Nutritional Intervention: What of the Future?

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Introduction

In the practice of nutritional intervention as it relates to the sick patient, the future is today! Predicting future developments in nutritional intervention depends on technical innovations, yet to be realized, which will facilitate the implementation of advances in nutritional support. These innovations include delivery devices, ranging from catheters to packaging and enhanced nutrient substrate composition, based on greater understanding of their function in health and disease.

But, by merely expanding the use of contemporary nutritional support to the field of obstetrics, heart disease, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) and bone marrow transplantation (BMT), we can immediately amplify our application of nutritional intervention, bringing the future to it. This would benefit patient populations in whom nutritional support is not routinely considered, despite medical evidence to the contrary.

Nutritional Intervention in the Field of Obstetrics

Global estimates of obstetrically related maternal mortality, as provided by the World Health Organization, exist up to 1995 [1] and are based on the absolute number of maternal deaths, the maternal mortality ratio (MMR), and the lifetime risk of deaths. Over 50% of worldwide maternal deaths occur in
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Fetal nutrient demand
Fetal size and growth trajectory

Maternoplacental nutrient supply
Nutrient availability and partitioning
Placental size and transfer capabilities
Uteroplacental blood flow

Fetal adaptations and developmental changes if demand greater than maternoplacental supply
Alterations in fetal body composition
Growth of specific organs
Alterations in fetal endocrine status
Fetal cardiovascular adaptations

**Fig. 1.** Framework for understanding the maternal regulation of fetal development and programming. From Barker [8].

Africa, 42% occur in Asia, ~4% in Latin America and the Caribbean Islands, and less than 1% in the more developed regions of the world. The frequency of complications during pregnancy remains high, contributing directly to fetal intrauterine malnutrition and resulting in dysmaturity. These sequences of intrauterine metabolic events have immediate profound adverse effects on the fetus and subsequently on adult disease later on in life, as proposed by Barker [2] in his ‘Fetal Origins’ hypothesis. An understanding of this concept permits the development of nutritional intervention strategies in obstetrics, which prevent the deleterious metabolic fetal intrauterine consequences and impacts on the frequency of future adult disease, as summarized in Figure 1.

**Fetal Nutrition and Adult Disease: ‘Fetal Origins’ Hypothesis**

This hypothesis was proposed by Barker [2]. It states that a stimulus or insult (termed ‘programming’), such as undernutrition, occurs at a sensitive or critical period during high fetal cell division or differentiation, causing changes in fetal nutrition and endocrine status and resulting in developmental adaptations that permanently change structure, physiology and metabolism, thereby predisposing individuals to cardiovascular, metabolic and endocrine disease in adult life (Table 1). Some effects of nutrition are direct consequences of alterations in substrate availability, while hormonal effects mediate others. These alter the development of specific fetal tissues, reflecting the plasticity of neural tissue during early sensitive periods of development [3]. Alternatively,
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Table 1. Fetal undernutrition with each trimester of pregnancy

<table>
<thead>
<tr>
<th>Trimester</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
<tr>
<td>Body proportions</td>
<td>Proportionately small</td>
<td>Thin</td>
<td>Short</td>
</tr>
<tr>
<td>Weight at 1 year</td>
<td>Reduced</td>
<td>Normal</td>
<td>Reduced</td>
</tr>
<tr>
<td>Adult life</td>
<td>↑BP</td>
<td>↑BP Non-insulin dependent diabetes</td>
<td>↑BP LDL cholesterol ↑Fibrinogen</td>
</tr>
<tr>
<td>Death</td>
<td>Haemorrhagic stroke</td>
<td>Coronary heart disease</td>
<td>Coronary heart disease Thrombotic stroke</td>
</tr>
</tbody>
</table>

BP = Blood pressure; LDL = low-density lipoprotein. From Barker [8].

Experimental data suggest that the response may lead to long-lasting changes in hormone secretion or tissue hormone sensitivity [4]. The fetal hypothalamus has been implicated as the key site, which is programmed by transient prenatal endocrine status. A wide range of organs and systems may be programmed by the intrauterine environment suggesting that programming reflects a general principle of developmental biology. Table 2 lists several key tissues and systems in humans indicating the effects of programming by nutrients and hormonal milieu on the fetus.

**Fetal Nutrition and Maternal Influences on Fetal Nutrition**

The dominant determinant of fetal growth in utero is the oxygen and nutrient supply and the ensuing hormonal environment, in which the fetus develops; the fetal genome plays a subordinate role [5]. Fetal size at birth is the product of the fetus’s trajectory of growth, as programmed by the fetal genome, and the materno-placental capacity to supply sufficient nutrients to maintain that trajectory. The mother’s birth weight, her dietary intake and
**Table 2.** Tissues and systems for which there is evidence of programming in humans

<table>
<thead>
<tr>
<th>Tissue/system</th>
<th>Examples of programming</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular and respiratory system</td>
<td>Vascular compliance, endothelial function, lung volume</td>
</tr>
<tr>
<td>Endocrine system</td>
<td>Hypothalamic-pituitary-adrenal axis, glucose/insulin metabolism, growth hormone-IGF-I axis</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>Age at menarchy, polycystic ovary syndrome</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Skeletal muscle/bone</td>
<td>Insulin resistance, glycolysis during exercise, bone mineral content</td>
</tr>
<tr>
<td>Kidney/liver</td>
<td>Renin/angiotensin system, cholesterol metabolism</td>
</tr>
<tr>
<td>Immune system</td>
<td>Thyroid autoantibodies, IgE concentrations</td>
</tr>
</tbody>
</table>

IGF-I = insulin-like growth factor I; Ig = immunoglobulin. From Godfrey and Barker [52].

