To Our Readers

We have been extremely encouraged by the enthusiasm and interest displayed by you all. The current (Seventh) issue of the Update Series covers two important areas which are likely to have considerable application in modern hospital-based nutrition intervention programmes - "Immunonutrition" and the role of "Nucleotides in Nutrition".

The first article on Immunonutrition underscores the important role that nutritional factors play in the immune status and how Immunonutrition influences both gut function and the immune system. The broad principles governing the role of nutritional factors as immunomodulators have also been highlighted.

The second article provides an overview of the clinical importance of nucleotides in nutrition and the biochemical factors involved in their functioning.

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Immunonutrition

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The disciplines of nutrition and immunology are becoming more closely inter-related, with current interest surrounding specific dietary components that may influence and correct immune dysfunction. Nutrition is essential for normal cellular metabolism, wound healing, immune competence and organ function but we now know that nutrients exert more than their established 'nutritive' effects on body function and metabolism. Deficiencies of individual nutrients are associated with profound impairment of cell-mediated immunity. As well as maintaining good health and diminishing the risk for chronic diseases, certain nutrients and 'non-nutrient' free radical scavengers such as polyphenols, flavanoids and phytoestrogens, in fresh vegetables, cereals and fruits, control important metabolic activities and can modify the immune response.

Nutritional factors play a major role in immunity, which appears to progressively decline with age, leading to increased infection and complication rates. Primary immune changes may not explain the increased incidence and severity of infections in the elderly. Indeed, environmental factors leading to secondary immune dysfunction may be more influential. These include cumulative antigenic influences, which reflect the illnesses, drug therapy, physical activity and nutritional quality of the diet, experienced throughout life.

The content and 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 hypercatabolic situations. Critical illness is often associated with a physiological immunosuppression leading to increased opportunistic infections, increased morbidity and a high risk of mortality. Impaired host immunity has been increasingly related to protein calorie malnutrition, which is known to depress antibody production, the functions of phagocytes, T-cells and levels of plasma complement. In trauma or surgery, energy requirements are affected by decreased physical activity and by the increased metabolic demands of injured tissues. Considerable increases in blood polymorph numbers are encountered in the immediate post-operative period, following the stress related cortisol release. Lymphocytes decrease both
in number and in responsiveness. Concentrations of the acute phase proteins, C-reactive protein, (relating to IL-6 activity) may have prognostic significance.

The term immunonutrition has been coined to describe diets that are specifically designed to enhance immune function. While the metabolic response to a brief period of starvation may be foreseen in the healthy patient presenting for elective surgery, it is clearly advisable to improve the nutritional status in patients with severe preoperative malnutrition. Failure to do so may affect immunocompetence, organ failure and late mortality in the critically ill. Immunonutrition may aid patients with pathological inflammatory responses by altering the composition of inflammatory mediators such as prostaglandins, 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.

Immunonutrition influences gut function as well as the immune system. The gastrointestinal tract is the most metabolically active organ following surgical trauma, which possesses immunoregulatory properties2, maintains immunological function and protects the body from invading pathogens. It involves not only the gut wall barrier but also macrophages, other phagocytic cells and mast cells. A lack of intestinal nutrient provision such as that induced by total parenteral nutrition (TPN), predisposes towards exaggerated cytokine mediator production and acute-phase response3. Withholding enteral nutrition (EN) in humans has also been associated with increased gut mucosal permeability and decreased villus height. These can be reversed with timely immunonutrition therapy.

Glutamine (GLN) is a major fuel for gut enterocytes and is essential for immune cells such as lymphocytes, macrophages, and neutrophils which all exhibit high rates of GLN consumption in culture4. GLN greatly enhances the in vitro bactericidal function of isolated human neutrophils and numerous studies have documented the requirement for GLN to support the proliferation of mitogen-stimulated lymphocytes from both rodents and humans5. Dietary GLN increases in vitro production of cytokines by up to four-fold in cell culture6. Thus, GLN may promote the development and activation of macrophages in vivo. The availability of cytokine assays allows their utilisation as surrogate markers of injury severity or predictors of complications and offers exciting potential for manipulation of the diet and thus the immune system in a variety of clinical situations.

