Review of Literature

REVIEW OF LITERATURE

The science and art of human nutrition focus on nourishing human life. The relationship between nutrition and health can be trace back to the ancient Indian scriptures as early as 5000 BC [*Chandra 1985a*]. From the moment of conception until death the body needs energy to carry out all vital functions, which must be constantly replenished by means of nutrition. Traditionally, each person develops food habits and ways of eating from birth and they are influenced by ethnic background, cultural patterns, family habits, socio-economic status, health situation, available food and personal like and dislikes. However, in current times, increasing ethnic diversity has influenced the food pattern with intermingling of varieties of foods and ideas of foods. Modern society is fast paced and competitive. The modern life stresses, either physical or psychological send out waves that wash over the human body often contributing to disease and malnutrition [*Williams and Anderson 1996*]. The human body strives continually to maintain balance between the conflicting demands of external and internal forces. Any challenge whether chemical, physical, biological or psychological produces metabolic stress and effects to restore homeostasis ensue [*Fish and Friedmann 1998*]. Throughout history, links between nutrition and the immune response has been demonstrated repeatedly by the simultaneous occurrence of pestilence and famine. During times of war or natural disasters, sources of adequate nutrition may be limited and consequently, nutritional depletion and subsequent immune-meditated changes can occur that potentially threaten the survival [*Chandra 1985b*]. Malnutrition in the hospital setting exists today despite numerous advances in the medical and nutritional arenas. Surveys have found that 40 – 50 % of patients admitted to hospitals are at risk for malnutrition and up to 12 % are severely malnourished [*Daniel and Mercy 2003*]. The incidence of hospital malnutrition is largely due to disease process itself and so the relationship between nutrition and disease is important, as it may affect recovery from illness, surgery, or injury. Infections can be more serious in the presence of malnutrition, and many infections precipitate malnutrition. Malnutrition can result in apathy, depression,

fatigue, and loss of morale and can decrease a patient's ability to cooperate in his or her management [*Pennington 1995*]. Malnutrition and nutrient deficiencies affect various part of the immune system. However, treating malnutrition can itself cause complications, which partly depends on the route of access.

There may be situations where patients may occasionally need to undergo various surgical procedures for treatment of medical problems or injuries. Severe surgical illness results in metabolic responses that mobilise substrate (amino acids and fatty acids) from body stores to support vital organs, enhance resistance to infection, and ensure wound healing. Central to this process is the redistribution of body protein, which moves from skeletal muscle to support the central viscera. If unsupported, this protein-wasting state could result in prolonged convalescence, diminished immunity, and poor wound healing [*Wilmore 2000*]. Thus, disease related malnutrition might contribute to increased mortality, morbidity, and length of stay in hospital [*Reilly 1988*]. Gastrointestinal surgeries affect mode of feeding to meet nutritional requirements for healing and must accommodate resulting changes in the normal gastrointestinal tract. Surgery related malnutrition can result in poor postoperative results, impaired and delayed wound healing, and a higher incidence of postoperative complications [*Hill 1992 ; Rana et. al., 1992*]. Malnutrition can even result in impaired cardiac function and in weak muscles that fatigue more easily, including respiratory muscles [*Fraccadori and Borghetti 1991*]. Cardio respiratory dysfunction from malnutrition increases the risk of chest infection and limits mobility, predisposing to thromboembolism and pressure sores. Thus, nutritional therapy in every step of diseased state must modify food intake accordingly in order to maintain body's optimal nutritional status [*Williams and Anderson 1996*].

In this chapter discussion has been initiated with importance of nutrients including electrolytes and energy metabolism in normal human body, changes that occur during surgical procedures including role of hormones, mode of diet administration with special focus on *specialised nutrition support* through diet formulations for the surgical gastrointestinal patients.

I. DIGESTION AND ABSORPTION IN THE GASTROINTESTINAL TRACT:

The gastrointestinal tract is a sensitive mirror of the individual human conditions its physiologic function reflecting physical and psychologic conditioning. The digestion

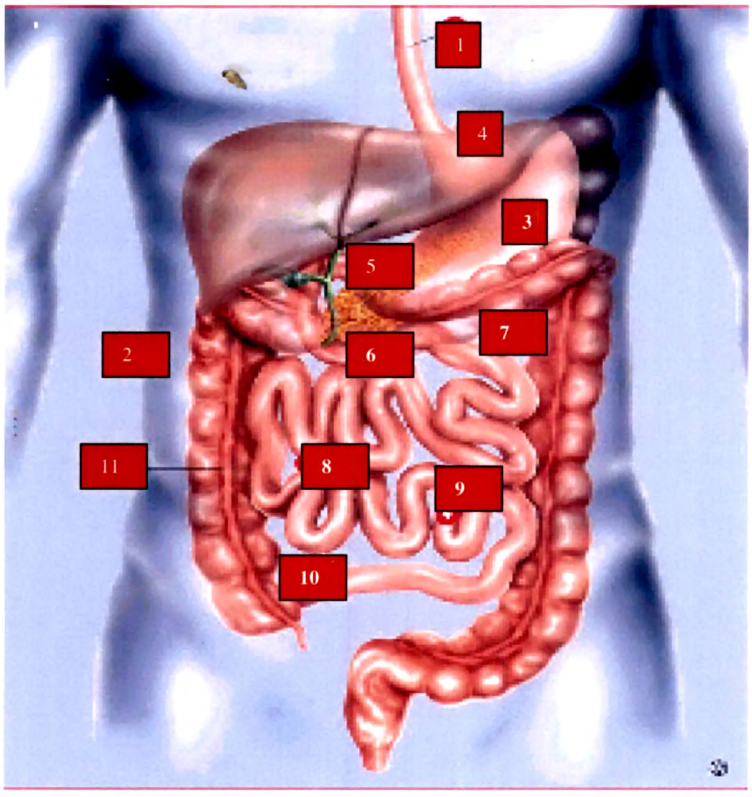
and absorption of food is accomplished in the gastrointestinal tract through a series of intimately related secretory and neuromuscular mechanism. Its vital absorptive process maintains protein metabolism as well as acts as a mechanical barrier so important in immune function. Sometimes many diseases may disrupt the normal functioning leading to some functional discomfort to serious disease even to complete obstruction needing even surgical procedures, which may lead to malnutrition.

1.The gastrointestinal tract:

It starts at the mouth, ends at anus and includes the salivary gland, the liver, pancreas and gallbladder [Fig 1]. Once the food is chewed and moistened, the bolus is moved passed the pharynx into the oesophagus by a swallow and is then propelled passes into stomach - an expandable reservoir where the food and digestive enzymes are churned together by powerful gastric contractions to form chyme. Approximately, every 30 seconds the chyme and the small food particles are emptied through the pyloric sphincter into the duodenum. The gastric emptying is controlled mainly by neural reflexes and gastrointestinal hormones [*Hunt and Groff 1990]*. There are number of gastrointestinal hormones like gastrin, Cholecystokin (CCK), secretin, gastric-inhibitory polypeptide (GIP), motilin, vasoactive intestinal polypeptide (VIP), glucagon, enteroglucagon, pancreatic polypeptide, bombesin and somatostatin who have different site of secretion like duodenum, proximal small intestine, small intestine, pancreas, and stomach [*Greene and Moran 1994*].

The small intestine has large mucosal folds, finger like projection through the mucosa (villi) and microscopic projections covering the villi (microvilli), a massive absorptive surface. The small intestine mucosa is comprised of a single cell thickness of mostly columnar epithelial cells, with endocrine cells, mucin cells, and Paneth cells interspersed between them. The absorptive capacity of the small intestine is greatly increased by the presence of villi, with corresponding crypts between them. The most mature cells occupy the tip of the villi, while immature cells are at the base of the villi, in the crypts. The immature cells proliferate and migrate to the tip, where they mature, then are reabsorbed or sloughed off into the lumen. The entire process takes only three to six days. This high rate of proliferation and turnover is usually well-regulated by nutrient availability, gastrin, growth hormone, bacterial flora, and neuro-regulatory activity. However, the presence of food passing through the

Fig 1 : THE HUMAN DIGESTIVE SYSTEM



1. OESOPHAGUS
2. ABDOMEN.
3. STOMACH.
4. A valve (allows the food to enter while keeping the acid-laden food from "refluxing" back into the esophagus,
5. PYLORUS
6. SMALL INTESTINE.
7. DUODENUM
8. JEJUNUM
9. ILEUM
10. Valve separates the small and large intestines to keep bacteria-laden colon contents from coming back into the small intestine.
11. LARGE INTESTINE.

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gastrointestinal tract seems to be the primary stimulus for regulation of this proliferative response, as it can affect all of the aforementioned regulatory systems [*Wilmore 1997].* After seven days of fasting, even with the use of TPN, gut mass can be reduced by as much as 50 percent [*Souba et. al., 1988 ; Souba 1988*]. Chyme moves through the ileocecal valve into the first portion of the colon (cecum). Some 80 – 90 % of the fluid that enters the colon is absorbed when the fecal matters enters the rectum. Feces are stored in the rectum until defecation [*Sullivan and Alonso 1999*].

2. Digestion and Absorption:

The food, which is, ingested, consists of carbohydrates, fat protein and small quantities of substances such as vitamins and minerals. These cannot be absorbed in their natural forms. Thus it is essential that these substances be digested into small compounds for absorption through a series of mechanisms.

a) Carbohydrate: There are three major sources of carbohydrate *viz.,* sucrose, lactose and starches in the normal human diet. In the process of digestion, starches are hydrolysed to disaccharides, which are further hydrolysed to the monosachharides glucose, galactose and fructose. Hydrolysis of starches begins in mouth under the influence of enzyme ptyalin (secreted in saliva) and the stomach containing the HCl also causes slight amount of hydrolysis further. The final hydrolysis occurs in the upper part of the small intestine by pancreatic amylase. The enzyme lactase, sucrase, maltase and isomaltase located in the brush border of epithelial cells digest the disaccharides to monosaccharides. The digestive products monosaccharides are then immediately absorbed into portal blood.

Absorption of carbohydrate is directly linked to the final stage of digestion Luminal carbohydrate digestion produces largely the diasaccharides molecules sucrose, lactose and maltose. During hydrolysis, they form monosaccharides, glucose, fructose and galactose. Sugars are co transported with sodium ions against their own concentration gradients, a process of great nutritional value. Once concentrated, within the enterocyte, the sugars pass by facilitated diffusion across the basolateral membrane into the interstitial spaces and from there diffuses into capillaries of the intestinal walls [*Williams and Anderson 1996*].

b) Fat: Most of the fat in the diet are in the form of neutral fat (Triglycerides). Diet also contains small quantities of phopholipids, cholesterol and cholesterol esters.

Though a minute amount is digested the stomach by gastric lipase, major digestion occurs in small intestine under the influence of pancreatic lipase. In this process, fat globules are emulsified by bile salts for the digestive enzymes to act. The bile salt micelles act as a transport medium to carry the monoglycerides and the free fatty acids to the brush borders of the epithelial cells. Fats being insoluble in water have absorption process. Absorption is a passive process and kinetics is largely dictated by lumen concentration of the lipid. Miceles produced by the action of bile salts is a carrier of lipid molecules to the enterocyte luminal membrane where the fatty acids and monoacylglycerols diffuse from the micelle through the lipid components of the membrane to enter the enterocyte cytoplasm. Once within the enterocyte, fatty acids and monoacylglycerols droplets are coated with a protein coat called apolipoproteins by which it makes the lipids more soluble. These coated droplets are called chylomicrons, which passes across the basolateral membrane of the enterocytes by exocytosis into the interstitial where they are inhibited from passing into villus capillaries by the basement membrane. Instead chylomicrons pass into the lacteals of the villus and, from there into the lymphatic system draining into the circulation at the great lymphatic duct behind the right atrium of the heart [*Williams and Anderson 1996*].

c) Protein: Digestion begins with the stomach by the action of enzyme pepsin splitting the proteins into proteoses, peptones and large polypeptides. They are further digested in the upper part of the small intestine under the influence of pancreatic enzymes (Trypsin, chymotrpsin and carboxylpolypeptides). Final products being the polypeptides are digested into aminoacids when they come in contact with the epithelial calls of the small intestine.

The amino acids produced from the protein digestion are absorbed by secondary counterpart with sodium ion. Some simple dipeptides remain within the lumen and these final peptide bonds are hydrolysed by aminopeptidase enzymes within the eterocyte luminal membrane [*Williams and Anderson 1996*].

d) Mineral absorption: Mineral absorption is more normally proportional to the dietary intake with two important exceptions, iron and calcium, the absorption of which can be regulated according to the needs of the body.

i) Sodium: The enterocyte membrane possesses carrier-protein for the transport of specific substrates. A specific sodium transporter exits on the enterocyte basolateral

membrane, exporting sodium from the cell by an energy dependent process. This effect of sodium transporter is to maintain a low intracellular sodium concentration. Sodium may pass by passive diffusion down its concentration gradient or may be transported by luminal transporter in association with nutrients such as glucose and aminoacids. It may also diffuse between the cells directly into the interstitial spaces. Water molecules follow sodium ions across the membrane. These frictional force between water and dissolved electrolytes drags sodium ions along with the movement of water. The jejunum, where intercellular junctions are large and osmotic forces greatest, solvent drag represents a significant portion of overall sodium absorption. Although, the intestine has a bi-directional sodium flux, it nonetheless is highly sodium preserving of the 250 – 300 $mEqd^{-1}$ of sodium consumed by the average adult over 95 % is absorbed is less than 5 $mEqd^{-1}$ excreted in the stool [*Williams and Anderson, 1996*].

ii) Potassium: It is most prevalent intracellular cation and only 2 % is located in ECF. It is crucial to maintain cell volume, hydrogen ion concentration (pH), enzyme function, protein synthesis and cell growth. In the ICF and ECF concentration gradient, potassium helps regulate neuromuscular excitability. Dietary potassium is absorbed in the small intestine. Urinary loss is the principle loss of potassium [*Humphreys, 1994*].

iii) Iron: A vital component of hemoglobin, transports oxygen to the various tissues of the body. All the intracellular iron is either hemoglobin or in the iron storage protein ferritin. Iron is rather unique in that nature regulates its absorption, because there is no mechanism that enables excretion of excess iron. Absorption of iron is a complex mechanism. Most dietary iron comes from ingested meat as myoglobin and hemoglobin. It is absorbed in the duodenum and proximal jejunum. There are separate transport mechanism for complexed (iron) (heme), which is most rapidly absorbed and for inorganic iron, which is preferentially absorbed in ferrous (Fe^2) form. Dietary ascorbic acid aids in iron absorption by reducing the ferric (Fe^3) ion to more absorbable ferrous form. The ferrous iron can than be complexed with apoferritin to form ferritin, an intracellular storage form of iron [*Williams and Anderson 1996*].

iv) Calcium: It constitutes 1.5 - 2% of the total body weight. About 10 – 30 % of the calcium in an average diet is absorbed. Absorption takes place in the small intestine.

chiefly in the duodenum. Controlled by the body's need for the calcium, vitamin D hormone stimulates a complex series of active transport mechanisms involving calcium-binding proteins, calcium channels and pumps. This transport complex arises the dietary calcium from the intestinal lumen into the mucosal cells (enterocytes) through the cell and across the basal membrane into blood circulation [*Mauchan and Noakes 1991; Newmark SR 1991*].

v) Phosphorus: It is closely associated with calcium free phosphate, absorbed in the jejunum of the small intestine in relation to calcium and is regulated by calcitriol [*Avioli 1988*]. In the typical feedback mechanism of hormone action, when serum phosphate level is low, kidney is stimulated to provide vitamin D hormone, which in turn enhance phosphorus absorption from the intestine.

vi) Magnesium: About 70 % of the 25 g in an adult is combined with calcium and phosphorus in the bone salts complex. Rest is distributed in various soft tissues and body fluids. Absorption of magnesium occurs throughout the small intestine and depends on the load present rather than a single factor (vitamin D). The process is accomplished by the positive diffusion and solvent drag [*Williams and Anderson 1996*].

e) Water Absorption: About 1.0 - 1.5 L of water is ingested each day with 5.0-10.0 L secreted by the G.I. tract in the form of salivary (1.2 - 2.0 L), gastric (2.0 - 3.0 L), biliary (0.5 L), pancreatic (1.0 - 2.0 L) and intestinal (1.0 L) secretions. About 80 % of this fluid is reabsorbed by the small intestine. Net water movement in or out of the lumen of the gut is determined largely by the tonicity of the enteral material. When meal is ingested, a large volume of fluid is added by the salivary glands and stomach and a hypotonic solution of chyme is deposited in the upper small intestine. In addition, the neutralization of stomach acid by bicarbonate from the pancreas decreases osmotic pressure of generating NaCl and H_2O. Because of the large intercellular force in the jejunum, water rapidly leaves the intestinal lumen, bringing enteric contents close to isotonicity. In the more distal intestine, the intercellular channels are smaller (3.0 - 3.5 A), creating a less porous membrane. Of the original 6.0 - 11.0 L of water entering the duodenum in 24 – hours less than 1.0L is delivered into the colon [*Williams and Anderson, 1996*].

II. METABOLISM:

1) Energy Metabolism and Energy Expenditure:

Energy metabolism is a sum of complex and integrated chemical reactions by which the body derives energy from the environment and maintains proper functioning of all biological processes [*Molina et. al., 1995*]

The human body requires a constant supply of energy to maintain homeostasis (life), was recognised as early as 18th century [*Kleiber 1961*]; the element oxygen of the air is taken up with the release of carbon dioxide and heat energy [*Bursztein et. al., 1989*]. In cellular metabolism of macronutrients, carbon dioxide is produced, oxygen is consumed and heat is generated in proportion to the amount of substrate being oxidised. The relationship among oxidation of substrate, oxygen consumption, carbon-dioxide production and release of heat are constant [*Becker 1984*]. The amount and types of food determines the pattern of substrate utilisation in healthy persons. In critically ill patients, substrate metabolism is markedly different as they have high-energy expenditure and catabolic rates than the normal persons [*Long et. al., 1990*].

Direct colorimetry [*Benedict and Carpenter 1910 ; Benzenger and Kitzinger 1963*], Harris and Benedict Equation [*1919*], Indirect colorimetry [*Jaquier 1981*], Double labeled water technique [1982], Fick Equation [*Liggett et. al., 1987*], Ireton and Jones Equation [*1992*], Swinamer Equation [*1990*] and Frankenfield [1994] have been developed by many physiologists and nutritionists for the measurement of energy expenditure in humans. Indirect colorimetry is the 'gold standard' for assessing energy expenditure as this method offers the most accurate evaluation for the critically ill patient's total energy expenditure to the clinicians and becoming an increasingly common tool for determining energy requirements of hospitalised patients [*Frankenfield et. al., 1994*]. Inspite of development of various equations, Harris Benedict Equation is most often quoted and used technique in assessing energy expenditure. Basal energy expenditure (BEE) is the minimum amount of energy the body needs to maintain homeostasis. In adults BEE is principally a function of body size or more specifically fat free mass [*Webb 1981].* BEE accounts for 60-70% of the total daily energy expenditure and due to sharing a large portion of total energy expenditure (TEE), attempts have been made to construct predictive standards. Now-a days effect of genetics, body composition, gender, age, physical

fitness and nutritional status are also being considered [*Ravussin and Bogardas, 1989*]. Many hospitalised patients are hypermetabolic and the degree varies from patient to patient and from day to day [*Vermeij et. al., 1989*]. Earliest work with critically ill patients, showed a more complex relationship between fever and energy expenditure [*Kenney and Roe 1962*] summarising 200 studies in Kinney's group, BEE of hospitalised patients was recommended to modify as 60 – 80 % of BEE for major tissue depletion, 110 % of BEE for major elective surgery, 110 – 125 % of BEE for multiple injury 120 – 150 % of BEE for major sepsis and 150 – 200 % of BEE for major burns [*Kinney et. al., 1968*]. Stress factor for hospitalised patients was suggested to calculate energy expenditure in modern intensive care unit [*Long et al., 1979*]. Studies showed that non-critical patients of cirrhosis, pancreatitis and Crohn's disease had negligible effect on expenditure [*Dickerson et. al, 1991 ; Stokes and Hill 1993*]. Critical medical illness is associated with hypermetabolism [*Liggett and Renfro 1990*]. Guillian-Barre' syndrome causes a hypermetabolic response on the order of 150 -168% of BEE [*Roubenoff et. al., 1992*] and sepsis order of 155 % of the BEE [*Kreymann et. al., 1993*]. Calculation of energy expenditure remains as important aspect of nutrition assessment in the hospital and is estimated with the assessment of BEE plus the allowance for activity and injury. Total energy requirements can be calculated by using stress equation: for mild and moderate infection, the energy requirement be increased by 20 - 30% and for severe infections the increase is about 50 % above the basal levels.

Energy is essential for maintenance of cellular integrity and functions, new tissue synthesis, thermoregulation and physical activity. The energy requirement of an individual varies with age, sex, body composition, physical activity and stress. A normal adult at rest, about 75 % of energy requirements reflect the energy needs of major organs *viz.,* brain 20 %, skeletal muscle 18 – 22 %, abdominal muscle 25 % and heart 11 %. However, with exercise, energy requirement of skeletal muscles increases and during a meal abdominal organs require more energy for digestion and absorption. The body derives energy by metabolism of carbohydrate, fat and protein provided exogenously in fed state and endogenously in post-absorptive state. A mixture of metabolic fuels including glucose, triacylglycerols, ketone bodies, non-stratified fatty acids and aminoacids present in the blood depends on fed or fast state

of the individual, extend of fuel stores and bodies recent and current metabolic demand. [*Bines 1998*].

Early concept as critical care nutrition of '***more calories being better***' has been changed and convention of 35 - 40 Kcal Kg^{-1} day^{-1} prevailed in 10 years ago has been reduced to 22 - 25 Kcal Kg^{-1} day^{-1}as optimum level of delivery in hypermetabolic settings. This was because of the fact that the patients during hypermetabolic state are unable to utilize excess calorie and despite deliver of adequate nutrient, endogenous glucose production is not reversed. The excess calorie delivery results in hyperglycemia, hyperinsulinemia, and hepatic steosis [*Martindale 2002*].

2. Carbohydrate:

Metabolic pathways have been developed to extract energy during the fed state and to provide needed energy during short term and long term deprivation. Glucose plays a key role in body metabolism .It is the preferred metabolic fuel for many tissues and is an essential fuel for the retina, red blood cells, renal medulla and the brain under normal conditions. Hormones notably insulin and the counter regulatory hormones glucagons, cortisol, growth hormone and epinephrine and substrates closely control carbohydrate metabolism. This control may be exerted by modifying an enzyme or by altering protein synthesis. These paths are further altered by disease, exercise and stress. In case of stress, the inherent control mechanisms are largely ineffective [*Elwyn and Bursztein 1993*].

