Nutritional correlates of human immunodeficiency virus infection

Daniel J. Raiten

This review is a presentation of extant knowledge about the impact of human immunodeficiency virus (HIV)-related disease on the processes of nutrition. There has been an inadequate amount of research to ascertain the exact nature of this relationship beyond the documentation of physiological phenomena having a nutritional component. Evidence is presented of nutritional problems that have been documented during all stages of the progression of HIV infection and the acquired immune deficiency syndrome (AIDS). The possible causes of these changes are examined and include changes in intake, metabolism, and potential iatrogenic factors such as drug-nutrient interactions. Particular attention is paid to factors that have confounded our ability to effectively interpret studies done to date. A conceptual model of the relationship between nutrition and HIV is offered along with suggestions for future investigations. A brief discussion is also included on the potential impact of suboptimal nutrition on the progression of HIV disease.

Keywords: Nutrition, human immunodeficiency virus, infection, metabolism, macro/micronutrients, diet, drug-nutrient interaction.

In 1990, the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) published a comprehensive review of existing knowledge on the relationship between nutrition and infection with the human immunodeficiency virus (HIV) [1]. At that time there was a paucity of peer-reviewed literature regarding specific aspects of this important area. This paper is an updated excerpt from that comprehensive review, focusing on mechanisms that underlie the precipitous wasting seen in HIV-infected individuals.

Among the most common observations in patients with HIV infection are profound weight loss and wasting reminiscent of the clinical manifestations associated with protein energy malnutrition (PEM). According to Torun and Viteri [2], "PEM results when the body's needs for protein, energy fuels or both cannot be satisfied by the diet." Consequently, the diagnosis of PEM in HIV disease is based on the underlying presumption that the reported weight loss and wasting in HIV disease is the result of malnutrition. Presumably, this malnutrition is associated with decreased intake, malabsorption due to gastrointestinal problems and/or increased energy or nutrient requirements as a consequence of changes in intermediary metabolism initiated and perhaps mediated by the HIV virus. Each of these situations can occur in chronic disease.

Conceptually, malnutrition in chronic disease is explained in terms of starvation malnutrition caused by stress or injury, and cachexia. Each has been well characterized in terms of metabolic and nutritional changes [2-4]. The essential difference between PEM and cachexia is that in the former, the body attempts to compensate metabolically for the nutrient deficit(s), whereas in the latter, the metabolic signals become uncoupled. Many of the metabolic changes seen in PEM can be explained in terms of preservation of lean body mass and visceral organ function. The changes in cachexia are qualitatively and quantitatively different from malnutrition (i.e., marked and almost immediate depletion of muscle mass) and may not be reversed by nutritional intervention. Consideration of the acute-phase response is also important, because at any time, a patient with a chronic disease such as the acquired immune deficiency syndrome (AIDS) may progress from one stage to another; for example, an HIV-infected patient may progress from asymptomatic to AIDS-related complex (ARC) or AIDS. The distinguishing features of these two conditions include the occurrence of various infections and the acute and chronic stress of the disease process.

Thus, in studies of patients with HIV infection, ARC or AIDS, if care is not taken to separate those experiencing an acute-phase response, results such as changes in plasma protein levels might be attributed inappropriately to the HIV virus or its nutritional ramifications rather than to the presence of severe stress or an acute infection. Whether the acute-phase response
seen in HIV-positive patients involve these well known phenomena or whether they are unique manifestations of the HIV infection remains to be established.

A conceptual model of the relationship between nutrition and HIV disease is shown in Fig. 1. This chapter reviews the evidence that the changes in body composition, intermediary metabolism or status of individual nutrients observed in HIV infected patients are the consequence of a decreased intake secondary to malnutrition of chronic disease, or are primarily caused by the HIV disease process. Potential mechanisms of malnutrition in HIV infection are also discussed.

Evidence for general malnutrition with HIV infection

Weight loss and body composition
Progressive involuntary weight loss typically appears in the early stages of the HIV infection and increases in severity as the disease progresses. Weight changes have been reported in most of the body composition studies, which have generally been descriptive and have involved only hospitalized AIDS patients. Weight loss and changes in anthropometric measures have also been reported in persons with HIV infection before the development of AIDS. For example, in a study of 30 men who were HIV seropositive but asymptomatic except for lymphadenopathy, Mantero-Aleienza et al. [5] found that two had significantly low body weight, triceps skinfold thickness and body mass index, while three were obese. The pattern of weight loss in HIV infection seems to indicate that stable AIDS or asymptomatic HIV-seropositive patients are able to maintain body energy stores, but that precipitous weight loss occurs if disease progresses.

Kotler et al. [6] were among the first to examine the body composition of ARC or AIDS patients with weight loss. They investigated body cell mass by measuring total body potassium (40K) content, total body water and extracellular water volumes, and the body fat content of 27 men and six women with ARC or AIDS. Data from these patients were compared with data from five healthy homosexual men and a previously studied laboratory reference group of 58 men and women without AIDS or ARC. They found that the 33 ARC or AIDS patients were significantly underweight compared with the five healthy homosexual men and 58 male and female laboratory controls (82±10, 101±7 and 103±6% of 'ideal body weight', respectively). In the immunodeficient patients, total body potassium to height ratios were 68±10% of normal while ratios for the two control groups were within normal ranges. These results indicated that body cell mass depletion was greater than body weight reduction in the patient group. Within the ARC- or AIDS-diagnosed group, potassium to height ratios (an index of lean body mass) were significantly lower in the 15 patients with diarrhea (62±9% of normal) than in the 16 patients without (74±9% of normal). These data indicate that the observed weight loss is associated not
only with total body water loss, but also with loss of lean body mass.

Kotler et al. [6] also found that compared with normal values (derived from a previous survey of 3000 adult males), body fat was depleted in the immunodeficient patients; values were, however, similar for the immunodeficient group and the healthy homosexual control group. The women in the immunodeficient group had significantly less body fat than the immunodeficient men (29 ± 20 and 71 ± 21% of normal, respectively), and their values were similar to those of women with eating disorders. The immunodeficient men, in contrast to the women, experienced a greater relative depletion of body potassium than body fat. The percentage of body weight as water was higher in the immunodeficient patients than in the control groups; intracellular water volumes were decreased in these patients, with a relative increase in extracellular water volume.