Glutamine (or its dipeptide precursors) has been shown to decrease negative nitrogen balance, maintain muscle mass and gut integrity after major surgery7, after bone marrow transplantation8, and in very low birth-weight babies9. Intensive care patients administered GLN-supplemented TPN (20-25g/d) exhibit improved nitrogen balance, increased lymphocyte recovery, greater cysteinyl leukotriene production by neutrophils, and decreased mortality10,11. GLN-enriched enteral nutrition (also containing Arginine) has recently been shown to decrease the frequency of pneumonia, sepsis and bacteremias in patients with multiple trauma12. Oral GLN (40g/d) plus antioxidants decreases the demand for endogenous GLN by HIV patients and results in weight gain, increased body cell mass, intracellular and total body water13. Because the immune system appears to have a requirement for GLN to retain optimal function, maintenance of plasma GLN concentrations in catabolic patients might have an added benefit of improving immune function and thus lead to enhanced resistance to infection. In metabolically stressed situations, plasma and muscle GLN concentrations are significantly decreased, reflecting the increased energy demand of these immune cells14. There is also a significant negative correlation between GLN levels and IL-6 production. Immune cells (including macrophages) share a GLN dependence for proliferation, function, and/or activation, but can the depression of plasma GLN levels experienced during catabolic states actually contribute to immune depression? Exhaustive exercise is one model which is followed by impaired natural immunity with high circulating levels of pro- and anti-inflammatory cytokines15. Nutritional supplementation with GLN certainly counteracts the exercise-induced decline in plasma GLN and, together with fish oil, vitamin E and vitamin C, has been shown to diminish the risk of upper respiratory tract infections in athletes16.
Over the past two decades, studies have shown Arginine (ARG) and its analogues, to be powerful mediators of multiple biological processes including hormone release, collagen synthesis during wound healing, antitumour activity, and immune cell responses. Ornithine demonstrates most of ARGs pharmacological properties, but cannot be substituted nutritionally in organisms that require ARG for optimal growth. Although citrulline can replace ARG nutritionally, exogenous citrulline has none of the latter’s pharmacological properties. There is increasing evidence that ARG influences the activity and interactions of macrophages and polymorphonuclear cells. At the cellular level, ARG is metabolised by a number of enzymes, including arginase and nitric oxide (NO) synthase that are implicated in immunomodulation. Arginase and NO synthase coexpression in macrophages may represent a regulatory mechanism to modulate NO synthesis and ARG use during sepsis or heightened inflammatory responses. ARG increases T-cell mitogenic responses when given in doses of 30 g/d (or 5–12 g of arginine/1,000 kcal) in volunteers and in severely ill patients. Meta-analysis of 12 prospective randomised studies involving more than 1,500 intensive care or postsurgical patients, who received ARG, fish oil and nucleotides, demonstrated that immunonutrition significantly lowers the risk of infections, the number of ventilator days and length of stay in ICU, but does not reduce mortality.

N-acetyl cysteine (NAC) is a substrate of cysteine, a precursor for the major anti-oxidant glutathione (GSH) that scavenges free radicals. Cysteine itself appears to cause destruction of intracellular GSH in hepatocytes, probably by production of peroxides associated with its oxidation to cystine. A slow release of cysteine for the GSH synthetic pathway from NAC may, however, maintain or replenish GSH. In protein-depleted rats given an inflammatory challenge of E Coli endotoxin, the liver and lung GSH levels were decreased, but were subsequently enhanced with a diet enriched with NAC. Oral NAC supplementation has been well tolerated by cervical cancer patients where it minimised the decreases in red blood cells and total lymphocyte counts.