In the fed state, glucose is derived from the digestion and absorption of carbohydrates provided in the meal. Fed state is characterised by increased blood concentration of glucose, aminoacids and fats. In the fed state, carbohydrate is delivered to the liver and other tissues especially skeletal muscles and brains. Some of the glucose and much of fructose is extracted by the liver for glycogen storage. *Gerard et. al.,* [*1993*] using nuclear magnetic resonance spectroscopy (MRS) found that 19 % of the glucose load is stored in the liver. Glucose is first metabolised (oxidised) to pyruvate and lactate under anaerobic conditions and then oxidised through Kreb's cycle in liver muscle and adipose tissues. Pyruvates oxidised into NADH + H_2 . FADH + CO_2. The NADH + H transports hydrogen to the respiratory chain when it is used to reduce oxygen to water. There are three important mechanism for this regulation: **a)** Insulin enhances glucose uptake into muscle and fat and stimulates glycogen synthesis. It inhibits lipolysis, glycogenolysis and

gluconeogenesis. High insulin level will decrease blood glucose while the low insulin level will rise blood glucose level by decreasing inhibition of glycogenolysis and reduced peripheral uptake of glucose. **b)** Glucagon increases liver glycogen breakdown, gluconeogenesis and ketogenesis from fatty acids. It also stimulates lypolysis from adipocytes in extra hepatic tissue. Result is the maintenance of blood glucose level. **c)** Neuroendocrine response to glucose deprivation in the brain rapidly increases glucose release from liver glycogen. About 40 % of glucose infused at 5 –6 $mg^{-1}kg\text{-}^{1}min^{-1}$ is oxidised [*Wolfe 1994*]. The actual oxidation rate varies with intake, degree of exercise and the tissue under study [*Shulman et. al., 1985*]. Most unoxidised glucose is stored as glycogen either directly or indirectly. In the indirect pathway, glycolysis and end product pyruvate and lactate are the substrates used for glycogen synthesis. Whether direct or indirect path predominates in the liver is not for certain [*Katz and Mc Garry 1984*]. *Gerara et al.,* [*1993*] observed that 74 % of the glycogen form directly from glucose and rest from pyruvate and lactate. Glycogen, a complex hydrated polymer arranged in a highly branched spherical form, allows glucose to be stored in large amounts without causing osmotic shifts. The terminal glucose molecules, within these branching structures are accessible to the enzymes mediating glycogen breakdown for rapid release of glucose in time of stress. The enzyme required for glycogen breakdown to glucose, glucose-6-phosphate, is present only in the liver. Muscle glycogen is metabolised by anaerobic glycolysis to form pyruvate and lactate. The lactate is then transported to liver where it acts as a precursor for gluconeogenesis which is called Cori cycle. The energy required for the resynthesis of glucose in the liver is derived from fatty acid oxidation. Several micronutrients *viz.,* thiamin, niacin, riboflavin, phosphorus and magnesium are required for carbohydrate oxidation. When they are short of supply, electrolyte imbalances and result an oxidation cannot continue. Insulin secretion increases the glucose load. The absolute glucose concentration and its rate of change are the principle regulators of the hormone, but other carbohydrates, certain aminoacids and fatty acids, metabolites and ketones also affect insulin concentration. Insulin improves transport of glucose into all tissues except the liver but has no effect on oxidation [*Jacobs et. al., 1990*].

When carbohydrate is supplied in sufficient quantities, lipogenesis eventually ensues and carbohydrate is stored as fat. Under normal healthy person, lipogenesis from

carbohydrate rarely happens but under overfeeding fat is synthesised from carbohydrates after maximal glycogen storage [*Jequier 1994*]. Fructose can enter the glycolysis pathway as fructose-1-phosphate. In the liver or fructose-6-phosphate in adipose tissues. Most of the fructose is metabolised by liver when serum glucose concentration are decreased, higher triglyceride, lactate and uric acid labels have been associate with fructose than the glucose feeding. In the liver, galactose is converted to glucose since galactose and its alcohol are toxic [*Stryer 1988*].

In post-absorptive state, the hormonal status of the body and the metabolic pathways change to ensure a continual supply of glucose [*Elwyn and Burstzein 1993*]. Glucagon derives hepatic glycogenolysis and gluconeogenesis to increase liver glucose output. Epinephrine promotes glycolysis in muscle and glucocorticoids enhance gluconeogenesis [*Rothman 1991*]. With prolonged starvation, the body gradually adapts by decreasing basal energy expenditure and protein turnover thus sparing protein store [*Waterlow 1986*]. Oxidation of fat provides more energy as the brain adapts to using ketones as fuels.

Metabolic Alterations of Carbohydrate in Stress and Disease:

Stress and disease conditions can alter the metabolism of carbohydrate. In post-operative stress, trauma and sepsis, hormonal control of metabolism is affected by increased cytokines and action of sympathetic nervous system [*Elwyn and Bursztein 1993*]. Glucagon, epinephrine and cortisol are increased. Energy expenditure rises with increase in body temperature and oxygen consumption, protein turnover is greater and despite ongoing protein synthesis, there is a net catabolism [*Cerra 1987*]. Alterations in carbohydrate metabolism are manifested as increased serum glucose and insulin increased protein breakdown and enhanced futile cycling. Hyperglycemia and hyperinsulinemia vary directly with the severity of injury or decreased stress [*Jeevanandam et. al., 1990*]. Liver does not respond to insulin and glucose concentrations that normally decrease gluconeogenesis and hepatic glucose output is enhanced [*Wolfe, 1994*]. Hypoglycemia of illness or injury is due to increased glucose production [*Elwyn and Bursztein 1993*]. Lipolysis and fat oxidation also increase with stress but ketone production is minimal. It was reported that more than 60 % of the cancer patients had abnormal glucose tolerance and the glucose intolerance is an early manifestation of the disease [*Rossi- Fanelli et. al., 1991*].

3. Proteins :

The proteins of the living matter act as organic catalysts (enzymes), as structural features of the cell, as messenger (peptide hormones) and as antibody. About 15% of the total body weight is made up of proteins of which half are intracellular and half are extracellular. Extracellular proteins include those that circulate in the bloodstreams (albumin, transferin and hemoglobin) and those that compose the intracellular matrix such as collagen and other fibrous proteins. Importance of protein in diet is primarily to act as a source of amino acids, some of which are *essential* (indispensable) dietary constituents because their carbon skeletons are not synthesised in the body of the animals. Other ones are *non-essential* (dispensible) because they can be made within the animal from carbon and nitrogen precursors. Protein consumed in the diet is enzymatically hydrolysed in the alimentary tract and passes into blood as free amino acid. Amino acids occur in the body in the free form and in the form of body proteins. The concentration of protein, bound amino acids in the tissues averages 2 M whereas the free amino acid pools are 0.01M [*Christensen 1964*] i.e., 0.5 % of the concentration of protein bound amino acid`. About half of body's nitrogen is contained in extra cellular tissues such as collagen and the remaining nitrogen is present in the lean muscle mass comprising skeletal and visceral muscles. The proteins within these tissues are constantly being broken down and resynthesised at a rate of 3.0 - 3.5 $g^{-1}Kg^{-1}day^{-1}$ in a young adult [*Bines 1998*]. The tissue concentrations of the free essential amino acids are very low whereas the concentrations of four of the non-essential amino acids are higher. In the fed state, amino acids are digested and absorbed in excess of the body's immediate requirements for incorporation into proteins or other molecules. They are oxidised for energy or metabolised to glycogen or fat and protein provides approximately 17 KJg^{-1} (4.2 Kcal g^{-1}). Prolonged fasting results in depletion in the liver and muscle glycogen stores. In the clinical setting, conversion of amino acids to glucose contributes to the glucose requirements of the brain. The transition to the metabolism of amino acids as an energy source is mediated by an alternations in the balance of insulin and glucagons. The breakdown of tissue protein of provide glucose results in a sustained loss of body nitrogen of approximately 12 g day^{-1} [*Bines 1998*].

Amino acids are subjected within the body to the series of metabolic reactions which are as: **a)** Part of the free acid pool undergoes catabolic reactions. This process

leads to the loss of the carbon skeleton as carbon-dioxide or its deposition as glycogen and fat, while the nitrogen is eliminated as urea. **b)** Some free amino acids are used for synthesis of new N -containing compounds *viz.,* purine bases, creatinine and epinephrine. These are subsequently, generally degraded without return of end products to the free amino acid pool. So, purines are degraded to uric acid, creatinine to creatinine and epinephrine to vanillylmandelic acid. In addition, the non-essential amino acids are made in the body using amino groups derived from other amino acids and carbon skeletons formed by reactions common to intermediary metabolism. Excess amino acids are degraded and carbons are oxidised to energy or are incorporated into glycogen or free fatty acids. In addition to metabolism, the existing proteins in the cell are continuously recycled, so the total protein turnover in the body is about 300 $gday^{-1}$. Since, vertebrates can reuse nitrogen with 100 % efficiency, obligatory nitrogen losses mainly as nitrogen occur. Nitrogen is lost mostly in urine in the form of urea (85 %) with lesser amount as creatinine and ammonia. Over relatively long periods, healthy adults maintain nitrogen equilibrium (zero nitrogen balance). A protein nitrogen balance occurs due to nitrogen intake exceeding the amount expelled while a negative balance often occurs during starvation, injury and severe infection. The metabolism of amino acids generates ammonia, one of the most toxic and reactive compounds in physiologic fluids. Ammonia levels in the blood are generally kept at non-toxic concentration (20 - 40 $\mu molL^{-1}$), primarily by the liver, which converts ammonia into urea, a non-toxic soluble compound. A large of the ammonia used for the urea synthesis arises from nitrogen catabolism in extrahepatic tissue. In these organs, ammonia is reformed but is either excreted (kidneys) or detoxified (liver). Liver has all the enzymes of urea synthesis and the enzymes are located only in the portal hepatocytes. Urea is highly soluble (2 mol L^{-1}), non-toxic molecule with high nitrogen content of 47 %. Urea accounts for 85 % of the total urinary with remaining 15 % contributed by the ammonia and creatinine. Urea synthesis is performed in the liver [*Kreb 1964*]. The biosynthesis of urea involves transamination, oxidative deamination, ammonia transport and the reactions of the urea cycle. Transamination, catalyst by enzymes transaminases or aminotransferases interconverts a pair of amino acids and a pair of ketoacids. Ammonia and carbon dioxide are formed from carbomyl phosphate, which reacts in turn with ornithine to give citrulline. This acquires another nitrogen from aspartic acid

to form arginosuccinate, which splits into arginine and fumarate. The fumarate goes back to the tricarboxylic acid cycle while the arginine splits by arginase into urea and ornithine. Ornithine thus released, participates in another cycle. The urea so formed is secreted directly into the urine but some passes in the lumen of the gut where urease causes release of ammonia. This ammonia returns via portal vein to the liver where urea is again formed. About 20 % urea is recycled through the gut flora [*Walser 1981*]

a. Role of Skeletal muscle in protein metabolism: Skeletal muscle is the largest tissue in the body [*Shils and Young 1988*]. It is the main site of metabolism of the branched chain aminoacid (leucine, isoleucine and valine). As muscle is also a major target for the action of insulin, insulin also promotes synthesis of muscle protein and reduces muscle protein breakdown. In man measurement of uptake and release of aminoacids indicates that fasting results in the release of large amounts equivalent to a loss of 50 g of protein daily from the muscles of 70 kg man [*Shils and Young 1988*] . Most of this takes the form of alanine and glutamine. The alanine formed by the transamination between pyruvate derived from glucose and aminogroups transferred from aminoacids present in muscle. In consequence, alanine becomes a carrier of nitrogen from muscle to liver, where its carbon skeleton enters the gluconeogenesis in the liver, where its carbon skeleton enters the gluconeogenic pathway whilst its aminogroup is converted into urea. The other carrier of nitrogen from muscle is glutamine formed when glutamic acid accepts nitrogen as its amide group. This glutamine passes to the intestine where about half undergoes transamination to alanine, which now goes to the liver. Following gluconeogenesis in the liver, some of the carbon comes back to muscle as glucose, the overall exchange between liver and muscle being named the glucose-alanine cycle. Measurement of the arteriovenous difference across the forearm has demonstrated that if a meal is given the output of aminoacid diminishes and that after a meal containing, it is completely reversed so the muscle actually gains protein [*Shils and Young 1988*].

b. Plasma protein metabolism: It can be more readily sampled in man and thus occupies a specific place. Most of the major proteins in the plasma are secreted from the liver, as most of them are glycoproteins with notable exception being serum albumin. The rate of plasma protein formation by the liver can be extremely high as 2

ghr^{-1} or as much as 50 $gday^{-1}$. A diet low in protein will show a progressive reduction in plasma albumin level due to reduced synthesis of plasma protein [*Shils and Young 1988*]. Addition of protein to the diet will stimulate protein synthesis followed by restoration of the level of albumin in the plasma. Serum albumin is thus too insensistive to serve as reliable indicator of subclinical malnutrition. *Shetty et. al., [1979]* have shown that plasma protein with more rapid turnover rates than albumin can be more sensitive indicators of protein or calorie depletion and repletion.

4. Lipids:

Fat has been regarded as a calorie-dense energy source. The surface area of ingested triglyceride (TG) is much increased by mechanical and emulsificaion mechanisms of chewing and gastric action. Lingual lipase and gastric lipase produces diglycerides (DGs) and fatty acids (FAs). The gastric chyme, which contains TG, DG and FA in small, oily droplets, is delivered intermittently in small amounts to the duodenum. The cells of the intestinal mucosa can absorb only two hydrolytic products of TG digestion, 2-monglycerides (2-MG) and free fatty acids (FFA). Partial hydrolysis of the TG and DG is accompanied by pancreatic lipase in the small intestine. The presence of the lipid components of chyme and acid pH in the duodenum induced release of cholecystokinin (CCK) and secretin. Pancreatic lipase continues the hydrolysis of the remaining TG and DG. The pancreatic lipase has greatest affinity for FAs. Affinity of enzyme for FAs is much less avid and so the products of these digestion are FA and 2-MG s. This products are incorporated into mixed micelles containing partial glycerides, FFA, bile-acids and cholesterol [*Kelley 1999*]. Free cholesterol in the diet requires no digestion but is emulsified by the components of bile. Cholesteryl esters (Cholesterol linked to FAs) are hydrolised to cholesterol plus FA by pancreatic cholesterol esterase. Phospholipids undergo hydrolysis of the FA by pancreatic phospholipase A_2. The resultant lysophospholipids, cholesterol and FA s are absorbed by the passive diffusion into enterocytes along with the products of the TG digestion [*Kelley 1999*].

Once inside the enterocyte, FA and MG are reesterified into TGs, which are then incorporated into chylomicrons. The chylomicrons, which contain cholesterol, cholestryl ester, phospholipids and protein, are secreted by the enterocytes into the local lymph vessels and enter the blood stream through the thoracic duct. Lipoprotein

lipase, found in the endothelial membrane hydrolyses the TG releasing FFA s that diffuse into the adipocytes where they are reesterified and stored as TG. In muscle, FAs may be reesterified or used immediately for energy. The process of digestion and absorption of TG is affected by the chain length of the FAs involved. When medium chain fatty acids are present, they require smaller amounts of bile salts and diffuse into luminal cells faster than TGs along with long chain FAs. Short-chain fatty are preferentially hydrolysed by pancreatic lipase [*Kelley 1999*]. FFA levels are lower or reduced in the fed state as compared with starvation. In the fed state insulin stimulates triglycerol synthesis. During fasting triaclyglycerol is converted into fatty acids and glycerol. Within days, glycerol and palmitate release increases by 2 - 3 times of fed levels. This release is regulated by hormone-sensitive lipase. Owing to the absence of glycerol kinase in the white adipose tissue, glycerol cannot be completely metabolised within the adipocytes and is transported to the liver where it is converted to glucose by gluconeogenesis. The FAs either are released from the adipocytes to be oxidised by the liver or other tissues or may be reesterified with glycerol 3-phosphate and reenter the cycle to form triaclyglycerol [*Bines 1998*]. FAs delivered to the liver may be oxidized or reesterified into triacylglycerols. FA oxidatiom is stimulated by the activation of carnitine / acyl carnitine translokase acyltransferase, which effects the transport of long chain fatty acids into the mitochondria. Most of the acetyl-CoA produced from FA oxidation is metabolised to acetoacetate, which in turn may be converted β–hydoxybutyrate and acetone. These products are ketone bodies, which are produced, in small quantities in fed state and they are generally metabolised by the liver and not releasesd in the circulation. During fasting, the rate of production acetoacetate and β–hydoxybutyrate significantly increases. These metabolites are released into the circulation and can be used by brain and other tissues as an alternative source [*Bines 1998]*

Fat metabolism during critical illness has been widely characterised. FFA levels near post-absorptive levels have been observed to increase. This was in response of increase in hormone concentration following injury. Elevation of epinephrine and glucagons would elevate FFA levels at the same time the insulin levels in response to increased gluconeogenesis and blood glucose concentration and subsequently attenuate the FFA elevating effects of these hormones. Insulin resistance frequently accompanies elevated insulin levels to glucose transport by muscle tissues. Lipolysis

can be inhibited by insulin and elevated catecholamines level can overcome the inhibition of lipolysis by higher insulin levels [*Schlichtig and Ayres 1988*]. The percentage of energy expenditure supplied by lipid and the lipid requirements of the nutrition support regimen is a matter of concern. Cohen [1994] concluded that fat oxidation accounted for 70 – 90 % of REE. In addition, while blood FFA levels may not be increase, the release of FFA from adipose tissue is increased. The liver uptake and reesterification of FFA are also increased. The situation is altered somewhat when stressed patients are fed [*Goran et. al., 1990*].

5) Fluid balance:

The average adult consumes 2.0 - 2.5 L of water daily. Of this amount 1.5 L is ingested as fluid. The remaining is extracted from solid food or is produced during oxidative metabolism [*Shires et. al., 1994*]. Approximately, 300ml of water is generated daily from the oxidation of carbohydrate, proteins and fats [*Horne and Swearingen 1993*]. Fluid losses occur via kidney, lungs, skin and gastrointestinal surgical drains, chest tubes, fistulas, large open wounds and hemorrhage are other contributors of fluid loss. The kidneys are the primary regulators of fluid and electrolyte status. Of the 180 L of plasma, the kidney filters daily about 1.5 L, which is excreted as urine [*Horne and Swearingen, 1993].* Urine osmolality is determined by the amount of metabolic waste it contains. The kidney have a maximal concentrating ability of 1400 $mOsmKg^{-1}$ of water. Renal contracting ability decreases with advancement of age.

Nearly 500 - 600 ml of fluid is lost through the skin everyday. Insensible fluid is essentially void of electrolytes and is considered free water loss; sensible loss via sweat varies with climate and activity levels and losses may be 2.0 $Lhour^{-1}$ in extreme case. Sweat contains appreciable amount of electrolytes (15-60 mEq $Na^{+}L^{-1}$) but hypotonic. Insensible fluid loss also occurs via lungs and may in the order of 400 ml per day [*Shire et. al., 1994*]. Despite 6.0 - 8.0L fluids, passes through G.I. tract daily only 100 – 200 ml is lost. The electrolyte concentration of gastrointestinal secretions, vary greatly but are generally isotonic or hypotonic. During illness of G.I. tract, considerable fluid losses via nasogastric suctioning, vomiting, diarrhoea and fistula drainage occurs. If these losses are not replaced, severe fluid deficit can result.

Insensible water loss and loss through urine, sweat and stool must be considered for fluid maintenance. Moreover, metabolic status is to be considered which affects the fluid requirements. In fever, fluid requirement is increased by 12.5 % for each rise of 1°C of body temperature above 37°C. Other factors are hypermetabolism and hyperventilation [*Shire et. al., 1994*]. Body's homeostatic mechanisms make necessary adjustment for maintenance of normal extracellular volume, composition and osmolality. This in turn ensures a relatively constant cell environment and facilitates normal cell function [*Horne and Swearingen 1993*]. Depletion of ECF volumes, hypovolemia occurs with abnormal losses from gastrointestinal tract, kidney and skin, hemorrhage, fluid deprivation and sequestration of third-space fluid. Water loss is accompanied by loss of electrolytes, causing imbalance in osmolar, acid-base and electrolytes. With severe dehydration, decreased tissue perfusion due to decreased ECF volume may lactic acidosis and acute failure [*Shires et. al., 1994*]. Expansion of ECF volume (hypervolemia) occurs with decreased renal excretion of sodium and water, excessive intervenous fluid administration or interstitial fluid-plasma fluid shifts [*Horne and Swearingen 1993*].

6. Electrolytes:

Electrolyte disorders, either concurrently or independently may result in abnormal electrolyte losses or gains or normal regulatory mechanisms may be rendered ineffective. Recognition and correction of these disorders is crucial to preventing a host of potentially life-threatening physiologic squeals.

a) Sodium: Sodium is mostly is intertwined with fluid balance and its changes in concentration stimulate a variety of regulatory mechanism to restore sodium and water homeostasis. Losses occur principally via urine sweat and gastrointestinal secretions. Sodium balance is maintained by the kidneys that are able to limit renal sodium losses to less than 1 mEq day^{-1}. Hyponatremia (Na^{+}<130 $mEqL^{-1}$) represents a relative loss of sodium in proportion of water or gain of water in proportion to sodium. Plasma osmolality and urinary sodium values are helpful in determining the cause of hyponatremia. Generally symptoms of hyponatremia are not manifested until serum concentration reached to 120 -125 $mEqL^{-1}$ .The severities of symptoms is affected by degree of hyponatremia and rapidity of onset.

Asymptomatic hypovolemic, hypotonic, hyponatremia is managed with administration of saline solution [*VanZee et.al.,1992*]. Cellular dehydration owing to the movement

of free water along a concentration gradient from the ICF to the ECF is the key feature of hypernatemia (Na^+>150 $mEqL^{-1}$) regardless of volume status. Hypernatremia can result from free water loss (gastrointestinal, renal cutanoeus and peritoneal losses or sodium gain). Drug treatment is required for both nuerogenic and nephrogenic diabetes insipidus. Hypervolemiac hypernatremia requires diuretics and water replacement along with dialysis.

b) Potassium: Potassium enters the body through food, medication and potassium containing intravenous fluid. The body also releases potassium into ECF when there is cell breakdown or when ECF pH drops. Losses occur through the gastrointestinal tract, kidneys and skin. Formed stools contain potassium 5 -10 $mEqday^{-1}$. Sweat contains 5 -10 $mEqL^{-1}$ and total daily volume is small [*Mc Donald 1995*]. Kidney is the principal regulator of potassium balance and hemostasis is maintained by excretion of urine. Obligatory renal loss is 5 –10 $mEqday^{-1}$ [*VenZee et al., 1992*].

