NUTRITION AND HIV INFECTION

November 1990

Prepared for
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, DC 20204

under
FDA Contract No. 223-88-2124
Task Order No. 7
NUTRITION AND HIV INFECTION:
A REVIEW AND EVALUATION OF THE EXTANT KNOWLEDGE
OF THE RELATIONSHIP BETWEEN NUTRITION AND HIV INFECTION

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prepared by
Daniel J. Raiten, Ph.D.
FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in relevant areas of biology and medicine.

This report was developed for the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA), in accordance with provisions of Task Order #7 of Contract No. 223-88-2124. The final report was prepared and edited by Daniel J. Raiten, Ph.D., Senior Scientific Consultant. The tentative report was prepared by Susan M. Pilch, Ph.D., formerly Senior Staff Scientist, LSRO, FASEB. The final report is based upon a review of available scientific literature as well as information submitted to LSRO and comments of scientists and others who reviewed the tentative report.

As announced by FASEB and FDA in the Federal Register (54:50822–50823), the LSRO requested submission of scientific data and information by January 31, 1990. Individuals and organizations that provided written materials and scientific data in response to this request are identified in Appendix B.

Subsequently, LSRO prepared a tentative report and announced its availability for public comment (Federal Register 55:13847) on April 12, 1990. LSRO also invited review of the tentative report by individuals with clinical and investigative experience in nutritional management of patients with HIV infection. Individuals and organizations that were asked by LSRO and those who responded to the request for comments on the tentative report are identified in Appendix C.

All data, information, and comments provided initially and on the tentative report in response to the announcements in the Federal Register were considered by LSRO in preparing this report. Copies of the submitted materials are available for public inspection at LSRO, FASEB, and the Dockets Management Branch, FDA (Docket No. 89N–0482). The evaluation of scientific literature, data, and information submitted to LSRO was made by LSRO independently of FDA and any other group, governmental or nongovernmental. The LSRO accepts responsibility for the accuracy of the report and the evaluation of the scientific data cited. The listing of individuals and organizations in Appendices B and C does not imply that they endorse any of the report conclusions or recommendations.

The final report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Federation Board. Upon completion of these review procedures, the report was approved and transmitted to FDA by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of the individual members of the FASEB Societies.

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office

November 30, 1990
Date
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I. INTRODUCTION

A. BACKGROUND

Acquired immunodeficiency syndrome (AIDS) has been identified as the number one public health priority in the United States and is rapidly becoming a major health priority throughout the world. By mid-1990, approximately 140,000 children and adults in the United States had developed AIDS. The Centers for Disease Control (CDC) reported that 85,430 persons died from this condition as of June 1990. Projections of U.S. health authorities suggest that by the end of 1991, a total of 300,000 to 485,000 cases will have been reported in the United States with the number of deaths increasing at a proportionate rate. In addition, 0.8 to 1.5 million persons are reported to be infected with the human immunodeficiency virus (HIV) as of mid-1990. In its May 1989 action plan, the Food and Drug Administration (FDA) outlined a variety of initiatives intended to contribute to the conquest of AIDS (Food and Drug Administration, 1989). These initiatives included a requirement for the Center for Food Safety and Applied Nutrition (CFSAN) to develop nutrition guidelines for HIV-infected and AIDS patients.

The clinical course of AIDS varies, but its manifestations include many symptoms or signs that affect food intake and or nutritional status. Oral and esophageal lesions may make eating painful; fevers may increase energy requirements and adversely affect food intake; nausea and vomiting also limit food intake; and a multiplicity of opportunistic intestinal infections, lesions, and other conditions may cause diarrhea and malabsorption. In addition, various drug treatments may interfere with nutrient absorption or metabolism, and conversely, inadequate nutrition may compromise drug therapy. These factors contribute to weight loss, various forms of undernutrition, failure to thrive in children, and severe metabolic wasting that cause debilitation in many patients with AIDS. Indeed, many AIDS patients appear to die from the consequences of progressive wasting rather than from the viral infection itself.

In the absence of adequate information on the nutritional aspects of HIV infection, recommendations on nutrition practices and support have been promulgated on the basis of principles derived from knowledge about the role of nutrition in other acute and chronic disease wasting states such as malabsorption syndromes and cancer; some advice has been in the form of unproven and questionable nutrition therapies. Recommendations regarding various aspects of nutrition and AIDS from individual health care providers, educators, and scientists and from various organizations have appeared in the recent scientific and lay literature. However, the scientific basis for many of these recommendations is intuitive and is derived from clinical experience with various diseases including AIDS. The nature of the disease and its rapid appearance as a major public health concern continue to interfere with investigators' abilities to conduct controlled experimental investigations and extensive prospective studies.

In order to obtain a scientific report on all aspects of nutrition and HIV-related disease for the use of health care providers, the CFSAN of FDA contracted with the Life Sciences Research Office of the Federation of American Societies for Experimental Biology to conduct a comprehensive review of the topic.

B. SCOPE OF WORK

The scope of work for this project explicitly requests the following:

1. The contractor shall devise a plan to secure state-of-the-art information on current theories and beneficial clinical practices concerning the role of nutrition support in the care of HIV-infected and AIDS patients. Toward this goal, it is expected that the contractor would contact a
wide variety of reputable health care providers, educators, and medical scientists who have research and clinical expertise in this area.

2. Subsequently, the contractor shall devise a plan to publicly distribute this information for critical and scientific peer review and for comment about the scientific merit and clinical appropriateness of the findings. The results of this second phase of the project, which is expected to provide the contractor with scientific critique and consensus, are to be published as a public report.
II. HIV INFECTION AND NUTRITION: CONCEPTUAL FRAMEWORK

A. HIV INFECTION

1. Etiology of HIV infection

The human immunodeficiency virus (HIV), earlier called lymphadenopathy-associated virus (LAV) and human T-cell lymphotropic virus type III (HTLV-III), has been identified as the etiologic agent of Acquired Immunodeficiency Syndrome (AIDS). AIDS is a clinical disorder representing the end point in a progressive sequence of immunosuppressive changes that render the body highly susceptible to life-threatening tumors and opportunistic infections. HIV infection is spread by: sexual contact, infected blood or blood products, perinatally (Fauci, 1988; Lifson et al., 1988), or by breastfeeding (World Health Organization, 1987).

Infected persons show a wide range of signs and symptoms over the course of their disease, because of the progressive nature of the immunosuppression associated with HIV infection. There is a growing consensus in the medical community that the term "AIDS" should be used only in those cases where there is at least one well-defined, life-threatening condition that is definitively associated with immunosuppression induced by the HIV (Hessol et al., 1989; Goedert and Blattner, 1988). In this report, for the purpose of consistency, the term HIV infection, rather than AIDS, will be used as the generic term describing the disease process.

The number of reported AIDS cases are but one indication of the larger epidemic of HIV infection; it is estimated that 1 to 1.5 million persons in the United States are infected with HIV. The incubation period for the appearance of HIV-related symptoms (excluding generalized lymphadenopathy) has been estimated at a minimum of two years and as many as eight for the development of AIDS (Hessol et al., 1989). The natural history of the infection may be influenced by a myriad of potential mediators such as behavioral response, genetic and other host- or virus-specific factors, treatment with antiviral agents (Hessol et al., 1989; Lifson et al., 1988), and effects of nutritional intervention on disease progression. Nonetheless, the number of persons with AIDS and other manifestations of HIV infection will continue to increase for the foreseeable future until more effective treatment modalities, and possibly preventive strategies, become available.

2. Groups at risk

In the United States homosexual and bisexual men comprise the group most affected by the disease, but intravenous (IV) drug users, their sex partners, and their children represent an increasing proportion of cases. Of AIDS cases reported before 1985, 63 percent were homosexual or bisexual men with no history of IV drug use, 18 percent were female or heterosexual male IV drug users, and 2 percent were the sex partners or children of IV drug users. In contrast, among the cases reported during the first 6 months of 1989, 56 percent were homosexual or bisexual men with no history of IV drug use, 23 percent were female or heterosexual male IV drug users, and 4 percent were the sex partners or children of IV drug users (Anonymous, 1989a). Transfusion recipients and persons with hemophilia continue to comprise a small proportion of total cases. While screening of the blood supply and heat treatment of clotting factor products (Goedert and Blattner, 1988), has substantially reduced the risk of infection in these groups, they have not been 100% effective (Donahue et al., 1990).
3. Mode of viral action

Since the identification of HIV as the etiologic agent of AIDS, much has been learned about the virus' mode of action. Although a wide variety of immunologic abnormalities have been associated with HIV infection, the major effect of the virus appears to be the selective depletion of the helper or inducer subset of T lymphocytes that express the CD4$^+$ phenotype (the T4 cells) (Fauci, 1988). The virus is thought to bind to the CD4 molecule, where it is internalized and uncoated. The viral RNA is then transcribed to DNA, and this proviral DNA is integrated into the host chromosomal DNA. One unique characteristic of HIV is that unintegrated proviral DNA accumulates in the cytoplasm of infected cells and may contribute to its cytopathic effect (Gallo and Wong-Staal, 1985). After integration, the infection may assume a latent phase, until activation by potential inducers such as antigens, coinfecting viruses, or cytokines occurs to cause viral replication that brings about death of the host cell (Fauci, 1988; Rosenberg and Fauci, 1988). This action alone can give rise to a variety of immune defects because the T4 lymphocytes are responsible for activation of macrophages; induction of the function of cytotoxic T cells, natural killer cells, suppressor cells, and B cells; and secretion of hematopoietic colony-stimulating factors, growth and differentiation factors for lymphoid cells, and factors which induce nonlymphoid cell function (Fauci, 1988). HIV can also infect monocyte or macrophage cells, which then can serve as a reservoir of the virus and as a transport vehicle to various organs and tissues, including the brain (Rosenberg and Fauci, 1989a). Abnormalities of immune function cells seen in HIV infection are given in Table 1. The measurement of CD4$^+$ cell numbers or the ratio of helper (T4) to suppressor (T8) lymphocytes is considered a useful indicator of immune system status during HIV infection (Lifson et al., 1988).

4. Diagnosis of HIV infection

While the virus can be isolated from the majority of HIV antibody–positive individuals, the diagnosis of HIV infection is most commonly made on the basis of detection of HIV antibodies in the serum or other body fluids. The two most common detection methods are the enzyme–linked immunosorbent assay (ELISA) and the Western Blot Technique. Current convention dictates that a diagnosis of HIV infection be confirmed by at least two independent methods (Centers for Disease Control, 1987).

5. Associated diseases

The severe alterations of the immune system resulting from HIV infection markedly increase the susceptibility of affected persons to various neoplasias and opportunistic infections caused by a variety of microorganisms. Neoplasias and opportunistic infections commonly seen in adults with AIDS are listed in Tables 2 and 3, respectively.

6. Classification schemes

One consequence of the variability in the clinical course of HIV infection has been the inability to arrive at a sensitive and specific classification scheme for use in population surveillance. A classification system for HIV infections in adults was developed by the CDC in 1986. Their revision of the definition of AIDS was released in 1987 (Table 4). Figure 1 represents a flow chart for the revised CDC case definition of AIDS. Another classification, developed at the Walter Reed Army Institute of Research (Redfield et al., 1986), that defines increasingly compromised laboratory or clinical immune function is shown in Table 5. There is also a separate CDC scheme for children (Table 6). Such schema are helpful, but require continual updating to reflect the dynamic nature of the disease process and the evolving knowledge of the manifestations and consequences of the disease.
Table 1. Abnormalities of Immune System Cells in HIV Infection.*

<table>
<thead>
<tr>
<th>Abnormalities of T Lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased number of T4 (helper) cells</td>
</tr>
<tr>
<td>Elevated, normal, or decreased numbers of T8 (suppressor) cells</td>
</tr>
<tr>
<td>Decreased delayed-type hypersensitivity responses</td>
</tr>
<tr>
<td>Elevated spontaneous proliferation in vitro</td>
</tr>
<tr>
<td>Decreased proliferative responses to mitogens and antigens in vitro</td>
</tr>
<tr>
<td>Decreased virus-specific cytotoxic lymphocyte function in vitro</td>
</tr>
<tr>
<td>Decreased ability to provide help to B lymphocytes in vitro</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormalities of B Lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated serum immunoglobulin level</td>
</tr>
<tr>
<td>Circulating immune complexes</td>
</tr>
<tr>
<td>Inability to mount appropriate serological response after immunization</td>
</tr>
<tr>
<td>Elevated spontaneous proliferation in vitro</td>
</tr>
<tr>
<td>Elevated numbers of spontaneous plaque-forming cells in peripheral blood</td>
</tr>
<tr>
<td>Enhanced responsiveness to B-cell growth factors in vitro</td>
</tr>
<tr>
<td>Refractoriness to normal in vitro signals for B-cell activation</td>
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</table>

<table>
<thead>
<tr>
<th>Abnormalities of Monocytes and Macrophages</th>
</tr>
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<tbody>
<tr>
<td>Decreased chemotaxis</td>
</tr>
<tr>
<td>Decreased monocyte-dependent T-cell proliferation</td>
</tr>
<tr>
<td>Decreased Fc receptor function</td>
</tr>
<tr>
<td>Decreased C3-receptor-mediated clearance of particles</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormalities of Other Cell Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased natural killer-cell activity</td>
</tr>
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</table>

* Adapted from Rosenberg and Fauci, 1989b.
<table>
<thead>
<tr>
<th>Neoplasia</th>
<th>Site</th>
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</thead>
<tbody>
<tr>
<td>Kaposi's sarcoma</td>
<td>Cutaneous, oropharynx, gastrointestinal tract, other viscera, lymph nodes</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>Central nervous system, gastrointestinal tract, disseminated</td>
</tr>
<tr>
<td>Cloacogenic or intra-epithelial carcinoma</td>
<td>Rectum</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>Oropharynx</td>
</tr>
<tr>
<td>Small-cell undifferentiated carcinoma</td>
<td>Rectosigmoid, pancreas, lung</td>
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*Adapted from Machet et al., 1988.*
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<th>Microorganism</th>
<th>Location</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protozoa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pneumocystis carinii</em></td>
<td>Lung, liver, spleen, lymph nodes, intestines, eye, ear, skin, disseminated</td>
<td>Pneumonia, splenomegaly, lymphadenopathy, choroiditis, otitis</td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>Brain, eye, lung, heart, adrenal, disseminated</td>
<td>Focal encephalitis, retino-choroiditis, myocarditis, pneumonia</td>
</tr>
<tr>
<td><em>Cryptosporidium spp.</em></td>
<td>Intestine, gallbladder, bile ducts, respiratory epithelium</td>
<td>Malabsorption and diarrhea, cholecystitis, biliary stenosis, sclerosing cholangitis</td>
</tr>
<tr>
<td><em>Microsporidium spp.</em></td>
<td>Intestine</td>
<td>Malabsorption and diarrhea</td>
</tr>
<tr>
<td><em>Isospora belli</em></td>
<td>Intestine, lymph node</td>
<td>Diarrhea, lymphadenopathy</td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em></td>
<td>Intestine</td>
<td>Diarrhea</td>
</tr>
<tr>
<td><em>Giardia lamblia</em></td>
<td>Intestine</td>
<td>Diarrhea</td>
</tr>
<tr>
<td><em>Acanthamoeba spp.</em></td>
<td>Brain</td>
<td>Meningoencephalitis</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Aspergillus spp.</em></td>
<td>Respiratory tract</td>
<td>Fungemia, pneumonia</td>
</tr>
<tr>
<td><em>Candida spp.</em></td>
<td>Oropharynx, esophagus, trachea, bronchi, lung</td>
<td>Thrush, stomatitis, esophagitis, pharyngitis, tracheobronchitis, pneumonia</td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>Brain, lung, lymph node, bone marrow, skin, blood, urine, disseminated</td>
<td>Meningitis, pneumonitis, skin lesions, lymphadenopathy, fungemia</td>
</tr>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>Lung, liver, spleen, lymph node, adrenal, bone marrow, eye, skin, blood, urine, disseminated</td>
<td>Pneumonitis, hepatosplenomegaly, lymphadenopathy, chorioRETinitis, skin lesions, pancytopenia, fungemia</td>
</tr>
<tr>
<td><em>Coccidioides immitis</em></td>
<td>Lung, brain, lymph node, liver, spleen, blood, urine, bone marrow, kidney, disseminated</td>
<td>Pneumonitis, meningoencephalitis, hepatosplenomegaly, lymphadenopathy, fungemia</td>
</tr>
</tbody>
</table>

* Adapted from Kovacs and Masur, 1988 and Macher et al., 1988.
Table 3. (Continued).

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Location</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fungi—continued</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporothrix schenckii</td>
<td>Skin, joint, lung, liver, spleen, disseminated</td>
<td>Cutaneous lesions, tenosynovitis, arthritis, pneumonia</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campylobacter spp.</td>
<td>Intestine, blood</td>
<td>Diarrhea, bacteremia</td>
</tr>
<tr>
<td>Cat scratch disease bacillus</td>
<td>Lymph node, skin</td>
<td>Lymphadenopathy, cutaneous lesions</td>
</tr>
<tr>
<td>Legionella spp.</td>
<td>Lung</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Meninges, blood</td>
<td>Meningitis, bacteremia</td>
</tr>
<tr>
<td>Mycobacterium avium-intracellulare, tuberculosis and kansasii</td>
<td>Lymph node, liver, spleen, bone, marrow, intestine, lung, skin, adrenal, blood, urine, disseminated</td>
<td>Lymphadenopathy, hepatosplenomegaly, pancytopenia, pneumonia, tuberculosis, diarrhea, mycobacteremia</td>
</tr>
<tr>
<td><em>Norcardia</em> spp.</td>
<td>Lung, pleura, pericardium, soft tissues, bone, brain, lymph node, spleen, kidney, disseminated</td>
<td>Pneumonia, empyema, pericarditis, retropharyngeal or subcutaneous abscess, draining sinus tract, encephalitis</td>
</tr>
<tr>
<td>Pneumococcus spp.</td>
<td>Lung</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>Intestine, blood</td>
<td>Diarrhea, bacteremia</td>
</tr>
<tr>
<td>Shigella spp.</td>
<td>Intestine, blood</td>
<td>Diarrhea, bacteremia</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>Lymph node, testis, brain</td>
<td>Lymphadenopathy, orchitis, neurosyphilis</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Esophagus, lung, adrenal, eye, brain, peripheral nerve, intestine, liver, seminal vesicle, blood, disseminated</td>
<td>Esophagitis, pneumonitis, retinochoroiditis, meningocerebral meningitis, reticulitis with polyneuropathy, diarrhea, viremia</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Location</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses—continued</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr</td>
<td>Lymph node, tongue, blood</td>
<td>EBV-positive non-Hodgkin's lymphomas, oral hairy leukoplakia</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Liver</td>
<td>Nausea, vomiting, fever, antigenemia</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Mucocutaneous, oral cavity, esophagus, bronchus, lung, disseminated</td>
<td>Ulcerative mucocutaneous lesions, stomatitis, esophagitis, bronchitis, pneumonia, encephalitis</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Mucocutaneous, disseminated</td>
<td>Multiple dermatomal zoster, Herpes zoster ophthalmicus</td>
</tr>
<tr>
<td>Papillomavirus</td>
<td>Mucocutaneous</td>
<td>Condyloma acuminitum, oral hairy leukoplakia</td>
</tr>
<tr>
<td>Polyomavirus</td>
<td>Brain</td>
<td>Progressive multifocal leuko-encephalopathy</td>
</tr>
<tr>
<td>Poxvirus</td>
<td>Mucocutaneous</td>
<td>Molluscum contagiosum</td>
</tr>
<tr>
<td><strong>Helminths</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Strongyloides stercoralis</em></td>
<td>Intestine, lung, brain, disseminated</td>
<td>Diarrhea, pneumonia, meningoencephalitis, recurrent polymicrobial bacteremias</td>
</tr>
<tr>
<td><strong>Arthropods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Sarcoptes scabiei</em> (burrowing mange mite)</td>
<td>Skin, disseminated</td>
<td>Norwegian scabies, secondary bacteremias</td>
</tr>
</tbody>
</table>
Table 4. Centers for Disease Control Classification System for Patients with HIV Infection.*

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td><strong>Acute HIV Infection</strong> (Patients with transient signs and symptoms of HIV infection.)</td>
</tr>
<tr>
<td>Group II</td>
<td><strong>Asymptomatic HIV Infection</strong> (Patients without previous signs or symptoms leading to classification in Group III or IV.)</td>
</tr>
<tr>
<td>Group III</td>
<td><strong>Persistent Generalized Lymphadenopathy</strong> (PGL) ( Patients with lymph nodes &gt;1 cm in diameter that persisted for &gt;3 months at two or more extrainguinal sites.)</td>
</tr>
<tr>
<td>Group IV</td>
<td><strong>Other HIV Disease</strong></td>
</tr>
<tr>
<td></td>
<td>Subgroup A: <strong>Constitutional Disease</strong> (Patients with one or more of the following: fever &gt;1 month, involuntary weight loss &gt;10%, diarrhea &gt;1 month.)</td>
</tr>
<tr>
<td></td>
<td>Subgroup B: <strong>Neurological Disease</strong> (Patients with dementia, myelopathy or peripheral neuropathy.)</td>
</tr>
<tr>
<td></td>
<td>Subgroup C: <strong>Secondary Infectious Disease</strong> (Patients diagnosed with infectious disease from the following categories.)</td>
</tr>
<tr>
<td></td>
<td>Category C–1: One of the 12 specified diseases listed in the CDC surveillance definition of AIDS—<em>Pneumocystis carinii</em> pneumonia, chronic cryptosporidiosis, toxoplasmosis, extraintestinal strongyloidiasis, isosporiasis, candidiasis (esophageal, bronchial, or pulmonary), cryptococcosis, histoplasmosis, mycobacterial infection with <em>Mycobacterium avium</em> complex or <em>M. kansasii</em>, cytomegalovirus infection, chronic mucocutaneous or disseminated herpes simplex virus infection, and progressive multifocal leukoencephalopathy.</td>
</tr>
<tr>
<td></td>
<td>Category C–2: Symptomatic or invasive disease with oral, hairy leukoplakia, multidermatomal herpes zoster, recurrent <em>salmonella</em> bacteremia, nocardiosis, tuberculosis, or oral candidiasis.</td>
</tr>
<tr>
<td></td>
<td>Subgroup D: <strong>Secondary Cancers</strong> (Patients diagnosed with cancers known to be associated with HIV infection.) Kaposi's sarcoma, non–Hodgkin's lymphoma (small, noncleaved lymphoma or immunoblastic sarcoma), or primary lymphoma of the brain.</td>
</tr>
<tr>
<td></td>
<td>Subgroup E: <strong>Other Conditions in HIV Infection</strong> (Patients exhibiting clinical findings which may be due to HIV disease.) Chronic lymphoid interstitial pneumonitis, constitutional symptoms not meeting Subgroup IV–A, patients with infectious diseases not meeting Subgroup IV–C, and patients with neoplasms not meeting subgroup IV–D.</td>
</tr>
</tbody>
</table>

* Adapted from Centers for Disease Control, 1986.
Figure 1. Flow diagram for revised CDC case definition of AIDS, September 1, 1987 (modified from Centers for Disease Control, 1987)
Table 5. Walter Reed Staging Classification for HIV Infection.¹

<table>
<thead>
<tr>
<th>Stage</th>
<th>HIV Antibody or Virus Isolation</th>
<th>Chronic Lymphadenopathy</th>
<th>CD4⁺ T Cells /mm³</th>
<th>DTH²</th>
<th>Thrush</th>
<th>Opportunistic Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>WR0</td>
<td>-</td>
<td>-</td>
<td>&gt;400</td>
<td>NL²</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WR1</td>
<td>+</td>
<td>-</td>
<td>&gt;400</td>
<td>NL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WR2</td>
<td>+</td>
<td>+</td>
<td>&gt;400</td>
<td>NL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WR3</td>
<td>+</td>
<td>+ or -</td>
<td>&lt;400</td>
<td>NL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WR4</td>
<td>+</td>
<td>+ or -</td>
<td>&lt;400</td>
<td>Partial</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WR5</td>
<td>+</td>
<td>+ or -</td>
<td>&lt;400</td>
<td>Anergy and/or</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>WR6</td>
<td>+</td>
<td>+ or -</td>
<td>&lt;400</td>
<td>Partial or anergy</td>
<td>+ or -</td>
<td>+</td>
</tr>
</tbody>
</table>

¹ Adapted from Redfield et al., 1986.

² DTH = delayed type hypersensitivity; NL = normal; partial anergy defined as induration of 5mm or greater in only one of the test antigens: tetanus, trichophyton, mumps, and candida.

Note: Boldface type indicate the essential criteria for each stage.

Table 6. Classification for HIV-Infected Children.*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-0</td>
<td>Indeterminate infection in perinatally exposed children younger than 15 months</td>
</tr>
<tr>
<td>P-1</td>
<td>Asymptomatic infection</td>
</tr>
<tr>
<td>P-2</td>
<td>Symptomatic infection (causes other than HIV excluded)</td>
</tr>
<tr>
<td></td>
<td>A Nonspecific findings</td>
</tr>
<tr>
<td></td>
<td>B Progressive neurological disease</td>
</tr>
<tr>
<td></td>
<td>C Lymphocytic intestinal pneumonia</td>
</tr>
<tr>
<td></td>
<td>D Secondary infectious diseases</td>
</tr>
</tbody>
</table>

* Abbreviated from Centers for Disease Control, 1987.
7. Clinical course of HIV infection

The clinical course of HIV infection varies substantially from individual to individual. Typically, there is a sudden onset of a mononucleosis-like syndrome (about one to two weeks long) that corresponds to the process of seroconversion. This condition, often referred to as "Primary" HIV infection, occurs between two and four weeks of exposure and can also include a myriad of neurological, dermatological and other pathophysiological problems (Tindall et al., 1990). This phase is followed by an asymptomatic period which may include a persistent generalized lymphadenopathy (PGL). The terms "persistent generalized lymphadenopathy" and "lymphadenopathy syndrome" have been used to describe the status of patients whose only sign was lymphadenopathy (lymph nodes greater than 1 cm in diameter) found at two or more extrainguinal sites for three months or more (Yarchaon and Pluda, 1988). This stage is often followed by the early manifestations of HIV infection. These include: fatigue, seborrhea, eczema, fevers, diarrhea, muscle pain, night sweats, weight loss, oral candidiasis, herpes zoster, and other opportunistic infections that are not life threatening. This constellation of signs and symptoms is often referred to as AIDS-related complex (ARC) and is the antecedent of AIDS.