The tripeptide glutathione (glycyl-glutamyl-cysteine) is, in quantitative terms, one of the most important antioxidants in human cells. Likewise, it has been suggested that glutathione plays an important role in the regulation of protein synthesis, vitamin C and vitamin E regeneration, protein degradation and detoxification. It could also protect skeletal muscle, liver and endothelial tissues against free radical-induced oxidative stress and tissue damage following shock, sepsis, pancreatitis and head or surgical trauma. It has become increasingly clear that muscle glutathione is reduced in post-abdominal surgery, and in patients with septic complications. Moreover, it has been demonstrated that septic patients with high nitric oxide (NO) concentrations not only develop cardiovascular dysfunction but also mitochondrial complex I and IV inhibition (cell respiration inhibition). This seems to be due to S-nitrosylation of these enzymes, which becomes progressively persistent as the cellular concentration of reduced glutathione (GSH) decreases.

Recent studies have also shown the possible relationship between GLN and GSH. Since GLN is efficiently transported across cell membranes, it may be a readily available precursor for GSH synthesis. Liver GSH levels improve after GLN supplementation to glutathione-depleted animals and after severe injury. Furthermore, GLN supplementation enhances plasma GSH concentration, and preserves gut GSH levels during intestinal ischaemia and reperfusion.

Even a moderate depletion of GSH impairs the integrity of mitochondria. Decreases in GSH have been found to correlate with a decrease in creatine phosphate (PCr) indicative of a decreased mitochondrial energy metabolism. Creatine facilitates the transfer of energy into cells and as (PCr) buffers against lactic acid production during metabolic stress. A decreased availability of PCr represents a reduction in the rate of ADP rephosphorylation to ATP, which in turn is associated with muscle atrophy. Motor neurone disease (MND), also known as amyotrophic lateral sclerosis (ALS), is a progressive and ultimately fatal disease. Muscle fatigue, impaired muscle function, immunosuppression and reduced tissue viability are classical symptoms of MND, which may be partially corrected with nutritional support. Immunonutrition with creatine, glutathione and/or its precursors is currently under investigation with a transgenic animal model of ALS.
The interrelationship between nutrition and laboratory parameters of immunity may have considerable practical applications. It is now clear that dietary composition can profoundly affect immune function, cell division and interaction, the response to pharmacological agents and other biological processes. The development of more sophisticated parenteral and enteral therapy in recent years has greatly improved the nutritional status of hospitalised patients but has not shown significantly decreased morbidity or mortality in the critically ill. Simply improving nitrogen balance without maintaining plasma or tissue glutamine levels and satisfying the dramatically increased requirements of the immune system could be detrimental. The use of specific nutrient supplements, singly or in combination, stimulates the immune response and should result in fewer infections, particularly in the elderly, low birth-weight infants and the malnourished critically ill.

Metabolic modulation of immunity by immunonutrition holds much future promise of improved clinical outcome. We are beginning to understand more about the biochemical effects and interrelationships of the wealth of nutrients that occur naturally in foods, but much more research is required. When we can determine the bioavailability and mechanism of action of individual pharmaconutrients used for immunomodulation, we shall be able to optimise the formulations and regimens for immunonutrition therapy.

REFERENCES

Nucleotides In Nutrition

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INTRODUCTION

Nucleotides are ubiquitous intracellular compounds of crucial importance to cellular function and metabolism. They have been demonstrated to have a wide variety of physiological effects such as antiviral, anti-proliferative, immunomodulatory and other such beneficial functions. Nucleotides can be synthesised endogenously and hence are not essential nutrients. However, their requirements go up in situations of stress like infection, surgery, tissue repair and/or when de novo synthesis may be inadequate. The need then arises for extraneous supplementation. Thus the nucleotides have come to be classified, in recent times, as 'conditionally essential nutrient' like the amino acid glutamine.