Hypokalemia (K^+< 3.5 $mEqL^{-1}$) results from a decrease in the total body potassium or shift of potassium from the ECF to the ICF. Most gastrointestinal secretions are potassium rich, so abnormally large gastrointestinal losses carry the risk of hypokalemia. Extracellular potassium decreases with anabolism, alkalosis and increased levels of insulin, epinephrine and aldosterone [*VenZee et al., 1992*]. Clinical manifestations include muscle weakness, leg cramps, nausea, vomiting, ileus and a weak, irregular pulse [*Whitmire 1999*]. Hyperkelemia (K^+>5.5 $mEqL^{-1}$) can result from an increase in exogenous or endogenous potassium load and extracellular potassium shift or indirect potassium excretion. Neuromuscular dysfunction dure to hyperkalemia accounts for cardiovascular and gastrointestinal symptoms. Electrocardiography abnormality, hypertension, ventricular fibrillation and diastolic cardiac arrest are the cardio vascular symptoms whereas nausea, vomiting, diarrhoea and intestinal coli are the gastrointestinal symptoms of hypokalemia [*Whitmire 1999*].

c) Calcium: This ion functions as an important regulation of most neuromuscular functions and enzymatic processes. Average adult's total body calcium is 1.0 - 2.0 Kg; nearly 90 % of it is in bone and teeth in the form of calcium carbonate or calcium phosphate [*VenZee et. al., 1992*]. Less than 1% is located in the ECF. Plasma calcium concentrations are regulated by parathyroid hormone and calcitonin. Low serum calcium levels stimulate release of parathyroid hormone which increases bone

reabsorption, stimulates renal conservation of calcium and activates vitamin D which in turn increases gastrointestinal calcium absorption [*Horne and Swearingen 1993*].

Three forms of plasma calcium, ionised, bound and complex localised calcium, is the most physiologically important and accounts for approximately 45% plasma calcium. Approximately 40% of plasma calcium is bound to protein as albumin and remaining 15% is the complex form of phosphate, citrate, sulphate, lactate and bicarbonates. The ratio of ionised to total calcium is affected by plasma pH and protein levels. Acidosis increases the ionised fraction and alkalosis decreases it [*Whitmire 1999*].

Symptomatic hypokalemia can occur with a decrease in total body calcium or a decrease in the fraction of ionised calcium. Hypocalcemia (total Ca^{++}< 8.0 $mgdl^{-1}$; ionised Ca^{++}> 4.5 $mgdl^{-1}$) can decrease calcium absorption, increase its loss or alter its regulation. Hypocalcemia symptoms are neuromuscular and include tetany, muscle weakness, muscle and abdominal cramps, hyperactive deep tandon reflexes and electrocardiographic changes [*Guise and Mundy 1995*]. Hypercalcemia (total Ca^{++}<11.0 $mgdl^{-1}$; ionised Ca $^{++}$> 5.5 $mgdl^{-1}$) can occur with either rise in total serum calcium or increase in the fraction of ionised calcium [*Horne and Swearingen 1993*]. The critical level for emergency treatment of hypercalcemia is more than 15 $mgdl^{-1}$ [*Shires et. al., 1994*]. Early symptoms of include fatigue, muscle weakness, anorexia, nausea, vomiting, constipation and depressions [*Horne and Swearingen 1993*].

d) Phophorus: Phosphorus is an important constituent of all body tissues and plays a vital role cellular bioenergetics. It is important structural component of bones and teeth, facilitates normal nerve and muscle function and act as an acid-base buffer in the urine. Approximately 85 % of it is in the bones and is exchangeable with small fractions in the ECF (~1%) The remaining 14 % is found in the soft tissues Plasma phosphorus exists almost as free or protein-bound phosphate. Free phosphate exits in univalent ($H_2PO_4^-$) and divalent (HPO_4^{--}) forms. Phosphate levels are affected by intake, intestinal absorption, renal excretion and hormonal regulation associated with bone metabolism [*Whitmire 1999*].

The hypophosphatemia (P < 2.0 $mgdl^{-1}$) occur gradually as a result of inadequate dietary phosphorus intake or impaired absorption. This can occur with alcoholism and prolonged use phosphorus-binding antacids. It can result from transient intracellular shifts, increased urine losses or sudden increase in phosphorus utilisation. Hypophosphatemia associated with refeeding syndrome can be severe and results

from sudden increase in phosphorus utilisation. Symptoms of sever phophorus depletion (P < 1.0mgdl^{-1}) include weakness, impaired myocardial and respiratory muscle function, acute respiratory failure, impaired WBC functions, confusion and coma [*Whitmire 1999*]. Hyperphosphatemia (P> 5.0mgdl^{-1}) is caused by acute and chronic renal failure. It can also result from endogenous release of phosphorus into the ECF due to significant self-destruction [*Horne and Swearingen 1993*].

e) Magnesium: It is essential in activity enzymes involved in protein and carbohydrate metabolism and ATPases involved in the intercellular electrolyte homeostasis (Na^+, K^+, Ca^{++} and protein pumps). It is vital in transmission of neuromuscular activity, central nervous system activity and myocardial function [*Horne and Swearingen 1993*]. Majority of total body magnesium is incorporated into bone (50 – 60 %). Only 1 % is located in the ECF, the remainder in the intracellular compartment. One third of plasma magnesium is protein bound; a small portion is complexed to citrate, bicarbonate and phosphate. The remainder is free or ionised, which is physiologically important [*Al-Ghamdi et. al., 1994*]. Magnesium levels are regulated by gastrointestinal absorption and renal excretion. Normally, one-third of dietary magnesium is absorbed. Renal excretion varies and is affected by sodium and calcium excretion. Magnesium excretion decreases with decreased calcium and sodium excretion. The kidneys have an amazing ability to conserve magnesium [*Shier et. al., 1994*].

Hypomagnesemia (Mg^{++}<1.5mEqL^{-1}) results from insufficient intake, impaired gastrointestinal absorption or excessive gastrointestinal loss and increased urinary loss. Hypomagnesemia can develop with acute pancreatitis, hyperaldosteronism, diabetic acidosis and thermal injury. The symptoms become evident as serum levels drop below 1.0-1.2 mEqL^{-1} [*Al-Ghamdi et. al., 1994*]. Magnesium deficiency can cause muscle weakness, hyperactive tendon reflexes, muscle tremors, tetany, cardiac arrhythmias, blood pressure elevation and vascular resistance [*Shier et al., 1994*]. Hypermagnesemia (Mg^{++}> 2.5mEqL^{-1}) occurs frequently in acute or chronic renal failure. Magnesium containing antacids or laxatives can result in symptomatic hypermagenesemia. Other conditions are adrenocortical insufficiency, early burn injury, severe trauma, surgical stress, severe dehydration and severe acidosis [*Ven Zee et al., 1992*].

f) Chloride and Bicarbonate: Chloride is distributed with sodium in the ECF where it functions to maintain fluid and acid-base balance. It functions as a constituent of hydrochloric acid in the stomach. Deficiency may result in alkalosis and impaired cognition [*Katz, 2003*]. Chloride ion absorption is managed passively and actively. The active sodium chloride counterpart or counter transport described earlier plays a role primarily in the ileum and is effective against a large electrochemical gradient. Passive diffusion of chloride can occur through paracellular spaces, since the interstitium is slightly electrically positive compared to the gut lumen. A significant portion of chloride transport involves reabsorption of chloride ion secreted as HCl by the stomach. Bicarbonate absorption in the jejunum involves the function of carbon-dioxide in the gut lumen from HCO_3 ion and secreted hydrogen ion. These generate the high partial pressure from carbon-dioxide in the gut lumen which diffuses back into the cell and reforms bicarbonate and hydrogen ion by way of carbonic anhydrase. HCO_3 diffuse into the blood whereas hydrogen ion is resecreted in exchange for chloride and assists in neutralizing stomach acid [*Koltun and Pappas 1996*].

7.Trace Elements

Small amounts of trace elements may act as necessary enzyme components in essential cell metabolic reactions. They act as structural molecule components and as building material inessential cell and tissue formations. Micronutrients or trace elements (TE) are present in the body in extremely small amounts (< 0.005% of the body weight). They are now known to have supple roles in metabolism and contribute to overall well being. Several TE have been identified to be essential for humans, i.e., they must be provided to the patient parenterally or enteraly. They are zinc (Zn), Chromium (Cr), Copper (Cu), manganese (Mn), selenium (Se), iron (Fe) iodine (I), cobalt (Co) and molybdenum (Mo). They are classified into three major groups – **a)** Cationic elements such as Zn, Fe, Mn and Cu which are absorbed from the gut with variable efficiency and whose homeostatic control is mediated by the liver and gastro intestinal tract, **b)** Anionic elements such as Cr, Se, Mo and I which are absorbed efficiently by the gut and excreted mainly in the kidney and **c)** TE that exists as organic complexes which affect their metabolism like selenoamino acids, Cr 'glucose tolerance factor', heme Fe and Co in cobalamine [*Sriram 2003*].

These trace elements carry out their functions in three ways – **a)** they amplify the full functions of the larger molecules which they are a part **b)** they are specified to the particular function involved and **c)** they contribute to the homeostatic regulation through their absorption-excretion balance and the degree of their carrier transport situation [*Braunschweig, 1999*]. TE are involved in cellular biochemistry at such fundamental levels that the deficiencies of any of these can cause metabolic alternations with an expected increase in morbidity and mortality. It is suggested that TE be considered for all patients on nutrition support for any duration greater than 7 days [*Sriram 2003*].

8.Vitamins:

They are organic compounds, the body requires in small amounts for metabolic processes but cannot produce endogenously. Vitamins are divided into water soluble and fat soluble groups. Fat-soluble are stored in the body in sufficient reserves so that daily intake is not required. They include A (retinols), D (calciferol), E (tocopherol) and tocotrienols) and K (derived from naphthoquinone for prothombin and blood clotting factor. Water-soluble are generally readily available in food supply and are well absorbed and stored to a very limited extent in the body. The water soluble vitamins include the B-complex– B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_5 (pantothenic acid), B_6 (pyrodoxine), B_{12} (cyanocobalamine), folate and biotin as well as vitamin C. In addition, some organic nutrients have vitamin-like properties but true requirement remain uncertain. They can be enlisted as choline, taurine, carnitine, myo-inositol, bioflavonoids, lipoic acid and co-enzyme Q [*Katz 2003*]. Fat soluble vitamins are primarily absorbed by micelles along with fats and exit the mucosal cell through chylomicrons to enter the lymph. Water-solubles are absorbed in the ileum and jejunum by various means. Vitamins C, B_1, and B_{12} and niacin use active transport mechanisms linked to sodium cotransport. Folic acid and vitamin B_2 are absorbed by facilitated diffusion. Pyridoxine is absorbed by facilitated diffusion. Vitamin B_{12} absorption requires a glycoprotein called 'intrinsic factor' which is produced by the parietal cells of the stomach. One intrinsic factor molecule binds two molecules of cobalamine and this complex attaches to a specific receptor and any compromise of the production of intrinsic factor, as occurs in patients after proximal gastrostomy, decreases vitamin B_{12} absorption. After absorption, the free vitamin is extruded from the cell and transported into the blood by B_{12} binding proteins called

transcobalamines. VitaminB_{12} is essential in DNA synthesis and deficiency leads to anemia.

9. Acid –Base Balance:

Maintenance of cellular and extra cellular pH is essential like since the activity of many processes (e.g enzyme activity) is pH dependent. Hydrogen ions are generated by cellulometabolism (independent of dietary acid load) and the major role of acid-base homeostasis is to prevent acidification occurring. Blood and tissue pH are tightly regulated by the presence of buffer system which alternate changes in acid load and the subsequent excretion of volatile acid by the lungs and fixed acids by the kidney [*Jardine and Kilpatrick 1999*]. Daily metabolism of carbohydrate, protein and fat generate 1mEqHkg^{-1} body weight [*Humphreys 1994*]. Acid-base equilibrium is maintained through the action of buffer systems, the regulation of H^+ and $HCO3^-$ (excretion and reabsorption by the kidneys and regulation of CO_2 eliminated by the lungs). When there is impairment of body's regulatory mechanism occur or when acid-base losses or gains exceeds regulatory capabilities, acid-base dysequlibrium ensues [*Whitmire 1999*]. Protein and phosphates are important in intracellular pH. Hemoglobin-oxyhemoglobin system is the primary intracellular buffer of RBC. The bicarbonate-carbonic acid system is the principle buffer of the ECF compartment and accounts for 50% of the body's buffering capacity. Inorganic or organic acids combine with bicarbonates to produce carbonic acid and sodium salt of the inorganic or inorganic acid. The carbonic acid dissociates into CO_2 and water and CO_2 eliminate through lungs. The inorganic acid anions are excreted by the kidneys with hydrogen or as ammonium salts.

Lungs excrete volatile acid (CO_2) by changes in the rate and volume of respiration. Respiratory 'dry' is regulated by respiratory centers in the brain stem which response to changes in pH and PCO_2 of cerebrospinal fluid and signals from chemoreceptors in the carotid and aortic bodies that are responsive to changes in pH and PCO_2 of the arterial blood [*Jardine and Kilpatrick 1999*]. Kidneys regulate acid-base balance by adjusting HCO_3^- levels and depends on an array of mechanisms that alter Na^+, H^+ and HCO_3^- excretion and reabsorption and rate of NH_4 synthesis. Excess CO_2 combines with water to form H_2CO_3, which dissociates into H^+ and HCO_3^-. Hydrogen ions are exchanged for Na^+ and excreted producing acidic urine. Bicarbonates combine with Na^+ and enter to peritubular plasma and returns to ECF [*Horne and*

Swearingen 1993]. The mechanism may be inhibited by dehydration and Na+ deficiency [*Ven Zee et al., 1992*]. When ECF becomes alkalotic, the kidneys conserve hydrogen H^+ and increase HCO_3^- excretion to produce alkaline urine. This mechanism is inhibited by deficiency of Na^+ or K^+. Metabolic acid-base disorder may occur due to metabolic acidosis, metabolic alkalosis and respiratory alkalosis. Metabolic alkalosis is caused by an absolute or relative increase in acid concentration. This can occur via addition of acid from exogenous sources, from endogenous acid generation or failure to excrete the acid load. Direct loss of HCO_3^- also causes metabolic acidosis. It is characterised by an arterial pH below 7.35 and serum HCO_3^- below 25 $mEqL^{-1}$. Strong acid reacts with $NaHCO_3$ forming Na^+ salt of the acid and HCO_3^-. In this process HCO_3^- is consumed resulting in decrease HCO_3^-. In addition, as H^+ move from the ECF to the ICF, K^+ is exchanged to maintain electroneutrality and moves from the ICF to the ECF [*Whitmire 1999*]. Metabolic alkalosis by an absolute or relative increase in alkali concentration. This can occur via addition of HCO_3^- or precursors or loss of acid or loss of fluid containing more Cl^- than HCO_3^- [*Horne and Swearingen 1993*]. Metabolic alkalosis can also occur with hypovolemia and severe K^+ depletion. Hypovolemia decreases renal perfusion, which stimulates reabsorption of Na^+ and water. Carbonic acid (HCO_3) is reabsorbed with Na+ generating metabolic alkalosis. In severe hypokalemia, K^+ moves from ICF to ECF. H^+ ions are exchanged resulting in intracellular acidosis and increased renal H^+ excretion. Metabolic alkalosis is characterised by arterial pH 7.45 and $HCO_3 > 25$ $mEqL^{-1}$. Respiratory alkalosis results from increased alveolar ventilation and elimination of CO2. It is characterized by hypocapnia ($PCO_2 < 40mmHg$) and pH above 7.40. Chronic respiratory alkalosis occurs in pulmonary and hepatic disease [*Whitmire 1999*].

III. GASTROINTESTINAL DISEASES:

The normal function of gastrointestinal tract may be disrupted with some functional discomfort to serious disease to complete obstruction. There may be number of problems right from the beginning of the tract and continue up to the end. There may be oral problems due to gingivitis (inflammation of gums), stomatitis (inflammation of oral mucosa), glossitis (inflammation of tongue) and cheilosis (a cracking and dry

scaling) or dental problem or disorders in salivary glands and salivation or swallowing disorders (dysphagia). There may be oesophageal problems, which may disrupt normal swallowing and food passage due to oesophageal spasm (uncoordinated contraction of the oesophagus), oesophageal stricture (narrowing caused by inflammation or tumor) and oesophagitis (inflammation). These conditions require medical attention for dilation or sometime surgery.

Gastrointestinal problems arising in the stomach include nausea and vomiting and peptic ulcer in a major clinical problem. Major complication of peptic ulcer in the older patients are bleeding, perforation and obstructions [*Katz 1991*]. There are multiple causes of malabsorption condition of small intestine, which results into maldigestion due to pancreatic disorders, biliary disease, bacterial overgrowth or ileal disease [*Caspary 1992*]. It may also result from intestinal steosis, mucosal alterations, intestinal resections or lymphatic obstruction. Inflammatory bowel disease (IBD) like crohn's disease and ulcerative colitis produce mucosal tissue lesions, are now wide spread diseases of the small intestine [*Hanauer 1996*]. Short-bowel syndrome (SBS) is a pattern of varying metabolic and physiologic consequences of surgical removal of parts of the intestine with extensive dysfunction of the remaining portion of the organ [*Friedman 1991*]. Diverticular disease of large intestine becomes problematic when infected and inflamed from fecal irritation and colon bacterial infection. In addition, there are irritable bowel syndrome (IBS) and constipation also in the large intestine.

The accessory organs of the gastrointestinal tract are liver, gallbladder and pancreas. Diseases of these organs can easily affect gastrointestinal function and cause problems in the normal handling of specific types of foods. Viral hepatitis like Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E and newly discovered Hepatitis G are the inflammation of liver which now-a-days major public health problems throughout the world affecting hundreds and million of people [*Martinot 1997*; *Koff 1997; Lee 1997*]. Among all diseases cirrhosis of liver is the leading nonmalignant cause of death in most of the developed world [*Silk, 1991*]. In addition, hepatic encephalopathy is a major serious complication of end-stage liver disease. Cholecystitis (inflammation of gallbladder) and cholelithiasis (the formation of gallstone) are diseases of the gallbladder. Acute pancreatitis and chronic pancreatitis are primarily caused by alcoholic abuse. Other causes include biliary disease malnutrition drug reaction, abdominal injury and genetic predisposition [*Williams and*

Anderson 1996]. Nutritional support is a primary therapy for patients who develop malnutrition secondary to intestinal disease such as enterocutenous fistulas, short bowel syndrome, inflammatory bowel diseases with systemic sepsis or slow growing malignant tumors associated with oropharyngeal or oesophageal obstruction.

IV.GASTROINTESTINAL SURGERY:

Pathophysiology of the catabolic response to surgery

More than half a century has passed since Cuthbertson observed that bone fractures cause a large increase in urinary nitrogen excretion, thereby establishing negative nitrogen balance as a metabolic hallmark of trauma. The cumulative net nitrogen losses after elective abdominal operations range between 40 and 80 g of nitrogen; complications that delay the use of the gastrointestinal tract may result in nitrogen losses of up to 150 g [*Kinney and Elwyn 1988*]. Patients suffering from multiple injury and septic shock lose more than 200 g of nitrogen, while nitrogen losses after severe burns can exceed 300 g. The clinical importance of this catabolic pattern can be appreciated more readily when one remembers that 1 g of nitrogen is the equivalent of 30g of hydrated lean tissue. Therefore, a loss of 50 g of nitrogen, as seen after uncomplicated cholecystectomy, would be the equivalent of 1500 g of lean tissue. The latter point is of utmost clinical relevance as the length of time for return of normal physiologic function after discharge from the hospital is related to the extent of loss of lean body mass during hospitalisation [*Wilmore 1999*]. Because protein represents both structural and functional body components, erosion of lean tissue may also lead to devastating consequences such as delayed wound healing, compromised immune function, and diminished muscle strength resulting in prolonged convalescence and increased morbidity [*Schricker 2001*].

Nitrogen balance studies reflect only net gain or loss of protein from the body. Nitrogen equilibrium, however, is maintained by the careful balance between rates of protein synthesis and degradation. Negative nitrogen balance, therefore, can occur if the protein breakdown and amino acid oxidation increase and synthesis remains the same, or if breakdown and oxidation rates remain unchanged and the rate of protein synthesis decreases. The use of isotopically labelled, non-radioactive amino acids allows for quantitation of the kinetics in whole body protein breakdown, synthesis, and amino acid oxidation. Studies employing this methodology have improved our

understanding of the pathophysiology of altered protein metabolism homeostasis after surgery. The principal underlying defect appears to be an accelerated rate of proteolysis and amino acid oxidation along with an insufficient increase in protein synthesis [*Shaw and Wolfe 1989*] Endogenous amino acid oxidation and amino acid release from the muscle after abdominal surgery have been shown to increase by 90 % and 30 %, respectively, while whole body protein synthesis increases by 10 % only [*Carli et. al.,1991*] The magnitude of this alteration is substantial considering the fact that muscle tissue represents approximately 45 % of body weight and contributes as much as 20% to total body protein synthesis [*Kinney and Elwyn 1988*]. These changes in protein metabolism are accompanied by stereotypical alterations in glucose metabolism, *i.e.,* stimulated whole body glucose production and impaired glucose utilisation resulting in hyperglycemia [*Schricker et. al., 2000a*] Gluconeogenesis is activated as a result of long fasting periods before surgery and concurrent depletion of hepatic glycogen stores. The rate of this process is further enhanced by the surgical stress induced over-production of catabolic hormones, which stimulates gluconeogenesis, particularly in the face of insulin resistance. Muscle protein becomes the major source of gluconeogenic precursors *via* the glucogenic amino acids released during proteolysis. A significant correlation between the amount of glucose production and the rate of protein breakdown could be demonstrated after abdominal surgery providing evidence of this interdependence of glucose and protein metabolism in surgical patients [*Schricker et. al., 2000b*] Furthermore, gluconeogenesis in the liver is an energy-consuming process and accounts for 50 % of hepatic oxygen consumption. Thus, any modification of hepatic gluconeogenesis assumes metabolic importance regarding the energy balance of the liver and whole body protein catabolism.

The biochemical factors initiating, regulating and sustaining the catabolic response to surgery have not been fully identified. However, it has been argued that much of the observed catabolic profile can be explained by specific hormonal alterations known as the neuroendocrine stress response [*Weissmann 1990*]. The endocrine milieu after surgical trauma is characterized by increased secretion of several pituitary hormones and activation of the sympathetic nervous system, resulting in elevations in the plasma levels of cortisol, epinephrine and norepinephrine. All of these hormones exert catabolic effects, either directly or indirectly by inhibiting insulin secretion and /

or counteracting the peripheral action of insulin leading to the impairment of tissue insulin sensitivity *[Schricker 2001]*. Marked insulin resistance is present after routine surgical procedures, even in the absence of sepsis or other complications, and may persist up to 20 days thereafter [*Brandi et.al.,1990*] The impact of insulin resistance upon carbohydrate and lipid metabolism, i.e., hyperglycemia, stimulated glucose production and lipolysis, has been well documented and gave rise to the term "diabetes of injury" [*Schricker 2001*].