Body composition exert major effects on the balance between fetal demand for nutrients and the materno-placental capacity to meet that demand, as shown conceptually in Figure 1. Failure to satisfy fetal nutrient requirements results in a range of fetal adaptations and developmental changes which benefit short-term survival, but lead to permanent changes in the body’s structure and metabolism and thereby to cardiovascular and metabolic disease in adult life [6]. Thus, low-birth-weight mothers tend to have thin infants with a low ponderal index (ratio of the individual’s height to the cube root of his/her weight) at birth; the probable mechanisms being alterations in the uterine or systemic vasculature. Paternal birth weight has an influence on crown-heel length, reflecting paternal imprinting of genes important for skeletal growth [7]. Women who consumed a high dietary carbohydrate diet in early pregnancy and who delivered at term had smaller placentas, particularly if combined with low intakes of protein in late pregnancy. These effects are independent of a mother’s body size, social class, and smoking status. These effects result in alterations in the ratio of placental weight to birth weight. Observations linking the intrauterine environment with later hypertension, diabetes, elevated blood cholesterol and fibrinogen concentrations, and polycystic ovary syndrome serve to illustrate some of the principles that underlie fetal programming.
Influence of Fetal Growth and Coronary Heart Disease

Coronary heart disease (CHD) occurs probably as a consequence of fetal adaptations to undernutrition, which is of benefit for short-term survival, although detrimental to health in postreproductive life [8]. Thus, low rates of fetal growth are associated with CHD in adult life, as shown in Table 1 [9].

High Blood Pressure and Hypertension

Studies of men and women who had detailed neonatal anthropometrics show that those who were disproportionately thin or short at birth tend to have high blood pressure and are at a greater risk of hypertension in adult life. Thus, hypertension is found in people who are small for gestational age rather than those born prematurely [8].

Type-II Diabetes and Insulin Resistance

An association between low birth weight and altered glucose metabolism exists [10]. The prevalence of type-II diabetes and impaired glucose tolerance falls progressively between those who are small and those who are large at birth. Similar to the hypertension data, the association between birth weight and later glucose tolerance is independent of adult lifestyle influences.

Cholesterol Metabolism and Blood Coagulation

Restricted intrauterine fetal growth leading to abnormal body proportions at birth and a short body in relation to the head size is associated with higher concentrations of total cholesterol, low-density lipoprotein (LDL), apolipoprotein B, fibrinogen, and factor VII. A low abdominal circumference at birth predicted high serum LDL-cholesterol and plasma fibrinogen concentrations in adult life [8]. Disproportion in body length relative to head size results from cranial redistribution of oxygenated blood away from the trunk to sustain brain metabolism impairing growth of the liver leading to permanent abnormalities in regulation and clotting factors [11].

Enteral/Parenteral Nutrition in Obstetrics and Gynecology

The indications for the use of nutritional intervention, including total parenteral nutrition (TPN) during pregnancy are maternal nonfunctioning of the gastrointestinal tract associated with disease. These include inflammatory bowel disease, pancreatitis, anorexia nervosa or uncontrolled diabetic keto-acidosis, patients who are undergoing post-gastric bypass procedure for morbid obesity, patients with active cancer who are receiving chemotherapy, and those with hepatorenal failure or brain tumors [12–14]. Another major category, in which nutritional intervention is indicated, is following maternal trauma (including blunt and penetrating injury), iatrogenic or spontaneous injury to the mesenteric vasculature, burns, coma and maternal brain death. Lastly, fetal intrauterine growth retardation, hyperemesis gravidarum, and
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eclampsia are large categories of intrauterine catastrophes, in which the baby tends to survive and in which nutritional intervention of the most sophisticated nature needs to be provided to the mother and the fetus. However, unlike traditional blood value markers of nutrient adequacy for nutritional intervention, these are absent in obstetrics due to the lack of a blood sampling facility in the fetus. Furthermore, the daily requirements of most nutrients, particularly of vitamins, mineral and micronutrients, during the different stages of development remain speculative. Thus, blood levels of marker in the mother serve as surrogate markers, while ultrasound measurements of numerous fetal bones and their ratios remain an estimate as to the adequacy of fetal nutrient provision and fetal growth [15–17]. Conventional markers of nutritional intervention adequacy continue to be used for the mother, ensuring that sufficient nutrients are given to meet her primary needs and to meet the need of her underlying condition.

Implication for the Future

As a consequence of maternal illness (hemorrhage or toxemia of pregnancy and indirect obstetrical causes such as inflammatory bowel disease, trauma, etc., as well as factors including a woman’s diet and body composition) many fetuses must adapt to a limited supply of nutrients. In doing so, they permanently change their physiology and metabolism. These ‘programmed’ changes are the origins of a number of diseases in later life including CHD and the related disorders, hypertension, stroke and diabetes (Table 1).

Thus via the use of nutritional intervention, physicians can and should optimize the intrauterine nutrient environment provided for the fetus. Because nutrients influence hormones, which alter fetal gene expression programming in fetal development and adult disease, it is imperative that clinicians focus on an enteral intervention program that ensures optimal nutrient intake of mothers during pregnancy. Such enteral products should reflect our most sophisticated knowledge of the effects of nutrients on tissue growth and on anabolism. Data suggest that such a wide-sweeping nutritional intervention program would have a profound effect not only on the health of the offspring, but also on the frequency of adult disease later on in life.

As emphasis on maternal health continues to expand, so too does the use of nutritional intervention, both enteral and parenteral, to prolong the quality of life of the mother. This will enable her to deliver a relatively healthy infant near term.

Nutritional Intervention in Heart Disease

As the population becomes older, heart disease becomes a more prominent health care issue. Intrinsic heart failure leads to malnutrition, and weight loss. Cardiac muscle fibers atrophy, the ventricular volume mass decreases, stroke
volume falls, cardiac output decreases, the QRS complex diminishes in size, there is a reduction in oxygen consumption and ultimately an increase in mortality occurs [18].