The building blocks of nucleotides are purine and pyrimidine bases attached to a sugar (ribose or deoxyribose). When phosphate moiety is also added, it is termed as nucleotide. Table I gives the nucleotide nomenclature.

NUCLEIC ACID SYNTHESIS

Nucleotides can be synthesised in two ways (a) de novo synthesis, and (b) salvage pathway. The de novo synthesis makes use of many precursors of amino acids like glutamine, aspartic acid, glycine, vitamins like folic acid as well as a metabolite of ribose-5-phosphate (PRPP). Considering the overall economy of the cell, this is a costly process and hence the salvage pathway, which makes use of breakdown products and exogenously added nucleotides, serves as an effective alternate pathway for the synthesis of nucleotides.

METABOLIC FUNCTIONS

Cellular nucleotides have many functions. Apart from being the genetic material to carry forward the heredity, they also are known to act as cellular messengers for signal transduction (Cyclic Amp), cellular "energy currency" (ATP), physiological mediators (cyclic GMP, ADP in platelet aggregation), cofactors for many enzymes (FAD, FMN, NAD), a role in detoxification processes (UDP sugar), as a constituent of s-adenosyl methionine (SAM), which acts as a methyl donor and cellular agonists to trigger intracellular signal transduction cascades including CAMP and inositol-calcium pathways. Evidence supports the existence of pyrimidine as well as purine receptors for this purpose.
Table I: Nucleotide Nomenclature

<table>
<thead>
<tr>
<th>Base Nucleoside</th>
<th>Ribonucleotide</th>
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<tr>
<td><strong>Purines</strong></td>
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<td></td>
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<tr>
<td>Adenine (A)</td>
<td>Adenosine</td>
<td>AMP</td>
</tr>
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<td></td>
<td></td>
<td>dAMP Guanine (G)</td>
</tr>
<tr>
<td>Hypoxanthine</td>
<td>Inosine</td>
<td>IMP</td>
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<td>Pyrimidines</td>
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<td>Cytosine (C)</td>
<td>Cytidine</td>
<td>CMP</td>
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<td>Uracil (U)</td>
<td>Uridine</td>
<td>dCMP</td>
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<tr>
<td>Thymine (T)</td>
<td>Thymidine</td>
<td>dTMP</td>
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</table>

NUCLEOTIDES IN NUTRITION

There are many dietary sources of preformed NTs coming from plant and animal sources. They are listed in Table II. Human milk is a very good source of nucleotides. The nonprotein nitrogen content of human milk is around 25 per cent of total nitrogen vis-a-vis only 5 per cent in the case of cow's milk. For this reason, human milk is always taken as the "Gold Standard" during any humanisation process of branded milk foods. Free and cellular nucleotides (primarily CMP and AMP) account for about 2-5 per cent of the NPN in human milk. Apart from NTs, NPN compounds present in human milk are mainly urea, N-acetylglucosamine, carnitine and others. Levels of nucleotides such as CMP, AMP, GMP and UMP are high in colostral milk (that is, two days after parturition), which gradually go down with advancing period of lactation. Still considerable level of NT is seen even after three months of lactation. Intensive research has been going on to understand the significance of free nucleotides present in human milk. One possible reason could be that it helps in the rapid tissue growth in the child, by augmenting nucleic acid synthesis. It also seems to enhance the humoral immune response to vaccination. An exogenous supply of dietary nucleotides may particularly be helpful to a premature child, in whom the metabolic pathways have not fully developed. Currently, many infant foods are being formulated and marketed in the west by inclusion of NT, which is expected to confer benefit to the child during its active growth phase. Thus nucleotides are now being considered as a functional food with its value-addition to the infant formula food.