Thus Physiologic Response to Surgery can be summarised as:

a. Endocrine changes and their metabolic consequences: One of the earliest consequences of a surgical procedure is the rise in levels of circulating cortisol that occurs in response to a sudden outpouring of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland. The rise in ACTH stimulates the adrenal cortex to elaborate cortisol. Cortisol has generalised effects on tissue catabolism and mobilises aminoacid from the skeletal muscle that provides substrates for wound healing and serves as precursors for the hepatic synthesis of acute-phase proteins or new glucose [*Burke et. al., 1955*]. Adrenal medulla is also stimulated simultaneously through sympathetic nervous system, with elaboration of epinephrine. In addition, nor-epinephrine levels rise during and following elective operative procedure. Urinary catecholamines may be elevated for the 24 - 48 hours after operation and may then return to normal. The major catabolic role of this regulatory system may be the stimulation of hepatic glycogenolysis and gluconeogenesis in concert with glucagons and glucocorticoids [*Souba and Wilmore 2002*]. Alteration in serum osmolarity and tonicity of the body fluids secondary to anesthesia and the operative stress stimulate the secretion of aldosterone and antidiuretic hormone [*Traynor et. al., 1981*]. The ability to excrete a water load after elective surgical procedure is restricted even in the presence of adequate hydration. Hence, weight gain secondary to salt and water retention is usual following operation. Administration of sodium containing solutions during operation replaces this functional volume loss as extra cellular fluid redistributes in the body. This third spaced fluid eventually returns to the circulation as the wound edema subsides and diuresis commences 2 to 4 days following the operation. Alterations occur in the response of the endocrine pancreas following elective operation. In general, insulin elaboration is diminished and glucagons

concentration rise thus accelerating hepatic glucose production and with other hormones gluconeogenesis is maintained. Current techniques of post-operative care minimise but do not reverse these responses [*Souba and Wilmore 2002*].

b. Stage of Surgical Convalescence: The period of catabolism (Adrenergic-corticoid phase) is followed by the onset of anabolism lasting for only 1 - 2 days [*Moore 1959*]. This phase of 'corticoid withdrawal phase' is characterised by a spontaneous sodium and free water diuresis, positive potassium balance and reduction in nitrogen excretion. Patient then enters a prolonged period of early anabolism characterized by positive nitrogen balance and weight gain. Protein synthesis is increased as a result of sustained enteral feedings and this change is related to the return of lean body mass and muscular strength. Final phase of surgical convalescence is late anabolism, with slower weight gain with positive carbon balance resulting from deposition of fat [*Souba and Wilmore 2002*].

V. POST-OPERATIVE GUT PHYSIOLOGY AND GUT VULNARABILITY:

Stomach is profoundly affected by rigors of surgery especially proximal and distal stomach is altered in different ways. Under normal conditions, the proximal stomach is mainly a digestive and storage organ. The distal stomach serves more as a propulsive organ, but the rate at which stomach contents are emptied depends on many variables (osmolarity, volume, fat content etc.). The absence of sufficient gastric peristalsis in the post-operative setting has precluded enteral feeding into the stomach. This is very true in patients whose ileus has developed. Typically, after surgery, small bowel function returns first, then gastric function and lastly colonic function. Typically the stomach regains the ability to empty itself of liquids approximately 3 - 8 hours after surgery and of solids 24 - 48 hours post-operatively. The small bowel regains normal propulsive activity in approximately 12 - 24hours. The colon most seriously affected by anaesthesia will regain function last (48 – 72 hours) after surgery [*Martindale 1998*].

In post-operative setting 3 factors determine how well the gut can perform its absorptive function - the quantity of intraluminal substrate, the capacity of the transport system and the ability of the enterocyte to metabolise substrate. When the luminal nutrients have not been supplied for 3 - 5 days or longer or on TPN,

propulsion can be adversely affected and bowel luminal receptors undergoe significant down-regulation. In addition, metabolic capability of enterocytes is reduced. There may be mucosal damage and loss of gut intergrity and thus gastrointestinal tract permeability is increased leading to translocation of opportunistic organisms and their by products.

Gut vulnerability post-operatively in part is the result of physiologic response to stress in which disproportionate splanichic vasoconstriction shunts blood away from a tissue that has a high metabolic requirement. Second, the mucosa is at risk as a consequence of anatomy. The villus is perfused by an end artery-like system making the villous tip the most hypoxic part of the villus. In addition, there is a counter current exchange mechanism, in which transport of oxygen across cells from the arterial into the venous circulation is facilitated by decreased blood flow as may be due to shunting. Third, the hemoglobin concentration in blood entering the villus is lower because of plasma skimming. However, within 30 min. of relative mesenteric ischemic, subendothelial edema may develop. Studies suggest that rapid cell proliferation and mucosal repair may be blunted as a result of fuel limitation in the face of hypoperfusion. Duodenal feeding may protect or restore mucosal blood flow and limit shunting [*Purcell et. al., 1993*]. Any anaesthetic agent has the potential to adversely affect bowel motility, with colon being affected to the greatest degree. With epidural anaesthesia, normal gut function can be preserved. Alpha-adregenic agents and antichlorinergic agents reduce gut motility. Use of triacyclic antidepressants during post-operative period may also produce an unwitting adverse effect, which may be due to, increased intraluminal pressure, thereby inhibit bowel function. Abrupt withdrawal of glucocorticoids post-operatively may induce retrograde peristalsis. The relationship between operative procedures and effect on G.I motility differs. In a primate model, ileus was found to be independent of the site, duration and extent of operation [*Grabber 1982].* Thus procedure may not be a salient factor. However, Kudsk [*1940*] reported that laparoscopic surgery might decrease the incidence of post-operative ileus. This involves reducing hypermetabolic response to stress as a result of smaller incision. Deaarangement of serum potassium, sodium, calcium and magnesium may hinder the return of normal bowel function during hypovolemia or hypervolemia. Bowel wall edema often results from massive resusciation. It may

require 3-5 days to normalize. Enteral feeding given before developing bowel wall edema helps preserve gut function [*Kudsk 1994 ; Berry et. al., 1995*].

VII. NUTRITION IN RELATION TO SURGERY:

Benefits of current advances in nutritional support of hospitalised patients have been derived by surgery. Previously surgical patients who would have died due to malnutrition, sepsis and MOF because enteral feeding was not possible or were not adequate now survive as they may now be fed safely, with varying degrees of effectiveness. There is reduced mortality rates due to advances in the nutritional management and the development of new antibiotics, the ability to screen, preserve and administer blood and blood products and improvementation, anesthesia and ventilatory support. Nevertheless, the ability to feed the patients who cannot or will not eat is a major advance in surgical care [*Shire 1980*]. Nutritional support is a primary therapy for patients who develop malnutrition secondary to intestinal disease such as enterocutenous fistulas, short bowel syndrome, inflammatory bowel diseases with systemic sepsis or slow growing malignant tumors associated with oropharyngeal or oesophageal obstruction.

In patients undergoing gastrointestinal surgery up to one third can be categorised as being "moderately" malnourished [*Detsky et. al., 1987*] This is of clinical importance because it is well recognised that malnutrition and weight loss are associated with alterations in cellular physiology and organ function [*Heys and Gardiner 1999*], which are of importance for the surgical patient. Furthermore, the consequences of pre-operative weight loss in terms of an increased post-operative morbidity and mortality are well recognised and are a major consideration for clinical practice.

Patients with greater than 10 % weight loss requiring an operative procedure constitute candidates for pre-operative nutritional support. These patients are usually normometabolic and gain weight when provided with adequate calories and nitrogen with weight gain and anabolism they become better surgical candidate [*Souba and Wilmore 2002*]. *Buzby et al.,* [*1980*] observed that patients who received at least 5 days pre-operative parenteral nutrition had 5 days fewer post-operative complications. All patients with post-operative complications had either a pre-operative serum albumin concentration of less than 3.5 gdl^{-1} or a serum transferin

concentration less than 150 $mgdl^{-1}$. Postoperative weight loss (a mean of 1.8 kg in patients receiving intravenous fluids in this study) is acceptable because short- term undernutrition (10 - 12 days) does not complicate convalescence after major surgery [*Sandstorm et. al., 1993*].This would therefore not be a reason for recommending routine postoperative nutritional support. In high-risk surgical patients, only an occasional previously healthy patients undergoing elective operation develops complications and require nutritional support. In general, well nourished elective surgical patients are also not considered to need nutritional support, unless postoperative complications prevent oral intake. The incidence of such complications such as bowel obstruction, anastomotic disruption, pancreatitis is observed to be low. [*Souba 1996*]. It is observed that well-nourished patients, undergoing elective operations suffer from one common problem as post-operative ileus. If ileus continues for more than for 5 - 7 days, intravenous feeding usually by peripheral vein should be initiated [*Souba and Wilmore 2003*].

Nutritional therapy for determining nutritional requirement is directed to a specific goal such as to diminish the rate of weight loss and body protein breakdown, to maintain body weight and protein stores and to achieve weight gains and anabolism. Total energy requirement are based on the basal metabolic rate, the degree of stress imposed by the diseases process and the amount of energy expended with activity. The principle influences on nitrogen balance in surgical patients are total energy intake, nitrogen intake and the metabolic state of the patient. Energy and nitrogen relationships are altered in the nutritionally depleted and hypermetabolic patients. Hypermetabolic, hypercatabolic patients, on other hand have a diminished protein economy and require much more protein [*Souba and Wilmore 2003*].

VIII. NUTRITION SUPPORT PATHWAY:

The goal of nutrition support is to maintain or improve nutrition status to avoid the adverse consequences of malnutrition [*Beir and Boesby 1996*]. The presence and degree of malnutrition and the clinical status of the patient should be evaluated since malnourished patients tend to have higher rates of morbidity and mortality [*Mullen et. al.,1978 ; Seltzer et. al., 1982*] and longer hospitalisation and nutritional status tends to decline with length of hospital stay [*Weinsier et. al., 1979*].

Gastrointestinal surgery patients are at a risk of nutritional depletion from inadequate nutritional intake, surgical stress and the subsequent increases in the metabolic rate. The small intestine mucosa is comprised of a single cell thickness of mostly columnar epithelial cells, with endocrine cells, mucin cells, and Paneth cells interspersed between them. The absorptive capacity of the small intestine is greatly increased by the presence of villi, with corresponding crypts between them. The most mature cells occupy the tip of the villi, while immature cells are at the base of the villi, in the crypts. The immature cells proliferate and migrate to the tip, where they mature, then are reabsorbed or sloughed off into the lumen. The entire process takes only three to six days. This high rate of proliferation and turnover is usually well-regulated by nutrient availability, gastrin, growth hormone, bacterial flora, and neuro-regulatory activity. However, the presence of food passing through the gastrointestinal tract seems to be the primary stimulus for regulation of this proliferative response, as it can affect all of the aforementioned regulatory systems [*Wilmore 1994*].

Studies of post-operative nutritional support have demonstrated reduced morbidity and reduced length of stay [*Asknazi et. al., 1986*]. Even studies have shown reduced infectious complications, improved wound healing in addition to shortened hospital length of stay [*Souba 1997 ; Moore et. al .,1992 ; Siga and Daly 1990*]. Evidence to support preoperative nutrition support though is limited but suggests that if malnourished individuals are adequately fed for 7-10 days pre-operatively then surgical outcomes can be improved [*The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group 1991*]. Therefore, timely nutrition intervention is necessary for patients with pre existing malnutrition to prevent nutritional depletions. *Woodcock et. al.,* [*2001*] suggested that choice of feeding route should be determined by the clinical assessment of the gastrointestinal function [Fig:2]. The integrity and functional capability of gastrointestinal tract should be assessed to determine the feasibility of feeding the patients by mouth. Oral feeding of standard diet is the best option when gastrointestinal tract is functional, accessible and 'safe to use'. Focus of post-operative ileus and the integrity of newly constructed anastomosis have led to the treatment typically entailing starvation with administration of intravenous fluids until the passage of flatus. There seems to be no clear advantage to keeping patients nil by mouth after elective gastrointestinal resection. After seven days of fasting, even with the use of TPN, gut mass can be reduced by as much as 50 percent [*Souba*

1988 ; Souba et. al., 1988]. Early enteral feeding following bowel surgery has been shown to significantly increase strength of anastomosis [*Heydock and Hill 1986 ; Moss et.al.,1980*]. Early feeding may be of benefit [*Stephens et. al., 2001*]. However, small intestinal motility recovers 6-8 hours after surgical trauma and moderate absorptive capacity exists even in the absence of normal peristalsis. The commonest observed adversed effects were gastrointestinal such as abdominal cramps and bloating [*Braga 2002*]. An appropriate delivery method should be selected depending on the anticipated duration of feeding; aspiration risk and the gastrointestinal anatomy.

1. Routes of administration for nutrition support:

The patient will not tolerate enteral feeding until a certain degree of intestinal motility has returned after surgery. If he is hemodynamically unstable or on vassopressor therapy, there is a high risk for intestinal ischemia. In such cases, it may be appropiate to delay enteral feeding until the patient is not receiving vasopressors and is fully resuscitated [*Mc Clare et. al.,1999*].

Enteral nutrition is the delivery of nutrition to the gastrointestinal tract via artificial means and is administered for the patients who have a functional gastrointestinal tract. But in patients inspite of functional intestinal tract, cannot or will not eat and in such cases EN delivered via a feeding tube is the method of choice as it promotes comparable better outcome [*Kudsk et. al., 1992*]. It has been shown to result in some specific clinical benefits including reducing the incidence of post-operative infection complications [*Saito et. al., 1987, Bier and Bosby 1996*], improved wound healing response [*Schroeder et. al., 1991*] including altering antigen exposure and influencing oxygenation of the gut mucosa [*Reynolds 1996*]. Enteral nutrition is claimed to be less expensive, safer and more physiologic in the sense that it preserves gut barrier function [*Sigurdsson 1997, Silk and Green 1998*]. Any patient who cannot tolerate adequate volumes of enteral nutrition, irrespective of diagnosis, should receive total parenteral nutrition preferably by peripheral route. Parenteral nutrition can be provided through a central vein that can acccomodate more concentrated solutions in smaller volumes or through a peripheral vein that accommodates large volumes of dilute solution [*Souba and Wilmore 2002*]. Authors conclude that perioperative TPN should be limited to severely malnourished patients in the absence of other specific indications [*Veterans 1991*]. Despite the controversy over who might benefit from

perioperative nutritional support, there is no doubt that the enteral route is preferable to the parenteral. *Muller et. al., [1982]* observed that, patients with cancer of gastrointestinal tract who received intravenous pre-operative feedings had reduced incidence of major post-operative complications. At least three clinical trials [*Kudsk et. al., 1992; Moore and Jones 1986; Moore et al., 1989*] and a meta-analysis have documented the superiority of immediate postoperative enteral feeding over parenteral nutrition in patients with blunt and penetrating trauma. Enteral feeding was initiated within 24 hours of injury, was well tolerated, and resulted in a significantly lower incidence of postoperative pneumonia, intra-abdominal abscess, and catheter sepsis. The routine use of post-operative TPN is contraindicated in the patients undergoing elective G.I surgery. A meta-analysis of eight prospective, randomised, controlled trials showed a 10% increase in septic and metabolic complications related to overnutrition [*Torossium 1999*]. However, severely malnourished patients requiring preoperative TPN may benefit from continuing TPN through the immediate post-operative period [*Bozetti et. al., 2000*]. The adverse effects of total parenteral nutrition on the gastrointestinal tract include decreased brush border hydrolase activity [*Guedon et. al., 1986*] reduced amino acid transporter activity [*Inoue et. al., 1993*], increased mucosal permeability, and a slight decrease in villus height [*Van der Hulst et. al., 1993*]. *Rombeau et. al.,[1982]* suggested that pre-operative parenteral nutrition was beneficial in patients requiring operation for inflammatory bowel diseases. A recent meta-analysis of 27randomised controlled trials concluded that TPN has no statistically significant effects overall on mortality or morbidity in surgical patients [*Heyland et. al., 2001*]. However, nutrition support of the surgical patients can be carried out with different modalities, depending on the underlying disease and on the patient's general condition. There are 4 main modalities of the artificial nutrition: oral supplementation of nutrients, enteral nutrition (EN), TPN; mixed parenteral and enteral nutrition. It should be remembered that, each route of delivery of nutritional support is associated with different complications substrates delivered by the enteral route are better utilised by the gut than those parenterally.

2. Aspects of Enteral nutrition:

Surgeons have known for more than a half century that malnourished patients are more likely to suffer post-operative complications resulting in increased morbidity and mortality [*Studley 1936*]. In 1980, a classic study was published that :

improved immune function with dietary supplementation in population of burned children [*Alexander et. al., 1980*]. Since then several compelling reasons for favouring early enteral nutrition over other modes of feeding have surfaced. High-risk surgical patients were found to have reduced septic morbidity rates with early post-operative enteral nutrition compared to TPN [*Saito et. al., 1987*]. EN is an effective option in severely malnourished patients with upper G.I cancer associated with fewer complications such as shorter post-op hospital stay [*Bozetti et. al., 2001*] and reduced costs compared to TPN [*Braga et. al., 2001*].

a) Routes Of Access: The commonly used routes for enteral feeding include transnasal (nasogastric, nasoduodenal, nasojejeunal) feeding catheters, and enterostomy feeding catheters (gastrostomy tubes, gastro-jejunostomy and jejunostomy). Nasogastric (NG) and Nasoduodenal (ND) / nasojejunal (NJ) routes are used for the short term basis and quite useful for supplemental feeding both for bolus or continuous feeding. Gastrostomy (GT) feeding is recommended for long term feeding when there is a functional stomach. Percutaneous endoscopic gastrostomy (PEG) and percutaneous endoscopic jejunostomy (PEJ) requires no surgery. It is recommended for long term feeding and is useful when access to or function of stomach is impaired [*Ideno 1995*] .

b) Feeding Tube: The ancient Egyptian used nutrient enemas to coat inflamed intestine and provide nutrients [Bliss 1882]. Earliest record of tube feeding date backs to 1617, when tube made of silver was used for nasogastric feeding [*Pareira et. al., 1954*] and later on leather or rubber tubes was used upto 19th century [*Rankin 1882*]. The lavin tube of 1921 led in 1950 to the development of polyethylene tube [*Wagner et. al, 1952].* Many changes have occurred since then in respect of easy insertion, comfort and in feature and equipment improvements. The newer feeding tubes are smaller, softer, more pliable and poses less risk of oropharyngeal and oesophageal infection [*Paine 1986*]. The consideration in selecting feeding tube includes tube material, length, diameters ports, weights, feeding guides or stylets and tips.

i) Nasoenteral Feeding Tube Insertion: The nasoenteral feeding tube is inserted through the nose and via the oesophagus, entering stomach or small intestine, depending upon the desired position. They are used when feeding is less than few weeks. Nasogastric feeding tubes are appropriate for alert patients. Nasoduodenal

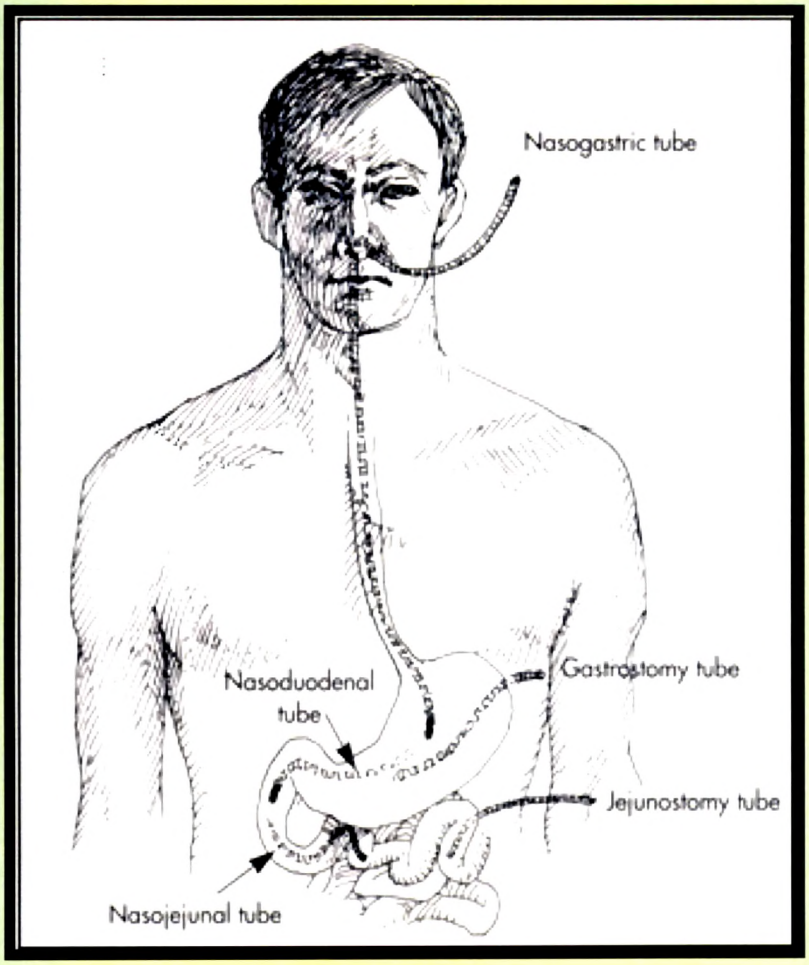

Fig 2: ENTERAL FEEDING ROUTES

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and nasojejunal feeding is done when the potential for aspiration is great or functioning of the proximal gastrointestinal tracts is impaired [*Hamson 1979*]. Special problems related to feeding include gastroesophageal reflux and aspiration, tube clogging, dislodgement and feeding intolerance.

ii) Enterostomy tube feeding: Surgically inserted feeding tubes include, the cervical oesophagostomy, gastrostomy, the percutaneous endoscopic gastrostomy (PEG) and percutaneous endoscopic jejunostomy (PEJ). The cervical pharyngostomy or oesophagostomy is made into oesophagus or larynx through which tube is passed into oesophagus or stomach. In gastrostomy, the tube is inserted into stomach for long term feeding and jejunostomy into the jejunum. Gastrostomy and percutaneous endoscopic gastrostomy (PEG) tubes can be placed to gastric decompression. If access into the jejunum is achieved, nutrients can be infused in the absence of bowel sounds immediately after laparotomy. The percutaneous endoscopic jejunostomy (PEJ) tube is placed through the stomach and into the proximal small intestine. Needle catheter jejunostomy is used for predigestion formula and is placed for enteral feeding post-operatively [*Strife et. al., 1985*]. In larger tubes (>7F) standard isotonic polymeric formulas are well tolerated [*Ford et. al.,1992*]. Complications include obstruction of the tube, wound drainage and infection, peritoneal leakage, unintentional removal, diarrhoea and vovulus.

c) Delivery System: Feeding can be delivered as intermittent or continuous schedule. *Ciocon et. al.,* [*1992*] reported that continuous intragastric feedings were safer with fewer episodes of diarrhoea and aspiration compared with intermittent feedings. Gravity feeding is acceptable when patients are medically stable, large volume of feeding formulas is necessary, viscosity is low, internal feeding tube diameter is wide and patients have adequate absorptive capacity. Continuous pump feedings are the preferred route for intrajejunal feedings. An infusion pump allows safe, accurate delivery of formulas of varying viscosities. They have audible alarms and usual displays that indicate occlusion, malfunction, low battery empty container or inadvertent rate change [*Lysyn and Samour 1999*]. Thus methods of feeding can be highlighted as

1. Pump feeding: this is where an electronic feeding pump delivers feed, via a giving set, at a set rate per hour over a pre set dose or time period.
2. Bolus feeding: this is where feed is administered directly into the feeding tube via a

syringe.