Loss of body weight decreases lean body mass, a major determinant of resting metabolic rate, which reduces metabolic rate and thus cardiac output, to protect the failing heart. In the presence of heart failure, without weight loss, there occurs a decrease in activity-associated energy expenditure, without a decrease in resting energy expenditure. But with weight loss both are reduced. The most significant determinant of wasting in heart failure is severe biventricular failure with increased right atrial pressure and tricuspid incompetence [19].

Patients with this condition have very low but fixed cardiac output. During nutritional intervention, e.g., TPN, where energy intake is increased either as carbohydrate or fat, oxygen consumption also increases, although only to a limited extent. Protein intake does not increase cardiac output. Thus energy intakes should be increased cautiously in marked malnutrition and severe heart failure.

With gradual refeeding in a protein calorie-malnourished patient with cardiac failure, cardiac fibers hypertrophy, the QRS complex normalizes, oxygen consumption increases, and cardiac output rises. But, if a malnourished patient with cardiac cachexia is rapidly fed, cardiac failure with tachycardia, anasarca, pulmonary edema, and shortness of breath ensue.

A number of micronutrient deficiencies also have induced cardiac malfunc-
tion [20]. Among these, thiamin deficiency, due to its role in pyruvate dehydrogenase activity, is responsible for converting pyruvate to acetyl CoA, which is then oxidized in the tricarboxylic acid cycle inhibiting glucose oxidation. Selenium and phosphorus deficiencies cause cardiomyopathy and heart failure. Deficient myocardial fiber concentrations of taurine, carnitine and coenzyme Q10 (CoQ10) are also associated with impaired cardiac function leading ultimately to cardiac death, while magnesium and potassium deficiencies induce lethal cardiac arrhythmias.

Effects of Energy Intake and Growth Hormone Supplementation in Heart Failure

In two studies, patients were given nutritional supplementation for prolonged periods of time. And, despite positive energy and nitrogen balances, cardiac wall thickness and cardiac function did not improve [21, 22]. In two different studies, growth hormone was given to patients with heart failure in an effort to increase the muscle mass of the heart and improve pumping efficiency [23, 24]. Growth hormones increased ventricular muscle mass, but did not improve cardiac failure. Thus, nutritional intervention, as protein and energy, together with the promotion of ventricular cardiac muscle growth via growth hormones, does not improve heart failure or cardiac function. This implies that an intrinsic metabolic/energetic imbalance is the basis of the
Abnormalities of Cardiac Mitochondrial Function in Cardiac Failure

In heart failure, the cardiac muscle is deficient in complex IV of cytochrome C oxidase and skeletal muscle energetics are abnormal; both conditions contribute to fatigue [27]. Thus, to address the issues of improving cardiac function, nutritional strategies need to be based on an understanding of the recognized abnormalities. These include: (i) promotion of optimal substrate oxidation; (ii) ensuring electron flow is facilitated; and (iii) prevention of mitochondrial injury.

Optimal Substrate Oxidation

Via the action of carnitine, long-chain fatty acids are cleaved from acryl CoA, freeing CoA and promoting oxidation of pyruvate derived from glycolysis resulting in glucose oxidation. In congestive cardiac failure, free carnitine in the cardiac muscle is reduced. Its concentration correlates with the patient’s ejection fraction [28]. The provision of free L-carnitine vs. placebo improves outcome in patients with cardiac failure and enhances survival [29]. In heart failure patients, the cardiac muscle is also deficient in CoQ10, and nutritional intervention with 2 mg/kg/day CoQ10 restores their cardiac levels. Functionally, CoQ10 concentrations in cardiac muscles correlate negatively with ventricular grade, such that nutritional intervention with CoQ10 vs. placebo in patients with class III–IV cardiac failure led to a shorter hospital stay and fewer episodes of pulmonary edema [30].

Prevention of Mitochondrial and Myocyte Injury

Taurine modulates voltage-dependent calcium channel activity and regulates Na/Ca exchange and Na-taurine cotransport, protecting cardiac myocytes from calcium cell injury. Taurine supplementation reduces muscle-free calcium and thus cardiac damage [31]. Another well-recognized cause of cardiac injury is oxidative stress that increases in relation to the degree of heart failure.

Figure 2 summarizes the multiple problems related to optimal substrate use in cardiac function in heart failure patients, indicating points at which nutritional intervention would be recommended. Since cardiac patients are usually on diuretics, thiamin is supplemented to prevent thiamin deficiency, which results in reduced glucose oxidation. Carnitine also aids glucose oxidation, while CoQ10 promotes electron flow and taurine, together with other antioxidants such as glutamine to protect mitochondria and myocytes from injury.

Cardiac function does not improve in patients with right heart failure and tricuspid incompetence, when fed protein and energy, primarily because the hearts in patients with cardiac failure have mitochondrial dysfunction. Jeejeebhoy and Sole [25], among others, have determined that the mitochondria are depleted of carnitine, CoQ10 and taurine, in which the severity
of depletion is related to the severity of heart failure. Repletion of carnitine, CoQ10 and thiamin improves outcome.

*Implication for the Future*

It is proposed that nutritional intervention in heart failure patients should not only be directed solely to the provision of sufficient energy and protein, but also directed to the replacement of carnitine, CoQ10, taurine, antioxidants and thiamin. The need to develop a range of enteral supplements specifically aimed at the cardiac patient seems of high priority. Such a supplement(s) should be high in protein, enriched with glutamine, arginine, glutathione, and carnitine, CoQ10, taurine and thiamin, contain an optimal balance between n-3 and n-6 fatty acids and provide a complex carbohydrate base, including fiber.