8. Clinical course and considerations in pediatric HIV-infected patients

As in adults, there is also a range of manifestations of HIV infection in infants and children from asymptomatic to critically ill. Most children with HIV infection have nonspecific findings such as lymphadenopathy, hepatosplenomegaly, oral candidiasis, low birth weight, failure to thrive, weight loss, diarrhea, chronic eczematoid dermatitis, or fever (Falloon et al., 1988). Serious bacterial infections with Streptococcus pneumoniae, Hemophilus influenzae, Salmonella spp., and other organisms are common manifestations of AIDS. Many HIV-infected children have heightened susceptibility to various opportunistic and pathogenic microorganisms because they never developed appropriate immunity prior to infection. A majority of children with HIV infection appear to be affected to some extent by a characteristic encephalopathy that results in developmental delay or deterioration of motor and intellectual function (Falloon et al., 1988). Lymphocytic interstitial pneumonitis, which is rare in adults, is common in children with AIDS; the reverse is true of Kaposi's sarcoma and HIV-associated lymphomas, which occur commonly in adults but rarely in children (Falloon et al., 1988).

Infants with HIV antibodies represent special cases, because most are born with passively acquired antibodies from their HIV-infected mothers (Goedert and Blattner, 1988). A definitive diagnosis of infection cannot be made by antibody detection alone in young infants because most conventional tests cannot detect the difference between passively acquired antibodies and those that have been endogenously produced. Moreover, viral detection may not be possible by ELISA or Western Blot techniques for at least six and in some cases as many as 15 months postnatally. Consequently, Goedert and Blattner (1988) suggested that HIV infection in very young children be defined "only by direct identification of live virus, HIV-specific nucleic acids, or HIV specific antigens, in addition to cases indirectly defined by virtue of AIDS or another condition that is closely related to HIV." Special considerations of current knowledge and practice with pediatric patients are reviewed in Chapter VI.

B. NUTRITION CONCEPTS

A role for nutrition in the HIV disease process is suggested by the involuntary weight loss or wasting indicative of severe protein-energy malnutrition (PEM), observed in many patients with HIV infection (Kotler, 1989a), and the intimate and inextricable role that nutrition and specific nutrients play in immunocompetence (Chandra, 1983). Evidence indicates that for many diseases, the
nutritional status of the individual will have an impact on morbidity and mortality irrespective of the disease process (Krause and Mahan, 1984). In addressing the nutrition and HIV disease relationship there are two questions to be answered:

1. What impact does nutritional status or specific nutrients have on the progression of the HIV infection?

2. What impact does the HIV virus and subsequent infections and or neoplasms have on general or specific nutritional needs?

A related issue is the potential of iatrogenic effects of currently available treatment modalities on nutritional status. A conceptual framework based in an understanding of fundamental concepts of nutrition and nutritional assessment is needed to address these issues. Accordingly, for purposes of this report it is essential that a framework of working definitions be used.

**Nutrition** may be defined as the sum total of the processes involved in the ingestion and utilization of nutrients that are subsequently involved in the growth, repair, and maintenance of the body's components and their functions. These processes include ingestion, digestion, absorption, metabolism, and functional utilization of nutrients. Furthermore, the acquisition of a balanced diet is influenced by an array of physical, sociocultural, economic, behavioral, genetic, and medical factors.

**Malnutrition** may be a consequence of changes in any of the processes involved in nutrition or in those factors affecting it, and may result in either over- or undernutrition.

**Undernutrition**, associated with deficiencies of one or more nutrients, may have the following five primary causes outlined by Herbert (1973): inadequate ingestion, absorption, and utilization, and increased excretion, and requirement.

The interpretation of studies about the relationship between nutrition and HIV infection relies on an appreciation of the processes involved in the selection of appropriate nutritional assessment methodologies. In general, the ability to select appropriate assessment techniques stems in part from an understanding of not only the processes of nutrition, but also the nature of the changes that are likely to occur during the course of a nutritional deficiency. Brin (1978) listed five stages of a nutritional deficiency progressing from such generalized manifestations as weight loss or lethargy, to specific biochemical and anatomic lesions and eventual death. Consequently, clinical assessments should progress from general, nonspecific, but sensitive, indicators of overall nutrient intake and nutritional status to specific and sensitive biochemical measures.

Of particular concern in the selection of a particular assessment method are those issues related to its sensitivity and specificity. Solomons and Allen (1983) have defined sensitivity as the probability that a given test for a specific nutrient will be positive in a malnourished individual, while specificity is the probability that a test will be negative in a well-nourished individual. Of additional concern is whether the test result reflects immediate intake or long-term status. Viewed within the context of the processes of nutrition and the progression of a nutritional deficiency, an assessment procedure should, whenever possible, reflect early changes in the function of a nutrient-dependent system. It is important that the test be a reflection of the functional status of the nutrient rather than a random measurement of the level of the nutrient. Also, the interpretation of a given biochemical assessment must be viewed within the context of the other processes of nutrition, in particular dietary intake, and use of dietary supplements and drugs (both recreational and therapeutic). For a given study these factors will determine both its internal validity (the study's ability to test the null hypothesis) and external validity (the ability to generalize the results to the larger population).
Before beginning the discussion of the available research on the relationship between HIV infection and nutrition, the reader should recall that, in this report, the convention, "HIV infection" is used to refer to all phases of the disease process culminating in AIDS. Furthermore, the rationale for this is best exemplified by a quotation from the Report of the Presidential Commission on Human Immunodeficient Virus Epidemic (1988):

"The term AIDS is obsolete. HIV infection more correctly defines the problem. The medical, public health, political, and community leadership must focus on the full course of HIV infection rather than concentrating on the later stages of the disease (ARC and AIDS). Continual focus on AIDS rather than the entire spectrum of HIV infection has left our nation unable to deal adequately with the epidemic."

It is important to keep this terminology in mind when reviewing the literature in this field because many authors have and continue to use the term AIDS in a generic sense. Consequently, many of the studies cited herein include only very ill patients with AIDS while others include groups of patients ranging in the clinical spectrum from HIV+ asymptomatic to AIDS but referred to as the "AIDS group." This is obviously more than a semantic issue as there can be a vast difference between the physiology, immunocompetence and nutritional status of patients who are HIV+ asymptomatic and those who have terminal stages of AIDS. Any conclusions drawn in studies that use the generic AIDS must be viewed with caution. In addition, generalizations drawn about changes seen in patients with AIDS and their applicability to all HIV+ infection patients should also be made carefully.

An additional caveat is necessary because most of the studies conducted to date, and particularly those cited in this report, have examined adult male patients with AIDS. Less than 35 percent of these studies are from peer-reviewed, refereed scientific journals. Within this group, fewer still are prospective studies with adequate numbers of subjects and appropriate control groups. Many of the studies are preliminary, have a limited number of subjects, are observational rather than investigative, and were published only as abstracts or letters to the editors.

This caveat is not meant to be critical of the efforts of investigators who are studying the role of nutrition in HIV-related disease and possible approaches to avoidance of disease manifestations such as involuntary weight loss. Rather, it is a caution that at this time, the body of extant knowledge derived from experimental studies on the role of nutrition in HIV infection and AIDS is limited. Knowledge is evolving rapidly but still relies heavily on reports of clinical observations, experience with other wasting diseases, and inductive reasoning.
III. EFFECTS OF HIV INFECTION ON NUTRITIONAL STATE

A. EVIDENCE FOR GENERAL MALNUTRITION WITH HIV INFECTION

Among the most common observations in patients with HIV infection are profound weight loss and wasting reminiscent of the clinical manifestations associated with PEM. According to Torun and Viteri (1988), "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 would be associated with decreased intake, malabsorption secondary 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 occurs with chronic disease conditions.

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 (Table 7). The three conditions may be defined as follows:

PEM—In this report a condition synonymous with starvation and results when the body's needs for protein, energy, or both cannot be met by diet (Torun and Viteri, 1988). The inability to meet these needs in HIV infection may be the primary result of inadequate intake, or secondary following malabsorption, decreased utilization or changes in metabolism.

Cachexia—A clinical syndrome characterized by a mixture of metabolic abnormalities that lead to weight loss through accelerated wasting of host tissue mass, and failure of adequate nutrient intake, absorption, and utilization (Kern and Norton, 1988).

Acute Phase Response—A term that refers to the metabolic changes occurring as a result of tissue injury, infection, or inflammation and is characterized by changes in the circulating levels of various plasma proteins (Fleck, 1988).

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 (Table 7). Many of the metabolic changes 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 interventions. The consideration of the acute phase response (APR) is important, because at any time, an individual with a chronic disease such as AIDS may progress from one stage to another; for example, an HIV-infected patient may progress from asymptomatic to ARC or AIDS. The distinguishing features of the latter two conditions involve the occurrence of various types of 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 document and partition those subjects experiencing an APR, results such as changes in plasma protein levels might be attributed inappropriately to the HIV virus or nutritional ramifications thereof rather than the presence of severe stress or an acute infection.

Whether the changes seen in HIV-positive patients involve these well known phenomena or whether they are unique manifestations of the HIV infection remain to be established. The following section provides a review of available evidence that the changes in body composition, intermediary metabolism, or status of individual nutrients observed in HIV infected persons are
Table 7. Metabolic Changes Associated with Malnutrition in Chronic Disease.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PEM\textsuperscript{1} Mild or Moderate</th>
<th>Severe</th>
<th>Cachexia (Cancer)\textsuperscript{2}</th>
<th>Acute Phase Response\textsuperscript{3,4} (including stress and infections)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (WT for HT)</td>
<td>Mild 80–89%. NCHS moderate 70–79%.</td>
<td>&lt; 70%</td>
<td>↓ persistent failure to gain weight despite nutritional compensation.</td>
<td></td>
</tr>
<tr>
<td>Lean body mass</td>
<td>↓ LBM</td>
<td>↓ LBM (Wasting)</td>
<td>↓ LBM ↓ Muscle wasting</td>
<td></td>
</tr>
<tr>
<td>Basal energy expenditure (BEE)</td>
<td>↓ Energy expenditure</td>
<td>↓ BEE</td>
<td>No or small elevations in BEE. May be tumor dependent. In sarcoma, patients were found to have ↓ BEE. Food intake will not effect change in metabolism.</td>
<td></td>
</tr>
<tr>
<td>Protein metabolism (Total protein, BUN)</td>
<td>↓ Branched chain amino acid ↓ Transferrin ↓ Albumin</td>
<td>↓ All blood prot. ↓ Free amino acids ↓ RBP, Transferrin</td>
<td>↓ Albumin – significantly ↓ protein turnover than malnourished.</td>
<td>Acute response is ↓ in most plasma proteins, followed by ↓. Moderate to severe infection → ↓ Albumin, transferrin, RBP, Pre-albumin ↓.</td>
</tr>
<tr>
<td>Glucose</td>
<td>NC</td>
<td>↓ (↓ Insulin)</td>
<td>↓ Gluconeogenesis – hypoglycemia glucose intolerance</td>
<td>↓ in moderate to severe infection. ↓ Insulin</td>
</tr>
<tr>
<td>Lipid metabolism</td>
<td>↑ Lipolysis</td>
<td>↑ Free fatty acids</td>
<td>Hyperlipemia ↑ Lipolysis</td>
<td>↑ Free fatty acids (stress)</td>
</tr>
<tr>
<td>Other</td>
<td>↑ Extracellular H\textsubscript{2}O enlarged lymph nodes ↑ Infections ↑ Total body K</td>
<td>Inability to adapt to ↓ intake Anorexia despite metabolic changes</td>
<td>Acute rapid ↓ in Plasma, zinc, &amp; iron ↓ Cell potassium ↑ Electrolyte loss ↑ Water</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{1} Turin and Viteri, 1988.
\textsuperscript{2} Kern and Norton, 1988.
\textsuperscript{3} Fleck, (1988).
\textsuperscript{4} McLaren, (1988).
the consequence of decreased intake, are 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.

1. **Body weight**

Progressive involuntary weight loss typically appears in the early stages of the HIV infection and increases in severity as the disease progresses.

As depicted in Table 8, weight change has been documented in the majority of the body composition studies, which generally have 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 prior to the development of AIDS. For example, in a study of 30 homosexual men who were HIV positive but asymptomatic except for lymphadenopathy, Beach et al. (1989a) and Mantero-Atienza et al. (1989a) found that two of the patients had significantly low body weight, triceps skinfold thickness, and body mass index, while three patients were obese. The pattern of weight loss in HIV infection seems to indicate that stable AIDS or asymptomatic HIV+ patients are able to maintain body energy stores, whereas precipitous weight loss occurs in ill patients as the disease progresses.

Generalization of the results of the studies noted in Table 8 to the whole HIV-infected population may be difficult because of complicating experimental issues such as reliance on data, often retrospective, compiled over periods of time (months and years). In such circumstances, consideration of factors such as use of zidovudine or other drug therapies, dietary habits or nutritional intervention; more importantly, the existence or occurrence of multiple infectious diseases prior to 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 (Rowland, 1990).

The issue of concurrent infections was addressed by Kotler (1989b), who reviewed information on a large number of infectious diseases, injuries, and tumors found in the gastrointestinal tract of patients with AIDS. Many of these diseases and disorders are associated with the malabsorption syndrome in the absence of HIV-infection or AIDS. Whether this malabsorption is related to other potential mediators of weight loss such as failure to maintain adequate dietary intakes; failure to control gastrointestinal infections; inadequate, inappropriate, or unsuccessful nutrition interventions; or HIV-infection per se remains to be clarified. To date, most studies suggest that when weight loss occurs in persons with diagnosed AIDS, problems with malabsorption and secondary infections of the gastrointestinal tract are probably involved.

The potential predisposition of high-risk groups for malnutrition constitutes an additional consideration in the design and interpretation of weight-loss studies. Kotler et al. (1984) 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 control subjects were seen for gastrointestinal problems. This is consistent with reports of a high incidence of gastrointestinal problems in this population (Baker and Peppercorn, 1982). The detrimental effects of various "recreational" drugs, including marijuana, cocaine, and heroin, on nutritional status were reviewed by Mohs et al. (1990). Tripp and Touger-Decker (1990) reported that HIV seronegative IV drug users (IVDU), 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 extent to which such predisposing factors exist and their potential for influencing the course of HIV infection must be considered in any studies of these populations.
Table 8. Weight Loss Studies.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Diagnostic Criteria 1</th>
<th>DOI 2</th>
<th>Nutritional Indices 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kotler et al., 1984</td>
<td>12 AIDS HS</td>
<td>CDC</td>
<td>NA</td>
<td>BW, Mid-arm circumference, % Ideal BW, Weight change</td>
</tr>
<tr>
<td>O'Sullivan et al., 1985</td>
<td>50 AIDS</td>
<td>NA</td>
<td></td>
<td>% Pre-illness weight, % Ideal BW, % Reference weight, (NHANES)</td>
</tr>
<tr>
<td>Kotler et al., 1985</td>
<td>28 AIDS</td>
<td>CDC</td>
<td>NA</td>
<td>(BW), Skinfold thickness, (TBK), (TBW)</td>
</tr>
<tr>
<td></td>
<td>5 ARC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 HS HIV(-)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>58 Lab controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 Eating disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dworkin et al., 1985</td>
<td>22 AIDS:</td>
<td>CDC</td>
<td>32 ± 29 weeks</td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>3 HS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 IVDU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 HS + IVDU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garcia et al., 1987</td>
<td>50 Male AIDS</td>
<td>NA</td>
<td>NA</td>
<td>Patient recall of &quot;usual weight.&quot; BW at death.</td>
</tr>
<tr>
<td>Chelluri and Jastremski, 1989</td>
<td>24 AIDS:</td>
<td>NA</td>
<td>NA</td>
<td>History of weight loss</td>
</tr>
<tr>
<td></td>
<td>1 HT, 5 HS, 15 IVDU,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 HS + IVDU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCorkindale et al., 1990</td>
<td>Group 1</td>
<td>CDC</td>
<td>NA</td>
<td>Nutrition history, Height, weight, (BMI), Skinfold thickness</td>
</tr>
<tr>
<td></td>
<td>13 HIV(+) ASYMP, 6 ARC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 ARC, 3 AIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mantero-Atienza et al., 1989a</td>
<td>30 HS HIV(+) ASYMP</td>
<td>Serology</td>
<td>NA</td>
<td>Weight, height, TSF, MUAC</td>
</tr>
<tr>
<td>Bergerson et al., 1990</td>
<td>48 HIV infected; HIV(+) ASYMP, HIV(+) + Kaposi, HIV(+) + infections</td>
<td>NA</td>
<td>NA</td>
<td>BW, Height, Skinfold thickness, TBK</td>
</tr>
<tr>
<td>Trujillo et al., 1990</td>
<td>48 AIDS, 6 ARC Male</td>
<td>NA</td>
<td>NA</td>
<td>% weight change from usual BEE EPR</td>
</tr>
<tr>
<td>Ysseldyke, 1990</td>
<td>50 AIDS Males</td>
<td>NA</td>
<td>17.7 mo. since diagnosis</td>
<td>Weight history</td>
</tr>
</tbody>
</table>

1 Subjects -
- HT - Heterosexual
- HS - Homosexual
- IVDU - Intravenous drug users
- BP - Blood products
- ASYMP - Asymptomatic
- ARC - Aids related complex
- AIDS - Aquired immunodeficiency syndrome
- HIV - Human immunodeficiency virus

2 Diagnostic Criteria -
- WR - Walter Reed
- CDC - Centers for Disease Control
<table>
<thead>
<tr>
<th>Diet Data</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>AIDS &lt; Controls for all measures</td>
<td>No diet data: all AIDS patients were experiencing AIDS-related illnesses, no drug treatment data given.</td>
</tr>
<tr>
<td>NA</td>
<td>62% has &gt; 10% weight loss from pre-illness, 84% &lt; 15th percentile compared to NHANES. Mean 16% weight loss during hospitalization.</td>
<td>Retrospective chart review No patient data given, i.e., DOI, diet, stage and illness, drug history.</td>
</tr>
<tr>
<td>NA</td>
<td>AIDS &amp; ARC &lt; control % IBW, TBK. Male: Female differences in composition of weight loss in AIDS &amp; ARC. Patients with diarrhea + AIDS had TBK less than patients with AIDS alone.</td>
<td>Heterogenous subject group. All chronically ill. No drug history or diet data.</td>
</tr>
<tr>
<td>NA</td>
<td>Mean weight loss 34 ± 19 lbs.</td>
<td>No correlation between DOI and weight loss. Time-frame for determination of weight loss not given. No available pre-HIV data or HIV(-) IVDU comparison group. Study focus was on GI status and diarrhea.</td>
</tr>
<tr>
<td>NA</td>
<td>Mean loss of 11.8 ± 7.6 kg</td>
<td>Chart review of 50 expired AIDS patients. No data on DOI, nutrition, history</td>
</tr>
<tr>
<td>NA</td>
<td>20 (91%) had history of weight loss. Actual weight loss 25 lbs.</td>
<td>Retrospective chart review. 87% had pneumocystic pneumonia. Baseline for history of weight loss not given. No data on DOI, IVDU treatments.</td>
</tr>
<tr>
<td>4-day diet records</td>
<td>Group 1</td>
<td>All subjects involved in clinical drug trial. Group 1 was in 2X blind crossover. The code was not broken so that authors did not know who was on drug or placebo during sampling period.</td>
</tr>
<tr>
<td>NA</td>
<td>1 Body wt., 1 % Body fat No change Macronutrient intake 1 in Group 1. No diet data for Group 2.</td>
<td>No nutritional history or diet data, DOI unknown.</td>
</tr>
<tr>
<td>NA</td>
<td>2 (7%) Had BW &lt; 80% IBW 3 (10%) were &gt; 120% IBW</td>
<td>Abstract - little detailed information. No diet data reported. No data re: drug use, sex, risk group.</td>
</tr>
<tr>
<td>NA</td>
<td>HIV(+) + Kaposi HIV(-) + infect differed from HIV(+)'s in BCM</td>
<td>Abstract - little detail available.</td>
</tr>
<tr>
<td>Kcal and Protein per day</td>
<td>BW for HIV(+) &gt; HIV(-) IVDU at risk despite HIV status</td>
<td>Abstract - all patients pooled. No data on disease stage. High incidence of G.I. problems, 44% diarrhea. All subjects hospitalized.</td>
</tr>
<tr>
<td>NA</td>
<td>67% &lt; IBW 77% had weight loss &gt; 10% of usual BW.</td>
<td>Abstract - all patients hospitalized. 48% died. 52% had diarrhea.</td>
</tr>
</tbody>
</table>

3 DOI = Duration of Illness

4 Nutritional Indices - BW = Body weight

TBK = Total body potassium
TBW = Total body water
BMI = Body mass index

MUAC = Mid-upper arm circumference
TSF = Triceps skinfold
BEE = Basal energy expenditure
EPR = Estimated protein requirement
To summarize, there is little doubt that weight loss occurs in AIDS patients. However, extant data concerning the actual weight losses in different patient populations, (i.e., HIV-seropositive asymptomatic, ARC, or AIDS) vary widely. Similarly the extent and composition of weight loss by individuals within patient groups (i.e., infected males versus females, IVDU versus homosexuals) also vary widely. Currently, the ability to determine the ranges of actual weight loss that might be expected and the predisposing factors or causes for this variability is limited by the lack of controlled studies addressing these issues.

2. **Metabolic changes in HIV infection**

Aside from documentation of 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. Irrespective of whether the malnutrition often seen in HIV infected patients is the direct result of the virus or the psychological and or physiological response to the constellation of problems associated with the infection, patients must be treated individually with regard for their clinical status. Because of the inconsistencies in study design and the absence of adequate control, results cannot be generalized to the whole population. However, consideration of the possible existence of mild to severe malnutrition in addition to the burden of infections in any given patient must be given high priority.

Other outcomes that would provide evidence of a metabolic anomaly associated with HIV infection are potential changes in circulating proteins and or lipids. Unusual changes in these parameters could indicate a mobilization or shifting of the relative energy storage pools.

a. **Body composition**

Kotler et al. (1985) were among the earliest investigators to examine the composition of weight loss in subjects diagnosed with ARC or AIDS. They investigated body cell mass by measuring total body content of potassium ($^{40}$K), total body water and extracellular water volumes, and body fat content of 27 male and 6 female subjects. Data from these 33 immunodeficient subjects were compared with data from 5 healthy homosexual males and a previously studied laboratory reference group of 58 adult men and women who did not have AIDS or ARC. Kotler et al. (1985) found that the 33 ARC or AIDS subjects were significantly underweight compared to the 5 healthy homosexual males and 58 male and female laboratory controls (82±10 percent, 101±7 percent, and 103±6 percent of "ideal body weight," respectively). The immunodeficient patients had total body potassium to height ratios that were 68±10 percent of ideal while ratios for the 2 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 percent of normal) than in the 18 patients without diarrhea (74±9 percent 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. (1985) also found that compared with normal values (derived from a previous survey of 3,000 adult males), body fat was depleted in the immunodeficient patients; however, values were 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±30 percent vs. 71±21 percent of normal), and their values were similar to those of women with eating disorders. In contrast to the women, the immunodeficient men 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 the patients, with a relative increase in extracellular water volume.
Repeat measures, conducted on 11 of the immunodeficient patients, indicated a progressive depletion of body potassium and body cell mass in 8 patients with AIDS but not in 3 patients 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 male AIDS patients was reminiscent of stress or injury. While dietary data are needed to make the differential diagnosis of the type of malnutrition these patients experienced, the preferential loss of lean body mass rather than body fat would be more reflective of cachexia than PEM. In subsequent studies of body composition of 24 patients in the terminal stages of AIDS, Kotler et al. (1987a, 1989a) 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 necessarily an inevitable consequence of HIV infection. When Kotler et al. (1990) studied energy balance and body composition of five clinically stable outpatients with AIDS, six HIV-seronegative homosexual, and six HIV-seronegative heterosexual males, they found that over the six-week study period, body weight losses of the five patients with AIDS averaged about 3 kg (5 percent of initial body weight) while body weights 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 when compared to either of the control groups. The actual composition of the weight loss was not clear. Baseline caloric and nutrient intakes of the subjects in the three groups, as measured by three-day diaries, were essentially similar. Interestingly, while the three groups did not differ 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 so that it is not possible to assess any changes in intake relative to subsequent weight loss in the AIDS group over the entire study period. Additional observations were a decrease in resting metabolic rate or hypometabolism in the AIDS patients along with a diminished intestinal absorption of both the pentose sugar xylose and the triacylglycerol triolein. These authors suggested that the apparently paradoxical effects of an imbalance in energy intake (in excess of energy expenditure) and weight loss were an appropriate adaptive response to malabsorption. The absence of significant progressive wasting indicated a metabolic adaptation that would be similar to that expected in starvation (see Table 7).

b. Circulating proteins

Several investigators have examined levels of serum proteins as indicators of nutritional status of patients with AIDS. Representative studies include retrospective review of serum albumin levels of hospital patients, total lymphocyte counts, retinol-binding protein (RBP), prealbumin, and C-reactive proteins.

Chelluri and Jastremski (1989) reviewed records of 24 hospitalized patients with AIDS and found that serum albumin levels were abnormal in 42 percent at admission, with 29.5 percent having moderately depleted levels (2.8–3.5 g/dL) and 12.5 percent having severely depleted levels (<2.8 g/dL). They also reported that most of the patients (84 percent) had total lymphocyte counts less than 1200 cells/µL and experienced deterioration of albumin status and lymphocyte count during hospitalization. Dworkin et al. (1985) also noted hypoalbuminemia in a group of 22 hospitalized patients with AIDS; mean serum albumin level was 3.3±0.8 g/dL. In a group of 12 homosexual men with AIDS, the mean serum albumin level was 2.7±0.3 g/dL, which was significantly lower than the mean of 4.0±0.2 g/dL in HIV seronegative homosexual control subjects (Kotler et al., 1984). Zumvilt and Schmidt (1989) reported lower serum albumin levels in 20 males with AIDS and 20 males with ARC than in a group of 20 healthy male controls.
Serum RBP concentration, total iron-binding capacity, and serum albumin concentration were significantly lower in a group of 33 men and women diagnosed with AIDS or ARC than in healthy controls (Kotler et al., 1985). RBP concentration was correlated with the total body potassium to height ratio (an indicator of lean body mass) and with iron-binding capacity, but not with serum albumin.