NTs are known to enhance taste perception and make the food more palatable. They are therefore being increasingly used as food flavours in food industry around the world. One earlier study has also reported that infants consumed increased quantities of cow's milk when NTs were added which could be due to improvement in taste.
Role of dietary nucleotides in neonatal and infant nutrition can be summarised as follows:
Yet to be proved unequivocally (Randomised Control Study)

- Accelerated physical growth
- Neurological development
- Better growth and development of their GI tract resulting in improved digestive and absorptive functions
- Immune augmentation
- Resistance to infection
- Lower bacterial and viral infection rates in infancy
- A more favourable intestinal microflora associated with a lower rate of infectious diarrhoea.

**PROVED**

- Better catch-up growth of severe IUGR term infants.
- Future studies will be needed in conditions of
  a) Prematurity,
  b) Foetal growth retardation,
  c) Intestinal injury,
  d) Limited nutrient intake.

**Table II: Purine and RNA Content of Selected Foods**

<table>
<thead>
<tr>
<th></th>
<th>Adenine (mg/10 g)</th>
<th>Guanine (mg/100 g)</th>
<th>Hypoxanthine</th>
<th>Xanthine (mg/100 g)</th>
<th>Total Purines</th>
<th>RNA (mg/100 g)</th>
<th>Protein(%)</th>
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<td>102</td>
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<td>26</td>
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<td>Pork liver</td>
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<td>71</td>
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<td>Chicken liver</td>
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<td>71</td>
<td>22</td>
<td>243</td>
<td>402</td>
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<tr>
<td>Chicken heart</td>
<td>32</td>
<td>41</td>
<td>12</td>
<td>138</td>
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<td>187</td>
<td>18</td>
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<td>Fresh seafood</td>
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<td>6</td>
<td>212</td>
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<td>24</td>
<td>12</td>
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<td>Mackerel</td>
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<td>26</td>
<td>5</td>
<td>152</td>
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<td>Salmon</td>
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<td>Sardines</td>
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GASTROINTESTINAL EFFECTS

A number of human and experimental studies have shown that nucleotides have many positive effects on the GI tract. They help in the growth and development of the intestines. Iijima et al have demonstrated that supplementation of a nucleoside and nucleotide mixture to a TPN solution can attenuate the initial mucosal atrophy and improve intestinal cell turnover after a massive bowel resection in male Wistar rats.2

In a detailed study, Tsujinaka et al showed the effect of supplementation of dietary nucleotides (nucleotides and nucleosides) in a group of Wistar rats and compared them with control group, given only the parenteral nutrition without NTs.3 Various parameters like mucosal wet weight, protein and DNA contents, villous heights, crypt depth, electron microscopic examination of intracellular junctions, proliferating activity of the mucosal cells, mucosal permeability, bacterial translocation and mucosal cathepsin activities were examined.

The wet weight, protein and DNA contents of jejunal mucosa as well as villous heights were significantly elevated. Many other indices like the activity of diamine oxidase, ratio of proliferating cell nuclear antigen positive cells were also significantly high in NTs supplemented groups indicating that the parenteral supplementation of nucleic acids supports mucosal cell proliferation and functions. However some authors have suggested that beneficial effects to the gut appear to depend on the type of damage sustained by the gut. Grimble indicates from animal studies that an exogenous supply of nucleotides (salvage pathway) can improve liver regrowth, immune responsiveness to a microbial challenge and gut morphology in diarrhoea models.4 It is worthwhile to remember that the gut receives its supply of NTs from the liver which is the main site of de novo synthesis. In humans, de novo synthesis is down regulated when dietary NTs are supplied.

Critically-ill patients, who cannot synthesize NTs de novo, need it exogenously. At the moment, there are not many preparations nor many studies on TPN or E regimens which generally include nucleotides and hence supply is restricted to the gut and immune cells in the critically-ill and artificially-fed patients. They need extra NTs in times of stress and hence such studies should be undertaken.

The selection of intestinal microflora can be influenced by dietary NTs. Bifidobacteria is predominant in the stools of breast fed infants, while gram-negative bacteria predominate in children given cow's milk infant formula. In vivo and in vitro reports have suggested that bifidobacteria growth can be stimulated and enhanced by NTs added to the formula milk.