*Perioperative Nutritional Intervention in Cardiac Surgery*

As affluence increases in emerging economies, an increasing number of patients avail themselves of cardiac surgery, as a means to address congenital and acquired-lifestyle cardiac disease. Numerous laboratory studies have shown that a high myocardial glycogen content offers a protective effect on
Table 3. Frequency of life-threatening post-operative cardiac complications

<table>
<thead>
<tr>
<th>Group</th>
<th>Post-operative substrate</th>
<th>mg glycogen/100 g heart</th>
<th>Atrial arrhythmia %</th>
<th>Ventricular arrhythmia %</th>
<th>Vasopressor %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>880 ± 47*</td>
<td>11.1</td>
<td>18.5</td>
<td>24.2</td>
</tr>
<tr>
<td>II</td>
<td>10% glucose</td>
<td>1,180 ± 50*</td>
<td>7.4</td>
<td>14.9</td>
<td>17.9</td>
</tr>
<tr>
<td>III</td>
<td>20% glucose</td>
<td>1,270 ± 50*</td>
<td>6.1</td>
<td>23.0</td>
<td>3.1</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous fat 1</td>
<td>1,509 ± 110*</td>
<td>8.1</td>
<td>22.8</td>
<td>5.2</td>
</tr>
<tr>
<td>V</td>
<td>Fat and glucose 20%</td>
<td>1,486 ± 74*</td>
<td>7.2*</td>
<td>4.4*</td>
<td>4.3*</td>
</tr>
</tbody>
</table>

*p < 0.001.
From Lolley et al. [33].

cardiac function during anoxia [32]. Based on these observations, the application of nutritional intervention to support the patient during perioperative cardiac procedures has been well established and documented to enhance survival [33]. Three hundred and twelve elective adult coronary artery surgery patients were divided into 5 groups differing as to preoperative glucose or fat loading (Table 3). The control group (n = 54) had a mean myocardial glycogen level of 880 mg/100 g heart weight, an 18.5% incidence of serious ventricular arrhythmias, 24.2% dependence on vasopressors, a mean peak postoperative serum glutamic-oxaloacetic transamidase (SGOT) level of 100 IU, and a 3.7% perioperative transmural myocardial infarction rate. The 10% glucose loading group (n = 67) had an elevated myocardial glycogen of 1,180 mg/1,000 g heart, 14.9% serious ventricular arrhythmias, but a lessened dependence on vasopressors (17.9%), a peak post-bypass SGOT of 74 IU, and 2.9% transmural infarction rate. A 20% glucose overnight loading group (n = 65) had a myocardial glycogen level of 1,270 mg/100 g heart, a 23.0% incidence of serious ventricular arrhythmias, a significant reduction in vasopressor dependence (3.1%), no transmural myocardial infarctions, and peak post-bypass SGOT of 53 IU. The intravenous fats (10% intralipid) group (n = 57) had the highest glycogen level of 1,509/mg/100 g heart, the lowest peak SGOT of 51 IU, no infarctions, a low vasopressor dependence (5.2%), but high rate of serious ventricular arrhythmias (22.8%). The oral fat and 20% glucose loading group (n = 69) had a myocardial glycogen of 1,486 mg/100 g heart, a low vasopressor dependence rate of 4.3%, no infarctions, a peak SGOT of 66 IU, and the lowest serious ventricular arrhythmia rate of 4.3%. These results suggest that it is possible to alter pre-bypass myocardial substrate levels against the stresses of cardiac surgery with fat and/or glucose loading and that myocardial protection is evident. The best clinical results occurred within a short preoperative period of a combination of fat and intravenous
glucose loading to achieve maximal and complete substrate enhancement and optimal myocardial glycogen concentration [34].

**Implication for the Future**

A more rational understanding of the pathophysiology of cardiac disease will help design specific nutritional intervention strategies directed at the early stages of cardiac disease. Data convincingly show that nutritional intervention in the form of glycogen loading, prior to cardiac surgery, diminishes postoperative life-threatening arrhythmias, enhances survival and optimizes outcome. These are the highest attributes of nutritional intervention.

**Nutritional Intervention in HIV and AIDS**

In the early 1970s, a few cases of a newly acquired cellular deficiency disease were reported in the *New England Journal of Medicine*, among other prestigious journals. These cases concerned the development of *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men, primarily patients from the US, Haiti, Africa and Europe. Within a decade, HIV was reported in all countries in patients of all races, ages, and social classes. Today, globally, 36.1 million adults and children are living with HIV and AIDS.

Figure 3 reflects the HIV epidemic in South Africa. Estimates of the national prevalence rate of HIV from 1990 to 1998 show a steady increase from 0.7% in 1990 to 22.8% in 1998. This indicates an increased rate more than 30 times higher than that found at the beginning of the epidemic. Overall in Sub-Saharan Africa, the adult HIV prevalence rate is 8.8%, while it is estimated that 25.3 million individuals are living with HIV/AIDS, of which 55% constitute women. It is estimated that newly infected cases constitute 3.8 million per year and that annual death rates due to HIV/AIDS are 2.4 million. Nutrition plays a major role in the progression of HIV disease [35, 36].

Nutritional deficiencies exacerbate the clinical immune deficiency, diminishing the quality of life for HIV-positive individuals. Malnutrition is a major contributor to morbidity [37]. Malnutrition causes a variety of immunological abnormalities similar to AIDS, and can thus predispose to opportunistic infection(s) causing or exacerbating AIDS [38]. The immunological abnormalities in AIDS include: a reversal in the ratio between helper and suppressor T cells, a decrease in lymphokine production and a decrease in the activity of cytotoxic cells. Furthermore, many patients with AIDS have weight loss, which may be preceded by the occurrence of opportunistic infections and tumors [39].

Since not all patients harboring the virus develop AIDS, a predisposing host factor plays an important role in determining the response [40]. Thus maintaining sound nutritional status plays a significant role in (i) diminishing susceptibility to the HIV, and (ii) delaying disease progression. Both enhance
well-being, and are compelling reasons for providing nutritional intervention (either enterally or parenterally, depending on the stage of the disease process) in HIV-positive individuals.