Huang et al. (1988) determined the serum concentrations of total protein, albumin, prealbumin (transthyretin), and RBP in 53 patients with AIDS, 27 HIV-seropositive individuals, and 23 uninfected controls. Other than diagnostic category and HIV antibody status, no other information (i.e., sex, or risk–group status) was available on the study participants. Albumin and prealbumin concentrations were lower in patients with AIDS than in HIV–positive individuals or controls, total serum protein concentrations were significantly greater in patients with AIDS and HIV–infection than in controls, and RBP levels did not differ among the three groups. In the absence of infection, RBP is a sensitive indicator of nutritional status (Fleck, 1988). However, the majority of changes in RBP levels have been in HIV–infected patients experiencing some form of acute or chronic infection. Therefore these results would appear to support an acute phase or perhaps early stage cachexic (muscle wasting) response (both of which are characterized by changes in circulating proteins) rather than primary PEM.

Beach et al. (1989a) and Mantero-Atienza et al. (1989a) found that in a group of 30 HIV–positive homosexual men who had no symptoms other than lymphadenopathy, 25 percent had serum RBP levels below the normal range of 3.0–5.0 mg/dL and 9 percent had serum albumin levels below the normal range of 3.5–5.5 mg/dL. Similar findings were reported in a smaller (25 HIV–seropositive asymptomatic males) study (Fordyce-Baum et al., 1988a) where 25 percent had significantly low RBP levels. In the Beach et al. (1989a) study, total serum protein levels were normal or high, perhaps as suggested by these investigators, a consequence of increased levels of immunoglobulins. Many more subjects had depressed serum RBP levels than had anthropometric evidence of malnutrition. These investigators also postulated that such outcomes might represent a sensitive (although not specific) indication of early stages of malnutrition. Such an interpretation would be premature without data on actual dietary intakes or infection status.

Changes in plasma amino acid profiles in subjects with AIDS or ARC have been explored. In a preliminary report, Althoff et al. (1989) compared values for 21 amino acids in plasma of 23 patients with AIDS (CDC Stage IV), 8 patients with ARC, and 121 controls. Again, none of the groups was characterized in terms of any other demographic variables except clinical status. Results indicated a uniform decrease of most circulating amino acids levels in the patients with AIDS (especially in those with a low body-mass index) as compared to patients with ARC or to control patients. Pronounced reductions were reported for serine, glutamine, valine, methionine, isoleucine, leucine, tyrosine, histidine, threonine, and tryptophan. The significance of these changes is uncertain, although decreased levels of plasma amino acids are associated with nitrogen imbalance and wasting of cancer cachexia.

While these several studies have documented changes in protein distribution in patients with AIDS, ARC, and HIV infection, the significance of these changes in regard to nutritional status is unclear. Many patients with AIDS have additional infectious diseases, and the stress of disease is known to produce changes in levels of circulating serum proteins (Fleck, 1988). 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, abnormal losses in pathogenic processes, and the state of body hydration (Heymsfield and Williams, 1988). In addition, Fleck (1988) 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. Fleck (1988) also suggested that it is inappropriate to use a decrease in any plasma protein as a measure of inadequate protein intake, especially when there is clinical evidence of the acute phase response to injury or infection.
Thus, because they are affected by nonnutritional factors decreased levels of circulating total protein, albumin, prealbumin, and RBP must be considered in the context of the overall condition of the patient.

Similarly, total lymphocyte counts may be an inappropriate measure of the nutritional status of patients with AIDS. While total lymphocyte count is useful in immune competent persons, individuals with HIV-infection and AIDS are already immunocompromised and their levels of circulating T cells are reduced; however, the extent of reduction is not known without knowledge of the pre-disease value (Rakower and Galvin, 1989).

c. Circulating lipids

Circulating lipid levels represent another dynamic energy pool that may be affected by diet or disease-related malnutrition. Changes in these compounds in HIV-infection have been assessed in a few studies with limited numbers of subjects. Hypertriglyceridemia has been the most commonly reported observation. Grunfeld et al. (1989) measured fasting serum lipid levels and body cell mass in 32 male patients with AIDS (all had opportunistic infections and or Kaposi's sarcoma), 8 asymptomatic subjects who were HIV antibody-positive, and 17 (9 heterosexual and 8 homosexual) HIV seronegative control subjects. Both the mean triacylglycerol concentration and the prevalence of hypertriglyceridemia (values >190 mg/dL) were significantly greater in patients with AIDS than in controls; values for asymptomatic HIV-positive subjects were intermediate. These authors concluded that increased levels of triacylglycerols seen in HIV infected patients may be unrelated to body wasting and speculated that these changes might be the consequence of the HIV virus itself rather than other opportunistic infectious organisms. Examination of lipoprotein classes in four patients with AIDS revealed that the excess triacylglycerols had accumulated in the very low density lipoprotein fraction, which is characteristic of bacterial and parasitic infections. Serum triglyceride levels were not correlated to body cell mass or the presence or absence of wasting in patients with AIDS or HIV infection. Finally, serum cholesterol levels did not differ among the three groups.

In contrast, Zumvalt and Schmidt (1989) reported that the serum cholesterol levels of 20 men with ARC and 20 men with AIDS were lower than the levels of 20 healthy controls. Whether these results reflect the general state of debilitation or are related directly to HIV infection remains to be established.

Bégin et al. (1989a,b) measured plasma lipids in 11 patients with "fully developed" AIDS and in 49 apparently healthy controls. No other patient or control group description was given. Total lipid levels were approximately 75 percent of normal in the patients with AIDS. Plasma concentrations of linoleic acid (18:2n–6), stearic acid (18:0), oleic acid (18:1n–9), and especially of eicosapentaenoic (20:5n–3), docosapentanoic (22:5n–3), and docosahexaenoic (22:6n–3) acids were significantly lower than normal; concentrations of the two n–6 C22 fatty acids were elevated significantly. Similar results were obtained for measures within the phospholipid fraction. Total lipid levels were below normal, and reductions were seen in most of the fatty acids in this fraction, with the most striking reductions in the C20 and C22 polyunsaturated fatty acids (omega–3 fatty acids). Contradictory results were reported by Chang et al. (1990) who found no significant differences in plasma fatty acid composition between a group of asymptomatic HIV-positive homosexual men (n=20) and a group of HIV-negative homosexual controls (n=7).

Andes et al. (1989a) observed a decline in serum cholesterol level that preceded seroconversion in a group of 14 patients with hemophilia who had used nontreated coagulation factor concentrates. In a group of 10 homosexual HIV-positive men and 4 seronegative male controls, Shoemaker et al. (1987) found significantly higher cholesterol levels in mixed leukocyte membrane in patients in Walter Reed stages 5 to 6 than in patients in stages 0 to 4. Because no differences in serum
cholesterol (or cholesterol intake) were seen between groups, these investigators suggested that increased cellular cholesterol was associated with the HIV virus rather than with dietary changes or nutritionally related metabolic changes.

Changes in bound and free fatty acid profiles and circulating concentrations could be significant because such changes suggest alterations in prostaglandin metabolism and possibly modifications of cell membrane composition and function. The studies of lipid metabolism in HIV infection have not been nutritional in the sense that none of them have assessed changes in intake or metabolism consequent to PEM. Consequently, at the present state of knowledge, changes in lipid profiles and concentrations are of limited relevance to the question of malnutrition in HIV infection.

3. **Summary**

Most studies report data that are indicative of relative changes in circulating metabolic energy pools. It is difficult to draw conclusions about the relationship between nutrition and HIV infection, ARC and or AIDS without adequate documentation of dietary intake patterns, medication use, or current status of infection. Many of the documented changes in body composition, circulating proteins and lipids are characteristic of cachexia and acute phase response. Several of the studies noted differences between AIDS, ARC, and HIV+ asymptomatic patients based on levels of circulating proteins and or lipids. It is conceivable that the reasons for these differences are related to clinical status, i.e., concurrent infections, rather than PEM. Without documentation of infection status, nutrition history and concurrent diet, the diagnosis of PEM caused by nutrient insufficiency is premature. The question of whether PEM is an inevitable concomitant of the HIV infection requires continued investigation.

B. **EVIDENCE FOR DEFICIENCIES OF INDIVIDUAL NUTRIENTS IN HIV INFECTION**

Studies that have assessed individual nutrient status in HIV infected patients are summarized in Table 9.

1. **Vitamins**

Body stores and circulating levels of several vitamins are recognized as possible indicators of nutritional status. Several investigators have assessed vitamin status of subjects at various stages of HIV infection. Folate and vitamin B12 are the two vitamins that have been studied most frequently because deviations from normal values were found.

Beach et al. (1988a) observed that plasma and erythrocyte folate levels were elevated significantly in a group of adults with HIV infection. In 100 homosexual males with no symptoms other than lymphadenopathy, 58 percent had plasma values and 75 percent had erythrocyte values above the values of 300 health professionals who served as the control group. Although actual intakes (combined dietary and supplemental sources) were not documented, the authors suggested that these high levels did not appear to be related to high intakes of supplemental folate.

Tilkian et al. (1988) noted that plasma folate levels, measured as 5-methyl tetrahydrofolate, may be elevated in vitamin B12 deficiency because vitamin B12 is required for the demethylation of 5-methyl tetrahydrofolate. However, in another population sample found that Beach et al. (1988b), although serum vitamin B12 levels were low in 25 percent of their subjects, B12 levels were not associated with folate levels. In contrast, Herbert et al. (1989a) found evidence of "negative folate
Table 9. Summary of Changes in Measures of Nutritional Status in HIV Infection, ARC, and AIDS.\(^1\)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Asymptomatic HIV Infection(^2)</th>
<th>ARC</th>
<th>AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Serum total protein ↑ (2)</td>
<td>Serum albumin ↓ (2)</td>
<td>Serum albumin ↓ (5); ↓↓ (1)</td>
</tr>
<tr>
<td></td>
<td>Serum albumin ↓ (1); normal (1)</td>
<td>Serum retinol-binding protein ↓ (1)</td>
<td>Serum retinol-binding protein ↓ (1)</td>
</tr>
<tr>
<td></td>
<td>Serum retinol-binding protein ↓ (1); Normal (1)</td>
<td>Total iron-binding capacity ↓ (1)</td>
<td>Serum total protein ↑ (1)</td>
</tr>
<tr>
<td></td>
<td>Normal (1)</td>
<td>Total iron-binding capacity ↓ (1)</td>
<td></td>
</tr>
<tr>
<td>Amino acids</td>
<td>Most serum amino acids ↓ (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipids</td>
<td>Serum triglycerides ↑ (1)</td>
<td>Serum cholesterol ↓ (1)</td>
<td>Serum triglycerides ↑↑ (1)</td>
</tr>
<tr>
<td></td>
<td>Plasma fatty acids normal (1)</td>
<td></td>
<td>Serum fatty acids ↓ (1)</td>
</tr>
<tr>
<td></td>
<td>Serum cholesterol ↓ before</td>
<td></td>
<td>Serum cholesterol normal (2); ↓ (1)</td>
</tr>
<tr>
<td></td>
<td>Seroconversion (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folate</td>
<td>Serum and erythrocyte folate ↑ (1)</td>
<td></td>
<td>Folate in CNS ↓ (1)</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Serum cobalamin ↓ (2)</td>
<td>Serum cobalamin ↓ (1)</td>
<td>Serum cobalamin ↓ (3)</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>Serum B6 ↓ (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>Serum zinc ↓ (4); normal (3)</td>
<td>Serum zinc ↓ (1)</td>
<td>Serum zinc ↓ (5); ↓↓ (3)</td>
</tr>
<tr>
<td></td>
<td>Erythrocyte zinc ↑ (1); normal (2)</td>
<td></td>
<td>Zinc-thymulin ↓ (1)</td>
</tr>
<tr>
<td></td>
<td>Zinc-thymulin ↓ (1)</td>
<td></td>
<td>Zinc taste test ↓ (1)</td>
</tr>
<tr>
<td>Selenium</td>
<td>Serum selenium ↓ (1)</td>
<td></td>
<td>Plasma or serum selenium ↓ (3)</td>
</tr>
<tr>
<td>Copper</td>
<td>Serum copper ↓ (1); normal (1)</td>
<td></td>
<td>Erythrocyte selenium ↓ (1)</td>
</tr>
<tr>
<td>Iron</td>
<td>Serum ferritin ↓ (1)</td>
<td></td>
<td>Cardiac selenium ↓ (1)</td>
</tr>
<tr>
<td></td>
<td>Serum iron ↓ (1)</td>
<td></td>
<td>Serum copper normal (1)</td>
</tr>
</tbody>
</table>

\(^{1}\) ↑ or ↓ = levels higher or lower than normal laboratory values or levels in uninfected control subjects; ↑↑ or ↓↓ = levels higher or lower than in controls and/or subjects with HIV infection; number in parentheses = the number of studies with similar findings.

\(^{2}\) Asymptomatic or lymphadenopathy only.
balance" in 100 consecutive (mostly drug abusing) male patients with AIDS. None had elevated serum or red blood cell folate levels. Serum folate levels suggestive of negative balance (<5 ng/mL) were present in 33 percent of patients; red blood cell folate levels suggestive of tissue folate depletion were found in 18 percent. Granulocyte lobe averages of >3.5 in 6 patients indicated impaired DNA synthesis. "Negative vitamin B12 balance" was also detected in 53 percent of these patients (Herbert et al., 1989b, 1990a).

Herbert (1990) suggested that drug abusers might have a high frequency of folate deficiency because their diet might include few folate–rich items (fruits, vegetables, and juices), while homosexual males could have a low frequency of folate deficiency, because their diet would be expected to include folate–rich items. Data on dietary intakes that would support this hypothesis were not presented. The term balance would indicate that there is a discrepancy between intake and output or availability of physiologically useful forms of these nutrients. It should also be noted that these studies were limited to hospitalized AIDS patients, the majority of whom were IVDU. There have been no reports on dietary intake, vitamin metabolism, or the pharmacokinetics of either folate or vitamin B12 in IVDU-seronegative or -seropositive patients without HIV-related disease or concurrent infections.

Low serum levels of vitamin B12 have also been reported by other investigators during HIV infection (Burkes et al., 1987; Harriman et al., 1987, 1989; Remacha, 1989). The observation of low serum cobalamin in a selected group of 10 patients with AIDS or ARC and hematological abnormalities led Burkes et al. (1987) to survey 40 randomly sampled homosexual men attending an AIDS clinic. Low serum cobalamin levels were observed in eight persons (20 percent) in this latter group. Serum cobalamin levels were correlated with serum folate and hemoglobin levels but not with mean corpuscular volume. Cobalamin absorption was tested in six individuals with low serum cobalamin levels; malabsorption was observed to be present in only one case. These six patients were also treated with cobalamin injections (dosage or time course not indicated). Burkes et al. (1987) reported no apparent clinical or hematological improvement.

In contrast, Harriman et al. (1987, 1989) observed impaired vitamin B12 absorption (abnormal Schilling's test) in 8 of 11 homosexual or bisexual men who had AIDS without a history of diarrhea, ten subjects had Kaposi's sarcoma, one had Kaposi's sarcoma plus pneumocystis carinii infection and 3 had low serum cobalamin levels. In a second study of 141 seropositive subjects (generically referred to as AIDS patients), these investigators (Harriman et al., 1989) found low serum vitamin B12 levels in 14 (5 patients had a history of GI infections, one patient had Kaposi's sarcoma of the duodenum and colon). Remacha (1989) also reported a high frequency of hypocobalaminemia in 56 hospitalized patients with AIDS; 9 patients were identified as having low levels and 9 as having borderline low levels. Herbert et al. (1990b) have reported a circulating antibody to intrinsic factor in 9 of 100 patients with AIDS. These investigators also noted a high frequency of elevated gastrin in this population sample, a condition associated with defective B12 absorption.

Beach et al. (1989b) and Mantero–Atienza, et al. (1989b) used available biochemical techniques for the assessment of several vitamins to examine the nutritional status of 50 asymptomatic HIV seropositive homosexual males. The results of these assessments were compared to a control group of HIV seronegative homosexual males and a set of undefined "normal" reference values. Although these authors had earlier reported weight loss and malnutrition in a similar group of HIV seropositive males (Mantero–Atienza et al., 1989a), they noted that in this sample none of the participants exhibited any clinical indications of malnutrition upon entrance into the study.

Vitamin B6 status was assessed by the stimulation of erythrocyte aspartate aminotransferase (ASAT), while dietary intake was measured by the use of a food frequency questionnaire. Thirty-five percent of the asymptomatic HIV+ subjects were reported to have an "overt" vitamin B6 deficiency when compared with a control group of male HIV(−) homosexuals. An additional 18 percent were described as marginally deficient despite adequate intakes of vitamin B6. Subjects
with indications of vitamin B6 deficiency had consistently lower CD4⁺ cell counts than did subjects with normal B6 status. The response of peripheral blood lymphocytes to phytohemagglutinin stimulation was related significantly and inversely to vitamin B6 status.

The interpretation of these observations is compromised by several factors related to the sensitivity and specificity of the assessment methodologies. Sauberlich et al. (1974) 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. (1988) attributed elevations of this enzyme in the serum of HIV infected patients to compromised 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 interpreted cautiously. Dietary intake was assessed by food frequency methods (Mantero-Atienza, 1990). The usefulness of food frequency questionnaires for the quantification of the intake of most nutrients including vitamin B6 has not been validated. The use of food frequency methods results in a loss of precision estimation of actual intake of foods and or specific nutrients when compared with quantitative daily intake methods (Anderson, 1986). Given these considerations, the possibility of a vitamin B6 deficiency in the HIV-infected population remains to be verified. Furthermore, since the potential for a toxicity from large doses of vitamin B6 exists (Schaumburg et al., 1983), caution should be taken before advocating the supplemental use of this nutrient in this population.

Beach et al. (1989b) also surveyed various indicators of other vitamins in the same study sample of 50 HIV-positive male homosexuals. Plasma vitamin B12 levels considered indicative of overt deficiency (<200 pg/mL) were found in 35 percent of the patients, and levels considered indicative of high risk (200-400 pg/mL) were found in 12 percent of the patients. In contrast, plasma and erythrocyte folate levels were elevated in 67 and 73 percent of the subjects, respectively. Indicators of thiamin, riboflavin, ascorbic acid, vitamin A, and tocopherol status were within the "normal" range.

The possibility of thiamin deficiency occurring in AIDS has been suggested by a case report of the discovery at autopsy of Wernicke's encephalopathy in an AIDS patient, without history of drug abuse or excessive alcohol consumption, who had developed cachexia, amnesia, and dementia (Soffer et al., 1989). Beach et al. (1989b) found no evidence of thiamin deficiency in their study of asymptomatic HIV infected patients. Similarly, the occurrence of riboflavin deficiency has been suggested. While there were no differences in the riboflavin status of HIV infected subjects (Beach et al., 1989b) the question is currently under investigation (Beach, 1990).

2. Minerals

Concentrations of several essential minerals in serum have been studied as possible indicators of nutritional status. Current information is summarized in Table 9.

A possible association of zinc deficiency with AIDS was suggested relatively early in the history of the epidemic (Beach and Laura, 1983; Weiner, 1984) and generated considerable interest (Shambaugh, 1988). Caselli and Bicocchi (1986) reported that serum zinc levels in patients with AIDS were substantially lower than those in normal subjects; patients with ARC or lymphadenopathy exhibited intermediate values. Similar findings were reported by Libanore et al. (1987) who found that serum levels were lower in patients than in controls, and that zinc levels decreased progressively with the worsening clinical and immunological condition represented in the progression from lymphadenopathy syndrome to AIDS. In addition, serum zinc levels in patients with ARC and AIDS were correlated with the CD4⁺ lymphocyte number.
Fabris et al. (1988) measured serum zinc levels and plasma concentrations of active (zinc-bound) thymulin and total zinc-saturable (active plus inactive) thymulin in 7 patients with AIDS, 12 subjects with lymphadenopathy syndrome, 10 healthy controls, and 9 drug users who were not infected with HIV. Compared to healthy controls, the serum zinc and active thymulin levels in patients with AIDS were significantly and markedly reduced; total zinc-saturable thymulin levels were similar in the 2 groups. Patients with lymphadenopathy syndrome had values for serum zinc and thymulin between those recorded for patients with AIDS and healthy controls. All three measures were similar in the drug-using subjects and the controls.

Serum zinc levels were also measured by Falutz et al. (1988) in subjects with HIV disease classified in CDC categories II, III, IV-C-1, IV-C-2, and IV-D, as well as in heterosexual and homosexual controls. They found that zinc levels were lower in patients with group IV HIV disease than in controls, except for subjects in group IV-C-2. Group IV-C-1 patients (who had opportunistic infections) had the lowest serum zinc values, but these were in the low normal range for the laboratory. Values for subjects in groups II and III did not differ from those in controls, and values for heterosexual controls and homosexual controls were similar to each other. Measures on additional subjects confirmed that serum zinc levels were significantly lower in patients with advanced HIV disease (groups IV-A, IV-D, and IV-C-1) than in HIV-negative controls (Falutz et al., 1989a), but also showed significantly lower zinc levels in group III patients than in consistently seronegative controls (Falutz et al., 1989b). Heise et al. (1989a) found severe hypozincemia in 2 of 31 patients with AIDS (groups IV-C-1 and IV-C-2); serum zinc levels were strongly correlated with albumin levels as might be expected. Whether hypozincemia is the result of hypoalbuminemia or the latter is causally related to the former is uncertain. Since both zinc and albumin levels are affected by infections and the acute phase response, the meaning of these results within a nutritional context is unclear.

In another study that compared serum zinc levels in 29 homosexual men (19 of whom were seropositive for HIV) and 16 heterosexual men (HIV status not reported), Bro et al. (1988) found that the variances for the homosexual and heterosexual groups differed significantly. However, there was no significant difference between zinc concentrations in homosexual men who were HIV-seropositive and those who were HIV-seronegative.

Isa et al. (1988) measured plasma and erythrocyte zinc levels in 54 drug addicts and 22 age-matched healthy controls. Among the drug-using subjects, 34 were seropositive for antibodies to HIV; 23 were asymptomatic and 11 were affected by lymphadenopathy syndrome/ARC. These investigators found no differences in plasma or erythrocyte zinc levels among drug addicts infected and uninfected with HIV and controls. There were also no differences between symptomatic and asymptomatic patients despite the immunological changes observed in the former group.

In a pilot study of male homosexuals with HIV infection classified according to T4:T8 cell ratio and the Walter Reed criteria, Millard et al. (1987a,b) and Shoemaker et al. (1988) measured several indicators related to zinc status. Serum zinc concentration was 0.93 to 0.96 μg/dL (14.2 to 14.7 μmol/L) in three subjects with T4:T8 cell ratios of 0.08 to 0.30 who were clinically well. In three patients with T4:T8 cell ratios of 0.04–0.10 who had current opportunistic infections, serum zinc levels ranged from 0.66 to 0.72 μg/dL (10.1 to 11.0 μmol/L) despite self-supplementation with zinc. The six remaining subjects had T4:T8 cell ratios of 0.60 to 1.20 and serum zinc levels in the range 0.69 to 0.99 μg/dL (10.6 to 15.1 μmol/L). Erythrocyte and leukocyte zinc were not correlated with serum zinc levels, T4:T8 cell ratios, absolute T4 cell number, or clinical condition.

Fordyce-Baum et al. (1989) examined trace mineral status in 50 HIV-positive male homosexuals with no manifestations other than lymphadenopathy. Plasma zinc levels indicative of overt deficiency were not seen, but marginal levels (0.70 to 0.85 μg/mL) were found in 23 percent of the subjects. They also reported that mean erythrocyte zinc levels were significantly higher in the subjects than in the seronegative homosexual controls, and 53 percent of the subjects had values greater than the upper limit of normal (>12.5 μg/mL).
Johnson et al. (1989) who performed zinc taste tests in 24 patients with AIDS and 10 HIV-negative controls. A significantly higher proportion of abnormal responses on the test were observed in patients than in controls; neither serum zinc nor diet differed in the two groups, although nutritional status was reported to be poorer in the patients. Chemotherapeutic status of study subjects was not reported. AZT as well as other commonly used therapeutic agents have been associated with distortions of taste (Ghiron et al., 1989a). Due to the common use of these drugs in this population, the sensitivity and specificity of the zinc taste test, as an index of zinc status, are compromised.

Assessing the significance of changes in zinc concentrations in serum or plasma is very difficult. The level of zinc in serum or plasma has been measured as a biochemical indicator of zinc status, but it lacks sensitivity and specificity because several factors such as circulating albumin levels and occurrence of infections influence the values (Pilch and Senti, 1984). Normal and deficient ranges are fairly well defined if fasting morning blood samples are collected and certain other conditions are taken into account. Few of the studies of HIV-infected subjects appear to have collected fasting morning blood samples. An expert group has recently recommended that "low" zinc levels be defined as serum values less than 60–70 (μg/dL) in otherwise healthy persons, depending on the time of sample collection and the fasting state of the subject (Pilch and Senti, 1984).

Some researchers have proposed that in certain high-risk groups impaired zinc status is a factor more closely related to life style that predisposes to the development of immune deficiency. Others hold that changes in zinc status occur secondary to HIV infection and that the causes are multifactorial. Lack of comparability among studies in the classification of patients in either disease stage or life-style risk group, contributes to the lack of clarity. No single indicator of zinc nutritional status is ideal; serum zinc is assessed most frequently, but is known to be affected by hypoalbuminemia, drugs that alter binding to plasma proteins, infection, as well as nutritional deficiency (Alpers et al., 1988). These factors and aspects of zinc metabolism suggest that the utility of serum zinc measurements as a measure of nutritional status in AIDS must be viewed with caution.

Selenium status has also been examined in HIV infection and in AIDS. Fordyce–Baum et al. (1989) found that when compared to controls, plasma selenium levels were significantly lower in a group of 50 HIV-positive homosexual men who were asymptomatic except for lymphadenopathy. Levels were considered deficient (<0.90 μg/mL) in 42 percent of the subjects and marginally deficient (0.90–1.20 μg/mL) in 22 percent of the subjects.