3. Gravity feeding: this is rarely used these days, and involves the feed bag attached, through a giving set, to the enteral feeding tube and feed drips in via gravity.

Feeding containers are usually made of vinyl or polyvinyl chloride with capacity of 500 - 2000 ml. Ideally the enteral feeding containers to be easy to fill close and hang, easy to read calibration, appropriate size, compatible with pump, easy to clean, leak proof, requires minimal storage space and recyclable [*Lysyn and Samour 1999*].

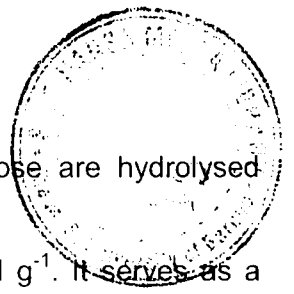
d. Enteral Feeding Formulations:

There are numerous enteral formulas available, which are designed for oral or tube feeding. The standard formulas are usually nutritionally complete. This generally provides 1.0 Kcal ml^{-1} of formula and contains approximately 50 – 55 % carbohydrates, 15 – 20 % protein and 30 % lipids. They are often isotonic.

a. Components of Nutrient Formulas:

i. Protein: Protein is considered the most critical component enteral formulas. It is provided in various enteral formulas as intact proteins, hydrolysed proteins and crystalline aminoacids. Intact proteins are whole proteins from food for protein isolates. Lactalbumin is a protein isolate derived from whey. Intact protein and protein isolates require normal level of pancreatic enzymes to catabolise large proteins to small polypeptides and free aminoacids [*Eisenberg 1989*]. Hydrolysed protein is a protein that has been enzymatically hydrolysed to smaller peptide fragments and to free aminoacids [*Ideno 1993*]. Formulas that contain di- and tri-peptides and crystalline aminoacids are often referred to as elemental or pre-digested formulas as they are absorbed directly into the blood stream. The different sources of protein such as lactalbumin, soy protein hydrolysate, whey, egg white, non - fat milk, whole milk, casein etc., have been used in various formulas.

ii. Carbohydrates: Carbohydrates provide 30 – 90 % of the total calories from enteral formulas and in most formulas it is the principal energy source. The main differences among the formulas are the form and composition of carbohydrate. In general, the longer carbohydrate molecules exert less osmotic pressure, taste less sweet and require more digestion than the shorter ones [*Ideno 1993*]. Oligosaccharides and polysaccharides are the most predominant forms of carbohydrate used in enteral formulas. They require pancreatic enzymatic breakdown



for digestion and rarely cause intolerance. Sucrose and maltose are hydrolysed rapidly while lactose, slowly [*Mac Brunney et. al., 1990*].

iii. Lipids: Fat is a calorie dense source which provides 9 kcal g^{-1}. It serves as a vehicle for fat soluble vitamins and provides essential fatty acids. Enteral formulas contain 2 – 55 % from fat. The essential fatty Acids (EFA) requirement of 3 – 4 % of total calories is met in most enteral formulas. Common fat sources are soybean, corn, safflower, canola oil, medium chain triglycerides (MCT), lecithin and milk fat. Other fat sources are fish oil, structured lipids and short chain fatty acids, (SCFA) [*Trijillo 1998*].

LCT contains linoleic acid, a precursor of arachidonic acid. Omega-3 fatty acids derived from marine oils that contain moderately large amounts of EPA and DHA may benefit immune system. MCTs prepared from palm kernel or coconut oil can be absorbed intact without appreciable pancreatic or biliary function and are subject to more rapid clearence from the blood stream. Structured lipids (a chemical mixture of LCT and MCT) offer the advantage of decreasing infection and improve survival by producing fewer inflammatory and immunosuppressive eicosanoids as compared to conventional triglycerdes. Short chain fatty acids are not currently used in enteral formulas, but have been investigated for potential benefit in critical illness as are the principle fuel source for the colon [*Sandstorm et. al., 1995*].

iv) Fibre: Fibre in the enteral formula has many potential clinical applications, including ameriolating constipation and proving mucosal healing in inflammatory bowel diseases, supporting the gut barrier and increasing intestinal adaptation in short-bowel syndrome [*Palacio and Rombean 1990*]. Fibre supplemented enteral formula have been shown to improve bowel regularly in stable patients by increasing the number of bowel movements per day [*Zarling et al., 1994*]. Use of Soy polysaccharides has been shown to improve bowel function [*Fredstorm et. al., 1991*]. Extensive epidemiologic evidence supports that fibre may protect against large bowel cancer [*Bingham 1990*]. The dietary fibre has been effective the reducing serum cholesterol and it may decrease serum lipids, lower blood pressure, improving glucose metabolism and aiding in weight control [*Geil and Anderson ,1992*]

Enteral Formulas with Fibre and Bowel Function:

The types of formulas that contains fibre are currently marketed as blenderised formulas, made from whole food and formulas supplemented with purified sources,

usually soy polysachharides .The amount of dietary fibre in the products varies: 1.9-3.3 g of total dietary fibre (TDF) per 250 ml blenderised formula and from 2.5 - 5.9 g of TDF per 250ml formulas containing soy polysaccharides. The breakdown of soluble and insoluble fibre, in the enteral products has been determined in blenderised formulas generally contain higher ratio of soluble fibre to insoluble fibre [Sunvold *et al.,* 1995]. As compared with other fibre sources available as supplements soy polysaccharides provides a broad range of positive functional nutritional and physiologic properties. Although soluble fibre content of soy polysaccharide is low (6 % of TDF), soy polysaccharide has been shown to reduce serum cholesterol in hyperlipidemic patients and to improve diabetes control [*Won 1996*]. Other purified fibre sources are being used in enteral products *viz.,* oat, pea, hydrolysed guar gum and sugar beet fibres. Some formulas use a mixture of fibre sources [*Sunvold et. al ., 1995*]. No recommendations exist for fibre intake in various disease states or for patient in long-term care facilities [*Slavin 1999*]. Recently, in enteral formulas, fructoligosaccaharides, a short-chain oligosaccharide may have a physiologic effect similar to those of soluble fibre [*Own et. al., 1996*]. Enteral formulas with fibre were used in the acute-care setting to prevent diarrhoea associated with tube feeding [*Frankfield and Beyer 1984*]. Dietary fibre is thought to normalize bowel function and reduce diarrhoea. Brown *et. al.,* [1993] concluded that soy polysaccharide reduced the duration of liquid stool excretion. However, soluble fibre (guar-gum) could lower the serum cholesterol and blood glucose level [*Fredstorm et al.,1994*]. However, despite compelling clinical, dietary fibre is a treatment of choice in constipation [*Hillemeier, 1995*] and as a treatment for diverticular disease [*Ozick et. al., 1994*].

v. **Micronutrients:** Most enteral formulas contain adequate vitamins and minerals in a volume of formula to meet energy and protein needs. Data are not much available on vitamin and mineral requirements in various disease states [*Trijillo, 1999*].

vi.**Immunonutrients:** Glutamine and branched chain aminoacid (BCAAs) (aminoacids found in skeletal muscle) have also been identified as key aminoacid in preserving nitrogen balance during stress and injury in recent clinical studies. Enteral formulas containing glutamine exists either bound to protein (*e.g* whole proteins and peptides) or as the free aminoacids. BCAAs enriched solutions have been used

principally in patients who have hepatic encephalopathy, the infusion of BCAAs lowers the aromatic aminoacids (AAAs)/BCAA ratio in plasma and may thereby decrease the penetration of AAA across blood-brain barrier as the synthesis of neurotransmitters is normalised [*Elia 1995*]. Arginine (semi-essential aminoacid) can be conditionally essential after an injury. Human and animal studies have shown an increased intake of arginine after trauma decreases nitrogen losses and accelerates wound healing [*Kirk et al., 1993*]. For patients under physiologic stress in combination with other nutrients such as omega-3 polyunsaturated FA (PUFA), glutamine and nucleotides, the arginine enriched enteral formulas have been associated with fewer wound infections and reduced length of hospital stay [*Moore et. al., 1994].* Nucleotides being precursors of RNA and DNA are added to some enteral formulas as immunity enhancers. In animals, dietary supplementation of nucleotides have been reported to facilitate growth and maturation of the developing gut [*Uauy et. al., 1990*] and dietary nucleotides appear to be modulators of intestinal development after chronic diarrhoea [*Bueono et. al., 1994*]. However, studies regarding the role of arginine and n - 3 fatty acids in gastrointestinal surgery patients have not yet been published.

v. **Water:** Intracellular and extracellular fluids make up the total body water. Water moves along osmotic gradient to maintain equilibrium between intra- and extracellular fluid [*Hauff 1991*]. A total daily fluid loss is approximately 2600 ml for adult, which are usually offset by endogenous water production and metabolism or intake of exogenous fluids. In a patient who relies on enteral nutrition, this amount of water must be supplied. A large amount of all the enteral formulas is free water. In general, a 1.0 Kcal ml^{-1} contain approximately 80 % free water whereas for 1.5 Kcal ml^{-1} and 2.0 Kcal ml^{-1} formulas, the free water content is 75 % and 69 %, respectively [*Trijillo 1999*].

b) Physical Characteristics:

The following physical characteristics of the enteral formula should be considered before administering the fluid solution to the patients.

i) Osmolality: Osmolality maintains the balance between intra- and extracellular fluids. Formulas with larger proportion of hydrolysed nutrients have higher osmolality.

The osmolality along with the rate of delivery may be associated with diarrhoea [*Heibert et. al., 1981*]. Lipids contribute minimally to the formula with the exception of MCT's owing to their water solubility. Minerals and electrolytes contribute significantly because of their dissociation properties and small size [*Krey and Lockett 1986*]. Isotonic formulas (280 - 320 mOsmol Kg^{-1}) were supposed to be better tolerated than hyper or even hypotonic formulas particularly with a dysfunctional gastrointestinal tract or short bowel syndrome, small bowel feeding with isotonic solution showed better [*Keohane et. al., 1984*]. The average osmolality of the commercial preparation is reported to be 450 - 10950 mOsm Kg^{-1} [*Dickerson et al., 1988*] and ranges from 270 -700 mOsm Kg^{-1} for enteral formulas Normal volunteers can tolerate full strength isotonic polymeric small bowel tube feedings at rates up to 340 mlh^{-1} without significant diarrhoea [*Kandil et. al., 1993*]

ii) Renal Solute Load (RSL): It refers to the constituents in the formulas that must be extracted by the kidney. Protein, sodium, potassium and chloride are the major constituents of the formula. As a formula becomes more concentrated or renal solute load increases, the patient requires more water [*Mac Burney et. al., 1990*]. Hydration status should be monitored daily especially in pediatric and gastric patients and those with excessive losses due to diarrhoea, amesis, fistulas or fever [*Trujillo 1999*].

iii) Calorie Density: The calorie density of enteral feeding formulas is generally 1.0, 1.2,1.5 or 2.0 Kcal ml^{-1}. The more nutrient-dense the formula is, less the moisture or water content. Gastro empty rate may be slowed by high-calorie density formulas [*Hunt and Stubbs 1975*].

iv) Hydrogen Ion Concentration (pH): Gastric motility is retarded when pH is lower than 3.5 [*Ideno 1993*] though the pH level of most of the formulas is above 3.5. The pH level of the formula can be contributed to clogging of feeding tube. However, incase of intact protein formulas, coagulation stars when acidified to a pH less than 5.0 [*Powell et. al., 1993*].

The choice of feed to be given via ETF is influenced by a patient's nutritional requirements, any abnormality of gastrointestinal absorption, motility, or diarrhoeal loss, and the presence of other system abnormality, such as renal or liver failure [*McAlter et. al.,1999*]. Most commercial feeds contain 1.0 Kcal ml^{-1}, with higher

energy versions containing 1.5 Kcal ml^{-1}. They are generally available in fibre free and fibre enriched forms.

f) Role of Special Tube Feeding Formulations includes – The choice of feed to be given via ETF is influenced by a patient's nutritional requirements, any abnormality of gastrointestinal absorption, motility, or diarrhoeal loss, and the presence of other system abnormality, such as renal or liver failure [*McAlter et. al.,1999*] Enteral formulations are divided into seven separate classifications that include blenderised, lactose-containing/lactose free, elemental, modular, specialised and supplemental.

Blenderised formulations are generally used with a combination of table foods with added vitamins and minerals. While kitchen-prepared feedings were traditionally used, these are not ideal for various reasons. Blenderised foods need to be given through large bore feeding tubes, with its attendant complications. Supply of feedings round the clock cannot be assured, there is a high risk of bacterial contamination, and the bioavailability of nutrients makes it difficult to supply "dose-specific" nutritional support. Finally, when the cost of preparation, transport, wastage, personnel time, and management of complications associated with large bore tubes is considered, kitchen prepared diets are not less expensive in the hospital environment. Thus there has been an increase in the availability of commercial enteral preparations, designed for use with small-bore feeding tubes. Formulas containing **lactose** are rarely used today. Lactose free diets (polymeric) basically designed for long term usage with complex form of carbohydrate, fats and proteins and thus require some degree of digestion, absorption; As they are categorized as polymeric diets, contain nitrogen as whole protein. The carbohydrate source is partially hydrolysed starch and the fat contains long chain triglycerides (LCTs). Their content of fibre is very variable and although most authorities recommend that fibre should be included [*McAlter et.al.,1999*] the evidence that higher levels are of real benefit is not strong. **Elemental** (monomeric and oligomeric) or chemically defined formulations are mainly for use with limited digestive capacity (diseases in which bowel's absorptive capacity is functionally or surgically reduced). They are delivered as free amino acids alone (monomeric) or free aminoacids, dipeptides and without prelimery intraluminal hydrolysis. Predigested feeds contain nitrogen as either short peptides or, in the case of elemental diets, as free amino acids. Carbohydrate

provides much of the energy content with the content variable in both quantity and the proportion provided as LCTs and medium chain triglycerides (MCTs). The aim of "predigested diets" is to improve nutrient absorption in the presence of significant malabsorption. Their importance is probably greater in maldigestive (for example, pancreatic disease) rather than malabsorptive states, and in patients with a short gut and no colon their high osmolality can cause excess movement of water into the gut and hence higher stomal losses [*McIntyre et.al.,1986*]. There are a variety of formulas available which are diseas specific for conditions such as pulmonary disease, renal failure hepatic failure. For e.g. Pulmonary formulas may be beneficial in the intubated patient with lung disease who may be difficulty to either oxygenate appropriately or wean from the ventilator. **Specialty diet products** are used for the patients with unique nutritional requirements and may lead to complications if used inappropriately. Glutamine has been shown to maintain small bowel mucosa when placed in parental solutions as compared with glutamine free parenteral formulations [*O Dwyer et. al., 1990]*. Arginine in supraphysiological amounts has been shown to increase nitrogen retention, accelerate wound healing and enhance immune function. Post surgical cancer patients who are tube –fed an enteral diet containing arginine, structutred lipids, RNA and menhaden oil improved in vitro immune response and nitrogen balance [*AGA 1994*]. **Modular diets** on the other hand exist as separate nutrient units mixed to create specific enteral formulations or can be added to the existing one to obtain higher levels of a particular nutrient. Supplements are also available for patients who cannot meet all their protein or calorie needs and are taken in the form of liquid, shake etc

vi. Complications Related with Enteral Nutrition:

Enteral nutrition is the preferred route of providing nutrition support when G.I tract is functional. Complications associated with enteral nutrition are minor but a few can be serious or life threatening.

A. Mechanical problem: Proper assessment of feeding tube placement can prevent feedings from being delivered to the wrong site. Techniques of determining feeding tube position include roentgenogram, tube aspiration (with assessment of pH, bile

volume of aspirate), use of special feeding tubes that measure pH or motility, ausculation and laryngoscopy [*Bohnker et. al., 1987; Miller et. al., 1985; Metheny 1993*].

I.Complications related to feeding tube placement: Upper airway injury during placement of feeding tubes may cause lacerations or bleeding of the nasal or oral cavity; lower airway injury during the placement of feeding tubes may cause perforation of the trachea or pulmonary parenchyma (pneumothorax) [*Miller et. al., 1985 ; Roubenoff and Ravich 1989*]; Gastrointestinal tract injuries during feeding tube insertion include perforation (peritonitis) or laceration with bleeding of the gastrointestinal tract; Contamination of the peritoneum can result to abdominal infection and abscess formation which can occur from perforation of the G.I tract, leakage following tube placement, or entry of bacteria during tube placement.; Respiratory compromise may occur during feeding tube placement as a result of interference with oxygenation or aspiration o f secretions.

II.Complications associated in the presence of feeding tube: Upper airway complications are associated with patients having nasopharyngeal erosions and necrosis, sinusitis, otitis media, loosening of teeth, bacteremia. Lower airway complications are associated with feeding into the trachea or lung with resultant pneumonia, respiratory distress, acute respiratory failure, emphysema and adult respiratory distress syndrome [*Montecalvo et. al., 1992*]. Gastrointestinal injuries may be one or combination of the following causes of oesophagus-erosions, aggravation of the varical bleeding, stomach erosions, ulcer bleeding, obstruction and volvulus and buried bumper syndrome, misplaced fasteners, necrotising fascitis, wound infection, cellulites, stomal leakage, hematoma, tube dislodgement, extrusion or migration of feeding tubes, subcutaneous emphysema and enterocutaneous fistula from PEG or surgical tube placement [*Bohnker et. al., 1987*].

III. Tube Clogging: It is more likely with intact proteins products and viscous products [*Marcuard and Perkins 1988, Caos and Gogel 1986 ; Hofstetter and Allen 1992*]. It may also be caused by product contamination leading to formula coagulation [*Kohn 1991*] or aspirating for residuals (gastric fluid coming in contact with formula in feeding tube) [*Powell et. al., 1993*] and medications [*Scanlan and Frisch 1992;*

Williams 1989 ; Holtz et. al.,1987]. Less clogging occurs with polyurethane tubes than with the silicon tubes. [*Metheny et. al., 1988; Hearne et. al., 1984; Petrosino et. al., 1987*]

IV. Aspiration: Aspiration is a potentially lethal complication. It can result in cough, bronchospasm, pulmonary edema, pneumonia, empyema and respiratory failure. Risk factors include decreased levels of consciousness diminished cough or gag reflex, neurologic injury in competent. Lower oesophageal sphincter reflux, gastroesophageal reflux, supine position, use of large bore feeding tubes, large gastric residuals, and gastroparesis [*Zaloga 1994*].

V. Miscellaneous: Other complications are tube knotting, perforation of the feeding tube with guide wire which also could perforate the bowel; inability to remove the guide wire because of knotting, kinking or poor lubrication and tube deterioration.

B. Metabolic and biochemical complications of enteral feeding:

Metabolic problems include a deficiency or excess of electrolytes, vitamins, trace elements, and water. Common problems include overhydration, which may develop in up to 25 % of tube fed patients and hypertonic dehydration in up to 10 %. Hyponatraemia is generally due to a dilutional state induced by excessive concomitant use of intravenous dextrose or water, while hypernatraemia is often due to free water loss, iatrogenic, due to excessive use of 0.9 % saline solutions, or albumin, or more uncommonly an inability to conserve free water secondary due to transient diabetes insipidus [*Valandingham 1981*]

Refeeding syndrome: Refeeding malnourished patients increases basal metabolic rate, with glucose being the predominant energy source. This anabolic response causes intracellular movement of minerals, and serum levels may fall significantly. These rapid changes in metabolism and electrolyte movement may lead to severe cardiorespiratory and neurological problems resulting in cardiac and respiratory failure, oedema, lethargy, confusion, coma, convulsions, and death [*Solomon and Kirby, 1990*] Patients at highest risk from the refeeding syndrome include those with chronic malnutrition, chronic alcoholics, and those on a prolonged fast or on intravenous hydration only [*Duncan and Silk 1997*].

C. Gastrointestinal complications of enteral tube feeding:

Complications directly related to the gastrointestinal tract are the most common complications of enteral tube feeding [*Payne and Silk 1990*]. Nausea, possibly related to smell, osmolality, altered gastric emptying, and too rapid administration of feed is common. Abdominal bloating and cramps may also be due to delayed gastric emptying Constipation is a common problem, and there is little conclusive evidence that lack of dietary fibre in enteral feed is the cause [*Patel et. al., 1985*]. Another commonest reported complication of enteral tube feeding is diarrhoea, which can occur in up to 30% of patients on general medical and surgical wards [*Cole et.al.,1998*] and 68% of patients on intensive care units [*Kelly et. al., 1983*]. A generally accepted scientific definition of diarrhoea is more than 250 g of stool per day Aetiology of enteral tube feeding related diarrhoea includes drugs and antibiotics [*Guenter et.al., 1991*] in part due to the "inert carriers" for the active compound, such as sorbitol, in part due to alteration of intestinal flora by antibiotics, including *Clostridium difficile* and its toxin.

D. Microbial contamination and infection of feed:

Enteral feed provides an excellent growth medium for bacteria. A variety of organisms have in the past been cultured from enteral feed [*Pearce and Duncan 2001*]. The risk starts as soon as the feed is opened, through a variety of routes, and involving handling type of delivery system, prolonged hanging time, and ascending spread of bacteria up the giving set [*Pearce and Duncan 2001*].Up to 36 % of enteral feeds given by continuous drip have been found to be contaminated in some studies [*Paynne 1992*]. Contamination can cause not just diarrhoea, probably the commonest manifestation, but also pneumonia and sepsis. Although oral or gastric feeding in a healthy individual rarely causes problems due to the antibacterial effects of saliva and gastric acid, contamination of nasoduodenal or jejunal feed which bypasses these mechanisms can result in serious morbidity. A similar effect can result in achlorhydria, either caused by drugs or pathology. There is some argument as a result in favour of the use of sterile feed [*Anderton 2000* ; *Bodoky 2000*]. At the very least, feed containers and giving sets should be changed every 24 hours, and some authors suggest a break between feeds to allow the gastric pH to fall [*Payne et. al., 1992*].