**Diminishing Susceptibility to the HIV**

AIDS is induced by an enveloped retrovirus. Enveloped viruses such as mixoviruses, paramixoviruses, arboviruses, and herpes viruses lose their inactivity under the influence of unsaturated free fatty acids, e.g. they become inactive with as little as 10 µg/ml of linoleic acid, arachidonic acid, and oleic acid, but are not affected by stearic acid [40]. The disintegration of the viral envelope accounts for their loss of infectivity. Although γ-linolenic acid (GLA) was not tested directly, it is likely that it also inactivates the virus by similar means. Moreover, both prostaglandin (PG) E₁ and PGA₁, derived from GLA, are known to inhibit viral replication and act as antiviral agents [41]. Furthermore, there is evidence that the antiviral effects of vitamin C and interferon result from controlled peroxidation of unsaturated fatty acids. Apart from exhibiting direct effects on the enveloped viruses, certain essential fatty acid (EFA) metabolites may enhance the ability of the host to resist infection by the AIDS agent, through modulation of immune response. Schlager and Meltzer [42]
demonstrated that lymphokine activity of macrophages was due to its ability
to increase the linolenic acid content of the macrophage two- to threefold
over control. It is apparent that EFA metabolism constitutes an important key
to understanding virucidal activity. The most important molecules in the n-6
family are γ-linolenic acid, di-homo-GLA and arachidonic acid, with α-linolenic
acid and eicosapentaenoic acid (EPA) having similar importance in the n-3
family. Thus it is possible that a deficiency in dietary EFAs or a defect in EFA
metabolism can make an individual more susceptible to develop AIDS.

It is likely that a deficiency in GLA can increase the susceptibility of an
individual to a viral infection. This is because GLA is not present in adequate
 amounts to inactivate viruses and because required amounts of PGE₁ and
PGA₁ cannot be formed to inhibit viral replication and enhance interferon
production and cell-mediated immune response [43, 44]. A deficiency in GLA,
due to either a dietary lack of α-linolenic acid or to the presence of inhibitors of
Δ⁶-desaturase enzyme activity, may enhance susceptibility to viral infections
and induce immunosuppression. To compensate for the lack of GLA and EPA,
the direct provision of GLA and/or EPA by nutritional intervention, either via
the enteral or parenteral route, is of particular value in AIDS patients. It is
postulated that an absolute or relative acquired deficiency in EFAs is related
to the development of AIDS. If this can be shown, then supplementing the
diet with GLA and/or EPA may be of some benefit in the prevention and in
the treatment of AIDS.

**Combating Malnutrition in HIV**

Nutritional intervention should be used as an adjunctive therapy for all
patients affected by HIV disease. Many of the nutritional deficiencies detected
in HIV are essential for various body functions (Table 4). Nutrient deficiencies
of vitamins A, B₆ and B₁₂ and zinc are associated with impaired immuno-
logical function and increasing progression of malignancies [45]. Specific
cognitive abnormalities have been attributed to vitamin B₁₂ and B₆ defi-
ciences. Vitamin B₁₂ and folate deficiencies produce anemia, exacerbating
dementia and neuropathy. Zinc deficiency interferes directly with CD4 T-cell
functioning, while magnesium deficiency is associated with fatigue, headaches,
and muscle aches. β-Carotene supplementation has been associated with
improved CD4 T-cell counts, while N-acetylcysteine, another antioxidant, has
been shown to have antiviral activity in vitro. Thus, multivitamin and mineral
supplementation should constitute part of the nutritional intervention program
in patients with HIV, since they affect quality of life and improve immune
status. However, when wasting becomes part of the clinical picture, intense
nutritional intervention including dietary counseling, vitamin/mineral supple-
mentation should be encouraged. Appetite stimulants (megastearol acetate)
including anabolic hormones, in addition to enteral and parenteral nutrition,
should be considered as well as cytokine inhibitors.
Table 4. Some useful vitamins and minerals in HIV disease

<table>
<thead>
<tr>
<th>Vitamin and minerals</th>
<th>Possible uses</th>
<th>Functions</th>
<th>Signs of deficiency</th>
</tr>
</thead>
</table>
### Table 4. (continued)

<table>
<thead>
<tr>
<th>Vitamin and minerals</th>
<th>Possible uses</th>
<th>Functions</th>
<th>Signs of deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate</td>
<td>Prevents iron-deficiency anaemia</td>
<td>Essential for transport of O₂ to tissues</td>
<td>Fatigue, pale skin, listlessness, irritability, and difficult swelling</td>
</tr>
<tr>
<td>(iron)</td>
<td>Stimulates bone marrow and production of Hgb</td>
<td>Maintenance of oxidative systems in cells</td>
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<tr>
<td></td>
<td>Forms part of enzymes and proteins</td>
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<td></td>
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<tr>
<td></td>
<td>Possibly stimulates immunity</td>
<td></td>
<td></td>
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<tr>
<td>Zinc</td>
<td>Antioxidant</td>
<td>Part of the molecular structure of more than 80 enzymes</td>
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<td></td>
<td>Promotes normal growth and development</td>
<td>including carbonic anhydrase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wound healing</td>
<td>Responsibility for combining CO₂ and H₂O in red blood cells</td>
<td></td>
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<tr>
<td></td>
<td>Promotes cell division, cell repair, and growth</td>
<td>Carbonic anhydrase is also present in GI mucus tubules and glandular epithelial cells</td>
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</tr>
<tr>
<td></td>
<td>Maintains normal level of vitamin A in blood</td>
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<tr>
<td>Magnesium</td>
<td>Aids in bone growth</td>
<td>Enzymatic activities</td>
<td>Muscle spasms and fatigue, convulsions, confusion, irritability, nervousness, skin problems</td>
</tr>
<tr>
<td></td>
<td>Necessary for skeletal muscle contraction and relaxation</td>
<td>Affects metabolism of proteins and nucleic acids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conducts nerve impulses</td>
<td>Important for sodium/potassium transport across cell membranes</td>
<td></td>
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<tr>
<td></td>
<td>Works as a laxative in large doses</td>
<td>Influences calcium levels (intracellular)</td>
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<tr>
<td></td>
<td>Antacid</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Strengthens tooth enamel</td>
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<td></td>
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<tr>
<td></td>
<td>Alleviates cardiac arrhythmias</td>
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<td></td>
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</table>