Dworkin et al. (1986) found that the red blood cell selenium level was 24 percent lower and the plasma selenium level was 59 percent lower in a group of 12 patients who met the CDC surveillance definition of AIDS than in a group of 27 healthy controls. Plasma albumin levels were also significantly reduced in the patients and were correlated with plasma selenium levels. Because selenium is transported on nonalbumin proteins, these results were judged to reflect depletion of selenium rather than an expression of protein malnutrition. Zasso et al. (1988) found that plasma selenium levels were below the normal range in 8 of 10 patients with AIDS and nonobstructive cardiomyopathy. Cardiac selenium levels were measured at autopsy in 8 patients who met the CDC criteria for AIDS and in 9 age-matched controls with histologically normal hearts; selenium levels were significantly lower in patients with AIDS than in controls (0.327±0.082 vs. 0.534±0.184 μg/g dry weight (Dworkin et al., 1989a).

Heise et al. (1989a) found that serum copper and magnesium levels were in the normal range in 31 patients with AIDS (groups IV–C–1 and IV–C–2). Mean plasma copper levels, however, were significantly lower in 50 HIV-positive male homosexuals with no symptoms other than lymphadenopathy than in controls; 55 percent were considered to have deficient levels (<0.85 μg/mL) and 22 percent were considered to have marginal levels (0.85 to 1.00 μg/mL) (Fordyce–Baum et al., 1989). This group also studied 61 HIV-positive patients and reported overt copper deficiency.
(<0.85 μg/mL) in 19.7 percent, as opposed to 0 percent in HIV-negative controls (Cabrejos et al., 1990). Ceruloplasmin levels were correlated with plasma copper levels but were within the normal range, even for subjects identified as having a copper deficiency.

Beck et al. (1989) measured serum concentrations of various trace minerals and the absolute number of T4 cells in 59 HIV-infected men. Levels of calcium, iron, and copper were significantly higher, and levels of phosphorus and selenium were significantly lower in infected subjects than in controls. Serum levels of potassium, magnesium, and zinc did not differ in the two groups. Trace element levels were not correlated with the Walter Reed stage. The absolute number of T4 lymphocytes was directly correlated with serum magnesium level.

Iron status indicators were assessed by Blumberg et al. (1984) who examined sera from homosexual men with AIDS (n=44) or persistent generalized lymphadenopathy (n=55) and four controls. In patients with AIDS, serum ferritin levels were significantly higher than those in patients with lymphadenopathy and were similar to those in the controls. Serum iron levels were lower in patients with AIDS than in patients with lymphadenopathy or controls and lower in patients with lymphadenopathy than in controls. Transferrin concentrations did not differ in the two groups of patients, but were lower than expected in patients with AIDS in view of the low iron levels. The authors suggested that rising levels of serum ferritin and falling levels of serum iron might herald progression from lymphadenopathy to AIDS; however, as noted by Kushner (1984) these changes occur in many infectious, inflammatory, and neoplastic states and are characteristic of the acute phase response. In a group of 12 homosexual men with AIDS, Kotler et al. (1984) found that the mean hemoglobin levels of 11.4±0.4 g/dL and iron-binding capacity of 213±14 μg/dL were lower than the values for a group of HIV-negative homosexual controls (14.5±0.4 g/dL and 293±21 μg/dL, respectively).

3. Summary

When viewed as a group, the studies of specific nutrient status 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. Future efforts designed to characterize the relationship between individual nutrients and HIV infection, should control those factors that might influence the status measures. In order to identify any predisposing factors that might influence their nutritional status, there is a need to further assess the relationship between the 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, the relevance of such deficits to the HIV-infected population remains to be determined.

C. MECHANISMS OF MALNUTRITION IN HIV INFECTION

Malnutrition leading to weight loss or nutrient deficiency may develop in HIV-infected patients through several mechanisms: reduced food intake, malabsorption of nutrients, and altered metabolism of nutrients. Because of the variable course of the disease in different patients, any one or more or none of these mechanisms may come into play.
1. Reduced food intake

In contrast to the numerous studies that report decrements 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. (1989a) who used 7-day records to compare dietary intake in 14 patients with AIDS and 14 patients with asymptomatic HIV infection, reported that patients with AIDS consumed an average of 266 kcal per day less than HIV-infected persons (2048±193 vs. 2314±117 kcal 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 percent) 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 6 women) 20–45 years old, Trufte et al. (1989) assessed dietary intake and weight changes at three stages: (A) prior to illness, (B) asymptomatic HIV positive, and (C) symptomatic HIV positive. Each patient was questioned retrospectively at stage C 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, (e.g., food frequency questionnaire, dietary recall measures). Similarly, there was no documentation of the subjects' relative condition at the time of the data collection (Stage C), in terms of GI symptomatology, neurological status or other clinical problems, that is, other infections or concurrent medications. Mean daily energy intake declined from 2500 kcal in stage A to 1440 kcal in stage B to 1200 kcal in stage C; mean protein intake declined from 80 to 46 to 43 g. Body weight declined 11 percent between stages A and B, followed by a further 5 percent weight loss between stages B and C.

In contrast, when Dworkin et al. (1989b) determined nutrient intakes based on 72-hour diet records in 17 clinically stable patients with AIDS, 9 patients with ARC, and 17 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, but 88 percent in each group were reportedly ingesting less than 50 percent of the Recommended Dietary Allowance (RDA) for at least one micronutrient. The validity of this finding is uncertain given the current limitations of available individual nutrient data bases (Hepburn, 1987). Based on data generated from three-day food records, Kotler et al. (1990) found that the energy, protein, carbohydrate, and fat intakes of five ambulatory, clinically stable, male patients with AIDS did not differ significantly from the intakes of homosexual and heterosexual controls.

Anorexia, a severe derangement in appetite regulation that results in profoundly reduced intake and that is caused by either manifestations of the disease process itself or chemotherapy, has been noted in some patients with HIV infection. Daily caloric intakes of less than 600 kcal, persisting for several months despite multiple attempts to supplement intake at home, have been reported in certain patients (Grunfeld, 1989).

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 the cytokines, tumor necrosis factor (or cachectin), interleukin-1, and the interferons can produce profound anorexia in animals (Grunfeld and Palladino, 1990). Use of the tumor necrosis factor and the interferons in humans as cancer chemotherapeutic agents was also 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 alpha have been detected in patients with AIDS (Abb et al., 1984; Lähdevirta et al., 1988).
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 are listed and their effects are described in Table 10.

Nausea and vomiting which also cause food avoidance, may result from 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-intracellular (Greene, 1988). Food intake may be reduced by dyspnea associated with respiratory complications (Budd, 1982) and by adrenal insufficiency (Greene, 1988).

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 (Kotler et al., 1990). A mediator for the latter process has not been identified, but its existence has been thought to contribute to the weight loss seen in other conditions of intestinal injury and disease. Such a process could provide an explanation for the clinical observation that food intake is often greatest in the morning in patients with AIDS and malabsorption (Kotler, 1990).

A variety of psychosocial factors in addition to neurological and psychological complications occur during HIV infection (Detmer and Lu, 1986–87) and interfere with food intake; depressed or anxious patients may experience a 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 (Brunetti et al., 1989; Price and Brew, 1990). In addition, opportunistic agents such as Toxoplasma gondii, Cytomegalovirus, and Cryptococcus spp. can produce a wide range of symptoms ranging from lassitude 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 (Price and Brew, 1990).

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 is 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 document these observations.

2. Drug–nutrient interactions

Some drugs commonly used in AIDS and their potential side effects that may influence food intake and have other nutritional consequences are listed in Table 11. Irrespective of the clinical rationale, the chronic use of drugs will affect many of the processes of nutrition. Patients with AIDS often receive 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, for example,
<table>
<thead>
<tr>
<th>Condition or Lesion</th>
<th>Location</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis</td>
<td>Oral or esophageal</td>
<td>Pain, dysphagia (difficulty swallowing), odynophagia (painful swallowing), dysguesia (impairment in sense of taste), nausea, esophagitis, decreased salivation</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Oral or esophageal</td>
<td>Dysphagia, odynophagia, esophagitis</td>
</tr>
<tr>
<td>Human papilloma virus</td>
<td>Oral</td>
<td>Oral warts, papillomas, condylomata and focal epithelia, hyperplasia</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Oral</td>
<td>Unilateral pain, vesicular eruption</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Oral or esophageal</td>
<td>Dysphagia, odynophagia (rare), esophagitis</td>
</tr>
<tr>
<td>Hairy leukoplakia</td>
<td>Oral</td>
<td>Usually asymptomatic</td>
</tr>
<tr>
<td>Cryptosporidiosis</td>
<td>Esophageal</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Premature progressive periodontitis</td>
<td>Oral</td>
<td>Irregular, generalized bone destruction</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>Oral</td>
<td>Halitosis, bleeding gums</td>
</tr>
<tr>
<td>Nonspecific esophageal ulcers</td>
<td>Esophageal</td>
<td>Odynophagia</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>Oral or esophageal</td>
<td>Dysphagia, obstruction</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>Oral or esophageal</td>
<td>Dysphagia</td>
</tr>
</tbody>
</table>

*Adapted from Chiron et al., 1989a.*
Table 11. Possible Side Effects and or Nutritional Interactions of some Drugs used in the Treatment of AIDS and AIDS–related Infections.*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Possible Side Effects or Nutritional Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azidothymidine</td>
<td>HIV infection, hairy leukoplakia, cytomegalovirus, Epstein–Barr virus</td>
<td>Severe megaloblastic anemia (non-nutritional), nausea, dysgesia, edema of tongue and lips, mouth ulcers, constipation, reduced serum Vitamin B12</td>
</tr>
<tr>
<td>Bromopirimine</td>
<td>RNA and DNA viruses, Kaposi's sarcoma</td>
<td>Nausea, vomiting, fatigue, diarrhea</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Herpes simplex</td>
<td>Diarrhea, nausea, vomiting, fatigue, sore throat, dysgesia, nephrotoxicity</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Cytomegalovirus, herpes viruses, retinitis</td>
<td>Nausea, anorexia</td>
</tr>
<tr>
<td>Dextran sulfate</td>
<td>HIV</td>
<td>Poor wound healing</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Cytomegalovirus, hepatitis B, herpes viruses, visna lentivirus</td>
<td>Renal dysfunction, anemia, nausea, headache, fatigue, neurologic impairment, calcium imbalance, hyperphosphatemia</td>
</tr>
<tr>
<td>Interferon</td>
<td>Cytomegalovirus, hepatitis B, respiratory infections, Kaposi's sarcoma</td>
<td>Flu–like symptoms, CNS disturbances, thrombocytopenia, leukopenia, depression, weakness</td>
</tr>
<tr>
<td>Suramin</td>
<td>Murine leukemia, sarcoma virus, avian myoblastosis virus</td>
<td>Gastrointestinal symptoms, dyspnea, reversible inhibition of hemoglobin synthesis</td>
</tr>
<tr>
<td>Rifabutin</td>
<td><em>Mycobacterium avium–intracellulare</em></td>
<td>Possible liver dysfunction, dysgesia, headache, anorexia, fatigue; absorption decreased when given with food</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td><em>Toxoplasma gondii</em></td>
<td>Nausea, vomiting, anorexia, diarrhea</td>
</tr>
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<table>
<thead>
<tr>
<th>Antiparasitic</th>
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<tbody>
<tr>
<td>Pentamidine</td>
<td><em>Pneumocystis carinii</em> pneumonia</td>
<td>Nephrotoxicity, nausea, vomiting, hypoglycemia, pancreatitis, folate deficiency, dysgesia, possible diabetes</td>
</tr>
<tr>
<td>Spiramycin</td>
<td>Cryptosporidiosis</td>
<td>Nausea, vomiting, diarrhea, acute colitis</td>
</tr>
</tbody>
</table>

* Adapted from Fields Neuman and Horn, 1988 and Ghiron et al., 1989a.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Possible Side Effects or Nutritional Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antifungal</strong></td>
<td></td>
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</tr>
<tr>
<td>Amphotericin B</td>
<td>Cryptococcal meningitis</td>
<td>Possible decreased potassium and magnesium levels, weight loss, anorexia, nausea, vomiting, diarrhea, severe nephrotoxicity</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Esophageal and oral candidiasis, cryptococcal meningitis</td>
<td>Possible nausea, vomiting, abdominal pain, decreased sodium; should not be given with antacids because it needs acidic environment for absorption.</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Candidiasis</td>
<td>Diarrhea, nausea, vomiting, fever, gastrointestinal distress</td>
</tr>
<tr>
<td><strong>Antibacterial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td><em>Pneumocystis carinii</em> pneumonia</td>
<td>Pancreatitis, anorexia, glucose intolerance, possible folate deficiency, glossitis, stomatitis</td>
</tr>
<tr>
<td>Trimetrexate</td>
<td><em>Pneumocystis carinii</em> pneumonia</td>
<td>Mucositis</td>
</tr>
<tr>
<td><strong>Immunomodulators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>HIV infection</td>
<td>Fever, anorexia, possible weight gain</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>HIV infection</td>
<td>Anorexia, vomiting, nausea</td>
</tr>
<tr>
<td>Sodium diethyl dithiocarbamate</td>
<td>HIV infection</td>
<td>Nausea, fever</td>
</tr>
<tr>
<td>Methionine enkaphalin</td>
<td>HIV infection</td>
<td>Nausea, abdominal cramps</td>
</tr>
<tr>
<td>Diethyldithiocarbamate</td>
<td>HIV infection</td>
<td>Nausea, fever, diarrhea</td>
</tr>
<tr>
<td><strong>Anticancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinblastine sulfate</td>
<td>Kaposi's sarcoma</td>
<td>Mucositis, anorexia, nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Kaposi's sarcoma</td>
<td>Anorexia, nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Bleomycin sulfate</td>
<td>Kaposi's sarcoma</td>
<td>Mouth ulcers, anorexia, weight loss, nausea, vomiting, stomatitis</td>
</tr>
</tbody>
</table>
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 (Stahl-Bayliss et al., 1986). Development of vitamin and mineral deficiencies may cause further decrease in appetite.

3. Malabsorption

Multifactorial nutrient malabsorption has been documented in several studies of patients with AIDS (Dworkin et al., 1985; Gillin et al., 1985; Kotler et al., 1984), but the consequences of nutrient malabsorption in AIDS are unsettled. Nutrient malabsorption results from small intestinal disease or injury, but during AIDS other gastrointestinal complications may occur involving the stomach (Lake-Bakaar et al., 1988), pancreas, liver, and colon (Kotler, 1987b; 1989a) 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 (Bartlett et al., 1988; Gelb and Miller, 1986; Haeney, 1987; Kotler, 1989a). 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 (3–10 watery, nonbloody 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 (Kapembwa et al., 1989). Another species of protozoa, Microsporidium, 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 (Smith et al., 1988); however, in some cases of AIDS-related enteropathy with diarrhea, no causative organism can be detected. HIV itself has been detected in the intestinal mucosa (Fox et al., 1989; Heise et al., 1989b; Nelson et al., 1988; Reka et al., 1989) and possibly causes direct injury to the small intestine (Ullrich et al., 1989).

Kotler et al. (1984) studied gastrointestinal structure and absorption in malnourished patients with AIDS in whom no bacterial or parasitic infections were detected. Diarrhea was seen in 7 of 12 patients. D-xylose absorption was lower in patients than in controls and lower in patients with diarrhea than in patients without diarrhea. Excess fecal fat was detected in 8 of 11 patients (including 3 without diarrhea) and in 1 of 11 control subjects. Patients with diarrhea had abnormal biopsy samples more frequently than patients without diarrhea and 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 intraepithelial lymphocytes. Similar lesions, also seen in graft versus host disease and inflammatory bowel disease, suggest immune-mediated intestinal damage (Kotler, 1987a).

Gillin et al. (1985) studied malabsorption and intestinal structure in patients with AIDS and without identifiable enteric pathogens or intestinal Kaposi’s sarcoma. In this series, 20 patients had diarrhea and weight loss and 10 did not. Malabsorption, as judged by abnormal D-xylose and 14C-glycerol–tripalmitin absorption tests, was common in the patients with diarrhea and weight loss. Duodenal biopsies in most of these patients showed nonspecific, 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. (1985) found impaired D-xylose absorption in 6 of 7 patients with intestinal infections and 2 of 7 patients without infection. Fecal fat was detected in 2 of 6 patients with infection and 2 of 8 patients without intestinal pathogens. Biopsies of the small bowel frequently showed pathogens and nonspecific inflammatory changes.

In four patients with AIDS and diarrhea associated with enteric infections (two with *Cryptosporidium*, one with *Microsporidia*, and one with *Isospora belli*), Modigliani et al. (1985) found evidence of impaired absorption of fat, D-xylose, and vitamin B12. Secretory diarrhea was present in three patients. An accumulation of fat in the enteric epithelia and lamina propria was noted; otherwise, only nonspecific changes in the histology of the small intestine were noted.

Miller et al. (1988) studied fat absorption and jejunal mucosal architecture in 20 homosexual men at various stages of clinical disease. Enteric pathogens were not detected in stool or jejunal biopsy. Twelve subjects had evidence of fat malabsorption based on results of the $^{14}$C-triolein breath test. Partial villus atrophy was the only histological abnormality detected. There was a significant correlation between the quantitative $^{14}$C-triolein breath test results and the villus atrophy index; both abnormal fat absorption and villus architecture were noted at all clinical stages of the disease. Kapembwa et al. (1990) also detected fat malabsorption (by $^{14}$C-triolein test) in 12 of 25 HIV-positive subjects. Mild pancreatic insufficiency detected in only 3 of these subjects, suggested that fat malabsorption in HIV infection is more commonly associated with problems of the small intestine.

Ulrich et al. (1989) studied the structure and function of the small intestine in 45 HIV-infected patients with gastrointestinal complaints. Enteric pathogens were detected in 21 patients. Seven of 12 patients tested showed evidence of lactose intolerance and 2 of 7 showed impaired absorption of D-xylose. Serum folic acid and vitamin B12 levels were abnormally low in 11 and 4, respectively, of 28 patients evaluated. Serum calcium levels were also low in 23 of 32 subjects tested. In 15 of 25 patients, no lactase activity was detected in the duodenal brush border; when measurable, lactase activity was lower than normal. Alkaline phosphatase activity was normal. In HIV-infected patients compared with controls, crypt depth was significantly greater, 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 maturational defect in enterocytes caused by HIV itself.

Other contributing causes of malabsorption and diarrhea in AIDS have been suggested. Diarrhea may develop in critically ill patients secondary to gastrointestinal mucosal edema associated with hypoalbuminemia (Brinson et al., 1987). 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 partially hydrolyzed protein, chemically defined diet which resulted in the restoration of the serum albumin levels (Brinson, 1985). As noted by Kotler et al. (1985), 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 biopsies and duodenal mucosal atrophy) contributes to nutrient malabsorption via diminution of the absorptive surface (Kotler, 1989b). 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 diminish further the absorption of nutrients such as lactose and triacylglycerols (Kotler, 1989b).
4. 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 reduction of basal metabolic rate or resting energy expenditure. Some clinically stable patients with AIDS have experienced this adaptive mechanism and thus conserved lean body mass even in the face of small losses in body weight arising from malabsorption (Kotler et al., 1987b; Kotler, 1990). During 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 (Cerra, 1987). The differences in resting energy expenditure (REE) and fuel utilization in starvation, hypermetabolism, and organ failure, as outlined by Cerra (1987), are illustrated below.

<table>
<thead>
<tr>
<th>Starvation</th>
<th>Hypermetabolism</th>
<th>Organ Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Adapted</td>
<td>Early</td>
</tr>
<tr>
<td>REE</td>
<td>↓</td>
<td>++</td>
</tr>
<tr>
<td>Glucose</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Fat</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Amino acids</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Hypermetabolism, with fever and rapid wasting, is common in AIDS. In patients with acute systemic illness or chronic infection, limited observations indicate that metabolic rates are 20 to 60 percent above predicted values (Kotler, 1990). Hommes et al. (1989) found that resting energy expenditure was higher in a group of 14 HIV-positive patients (eight with ARC and six with AIDS) who were slowly losing weight but had no evidence of acute infection or malabsorption than it was in a healthy control group. This difference was not associated with higher levels of catecholamines or triiodothyronine. Energy balance was not assessed.

Stein et al. (1990) studied protein and glucose metabolism in nine asymptomatic AIDS patients (six homosexual and three IVDU, who were all receiving chemotherapy at the time of the study). In a comparison with 13 age- and sex-matched control subjects (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 reduced ratio of essential to nonessential amino acids, were metabolic adaptations related to malnutrition. However, Stein et al. (1990) concluded that while these changes were probably caused by insufficient intake, any suggestions about the causes of the decreased intake, such as anorexia from cachexia, would be premature (Stein, 1990).

Alterations in lipid metabolism, such as fasting hyperlipidemia are also seen in various infections (Beisal, 1988). Fasting hypertriglyceridemia was observed in a cross section of HIV-seropositive subjects and patients with AIDS (Grunfeld et al., 1989). However, a relationship between wasting and hypertriglyceridemia was not detected. The authors noted that serum lipids reflect 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 (Anonymous, 1989b).

Many aspects of metabolic regulation, including lipid metabolism, are modulated by cytokines such as tumor necrosis factors, interferons, and others. For example, tumor necrosis factor, interleukin-1, and the interferons α, β, and γ inhibit lipid catabolism by lipoprotein lipase in fat cells in vitro (Beutler and Cerami, 1985; Keay and Grossberg, 1980; Patton et al., 1986; Price et al., 1986). Tumor
necrosis factor alpha, tumor necrosis factor beta, interleukin-1, and interferon alpha stimulate hepatic lipogenesis in vivo (Feingold and Grunfeld, 1987; Feingold et al., 1989). The localization of HIV to macrophages (Gartner et al., 1986) and the changes in gene expression in HIV-infected macrophages (Folks et al., 1987) have suggested that abnormal release of various cytokines may occur in AIDS. Indeed, increased serum concentrations of interferon alpha have been observed in patients with AIDS (Abb et al., 1984; Buimovici-Klein et al., 1986; DeStefano et al., 1982; Eyster et al., 1983), as have elevated serum levels of tumor necrosis factor (Lähdevirta et al., 1988). In the latter study, no correlation between weight loss and tumor necrosis factor level was detected.

More recent evidence has indicated that tumor necrosis factor alone does not induce cachexia (Grunfeld and Palladino, 1990). Nonetheless, it can contribute to the "futile cycling" of free fatty acids and triacylglycerols by increasing total body lipolysis in vivo and by increasing hepatic lipid synthesis and production of very low-density lipoprotein. Thus, fatty acids are released from fat, returned to the liver where they are re-esterified into triacylglycerols and secreted in the form of very low-density lipoprotein to return to the fat cell for breakdown and restorage as triacylglycerol (Grunfeld et al., 1989). The hypothesized action of tumor necrosis factor (in synergy with other cytokines) of stimulating overproduction of lipid by the liver and subsequent storage in adipose tissue could explain how fat mass is sustained throughout a period of weight loss during AIDS (Anonymous, 1990; Grunfeld, 1989). 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 nutrition support alone. In cancer cachexia, parenteral nutrition support generally has not maintained lean body mass, improved response to therapy, or increased survival (Kern and Norton, 1988). These authors have suggested that effective treatment for the metabolic derangements seen in cancer cachexia will require manipulation of intermediary metabolism as well as feeding. The same will likely prove be true for the metabolic changes of cachexia in AIDS.

5. Summary

There is little doubt that patients with HIV infection will be increasingly compromised nutritionally as the disease progresses. The role that the HIV virus plays in the nutritional problems seen in this population is less clear. In any individual, attention must be paid to the assessment of factors that might compromise any or all of the processes of nutrition from ingestion through utilization. Inconsistencies in study design and a lack of replicable results, make difficult the ability to draw conclusions about the impact of HIV infection on nutrient status except to say that the nutritional problems facing any patient with HIV infection should be given high priority as part of an aggressive clinical management strategy. The following sections will describe the potential impact of malnutrition on the health and outcomes of patients with HIV infection.
IV. EFFECTS OF NUTRITIONAL STATE ON HIV INFECTION

Nutrition may impact on the course of HIV infection in several ways. 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 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 (1977) concluded that malnutrition has an impact on 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 were shown 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, one must be cognizant of the interaction between nutrition and these functions. 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 or it 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 AIDS and the progression of HIV infection has not been studied extensively. However, the probability that malnutrition contributes to immune dysfunction, morbidity or debilitation, and mortality is high. 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 such interactions exist in nutritionally compromised individuals, and that this topic deserves additional attention. The following paragraphs contain a discussion of the available literature on the role of nutrition in immunity and clinical outcomes in patients with HIV infection. This chapter includes a review of those studies that have attempted nutritional interventions and concludes with a discussion of the role of food safety.

A. ALTERED IMMUNE SYSTEM FUNCTION

Relatively soon after the recognition of the disease, some striking similarities in immune system dysfunction in patients with AIDS and those with protein-energy malnutrition were noted (Table 12) (Gray, 1983; Jain and Chandra, 1984). Gray (1983) observed that patients with AIDS and children with protein-energy malnutrition both experience multiple opportunistic infections of viral, bacterial, parasitic, and mycotic origin. In addition, Kaposi's sarcoma and tumors similar to Burkitt's lymphoma, which are common in patients with AIDS, are also found in children and young adults in East Africa where protein-energy malnutrition commonly occurs. *P. carinii* pneumonia, which is very rare in immunocompetent persons, has been reported in malnourished African children (Hughes et al., 1974). Malnutrition has been proposed as a cofactor influencing both susceptibility to HIV infection and progression of HIV disease by impairing systemic and organ-specific (gastrointestinal and pulmonary) immune function (Beach et al., 1989c; Chlebowski, 1985; Colman and Grossman, 1987; Hebert and Barone, 1988; Jain and Chandra, 1984; Moseson et al., 1989; Pifer et al., 1987).