Repeat measurements, conducted on 11 of the immunodeficient patients, indicated a progressive depletion of body potassium and body cell mass in eight patients with AIDS but not in three with ARC. The authors suggested that severe, progressive loss of lean body mass is a common occurrence in patients with AIDS. Moreover, they suggested that in contrast to infected women who appear starved, the weight loss seen in men with AIDS was reminiscent of stress or injury. While dietary data are needed to make a differential diagnosis of the type of malnutrition these patients experienced, the loss of lean body mass rather than body fat is more indicative of cachexia than of PEM. In subsequent studies of the body composition of 24 patients in the terminal stages of AIDS, Kotler [7,8] observed that body cell mass was depleted to a greater extent than body weight; wasting was progressive and ultimately irreversible. These results suggest that the changes occurring in end-stage AIDS resemble the cachexia seen in other chronic debilitating diseases.

Changes in body composition are not an inevitable consequence of HIV infection. When Kotler et al. [9] studied the energy balance and body composition of five clinically stable outpatients with AIDS, six HIV-seronegative homosexual and six HIV-seronegative heterosexual men, they found that over the 6-week study period, body weight losses of the five patients with AIDS averaged about 3 kg (5% of initial body weight) while those of the two HIV-seronegative control groups were essentially stable. In the ambulatory patients with AIDS weight loss was not accompanied by significant changes in total body potassium, body fat content, or total body intracellular or extracellular water volumes compared with either of the control groups. The actual composition of the lost weight was not clear. Baseline caloric and nutrient intakes of the patients and volunteers in the three groups, measured by 3-day diaries, were essentially similar. Interestingly, while there was no difference between the three groups in terms of total macronutrient intake, when caloric intake was corrected for body surface area differences, the AIDS patients consumed more (albeit not significantly) calories than either control group. The dietary data were collected during the first week of the study, which made it impossible to assess any changes in intake relative to subsequent weight loss in the AIDS group over the entire study period. A decrease in resting metabolic rate (hypometabolism) in the AIDS patients along with a diminished intestinal absorption of both the pentose sugar xylose and the triacylglycerol triolein were also observed. The authors suggested that the apparently paradoxical observations of an imbalance in energy intake (in excess of energy expenditure) and weight loss indicated that an appropriate adaptive response to malabsorption was taking place. The absence of significant progressive wasting indicated a metabolic adaptation that would be similar to that expected in starvation.

To summarize, there is little doubt that weight loss occurs in AIDS patients. Data concerning the actual weight losses in different patient populations (i.e. HIV-seropositive asymptomatic, ARC or AIDS), however, vary widely. Similarly, the extent and composition of the weight loss by individuals within patient groups (i.e. infected males versus females, intravenous drug users versus homosexuals) also vary widely. Currently, the lack of controlled studies makes it difficult to determine the factors that predispose patients to weight loss, the ranges that might be expected or the causes of this variability.

Macro- and micronutrients
Aside from weight loss as the cardinal sign of malnutrition, the qualitative aspects of the loss and resulting changes in body composition provide some insight into the potential metabolic complications of the disease process. Other outcomes that would provide evidence of a metabolic anomaly associated with HIV infection are potential changes in circulating protein and/or lipid levels. Unusual changes in these parameters could indicate a mobilization or shifting of the relative energy storage pools.

The validity of most of the studies that have reported relative changes in circulating metabolic energy pools has been compromised by a lack of adequate documentation of dietary intake patterns, medication use or status of infection. Many of the documented changes in body composition and circulating protein and lipid levels are characteristic of cachexia and the acute-phase response. Several studies have reported differences between AIDS, ARC and HIV-seropositive asymptomatic patients, based on levels of circulating proteins [6,10–12] and/or lipids [13–15]. The studies on lipid metabolism in HIV infection have not been nutritional in the sense that none has assessed changes in intake or metabolism caused by PEM. The relevance of studies of circulating protein levels to mal-
nutrition is confounded by several issues related to the clinical status of the study participants.

While these studies have revealed changes in protein distribution in patients with AIDS, ARC and HIV infection, the significance of these changes in regard to nutritional status is unclear. The differences in circulating protein in patients with HIV disease may be related to clinical status, i.e. concurrent infections, rather than PEM. Many patients with AIDS have additional infectious diseases, and the stress of disease is known to produce changes in levels of circulating serum proteins [4]. The level of total protein in serum is determined by the rate of synthesis and catabolism of individual components, the volume and compartmentalization in the body, as well as the state of body hydration [16]. In addition, Fleck [4] has concluded that after injury or during infection decreased concentrations of serum proteins such as albumin and transferrin are likely to be related to altered vascular permeability. He also suggested that it is inappropriate to use a decrease in any plasma protein as a measure of inadequacy of protein intake, especially when there is clinical evidence of the acute-phase response to injury or infection. Thus, because they are affected by non-nutritional factors, decreased levels of circulating total protein (i.e. albumin, prealbumin and retinol-binding protein) must be considered in the context of the overall condition of the patient. Without a record of infection status, nutrition history and diet, the diagnosis of PEM caused by nutrient insufficiency is premature.

Studies of groups of nutrients such as vitamins and trace minerals suggest that deficiencies are a common occurrence in HIV infection, especially in the advanced stages of the disease. The extent of overt or marginal deficiency with respect to specific nutrients is less clear [1]. Minerals that have received attention include zinc [17–21], selenium [22–24] and iron [25,26].

Of the vitamins, B12 has received most attention. Low serum levels of vitamin B12 in HIV infection have been reported by several investigators [27–29]. Herbert et al. [30] reported a negative vitamin B12 balance in 53% of their study sample. According to another study by Herbert et al. [31], this phenomenon may be explained in part by a circulating antibody to intrinsic factor. An additional observation by these authors was a high frequency of elevated gastrin levels in their study group, a condition associated with defective vitamin B12 absorption [31].