Recently, studies have been carried out in intestinal cultures and the effect of addition of NTs in them. Not only have they demonstrated the efficacy of using such systems, but have also revealed that exogeneous NT may increase the growth and maturation of normal enterocytes. This intestinal cell culture system is a
very good model to delineate the effect of NTs on the GI tract.

MECHANISM OF ACTION OF NUCLEOTIDES

It has been postulated that dietary effects of nucleotides on intestinal mucosa as well as on immunity act at the gene transcription level. These nutrient-gene interactions are being actively pursued and now the techniques of molecular biology have facilitated the exploration and explanation of how dietary factors, such as glutamine, short chain fatty acids and nucleotides affect normal and pathologic mucosal development, function, adaptation and repair.

IMMUNITY

Yamamoto et al have shown in in vitro immune studies that NTs increased delayed type cutaneous hypersensitivity and the popliteal lymph node blastogenic response to antigens, allogens and mitogens5.

Lymphocytes are capable of synthesising their own requirements of NTs by both de novo as well as salvage pathways and any exogenous supply serves to increase the concentrations of intracellular NTs and turnover of cells. This is especially true in the case of proliferation of lymphocytes. The following effects on immunity have been demonstrated in humans and animals on feeding NTs.

Cellular Immunity

Mice

Feeding NT supplemented diet to mice has been associated with increase in the following immune parameters:

- Graft vs host disease mortality
- Rejection of allogeneic graft
- Delayed cutaneous hypersensitivity
- Alloantigen-induced lymphoproliferation
- Reversal of malnutrition and starvation-induced immunosuppression
- Natural killer cell activity and IL-2 production
- Resistance to challenge with Staph. aureus and Candida albicans
- Macrophage phagocytic ability
- Spleen cell production of IL-2 and expression of IL-2 receptors

(In most of these studies, addition of RNA or uracil restored immune function, which attests to the ability of lymphocytes to salvage pyrimidines)

Humans

Infants given NT-supplemented milk formula showed increased natural killer cell activity and IL-2 production.

Humoral Immunity

Various in vitro studies have suggested that polynu-cleotides addition produces the following effects:

- Influence on T-helper cells for generating antibodies.
- Modulation of humoral immune response by interaction with cell surface molecules of T-cells.
- Ensuring specificity of T-B cell cooperation, by suppressing nonspecific stimulation of T-cells.
In the absence of NTs in the diet, it was shown that the number of IgM and IgG secreting cells in spleen in mice is lowered. In the case of humans, most of the dietary nucleotides are probably retained in the intestinal tissue itself, which also contributes to body's immunity.

HEPATIC EFFECTS

Liver is the major site of synthesis and release of NTs in the body. In fact, the supply of this critical nutrient to the intestinal cells with its rapid turnover is from liver only. Other body cells also receive their supply of NT from hepatic source. This is accomplished by both de novo as well as salvage pathways. Any injury to the liver results in the stimulation of these pathways to manufacture new RNA and DNA.

Investigations in animals have shown parenterally administered NT/NS mixture improve hepatic function and promotes positive nitrogen balance following liver injury or partial hepatectomy in rats. Novak et al also observed that weanling mice fed NT-free diet had increased hepatic cholesterol, lipid phosphorus, and serum bilirubin and decreased liver weight and glycogen when compared to animals supplemented with 0.21 per cent w/w/NT6.

The role of exogenously administered nucleotide on hepatic function is an area which requires a lot of attention. This will be especially relevant in situations when liver's capacity to synthesise NTs de novo is affected due to disease or injury. Culture systems akin to what is already being attempted in the case of intestinal cells may prove to be good models for such investigations.