Deficiencies and excesses of specific nutrients in addition to general malnutrition affect the function of various components of the immune system and influence resistance to infection. These relationships have been reviewed (Beisel, 1988; Beisel et al., 1981; Chandra, 1983; Cunningham-Rundles, 1982; Good et al., 1976; Gottschlich, 1990; Myrvik, 1988) and are summarized in Table 13.
Table 12. Immunological Changes Associated with AIDS and Protein-energy Malnutrition.*

<table>
<thead>
<tr>
<th>Immunological Systems</th>
<th>AIDS</th>
<th>Protein-energy Malnutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cellular Immunity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T cells</td>
<td>Decreased (++)</td>
<td>Decreased (++)</td>
</tr>
<tr>
<td>Helper T cells</td>
<td>Decreased (++)</td>
<td>Decreased (++)</td>
</tr>
<tr>
<td>Helper:suppressor T-cell ratio</td>
<td>Inverted</td>
<td>Inverted</td>
</tr>
<tr>
<td>Delayed cutaneous hypersensitivity</td>
<td>Anergy (+)</td>
<td>Anergy (++)</td>
</tr>
<tr>
<td>Immature T cells</td>
<td>Increased (++)</td>
<td>Increased (++)</td>
</tr>
<tr>
<td>Lymphokine production</td>
<td>Decreased (+)</td>
<td>Decreased (+)</td>
</tr>
<tr>
<td>Cytotoxic T cells</td>
<td>Decreased (+)</td>
<td>?</td>
</tr>
<tr>
<td>Alloreactivity</td>
<td>Decreased</td>
<td>?</td>
</tr>
<tr>
<td>Helper T-cell activity</td>
<td>Decreased (++++)</td>
<td>Decreased (+)</td>
</tr>
<tr>
<td><strong>Humoral Immunity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum immunoglobulins</td>
<td>Increased (++)</td>
<td>Increased (++)</td>
</tr>
<tr>
<td>Immune complexes in serum</td>
<td>Present (++++)</td>
<td>Present</td>
</tr>
<tr>
<td>Primary antibody response</td>
<td>Diminished (++)</td>
<td>Diminished (+)</td>
</tr>
<tr>
<td>Circulating immunoglobulin secreting B cells</td>
<td>Increased (++++)</td>
<td>Increased (++)</td>
</tr>
<tr>
<td>Antibody affinity</td>
<td>Decreased (++)</td>
<td>Decreased (++)</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymic hormones</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Serum complement</td>
<td>Normal</td>
<td>Decreased (++)</td>
</tr>
<tr>
<td>Inhibitory factors in serum</td>
<td>Present (++)</td>
<td>Present (++)</td>
</tr>
</tbody>
</table>

* Adapted from Jain and Chandra, 1984.
+ Mild
++ Moderate
+++ Severe
? No information reported.
<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Functions Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Deficiency affects all components of the immune system including depressed cell-mediated immunity, B-cell function, macrophages, neutrophils, and complement.</td>
</tr>
<tr>
<td>Amino acids</td>
<td>Arginine deficiency compromises cellular immune mechanisms, particularly T-cell function. Supplemental arginine increases thymic size and number of T lymphocytes, suppresses tumor growth, and decreases incidence of infection. In general, isolated deficits or excesses, as well as imbalances, in essential amino acids lead to functional changes in humoral immunity; continued deficiencies of branched-chain or sulfur-containing amino acids produce depletion of cell from lymphoid tissues.</td>
</tr>
<tr>
<td>Lipids</td>
<td>Linoleic acid deficiency causes dermatitis and impaired wound healing; excess is immunosuppressive and stimulates suppressor T-cell activity. Prostaglandin E(_2) (a metabolite of linoleic acid) may depress cytostatic functions, lymphocyte mitogenesis, production of lymphokines, cytolysis, facilitate tumor growth, and prolong allograft survival. Omega-3 fatty acid deficiency may induce neurological deficits, dermatitis, and immunological changes; excess improves cell-mediated immune responses and opsonic indices, increases splenic weight, and inhibits production of immunosuppressive dienois prostaglandins.</td>
</tr>
<tr>
<td>Nucleotides</td>
<td>Deficiency suppresses cardiac allograft rejection in animals, delays the onset of experimental graft vs. host disease, impairs the onset of macrophage phagocytic function, suppresses cellular immune responses in vitro, and increases susceptibility to infection.</td>
</tr>
<tr>
<td>Zinc</td>
<td>Deficiency produces marked atrophy of the thymus; reduction in leukocytes (especially T-cell percentage) and antibody-mediated, cell-mediated, phagocytic, and delayed-type hypersensitivity responses; and increased susceptibility to infection. Excessive intake causes specific defects in the function of T lymphocytes and granulocytes.</td>
</tr>
<tr>
<td>Iron</td>
<td>Deficiency produces impaired bacterial killing ability of phagocytic cells, impaired lymphocyte response to mitogen stimulation, and decreased rosette-forming T cells. Excess iron can increase bacterial virulence, alter polymorphonuclear cell function, and increase host susceptibility to infection.</td>
</tr>
<tr>
<td>Selenium</td>
<td>Deficiency may impair antibody production and the bactericidal activity of neutrophils; slight excess may reduce susceptibility to infection and enhance antibody production and splenic plaque cell formation (immunostimulatory actions may be potentiated by vitamin E).</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Deficiency can cause thymic hyperplasia, decrease serum IgG levels, and reduce hemagglutinin responses.</td>
</tr>
<tr>
<td>Copper</td>
<td>Deficiency prevents normal response of reticuloendothelial system to infection.</td>
</tr>
</tbody>
</table>
Table 13. (Continued).

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Functions Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Deficiency may increase susceptibility to infection, cause atrophy of lymphoid tissues, decrease lymphocyte counts, suppress antibody production after immunization and splenic plaque-forming cell response to immunization, reduce in vitro lymphocyte response to mitogens, suppress delayed dermal hypersensitivity, reduce mobilization of peripheral macrophages, and increase the serum concentration of hemolytic complement. Excess may diminish susceptibility to infection, enhance antibody production after immunization and splenic plaque-forming cell response to immunization, increase in vitro lymphocyte response to mitogens, suppress delayed dermal hypersensitivity, and shorten allograft survival.</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>Deficiency depresses antibody production after immunization, splenic plaque-forming cell response to immunization, and delayed dermal hypersensitivity, and may cause atrophy of lymphoid tissues, decreased lymphocyte counts, and diminished inflammatory response.</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Deficiency may increase susceptibility to infection, reduce the percentage of T cells, prolong allograft survival, suppress the recall mechanism of delayed dermal hypersensitivity, impair the function of neutrophils and macrophages, reduce thymic humoral factors, and enhance complement concentration. Excess may reduce the duration of symptoms of the common cold, decrease the percentage of B cells, increase serum immunoglobulin concentration, and stimulate neutrophils and macrophages.</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Deficiency depresses immunological responses to antigens, lymphocytic proliferative responses, delayed dermal hypersensitivity, and general resistance. Slight excess enhances antibody responses to vaccines, delayed dermal hypersensitivity, clearance of particulate matter by the reticuloendothelial system, and general resistance. Large excesses inhibit many immune functions.</td>
</tr>
<tr>
<td>Folacin</td>
<td>Deficiency may depress lymphocyte counts, antibody response to immunization, splenic plaque-forming cell response to immunization, in vitro lymphocyte responses, and delayed dermal hypersensitivity.</td>
</tr>
<tr>
<td>Thiamin</td>
<td>Deficiency may depress splenic plaque-forming cell response to immunization.</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>Deficiency generally depresses primary response of antibody production after immunization.</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>Deficiency generally depresses antibody response to immunization and may depress splenic plaque-forming cell response to immunization.</td>
</tr>
<tr>
<td>Biotin</td>
<td>Deficiency may depress antibody response to immunization and splenic plaque-forming cell response to immunization.</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Deficiency may depress in vitro lymphocyte responses and neutrophil functions.</td>
</tr>
</tbody>
</table>

Adapted from Beisel, 1982, Beisel et al., 1981, and Gottschlich 1990.
Single nutrient deficiencies are relatively rare, and clinical studies of nutritionally impaired immune function usually involve multiple deficiencies. Therefore, most of the information about effects of single nutrients on the immune system has been derived from animal studies; however, associations between a few specific nutrients and immune function in HIV infection and AIDS have been documented.

Javier et al. (1990) assessed the status of antioxidant nutrients (vitamins A, E, and C and selenium) and measures of immune function in 70 HIV-positive homosexual men who had no symptoms or signs other than lymphadenopathy. Neither intake nor any other measure of nutritional status was reported. Serum vitamin A correlated significantly with total natural killer cell count and with levels of circulating IgG. Correlations between vitamin E status and immune function measures were not detected. Serum vitamin C and selenium were both correlated with IgM levels. These authors suggested a relationship between antioxidant nutrients and both humoral immunity and natural killer cytotoxicity. Whether these associations have any functional significance or are maintained throughout the course of HIV disease requires further study.

In a comparison of 10 AIDS (6 men, 4 women), 25 ARC (17 men, 8 women), 39 HIV+ with lymphadenopathy (32 men, 7 women) and 40 controls (male:female ratio unknown), Libanore et al. (1987) reported that serum zinc levels were significantly and positively correlated with the level of CD4+ helper cells; however, neither risk group status, nor chemotherapy usage was reported. No separate analysis by sex or multivariate analysis of variance was performed. Interpretation of these results is difficult because the uncontrolled factors of sex, risk group, and chemotherapy can be expected to impact on zinc status.

Falutz et al. (1989a) found that serum zinc levels correlated significantly to the proliferative response of isolated mononuclear cells to phytohemagglutinin in patients with advanced HIV disease (CD₄ stages IV-A, IV-D, and IV-C-1). Proliferative response, however, was not correlated to a CD4+ cell number or to serum albumin. In vitro stimulation of the proliferative response of isolated mononuclear cells to phytohemagglutinin by exogenous zinc was much greater for cells from HIV-positive patients with low serum zinc than for cells from HIV-negative controls (Falutz et al., 1989c). Harper et al. (1989) found that zinc-induced in vitro proliferation of mononuclear cells from 30 HIV-infected persons was inversely related to the Walter Reed stage of the disease.

As discussed in Chapter III, Mantero-Atienza et al. (1989b) found that subjects with evidence of a B6 deficiency had consistently lower CD4+ cell counts than did subjects with normal B6 status. The response to phytohemagglutinin stimulation by peripheral blood lymphocytes was significantly and inversely related to vitamin B6 status. There is precedence for a role of vitamin B6 in immune function. Ha et al. (1984) reported depressed numbers of murine T cells in vitamin B6 deficiency. Consequently, while the results reported by Mantero-Atienza et al. (1989b) are highly suggestive, they should be replicated by the use of appropriate vitamin B6 assessment methodologies.

Scevola et al. (1989) reported a relationship between the incidence of nutritional deficits (based on anthropometric measures of nutritional status such as body composition and body mass index) and the occurrence of opportunistic infections in patients with AIDS; they suggested that nutritional status was an important determinant of infection. Dietary intake, duration of illness, type or history of infection, sex, or risk-group status were not reported.

While the effects of nutritional status on immune function during the course of HIV infection are not well characterized, experience with other chronic diseases suggests that optimal nutritional status should be maintained in order to avoid unnecessary insults to the immune system that may either contribute to susceptibility to infection or exacerbate a preexisting problem.
B. INCREASED MORBIDITY AND MORTALITY

Malnutrition during the course of HIV infection may influence morbidity and mortality in a variety of ways. These include altered organ function, impaired tolerance to treatment, greater duration of hospitalization, decreased quality of life and mortality.

1. Altered organ function

One of the most potentially detrimental consequences of malnutrition is muscle wasting. Atrophy of the heart and respiratory muscles may result in decreases in cardiac and respiratory functions, respectively. Other organs may also be affected. Starvation may impair digestion secondary to inadequate pancreatic enzyme production (Bentler and Stanish, 1987). It has been suggested that nutritional deficiencies contribute to the cortical degeneration seen in pediatric patients with AIDS (Belman et al., 1985).

2. Impaired tolerance to treatment

Malnutrition compromises the integrity of the GI tract, thereby affecting drug absorption. In addition, the metabolism and biotransformations required for the activation and elimination of most drugs are dependent on adequate amounts of available macronutrients (e.g., protein, fat and carbohydrate) and micronutrients such as vitamins and minerals (Becking, 1976; Bidlack and Smith, 1984). Nutritional deficiencies can interfere with the delivery and metabolism of drugs (Campbell, 1977). Malnutrition associated with HIV-related disease may alter the pharmacokinetic and pharmacodynamic responses to the drug therapies used to decrease viral replication, boost immune response, and treat opportunistic infections (Janson and Teasly, 1988). The loss of body cell mass, increase in extracellular body water, and other changes in body composition that have been observed in patients with AIDS (Kotler et al., 1985) can lead to changes in the volume of distribution of drugs, depending on their physical and chemical properties and ability to bind to macromolecules. The risk of susceptibility to drug toxicity may also be increased by malnutrition (Hayes and Borzelleca, 1985).

Bygbjerg et al. (1988) found that supplemental folic acid, but not folinic acid, was effective in ameliorating the significant decline in leukocytes, neutrophiles, and hemoglobin level commonly seen during administration of the drug co-trimoxazole for P. carinii pneumonia. In vitro evidence also suggests that folate or vitamin B12 deficiency may potentiate the inhibition of DNA synthesis in bone marrow by AZT (Herzlich et al., 1988, 1990). The authors indicated that further study would be required to determine whether supplemental folate or vitamin B12 can partially overcome the hematologic toxicity of AZT and whether the benefits of such therapy may exceed the risks. However, McCutchan et al. (1989) and Navarette et al. (1989) found that supplemental vitamin B12 (given intramuscularly) was not helpful in preventing hematological toxicity induced by AZT.

3. Greater dependency and duration of hospital stay

Malnutrition is a frequent concomitant of prolonged hospitalization (McLaren, 1988). Nosocomial or hospital-derived infections are also frequently encountered (Ross, 1990). The HIV-infected individual is at particular risk for both of these problems. Little quantitative evidence on the relationship of nutritional status to patient dependency and duration of hospital stay has been generated. Clearly, if malnutrition contributes to debilitation, it will also generate increased susceptibility to infection. As a consequence, the need for care and assistance in the activities of
daily life and possibly duration of hospitalization will be increased, further straining the (already heavy) financial burdens of the disease.

The potential benefits of aggressive nutrition intervention are supported by the study of Bodnar and Beaulaurier (1990) who reported a decrease on patient teaching time, a decrease in hospitalization stay and an increase in patients' quality of life with the use of an enteral formula in advanced AIDS patients. This approach was further supported by the work of Weaver et al. (1990) who reported that administration of 3000–4000 kcal and 150 grams of protein per day via total parenteral nutrition (TPN) and fat emulsions resulted in average weight gains of 13 percent and improvement in quality of life indicators in AIDS patients with severe bacterial diarrhea. These reports suggest that nutrition support, even in very ill patients, can improve function and decrease the length of hospital stays.

4. Decreased quality of life

Undernourished but clinically stable patients with AIDS have been found to be hypometabolic (Kotler et al., 1990). Hypometabolism may be manifest clinically as a decrease in activity and, thus, may be responsible for the apathy and listlessness described in some patients with AIDS (Gabuzda and Hirsch, 1987; Navia et al., 1986) and usually attributed to organic neurological complications.

In a study tracking the nutritional status of clinic outpatients with ARC or AIDS, Broderick and Nesset (1989) briefly noted "a positive correlation between nutritional status and quality of life parameters." The previously mentioned study of Weaver et al. (1990) noted that the response to aggressive nutrition intervention resulted in an improvement in several indicators of quality of life including, a more positive attitude, improved appetite, unassisted ambulation, and increased energy level.

5. Mortality

The most straightforward evidence relating nutritional status and outcome in HIV related disease has been studies of the magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS patients (Kotler et al., 1987b, 1989a). Data for 43 nutritional assessments on 32 patients were evaluated within 100 days of death from a wasting disease. The patients had a variety of disease complications including infections, tumors, and dementia and had not received sustained nutrition support. Total body potassium ($^{40}K$) was assessed as a measure of body cell mass; normalized determinations were plotted as a function of time before death and were analyzed by regression. A progressive depletion of body cell mass until death was seen; extrapolated and observed values for body cell mass at death were 54 percent of normal. A similar relationship with time of death was seen for normalized body weight. The extrapolated body weight at death (66 percent of ideal), indicated a relatively greater degree of depletion of body cell mass. At 100 days prior to death, the extrapolated body cell mass was 71 percent of normal while extrapolated body weight was 90 percent of normal. Body fat content was not related to time of death.

These results, which are similar to those found in several studies of starving populations, (Torun and Viteri, 1988) suggested that the timing of death from wasting in AIDS was related to depletion of body cell mass to a critical level, rather than to specific disease processes. In this regard, AIDS does not differ from other chronic debilitating diseases. As noted by Kotler (1989a), "The observation that death as a result of starvation and death as a result of AIDS may occur at an identical degree of body cell mass depletion highlights the paradox between the common notion of AIDS as an aggressive, overwhelming illness and its more frequent clinical course as a chronic, progressive, debilitating illness."
Chlebowski et al. (1989b) also concluded that nutritional status may be a major determinant of survival in AIDS. They evaluated the clinical course of 71 patients with AIDS and found that both body weight loss and serum albumin level were strongly associated with life-table analysis of survival. At baseline, 98 percent of the patients had experienced weight loss and 83 percent had hypoalbuminemia (<3.5 g/dL), together with a variety of gastrointestinal symptoms. Median survival was significantly different in patients with weight loss <10 percent and those with weight loss >20 percent at baseline (520 and 48 days, respectively) and in patients with serum albumin levels >3.5 g/dL and those with levels <2.5 g/dL (>960 days and 17 days, respectively). Based on initial albumin level and the rate of albumin decrease, a projected time for the development of a level <2.5 g/dL was calculated and was found to be similar to actual median survival time.

Malnutrition (assessed as low serum albumin) was found to be the most important determinant of mortality (Nwiloh et al., 1989) in a group of 80 patients with AIDS, ARC, and other disorders who underwent surgical drainage of infections in the pleural space or lung.

Clearly, nutritional state will impact on the quality of life of a given patient. Whether there is a unique relationship between nutritional factors and the course of HIV infection is unknown. In spite of this lack of evidence, there is no reason to treat HIV-infected patients any less aggressively than other seriously ill patients. In all probability, it is likely that nutritional adequacy can improve the patients' ability to withstand the rigors of the disease process and treatment. Consequently, nutritional rehabilitation must be given a high priority in the care of the HIV-infected patient.

C. NUTRITIONAL INTERVENTION TRIALS

In assessing the role of nutrition therapy for the reversal of malnutrition in AIDS, the importance of treating complications of the disease is an important consideration. For example, Kotler et al. (1987a) observed the effects of ganciclovir treatment on body composition in patients with cytomegalovirus infections. Total body potassium and body fat were measured in five patients who had not been treated and nine treated patients every four to six weeks when possible until death or the development of another complication. The untreated group lost total body potassium and body fat while the treated group gained total body potassium and body fat. Six of the nine treated patients were able to replete total body potassium on ad libitum oral intake. Based on the differences in the changes in body composition in the two study groups, ganciclovir treatment of cytomegalovirus infection was calculated to result in a net increase of about 600 kcal to daily energy conservation. The authors observed that the striking ability of patients with AIDS to replete mass spontaneously during ganciclovir therapy indicates that wasting in AIDS is more likely secondary to complications than to the underlying disease process.

1. Administration of specific nutrients or diets

There has been a limited number of therapeutic trials of specific nutrients in HIV-infected patients. The most likely reason for this lack is a dearth of supporting pilot data indicative of specific nutrient related problems. The following section is a review of the few available clinical trials.

Golden et al. (1989) treated five patients with Kaposi's sarcoma with a combination of "metabolically activated" essential fatty acids formulated to increase tissue levels of dihomo-α-linoleic acid relative to arachidonic acid. Regression was seen in early lesions, but not in advanced disease, after 2 to 6 months of treatment. Kahl et al. (1989) tested the effects of essential fatty acids in 18 patients with ARC in a 6 month, double-blind, placebo-controlled trial. Each patient's clinical condition was assessed by a physician using CDC criteria for ARC and ranked on a subjective scale ranging from significantly improved (+2) to significantly worse (~2). The average score for the treated group was
positive and significantly higher than that for the placebo group; similar effects of treatment were
found whether or not patients were taking AZT. Clinical improvement was not correlated with
helper or suppressor T-cell counts.

Burke et al. (1987) treated five patients who had AIDS and low serum cobalamin levels with
cobalamin injections. Hematological indices were not altered and clinical improvement was not
noted. In three adult patients with ARC, Mathé et al. (1986a,b) reported improvement in T4:T8
ratio after administration of zinc gluconate, 125 mg twice daily orally for three weeks. Quinones
et al. (1989) reported results of a preliminary study in which chronic diarrhea in five patients with
AIDS was resolved by feeding a gluten-free diet.

2. Enteral formulas

There is ample precedent for the use of enteral feeding paradigms for the amelioration of the
malnutrition associated with chronic disease (Koruda et al., 1987); however most studies of trials
with HIV-infected patients have been reported as abstracts. Ferraro et al. (1989a,b) presented
initial results of an open trial of enteral nutritional therapy in five patients with AIDS. The
patients were not described except that they had lost more than 10 percent of body weight, had
dietary intakes less than 80 percent of requirements, showed adequate xylose absorption, and did
not have any severe active complications, (i.e., infections, diarrhea, or other GI disturbances) that
might explain their decreased intake. After receiving a hydrolyzed protein solution via a
percutaneous endoscopic gastrostomy tube (presumably in addition to regular oral alimentation) for
two months, the patients showed significant increases in body weight, total body potassium, body fat
content, and intracellular water volume. No data were supplied as to the caloric, vitamin, or
mineral content of this regimen. This evidence of body mass repletion was not accompanied by
changes in total or CD4+ lymphocyte counts or changes in serum immunoglobulin concentrations.
No other outcomes reflecting changes in the quality of patients’ lives were reported. Kotler et al.
(1991) have reported the results of an open trial of a defined enteral formula fed via a gastrostomy
tube to severely malnourished (defined as weight loss >10 percent of ideal body weight) AIDS
patients. This study of 8 seriously ill patients (7 males and 1 female, risk group status unknown)
demonstrated an increase in total body potassium and body fat content. In addition to the body
composition changes, these authors noted improved mental status and the ability to discharge all
except one of the patients who finished the study.

The difficulties in selecting an appropriate enteral formula are illustrated in the case report
described by Mandau and Palac (1989). The patient had been admitted to the hospital with
aspiration pneumonia, dehydration, severe dysphagia, diplopia, back pain, and hoarseness as a result
of vocal cord paralysis. He had lost 6.3 kg in the preceding two months and had experienced
episodes of nausea and vomiting after outpatient chemotherapy for Burkitt's lymphoma, but stated
no history of diarrhea or malabsorption. Enteral nutrition via nasogastric feedings was instituted,
but three different formulas—a lactose-free, polymeric solution; an isotonic, lactose-free, polymeric
solution; and a monomeric solution—provoked diarrhea that could not be controlled with
medication and led to substantial weight loss during hospitalization. When a high-residue,
blenderized feeding formula was initiated, the diarrhea resolved, anti-diarrheal medications were
discontinued, and body weight stabilized. The patient was discharged on home enteral nutrition
support and maintained weight until he died of medical complications. The fermentable fiber and
complex carbohydrate content of the blended formula may have contributed to reducing
diarrheal output, but an apparently appropriate formula was identified only after a substantial
period of trial and error.

Preliminary results of a trial in HIV-positive adults (uncharacterized with respect to disease stage)
with chronic or intermittent diarrhea indicated that a low-fat, low-residue, defined formula diet
reduced the number of bowel movements 65 percent (from 2.6 to 0.9 per day) compared with the
patients' usual diets (King et al., 1989). The diet was well tolerated, but adjustment of diet strength was required. Five of seven patients maintained or increased body weight during the 10 days they were given the test diet. There were no consistent effects of diet on pain, vomiting, bloating, nausea, and appetite.

As described previously, a defined formula also was used successfully, via nasointestinal and oral routes, to restore nutritional status and improve the quality of life in a patient with P. carinii pneumonia (Weaver and Hickey, 1989).

The potential benefits of enteral feeding paradigms have been described for the treatment of malnutrition associated with surgery, trauma, gastrointestinal disease and cancer cachexia. Enteral feeding aided in the reestablishment of gastrointestinal function and integrity (Koruda et al. 1987). While several studies have supported its utility in critically ill patients, the effectiveness of enteral feeding in some populations has been questioned (Cerra et al., 1988; Koretz, 1986). Given the proposed benefits, enteral feeding would be appropriate in the case of HIV patients who are anorexic, cachetic, or experiencing idiopathic weight loss. More research is needed to establish the timing in terms of disease stage and clinical suitability of this treatment for the amelioration of malnutrition associated with HIV infection.

3. Parenteral nutrition

The decision to initiate parenteral nutrition in a patient with AIDS is problematical because of the danger of infection accompanying the use of catheters in these patients (Henry et al., 1989; Raviglione et al., 1989). Case histories and clinical studies have indicated variable results of parenteral nutrition support in AIDS, depending in part on the stage of the disease.

Culpepper-Morgan et al. (1988) measured body weight, total body potassium, and body fat longitudinally in nine malnourished patients with AIDS and a variety of clinical problems during total parenteral nutrition support (TPN). Eight of the nine patients showed an increase in body fat and six showed an increase in body weight, while only four of the nine showed an increase in total body potassium. Two patients showed marked increases (43 and 22 percent over initial values) in total body potassium on TPN, which were associated with significant functional improvement. No distinguishing characteristics identified the patients who responded favorably. The authors concluded that TPN alone was not sufficient to reverse malnutrition in patients with AIDS, but that it might be helpful in selected patients.

Kotler et al. (1989b) studied the effects of home TPN on body composition in 12 patients with AIDS. Two patterns of response were observed. In six patients, body weight, total body potassium, and body fat content were increased; the greatest effect was seen in two patients with severe small intestinal injury and in one patient unable to eat because of an esophageal ulcer. The remaining six patients, all of whom had serious opportunistic infections, gained weight and fat but not total body potassium. The authors concluded that home TPN could replete body mass in patients with problems of nutrient intake or absorption.

Various case reports also indicate that parenteral nutrition fails to restore normal nutritional status in patients with AIDS in the face of overwhelming infection (Anonymous, 1988a). However, parenteral nutrition maintains or improves status and or function when malabsorption or eating problems are the most prominent manifestations (Dolmado and Natividad, 1986; Janson and Teasley, 1988; Pomp et al., 1988; Udine, 1990).

Bodnar and Beaulaurier (1990) concluded that, for appropriate patients, a two-stage program of patient education in the hospital and a follow-up at home for administration of parenteral nutrition by a programmable pump could permit a decrease in length of hospital stay and an increase in the
quality of life. The ability of aggressive nutritional support to improve the quality of life in patients with cryptosporidial diarrhea and severe weight loss was reported by Weaver et al. (1990). The number of patients treated was not recorded, but the authors indicated that administration of 3000–4000 kcal and 150 g of protein per day via TPN and fat emulsions for approximately 14 days resulted in an average weight gain of 13 percent. Treated patients regained appetite, ambulated without assistance, had fewer stools, and reported subjective improvements in attitude and functioning.