Another vitamin that has received attention is vitamin B6. Baum et al. [32] assessed vitamin B6 status by stimulation of erythrocyte aspartate aminotransferase (ASAT) in 44 asymptomatic HIV-seropositive homosexual men. Dietary intake was measured by the use of a food frequency questionnaire. Thirty-four per cent of the group were classified as showing evidence of vitamin B6 deficiency based on the increase in ASAT level after coenzymatic stimulation. An additional 17% were described as marginally deficient despite adequate intake of vitamin B6. Significant positive associations were found between ASAT activity and response to selected mitogens; in multivariate analyses there was also a significant association between vitamin B6 status and measures of functional immunity, for example a response by peripheral blood lymphocytes to specific mitogens and natural killer cell cytotoxicity. In contrast to an earlier report by this same research group [33], there were no differences in immune cell subpopulation counts, for example CD4 cell number, between groups, based on vitamin B6 status.

The value of these observations is compromised by several factors related to the sensitivity and specificity of the assessment methodologies. Sauberlich et al. [34] cautioned against the use of the erythrocyte ASAT test in surveys or as the sole indicator of vitamin B6 status, because of the large variability in both the activity and in vitro stimulation of the enzyme. Moreover, transaminases may be affected by non-nutritional factors such as those seen in the acute-phase response. Huang et al. [12] attributed elevations in the concentration of this enzyme in the serum of HIV-infected patients to impaired liver function. Given the array of clinical complications in this population and the questionable specificity of this measure as the sole indicator of vitamin B6 status, these results must be regarded with caution. Dietary intake was assessed by food frequency questionnaires although the usefulness of this method for measuring the intake of most nutrients, including vitamin B6, has not been validated. Food frequency methods result in a loss of precision in estimates of the actual intake of food and/or specific nutrients compared with quantitative daily intake methods [35]. Given these considerations, the possibility of a vitamin B6 deficiency in the HIV-infected population remains to be verified. Furthermore, since large doses of vitamin B6 can be potentially toxic [36], caution should be taken before advocating the supplemental use of this nutrient in this population.

Future efforts designed to characterize the relationship between individual nutrients and HIV infection should control those factors that might influence the measurement of nutrient status. In order to identify any predisposing factors that might influence their nutritional status, there is a need to further assess the relationship between risk-group membership and individual nutrients. Other confounding variables such as chemotherapeutic agents, disease and infection status must also be considered. There is a plethora of ways in which the nutritional status of any HIV-infected individual may be compromised. Each patient must be viewed within the context of their disease and lifestyle. The functional ramifications of nutrient deficits have been well documented, but the relevance of these deficits to the HIV-infected population remains to be determined.
Mechanisms of malnutrition in HIV infection

Malnutrition leading to weight loss or nutrient deficiency may develop in HIV-infected patients through several mechanisms: a reduced food intake, iatrogenic effects (drug–nutrient interactions), malabsorption and alterations in metabolism. Because of the variable course of the disease in different patients, any one or more, or none of these mechanisms may come into play.

Reduced food intake

Compared with the numerous studies reporting decreases in body composition or individual nutrient status, relatively little information has been generated on dietary intake during HIV infection, either as an independent phenomena or in support of the various hypotheses on the antecedents of weight loss. Chlebowski et al. [37], who used 7-day records to compare dietary intake in 14 patients with AIDS and 14 with asymptomatic HIV infection, reported that patients with AIDS consumed an average of 1112 kJ per day less than HIV-infected persons (2048 ± 193 versus 9577 ± 489 kJ per day, respectively). The intakes of protein and carbohydrate were similar in the two groups, but fat intake was lower in the patients with AIDS. The patients with AIDS experienced significant weight loss (8.7 ± 4.0%) and had decreased serum albumin concentrations and decreased CD4 + cell numbers; these changes were not evident in the HIV-positive patients.

In a study of 40 patients (34 men and six women, aged 20–45 years), Truffe et al. [38] assessed dietary intake and weight change at three stages: before the illness; asymptomatic HIV-positive; and symptomatic HIV-positive. Each patient was questioned retrospectively at the symptomatic stage about his or her dietary practices during the preceding two stages. These authors did not report the mean duration of the individual stages or the method of measuring dietary intake, (for example, food frequency questionnaires, dietary recall measures). Similarly, there was no record of the patient’s relative condition at the time of data collection at the symptomatic stage, in terms of gastrointestinal symptoms, neurological studies or other clinical problems (other infections or concurrent medication). Mean daily energy intake declined from 10 455 kJ before the illness to 6022 kJ in asymptomatic HIV-positive patients and 5018 kJ in symptomatic HIV-positive patients; mean protein intake declined from 80 to 46 and 43 g, respectively. From illness to the asymptomatic HIV-positive stage, body weight declined by 11%, followed by a further drop of 5% between this stage and the symptomatic HIV-positive stage.

In contrast, Dworcin et al. [39] determined nutrient intakes based on 3-day diet records in 18 clinically stable patients with AIDS, 12 with ARC and 13 asymptomatic HIV-positive controls, they found no differences in energy intake (on a kcal/kg per day basis) among the three groups. Protein intakes were adequate in all groups, although 88% in each group were reportedly ingesting less than 50% of the recommended dietary allowance for at least one micronutrient. Curiously, the AIDS group had a lower mean number of deficient nutrients than either of the other groups. There were no significant correlations between macronutrient intakes (protein or fat) and anthropometric measures, although the validity of this finding is uncertain given the current limitations of available individual nutrient databases [40]. From an analysis of three-day food records, however, Kotler et al. [9] found that the energy, protein, carbohydrate and fat intakes of five ambulatory, clinically stable men with AIDS did not differ significantly from the intakes of homosexual and heterosexual controls.

Anorexia, a severe disturbance in appetite regulation that results in a profoundly reduced intake and is caused by either manifestations of the disease process itself or chemotherapy, has been reported in some patients with HIV infection. Daily caloric intakes of less than 2509 kJ, persisting for several months despite multiple attempts to supplement intake at home, have been reported in some patients [13].

Chemical signals produced during the course of disease processes may be responsible for the anorexia seen in HIV infection. For example, recent evidence indicates that two cytokines, tumor necrosis factor (or cachectin) and interleukin-1, and the interferons can produce profound anorexia in animals [41]. The use of tumor necrosis factor and interferons in humans as cancer chemotherapeutic agents has also been associated with severe anorexia. Although experimental evidence indicates that the anorexia caused by tumor necrosis factor is transient, the anorexia induced by the interferons and interleukin-1 can be persistent. Elevated levels of tumor necrosis factor and interferon α have been detected in patients with AIDS [42,43].