BRAIN

The beneficial effect of supplementation of NTs in improving brain function has been demonstrated by Yamamoto et al5. Brain has very limited de novo synthesising capacity of purine and pyrimidine bases. These authors showed that memory deficient senescence accelerarated mice and mice with dementia showed improved memory with dietary NTs supplementation.

In an excellent review, Neary et al7 have narrated the trophic actions of extracellular NTs on glial and neuronal cells. Besides being neurotransmitters and neuro modulators, NTs can also act as trophic factors in both central and peripheral nervous systems.

Specific extracellular receptor subtypes for these compounds are expressed on nervous, glial and endothelial cells, where they evince different effects. This can range from induction of cell differentiation and apoptosis, mitogenesis and morphogenetic changes to stimulation of synthesis or release or both of cytokines and neurotrophic factors, both under physiological and pathological conditions. NTs may be involved in the regulation of development and plasticity of the nervous systems and in the pathophysiology of neurodegenerative disorders.

Receptors for NTs could represent a novel target for the development of therapeutic strategies to treat incurable diseases of the nervous system, including trauma and ischemia associated neurodegeneration, demyelinating and ageing associated cognitive disorders.
HEMOPOIESIS

Yamamoto et al have shown in experimental animals that NTs stimulate hemopoiesis and increase in peripheral neutrophil counts in mice treated with cyclophosphamide.

EFFECTS ON LIPIDS

Human and animal studies have shown that feeding a NT-supplemented formula results in the increase in long chain polyunsaturated fatty acids in erythrocytes of term and preterm infants and in the plasma of term infants and in rats. It is likely that dietary NTs play a role in the conversion of 18 C essential fatty acids to 20-22 C very long chain PUFA.

NTs IN ENTERAL AND PARENTERAL SOLUTIONS

Management of the critically-ill patient remains a significant challenge to clinicians. The ultimate objective is to augment host barriers and immune functions and improve survival. Many nutrients have been under intense scrutiny for this purpose. Among them vitamins E, and C, albumin, arginine, glutamine and omega 3-fatty acids show great promise. Close on their heels, are short chain fatty acids and nucleotides. Hence pharmaceutical companies have been vigorously pursuing the idea of enriching parenteral or enteral preparations with nutrients like glutamine, nucleotides, vitamins and others. It is worthwhile to mention three such preparations in this connection (i) OG-VI (ii) Impact (iii) NNM from Japan.

OG-VI Composition

30 mM Inosine
30 mM Sod.
5’ guanylate
30 mM Cytidine
22.5 mM Uridine
7.5 mM Thymidine

Since dietary NTs play an important role in the growth and development of the intestines, supplementation of a nucleic acid solution (OG-VI) may support the optimal growth and integrity of the intestines under TPN. Supplementation of OG-VI to a TPN (a) improved mucosal morphological and functional changes, (b) increased mucosal proliferation, and (c) decreased mucosal permeability of the intestines. After 80 per cent small bowel resection, OG-VI supplementation to a TP solution attenuated the initial mucosal atrophy and improved intestinal cell turnover. Thus, nucleic acid supplementation may be clinically beneficial in certain situations.

Impact (Sandoz)

One of the enteral branded preparation available to the clinician is 'Impact' which contains among other ingredients, arginine, omega 3-fatty acids and dietary nucleotides. Senkal et al8 have carried out a study in surgical patients to determine if early post-operative feeding of patients with upper GI tract malignancy using Impact results in an improved clinical outcome, that is, reduced infections and wound complications and decreased treatment costs, when compared with an isocaloric, isonitrogenous control diet. The study was designed as a prospective, randomised, placebo controlled, double blind, multicentre trial for the clinical outcome and a retrospective cost-comparison analysis. The results unequivocally indicated that in patients who received the supplemented diet, a significant reduction in the frequency rate of late post-
operative, infections and wound complications was observed. This also resulted in substantial reduction in treatment cost.