E. Metabolic Complications:

Hyperglycemia: It may occur in some patients because of underlying diabetes mellitus or insulin resistance (precipitated by the illness or by use of medications such as glucocorticoids). This condition should be treated because it impairs immune function, increases the risk of infection, increases post ischemic neuronal damage and results in fluid and electrolyte loss.

Electrolyte and Mineral deficiencies: Electrolytes are lost via stool, ostomies, fistulae, urine and through the skin. Potassium, magnesium and phosphorus are required for optimal protein synthesis. The kidneys are primarily responsible for excretion; intake of these ions may need to be decreased in patients with renal insufficiency or failure.

a) Sodium, primary extracellular cation in the body, is the major controller of the osmolality. Altered circulating levels of sodium primarily reflect the status of body water. The most common cause of hyponatremia in hospitalised patients is excess secretion of antidiuretic hormone (which results in retention of water in excess of sodium) and dehydration because of water loss in excess of sodium (e.g. excess sweating, excess urinary loss of water because of osmotic diuresis or limited water intake. Hypernatremia or hyponatremia also can be caused by high and low sodium intake in relation to output. Table salt may be judiciously added to the formula or the flush solution. Conversely, sodium content of IV fluids must be checked when hypernatremia is evaluated.

b) Potassium is the primary intracellular cation in the body and is the major determinant of electrical membrane potential. Decreased concentrations result in cardiac arrhythmias, muscle weakness and impaired protein synthesis. Deficiency results from loss of potassium in the stool, gastrointestinal secretions and urine (especially diuretics).

c) Calcium is the primary divalent cation of the extracellular fluid and is essential for regulating processes that require movement in the body. Calcium circulates in the blood in three fractions: ionised, chelated and protein bound. It is not required in the diet over the short term because it can be mobilised from bone.

d) Phosphorus is important as a source of cell energy (eg, adenosine triphosphate, creatine phosphate), a component of cyclic adenosine-monophosphate and cyclic

guanosine-monophosphate (important intracellular messengers), a component of 2,3-diphosphoglycerate(important for oxygen off loading from hemoglobin),and synthesis of nucleotides. Most circulating phosphorus is in the ionised form. Respiratory arrest can occur with severe phosphorus depletion. Common causes of hypophosphatemia are administration of large amounts of carbohydrate (phosphorus shifts intracellularly when glucose enters the cell), administration of drugs (insulin, epinephrine, phosphate-binding antacids, sucralfate), and phosphate loss from the GI tract and kidneys, if levels are severely low, IV phosphorus should be administered.

e) Magnesium is an important cofactor for many essential enzymes. Depletion results from loss of magnesium from the body in GI fluids or urine or from decreased intake in the diet.

3. **Vitamin deficiencies** may develop in patients who receive nutrition support. Deficiencies commonly result from inadequate vitamin intake (which fails to match requirements or losses). Malnourished patients are at higher risk because of the presence of a depleted state when nutrition support is initiated. Fat-soluble vitamins (A, D, E, and K) require pancreatic enzymes and bile for absorption. Concentrations may be low in patients with pancreatic insufficiency, cirrhosis and malabsorption syndromes. Gut bacteria synthesise vitamin K and concentrations may be decreased in patients who receive antibiotics. Water-soluble vitamins the most common deficiencies are of folate, ascorbic acid, and thiamine.

4. **Dehydration:** It is common in patients who receive enteral nutrition. Water needs average 1ml per calorie consumed. Dehydration may result from the use of concentrated formulas.. In addition, high-protein feeds may cause a urea diuresis and loss of body water. It may result when body-water losses are not met by water intake (eg, water loss from skin during fever, from urine or from stool). An increasing serum sodium concentration, BUN, or BUN / creatinine ratio suggests dehydration. Treatment is aimed at restoring intravascular volume and water balance.

Nutrition support, in addition to providing sufficient essential nutrients, vitamins and trace elements to meet recommended dietary allowances, should also provide adequate nitrogen to achieve nitrogen balance [*Barton 1997*] The content and the type of protein plus the concentration of individual amino acids, lipids, trace elements and vitamins in the diet, have been shown to effect immunocompetence and

influence patient outcome in hyper catabolic patient [*Hardy 2002*]. Following review links the unique relationship between 'nutrition and its contribution towards protecting the human body from external insults'

IX. NUTRITION AND IMMUNITY:

History links between nutrition and immune system response by demonstrating examples of simultaneous occurrence of persistence and famine [*Chandra 1985*]. During times of war or natural disasters, sources of adequate nutrition may be limited, consequently nutritional depletion and subsequent immune-mediated changes can occur that potentially threaten survival. [*Chandra 1985a*]. Malnutrition and nutrient deficiencies affect various parts of the immune system [*Biesel 1982 ; Santos and Falcao 1990*]. For example, altered nutrition status can impair the ability of immune cells to recognize foreign stimuli, alter the proliferative responses of the various cells, impair antigen presentation, reduce phagocytic and cytolytic capacity, change membranes or enzymes, or perturb the cooperative interactions between the various types of immune system cells.

Immunoglobulins are glycoproteins and therefore are dependent on adequate protein nutrition, as well as on the enzymes and cofactors essential to protein metabolism. Normal immune function is dependent as well on cytokine and complement, chemical messengers orchestrating the response of immune cells. The entire immune system is subject to neuro – endocrine regulation, which in turn is influenced by nutritional status. Nutrition is essential for normal cellular metabolism, wound healing, immunocompetence and organ function but now it is more clearly established that nutrients exert more nutritive effects on body function and metabolism. Deficiencies of individual nutrients are associated with profound impairment of cell - mediated immunity. Certain nutrients have been identified which may affect organs function, independent of the general nutritional effects. The target cells for the action of these nutrients appear to be T-lymphocytes and macrophages. It has also been found that certain nutrients and non- nutrient free radical scavengers such as polyphenols, flavonoids and phytoestrogens in fresh vegetables, cereals and fruits, control important metabolic activities and can modify the immune response [*Hardy 2002*].

Immunity and Stress response:

Any critical illness is often associated with immunosuppression leading to increased opportunistic infections, increased morbidity and a high risk of mortality. Malnutrition in surgical patients is often associated with an increased incidence of postoperative septic complication, morbidity and mortality. In trauma or surgery, lymphocytes both decrease in number and in responsiveness. This may suggest an impaired ability to duplicate and differentiate [*Hardy 2002*]. Concentrations of the acute phase proteins increase and the concentration of C-reactive protein (relating to IL-6 activity) has prognostic significance. Considerable increases in blood polymorph numbers are encountered in the 24 - hours postoperatively, following stress related cortisol release. Subset distribution of T and B cells are altered and this largely contributes to the apparently reduced immunocompetance of the patient, as measured by in vitro nitrogen transformation studies with peripheral blood lymphocytes. During stress or after major surgery, plasma and muscle glutamine concentrations are significantly decreased, reflecting the increased demand of these immune cells, which cannot be always met by protein breakdown. There is also significant negative correlation between glutamine levels and IL-6 production noted in many studies. [*Newsholme and Par Billings 1990*]. Thus it is essential to have a clear understanding of the various nutrients and their role in immunity.

ix. NUTRIENTS AND NUTRICEUTICLES – *Their Role in Immunity*

Epidemiological data reveal that total leukocyte count to be potent predictors of various morbities and all-cause mortality. Leukocyte activity generates reactive oxygen moieties, a possible mechanism for adverse effects. Reactive oxidant specifies such as H_2O_2 and HOCl exert an inhibitory influence on both T and B lymphocyte and natural killer cells. Dietary intake levels and serum levels of several antioxidants including vitamin C, vitamin E and B-carotene are inversely correlated with neutrophil and total leukocyte counts. Thus, the WBC count may emerge as a convenient gauge of the adequacy of antioxidant intake.

1. Essential Aminoacids:

Essential aminoacid deficiency of any one appears to suppress humoral immunity, whereas intake of non-essential aminoacids appears not to be limiting given

adequate total protein intake. Animal studies suggest that imbalances of protein intake can impair immunity even in the absence of overt deficiency; excessive dietary leucine has been shown to reduce antibody responses in animals.

Sulphur Amino Acids such as Cysteine, Methionine and Taurine are recently identified as conditionally aminoacids function of which is found to be immunostimulatory [*Mowat Viney 1997*]. Such as arginine, glutamine, and taurine and other essential aminoacids that may be of beneficial in improving the immune function.These act as substrates for acute phase protein and immunoglobulin synthesis. During infection, demand for these can exceed production so dietary intake is extra-important. These amino acids are also useful for glutathione production, which protects tissue against pro oxidant inflammation, and augments the activation of Tc cells. Sulfur containing aminoacids involved in the synthesis of glutathione may be in particular demand during infection/ inflammation due to the increased oxidative stresses, suggesting that supplementation might be beneficial [*Alexander et. al., 1980*]. Insufficient sulphur amino acids results in a proinflammatory influence and reduces overall immune efficiency [*Martine 2003*].

Taurine is sourced from the diet or made from cysteine and methionine. It is rare to have a deficiency, unless in times of very poor immunity. Taurine constitutes ¾ of the amino acid pool in the neutrophils. It preserves neutrophil phagocytic activity that has been decreased by hyperlipidemia. Taurine helps kill bacteria by reacting with hydrochlorus acid produced by the neutrophils. A deficiency is seen in cats and results in defective phagocytic function and lymph node regression [*Martine 2003*].

Lactalbumin has been shown to elevate humoral and cell mediated immune response in mice compared to other protein sources. Merely increasing the dietary protein from 15% to 23% for children with severe burns resulted in significantly higher levels of complement C3 and immunoglobulin with survival increased from 56% in the control group to 100% in high protein group [*Alexander et. al., 1980*].

2.<u>Minerals</u>:

a) <u>Zinc</u>: Zinc deficiency is considered as one of the most prevalent nutritional deficiencies worldwide, due to both limited dietary intake and presence in the food supply of phytic acid, a zinc chelator. In relation to immune function, it acts as an essential cofactor for many enzymes and cellular function. Zinc itself can act as an

immunostimulant of leukocyte activities and there is some evidence to suggest that it prevents cells from undergoing apoptosis. Zinc deficiency is accompanied by thymic atrophy and high frequency of bacterial, viral and fungal infections; under these conditions, chemotaxis and oxidative burst generation are impaired. Studies suggest that deficiency leads to chronic elevation cortisol is thought to augment apoptosis of pre-lymphocytes in the bone marrow. Zinc repletion appears to restore normal immunity in zinc deficient organisms within as little as 2 weeks. In preterm infants, zinc deficiency causes reduced T-cell counts, lymphocyte response, NK cell activity and phagocyte dysfunction, which can be corrected by zinc supplements, facilitating recovery of the immune system [*Fraken et.al., 1986*]. However, a fine balance of zinc is very important as excessive supplementation can have an inhibitory effect on T cell function [*Rink and Kirchner 2000*]

b) Iron: Iron deficiency is associated with impaired cell mediated immunity. If deficiency occurs in the context of general malnutrition, protein deficiency will suppress levels of transferin. Under such circumstances, repleted iron is readily available to microorganisms, therefore, iron repletion before protein repletion might be harmful, promoting bacterial replication. Iron in excess is associated with impaired immunity and susceptibility to tumorigenesis. In relation to immunity it plays an important role for the optimal functioning of NK cells, neutrophils and lymphocytes [*Wawbayashi et.al., 1988*].

c) Copper: Copper deficiency has been seen to suppress lymphocyte function [*Mulhern and Kolher 1989*] and selenium which also acts as an antioxidant via its cofactor role in glutathione peroxidase, enhances lymphocyte activity [*Larsen et.al.,1988*].

3.Vitamins:

Various micronutrients have shown to have immuno-stimulatory properties.

Vitamin A: Vitamin A deficiency is associated with disruption of mucosal and epithelial barriers as well as impaired antibody responses. Vitamin A supplementation in mice can reduce the immunosuppresion caused by UV radiation and restore antibody production in Vitamin A deficient rats [*Pasatiempo et.al.,1987*]. However, carotenoid supplementation particularly B-carotene has been studied as a means of reducing cancer risk. Vitamin B can prevent a reduction in lymphocyte from rats fed on immunosuppresion diet [*Sinkeldem et.al.,1988*]. Vitamin C is an important

antioxidant, which enhances the nitrogen dependent blastogenesis of lymphocytes [*Oh and Narkano 1988*]. Vitamin E is important to immune function both in its role as antioxidant and as cell membrane constituent. It is known to stimulate immunoglobulin production and have an enhancing effect on humoral and cellular immunity [*Haberial et.al.,1997*]. Vitamin E may be of particular importance in combination with n-3 fatty acids. The recommended dietary allowances (RDA) level of vitamin E intake may not be optimal with regard to immune function particularly in the elderly [*Behark et.al., 1997*]. A randomised trial of vitamin E supplementation for 4 months in healthy elderly subjects demonstrated enhancement of clinically relevant measures of T-cell function [*Meydaini et.al.,1997*]. Others such as Uracil, the ribonucleotide is manufactured from ingested aminoacids and is not considered to be an essential nutrient. However, certain studies show its beneficial function to immune function during the states of high metabolic stress.

4. <u>Essential Fatty Acids:</u>

Fatty acids serve as a major component of the cell membrane and are involved in catalyzing a number of processes including dilation and contraction, inhibition and promotion of clotting and cell division and growth [*Katz 2001*]. Omega-3 fatty acids, EPA and DHA, aid the immune system by competing with arachidonic acid for cyclo-oxygenase metabolism at the cell membrane. These effects may be beneficial in the sites of chronic inflammation. . However, n-3 fatty acids have the trend to suppress T-cell function, the effect may be mitigated by vitamin E supplementation [*Wu and Maydani 1998*]. Arachidonic acid (AA) is an omega-6 fatty acid that at high levels suppresses the immune function and promotes inflammation. Diets high in n-6 PUFA appear to promote tumorigenesis. Modifying the omega-6 to omega-3 content of cell membrane affects T-cell proliferation, cell-to-cell adhesion, plasma membrane fluidity and cytokine production. [*Field 2000*].

XI. GASTROINTESTINAL TRACT AND IMMUNITY:

Recent research developments have identified that G.I. tract as the most metabolically active organ following surgical trauma, which possess immunoregulatory properties [*Grimble and grimble 1998*] maintains immunological functions protects from invading pathogens. This is a complex process since it not

only involves the gut wall barrier but also macrophages and other phagocytic cells, as well as specialised cells, including mast cells. The gastrointestinal mucosa has an important function in preventing translocation of microbial products to the portal circulation [*Wilmore et.al.,1988*]. Diminished barrier function is thought to play a key role in the pathogenesis of multiple organ failure [*Carrico and Meakins 1986 ; Wells et.al.,1989*]. The intestinal barrier is composed of several elements i.e. mucous layer; the epithelium with tightly connected enterocytes and gut associated lymphoid tissue (GALT) [*Wells et.al.,1989*]. The recognition that the gut may be central to the processes of inflammation [*Wilmore et.al.,1988*] that may ultimately progress to multiple organ failure has resulted in a concentrated effort among clinicians to support gut structure as well as barrier and absorptive functions as the patient recovers from injury and infection [*Barton 1997*].

Maintaining an intact gut barrier is ascribed to specific aminoacid thus immune activation due to oxidative stress in the gut can be prevented and the production of cytokines which, may increase intestinal permeability [*Anesthesiologic and Intensivmedizin 1997*] is diminished.

Gut Microflora: Oral tolerance is important as some bacteria require eradication, and others are beneficial for example probiotics. Probiotics break down food that the small intestine couldn't and they help maintain mucosal immunity. They prevent colonisation of pathogenic microorganisms and stimulate the generation of the mucosal barrier. Malnutrition affects the microorganism balance and causes infection to occur. The ability to adhere to mucosal surfaces appears to be important for optimal function of probiotic bacteria – a yoghurt bacterium does not adhere. Lactobacillus plantarum is a common helpful bacterium. It is able to stick to the mucosa, colonise the intestines and inhibit pathogens. It can tolerate lower pH than other microorganisms. It is found in fermented foods, vegetables, fish and meat, sourdough, sauerkraut, green olives, wines and beer. It is often used by the food industry as a preservative against pathogens, and it can even produce omega-3. Lactobacillus is dependent on glucose and arginine for growth – arginine degrades to nitric oxide which is essential for GI immune functions, for example bacteriostasis, stimulation of immune defense and mucus secretion-all these control Ecoli, salmonella, H-pylori and parasites. Lactobacillus binds to the mucosal surface through a mannose-specific adhesion, which competes with other gram-negative

bacteria or pathogens for receptor sites. This is how it is able to repopulate the gut with healthy bacteria [*Martine 2003*].

XII. IMMUNONUTRITION:

Nutrition support, in addition to providing sufficient essential nutrients, vitamins and trace elements to meet recommended dietary allowances, should include adequate calories, but should not exceed energy requirements. It should also provide adequate nitrogen to achieve nitrogen balance [*Barton 1997*]. The content and the type of protein plus the concentration of individual aminoacids, lipids, trace elements and vitamins in diet, have been shown to effect immunocompetence and influence patient outcome in hypercatabolic patient [*Hardy 2002*]. One area that has attracted considerable interest has been the question as to what the composition of the nutritional support should be. This is because it has been realised that certain nutrients, when given in amounts in excess of normal requirements, can modulate a variety of immune, inflammatory and metabolic processes [*Heys et. al.,1996*]. They may affect organs function, independent of the general nutritional effects. The target cells for the action of these nutrients appear to be T-lymphocytes and macrophages. Such an approach to the use of nutrients has been termed "nutritional pharmacology" or "targeted nutrition". In enteral nutrition enriched with such nutrients is celled immunonutrition. It may aid patients with pathological inflammatory responses by altering the composition of inflammatory mediators such as prostaglandin's and by increasing immune responses thus reducing risk of infection. Sepsis as a post-operative complication may require exogenous immunoglobulin support as well as specialised nutrition support [*Hardy 2002*]. Recent evidence has suggested that an immunonutrition can have a beneficial effect on the prevention of infection complications and SIRS and reduction of ventilator days and hospital stay [*Anaesthesiologic* and Intensivmedizin *1997*]. Several trials that suggest preoperative immunonutrition supplementation improves outcomes and is cost-effective by reducing complications [*Harry 2005*]. Thus the term '*immunonutrition*' refers to the nutrition that protects and stimulates immune function. The immune enhancing nutrient in immunonutrition provides identifiable salutary effects upon the immune system. Of the many immune enhancing nutrients identified in numerous human clinical trials important are: Arginine, Glutamine, Omege-3 fatty acids, Nucleotide.

1. ARGININE

Biochemistry and Physiology: Arginine is a dibasic aminoacid (2-a amino-5-guanidino pentanoic acid). It is a non-essential aminoacid in adult humans but under certain physiological condition, especially during stressful periods such as growth, illness or metabolic stress, it is considered to be a dietary conditionally dispensable aminoacid [*Rose 1937*]. It is synthesized endogenously from ornithine via citrulline as a result of interorgan reaction. The quantities produced, sufficient to maintain muscle and connective tissue mass may be less than that required for optimal protein biosynthesis and growth. In terms of severe stress and nitrogen overload endogenous synthesis of arginine is insufficient to meet the increased demands that increased protein turnover requires. Arginine is a normal constituent of numerous body protein and is associated with a variety of essential of intermediatary metabolism. The intestinal absorption of arginine involves a transport system shared with lysine, ornithine and cystein. Arginine serves as a vehicle for the transport, storage and excretion of nitrogen. The transamidation between arginine and glycine results in guendinoacetic acid, which is further methylated to form the high-energy phosphogen creatine phosphate. The reversible release of fumaric acid by dismutation of arginosuccinic acid further links arginine metabolism with cellular energetics via the TCA cycle.

The urea cycle represents the major metabolic pathway for ammonia detoxification and arginine plays a key regulatory role within this cycle. Any condition that increases the demand for ammonia detoxification is likely to increase arginine requirements. Recently arginine has been shown to be the unique substrate for the production of the biological effector molecule nitric oxide (NO). Nitric oxide is putative neurotransmitter and cytotoxic effector molecule. Nitric oxide is formed by oxidation of one of the two identical terminal guanidine groups of L-arginine by the enzyme. Nitric oxide synthase, a di-oxygenase of which there are at least two identified isoforms. Both isoforms of nitric oxide synthetase have been identified as flavoproteins [*Mayer et. al., 1991; Stuehr et. al.,1991a*] each containing flavine adenine-dinucleotide and flavin adenine mononucleotide and both are inhibited by diphenylneidonium flavoprotein inhibitor [*Stuehr et. al.,1991*b].

Arginine and Hormone Secretagogue Activity: Increased levels of arginine lead to enhanced secretion of several hormones including insulin, glucagons, growth hormones, prolactin and adrenal catecholamine [*Barbul 1986*]. Recent demonstration of nitric oxide synthetase immunoreactivity and functional activity in several secretory organs suggest that nitric oxide is involved in arginine induced hormone secretion. Nitric oxide synthetase immunoreactivity on functionality has also been located in the adrenal gland. Nitric oxide modulates adrenal medullary vasodilation and may increase the release of adrenal hormones during increased perfusion. In addition, L-arginine as well as other agents that increase intracellular cyclic guanosine monophosphate (cGMP) levels such as Nitric oxide, stimulates catecholamine release from the adrenal gland [*Dohi et.al.,1983 ; O'Sullivan and Burgoyne 1990*].Increased Nitric oxide synthesis may be the mechanism by which arginine levels to enhanced hormone secretion.

Arginine and Post-Traumatic Nitrogen Metabolism: L-Arginine is one of the higher nitrogen containing aminoacds and supplementation appears to improve nitrogen balance in critically ill patients. Arginine has been shown to reduce nitrogen loss in post-operative patients. Thus elective surgery patients given arginine hydrochloride intravenously for the first 3 days post cholecystectomy had a 60% reduction in urinary nitrogen excretion. Following major abdominal surgery for gastrointestinal malignancies, patients receiving immediate enteral feedings supplemented with arginine had a mean positive nitrogen balance when compared with glycine-supplemented control [*Bucknall 1984*].