In addition to the metabolic anomalies responsible for anorexia, frequently occurring mechanical impediments to food intake are another cause of severe dietary restrictions. Oral and/or esophageal conditions or lesions often associated with HIV infection make eating difficult, unpleasant or painful. Lesions throughout the oral cavity and esophagus may cause infants to refuse to suck bottles, older children to reject solid food and adults to restrict food intake. Common oral and esophageal conditions or lesions associated with AIDS that may interfere with eating behavior have been listed and their effects described [1].

Nausea and vomiting, which also cause food avoidance, may be a result of infectious complications, obstructions caused by tumors or drug therapy. Early satiety may occur with massive hepatomegaly or splenomegaly caused by several complications of AIDS or by infiltrative diseases of the stomach and small bowel, such as Kaposi’s sarcoma, lymphoma or Mycobacterium avium intracellulare [44]. Food
intake may be reduced by dyspnea associated with respiratory complications [45] and by adrenal insufficiency [44].

Diarrhea may also depress food intake, either because patients attempt to reduce fecal output by restricting food consumption or because of specific suppression of appetite as a response to the presence of unabsorbed nutrients in the lower intestine [9]. No mediator for the latter process has been identified, but its existence has been thought to contribute to weight loss in other conditions of intestinal injury and disease. This could explain the clinical observation that food intake is often greatest in the morning in patients with AIDS and malabsorption [9].

A variety of psychosocial factors in addition to neurological and psychological complications occur during HIV infection [46] and interfere with food intake; depressed or anxious patients may experience loss of appetite. Infection of the central nervous system by HIV results in the AIDS dementia complex, a progressively debilitating syndrome characterized by severe motor, behavioral and cognitive problems that may occur even in the absence of opportunistic infections [47,48]. In addition, opportunistic agents such as Toxoplasmosis gondii, Cytomegalovirus spp. and Cryptococcus spp. can produce a wide range of symptoms, ranging from latitude and weakness to profound dementia. Weak or fatigued patients may find it too difficult to shop for food and prepare meals. Demented patients may forget to eat and may experience apathy, social withdrawal, attention and concentration difficulties, irritability, and psychosis. In later stages of AIDS-related encephalopathy, signs may include tremor, confusion, disorientation, seizures, myoclonus, mutism and coma [48].

In addition to the pathophysiological and psychological causes of anorexia described above, economic and social factors may also contribute to decreased food intake. Many patients, who may be too ill to work, cannot obtain medical insurance, find their insurance coverage exhausted or cannot afford the increased cost of insurance once they are diagnosed with HIV or AIDS. Their finances may be depleted by insurance costs and/or medical expenses, and they may have inadequate money for food. Patients who are too weak to shop for food or too depressed or disoriented to prepare or eat food may lack support for such activities of daily living. The exact impact of these factors has received little attention. There is a need for quantitative data to support these observations.

Drug–nutrient interactions

Table 1 lists some drugs commonly used in AIDS and their potential side effects that may influence food intake and have other nutritional consequences. Irrespective of the clinical rationale, chronic use of drugs affects many nutritional processes. Patients with AIDS often take a wide variety of drugs for prophylaxis or treatment of complications; many of these drugs have the potential for serious side effects that affect appetite or eating behavior [49], for example stomatitis, dysgeusia, nausea, vomiting, and mucositis. A case in point is the weight loss in AIDS resulting from diabetes caused by pentamidine therapy for Pneumocystis carinii pneumonia [50]. The development of vitamin and mineral deficiencies may cause a further decrease in appetite [51].

Baum et al. [52] have recently reported a longitudinal study of changes in nutrient status in HIV-seropositive patients taking varying doses of zidovudine. A close examination of this paper is warranted because of the paucity of data in this area and the importance and widespread use of this treatment. This was a non-randomized, non-blinded observational study of 15 HIV-positive homosexual men (Centers for Disease Control (CDC) stage III) who were asymptomatic except for persistent generalized lymphadenopathy treated with zidovudine. The control untreated group (n = 22) were homosexual men matched for age, race, education and socioeconomic status. All participants were part of a larger cohort (n = 130) being followed by these investigators. The criteria used to select subjects for inclusion in this study were not given. Anthropometric measures of weight and height, hematology (SMAC-26 and complete blood counts), enzymatic stimulation assays for assessment of vitamins B1 (thiamine), B2 (riboflavin) and B6 (pyridoxine), plasma levels of trace elements, zinc, copper and iron, and vitamins C (total ascorbate) and B12, and folate, erythrocyte folate and total serum levels of vitamins A and E were used to assess the group. Diet history was evaluated with the use of a semiquantitative food frequency questionnaire. Immunological measures were similar to those reported in an earlier study of vitamin B6 by this group [32].

The treated group had significant hematological changes consistent with a macrocytic anemia (decreased hemoglobin and hematocrit and increased mean corpuscular volume); however, these findings were not discussed within the context of the nutrients studied, e.g. vitamin B6, folate, vitamin B12 or iron. The authors reported that there were no statistical differences between groups for vitamins B1, B12, B6, A or E. There was a significant difference in total plasma vitamin C and, as reported, a significant increase in the levels of vitamin B3 in both treated and untreated groups over time. However, the assessment technique used for vitamin B3 was an enzyme stimulation assay, not a direct measure of vitamin levels. The enzyme activity of glutathione reductase is measured in vivo before and after the addition of the coenzymatic form of the vitamin, flavine adenine dinucleotide. After addition of the cofactor, an increase in the activity beyond an accepted cutoff is indicative of a deficiency. Therefore, an increase in this activity in actuality is indicative of a decrease in available cofactor, rather than an increase in the levels of the vitamin.
As mentioned above in commenting on a previous study on vitamin B6 [32], the use of food frequency questionnaires to measure specific micronutrient intakes requires validation. Data on the vitamin B6 content of specific foods is limited, so that estimates by food frequency techniques may underestimate the actual intake to an unknown extent.