Brolin et al. (1990) reviewed the results of parenteral or enteral nutrition support given during 32 admissions of 54 consecutive patients with AIDS hospitalized 75 times over a 4-year period. Decreased body weight or low serum albumin levels occurred in 79 percent of these patients. Retrospectively, the use of nutrition support was positively correlated with weight loss of 10 percent or more, body weight 90 percent or less of ideal, admission hemoglobin levels of 10 g/dL or less, and hospital stays of 21 days or more. Nutrition support was not correlated with survival and survival was significantly lower in patients who received parenteral versus enteral support. Survival was negatively correlated with length of hospital stay and with continuous daily fever for 6 days or more. These results suggested that nutrition support was generally given to the sickest patients with AIDS and led the authors to recommend early nutritional assessment in hospitalized patients with AIDS.

Data for four years (beginning in 1984), from the OASIS Registry of home parenteral nutrition outcomes, included studies of 56 HIV-positive patients (Howard, 1990). These cancer patients, as with patients, required frequent rehospitalization, chiefly for complications unrelated to parenteral nutrition. Most of them experienced little rehabilitation; 95 percent died within one year.

The research reported to date indicate the HIV-infected patients, especially those in the advanced stages of immunoincompetence, are at risk for malnutrition to a degree that requires intervention. The nature of that intervention has not been investigated adequately. There is some controversy within other clinical disciplines about the relative efficacy of enteral versus parenteral nutrition (Lo and Walker, 1989; Moore et al., 1989). Aside from nutrient repletion, the cited benefits of enteral as opposed to parenteral feeding relate to the reestablishment of gastrointestinal morphology and functional integrity, and the decreased chance of further infection (Koruda et al., 1987). An additional consideration is the cost; enteral nutrition is considerably cheaper (Bower et al., 1986). All of these factors indicate that enteral nutrition would be particularly beneficial to the nutritionally compromised HIV-infected or AIDS patient. The relative benefits of enteral versus parenteral nutrition need to be explored further in the HIV-infected population.

D. FOOD SAFETY

Intestinal diseases are responsible for a considerable amount of the morbidity and mortality associated with AIDS; food is a probable vector for some of the enteric infections seen in AIDS (Archer, 1989). Archer and Young (1988) have described the variety of food-borne pathogens which include various bacteria (Salmonella spp., Listeria monocytogenes, Yersinia spp., Campylobacter spp., Aeromonas spp., Vibrio spp., Bacillus cereus, Shigella spp., and other gram-negative bacteria), protozoa, and viruses. HIV-infected patients are at greater risk for infections from these organisms than are persons without compromised immune function. In a study in San Francisco, Celum et al. (1987) found that the average annual incidence of salmonellosis in men 15 to 60 years old with AIDS was 384 per 100,000 while the average annual incidence for men without AIDS of the same age was only 20 per 100,000. Salmonella bacteremia was more common in patients with AIDS (45 percent) than in those without the disease (9 percent). Less common serotypes of Salmonella, specifically S. dublin and S. newport, were more common in patients with AIDS. In describing a number of case reports of salmonellosis in patients with AIDS, Jacobs et al. (1985), Profeta et al. (1985), and Smith et al. (1985) noted that the infections were particularly severe in these patients and were frequently associated with bacteremia. Infections with Listeria monocytogenes and with Campylobacter jejuni
have also been reported in patients with AIDS (Mascola et al., 1988; Perlman et al., 1988). The potentially life-threatening nature of such enteric infections in AIDS has led to the recommendation that persons with HIV-infection be counseled on ways to avoid food-borne infections (Archer, 1989; Griffin and Tauxe, 1988).

E. SUMMARY

Clearly, the nutritional status of a given individual will profoundly impact on their ability to resist and withstand the infection and debilitation of the HIV infection. As a population, HIV patients are susceptible to the same ramifications of general or specific nutrient deficiencies as non-HIV infected populations. The incidence of specific nutrient deficiencies cannot be predicted based on current evidence. There is no doubt that such problems will occur in any chronically ill population and should be given appropriate attention in order to maintain the highest levels of therapeutic efficacy and quality of life.
V. AVAILABLE INFORMATION AND CURRENT NUTRITION PRACTICES IN THE HIV COMMUNITY

Nutrition education materials and evidence about current practices with respect to nutritional therapy in AIDS are described below.

A. NUTRITION INFORMATION AVAILABLE TO PATIENTS AND HEALTH CARE PROVIDERS

Patient education materials on nutrition in AIDS are available from hospitals (Alvari and Jurecki, 1988; Cleveland Clinic Foundation, 1988; Coghlin et al., 1988a,b; Lee and Bryan, 1988; Mkandawire, 1989; Smerko, 1989), state and local health departments (New York City Department of Health, 1987, 1989; San Diego County Department of Health Services, 1989; Wickwire, 1989), and private organizations (Carrot Top Nutrition Resources, 1988; Collins, 1988; Collins and Garcia, 1989; Holmes et al., 1988; Taber–Pike et al., 1987). The Task Force on Nutrition Support in AIDS (1989) organized by, Norwich Eaton Pharmaceuticals, established guidelines for patients and health care providers that recommended three primary goals: preservation of lean body mass, provision of adequate levels of all nutrients, and minimization of symptoms of malabsorption. These guidelines were published or publicized in various journals (AMS Committee on AIDS, 1989; Anonymous, 1989c,d,e,f; Task Force on Nutrition Support in AIDS, 1989) and have been used widely by health care providers as a patient information brochure. Videotapes on nutrition and food safety issues in AIDS are also available (Food and Drug Administration, 1989; Gordon, 1989).

Various recommendations from individual clinicians and researchers have appeared in nutrition, nursing, and other publications (Bentler and Stanish, 1987; Budd, 1982; Crocker, 1988; Ghiron et al., 1989a,b; Greene, 1988; Hickey and Weaver, 1988; Hickson and Knudson, 1988; Hopefl, 1988; Hyman and Kaufman, 1989; Keithley and Kohn, 1990; Kotler, 1989a; Maring Klug, 1986; Probart, 1989; Rakower and Galvin, 1989; Resler, 1988; Taber, 1989; Taber–Pike, 1988). Bibliographies on nutrition and AIDS have been compiled recently (Education Programs Associates, 1989; Horn, 1988, 1989; Horn et al., 1989a,b).

Workshops, conferences, and courses sponsored by scientific and clinical societies and other groups have dealt with various aspects of nutrition and AIDS (American Dietetic Association, 1989; American Society for Clinical Nutrition, 1989; Anonymous, 1989g; Task Force on Nutrition Support in AIDS, 1989; Brunson, 1990; The Cutting Edge, 1988; The Cutting Edge and Stanford AIDS Education Project, 1989; Janson and Thompson, 1990; Mueller, 1987). An information support system for health care professionals dealing with the nutritional needs of patients with HIV infection or AIDS is provided by the National AIDS Nutrition Network (Matheny et al., 1989); a similar network also functions in California (Horn et al., 1989b). The National AIDS Information Clearing House (P.O. Box 6003, Rockville, Maryland 20850, 1–800–458–5231) is another source of materials on nutrition and AIDS.

The sources of information noted above are a representative list of the range of educational resource material currently available. Most of the current information and advice concentrates on eating to maintain adequate nutritional status, dealing with special problems associated with AIDS, and indications for special enteral support or parenteral nutrition. Food safety considerations are also included in many of these materials. In addition to advice based on accepted nutrition principles, unconventional nutritional therapies have been also promoted for persons with HIV infection and AIDS or are known to affected persons through the lay literature. Some of these are described on the following pages.
B. NUTRITIONAL THERAPY IN HIV INFECTION AND AIDS: CURRENT PRACTICES

Although much sound information on nutrition education and therapy in AIDS is available to both health care providers and patients, the actual extent of use of these materials is not known. How well the advice contained in these materials is accepted, understood, and followed is also unclear. Supplementation with vitamin and mineral preparations is thought to be widespread in persons with HIV infection, but little documentation has been available.

1. Nutrition practices of persons with HIV infection

Lovejoy et al. (1988) surveyed self-care behaviors and information needs in a self-selected sample of 178 well-educated, seropositive, homosexual or bisexual men in San Francisco. There were no comparison groups of either heterosexual or homosexual HIV-seronegative males matched for age and socioeconomic status (SES). A large majority of those surveyed reported dietary changes; 92 percent of the subjects with AIDS and 94 percent of the seropositive subjects without AIDS reported eating "a well-balanced diet" more often in 1987 than in previous years. Multivitamins were consumed more often in 1987 than in previous years by 74 percent of those with AIDS and 87 percent of those with ARC or asymptomatic HIV infection. Subjects were most interested in information on nutritional practices that might support or strengthen their health and immune systems. Various nutritional practices were perceived as influencing health. Positive effects on health were ascribed to dietary supplements such as Chinese herbs, herbal teas, garlic, shiitake mushrooms, "wheat grass," and sulfur-rich foods; macrobiotic diets; massive doses of vitamin C (20–25 g/day); AL 721; vegetables, fruits, and high-fiber foods; and "lots of water." Subjects surveyed by Lovejoy et al. (1988) indicated that coffee, sugar, red meat, unwashed fruits and vegetables, and processed foods were regarded as unhealthy and were avoided.

The dietary practices of 25 clients at an inner city HIV clinic, 60 percent of whom were intravenous drug users, were surveyed (Forrester et al., 1989). There were no comparison groups of either HIV seronegative heterosexual or IVDU nor was the stage of the HIV infection documented. This mixed sample of HIV-infected patients used vitamins and nutrition supplements rather than dietary modification to improve nutritional status; 75 percent were using vitamins and 40 percent were using liquid nutritional supplements of undetermined composition. Of the 40 percent of clients who had lost >5 kg in the six months preceding the study, 90 percent were using vitamins. Only 12 percent reported having received nutrition information at the two clinic visits prior to enrollment in the study. The applicability of these data to the general HIV-infected population is limited because of the lack of comparison groups and insufficient documentation of cohort characteristics.

Beach et al. (1988c) surveyed 25 homosexual males in the Miami area who were HIV positive but asymptomatic except for lymphadenopathy. There was no comparison group of SES matched seronegative homosexual or heterosexual males. A majority (85 percent) reported that they had made "major dietary modifications" and 57 percent had begun to consume high doses of vitamin and mineral supplements. Subjects were consuming many times the recommended dietary intake for vitamins A, D, and E, as well as several of the water-soluble vitamins—thiamin, vitamin B12, and ascorbic acid; few subjects had knowledge of the doses they were taking, the recommended intake, or the possible toxic consequences. Evidence of toxicity, in the form of hypertriglyceridemia, was detected in 20 percent of subjects consuming the highest levels of vitamin A (Fardyce-Baum et al., 1988b).

In another report on a larger number of subjects from this population (n=75), Mantero-Atienza et al. (1989c) found that 90 percent had made dietary changes after diagnosis of HIV infection. Changes most often cited were decreased intakes of red meat (37 percent), alcohol (33 percent),
whole milk (31 percent), and butter (21 percent) and increased intakes of vegetables (33 percent), fruits (32 percent), whole wheat bread and whole grains (21 percent), and seafood (20 percent). An increase in the use of vitamin and mineral supplements was reported by 59 percent of the subjects; 87 percent felt that such supplements could favorably influence their immune function. Only 10 percent had knowledge of daily requirements for vitamins and half of those using supplements did not know the doses they were taking. The most common sources of nutrition information were friends (75 percent) and newspapers and magazines (48 percent). The subjects clearly viewed nutrition and diet as important in maintaining immune function but made dietary changes on the basis of an inadequate information base. As in the previous reports, there were no contrast groups, nor was the study cohort adequately characterized in terms of education or income.

Some patients may reject the advice to consume enough food to reach or maintain ideal body weight because of a desire to remain slim. Cochrane et al. (1990) observed such a "weight consciousness syndrome" in a number of homosexual men whom they have seen in their public health nutrition program for HIV-positive persons. However, Cope (1990) noted that many of his HIV-positive patients are highly motivated to use nutrition support to avoid "externalization" of the disease manifested in weight loss.

In order to create an effective nutrition support system in terms of educational resource material, research efforts should continue to characterize the relevant attitudes and beliefs in the HIV-infected population. Because of the diversity in this population, future studies must focus on specific sub-sets of the population rather than attempt to make generalizations about the whole HIV-infected population. Furthermore, these studies must control for those factors that will impact on nutritional practices such as education, income, sex, risk group, and age.

2. Nutrition support for persons with AIDS

Very few data are available, but anecdotal information suggests that nutrition support in AIDS is not considered a priority in many hospitals settings. Nutrition support is not a component of early aggressive treatment but may be attempted after patients exhibit significant weight loss. O'Sullivan et al. (1988), in a study of patients with AIDS treated in New York City hospitals, noted that although a large percentage of patients were considered underweight at admission, 66 percent received routine oral diets without supplementation. Only a slight increase in enteral and parenteral feeding was noted during the hospital stays even though weight loss during hospitalization averaged 16 percent of admission weight.

In a commissioned telephone survey of 150 physicians and dietitians in 10 metropolitan areas with a high incidence of AIDS, the Task Force on Nutrition Support in AIDS (1989) found that 80 percent of the hospitals did not have a nutritional management protocol for AIDS (Anonymous, 1988b). Although nutrition support was identified as an important issue by 93 percent of health care providers caring for patients with AIDS, only 44 percent of hospitalized patients received nutrition support. In addition, 33 percent of hospitalized patients received total parenteral nutrition rather than enteral nutrition despite the fact that 60 percent of the respondents indicated that infection was a concern with parenteral nutrition. Thus it appears that even though the value of nutrition support in AIDS is well accepted, nutritional assessments and interventions are not performed routinely.

3. Unproven nutritional therapies and unconventional diets

Because of the irreversible and inevitable course of AIDS, lack of a curative therapy, social stigma and discrimination associated with the disease, and desire of many patients to control their own
treatment, HIV–affected persons are particularly susceptible to the claims made by proponents of unproven therapies (Dwyer et al., 1988). Aside from the fact that many of the claims made by advocates of unproven therapies are misleading and may result in unrealistic expectations, the use of large supplemental doses of specific nutrients may interfere with or otherwise compromise effective treatment. For example, a clinical examination could reveal a peripheral neuropathy that might be attributed to some aspect of the HIV–disease process, however the patient may have been taking a megadose of vitamin B6. Such a practice could result in a toxicity presenting as an idiopathic peripheral neuropathy (Shaumberg, et al., 1983). Similarly, tests for occult blood loss in stool or urine samples can be compromised by the use of supplemental vitamin C (Levine, 1983).

In addition to these clinical considerations, any investigation of the biochemical or metabolic manifestations of HIV infection, should include documentation of nutrient supplement usage. The current knowledge concerning vitamin and mineral toxicity has been recently reviewed (Alhadeff, et al., 1984; National Research Council, 1989a,b). In a study of lipid metabolism, such results as elevations in triacylglycerol or lipoprotein fractions might be affected by the use of zinc supplements (Fosmire, 1990). Alvari and Jurecki (1988), Coghill et al. (1988a,b), Dwyer et al. (1988), Rakower and Galvin (1989) and Taber–Pike (1988b) have described and evaluated some of the common unproven nutritional therapies and unconventional diets used by patients with HIV–infection. These include:

- **Megadoses of vitamins A, E, C, and B12, selenium, and zinc.** Large doses of these nutrients have been recommended to restore cell-mediated immunity by increasing T–cell number and activity, but efficacy and outcomes of these interventions have not been established in controlled clinical trials. Further, toxicity can occur with chronic intakes of vitamin A in excess of 50,000 IU per day as well as acutely with a large single dose (Olson, 1988). Chronic intakes of zinc as little as 25 mg per day, have been associated with nausea, gastrointestinal distress and dysgeusia (Solomons, 1988). Fosmire (1990) reviewed other aspects of zinc toxicity including impaired immune function and elevations in blood lipid indices. Selenium is also toxic in high chronic doses, but the critical level of intake is uncertain (Levander, 1988).

Blakeslee et al. (1985) observed that the chemically induced in vitro expression of HIV virus genes in cultured cell lines was inhibited by retinoids, ascorbic acid, and tocopherol (vitamins A, C, and E respectively). Protocols have been proposed for testing high doses of vitamin A as therapy for AIDS based on its beneficial effects in mice affected by stress–induced immune suppression (Fryburg et al., 1984) and based on the enhanced survival caused by vitamin A supplementation during murine AIDS (Watson et al., 1988). Oral 'hairy' leukoplakia in patients with AIDS has been treated successfully with topical application of 0.1 percent vitamin A acid solution (Schöfer et al., 1987).

Cathcart (1984, 1985) has promoted the use of vitamin C in the treatment of AIDS in combination with usual treatments for secondary infections. He reported that patients taking massive doses ("titrated to bowel tolerance") of 50 to 200 grams of ascorbate per 24 hours experienced suppression of their disease and marked reduction in secondary infections, even though helper:suppressor cell ratios may remain low. It is not clear from his report how many patients were treated with this regime, how many benefited, how the severity of illness was assessed, or what symptoms were affected. Moreover, intakes levels such as those recommended by Cathcart (1984, 1985) may be associated with toxic side effects in certain individuals (Rivers, 1989).

The usefulness of zinc salts against HIV was proposed by Sergio (1988) based on their known antiviral capabilities. Uncontrolled trials of the administration of zinc gluconate to immunocompromised patients with either cancer or ARC suggest some degree of immunorestitution (Mathé et al., 1986a,b). T4 cell number increased slightly but not significantly; T8 number was increased in patients who initially had low levels, and the T4:T8 ratio was significantly increased.
• **β-carotene.** Large doses have been used as a chemopreventive agent against cancer in animal models; clinical trials sponsored by the National Cancer Institute are in progress. There is currently no evidence of toxicity of β-carotene even in very large doses. Watson et al. (1989) found an increase in the number of cells with natural killer (NK) markers and markers of activation after 3 months of treatment with 30 mg per day of β-carotene.

• "Dr. Berger's Immune Power Diet." In his popular book, Berger (1985) asserted that poor health is caused by an "immune hypersensitivity" to many foods such as cow's milk, wheat, corn, yeast, soy, sugar, and eggs. A 21-day elimination diet for foods believed to cause allergies, followed by a reintroduction phase, then a maintenance diet is recommended to prevent food sensitivities and "revitalize" the immune system. The efficacy of this regimen has not been tested systematically. The restricted diet (high in fruits and vegetables and low in fat and calcium) may produce undernutrition, and the suggestion that moldy food be consumed to test for allergy to molds may be dangerous to persons who are immunocompromised.

• **AL 721.** This compound, developed in Israel, is composed of "active lipids" (AL) mixed in a ratio of 70 percent neutral lipid, 20 percent phosphatidylcholine (lecithin) and 10 percent phosphatidylethanolamine (hence the 721 designation). Sarin et al. (1985) hypothesized that AL 721 can reduce or inhibit HIV infection of lymphocytes in vitro. It has extracted cholesterol from cellular membranes, and made it more difficult for a virus to attach to receptor sites by increasing membrane fluidity (Lyte and Shinitsky, 1985). Such membrane modification has been suggested as a therapeutic approach to AIDS (Yatvin, 1988). Preliminary studies in patients have suggested some beneficial effects (Antonian et al., 1987; Grieco et al., 1988; Skornick et al., 1987). AL 721 was approved by the FDA for clinical trials (Bennett, 1988). In an open-label dose-ranging trial of AL 721 in 40 patients with lymphadenopathy or ARC, Mildvan et al. (1989) found little toxicity, but no consistent trends in T-cell quantitation or HIV cultures. Increases in body weight and serum total, HDL, and LDL cholesterol levels were observed. Homemade AL 721 can be made or obtained (James, 1987a,b) but it is of unknown purity. Although the compound is relatively nontoxic, it can spoil easily if stored improperly.

• **Lecithin.** This phospholipid compound is reputed to be the active ingredient of AL 721. The rationale for its use is similar to that of AL 721, but the purported ability of this lipid to destroy HIV by "membrane fluidization" has not been demonstrated (James, 1989).

• **Butylated Hydroxytoluene (BHT).** BHT has inactivated lipid-coated viruses like HIV in vitro (Snipes et al., 1975). To date there have been no studies performed on the efficacy of BHT in inhibiting the growth of the HIV virus (James, 1989). Concerns about the safety of supplemental BHT have been expressed by Shlian and Goldstone (1986).

• "Maximum Immunity Diet." Weiner (1986) suggested megadoses of vitamin C to strengthen the immune system. Its efficacy has not been established; rebound scurvy has occurred upon cessation of megadosing.

• **Laetrile.** In combination with a strict vegan diet and vitamin supplements, laetrile is supposed to destroy a tumor enzyme (β-glucuronidase); however, its lack of efficacy has been demonstrated. The diet is low in energy and may supply inadequate amounts of calcium, iron, niacin, and vitamin B12 and excessive thiamin, vitamin C, vitamin A, and zinc (Dwyer et al., 1988).

• **Gerson Method.** This program restricts all foods other than oatmeal and uncanned fresh fruits and vegetables and advocates regular enemas, especially coffee enemas, to create an internal milieu hostile to malignant cells. Efficacy has not been demonstrated; the adequacy of the diet is uncertain (Dwyer et al., 1988).
- **Kelley Regime.** To overcome a putative pancreatic enzyme deficiency, meat, milk in all forms except yogurt, and peanuts are excluded from the diet, almonds are substituted for meat, and nutritional supplements including vitamins and minerals are recommended. Toxicity has not been reported, but deficiencies of protein and calcium, fluid and electrolyte losses, and vitamin A toxicity are possible (Dwyer et al., 1988).

- **Yeast–free Diet.** This diet (Crook, 1985), which excludes high–carbohydrate and yeast–containing foods, is supposed to prevent opportunistic yeast infections such as candidiasis. Its underlying theory has been characterized as speculative (American Academy of Allergy and Immunology, 1986). As is true for any restricted diet, undernutrition is possible.

- **Macrobiotic Diet.** The diet, based on oriental philosophy, is supposed to restore balance and harmony between yin and yang forces and thereby ameliorate disease (Muramoto, 1988). The diet is very low in fat and high in bulk: 50 percent by volume whole grain cereals, 20 to 30 percent vegetables, 10 to 15 percent cooked beans or seaweed, and 5 percent miso (fermented soy paste) or tamari broth soup. The diet has been known to promote protein–energy malnutrition and deficiency of calcium and several vitamins in children and adults.

- **Herbal Remedies.** Badgy (1987) indicated that herbs can regenerate the immune system, but there have been relatively few studies to investigate this assertion. Smith (1988) discussed the potential benefits of combined acupuncture and herbal therapy in patients with AIDS.

Garlic has been credited with unique antiviral, antiparasitic characteristics and has been used in Chinese medicine for the treatment of cryptococcal meningitis (Hunan Medical College, 1980). In addition, Abdullah et al. (1989) reported an uncontrolled preliminary trial of garlic as an immune modulator in 10 patients seropositive to HIV. The patients consumed 5 g daily of an aged garlic extract for 6 weeks, then consumed 10 g daily for an additional 6 weeks. Seven patients completed the regimen and showed increased natural killer cell activity and some improvement in the helper:suppressor cell ratio.

Glycyrrhizin, a compound found in licorice, has had an inhibiting effect on HIV–induced plaque formation in MT–4 cells (Ito et al., 1987). The results of a preliminary study of three patients with AIDS and hemophilia who received large intravenous doses of glycyrrhizin (400 to 1600 mg per day) on six occasions over more than a month suggested inhibition of viral replication in vivo without serious side effects (Hattori et al., 1989). In another study, Ikegami et al. (1989) gave glycyrrhizin (150 to 225 mg) in daily oral doses to 10 asymptomatic HIV–positive patients for 12–24 months. Over that period of time, disease progression did not occur in these patients. Long–term use of excessive amounts may result in a syndrome resembling aldosteronism, with high blood pressure and water retention.

- **Coenzyme Q.** Ubiquinone or coenzyme Q, a product of cellular respiration, is concentrated in cardiac muscle. Its efficacy as a treatment for cardiovascular disease has been reported by Langsjoen et al., 1985. Its effect as an immune system stimulant has been studied (Folkes et al., 1982). Anecdotal reports indicate subjective improvement, but its efficacy in AIDS and ARC has not been established (James, 1989).

### C. SUMMARY

Table 14 is a comprehensive listing of the types of alternative therapies and approaches being touted as treatments for HIV infection. While it is conceivable that there are nutrients and or other dietary substances that may ameliorate some of the symptoms associated with HIV infection, it is too early in our understanding of the disease process to make recommendations about supplementation. Because the potential nutritional problems in HIV–related disease vary from
<table>
<thead>
<tr>
<th>Examples</th>
<th>Description</th>
<th>Claimed Rationale</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunological Claims</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamins A, C, E, B12</td>
<td>Megadoses</td>
<td>Restore cell-mediated immunity by increasing T-cell number and activity</td>
<td>Toxicity associated with chronic vitamin A intakes over 50,000 IU per day</td>
</tr>
<tr>
<td>Minerals</td>
<td>Selenium</td>
<td></td>
<td>Toxicity associated with chronic elevated selenium intakes. Toxic amounts unknown</td>
</tr>
<tr>
<td>Zinc</td>
<td></td>
<td></td>
<td>Toxicity associated with chronic zinc intakes. Undesirable side effects reported at 25 mg per day</td>
</tr>
<tr>
<td>Diet</td>
<td>Dr. Berger's Immune Power Diet¹</td>
<td>21-day elimination diet for foods purporting to cause allergies, followed by a reintroduction phase then a maintenance diet with a 4-day cycle</td>
<td>? undernutrition</td>
</tr>
<tr>
<td>Maximum Immunity Diet²</td>
<td>Vitamin C megadoses</td>
<td>Strengthens the immune system</td>
<td>Toxicity in susceptible individuals. ? rebound scurvy upon cessation of megadoses</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Dietary supplements</td>
<td>Strengthen the immune system</td>
<td>? purity</td>
</tr>
<tr>
<td><strong>Inhibitors of Cancer Growth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laetrile</td>
<td>Strict vegan diet with vitamin supplements</td>
<td>Supposedly destroys a tumor enzyme (β-glucuronidase)</td>
<td>Possible deficiencies of calcium, iron, vitamins B2, B12, D, energy; toxicities of zinc, B1, C and vitamin A</td>
</tr>
<tr>
<td>Gerson Method</td>
<td>Restrict all foods other than uncanned fresh fruits, vegetables and oatmeal; use enemas, especially coffee enemas</td>
<td>Detoxifies and creates internal milieu hostile to malignant cells</td>
<td>?</td>
</tr>
</tbody>
</table>

Table 14. Unproven Nutritional Therapies for AIDS (Adapted from Dwyer et al., 1988).
Table 14. (Continued).