(continued overleaf)
Table 4. (continued)

<table>
<thead>
<tr>
<th>Vitamin and minerals</th>
<th>Possible uses</th>
<th>Functions</th>
<th>Signs of deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper</td>
<td>Promotes normal RBC formation</td>
<td>Essential for a number of proteins and enzymes</td>
<td>Anemia, low white blood cells, and associated with reduced resistance to infections, bone demineralization</td>
</tr>
<tr>
<td></td>
<td>Acts as catalyst in storage and release of iron to form hemoglobin for RBCs</td>
<td>Especially important for cytochrome oxidase and dopamine hydroxylase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Assists in production of enzymes involved in respiration</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Promotes central nervous system function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selenium</td>
<td>Complements vitamin E as antioxidant</td>
<td>Enhances primary hormonal response to infections</td>
<td>Myocardial abnormalities</td>
</tr>
<tr>
<td></td>
<td>Promotes normal growth and development</td>
<td>Important for mitochondrial ATP biosynthesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antioxidant, in itself</td>
<td>Prevents wide variety of diseases in animals</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May enhance immune responsiveness</td>
<td>Antioxidant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May prevent diseases (seen in animals)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From Berger [53].

Implication for the Future

Malnutrition is a leading cause of morbidity in HIV disease. Early nutritional intervention directed at prevention, as well as treatment strategies in conjunction with antiviral medication, should remain the mainstay of therapy.

Nutritional Intervention in Bone Marrow Transplant

BMT is increasingly being performed in the population of emerging economies. It is perceived by both the medical community and by sophisticated patients as the natural next step in the treatment of a variety of hematopoietic conditions, particularly lymphoblastic and myoblastic anemias,
that have failed or have become refractory to conventional chemotherapeutic therapy. More recently, it has been employed in patients with aplastic anemia or acute leukemia and at present it is being advocated for young mothers with metastatic breast cancer.

The treatment consists of high-dose chemotherapy and total body radiation followed by autologous transplantation of bone marrow. The classical post-transplant clinical course includes anorexia, nausea, vomiting, diarrhea, malabsorption, negative N balance and weight loss occurring in the first 30 days, as a result of post-transplant complications, including infection or graft-versus-host disease [46]. Animal studies have demonstrated that hematopoietic recovery is compromised without an adequate nutrient intake [47]. Survival analysis of 33 patients who depended on oral nutrient intake averaged 10 months [48]. Therefore, due to the unreliability of the enteral route in these patients, intravenous nutritional intervention of BMT recipients has become routine [49]. The goal of nutritional intervention in most BMT patients is the maintenance rather than repletion of body cell mass, because their nutritional status is generally good at the start of treatment.

Szeluga et al. [50] measured serial nitrogen balance and concomitant energy intakes (kcal/kg/day) in 84 patients (age 4–49 years). For each patient a simple linear model (nitrogen balance vs. energy intake) was used. A simple linear model was constructed with nitrogen balance as the dependent variable (Y) and energy as the independent variable (X) for each of 84 patients, to determine the patient’s predicted energy requirement during the first 30 post-transplant days (EReq30). The X intercept corresponds to the predicted energy intake (kcal/kg/day) necessary to maintain nitrogen balance equal to 0 during the first 30 post-transplant days (EReq30). With no energy intake, nitrogen balance equaled $-29 \text{ g/day}$. To maintain 0 nitrogen balance the median requirement was 44 kcal/kg/day for the group of adult patients. For the group of adolescents the median was 53 kcal/kg/day, and for the group of children the median was 79 kcal/kg/day.

The positive effect of prophylactic TPN on long-term outcome of BMT was clearly demonstrated by Weisdorf et al. [51]. In a randomized trial, the impact of providing TPN to BMT patients during their cytoreductive therapy and for 4 weeks following BMT on 8 parameters of outcome was followed. A total of 137 patients over 1 year of age and with normal nutritional status were randomized to receive TPN, starting 1 week prior to transplant or to receive hydration with a 5% dextrose solution containing electrolytes, minerals, trace elements and vitamins. TPN was required for 40 of the 66 control patients, when nutritional depletion was documented. The average total calorie and protein intake was significantly higher for the TPN group than for the control. Minimum follow-up was 1 year and the median was 2 years. Overall survival, time to relapse and disease and disease-free survival was significantly improved in the TPN group.

Life
table curves for overall survival in the TPN prophylaxis \emph{vs.} control group, engraftment, duration of hospitalization, and incidences of acute and chronic graft-\emph{versus}-host disease and bacteria were not different. But nutritional intervention during BMT had a positive effect on long-term outcome. This indicates that well-nourished individuals survived longer during cytoreduction and BMT.

\textit{Implication for the Future}

During the early critical stages following high-dose chemotherapy and total body radiation followed by autologous transplantation of bone marrow, the patient needs to be aggressively supported via nutritional intervention using TPN for approximately 7–10 days. This has a profound influence on ultimate survival. During this time, the classical post-transplant clinical course including anorexia, nausea, vomiting, diarrhea, malabsorption, negative nitrogen balance and weight loss is minimized. In addition, as the gut lining regenerates, aggressive nutritional intervention using state-of-the-art enteral formulae should be simultaneously instituted.