The results reported by Baum et al. [52] raise additional questions concerning micronutrient nutrition in HIV-seropositive patients. For example, the intakes of all nutrients studied were well above the respective recommended dietary allowances [53]. Consequently, the relevance of the biochemical observations and the nutritional status of both patients and controls is unclear. In addition, given the use of single non-specific indices of nutrient status, such as enzyme stimulation assays as the sole indications of nutrient status, it is not clear what aspect of nutrition (absorption or metabolism), might be involved in these outcomes. Moreover, given the numerous factors studied and the variety of effects seen in both groups, the role of the therapy in producing these effects must remain speculative. The biochemical findings may represent non-specific outcomes of the HIV disease process. The inability to replicate the earlier findings of associ-
ations of vitamin B₆ by measures of immune function in an essentially identical sample of patients [32] lends support to this conclusion.

**Malabsorption**

Multifactorial nutrient malabsorption has been reported in several studies of patients with AIDS [11, 26, 54], but the consequences of nutrient malabsorption in AIDS have not been definitively settled. Nutrient malabsorption is a result of small intestinal disease or injury, but during AIDS other gastrointestinal complications may occur, involving the stomach [55], pancreas, liver and colon [8, 56], that affect the digestion of food or may contribute to diarrhea.

Protozoal, parasitic, bacterial and viral infections may affect the small intestine and contribute to the diarrhea and malabsorption often seen in persons with HIV infection [8, 57–59]. Cryptosporidium spp., the most common enteric pathogen in patients with AIDS, causes a massive secretory, cholera-like diarrhea but more often produces a syndrome like persistent ileal dysfunction (three to 10 watery, non-bloody bowel movements per day, with volume increased after eating). The sporozoite is found in the cytoplasm of epithelial cells and interferes with solute transport at the microvillus membrane. A similar infection, with similar outcomes is caused by Isospora belli. These two pathogens may impair ileal absorptive function [60]. Another species of protozoa, Microsporidium sp., has been detected in small bowel biopsies. Cytomegalovirus enteritis may give rise to steatorrhea and chronic diarrhea that may be watery, bloody or associated with excessive mucus if the colon is also involved. Mycobacterium avium intracellulare can also act as an enteric pathogen, with infiltration of the macrophages of the lamina propria. Other bacteria such as Salmonella spp. and parasites such as Giardia lamblia can also impair function of the small intestine.

Thorough diagnostic evaluation can lead to the identification of pathogens in a high percentage of patients with AIDS and diarrhea [61]. In some cases of AIDS-related enteropathy with diarrhea, however, no causative organism can be detected. HIV itself has been detected in the intestinal mucosa [62–64] and possibly causes direct injury to the small intestine [65].

Kotler et al. [26] studied gastrointestinal structure and absorption in malnourished patients with AIDS in whom no bacterial or parasitic infections were detected. Diarrhea was seen in seven out of 12 patients. D-xylene absorption was lower in patients than in controls and lower in patients with diarrhea than in those without. Excess fecal fat was detected in eight out of 11 patients (including three without diarrhea) and in one out of 11 controls. The patients with diarrhea had abnormal biopsy samples more frequently than those without diarrhea and the controls. Jejunal and rectal biopsies were abnormal in all patients with diarrhea; jejunal changes included partial villus atrophy with crypt hyperplasia and increased numbers of intra-epithelial lymphocytes. Similar lesions, also seen in graft versus host disease and inflammatory bowel disease, suggest immune-mediated intestinal damage [7].

Gillin et al. [54] studied malabsorption and intestinal structure in patients with AIDS and without identifiable enteric pathogens or intestinal Kaposi’s sarcoma (20 patients with diarrhea and weight loss and 10 without). Malabsorption, characterized by abnormal D-xylene and 14C-glycerol-tripalmitin absorption tests, was common in the patient with diarrhea and weight loss. Duodenal biopsies in most of these patients showed non-specific, mild-to-moderate chronic inflammation; in several, a dense histiocytic infiltrate containing numerous acid-fast organisms was detected. Several asymptomatic patients also showed signs of chronic inflammation.

In a group of 22 patients with AIDS and various gastrointestinal manifestations (infections and Kaposi’s sarcoma), Dworkin et al. [11] found impaired D-xylene absorption in six out of seven patients with intestinal infections and two out of seven without infection. Fecal fat was detected in two out of six patients with infection and two out of eight without intestinal pathogens. Biopsies of the small bowel frequently showed pathogens and non-specific inflammatory changes.

In four patients with AIDS and diarrhea associated with enteric infections (two with Cryptosporidium spp., one with Microsporidium and one with Isospora belli), Modigliani et al. [66] found evidence of impaired absorption of fat, D-xylene and vitamin B₁₂. Three patients had secretory diarrhea. An accumulation of fat in the enteric epithelia and lamina propria was reported; otherwise, only non-specific changes in the histology of the small intestine were reported.

Miller et al. [67] studied fat absorption and jejunal mucosal architecture in 20 homosexual men at various stages of clinical disease. Enteric pathogens were not detected in the stool or by jejunal biopsy. Twelve of these patients had evidence of fat malabsorption based on results of the 14C-triolein breath test. Partial villus atrophy was the only histological abnormality detected. There was a significant correlation between the 14C-triolein breath test values and the villus atrophy index; abnormal fat absorption and villus architecture were found at all clinical stages of the disease. Kapembwa et al. [60] also detected fat malabsorption by (14C-triolein test) in 12 out of 25 HIV-positive patients. Mild pancreatic insufficiently detected in only three of these suggested that fat malabsorption in HIV infection is more commonly associated with problems of the small intestine.

Ullrich et al. [65] studied the structure and function of the small intestine in 45 HIV-infected patients with gastrointestinal complaints. Enteric pathogens were detected in 21. Seven out of 12 patients tested showed
evidence of lactose intolerance and two out of seven showed impaired D-xylene absorption. Serum folic acid and vitamin B₁₂ levels were abnormally low in 11 and four, respectively, of 28 patients evaluated for these parameters. Serum calcium levels were also low in 23 out of 32 patients tested. In 15 out of 25, no lactase activity was detected in the duodenal brush border and, when measurable, lactase activity was lower than normal. Alkaline phosphatase activity was normal. In HIV-infected patients, crypt depth was significantly greater than in controls, the villus surface was slightly smaller and the number of mitotic figures per crypt was similar. Patients who had no detectable intestinal infections other than HIV had a significantly reduced number of mitotic figures per crypt and normal crypt depth. These factors suggest a maturation defect in enterocytes caused by HIV itself.