<table>
<thead>
<tr>
<th>Examples</th>
<th>Description</th>
<th>Claimed Rationale</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelley Regime</td>
<td>Nutrition supplements including vitamins, minerals, almonds to replace meat and pancreatic enzymes; diet is devoid of meat, milk in all forms (except yogurt), and peanuts</td>
<td>Overcomes putative pancreatic enzyme deficiency</td>
<td>Possible deficiencies of protein, calcium; fluid and electrolyte losses; megadoses of vitamin A and possible toxicity; no toxicities to date</td>
</tr>
<tr>
<td>β-Carotene</td>
<td>Megadosing</td>
<td>Chemopreventive in animals; clinical trials now in progress</td>
<td>No toxicities to date</td>
</tr>
</tbody>
</table>

**Antiviral, Anti-Infective and Homeostatic Claims**

<table>
<thead>
<tr>
<th>Homemade AL 721 (Antiviral)</th>
<th>Made from soy or egg yolk lecithin</th>
<th>Reduces or inhibit HIV replication</th>
<th>AL 721 is approved by FDA for clinical trials. Homemade AL 721 of unknown purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHT (butylated hydroxytoluene) (Antiviral)</td>
<td>Oral supplements</td>
<td>Kills HIV by attacking the &quot;coating&quot; on virus</td>
<td>?</td>
</tr>
<tr>
<td>Lecithin (Antiviral)</td>
<td>Oral supplements</td>
<td>Kills HIV by &quot;membrane fluidization&quot;</td>
<td>?</td>
</tr>
<tr>
<td>Yeast-free diet (Anti-infective)</td>
<td>Eliminate high carbohydrate and yeast-containing foods in diet</td>
<td>Prevents opportunistic yeast infections, such as candidiasis</td>
<td>? undernutrition</td>
</tr>
<tr>
<td>Macrobiotic diet (Homeostatic)</td>
<td>Diet includes: 50% by volume whole grain cereals; 20–30% vegetables; 10–15% cooked beans or seaweed; 5% miso (fermented soy paste) or tamari broth soup. NOTE: This diet is very low in fat and high in and bulk.</td>
<td>Restores balance and harmony between yin and yang forces and therefore ameliorate disease</td>
<td>Possible protein calorie malnutrition; inadequate intake of riboflavin, niacin, calcium in adults; inadequate intake of above, as well as pyridoxine, vitamins B12 and D in children</td>
</tr>
</tbody>
</table>

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patient to patient, dietary and nutritional interventions must by necessity be individualized. There are ample sources of reliable information available to health professionals and patients concerning nutritional approaches throughout the course of HIV infection. Efforts to continue the development of these resources should continue. Alternative therapies that show positive results in carefully controlled clinical trials also require further study.
VI. SPECIAL CONSIDERATIONS FOR PEDIATRIC PATIENTS WITH AIDS

The manifestations of HIV disease that influence the development of malnutrition in adults (anorexia, oral lesions, diarrhea and malabsorption, and chronic infections) also affect children (Maring Klug, 1986). Likewise, the synergism between the malnutrition associated with chronic disease and the immunological deficits caused by the HIV infection will further predispose patients to infection and malabsorption. The exact role that nutrition plays in the development of AIDS in HIV infected children is unknown nor has the nature of the impact of the HIV infection on nutritional status been characterized. To date there have been no peer reviewed studies comparing the impact of such factors as maternal risk group, disease stage, and nutritional status on the disease course in HIV-seropositive versus seronegative children.

Congenital AIDS generally occurs in children less than one year old and is characterized by weight loss, diminished stature, delays or loss of developmental milestones, hepatosplenomegaly, lymphadenopathy, persistent oral candidiasis, a longstanding history of infections, and a positive maternal history for HIV infection or risk factor (Grossman, 1990). Nutritional deficits, primarily reflected in weight loss or decelerated weight gain and poor growth, are common in children with AIDS.

It has been suggested that nutritional deficiencies contribute to the cerebro-cortical degeneration seen in pediatric patients with AIDS (Belman et al., 1985). In children, neurological complications may be manifested as developmental problems that affect feeding behavior. For example, children 3–4 years old may require feeding with a spoon or bottle feeding (Bentler and Stanish, 1987). The developmental delays or regressions may be related to lack of appropriate stimulation or the depressed response of a sick child, as well as to some degree of neurological dysfunction.

The term most commonly used to describe the growth and developmental deficits in HIV infected children is failure to thrive (FTT) syndrome. FTT has been described as a wasting without obvious underlying organic cause (Drotar, 1988) and has been reported in both apparently nourished (in terms of adequate caloric intake) HIV infected children who have been free of opportunistic infections and in children with AIDS (Wilkinson and Greenwald, 1988).

Adequate nutrition is a recognized prerequisite for normal growth and development. However, the study of the impact of only malnutrition on growth and development in humans is confounded by the factors comprising the sociocultural milieu of a given group of children. Factors such as socioeconomic status, maternal risk group status, and maternal and child interaction patterns all contribute to developmental outcome and are all factors in the FTT scenario (Drotar, 1988).

Another component that may be related to neurological function and cognitive and or behavioral outcomes is the critical period concept of development. Briefly stated, developmental psychologists contend that there are discrete windows of opportunity during which developmental milestones in cognition and behavior occur (Piaget, 1971). Read (1982) described the impact on brain growth parameters of prenatal and postnatal nutritional insults. Morphological or metabolic insults to the nervous system occurring during any of these time periods may result in neurophysiological and developmental problems (Thatcher et al., 1986). Future studies need to focus on the interaction between nutritional status and timing of the HIV infection and disease course on developmental and or neurological changes in perinatally infected infants and children infected at different stages of growth and development. These types of studies would help to determine the difference, if any, between FTT in infants and wasting, growth retardation and cognitive or behavioral problems in older children. In addition, any studies designed to describe changes in development consequent to HIV infection must control for age differences in the subject population as changes resulting from insults during infancy will be different than those occurring later in childhood.
As was the case with the cachexia versus PEM (starvation) issue in adults, the question of whether HIV-infected children are malnourished due to diminished intake or are developmentally stunted and or wasted as a result of a metabolic derangement needs to be addressed. Grossman (1990) noted that 75 to 80 percent of pediatric HIV infections are acquired perinatally. There have been no reports involving the systematic assessment of anthropometric measures of nutritional status in seropositive perinatally infected infants and or children. Moreover, there has been no attempt to compare nutritional indices in asymptomatic HIV-seropositive children to those seen in children with AIDS. Similarly, there have been no reports of studies that utilized control groups consisting of either normal infants or infants matched by maternal risk category for the study of nutrition in pediatric HIV infection.

There have been several reports about body composition and growth of children with hemophilia. Warrier et al. (1988) reported that in 66 children (1 to 18 years old) with hemophilia whose HIV status was known, either weight or height deficits or both occurred in 61.5 percent of the 26 children who were HIV positive. Eight (20 percent) of the 40 children who were HIV negative were either underweight or had height deficits. The same group of researchers (Kuvibidila et al., 1989; Warrier et al., 1989) performed additional evaluations of nutritional status in 42 male children (22 months to 18 years old) with hemophilia. None had symptoms of AIDS; however, 20 were HIV positive and 22 were HIV negative. A significantly higher percentage of HIV-positive children (40 percent) than HIV-negative children (4.5 percent) were below the fifth percentile of height for age; the percentages below the fifth percentile of weight for age did not differ in the two groups. While the wide age ranges across developmental periods and the lack of any dietary intake data preclude any generalizations about HIV infection, these data suggest a potential synergism between HIV status and hemophilia in children. The data also indicate the potential impact of the HIV virus per se on growth. Because of the metabolic requirements for growth in children, weight gain and maintenance and the adverse consequences of weight loss require further examination in regard to a possible role for nutrition intervention.

Much of the early evidence linking PEM to HIV infection is from reports comparing the immunological effects of malnutrition to AIDS in Africa and Haiti. In fact, whether the immune deficiency seen in children in Haiti and African countries was caused by AIDS or by malnutrition has been debated (Goudsmit, 1983; Lapointe et al., 1983; Lesbordes et al., 1986; Mellors and Barry, 1984; Pape et al., 1984; Schuerman et al., 1988). AIDS and malnutrition often occur together; Excler et al. (1987) found HIV infection in 45 percent of 40 malnourished children in a Burundi hospital.

There have been several attempts at generating metabolic evidence of malnutrition in infected children. As in the adult studies, the interpretation of these data must be tempered by the use of nonspecific markers (e.g., albumin and RBP) and a lack of corroborating dietary or other nutritional evidence. In a group of 42 children with hemophilia and without symptoms of AIDS, Kuvibidila et al. (1989) found significantly lower levels of plasma retinol-binding protein and prealbumin in HIV-positive subjects (n=20) than in HIV-negative subjects (n=22). These abnormal levels were judged to result from protein-energy malnutrition rather than inflammation, because plasma levels of C-reactive protein and α-1-acid-glycoprotein did not differ in the two groups.

Andes et al. (1989b) studied 13 patients with hemophilia who had used nontreated coagulation factor concentrates. They observed an 11 percent decline in serum albumin levels, a 28 percent decline in serum prealbumin levels, and a 7 percent increase in serum retinol-binding protein levels that preceded seroconversion.

Several studies have looked at changes in the levels of specific nutrients in HIV-infected children. Smith et al. (1987) found depressed levels of folate in the cerebrospinal fluid of two children with neurological disease due to congenital infection with HIV. Serum and erythrocyte folate levels were low or normal. Tong et al. (1986) presented a case report of a child with AIDS who was originally diagnosed as having acrodermatitis enteropathica. Kavanaugh-McHugh et al. (1989) obtained
echocardiograms and serum selenium levels for nine pediatric patients who were undergoing treatment with azidothymidine for symptomatic HIV disease. Five of nine patients had low selenium levels, all five had other evidence of malnutrition, and four of the five had evidence of cardiomyopathy. Two of the four patients with normal selenium levels also had evidence of cardiomyopathy.

A two-year-old child with HIV infection and low serum zinc levels was treated with IV zinc (2 mg/day for three weeks) (Caselli and Bicocchi, 1986); treatment was associated with increases in serum zinc level, T4:T8 cell ratio, and total lymphocyte number. However, in another pediatric patient with AIDS, cell mediated immunity was still found to be impaired after successful treatment of zinc deficiency (Tong et al., 1986).

Although limited, the available literature on pediatric AIDS indicates that malnutrition, particularly undernutrition of calories is a recurring problem (Grossman, 1990). Aside from the impact of the disease on the processes of nutrition and subsequent nutritional status, growth and development, is the impact of nutrition on the course of the HIV infection. Several reports of pediatric HIV-infected population indicate that the latency period for development of AIDS varies (Grossman, 1990; Wilkinson and Greenwald, 1988). Blanche et al. (1989) prospectively studied the development of AIDS in infants born to HIV seropositive mothers and found that 27 percent of these children developed signs of HIV infection or AIDS by 18 months postnatally. The majority of evidence indicates that intrauterine transmission is responsible for most pediatric cases of HIV infection (Grossman, 1990). Perinatal transmission has been estimated to occur in 25 to 50 percent of infants of HIV-infected mothers (Johnson, et al., 1989). Factors that may influence the onset of AIDS in HIV-infected children might include maternal nutritional status as well as postnatal feeding practices.

One issue that has received little attention is the role of breast-feeding both as a source of nutrition and as a potential source of HIV infection. The HIV virus has been isolated from the cell-free fraction of breast milk (Thiry et al., 1985) and several case reports document the development of AIDS in breast-fed infants whose mothers were thought to be infected by a postnatal blood transfusion (Lepage et al., 1987; Weinbreck et al., 1988; Ziegler et al., 1985). The risk of breast milk transmission is unknown, but is probably low compared to other known routes of infection. In view of the uncertainty, most investigators agree it is prudent to recommend that HIV-positive mothers should be discouraged from breast-feeding (Anonymous, 1988c). However, given the psychosocial impact of intimate maternal child interaction, breast-feeding may still be preferable, irrespective of the mother’s HIV status, if safe and effective use of alternatives is not possible (as may be the case in developing countries) (World Health Organization, 1987).

A. GENERAL CLINICAL RECOMMENDATIONS

Bentler and Stanish (1987) have recommended that nutritional assessments be performed routinely in pediatric patients with AIDS, so any problems can be identified and treated as they occur and nutritional deficits can be minimized. Assessment should include anthropometric measures, plasma protein evaluation, complete blood counts, and evaluations of appetite and intake. Eating ability should be determined and the social situation evaluated (Carrot Top Nutrition Resources, 1988). In many cases, the child’s home environment may be disordered; the parents may be intravenous drug users or the mother may be seropositive or have AIDS and may not be able to provide the necessary care.

Providing sufficient calories and protein to maintain linear growth and weight gain in HIV seropositive children with AIDS is sometimes difficult. Guidelines are available to estimate the range of caloric and protein requirements (Bentler and Stanish, 1987; Carrot Top Nutrition Resources, 1988; Wilkinson and Greenwald, 1988); for example, increasing protein intake 50 to 100
percent over the RDA has been recommended. However, needs are individual and should be monitored on an individual basis. Some suggestions to provide supplemental caloric and nutrient intake are listed below (Bentler and Stanish, 1987; Maring Klug, 1986).

- Use a calorically dense formula (24 to 27 kcal/oz.) for infants. Add glucose polymers or medium-chain triacylglycerol oil to formulas or reduce the amount of water added to powdered formulas to boost calories.
- Try food supplements that are high in calories and protein.
- Encourage children to eat nutrient–dense snacks such as raisins and peanuts.
- Add fats such as butter or mayonnaise to foods to boost calories.
- For the older, lactose-tolerant child, add skim milk powder to whole milk.
- Make adjustments in diet content, consistency, and temperature (as described above for adults) to overcome eating difficulties associated with disease complications and eating difficulties.

Lactose intolerance occurs frequently in children with AIDS, as a result of long-term antibiotic therapy and chronic gastrointestinal infections (Bentler and Stanish, 1987; Maring Klug, 1986). In such cases a lactose-free diet is indicated (Maring Klug, 1986), and the suggestions below may be helpful.

- For infants, lactose-free, soy-based infant formulas may be used instead of milk.
- Adding Lactaid® to milk products reduces the lactose content and permits improved digestion.
- Some children can tolerate low-lactose dairy foods such as yogurt.

Supplementation of vitamins and trace minerals in amounts one or two times the RDA may offset possible deficits and contribute to meeting increased requirements during hypermetabolic states (Bentler and Stanish, 1987). Attention should also be given to drug–nutrient interactions and other effects of drugs on nutritional status.

B. ENTERAL AND PARENTERAL NUTRITION

If oral intake is inadequate, tube feeding may be used to provide total or partial nutritional support in the presence of a functioning gastrointestinal tract (Bentler and Stanish, 1987). The potential benefits of aggressive intervention in infants with AIDS was described in several case reports documented by Fennoy and Leung (1990). A continuous drip using an enteral feeding pump may be preferable to bolus feedings which may not be tolerated or may exacerbate diarrhea. Nasogastric or nasoduodenal routes of feeding may be used as the gastrostomy tube site heals poorly in immunocompromised children. Wilkinson and Greenwald (1988) noted that the nasoduodenal route is preferred in the setting of a pediatric intensive care unit to reduce the risk of gastroesophageal reflux and pulmonary aspiration of stomach contents. These considerations are especially important for children with uncuffed endotracheal tubes or impaired neurological function and those treated with neuromuscular blocking agents.

Often caloric intake goals cannot be achieved secondary to fluid restrictions, malabsorption, or chronic or osmolar diarrhea (Wilkinson and Greenwald, 1988); if oral or enteral feedings are inadequate or contraindicated, parenteral nutrition support may be instituted. Severe esophageal candidiasis and chronic diarrhea are common indications for parenteral nutrition in children with AIDS (Berry, 1988). However, the potential nutritional benefits must be balanced against the
serious risk of catheter-associated infection (Shannon and Ammann, 1985). Wilkinson and Greenwald (1988) recommend the internal jugular and subclavian veins as sites for central venous access for the administration of total parenteral nutrition. To avoid catheter-related sepsis, catheters should be replaced every 4 to 5 days and the site should be changed every 8 to 10 days (Wilkinson and Greenwald, 1988). For extended periods of total parenteral nutrition, a surgically placed Silastic central venous nutrition catheter may be preferred (Wilkinson and Greenwald, 1988).

If possible, during total parenteral nutrition, tube feedings or oral alimentation should be encouraged to maintain sucking, chewing, and swallowing ability; to promote repair of the intestinal mucosa; and to prevent liver damage (Bentler and Stanish, 1987). Feeding therapy may also be helpful.

C. FOOD SAFETY

For infants being bottle fed, proper procedures for sanitary formula preparation must be followed. Infants should not be put to bed with a bottle of milk or juice, because these liquids can easily become contaminated by bacteria growth. Unpasteurized milk and milk products should be avoided as they may be sources of Salmonella spp. that can cause intestinal infections (Berry, 1988).

Children eating solid foods should not be fed directly from the jar to avoid possible bacterial contamination from the mouth, which can cause spoilage of leftover food. Food in opened jars should be refrigerated and used within 24 hours. Fruits and vegetables should be peeled or cooked, and meats should be well cooked. All utensils and dishes should be washed in a dishwasher or in hot sudsy water and air dried (Berry, 1988).

D. SUMMARY

The cause of malnutrition in pediatric HIV-seropositive and AIDS patients has not been characterized, although, as in adults, available evidence indicates a multifactorial pattern that includes anorexia, recurrent infections, gastrointestinal problems and neurological complications. Of additional concern in the pediatric population is the profound influence of the psychosocial context of the disease. Lack of appropriate nurturing, long-term and or chronic hospitalization may also contribute to developmental delays in cognition and behavior in these sick children. Efforts at identifying the prominent risk factors for malnutrition and the role of nutritional state in the development of AIDS in perinatally infected infants must continue in order to ensure the highest quality of life for the HIV-infected child.
VII. GENERAL CONCLUSIONS AND RECOMMENDATIONS

The following material includes general conclusions and recommendations that have been derived from a review of available scientific literature, information submitted to LSRO, and comments of individuals and organizations who reviewed the tentative report. Additional specific suggestions for research have been made in Chapters II through VI. Appendix A presents practical considerations for dietary management of HIV-infected persons and patients.

A. SUMMARY STATEMENTS ABOUT THE RELATIONSHIP BETWEEN NUTRITION AND HIV INFECTION

1. Impact of HIV infection on nutritional status

Available information indicates that the documented changes in nutritional status are multifactorial in origin and are related to organic and psychological manifestations of the HIV disease process. In terms of the relationship between the occurrence of HIV infection and its impact on nutritional status, the following conclusions can be drawn:

- If the HIV virus has a direct impact on gastrointestinal morphology and integrity as suggested by Kotler (1989b), then such changes could be expected to influence absorption and availability of macro- and micronutrients. The evidence for this scenario is suggestive but limited.

- If the HIV virus has a direct effect on neurological function as suggested by Price and Brew (1990), then the resulting AIDS Dementia Complex will affect nutrient intake because of behavioral, and possibly neuroendocrinological changes. To date no studies have addressed this possibility.

- Conclusive evidence of a metabolic derangement caused primarily by the HIV virus that results in increased nutrient requirements is lacking. Clearly, metabolic changes resulting in wasting occur in HIV seropositive patients. The exact relationship between the viral infection per se and nutritional needs is less clear.

- Evidence indicates a predisposition towards malnutrition in certain high risk groups (e.g., IVDU and infants born to IVDU) that is independent of HIV status. Whether changes in individual macro- or micronutrient status are associated with risk group or lifestyle rather than HIV related disease is unknown because of the incomplete characterization of the nutritional status of uninfected risk groups.

- Pharmacological interventions for the treatment of HIV-related disease have acute and long-term effects that can influence the processes of nutrition. The consequences of currently available drug therapies for the treatment of HIV-related disease on nutritional status have not been characterized.

2. Impact of nutritional status on the course of HIV infection

Overall nutritional status as well as the availability of physiologically active forms of specific micronutrients will affect an individual's ability to function optimally irrespective of HIV status. Conclusions about the interaction between nutritional status and the course of the HIV disease process may be summarized as follows:
• The role of nutritional status in the development of AIDS in HIV–infected adults or perinatally exposed children has been inadequately investigated.

• It is unknown whether changes in such specific functional domains as immunocompetence, behavior or cognition, or work performance as seen in HIV patients are primarily the result of the HIV infection, opportunistic diseases, nutritional factors or interactions of these contingencies.

• The efficacy of pharmacological treatment protocols may be affected by the nutritional status of any individual, irrespective of HIV status. The influence of nutritional status of HIV infected patients on the efficacy of currently available drug therapies has not been characterized.

• Data to support the utility of any of the proposed alternative nutritional therapies discussed in Chapter V or supplements of individual nutrients, beyond the amounts that are deemed adequate for good health, are limited. The absence of definitive data does not preclude the possibility that changes in individual nutrient requirements occur consequent to the development of HIV–related disease or that alternative treatments may be useful. Knowledge in this topical area requires conduct of well–designed prospective studies and clinical trials.

B. THE ROLE OF NUTRITION IN HEALTH CARE

Our knowledge of the nutritional needs of HIV–infected and or AIDS patients comes more from clinical experience with other chronic debilitating diseases than from any fundamental understanding about the relationship between nutrition and HIV infection. Available evidence indicates that the wasting and loss of endogenous fuels, can be attenuated by early aggressive nutritional intervention, education, and counseling in the early stages of HIV infection. The goals of such strategies should be to maintain macro– and micronutrient balance throughout the progression of the HIV disease process. As the patient progresses through different stages and manifestations of the disease, interventions should be individualized, continually monitored, revised, and supported by appropriate nutritional assessment methodologies.

An additional concern for both the HIV–infected patient and the health care provider is the importance of food safety. The patient and caregiver must be educated and trained in methods of food preparation and storage in order to ensure optimal safety of the food supply. Available sources of educational materials regarding nutritional care of HIV infected patients are listed in Chapter V. Additional recommendations about practical aspects of dietary and nutrition–related issues has been included in Appendix A.

C. SUGGESTIONS FOR FUTURE CONSIDERATION

While specific recommendations about future research needs have been made throughout the body of this report, several recurring themes emerge; the most prominent of these concerns issues related to experimental design.

1. Experimental design

Because of the urgency of the HIV epidemic, there are immediate needs for valid, reliable information which must come from well–designed prospective studies. Currently, the majority of reports have been from uncontrolled observations. Consequently, information about the nature of the nutrition and HIV relationship derived from well–designed prospective studies is limited.
Because of limited access to patients, the complex nature of the interaction between nutrition and HIV infection, and the potential complications with other factors (e.g., risk group, economics, pharmacology), many studies will continue to be descriptive rather than experimental. In those cases where available information suggests the potential efficacy of a particular intervention, clinical trials should be considered. Approaches to the design of clinical trials to test treatments of HIV-related disease have been discussed (Merigan, 1990; Byar et al., 1990). Ethical and clinical concerns notwithstanding, it is essential that fundamental concepts of experimental design be utilized to avoid creating unrealistic expectations about treatment modalities that are based on unreliable and invalid data. Below are some specific suggestions about future studies:

- Include appropriate comparison groups, for example, HIV-seronegative IVDU adults, in studies of HIV-seropositive IVDU. Similarly, defining the populations to be studied as AIDS patients in the generic sense should be avoided. Patient groups should be clearly designated and, unless post-hoc analysis dictates, patients with end-stage disease and asymptomatic HIV-infection should not be pooled. The use of appropriate controls will enable future efforts to be more focused on the specific relationship between the HIV infection and dependent variables such as changes in body composition and or metabolism.

- In those cases where patient recruitment, time, or urgency dictate that data be collected without necessary design considerations, in the analysis of all data include some multivariate procedures to test for main effects and interactions of all potential mediators of the dependent variables. For example, gender, age, risk factors, stage of illness, and concurrent drug therapies should all be accounted for in analysis of any data in the HIV-infected population.

- Select sensitive and specific indices of nutritional status for study. Wherever possible attempts should be made to avoid the use of measures such as the acute phase reactants albumin or RBP, that will be affected by nonnutritional factors. In addition, where possible, at least two corroborating dependent variables for each nutritional outcome should be assessed. Similarly, efforts should be made to choose variables that reflect nutrition or the processes of nutrition rather than disease activity alone.

- In assessing any specific nutrient (i.e., vitamin or mineral), make every attempt to have at least two indicators of biochemical status. Whenever possible use a functional test of nutrient status. For example, when studying riboflavin status the best indices might be excretion of riboflavin to assess intake and the stimulation assay, glutathione reductase which serves as a functional test of riboflavin status and long-term intake patterns (Sauberlich et al., 1974).

- All biochemical measurements should be supported by the best available assessment of nutrient intake. The choice of such indicators will be predicated by such factors as cost or invasiveness, as in the case of assessment of actual intake with the use of matched food homogenates. Other considerations will be the competency of record keeping by either the patient or caregiver. In any case, it is essential that appropriate dietary assessment tools be chosen for the conditions of the particular study. By taking such an approach the investigators can best address the possibility of changes in any of the processes of nutrition that may be responsible for changes in nutrient status.

2. Risk groups

The largest growing segments of the HIV-infected population are women, children, and adolescents. These groups, especially women, have been seriously underrepresented in the research efforts to investigate the role of nutrition in the disease process. Women of childbearing age are at increased risk for the development of dietary deficiencies of several essential nutrients including iron, irrespective of risk group or HIV status. Of all of the studies cited in this report, only one examined
HIV-infected women as a separate group. Kotler et al. (1985) observed that, under the conditions of that study, women differed from HIV-infected men in terms of the composition of weight loss. Clearly, there are many questions regarding nutrition and HIV infection in women that must be addressed. In order to be able to offer the full range of best available health care, women should be characterized in terms of their specific needs and not just with respect to their role as bearers of HIV infected infants.