Nucleoside Nucleotide Mixture (NNM composition: in g/lit).
(Inosine = 230, Cytidine = 210, Guanidine monophosphate 2 Na = 350, Uridine = 160, Thymidine = 30). It has been shown to augment T-cell immunoproliferation in SAM mice.

Table III: Reported Effects of Dietary Nucleotides in Humans and in Animals

<table>
<thead>
<tr>
<th>Human</th>
<th>Animal</th>
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<tbody>
<tr>
<td>Promotion of small intestinal growth</td>
<td>+</td>
</tr>
<tr>
<td>Increased small intestinal disaccharidase activity</td>
<td>+/-</td>
</tr>
<tr>
<td>Intestinal hyperemia</td>
<td>+</td>
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<tr>
<td>Protection against diarrhoeal disease</td>
<td>+</td>
</tr>
<tr>
<td>Effects upon stool flora</td>
<td>+</td>
</tr>
<tr>
<td>Enhanced cellular immunity</td>
<td>+</td>
</tr>
<tr>
<td>Enhanced humoral immunity</td>
<td>+</td>
</tr>
<tr>
<td>Effects upon hepatic composition</td>
<td>+</td>
</tr>
<tr>
<td>Increased blood levels of long chain polyunsaturated fatty acids</td>
<td>+/-</td>
</tr>
<tr>
<td>Effects upon serum lipoproteins</td>
<td>+/-</td>
</tr>
</tbody>
</table>

SIGNALLING BY EXTRACELLULAR NTs

ATP and other NTs can be released from cells through regulated pathways or following the loss of plasma membrane integrity. Once outside the cell, these compounds take on new roles as intracellular signalling molecules that elicit a broad spectrum of physiological responses through the activation of numerous cell surface receptor subtypes. ATP and other NTs act on a large and diverse family of P2 purine receptors, four of which have been cloned. These can act through calcium channels at G2 protein linked P2 receptor signals. These receptors are widely distributed in different tissues like neurons, muscles, platelets, and immune cells.

While considering the effects of dietary NTs, it should be borne in mind that it is a mixture of nucleotides and nucleosides. There have been several investigations on the effects of individual nucleotides also. The predominant purine and its analog that have been studied are adenine, adenosine and adenosine phosphate. Intravenous administration of adenosine has been found to influence significantly the activities of vascular, cardiac and neuronal tissues. Most of adenosine's biologic effects are due to its role as a potent vasodilator. Of all the purine and pyrimidine bases, adenosine is the one that plays a vital role in intestinal epithelium. Apart from adenine base, the other purine which has received some attention is inosine phosphate which appears to have immunomodulating activities. Very little work is, however, available on individual pyrimidines. Uracil is known to influence the performance of lymphocytes, as mentioned earlier. In addition, it may be needed in the metabolic activities of other tissues also.
This area of individual nucleotides and their physiological role in the body needs in-depth studies. Once specific roles are identified for individual purine and pyrimidine compounds, it might be possible to customise their use for individual needs in different organ systems in the body.

CONCLUSION

Dietary nucleotides seem to have significant effects on lymphoid, hepatic and intestinal tissues and also in lipid metabolism10 (Table III, previous page).

While the supply of NTs, generated by de novo and salvage pathways may be able to meet the needs of the body tissues during normal times, it may prove to be grossly inadequate during other times of stress and strain, like infection, toxic injury and critically-ill situations. It is now increasingly recognised that extraneous supply of NTs needs to be given to bolster the vital metabolic pathways in the body. This can be resorted to by augmenting the dietary intake or value addition to various products like infant formulae or enteral and parenteral nutrient media. While intense research has been going on in this area of Nucleotides in Nutrition, there are many more grey areas which need to be addressed. These include detailed investigations on the effect of supplementation of dietary NTs on morphology and physiology of enteral cells in health and disease, gut associated lymphoid tissue, infant formula milk while attempting to simulate breast milk and, last but not the least, the role of individual purine and pyrimidine compounds in conferring benefits.

REFERENCES