Other factors contributing to malabsorption and diarrhea in AIDS have been suggested. Diarrhea may develop in critically ill patients secondary to gastrointestinal mucosal edema associated with hypoalbuminemia [68]. Diarrhea developed in several patients with AIDS and hypoalbuminemia but with no evidence of bacterial, parasitic or histological changes in the gastrointestinal tract. The condition was resolved by feeding a chemically defined diet of partially hydrolyzed protein, which resulted in the restoration of the serum albumin levels to normal [69]. As indicated by Kotler et al. [6], malnutrition itself may impair intestinal function; protein turnover, which is normally very high, may be reduced, and decreased food intake can result in decreased pancreatic enzyme secretion and intestinal brush border enzyme activities.

Injury to the small intestine in AIDS patients (partial villus atrophy and crypt hyperplasia in jejunal biopsy samples and duodenal mucosal atrophy) contributes to nutrient malabsorption by diminishing the absorptive surface [70]. Absorption may be further impaired in cells damaged directly by infection. A functional immaturity of epithelial cells is suggested by the crypt hyperplasia and rapid cell turnover in the villus, which would further diminish the absorption of nutrients such as lactose and triacylglycerols [70].

Altered metabolism
The wasting associated with cancer cachexia and chronic infections is characterized by a loss of lean body mass, especially muscle. This process differs from the weight loss seen in starvation, in which lean body mass is preserved relative to fat by the adaptive mechanism of a reduction in the basal metabolic rate or resting energy expenditure. Some clinically stable patients with AIDS have experienced this adaptive mechanism and have thus conserved lean body mass even in the face of small losses in body weight arising from malabsorption [7, 71]. In some AIDS-associated illnesses, this mechanism appears to be inoperative and patients experience a hypermetabolic state in which excessive calories are burned. A similar hypermetabolic state is also seen in stressed states such as sepsis, trauma and surgery and may lead to organ failure [72]. The differences in resting energy expenditure and fuel usage in starvation, hypermetabolism and organ failure, as outlined by Cerra [72], are illustrated in Table 2.

Hypermetabolism, with fever and rapid wasting, is common in AIDS. Limited observations carried out in patients with acute systemic illness or chronic infection indicate that metabolic rates are 20–60% above predicted values [71]. Hommes et al. [73] studied resting energy metabolism in asymptomatic HIV-infected patients. Exclusion criteria included fever, renal problems or known endocrinologic disease; risk group history or demographic characteristics were not reported. These investigators found that resting energy expenditure was higher in the 11 HIV-positive patients (CDC group I or II) who were slowly losing weight, but had no evidence of acute infection or malabsorption, than it was in the age- and body composition-matched healthy control group. Of the energy substrates studied only fat oxidation rates differed significantly; the patients had higher rates than controls. This difference was not associated with higher levels of catecholamines, cortisol or thyroid hormones. Both norepinephrine and interleukin-6 levels were significantly different (lower and higher, respectively) in patients compared with controls. In an analysis of diet records in five patients and nine controls there was no difference in energy intake.

Stein et al. [74] studied protein and glucose metabolism in nine asymptomatic AIDS patients (six homosexual and three intravenous drug users, who were all

Table 2. Differences in resting energy expenditure and nutrient utilization with altered metabolism.

<table>
<thead>
<tr>
<th></th>
<th>Starvation</th>
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<th>Hypermetabolism</th>
<th></th>
<th>Organ failure</th>
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<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Adapted</td>
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<td>Resting energy</td>
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<tr>
<td>expenditure</td>
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<td>↓↓</td>
<td>↓</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Glucose utilization</td>
<td>++</td>
<td>+</td>
<td></td>
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<td>+</td>
<td></td>
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<tr>
<td>Fat utilization</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td></td>
<td>+</td>
<td>±</td>
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<tr>
<td>Amino acid utilization</td>
<td>++</td>
<td>+</td>
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</tbody>
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undergoing chemotherapy at the time of the study. In a comparison with 13 age and sex-matched controls (uncharacterized in terms of risk group) these authors concluded that in the experimental group, differences seen in substrate metabolism, decreased glucose cycling, protein synthesis, plasma amino acids and a reduced ratio of essential to non-essential amino acids were metabolic adaptations related to malnutrition. However, Stein et al. [74] concluded that while these changes were probably caused by an insufficient food intake, any suggestions about the causes of the decreased intake, such as anorexia from cachexia, were premature [74].

Grunfeld et al. [75] studied resting energy expenditure, caloric intake and short-term weight change in 16 asymptomatic AIDS patients. All patients were free of apparent secondary opportunistic infections. Exclusion criteria included dyspnea, hypoxia, sputum production, sinusitis, urinary tract problems, pathogenic culture or respiratory pathology. Nine patients with opportunistic infections, 14 HIV-seropositive asymptomatic and 15 age-matched controls were also studied. All were men; risk group, medications and demographic status were not reported. Patients and participants were admitted to a metabolic ward and allowed a free diet. A crude evaluation of intake (observations of the percentage of presented food that was eaten) was used to assess caloric intakes. All three HIV-seropositive groups had a significantly higher resting energy expenditure than controls, the difference increasing with the severity of the disease (AIDS patients with infections >AIDS asymptomatic >HIV-seropositive patients). Caloric intake was significantly decreased in only the symptomatic AIDS group, who consumed 17% less than their resting energy expenditure. Asymptomatic AIDS and HIV-seropositive patients were able to compensate for an increased resting energy expenditure without a short-term weight loss. These authors [75] found that resting energy expenditure was uncoupled from caloric intake, so that a decreased intake was not associated with a compensatory decrease in resting energy expenditure, a pattern consistent with cachexia.

Alterations in lipid metabolism, such as fasting hyperlipidemia, are also seen in various infections [76]. Fasting hypertriglyceridemia was observed in a cross-section of HIV-seropositive patients and patients with AIDS [77]. No relationship between wasting and hypertriglyceridemia, however, was detected. The authors found that serum lipid levels reflected the absorption of fat (which can be decreased in AIDS) and hepatic production and peripheral clearance, both of which are altered during infection and are affected by tumor necrosis factor [78].