Adolescents as a group have been largely ignored in research efforts to date. Hein (1989) commented on various issues relevant to the study of this high-risk group. Because of the latency period in the development of HIV-related disease, most HIV adolescents will not receive attention until they are adults. Available data from dietary surveys have identified segments of this age group as being at increased risk for specific nutrient deficiencies. Future efforts should focus on identifying potential risk groups within the larger group of adolescents and on characterizing these groups in terms of potential mediators of nutritional status.

Infants and children have also been understudied. Future prospective studies should focus on those factors that are associated with seroversion of infants born to HIV-infected mothers. The timing of seroconversion and or exposure should also be considered in studies assessing the impact of HIV-related disease on development. Because breast-feeding is the best source of nutrition for the neonate, efforts should be made to advance our understanding of the risk and benefits of this practice in HIV disease. While there have been concerted efforts to insure the safety of breast milk banks, as reflected by the guidelines for establishment and operation of a human milk bank (Human Milk Banking Association of North America, 1990), the potential benefits of this nutrient source have not been explored in HIV-infected children.

3. Other topics

- The efficacy and safety of current enteral and parenteral feeding protocols need to be explored further. Whenever possible, alternative strategies such as those discussed in Appendix A need to be developed and tested in well-designed clinical trials. An additional consideration might be the potential benefits of "disease specific" versus commonly available, nutritionally balanced enteral formulas for the HIV-infected population.

- A greater focus on the physiological and biochemical consequences of the early stages of the HIV infection process is needed. Prospective studies should be designed to assess the progression of the disease process and to begin to understand the impact of the HIV virus on nutritional status. As in all stages of the HIV disease process, classical balance studies need to be performed in order to assess the potential changes in nutrient requirements. Such studies are necessary not only for macronutrients such as energy or protein but also for vitamins and minerals.

- Quantitative data on the impact of economic and social factors on the ability of HIV-infected patients to nourish themselves or obtain adequate nutritional care are needed. Related factors include better understanding of attitudes, beliefs and nutritional practices of HIV-infected patients as well as definitive data on the influence of availability of medical insurance, food, and assistance in daily activities.

4. Collaborative ventures

There is a tremendous resource of expertise in all of the particular areas of nutrition discussed in this report. There are also administrative structures available that would enable a more efficient utilization of these resources. Attempts have been made to identify appropriate treatment approaches and topics that warrant future study. There has not, however, been a structure through
which investigators who wish to address specific nutritional issues might gain access to state-of-the-art methods and assessment techniques. Such a structure could be created through the auspices of national and international scientific organizations like the American Institute of Nutrition and its affiliate the American Society for Clinical Nutrition. At annual scientific meetings, groups devoted to research on particular nutrients meet to present research results and discuss topics of interest. These groups communicate throughout the year in a cooperative effort to advance the extant knowledge about their particular areas of interest. A national network could be established through which these groups could act as the resource needed to effectively address those nutrition issues that, until now, have received incomplete attention.

The questions and suggestions previously made about issues related to experimental design might also be addressed in a similar cooperative manner. A novel approach used by the National Academy of Sciences to circumvent some of the many problems in the study of a similarly controversial topic, diet and hyperactivity, was the establishment of specific study criteria (The National Advisory Committee on Hyperkinesis and Food Additives, 1975). Again, the expert groups from the relevant disciplines could contribute to the development of universal standards of study design.

An additional component of this cooperative venture would be the establishment of a communication network among clinical research centers throughout the country. Such a network would not only facilitate the distribution of information but could also be used as a subject pool that would expand the numbers of and increase the power of future studies, and thereby enhance the efficient use of already limited resources. One currently available source of information for those wishing to conduct a clinical trial is the computer based AIDS Clinical Trials Information Service, which is accessible through a Public Health Service toll free telephone line at 1-800-Trials-A. More information on this service is available by contacting the FDA's AIDS Coordination Staff at 301-443-0104 (Food and Drug Administration, 1990).
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APPENDIX A

PRACTICAL CONSIDERATIONS IN NUTRITIONAL MANAGEMENT OF HIV-INFECTED PATIENTS

The scope of work identified by FDA focused on current theories, a critical review of the existing research and an evaluation of clinical practices for nutritional support of individuals with HIV infection. Thus, this report addresses current knowledge of the role of nutrition in the disease process. However, in reviewing the available scientific and clinical information and in considering the comments on the tentative report submitted by most reviewers, LSRO became aware of the need for and anticipation of, suggestions on dietary practices and information on nutritional management of persons who are HIV positive and individuals with more advanced stages of the disease.

Chapter V identifies sources of available information that should be consulted for additional information on current nutritional approaches and practices available to health care providers and patients (see page 55). These sources, as well as materials and comments submitted to LSRO, contain considerable information on identification and management of nutritional needs, dietary approaches to providing adequate nutrient intakes, and possible complications and problems that may be encountered. This information has been summarized in this Appendix because it has immediate practicality to the health care providers. In general, the Appendix makes suggestions related to eating difficulties and special needs of individuals with HIV infection or AIDS. Clearly, the usefulness of this information for each individual should be evaluated as part of proper medical advice and counsel.

A. OBJECTIVES OF NUTRITION EDUCATION AND INTERVENTIONS

Designation of the most appropriate approaches to the identification and treatment of malnutrition in HIV related disease has been inhibited by the complexity of the problem (Kotler, 1989b). Because of the multifactorial causes of malnutrition in HIV infection, nutritional recommendations and support must be individualized and must be integrated with other therapeutic interventions. A comprehensive view of the disease process, use of medications, and the patient's wishes is necessary.

B. GENERAL NUTRITIONAL AND DIETARY RECOMMENDATIONS FOR PERSONS WITH HIV INFECTION

Nutritional screening of HIV-infected patients should be an essential component of health care. Consideration of maintenance or restoration of nutritional status should begin as soon as a patient is diagnosed as HIV seropositive (Kotler, 1989b). Ideally, nutritional screening should be performed at the time of first contact with a health professional, and any nutrition related problems should be evaluated so that a care plan can be designed, implemented, and adapted as necessitated by changes in the patient's clinical condition (Ghiron et al., 1989a).

1. Nutritional assessment

Nutritional assessment should be performed to detect the possibility of malnutrition; if detected, seek the specific cause(s) of malnutrition (Kotler, 1989b). Initial assessments should proceed from...
general to specific indices of nutritional status and should include medical history, anthropometric measurements, biochemical indices (only when available as part of general medical profile), and history of past and current drug use. A dietary history should be obtained, including use of nutritional supplements, to ascertain if diet composition is appropriate and to evaluate eating ability. A history of recent weight change is also useful. Because of their invasiveness and potential for introducing infections, specific biochemical measures of individual nutrients involving blood samples should be avoided unless the initial screening identifies a problem. Specific suggestions for assessments are provided by Carrot Top Nutrition Resources (1988), DeFoog (1988), Ghiron et al. (1989a), Taber–Pike (1988), and Task Force on Nutrition Support in AIDS (1989).

Any significant recent weight loss should be evaluated; such a loss should not be ascribed to HIV infection until complicating illnesses have been ruled out as contributors (Greene, 1988). Several concomitant mechanisms producing weight loss and malnutrition may be operating in any patient; each one must be evaluated on an individual basis, with attention to presenting symptoms (Greene, 1988). Possible causes noted by Greene (1988) include the following:

- Voluntary inadequate intake (restricted dietary regimens).
- Early satiety caused by a variety of AIDS complications.
- Drug–nutrient interactions and other drug side effects.
- Anorexia resulting from neuropsychiatric, endocrinological, and gastrointestinal conditions.
- Chronic fever and infection producing metabolic alterations.
- Diarrhea and malabsorption.

If possible, any detected complications that represent underlying causes of malnutrition should treated with appropriate medical intervention as well as nutritional therapy. Continued nutritional assessments throughout the course of the disease are required to detect changes in status that necessitate modification of nutritional management.

A behavioral and psychological evaluation and an assessment of social and financial support are also appropriate for designing a nutritional care plan and for integrating the plan with other therapies.

2. Nutrition counseling and education and recommendations for oral intake

Nutrition education plays an important role in the maintenance of adequate diet and nutritional status at all stages of HIV infection. In the asymptomatic stage, nutrition counseling must aim to promote an adequate and balanced diet for maintenance of weight and prevention of malnutrition. In later stages, nutrition recommendations may include various forms of nutrition support. Because of the complex nature of the disease, a multidisciplinary team approach is recommended for optimal nutrition management (Kotler, 1989b). Various publications offer suggestions for dietary enhancement in HIV infected persons (Alvar and Jurecki, 1988; Carrot Top Nutrition Resources, 1988; Cleveland Clinic Foundation, 1988; Coghlin et al., 1988a,b; Hickson and Knudson, 1988; Holmes et al., 1988; National Cancer Institute, 1987).

As noted by Ghiron et al. (1989a), "The goal of nutrition counseling is to make the fewest changes in the patient's life-style and habits that are necessary to promote optimal nutritional status while maximizing comfort and quality of life." The success of dietary intervention depends on the patient's motivation and ability to achieve the recommended diet changes. The provider can assist the process by prioritizing diet changes, providing explanations for suggested changes, giving encouragement and practical suggestions and aids for integrating changes into the patient's routine,
introducing information in manageable steps in order of complexity and difficulty, and involving the patient's family, friends, and caregivers (Ghiron et al., 1989a). Depending on the patient and the stage of the disease, instructions for the home diet or nutrition regimen may be verbal or written and may include detailed menus, recipes, shopping lists, and eating hints. The materials used should be individualized for the patient (Carrot Top Nutrition Resources, 1988).

Health care providers need to be sensitive to the special social and psychological issues that confront persons with HIV infection, and to how these stresses may influence the patient's and caregiver's attitude and compliance to treatment (Ghiron et al., 1989a). The need for assistance with activities of daily living (such as food shopping and preparation) and appropriate referrals should be evaluated and provided. Financial issues may also be a concern; patients should be encouraged to use the food assistance programs available to them, such as food stamps, commodity programs, food pantries, and local meals on wheels. Many AIDS support groups can provide information on local food program resources and some groups provide such services.

3. **Food safety considerations**

Precautions for home food preparation, serving, and storage are designed to protect the person with HIV infection against the possibility of food-borne infections (Holmes et al., 1988). Some food preparation and storage guidelines for food safety are provided below (Dhundale and Hubbard, 1986; Ghiron et al., 1989b; Holmes et al., 1988; Wickwire, 1989).

- Avoid raw protein foods, such as uncooked eggs, rare meat, and sushi. Cook meat and eggs thoroughly.
- Do not use cracked eggs.
- Thaw frozen meats in the refrigerator or microwave, not at room temperature.
- Wash fruits and vegetables thoroughly.
- Use only pasteurized milk.
- Keep hot foods hot (cooked to 165°F and held at 140 to 165°F).
- Keep cold foods cold (refrigerator temperature should be 35 to 40°F; freezer should be 0°F).
- Do not allow foods to stand at temperatures between 45°F and 140°F for more than 2 hours.
- Refrigerate perishable foods immediately upon return from the store. Store foods that have been opened in airtight containers or a moisture/vapor proof wrap. Don't crowd or overpack foods in the refrigerator.
- Avoid moldy or spoiled foods.
- Do not use foods after the recommended expiration date on the label.
- Always wash hands before handling food.
- Use different cutting boards for raw and cooked foods.

HIV infection is not spread by food or water. In the hospital, disposable utensils, dishes, and trays are not needed for patients with HIV infection. Use of regular dishes improves temperature control of foods and makes meals more attractive. Routine sanitation standards for food preparation, storage, should be maintained for serving, dishwashing and cleaning procedures (Collins and Garcia, 1989; Resler, 1988).
It has been suggested that sterile or low-microbial diets may be beneficial for immunosuppressed patients (Aker and Cheney, 1983), but such diets have not been studied in HIV-infected patients. Ghiron et al. (1989b) have concluded that, given the lack of conclusive evidence of benefit, these diets are unwarranted for patients with HIV-infection for practical reasons alone.

C. NUTRITIONAL RECOMMENDATIONS FOR PATIENTS WITH SYMPTOMS OF HIV-RELATED DISEASES

Oral dietary intake is the preferred method for meeting nutritional requirements. A variety of changes in the types, amounts, and temperature of foods; timing of meals; and other factors may help to alleviate food consumption difficulties that may be encountered during the course of HIV infection. These are described below. If requirements cannot be met by oral intake despite all efforts, enteral tube feeding and or parenteral nutrition can supplement or replace dietary intake.

1. Food choices and dietary recommendations to ameliorate specific problems related to eating

Because patients may experience multiple complications and because appropriate suggestions for addressing one sign or symptom may be inappropriate for another, care must be taken to individualize such recommendations.

Anorexia may result from depression, drug side effects, fever, and other causes. Some practical suggestions for overcoming reduced intake caused by lack of appetite that may be offered to the patient and or caregiver are listed below (Carrot Top Nutrition Resources, 1988; Holmes et al., 1988; Resler, 1988; Taber, 1989; Task Force on Nutrition Support in AIDS, 1989; Wickwire, 1989).

- Eat small meals frequently throughout the day. Try to eat by the clock.
- Include high-calorie snacks and or commercially prepared supplements (liquids or bars).
- Indulge desires for favorite foods.
- Consume more nutrient-dense foods and beverages, rather than filling up on low-calorie items.
- Drink liquids a half hour before eating instead of with meals.
- Prepare meals (such as soups or casseroles) ahead of time so that they can be divided into individual servings and frozen until ready for use.
- Keep easy-to-prepare foods on hand, such as frozen dinners, canned foods, and eggs.
- Make food presentation and service appealing.
- Encourage dining with friends or family in pleasant surroundings.
- Get family members and friends involved in meal preparation; the warm atmosphere they can provide may stimulate the patient's appetite.

When oral and esophageal lesions from candidiasis, herpes simplex, hairy leukoplakia, and Kaposi's sarcoma that make chewing and or swallowing food painful or difficult are present, the suggestions that follow may be helpful (Carrot Top Nutrition Resources, 1988; Coghlin et al., 1988a,b; Holmes et al., 1988; Taber, 1989; Task Force on Nutrition Support in AIDS, 1989; Wickwire, 1989).
• Eat soft, nonirritating foods such as eggs, cream soups, ice cream, puddings, ground meats, baked fish, soft cheeses, cooked fruits, and noodle dishes.

• Avoid hard, dry, crisp, or rough-textured foods.

• Avoid irritating lesions by eliminating spicy foods and acidic foods such as citrus fruits and juices.

• Avoid very hot or cold foods when lesions are present; consuming foods at room temperature may be soothing.

• Use a straw for drinking liquids to avoid irritating lesions or causing soreness.

• Drink nutritionally complete, commercially prepared supplements and blender drinks.

• Practice good oral and dental hygiene.

• Rinse with a topical anesthetic.

• Use hard candy or chewing gum to stimulate saliva production if mouth is dry. (Artificial saliva may be prescribed.)

• Soak dry foods in liquids such as gravy, sauces, coffee, tea, or milk.

• If swallowing is badly impaired and there is danger of aspiration:
  
  - Thin liquids may need to be omitted.

  - Thickening liquids to a semi-soft consistency with powdered milk, mashed potatoes, cornstarch, or oatmeal should be tried, if liquids cause choking.

  - Eliminate solid food and foods such as stews.

  - Avoid foods that stick to the palate, such as peanut butter and white bread, and slippery foods, such as bologna, macaroni, and gelatin.

  - Try seasonings and serve food hot or cold to stimulate mouth sensation.

  - Consult with a specialist such as a speech therapist.

Drug treatments and oral complications may also cause changes in taste; the suggestions that follow may help overcome unpleasant or reduced taste sensations (Cleveland Clinic Foundation, 1988; Coghlin et al., 1988a,b; Task Force on Nutrition Support in AIDS, 1989).

• Try new foods.

• Experiment with herbs and spices to enhance flavors.

• Alter the sweetness or saltiness of usual foods.

• Add beer and wine to soups to improve taste.

• Enhance taste with tart foods (if not otherwise contraindicated).

• Try other sources of protein such as eggs, chicken, fish, or tofu if red meat does not taste the same.
If fatigue makes it difficult to spend the time and energy necessary to prepare meals and maintain adequate intake (Holmes et al., 1988), the following steps may be helpful.

- Eat frequent small meals.
- Prepare meals ahead of time when feeling well and freeze them in individual servings.
- Keep easy-to-prepare foods on hand.
- Accept offers of family and friends to help prepare meals.
- Try take-out foods from restaurants or prepared food from grocery stores.
- Utilize home food delivery services.
- Direct the patient to support services in the community; sources of information on available food programs may include outpatient dietitians at local hospitals or public health department nutritionists.
- Carry powdered forms of liquid dietary supplements as they may be easier to carry than ready-to-use forms.

In *Pneumocystis carinii* pneumonia, respiratory symptoms such as shortness of breath or labored breathing can cause fatigue, and the need to wear an oxygen mask can interfere with eating. The patient with dyspnea may experience anxiety about eating and breathing and may be assisted by the recommendations below (Carrot Top Nutrition Resources, 1988; Taber, 1989).

- Eat small meals frequently.
- Keep a cold high-calorie beverage available during the day.
- Consume high-caloric protein shakes such as milk shakes, ice cream, sandwiches, and commercially prepared enteral supplements or modular supplements added to liquids.
- Avoid low-calorie foods.
- Use home-delivery and carry-out food services.

If the patient is experiencing nausea, the problem may be alleviated by antinausea medication and or the following suggestions (Alvari and Jurecki, 1988; Carrot Top Nutrition Resources, 1988; Coghlin et al., 1988a,b; Holmes et al., 1988; Taber, 1989; Task Force on Nutrition Support in AIDS, 1989; Wickwire, 1989).

- Eat larger meals at times when feeling better. Reschedule meals if nausea consistently occurs at the same time of day.
- Avoid favorite foods during nausea to prevent the development of taste aversions for these foods.
- Eat saltier foods.
- Avoid very sweet foods.
- Avoid greasy or fatty foods.
- Try cold entrees rather than hot ones; they are less aromatic and often better tolerated.
- Eat smaller portions of food throughout the day.
Stay out of the kitchen while food is being prepared if food odors provoke nausea.

Eat dry foods, such as toast or crackers, especially if nausea occurs in the morning (unless oral or esophageal lesions are present or salivary flow is impaired).

Eat soft, bland foods that are easier to tolerate, such as rice, soft-cooked or poached eggs, apple juice, nectars, and custards.

Time meals and medications to avoid anticipatory vomiting.

Provide antiemetic drugs prior to meals.

Replace fluids and salt by consuming broths, ginger ale, and juices if vomiting occurs.

Drink fluids through a straw between meals, rather than with meals.

Chew foods thoroughly and eat slowly.

Rest after meals, but avoid reclining or lying down immediately after eating.

Diarrhea is common in patients with HIV infection and may be resistant to treatment (especially if caused by cytomegalovirus, atypical Mycobacterium spp., Cryptosporidium spp., and Isospora belli). However, a causative intestinal pathogen should always be sought, because many do respond to treatment. Long-term suppressive therapy may be necessary because intestinal infection recurs frequently. Emotional stress, some drugs, contaminated foods or tube-feeding formulas, and hypoalbuminemia may exacerbate diarrhea. For some patients, taking antidiarrheal drugs and making dietary modifications may help to control diarrhea (Taber, 1989). Although diarrhea in AIDS often cannot be alleviated by dietary changes, some that may be helpful include those listed below (Alvari and Jurecki, 1988; Carrot Top Nutrition Resources, 1988; Coghlin et al., 1988a,b; Holmes et al., 1988; Wickwire, 1989).

Try small, frequent meals served at room temperature.

Replace fluids and electrolytes with: water, broth, fruit juices, gelatin, ice pops, commercially available electrolyte drinks, and high-potassium foods such as bananas, meat, potatoes, apricot and peach nectars. Watch for signs of dehydration.

Consume a low-lactose diet; use Lactaid® to reduce lactose in milk, and try yogurt and cheese in small amounts.

Consume a low-fat diet; use leaner foods, such as low-fat cottage cheese, part skim milk, low-fat cheeses, and leaner cuts of meat.

Avoid caffeine-containing foods such as coffee, tea, chocolate, and some carbonated beverages.

Limit consumption of bran-type fibers, seeds, and husks of grains. Try foods that are good sources of pectins and gums, such as oatmeal, cooked dried beans, apples, pears, potatoes, and other fruits, vegetables, and grains.

If cramping is a problem, avoid foods that may cause gas and or cramps, such as carbonated drinks, beans, cabbage, broccoli, cauliflower, highly spiced foods, too many sweets, and sorbitol-sweetened chewing gums.

Infection and fever increase both protein and energy requirements. Keeping the patient well hydrated and offering high-calorie and high-protein fluids and snacks may be helpful (Carrot Top Nutrition Resources, 1988).
Impairment of renal or hepatic function may require the adjustment of protein and sodium intake (Carrot Top Nutrition Resources, 1988).

Neurological manifestations in AIDS may result from the disease process itself or from the effects of malnutrition on the central nervous system; ascertain the cause (Task Force on Nutrition Support in AIDS, 1989). The following suggestions may help to maintain oral intake (Taber, 1989).

- Obtain help at mealtimes.
- If swallowing is impaired, speech and or physical therapy may help to restore this function.
- Occupational therapy and the use of specially designed utensils can permit self-feeding if motor functions are impaired.

If adequate oral intake cannot be maintained, guide the decision to pursue more aggressive forms of nutrition support by indications as to whether or not improved nutritional status, improved quality of life, and or patient comfort will result (Ghiron et al., 1989b).

2. **Enteral nutrition**

If voluntary oral intake is inadequate and the gastrointestinal tract is functioning, enteral feeding is indicated (Kotler, 1989b). For long-term use, enteral feeding is preferable to parenteral support (Kotler, 1989b) to avoid catheter-associated infections and to prevent atrophy of the gut. The enteral formula should be lactose-free and may need to be restricted in fat. Whether a defined formula diet offers an advantage is not yet clear (Hickey and Weaver, 1988; Kotler, 1989b), but probably depends on the specific clinical problems present. The choice of a transnasal route or surgically placed tube may be dictated by the clinical condition or may be influenced by patient preference.

Indications for enteral tube feeding include the situations cited below (Task Force on Nutrition Support in AIDS, 1989).

- When appetite is so poor or anorexia is so profound that nutrient intake is inadequate or weight loss occurs, tube feeding of a calorically dense enteral formula may be used to supplement oral intake. A nasogastric tube allows for various feeding schedule options including intermittent or continuous nocturnal feeding.
- If oral intake is impaired by oral or pharyngeal lesions for more than several days, consider intermittent or continuous tube feeding of a balanced formula to meet caloric requirements. If esophageal lesions are present, the use of the transnasal route is contraindicated. In this case, if impairment of oral intake is expected to be prolonged, consider the use of a surgically placed feeding tube (percutaneous endoscopic gastrostomy or jejunostomy).
- If nausea and vomiting are expected to reduce oral intake for two weeks or more (i.e., in the case of drug therapy) or significant unintentional weight loss has occurred, use an enteral formula introduced into the small intestine and adjusted for osmolality.
- When diarrhea cannot be managed by modification of diet, enteral feeding is appropriate except in the case of total small bowel disease that is accompanied by severe malabsorption. In partial small intestinal disease, a defined formula diet low in residue, fiber, lactose, and fat (<5 percent) is appropriate. (Fat in the form of medium-chain triacylglyceroles may be helpful in alleviating malabsorption.) A similar formula can be given to patients with disease of the large bowel. A low-lactose, low-fat (as tolerated) formula may be suitable for patients with nonspecific enteropathy; if there is no improvement, a less complex formula may be indicated.
When nutritional needs cannot be met orally in patients with infection and sepsis, use of an iso-osmolar formula is suggested, with monitoring for hyperosmolar complications and glucose intolerance.

3. Parenteral nutrition

Parenteral nutrition support should usually be considered as a final option, because of its expense and risk. However, it can be a feasible and effective method for providing calories. Partial parenteral nutrition with varying amounts of dextrose, amino acids, fat, vitamins, and minerals may be considered for short periods (about 2 weeks) when negative energy balance is expected (Kotler, 1989b). For example, such support might be used when inadequate intake caused by nausea and vomiting could be expected for a defined period of time, as during drug treatment (Task Force on Nutrition Support in AIDS, 1989). During systemic infection, the success of parenteral nutrition therapy will be dependent on diagnosis and treatment of the infection (Kotler, 1989b). Parenteral iron should not be administered during sepsis. Because of the risk of catheter-related sepsis, parenteral nutrition should usually be reserved for situations in which aggressive nutritional repletion is desired for more than 7–10 days and the gastrointestinal tract is not functioning, for example, when there is intestinal obstruction. A short course of parenteral nutrition together with a diet of bananas, rice, apples, and tea or toast (BRAT diet) may be helpful for some patients with diarrhea (Hickey, 1988).

Total parenteral nutrition is indicated as the first method of choice for severe malnutrition associated with total small intestinal disease and malabsorption, or in patients who cannot achieve adequate caloric intake via any other route (Hickey and Weaver, 1988; Kotler, 1989b; Task Force on Nutrition Support in AIDS, 1989a). During total small-bowel disease, serum albumin should be monitored and nitrogen intake adjusted to promote repletion.

Peripheral parenteral nutrition is judged to be appropriate when short-term, in-hospital support is needed. Central parenteral nutrition is preferred for patients with nonfunctioning gastrointestinal tracts and can also be used concomitantly with enteral feeding (Task Force on Nutrition Support in AIDS, 1989).

Home parenteral nutrition is a possibility if the patient and or care giver is able and willing to manage the procedure and equipment for nutrition support (Ghiron et al., 1989b). Cycling parenteral nutrition to last only 12 hours during the evening and night may not always be possible, but it is desirable in order to improve patient mobility during the day, adherence to treatment, and quality of life (Ghiron et al., 1989b; Worthington, 1987).

Although there is a risk of infection for patients, Asjo and Wahren (1986) have concluded that there is very little risk to care givers of nosocomial infection with HIV during administration of intravenous nutrition therapy in HIV-infected patients if hygienic precautions and isolation procedures are followed.
NOTE: The following persons and organizations submitted reference materials in response to announcement of the study in the Federal Register (55:50822-50823), December 11, 1989 and comments on a tentative report released on April 2, 1990 as announced in the Federal Register (55:13847), April 12, 1990 [Docket No. 89N-0482]. The names of several individuals and organizations were inadvertently omitted from the final report. The LSRO sincerely regrets any inconvenience resulting from this omission.

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