Arginine and Wound Healing: Successful wound healing is the cornerstone of recovery following surgical procedures. Nearly half of all post-operative morbidity involves wound complications. Both animal and human experimental evidence demonstrates that arginine can positively modulate the wound healing process, mainly by enhancing wound collagen deposition. Previous studies suggest an increase deposition of collagen early in the wound healing process correlates with an increase in wound strength. T-cell dependent immune system has been shown to have an important role in the regulation of wound healing [*Sung et.al.,1991*]. T-lymphocytes are necessary for the progression and orderly outcome of the normal wound healing process. Activated T-lymphocytes are capable of recruiting,

expanding and activating the fibroblasts that are primarily responsible for the repair process. Supplementation with arginine in human trials of postoperative patients results in beneficial effects on T cells [*Daly et. al., 1988*] and wound healing [*Barbul et. al., 1981 ; Kirk et. al.,1993*]. Use of immunonutrition solutions with arginine concentrations of ~6gL^{-1} (~2% of energy) has generally led to negative results [*Brown et al., 1994*], whereas the use of solutions containing arginine in amounts >12 gL^{-1} (>4% of energy) often gave positive results. Addition of arginine alone as a supplement to enteral nutrition was not beneficial in a study of patients in a medical intensive care unit (ICU)[*Caparros et. al., 2001*].

Arginine and Immune Function: Depressed immune responsiveness is a prominent feature of critical surgical illness, significant trauma and burn injury. Arginine plays a key role in the metabolic intracellular activity of lymphocytes and is also required for the effective induction of cytotoxic T-cell function in vitro [*Morigichi et.al.,1987*] and thereby benefiting the immune reaction. Arginine supplementation has been associated with improved thymic mass, increased thymic lymphocyte content after injury, improved lymphocyte proliferation in response to mitogenic and alloantigenic stimulation, enhanced macrophage and natural killer cell lysis of tumor targets and increased lymphocyte interleukin-2 production and receptor activity [*Daly et. al., 1988 ; Kirk and Barbul, 1990*]. It has been also been found to enhance lymphocyte blastogenesis and increase CD_4 lymphocyte populations in a pre-operative surgical populations.

2. GLUTAMINE

The non-essential aminoacid 'glutamine' has recently been the focus of extensive scientific interest because of its importance in cell, tissue culture and its physiologic role in animals and humans. The first hint about the presence and function of glutamine in the human organism came from Thierfelder and Sherwin in 1914. Twenty years later, Krebs and coworkers succeeded with in vitro glutamine synthesis in an incubation model employing glutamic acid and ammonium ions with liver specimens. [*Krebs,1980*].

L-glutamine is also known as 2-aminoglutaramic acid, levoglutamide, (S)-2,5-diamino-5-oxopentanoic acid and glutamic acid 5-amide. Its one-letter abbrevation is Q and it is also abbreviated as Gln [*Glutamine 2004*]. It has a molecular weight of

146.15 and an elementary composition of carbon (41.09 %), hydrogen (6.90 %), oxygen (32.84 %) and nitrogen (19.17%). It has two amine moieties an amino group and an easily hydrolysed terminal amide group. Glutamate is formed when the terminal amide group is cleaved. The remaining α-amino group plays a role in the production of various other α-amino acids via transamination. In the process, α-ketoglutarate is produced, which can enter the citric acid cycle and generate energy. Thus, the five-carbon aminoacid yields 30 mol of ATP, an amount comparable to the 36 mol of ATP produced from glucose, six-carbon sugar [*Souba et. al., 1985*].

Glutamine in Diet: Glutamine is a non essential (dispensable) amino acid, as it can be readily synthesised de novo in virtually all tissues in the body, it has been assumed that glutamine is not required in the diet, as glutamine is present virtually in all dietary proteins. Most naturally occurring food proteins contain 4 to 8% of their amino acid residues as glutamine; therefore less than 10g of dietary glutamine is likely to be consumed daily by the average person [*Souba and Labow 2001*]. However, this aminoacid becomes quite depleted during the course of a catabolic insult such as injury or infection indicating that the ability of glutamine production to meet demands during a variety of surgical illness is impaired. Studies in stressed patients indicate that considerably larger amounts of glutamine (20 - 40g day^{-1}) may be necessary to maintain homeostasis. Thus from nutritional standpoint, glutamine may be thought as a drug as well as a nutrient [*Labow and Souba 2001*].

Physiologic Function of Glutamine:

Body pool of Glutamine: Glutamine is the most prevalent free protein aminoacid in the human organism. In extracellular fluid, glutamine constitutes approximately 25% and in skeletal muscle more than 60% of the tissues-free aminoacid pool. Consequently, the transmembrane gradient over the muscle cell membrane is high approximately 34:1 (intra: extra cellular). Total glutamine content of the body protein is unknown, since measurement was not possible in the past. Muscle represents the major body protein pool and thus constitutes the prevalent endogenous source of glutamine. Calculating with the assessed glutamine content in the muscle protein and assuming that 40% of body weight is muscle tissue, the muscle glutamine corresponds to approximately 240 g [*Labow and Souba 2001*].

Pharmacokinetics: Following ingestion, L-glutamine is absorbed from the lumen of the small intestine into the enterocytes. Absorption is efficient and occurs by an active transport mechanism. Some metabolism of the amino acid takes place in the enterocytes. L-glutamine that is not metabolised in the enterocytes enters the portal circulation from whence it is transported to the liver, where again some portion of the amino acid is metabolised. L-glutamine not metabolised in the liver enters the systemic circulation, where it is distributed to the various tissues of the body [*Labow and Souba 2001*].

Function and Metabolism: It acts not only as a precursor for protein synthesis but is an important intermediate in large metabolic pathways. It is a precursor that donates nitrogen for synthesis of purines, pyrimidines, nucleotides and aminosugars and importantly serves as a glutathione precursor. It is the most important substrate for renal ammonegenesis thus taking part in regulating the acid-base balance. As the most concentrated amino acid in the blood stream, glutamine serves as a nitrogen transporter between various tissues. Due to its diverse participation in transamination reactions, glutamine can be classified as true regulator of amino acid homeostasis [*Sries and Haussinger 1984*].

Glutamine represents an important metabolic fuel for the cell of the gastrointestinal tract (enterocytes, colonocytes) [*Souba 1991 ; Windmuellar and Spaeth 1980*]. It also serves as energy source for the immune function. The gastrointestinal tract is continuously exposed to the exterior environment of the body via food, liquid, and swallowed salivary and mucus secretions, and therefore contains a large number of immune cells along its length. Glutamine's positive effects on the GI tract appear to stem from its ability to "feed" immune cells as well as mucosal cells. The essential importance of cellular hydration state as determinant of protein catabolism in health and disease has recently been established. It is postulated that an increase in cellular hydration (swelling) acts as an anabolic proliferative signal, whereas cell shrinkage is catabolic and antiproliferative. It is demonstrated that muscle cell water content and whole body nitrogen balance had an inverse relation in patients with various disorders [*Haussinger et.al., 1993*]. The concentrative uptake of glutamine into muscle and liver cells would be expected to increased cellular hydration, thereby

triggering a protein anabolic signal and subsequently modify or reverse catabolic changes [*Furst et.al., 1997*].

Transport characteristics of glutamine in human intestinal brush-border membrane vesicles: The existence of two carrier-mediated transport processes for glutamine (Gln) in the human intestinal Brush border membrane vesicle (BBMV), one is Na+ dependent and the other is Na^+ independent. Furthermore, the results suggest that Gln transport by the Na^+-dependent process probably occurs by a glutamine-sodium co-transport mechanism [*Said et.al., 1989*].

i) <u>Glutamine and Skeletal Muscle:</u> Glutamine constitutes 60% of the aminoacid pool (excluding taurine) in the skeletal muscle [*Berstorm 1974, Askanazi 1980*] and exists in humans at a concentrations of 20mmol /L of intracellular water. This large gradient favours glutamine export from cells. Glutamine and alanine are the major compounds that transport amino nitrogen from skeletal muscle to visceral organs. Following the stress of an operation, accidental injury or sepsis, glutamine is released by skeletal muscle at increased rates [*Kapadia et. al., 1982; Muhlbacher et. al., 1984*]. The intracellular glutamine concentration are depleted by 50% [*Wilmore 1983]* while plasma levels fall only by 20 – 30 % below normal during these catabolic states. The decline in the intracellular concentrations of glutamine exceeds that of any other aminoacid and persists during recovery, after concentrations of all other aminoacids have returned to normal. The quantity of glutamine released by skeletal muscle is greater than the amount in both the intracellular pool and that incorporated into proteins. This indicates that accelerated synthesis of glutamine occurs during catabolic states. Depletion of muscle glutamine is not prevented by administration of standard aminoacid containing nutritional solutions [*Vinnars et. al., 1983*]. However, post-operative glutamine supplementation was found to reduce the skeletal muscle efflux of glutamine [*Kapadia et.al, 1982 ; Karner et.al.,1989*] aminoacids in general and the fall of glutamine in the fall in synthesis of skeletal muscle polyribosomes [*Hammarqvist et.al., 1989*].

ii) <u>Glutamine and Gastrointestinal tract:</u> Reports in the 1960s suggested that glutamine was being utilised by the G.I tract of the rat [*Finch and Hird 1960;Addae and Lotspeich 1968*], the rabbit [*Neptune 1965*] and the dog [*Addae and Lotspeich*

1968]. *Windmuellar and Spaeth* [*1980*] demonstrated that glutamine was the major respiratory fuel for the intestinal tract of several animal species. Colonocytes and enterocytes were found to utilize glutamine to greater extent than any other fuel source, even glucose [*Windmuellar,1982 ; Ardawi1985*]. The uptake of the glutamine by the bowel may be accelerated during disease. Thus beyond its role in digestion and absorption of nutrients, the GI tract is now known to modulate the general protein catabolic response to stress [*Wilmore et. al., 1988*]. With operation or injury, the intestinal tract increases its rate of glutamine consumption. This appears to be regulated in part by corticosteroids, administration of exogenous steroids increases the bowel consumption of it and simultaneously induces the increase of glutaminase [*Rennie et. al., 1986*]. Morlion [*1998*] demonstrated that addition of glutamine to parenteral nutrition regimen given to patients after elective abdominal surgery results in reduced length of hospital stay and reduced costs. This is accompanied by an improved nitrogen balance and quicker lymphocyte recovery.

Glutamine has also been shown to maintain intestinal permeability in post-operative patients [*Jiang et.al., 1999*]. Studies also report that glutamine modulates intestinal permeability and reduces bacterial translocation in an animal model of experimental biliary obstruction and may increase bacterial killing by the immune system [*White et.al., 2005*]. One potential consequence of increased intestinal permeability is microbial translocation. Trauma, infection, starvation, chemotherapy, and other stressors are all associated with a derangement of normal intestinal permeability. Bacteria, fungi, and their toxins can subsequently translocate across the mucosal barrier into the bloodstream and react with the reticuloendothelial system. Cytokines produced from this reaction stimulate the hypothalamic-pituitary-adrenalaxis, resulting in cortisol release from the adrenals [*Souba 1992 ; Wilmore et. al.,1988*]. Cortisol increases glutaminase activity in intestinal enterocytes, stimulating increased breakdown and utilisation of glutamine in the small intestine. Cortisol also causes increased proteolysis in other tissues, and a release of glutamine from skeletal muscle [Fig 3: Interorgan flow of glutamine]. Although this adaptation response provides metabolic assistance to help heal hyperpermeable gut tissue, severe damage to the mucosa or other tissue utilising glutamine for healing, or prolonged stress can deplete skeletal muscle glutamine and consequently deprive enterocytes (which are using more glutamine in their stressed state) of their vital supply of

glutamine [*Miller 1999*]. In numerous animal studies, the addition of glutamine or glutamine dipeptides (stable dipeptides of glutamine with alanine or glycine) in experimentally-induced intestinal hyperpermeability improves gut barrier function, as well as immune activity in the gut [*Panigrahi et. al., 1997 ; Chun et. al.,1997*].

iii) Glutamine and the kidney: Glutamine is the substrate that allows the kidneys to excrete an acid load and thus protect the body against acidosis [*Golstein et.al., 1980*]. This is accomplished by the production of ammonia, which binds a hydrogen ion, thereby facilitating the urinary excretion of excess proteins. Glutamine principally released by muscle is transported into the cells of the distal tubules where it hydrolysed to glutamine and ammonia .the ammonia diffuses into the lumen of the tubule where it combines a proton to produce the ammonium ion. Along with an anion such as chloride, the ammonium ion is excreted in the urine. Simultaneously, a bicarbonate ion is released into the blood stream. In individuals with normal renal function, urinary ammonia accounts for $^{2/3}$ to ¾ of the hydrogen ions eliminated from the body . As expected, the rate of glutamine utilization by the kidney is increased during acidosis and decreased alkalosis [*Newsholme and Leech 1983*]. During extreme acidotic conditions, glutamate can give rise to additional ammonia upon its conversion to ketoglutarate (*via* the enzyme glutamate dehydrogenase) [*Pitts 1964 ; Welbourne1987*].

Iv) Glutamine and the liver: Under physiologic conditions, glutamine does not appear to be an important respiratory substrate for the liver [*Kovacevic and Mc givan 1983*]. However, blood concentrations of glutamine (when elevated or depressed) are homeostatically maintained in large part of the liver [*Windmuellar and Spaeth 1980*]. Thus the liver actively participates in the synthesis and /or degradation of glutamine, and this process is closely coupled with the disposal of glutamine nitrogen through pathways of this amination and/or ureagenesis. A fairly strict anatomic border separates hepatic cells that generate urea and those involved in glutamine synthesis .The portal bloodstream initially comes into contact with high capacity cells that take up the ammonia and synthesise urea. Ammonia that has escaped this initial extraction is captured by high affinity cells located close to the hepatic vein. These cells act as scavengers for ammonia and they are highly efficient in extracting this compound before the portal blood reaches the systemic circulation. These cells also

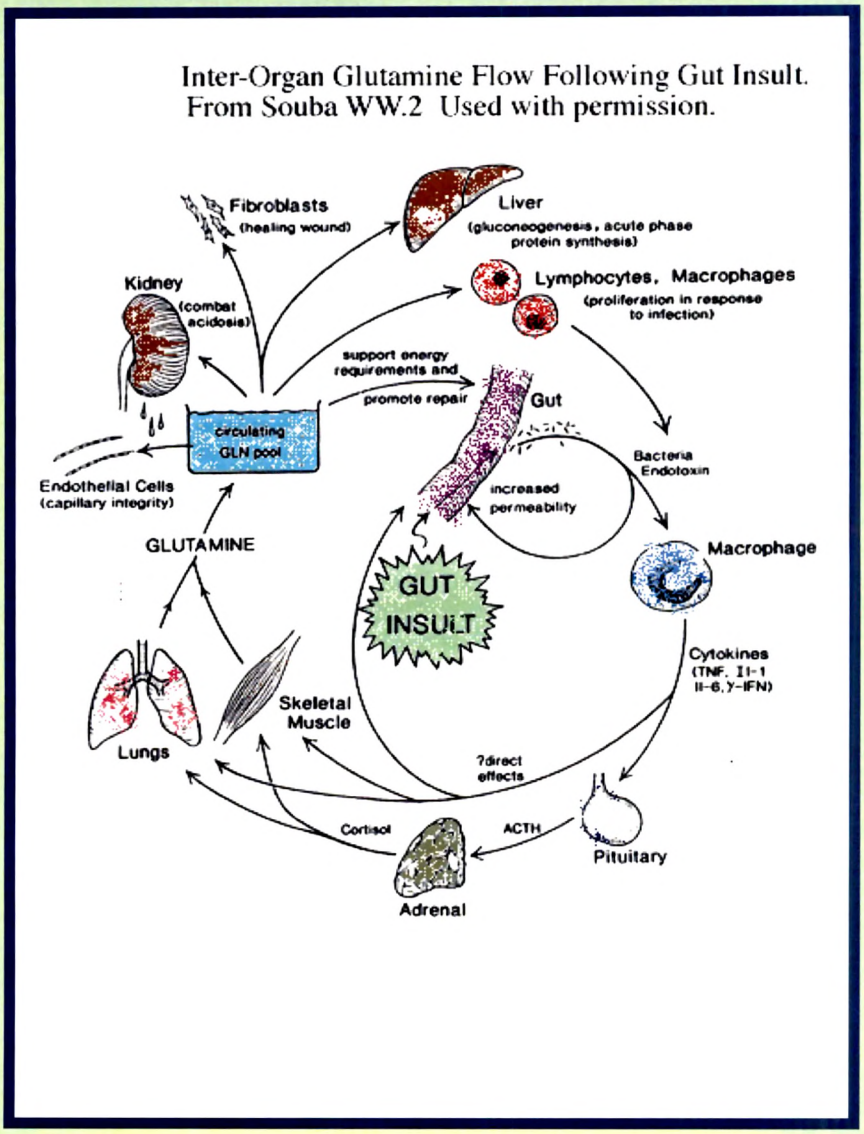


Fig 3: After a gut insult, increased permeability causes bacterial translocation. Leukocyte migration and cytokine release cause a further increased permeability, which triggers the hypothalamic-pituitary-adrenal (HPA) axis to induce a release of glutamine from skeletal muscle and lungs into the circulating glutamine pool. It is subsequently taken up by the gut to be utilised for repair of the damaged intestinal barrier

contain glutamine synthetase and thus convert the ammonia to glutamine. Furthermore, during acidosis, urea synthesis is decreased and glutamine synthesis is favoured in order to provide glutamine for renal buffering of the acid load [*Haussinger 1989*]. In addition, glutamine appears to stimulate hepatic glycogen synthesis and lipogenesis while inhibiting ketone body production [*Lavoinne et. al., 1987*] and lipolysis [*Cersosimo et. al., 1986*].

v) Role of Glutamine in Acid-Base balance: Muscle, adipose tissue, and the lungs are the primary sites of glutamine synthesis and release. During normal acid-base balance, the small intestine and the liver are the major sites of glutamine utilisation. The periportal hepatocytes catabolise glutamine and convert ammonium and bicarbonate ions to urea. In contrast, the perivenous hepatocytes are capable of synthesising glutamine. During metabolic acidosis, the kidney becomes the major site of glutamine extraction and catabolism. This process generates ammonium ions that are excreted in the urine to facilitate the excretion of acids and bicarbonate ions that are transported to the blood to partially compensate the acidosis. The increased renal extraction of glutamine is balanced by an increased release from muscle and liver and by a decreased utilisation in the intestine. During chronic acidosis, this adaptation is sustained, in part, by increased renal expression of genes that encode various transport proteins and key enzymes of glutamine metabolism. The increased levels of phospho*enol*pyruvate carboxykinase result from increased transcription, while the increase in glutaminase and glutamate dehydrogenase activities result from stabilization of their respective mRNAs [*Norman and Curthoys 2004*].

vi) Role of Glutamine in Cerebral nitrogen metabolism and ammonia neurotoxicity: Ammonia enters the brain by diffusion from the blood or cerebrospinal fluid or is formed in situ from the metabolism of endogenous nitrogen containing substances. Despite its importance in nitrogen homeostasis, excess ammonia is toxic to the CNS and its concentration in the brain must be kept low. This is accomplished by the high activity of the glutamine synthetase, which is localised in the astrocytes and which permits efficient detoxification of the incoming or endogenously generated ammonia. The location also permits the operation of an intercellular glutamine cycle. In this cycle, glutamate released from nerve terminals is taken up by astrocytes where it is converted to glutamine. Glutamine is released to the extracellular fluid to be taken up into the nerve cells, where it is converted back to glutamate by the action

of glutaminase. Most extrahepatic cells lack a complete urea cycle and for many organs, including the brain glutamine represents a temporary storage form of waste nitrogen. However, recent evidence suggests that excess glutamine is neurotoxic. Evidence has been presented that hyperammonia results in increased formation of glutamine directly in astrocytes, thereby generating an osmotic stress to these cells. This osmotic stress results in impaired astrocyte function, which in turn leads to neuronal dysfunction.

vii. Glutamine Metabolism during Stress: During stress hypercatabolic and hypermetabolic situations are associated with profound glutamine deprivation. During prolonged starvation [*Elwyn et.al.,1981*] after elective operation, major injury, burns, infections [*Furst,1983 ; Hammarqvist et. al., 1990 ; Stehle et. al., 1989*] and pancreatitis [*Kanner and Roth 1990*], intramuscular glutamine concentrations decline considerably, regardless of nutritional efforts following stress contributing to glutamine depletion. Studies indicate that glutamine is an essential dietary component for the maintenance of gut metabolism, structure and function, when the gut mucosal barrier may become compromised especially in critically ill.

Ix:Glutamine and Immune system: Glutamine is utilised at a high rate by cells of the immune system in culture and is required to support optimal lymphocyte proliferation and production of cytokines by lymphocytes and macrophages. Macrophages-mediated phagocytosis is influenced by glutamine availability. In man plasma and muscle glutamine levels are lowered in sepsis, injury, burns, surgery and endurance exercise and overtrained athelete. The lowered levels are most likely the result of demand for glutamine (by the liver, kidney, gut and immune system) exceeding the supply (from the diet and from muscle). However, supplementation with glutamine in such cases shown to add a benefit in maintaining immune function. Exogenous glutamine augments the functions of lymphocytes and macrophages. Neutrophils reportedly utilise glutamine at a significant rate. Recent studies demonstrated that glutamine enhances neutrophil function. In addition, increases production of reactive oxygen intermediates (ROI) by neutrophils. Thus, glutamine supplementation may improve bacterial function of neutrophils by increasing both phagocytes and ROI production [*Calder and Yaqoob 1999*] .

A clinical benefit of glutamine supplementation was first demonstrated by Ziegler *et. al.,* [1992] in patients undergoing bone marrow transplantation. Patients receiving glutamine were found to have a reduction in their hospital stay (by 20%) and developed less infectious complications, when compared with non-supplemented patients. The effects of glutamine supplementation on post-operative complications in patients undergoing elective surgery has also been examined. Twenty-eight patients who underwent non emergency surgery for colorectal cancer were randomised to have either glutamine-supplemented total parenteral nutrition (TPN) or an isonitrogenous, isocaloric TPN for five days after surgery [*Haussinger 1993*]. The most striking effect reported was a reduction in their length of hospital stay by almost one third. This study has been criticised, however, because of the lengthy of stay in patients in the control group and also the surgeon deciding the time of discharge, possibly being a source of bias. Furthermore, the criteria for discharge were not clearly laid out and this may have caused some difficulty in assessment of outcome. Another area where glutamine supplementation may have beneficial effects is on the gastrointestinal tract. Firstly, in view of its possible role in increasing intestinal absorption it has been postulated that L-glutamine may have a therapeutic role in patients with short bowel syndrome. A preliminary study of patients with short bowel syndrome had suggested that intestinal function and absorption of nutrients could be stimulated by a combination of oral glutamine, growth hormone and a high-carbohydrate, low-fat diet . Growth hormone was included in this cocktail because it is known to enhance intestinal growth and the uptake of nutrients across the intestinal wall [*Scolapio et.al., 1997*].