Many aspects of metabolic regulation, including lipid metabolism, are modulated by cytokines such as tumor necrosis factors, interleukin-1 and the interferons α, β and γ inhibit lipid catabolism by lipoprotein lipase in fat cells in vitro [79–82]. Tumor necrosis factors α and β, interleukin-1 and interferon α stimulate hepatic lipogenesis in vivo [83,84]. The localization of HIV to macrophages [85] and the changes in gene expression in HIV-infected macrophages [86] have suggested that an abnormal release of various cytokines may occur in AIDS. Indeed, increased serum concentrations of interferon α have been observed in patients with AIDS [42,87–89], as have elevated serum levels of tumor necrosis factor [43]. In the latter study, no correlation between weight loss and tumor necrosis factor levels was detected.

More recent evidence has indicated that tumor necrosis factor alone does not induce cachexia [41]. Nonetheless, it can contribute to the 'futile cycling' of free fatty acids and triglycerol and by increasing total body lipolysis in vivo and by increasing hepatic lipolysis and production of very low-density lipoprotein. Thus, fatty acids are released from fat and returned to the liver, where they are re-esterified into triglycerol and secreted in the form of very low-density lipoprotein to return to the fat cell for breakdown and restore as triglycerol [13]. The proposed action of tumor necrosis factor (in synergy with other cytokines) in stimulating overproduction of lipids by the liver and subsequent storage in adipose tissue could explain how fat mass is sustained throughout a period of weight loss in AIDS [13,90]. The hypothesis should be explored in a well-characterized sample of HIV-positive patients.

Clearly, much remains to be explained about the mechanisms underlying the changes in metabolism that accompany cachexia and appear to contribute to wasting in the end stages of HIV infection. These changes may not be amenable to modification by nutritional support alone. In cancer cachexia, parenteral nutrition support has generally not maintained lean body mass, an improved response to therapy or increased survival [3]. These authors have suggested that effective treatment for the metabolic malfunctions seen in cancer cachexia will require manipulation of intermediary metabolism as well as feeding. The same will likely prove to be true for the metabolic changes of cachexia in AIDS.

Summary and discussion

There is still a shortage of research, both basic and clinical, on the relationship between nutrition and HIV infection. A universal problem has been that the population available for longitudinal studies is often limited in number. Furthermore, the progressive nature of the disease process limits the ability and willingness of people to participate. Moreover, the transition from one disease stage to the next occurs with no consistent pattern, which presents a further obstacle in study design and data interpretation. Perhaps one solution would be to design more intrasubject design protocols using time series and repeated measures analysis.
Currently, it is difficult to generalize from most of the available study results to the whole HIV-infected population, because of complicating experimental issues such as a reliance on data, often retrospective, that have been compiled over months and years. Under these circumstances, factors such as the use of zidovudine or other drug therapies, dietary habits or nutritional intervention and, more importantly, the existence or occurrence of multiple infectious diseases before or during the study period are often overlooked. Many of these studies have relied on self-reported changes in weight, a method of questionable reliability [91].

The potential predisposition of high-risk groups to malnutrition constitutes an additional consideration in the design and interpretation of studies of the relationship between nutrition and HIV. Kotler et al. [26] observed that homosexual men with diagnosed AIDS and a control group of HIV-seronegative homosexual men had mean mid-arm circumference measurements in the 5th and 20th percentiles of normal values. Both values are indicative of low lean body mass and energy reserves. Additionally, 10 of the 11 controls were seen for gastrointestinal problems. This is consistent with reports of a high incidence of gastrointestinal problems in this population [92]. The detrimental effects of various 'recreational' drugs, including marijuana, cocaine and heroin, on nutritional status were reviewed by Mohs et al. [93]. Tripp and Touger-Decker [94] reported that HIV-seronegative intravenous drug users, particularly 'crack' cocaine users, are at nutritional risk based on anthropometric and clinical assessments. The results of these studies suggest that the lifestyles of high-risk population groups may be associated with limited nutrient reserves in terms of lean body mass irrespective of HIV status. The prevalence of these possible predisposing factors and their potential for influencing the course of HIV infection must be considered in any studies of these populations.

There is little doubt that patients with HIV infection will be increasingly compromised nutritionally as the disease progresses. Whether the observed changes in nutritional parameters are a non-specific response to the progression of the disease or a specific response to the HIV infection is less clear. In any patient, attention must be paid to the assessment of factors that might adversely affect any or all of the processes of nutrition, from ingestion to actual usage. Inconsistencies in study design and lack of replicable results make it difficult to draw conclusions about the impact of HIV infection on nutrient status, apart from the obvious recommendation that the nutritional problems facing any patient with HIV infection should be given high priority as part of an aggressive clinical management strategy.

In addition to the impact that HIV infection can have on nutritional status and metabolism, there is a per-

haps equally critical question regarding the impact of nutritional status on the development and outcome of this disease process. Nutrition may affect the course of HIV infection in several ways. A nutrient insufficiency or imbalance may (1) influence specific systems involved in the progression of the disease, (2) influence the susceptibility to opportunistic infections and (3) contribute to the severity of the response to HIV-related diseases. Irrespective of any possible specific relationship between nutrition and the HIV process, malnourished patients will be debilitated and unable to function optimally. A report of the National Academy of Sciences [95] concluded that malnutrition affects five areas of functionality: reproductive competence, immunocompetence, work performance, social and/or behavioral performance and cognition. The latter four of these functions have been studied in the HIV-infected population and are known to be compromised. The role that nutrition plays in the changes seen in HIV-related disease is unclear at this time. In investigating the changes associated with HIV infection, the interaction between nutrition and these functions must be taken into account. Poor nutrition may increase susceptibility to infection, affect the latency period before the development of ARC or AIDS, exacerbate the problems associated with HIV infection and may cause other problems that are independent of the infection but nevertheless compromise the already sick patient and might be attributed to the virus. Irrespective of the potential role of nutrition on specific functional domains in the HIV infection, nutritional adequacy must be an integral component in patient care.

Assessment of the importance of malnutrition in the development of AIDS and the progression of HIV infection has not been studied extensively. There is a high probability, however, that malnutrition contributes to immune dysfunction, morbidity or debilitation, and mortality. While there have been no studies assessing the interaction between nutritional status and neurological function (i.e. behavior, cognition and work performance) in HIV-infected persons, clinical observations indicate that these interactions occur in nutritionally compromised patients, and that this topic deserves additional attention.