We began by asking the question: What is the future of nutritional intervention? The answer lies clearly in the present. By expanding its application on a routine basis to the practice of obstetrics, heart disease, HIV/AIDS and BMT, we bring the present to the future, which in turn will invest in the future in unpredictable ways.

\textbf{References}

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**Discussion**

**Dr. Okada:** Dr. Meguid has discussed three topics such as obstetrics, heart disease, and AIDS. I propose discussing each category. First, obstetrics.

**Dr. Segal:** Barker’s hypothesis is that undernutrition or malnutrition *in utero* and in early infancy could lead in later years to specific diseases, particularly cardiovascular and endocrine diseases. His studies were done in the United Kingdom. However, 75% of the world comprises developing populations, and we know that in Africa undernutrition and malnutrition in early life is rampant. Nevertheless, those diseases don’t occur. In the urban situation, coronary artery disease is very uncommon. In the rural situation, type-II diabetes and hypertension are also very uncommon. So with due respect, I think that his hypothesis may be simplistic: it does not take into account all the other factors that are involved in early infancy; also it does not take into account that coronary artery disease worldwide is declining, which is at present inexplicable. So I just want to say that I don’t think one can accept Barker’s hypothesis *ipso facto*.

**Dr. Meguid:** I appreciate your comment. When I initially came across his hypothesis I too was very skeptical, but the more I read of his work, the less skeptical I became. He has a large following of people who approve his hypothesis, though there is equally a large body of people with whom you would feel comfortable! So obviously the
theory is not as simplistic as all that. It is not purely about nutrient intake; it is a combination of nutrient partitioning, oxygen supply, and placental development—a very complicated scenario. This year marked the first international conference on this subject, so momentum is gathering. It reminds me of Dennis Burkitt and the Burkitt tumor—it took a long time for people to accept that fiber was significant in our diet.

**Dr. Labadarios:** I have a comment in relation to Dr. Segal’s remarks. It may take some time before relationships of the kind shown by Barker start to manifest themselves, because the environment from the nutritional point of view, both pre- and postpartum, is different here from that in England in relation to the time Barker’s research focused on. We are facing a high rate of stunting—a quarter of our children below the age of 9 are stunted here—and we are seeing an extremely concerning rise in obesity. There is the experience elsewhere in the world in populations in transition from a stage of undernutrition to a stage of relative overnutrition with associated obesity, Chile being the best example [1]. Also, the prevalence of diabetes here is now increasing. So maybe as circumstances in the African continent change for the better, the Barker relationships will start to become more obvious. Diabetes is probably a good indicator of what we may be facing in the future. There are also data showing that syndrome X, which was referred to earlier, is relatively common here. There are data showing that it is occurring at a much higher frequency than would be expected even among rural populations. So though I share Dr. Segal’s skepticism, it may be that we have to be a little more patient in gaining experience of the behavior of populations in transition.

**Dr. Meguid:** I would like to add a further note for Dr. Segal. One of my colleagues has been doing some very elegant work looking at the hypothalamus in pup fetuses, where the maternal rat is fed diets varying in nutrient composition. The expression of different genes in the fetal hypothalamus—for galanine, neuropeptide Y and so on—is markedly affected by maternal diet. This is the kind of basic scientific research that is underpinning Barker’s hypothesis.

**Dr. Segal:** In relation to Dr. Labadarios’s comment on obesity, I accept that the incidence is increasing, but only among women, and we don’t see the associated features such as hypercholesterolemia. Therefore obesity may have different implications here.

**Dr. Meguid:** However, we need to have a hypothesis to prove or disprove, and it is healthy skepticism that keeps us balanced and allows us to move forward.

**Dr. Okada:** Well, let us move on to the second topic, heart failure.

**Dr. Endres:** In reference to the cocktails containing coenzyme Q for the treatment of cardiac failure, has coenzyme Q ever been used without taurine and carnitine. In pediatrics we have never seen any benefit except to the producing company!

**Dr. Meguid:** There are data in the literature showing that if you give coenzyme Q to a patient with a failing heart, cardiac function improves and the coenzyme Q concentration in the myofibrils increases [2].

**Dr. Endres:** Could you say something about nutrition intervention before surgery?

**Dr. Meguid:** We used to give nutritional support prior to surgery. We published the data in conjunction with Dr. Jeejeebhoy, using adductor pollicis muscle power as an index of nutritional sufficiency, which was a very sensitive test [3]. These were malnourished patients with cancer, who were going to have surgery. We found that giving supplementary nutrition for 5 and 7 days was sufficient to convert contraction of the adductor pollicis muscle, from a pattern consistent with malnutrition and malfunction, to one consistent with normal muscle function. This was the end point of our study and told us that the patients were ready for surgery. Unfortunately we are unable to keep patients in the hospital for such long periods, so the concept of giving patients an oral load 2 hrs before surgery is being explored by Lindqvist in Sweden. The data I presented, which we have been aware of for a number of years, show
that giving patients intravenous fat or glucose the night before surgery increases the glycogen content of the myocardium and also protects the heart from infarction and other complications during surgery and postoperatively. So I would call this prevention rather than early intervention.

**Dr. Shenkin:** I think you raised some very controversial points in relation to the use of specific nutrients in particular conditions, for example this cocktail in congestive cardiac failure. I'm concerned that we haven't yet fully addressed these different situations – on the one hand one may be trying specifically to correct a state of depletion, for example of protein, or energy, or a micronutrient such as vitamin C or thiamine; on the other hand there are situations, where you may want to provide an excess of a nutrient to produce some other effect, such as an antioxidant effect. Are these aims mutually compatible?

**Dr. Meguid:** One should address the major energy and protein issues first. In cardiac failure, provision of energy alone has not solved the problem, and growth hormone has not solved the problem either, so we have to explore the use of other nutrients, which are associated with energy states.