XIII. NEW DEVELOPMENT IN GLUTAMINE DELIVERY:

Numerous studies demonstrate that free glutamine can be added to commercially available crystalline amino acid-based preparations before their administration. Instability during heat sterilization and prolonged storage and limited solubility (35 g/L at 20°C) hamper the use of free glutamine in the routine clinical setting. Indeed, there are many well-controlled and valuable trials with free glutamine, yet its use is restricted to clinical research. Synthetic glutamine dipeptides are stable under heat sterilization and highly soluble; these properties qualify the dipeptides as suitable constituents of nutritional preparations. Industrial production of these dipeptides at a reasonable price is an essential prerequisite for implications of dipeptide-containing

solutions in clinical practice. Recent development of novel synthesis procedures allows increased capacity in industrial-scale production. Basic studies with synthetic glutamine-containing short-chain peptides provide convincing evidence that these new substrates are cleared rapidly from plasma after parenteral administration, without being accumulated in tissues and with negligible loss in urine. The presence of membrane-bound as well as tissue-free extracellular hydrolase activity facilitates a prompt and quantitative peptide hydrolysis, the liberated amino acids being available for protein synthesis and/or generation of energy. In the clinical setting, glutamine dipeptide nutrition beneficially influences outcome (nitrogen balance, immunity, gut integrity, hospital stay, morbidity and mortality). The provision of conditionally indispensable glutamine should be considered a necessary replacement of a deficiency rather than a supplementation

The glutamine containing dipeptides L-alanyl-L-glutamine (Ala-Gln) and glycyl-L-glutamine are available products and today are an integral part of routine clinical practice. These preparations, Dipeptiven and Glamin (Fresenius Kabi, Uppsala, Sweden), are innovative products; the result of many years of intensive research in the field of clinical nutrition. Dipeptiven is a 20 % solution of the glutamine-containing dipeptide *N*(2)-L-alanyl-L-glutamine (Ala-Gln). It is stable during heat sterilisation and storage, and it is highly soluble (568 gL^{-1}). Glamin is a complete, well-balanced amino acid solution containing 30.27 gL^{-1} stable glycyl-L-glutamine (Gly-Gln). Basic studies in humans and animals provide firm evidence that both glutamine dipeptides are readily used. Importantly, infusion of Dipeptiven or Glamin is well tolerated and not accompanied by any side effects or complaints. The dipeptide concept is based upon the premise that improvement in the quality of available amino acid solutions, currently lacking glutamine, is a major step in resolving the problem of how to formulate and prepare a complete, well-balanced amino acid [*Taylor and Curthoys 2004*].

Biochemical indications of glutamine dipeptide: Generally, poor nutritional status as assessed by body weight, body mass index, anthropometric measures and low plasma albumin, and severe loss of nitrogen and functional tissue, is a useful indication for glutamine dipeptide therapy. Poor immune status is always a strong signal of glutamine deprivation. Decreased body cell mass, in combination with decreased intracellular and increased extracellular water, favor glutamine dipeptide

administration. Please note that plasma-free glutamine concentrations do not always reflect body glutamine status. A normal plasma glutamine level might be associated with severe intracellular glutamine depletion [*Furst 2001*]

Enteral Nutrition and Glutamine: To date, tube-feeding trials show that hypocaloric glutamine-supplemented enteral diets will not provide the requisite amounts of glutamine that can escape the splanchnic bed to elevate blood and muscle concentrations. The reasons for the unfavorable results with enteral glutamine supplementation are multifactorial. Theoretically, the presence of bacterial overgrowth in stressed patients might in part explain the observed low circulating glutamine concentrations, because it is well known that bacteria readily consume glutamine as a preferred substrate. It is also possible that splanchnic glutamine use may contribute to the inability of glutamine-enriched enteral feeds to increase the plasma glutamine levels. Glutamine is absorbed in the upper part of the small intestine and subsequently metabolised in the liver, and, thus, it may not be available in sufficient quantity for the target mucosal tissue at the lower sites of the intestine [*Fürst 2000b*]. It is notable that enteral glutamine nutrition, which initially did not raise the blood glutamine concentration, has been shown to improve the outcome in premature infants; for example, the frequency of sepsis decreased and immunity increased after 0.3 gkg^{-1} body enteral supplementation of glutamine [*Neu et al. 1997*]. These beneficial effects presumably reflect increased bowel maturation, indicating that enteral glutamine can act on the gastrointestinal tract without exerting direct systemic effects [*Wilmore and Shabert 1998*]. In adult patients, glutamine has been shown to have a beneficial effect on intestinal barrier function when given orally (30 g/d) for several weeks after high dose chemotherapy or radiotherapy for esophageal cancer [*Yoshida et al. 1998*]. Another confirmation that enteral glutamine is effective in preventing infective complications has been recently reported in 60 patients with severe multiple trauma [*Houdijk et al. 1998*]. There was a significant reduction (~50%) in the 15-d incidence of pneumonia, bacteremia and severe sepsis. The strengths of this study are in the relatively homogeneous population of patients studied and the fact that the study did not suffer from the confounding factors present in multicenter studies. The results of this fascinating study require confirmation.

There is some evidence that the body glutamine pool is slower to recover when the same dose of glutamine is given enterally (orally) as opposed to parenterally [*Fish et. al. 1997*]. The enteral route may be ideal when given early to the noninfected patient to improve gut-associated lymphoid tissue function and immune defense against infection, but for already severely stressed or infected ICU patients, enteral supplements alone may be inadequate, and parallel parenteral support is likely to be required. It has been clearly shown that during intensive care parenteral supplementation of enteral nutrition with glutamine does not increase the risk to the patients and may ensure a better overall outcome. It should, however, be borne in mind that enteral supplementation with glutamine is a potential hazard because such formulations may form a vigorous cultural medium for microorganisms if strict care is not taken [*Griffiths 1999*].

3.OMEGA-3 FATTY ACIDS:

Dietary lipid is a carrier of fat-soluble vitamins and provider of essential fatty acid's linoleic and linolenic acids. All of the long chain fatty acids share the same enzyme system, as they are elongated and desaturated with each pathway competitive, based on substrate availability. Dietary fatty acids modulate the phospholipid cell membrane composition and the type and quantities of eicosanoids produced. Prostaglandins of the 3 series (PGE_3) and series 5 leukotrines have proven to be anti-inflammatory and immune enhancing agents [*Ninneman and Stockland 1984 ; Moncada 1983*]. Also PGE 3 is a potent vasodilator [*Britter et.al.,1988*]. These concepts have received considerable attention for the potential of n-3 fatty acids ability to enhance immune function and reduce chronic and acute inflammation. They also influence membrane stability, membrane fluidity cell mobility, the formation of receptors, binding of ligands to their receptors, activation of intracellular signaling pathways either directly or through the formation of eicosanoids, gene expression and cell differentiation. In general, eicosanoids formed from omega-3 fatty acids are much less potent in causing biological responses [*Alexander 1998*] than those from omega-6 fatty acids, including stimulation of cytokine production and inflammatory responses.

Many well- controlled clinical studies documented that n-3 fatty acids play an important role in CVD and diabetes mellitus in reducing arrthymias and hypertension,

protection from renal disease, improvement in rheumatoid arthritis, improvement in inflammatory bowel disease, reduced episodes of infection and impair platelet aggregation. Omega-3 fatty acids from dietary sources or supplements may also be useful in decreasing intestinal inflammation and in preventing intestinal cancer [*Hickman 1998*].

Biochemical and Pharmacological Aspects of Omega-3 fatty Acids: Fatty acids are characterised by number of C-atoms, the number of double bonds and position of the first double bond, calculated from the methyl end of the molecule e.g C-18: 2 w-6 (linoleic acid). The most important of omega-6 fatty acids derived from linoleic acid are γ linolenic acid and arachidonic acid (AA), while alpha-linoleic acid is the parent substance of the long-chain omega-3 fatty acids eicosapentanoic acid (EPA) and DHA. The chloroplasts of plants display an enzyme system that adds a further double bond into linoleic acid (C 18:2 ω-6) in position 3 creating alpha-linolenic acid (C18: 3 ω-3) Long chain omega-3 fatty acids, such as eicosapentanoic acid and docosahexanoic acid, are built up in algae and plankton and fish living on them. Deep sea fish and fish oils produced from them provide the main source for humans of omega-3 fatty acids, since the human organism is only able to synthesise small amounts of EPA from alpha-linolenic acid though desaturation and chain lengthening. Omega-3 fatty acids, such as EPA (C,20 :5 ω-3) and DHA (C22;6 ω-3) are contained in deep sea fish in percentage weights of 0.1-1.2% each [*Sinopoulus et.al.,1986*]. Omega-3 fatty acids, such as linoleic acids (C18:2 ω-6) and arachidonic acid (C20:4 ω-6)) which occur in vegetable oils and in the depot of fat of mammals, make up the largest part of fatty acid intake in the nutrition of populations in industrialised states [*Sinopoulus et.al.,1986*].

Metabolism Of Omega-3 fatty acids and Omega-6 fatty acids: As important precursors of eicosanoids, arachidonic acids and EPA are released from the phospholipids in cell membranes by the enzyme phospholypase A2. Since, the only difference between arachidonic acid and EPA is a double bond, both fatty acids are in competition for metabolisation by the same enzyme systems and can displace one another through their respective properties [*Weber et.al.,1986*]. Depending on the enzymes pattern of the respective cell (e.g. thrombocytes, endothelial cells, leucocytes etc.) these fatty acids turn into endoperoxides through the enzymes

cycloxygenase from which prostaglandins, prostacyclins and thromboxanes are formed. The enzyme lipoxygenase creates hydroperoxides as a first step, which finally produce leukotrines [*Wolfram 1995*]. The derivatives formed from EPA are differentiated in their structure and biological activity from the analogues aminoacids derivatives [*Needleman et.al.,1979*]. The cycloxygenase product of the 3-series, TXA_3, derived from EPA, shows a considerable reduction in proaggregatory and vasoconstrictive qualities in comparision with the TX_2 derived from aminoacid, while PGI_3 is comparable to PGI_2 in terms of its antiaggretory and vasodilatory effectiveness. This means that the introduction of omega-3 fatty acids into the prostanoids metabolism results inreduced proaggregatory as well as vasodilatory effect. In cells of granulopoises and of monocyte-macrophages system, arachidonic acid is metabolised into the leukotrines of the four series (LTB_4, C_4, D_4, E_4) that work as potent mediators of leococyte activation, chemotaxis and degranulation. EPA even provides a preferred substrate of 5-lipoxygenase [*Lee et. al.,1985 ; Prescott 1985*] in relation to aminoacid when inserted pro-inflammatory characteristics incomparision with aminoacid derivatives arise at the end of the enzymatic transformation [*Lewis et.al.,1986*] Thus, LTB_5 possesses a considerably reduced vasoconstrictive and chemotactic potency in comparision to LTB_4 [*Lee et.al.,1985 ; Goldman et.al.,1983*]. The formation of the platelet activating factors (PAF), which has a strong proinflammatory, and platelet aggregating effect is also reduced by EPA. In doing so, EPA interferes with the PAF precursor poor as in eicosanoid synthesis [*Weber et. al., 1991*]. Beyond this, the inhibition of the production of pro-inflammatory cytokines such as interleukin -IL1and tumor necrosis factor (TNF-α) is known.

Omega-3 fatty acids and Immune System: Increased intake of long chain omega-3 fatty acids affects the function of the immune system at several levels. Omega-3 fatty acids influence defensive functions by their incorporation into the cell membrane and through their modification of the eicosanoid spectrum. This modulation is characterized by the reduced formation of prostaglandins E_2 and Leukotriene B_4, with the simultaneously increased synthesis of eicosanoids, such as prostaglandins E_3 and leukotrine B_5 with an immunomodulatory and anti-inflammatory effect. Even following hemorrhagic shock, omega-3 fatty acids prevents an increase in the release of PGE_2 and maintenance of the normal defensive function of splenocytes and

macrophages as well as proliferation, antigen presentation and IL-1 and IL-2 secretion [*Ertel et.al.,1993*]. Sepsis, SIRS and endotoxinemia are associated with reduced perfusion of organs and tissue. Often lactacidosis develops due to impaired liver function. The omega-3 fatty acids and omega-6 fatty acids play an important role as eicosanoids precursors in connection with the genesis of these symptoms. With the administration of omega-3 fatty acids, the proportion of TXA_3 / TXA_2 as well as of LTB_5 / LTB_4 increases which results in reduced vasoconstriction and platelet aggregation [*Psheidl et. al., 1992]*. While the vasodilatory effects of prostaglandins PGI_2 and PGI_3 are comparable. Changes in local blood flow, especially hypoperfusion in the splanchinic area, play an important role in the pathogenesis of sepsis and multiple organ failure. Intestinal ischemia results in damage to the intestinal mucosa, with loss of barrier function for endogenous bacteria. Omega-3 fatty acid prevents the destruction of the intestinal barrier function associated with ischemia. Crohn's disease like ulcerative colitis, is a chronic inflammation of the bowel affecting large areas of the intestine. Administration of ω-3 fatty acids produces a shift of the lipid mediator spectrum toward leukotrienes of the 5 series, with reduced pro-inflammatory and chemotactic activity [*Lobos et. al., 1993*].

4.NUCLEOTIDE

Nucleotide results from the combination of purine or pyrimidine base, the sugars, ribose deoxyribose and a phosphate moiety. They serve as the structural units for DNA, RNA, ATP cyclic AMP and other substances important energy transfer such as NAD, NADP and FAD addition to their critical functions in maintaining and transferring the genetic code as well as energy transfer, nucleotides are thought to have important immunomodulatory properties. They were previously excluded from nutritional supplements because it was thought that the body could make the required amount itself. However, it has recently emerged that adequate levels of nucleotide are required for the body to mount an effective immune response to injury when critically ill. Dietary nucleotides are thought to enhance natural killer cell activity and have been shown to reverse the depressed T-lymphocyte function resulting from a protein-free diet [*Carver et.al.,1990 ; Van Buren et.al.,1990*].

Nucleotide and Wound Healing: In patients with cancer, the administration of Polyadenylic Polyuridylic acid (PAPU) has immunoregulatory effects, stimulation of

both T and B lymphocyte function, most likely due to induction of immunoregulatory cytokine production has been documented [*Hovanssian et.al.,1985*]. Dietary supplementation with of nucleotide promotes healing of small bowel ulcers [*Sukumar et.al.,1997*]. In intestinal mucous, nucleotide have been shown to enhance the production of repair cells, known as enterocytes [*Ortega et.al.,1995*] and also to prevent the loss of important bacteria in the gut. Some quantity of nucleotide may be necessary to maintain immunocompetance but not all studies clearly demonstrate benefit deriving from a nucleotide enriched formula or supranormal supplementation of nucleotides. Uses of dietary nucleotides have been less successful than glutamine supplements alone as stimulators of immune system.

XIV CLINICAL EFFECTS OF IMMUNO-ENHANCING DIETS :

An alternative approach to supplementation with a single nutrient has been to combine several of these key nutrients to produce an 'immuno-enhancing' diet. For example, combinations of L-arginine (with or without L-glutamine), EFAs and ribonucleic acid, with other nutrients, are available for use in the clinical situation. These diets contain some nutrients, which stimulate and others (e.g EFAs), which can inhibit the immune system. However, the basis for their use has been that initial clinical studies had demonstrated that such a mixture of nutrients could result in a stimulation of a range of immune functions when compared with those of patients taking a standard diet [*Cerra et. al., 1990 ; Kemen et. al., 1995*]. Following from these initial immunological studies, randomised controlled trials have examined the effects of such immuno-enhancing regimens, comparing them with standard diets, on clinically relevant indicators of patient outcome. These outcome indicators have included post-operative complications, length of hospital and/or intensive care unit stay and mortality. Several clinical studies on the effect of immunonutrients in surgical patients have been studied; the majority of these trials focus on the clinical outcome of G.I cancer patients undergoing elective surgery. Since these analyses have been carried out another study has been published by Braga *et. al.,* [1999] which has examined the effects of an immuno-enhancing nutritional regimen. A total of 206 patients with tumours of the stomach, pancreas or colorectum were studied. Patients were randomised to receive either the immuno-enhancing diet or a standard diet, which was given for 7 days prior to surgery and continued for 7 days after

surgery. Both groups of patients appeared to be comparable in terms of diagnosis, baseline nutritional status, disease stage and the surgery that was undertaken. The results demonstrated that patients receiving immuno-enhancing nutrition had a significant reduction in major infectious complications (14 % versus 30 %), and a significant reduction in overall hospital stay of 1.8 days. Inpatients undergoing elective major surgical procedures pre-operative administration of an IED for 5 - 7 days before elective surgery appears to improve clinical outcome.

Despite these promising results there are still many questions to be answered regarding the role of immuno-enhancing nutritional regimens. For example, should all patients receive them, does baseline nutritional status alter the effects, should they be given in the pre- and/or post-operative periods, how much should be given and for how long? Furthermore, many of these immuno-enhancing diets have contained a greater quantity of other nutrients, which are known to stimulate the immune system, eg selenium, vitamins A and E, than have the control diets. Therefore, it is still not entirely clear which are the key nutrients responsible for the possible beneficial effects that may have been documented. [*Heys and Gardner 1999*]. However, in case of surgical patients, patients who would benefit from early enteral nutrition with IED are malnourished elective G.I surgical patients (Albumin <3.5g dl^{-1}) for upper G.I tract and < 2.8g dl^{-1} for lower G.I tract). Even ventilator dependent non-septic medical and surgical patients are generally at risk for subsequent infectious morbidity and so are good candidates for IED [*Proceedings from the summit 2001*]. Once started IED should be aggressively administered with the goal of providing at least 50 - 60% of the patients calculated daily nutrient goal and continued for at least 5days with subsequent reevaluation [*Proceedings from the summit 2001].*

XV COST AND IMMUNOENHANCING NUTRIENT:

Cost is often quoted as a reason for sub-optimal nutritional support. However, on careful analysis, one sees that patients are often unnecessarily kept in the hospital (both pre- and post operative), undergo unwarranted investigations, which do not alter the management plan and receive non-indicated medications. Examples include multiple does of antibiotics for prophylaxis when only one dose may be sufficient; or an IV route of administration when the oral route will suffice. Additionally, PN is used

when EN is possible. When these factors are considered, one will realise that it is not the cost factor but the lack of sensitivity on the part of the physician that results in neglect nutritional support. Immunoenhancing formulas were found to be costing 10times more than the standard formulas. Studies have focused upon specific patient populations, however, (*i.e* severe trauma, malnourished GI surgery) have routinely identified reductions in infectious complications, length of hospital stay, antibiotic days, ventilator days and incidence of MOSF with a trend towards improved survival that would make the therapy cost effective [*Eastern Associated for Surgery of Trauma 2003 ; Proceedings from the summit 2001*]. Table representing costs of commercially available EN products are presented.

XV. BLENDERISED KITCHEN BASED POLYMERIC ENTERAL DIETS:

Blenderised kitchen based diets are used in many developing countries primarily because it is cheaper than commercially prepared feeds. Although is generally not used in the developed world. It is viscous and chunks of food and has the chances that it may block the feeding tube. Although larger bore tubes can be used, this increases the risk of many feeding related complications if not planned properly. Even there may be chances of feed contamination, is a further reason why blenderised feed is not used, particularly in immunocompromised patients or those patients with achlorhydria. Even feed of this type is considered unsuitable for jejunal feeding. Although blenderised feed may be used, generally commercially prepared polymeric feed is most commonly given to patients. Elemental and disease specific feeds are increasing in use, but at the moment are principally research based. Singh and Garg [*1999*] have reported that typical Indian vegetarian diet and dietary components such as cereals, grains, pulses, vegetables and spices have been analysed for 19 elements (Br, Cl, Co, Cr, Cu, Fe, Hg, K, Mn, Mo, Na, P, Rb, Sb, Sc, Se, Sr, Th and Zn) by instrumental neutron activation analysis (INAA). Several Standard Reference Materials (SRMs) were analysed for quality assurance. Based on the elemental contents, the daily dietary intake has been calculated and the data compared with those from other countries, Recommended Dietary Allowances (RDAs) and permissible body burden. It has been observed that, although vegetarian, the Indian diet has an adequate content of essential trace elements

compared to non-vegetarian oriental (Japan and Taiwan) and western (Germany, Denmark and USA) diets.

RESEARCH TRIALS ON KITCHEN-BASED POLYMERIC DIETS

Since India is also a developing with majority of the population under poverty line; commercial enteral feed available in the market are too costly to be used by the downtrodden people of the society. Hospitals are also not financially so sound to administer such commercial products and they are compelled to support them with lower energy level. This requires working with a low cost enteral feeding formula that can be within easy reach of the patients critically ill and needing to undergo surgical procedures. Research studies had been conducted with an intention to develop low cost Kitchen-based enteral formulas benefiting the lower socioeconomic critically patients **by Deparment of Foods and Nutrition & A WHO Collaborating Centre, The M.S University of Baroda, Vadodara**. Studies have been conducted by Mani *et. al.,* between the year *1997 - 2000*, had done deeper research studies on critically ill (organophosphate ingested) patients where they reported that kitchen based cereal pulses (consisted of rice flour, Bengal gram flour, sugar, oil, milk, and ragi supplied 1149 Kcal $500ml^{-1}$) based enteral diet had a trend for improvement increasing the total protein but also at the same time reduced the serum glucose, triglyceride level, Cholesterol level, creatinine, SGPT, and total bilirubin compared to the patients on routine hospital enteral diet. These diets were low cost (Rs: 10.00 p) at the same time and could be easily prepared in the kitchen set up.

Thus, from the above it is very clear that further research is required to clearly identify which surgical patients will significantly benefit from specific nutritional intervention. This is problematic as assessment of nutritional status is not straightforward and there is also an absence of a standardised definition of nutritional depletion. Such validated definition of nutritional depletion would enable nutrition support to be targeted to those surgical patients most likely to derive significant clinical benefit in terms of improved postoperative outcome. This would also facilitate direct comparison of trial data for large meta-analyses involving "malnourished" patients to provide robust, evidence-based guidelines for nutritional support of surgical patients.

In this present study, an effort had been made to know whether enteral nutrition support venture if planned based on kitchen based items, using protein sources from soy and milk with subsequent substrate enrichment with immunoenhancing nutrient

(IEN) specifically enteral glutamine, proves some promising results specifically for patients undergoing gastrointestinal surgical procedures. Soybean on an average contains 40 % protein, 23 % carbohydrate, 20 % oil, 9 % moisture and 5 % minerals and 3 % fibre. As per PDCAAs (the Joint Expert Consultation of FAO and WHO - 1989 recommended protein digestibility- Corrected Aminoacid Score) for evaluating protein quality has confirmed that it can replace meat and fish protein [*Subbulakshmi 2004*]. The protein of the milk is also considered as functional food with immunoenhancing properties [*Marshall 2004*]. Both are good natural sources of natural glutamine. Studies report that soy protein contains naturally higher levels of arginine and glutamine than milk protein or casein or egg white [*Subbulakshmi 2004*].

The following chapters presents detailed outline of the research study undertaken and its outcomes.