Annotated references

- Of interest
- Of outstanding interest


Excellent review of PEM.

   Excellent review of cancer cachexia.

   Excellent review of a poorly understood and under-appreciated physiological phenomenon.

   Observational study of asymptomatic HIV-positive patients.

   An important study, the first conscientious attempt to describe changes in body composition in the HIV patient.

   Good review.

   Good review.

   Good clinical study on stable AIDS patients.

    Early observations about nutrition and HIV infection.

    Good observational study.

    Good study of biochemical manifestations of HIV infection.

    Observations about metabolic changes in HIV infection.

    A metabolic study that is difficult to view within context of nutrition alone.

    Metabolic study, not nutritional in traditional sense; however, findings could lead to further studies about changes in metabolic pools.

    Review of general assessment techniques in clinical nutrition.

    Early observation about zinc status in HIV infection.

    Speculation about the importance of zinc in the HIV disease process based on preliminary observations.

    Comparison of zinc levels in one HIV risk group.

    Observational study about zinc in HIV.

    Speculation about the importance of zinc in HIV infection.

    Early observations about selenium in HIV.

    More focused observations about the potential role of selenium in HIV; nutritional relevance is not clear.

    Speculation about selenium-HIV link.

    Early observations about iron metabolism in HIV infection.

    One of the earliest reports describing gastrointestinal manifestations of HIV infection.

    Observational study of vitamin B12 status.

    Observations of possible impairment of vitamin B12 absorption.

    Investigation of vitamin B12 status with follow-up intervention and metabolic studies. Confounded by multiple risk factors, different stages of disease, and concurrent therapies.

    Examination of vitamin B12 status by one of the most experienced nutritional biochemistry groups with particular expertise in vitamin B12 nutrition.

31. HERBERT V, SHAW S, JAVATELLESE E, LAM P, GILKE V: Evidence in serum for food vitamin B12 (cobalamin) malabsorption in AIDS: high gastrin, low cobalamin on transcobalamin II, and circulating antibody to intrinsic factor despite nor-


The only study to focus on this important vitamin.


Abstract describing early observations of possible changes in immune status associated with vitamin B12 status in symptomatic HIV-positive patients.


Still stands as one of the best compendiums of laboratory assessment techniques for nutritional status, especially vitamins.


A guide to the use of dietary surveys.


An important first observation of the potential toxicity of what was previously considered to be an innocuous vitamin.


Abstract describing early observations on changes in dietary intake in HIV patients.


Observations about dietary changes associated with the transition through continuum of the HIV disease process.


Comparisons of dietary intake across stages of HIV infection.


Review of the use and limitations of food consumption surveys and nutrient databases.


Excellent coverage of the potential impact of this metabolically significant compound.


Interesting observations with potential, albeit tenuous, nutritional significance.
Position paper by a leader in the area of nutrition and HIV disease.


Coverage of factors associated with gastrointestinal complications of HIV disease.


Coverage of the impact of various infections on gastrointestinal integrity in HIV disease.


Review of gastrointestinal complications of HIV disease.


Observations about factors affecting gastrointestinal function in HIV disease.


Documentation of the diversity of gastrointestinal pathogens found in HIV infection.


Important observations about the potential of a direct impact of the HIV on gastrointestinal function and integrity.


Abstract documenting presence of HIV in intestine of HIV-infected patients.


Early confirmation of the presence of HIV in gastrointestinal tissue.


Important study of the direct impact of HIV on gastrointestinal function. Particular attention paid to changes in morphology and impact on particular nutrients.


Observations, on a small sample of patients, of potential specific nutritional problems associated with gastrointestinal infection in HIV disease.


Potential mechanisms for fat malabsorption in HIV disease. Particular focus on jejunal histology.


Examination of clinical factors associated with critical illness with particular reference to diarrhea.


Focus on the factors presented in [48] and their relevance to HIV disease. Includes data about the efficacy of nutritional intervention.


Good review.


Good review of nutrition from clinical perspective of an active researcher in this area.


Excellent presentation of metabolic changes that may accompany stress of illness.


Recent study documenting changes in bioenergetics and substrate metabolism that occur in early stages of HIV infection.


Report on changes in substrate metabolism in AIDS patients.


Comprehensive study of weight loss, intake and energy metabolism in symptomatic and asymptomatic AIDS patients.


Excellent review of the nutritional correlates of infection.

77. Grunfeld C. Metabolic mechanisms for wasting in AIDS.


Coverage of proposed mechanisms for weight loss in AIDS.


Hypothesized mechanisms for weight loss in AIDS.


Study of a potential mediator in observed anomalies in lipid metabolism.


Report on the mechanism of cytokine regulation of lipid metabolism.

Supports the hypothesized role for cytokines as mediators of the changes in lipid metabolism reported in HIV infection. As with [79] and [80], the relevance to HIV infection is speculative.


One of the early studies of the role of cytokines in changes in lipid metabolism in HIV infection.


Early investigation of a potential specific mediator of changes in lipid metabolism in HIV disease.

84. Frenkel KR, Sjoberg M, Siren MK, Musier AF, Dinarello CA.


Follow-up to [85].


Report of basic mechanism of HIV activity.

86. Flesch TM, Jennessen J, Knitter A, Dinarello CA, Fauci AS.


Molecular biology of HIV.


Documentation of increased cytokine concentrations in HIV.

88. DeStefano E, Friedman RM, Friedman-Kien AE, Goodlett JI.

Henderson D, Freiberg AT, et al: Acid-labile human leuko-


One of the earliest reports on the molecular biology of HIV.

89. Eyster ME, Goodlett JI, Poon MC, Freiberg AT: Acid-labile 


Suggestions about the clinical utility of alpha interferon as a marker for HIV infection.


Review.


An important discussion of potential sources of error in studies of an anthropometric change in clinical populations.


Important consideration of a potentially important covariate in the study of nutrition and HIV infection.


One of the few reviews of this important area.


Abstract supporting the contention that drug use as a risk factor may by itself result in a nutritionally compromised clinical population.


An unrecognized landmark in our appreciation of the impact of nutrition on health.