**Dr. Waitzberg:** What are your thoughts about giving amino acids during surgery? I believe there have been Swedish studies giving branched chain amino acids during surgical interventions to decrease deleterious metabolic responses.

**Dr. Meguid:** I am not familiar with those data, but let me tell you about a study of our own. We tried to do a study, where we randomized patients to receive intravenous nutritional support consisting of glucose, amino acids, fat, electrolytes, trace elements and vitamins during major abdominal surgery. We randomized about 7 patients, but the study was stopped by the anesthetists, because they recorded a higher frequency of intraoperative cardiac arrhythmias in the supplemented group. They considered that this was due to the long-chain fatty acids. Once that kind of objection has been raised, it is very difficult to overcome the apprehension about continuation of the study, so we abandoned it. I fully understand the biochemistry of amino acids, but in this situation I don’t completely understand the advantages for using branched chain amino acids.

**Dr. Beaufrère:** Branched-chain amino acids have a very specific positive effect on initiating translation in the protein synthesis machinery. However, branched-chain enriched solutions have been on the market for some years and have not really been successful in clinical practice. My feeling is that the lack of success might have been due to the way they were used – they were employed in all sorts of patients using different rates of infusion and so on. I think more work needs to be done in this area.

**Dr. Okada:** My understanding is that they are very important for cardiac muscle. There are also several reports describing the effects of branched chain amino acids particularly “valine” in catabolic states.

**Dr. Griffiths:** I know about the Swedish branched-chain amino acid study. It was done by an anesthetist called Selden at the Karolinska Institute, and the issue there was anesthetic hypothermia. She used amino acid mixtures for their thermic effect. It has been shown that providing external heat to patients can reduce the incidence of complications, and this study sought to show whether increased endogenous heat production would also be beneficial. Thermoregulatory control is impaired during anesthesia.

**Dr. Okada:** Thank you. Let’s move on to AIDS.

**Dr. Charlton:** I think the hypothesis about the progression of HIV to AIDS being exacerbated by a polyunsaturated fat deficiency is intriguing. South African cross-sectional data on HIV were presented recently, and the authors found in a fairly large sample that HIV-negative subjects had a higher dietary fat intake than HIV-positive subjects. However, the problem of confounding prevented the authors from making much sense of the data. My question is, do you think there may be a role
for supplementing HIV-positive people with polyunsaturated fatty acids before they progress to AIDS?

**Dr. Meguid:** It is certainly what the data would suggest. I was intrigued to know why some of my patients with HIV remained relatively healthy and only needed intense nutritional support, when they developed influenza or a cold, or in the summer time when they got dehydrated. I think it is a plausible hypothesis, and you are just adding some more data to it. Can one extrapolate from that and say we should consider providing a supplement to patients who are HIV positive? Patients are supplementing themselves with all sort of things, sometimes taking desperate measures, so I don’t see why we shouldn’t do that.

**Dr. Charlton:** With the problem of not being able to provide cocktail drugs and antiretroviral therapy for the majority of AIDS patients in sub-Saharan Africa, a lot of energy has been devoted to looking at indigenous plants as potential sources of therapy for HIV-positive patients. There is one plant product, made from plant sterolin (the brand name is Moducare and it is produced locally), which is now being marketed as having immuno-enhancing effects. There is also another agent just coming on to the market called Hypoplus, which has apparently received quite a lot of funding from our medical research council for randomized controlled trials. Do you have any experience with the use of plant sterols or sterolins in the USA?

**Dr. Meguid:** No I don’t, but I’m remiss in not mentioning that part of the treatment that we now use in the USA, and I am told you use here as well, namely probiotics. I believe the use of probiotics is a great advance in treating patients who have HIV.

**Dr. Labadarios:** I have seen some of the data on Moducare. Sterolins enhance lymphocyte activity quite remarkably, but we don’t know whether or not this alters the course of disease and I think we should be careful about that. As for the other products that are emerging, we must not raise false hopes; we know very little about the efficacy of these products.

**Dr. Haschke:** I want to add some data on HIV nutrition in infants. In Johannesburg, a study was conducted during the last 2 years, which is now completed, and a second study is under way, looking at nutrition of infants who are born to HIV-positive mothers who have decided not to breast feed. This was a randomized controlled study comparing a regular infant formula with a formula, which was acidified biologically and fortified with probiotics. The interesting outcome was that growth – which is the major outcome variable reflecting the health of children in environments like this – was better on the acidified formula after 6 months of exclusive formula feeding, than on the regular infant formula. We are doing a second study now to try to confirm this result. This would support a role for probiotics.

**Dr. Meguid:** Thank you, I appreciate your adding that information.

**Dr. Winter:** There is some concern about the use of probiotics in immune-compromised patients. Recently we have had a lot of difficulty in getting one of these studies on HIV-positive children through our ethics committee. What is your feeling about this?

**Dr. Meguid:** You have got to define what class of probiotics you are using. With the acidophilic kind, which are found primarily in products such as yogurt, we have not had problems with our ethics committee.

**Dr. Seidman:** I have a comment about bone marrow transplantation. Our nutritional support service was preoccupied 10–15 years ago with nutritional support for HIV-positive children, but now we virtually don’t see them any more, because they are all on effective pharmacological therapy. Our new challenge is bone marrow transplantation. This is an interesting future area of nutrition. Unlike the other situations we have discussed, in this situation you have a patient who has no immune system for several weeks. Thus we are not really talking about immunonutrition, because there
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is no immune system other than a developing one; furthermore the gastrointestinal complications are as challenging as they were in the AIDS populations.

Dr. Meguid: Thank you for raising that issue. When I went on the internet I was amazed to discover what a huge waiting list there is in South Africa for bone marrow transplants. So this is a very current problem that exists here in South Africa, but it is treated primarily with total parenteral nutrition and not enteral feeding, at least for the first 30 days.

References