The Wasting Report:
Current Issues in Research and Treatment of HIV-Associated Wasting and Malnutrition

by Tim Horn & David Pieribone

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Treatment Action Group
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The Treatment Action Group (TAG) fights to find a cure for AIDS and to ensure that all people living with HIV receive the necessary treatment, care and information they need to save their lives. TAG focuses on the AIDS research effort, both public and private, the drug development process, and our nation's health care delivery systems. We meet with researchers, pharmaceutical companies and government officials, and resort when necessary to acts of civil disobedience, or to acts of Congress. We strive to develop the scientific and political expertise needed to transform policy. TAG is committed to working for and with all communities affected by HIV.

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Design & Production: Joy Episalla
This report is dedicated to Kiki Mason (1960-1996)
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Introduction

Wasting syndrome can be a chronic and deadly manifestation of HIV. Multiple studies demonstrate that progressive weight loss and wasting are highly predictive of disease progression and death. However, wasting syndrome has been underemphasized, not only in clinical care, but also in basic clinical research. Currently, no standard of care exists for monitoring HIV-infected people for malnutrition, wasting and weight loss, and there is no clear consensus regarding the optimal ways to diagnose and treat these complications of HIV disease.

Progressive weight loss and wasting during the course of infection and illness is not a new phenomenon. In fact, much of the data generated by those investigating HIV-related wasting are based on research into cancer, sepsis, and the social ills of poverty. Unfortunately, given the complexities of HIV pathogenesis and its related opportunistic infections, weight loss and wasting in the course of HIV infection poses characteristics unseen in other diseases causing weight loss.

Despite the tremendous progress made in developing antiretroviral therapies, prophylaxis, and treatments for opportunistic infections, the prevalence of wasting syndrome is increasing. Two studies have reported that a ten-fold increase in wasting syndrome as the initial AIDS-defining illness has occurred since 1987 (Hoover 1993, Weiss 1993). The current CDC definition of wasting as an AIDS-defining illness may be misguided in light of the recent research into this multifactorial complication and so data from AIDS related weight loss and wasting epidemiology studies may be highly under-reported.

Research into HIV-related wasting syndrome has yielded advancement in understanding the epidemiology, multifactorial etiology and pathogenesis, and its potential treatments. However, much like HIV-disease itself, there is a great deal more to learn about the complexities of wasting syndrome and the ways in which it can be managed.

The aim of this report is three-fold: First, to put the complexities and current understanding of weight loss and wasting into a useful context for non-nutrition scientists, people with HIV/AIDS and their caregivers. Second, to evaluate the data thus far accumulated in its epidemiology, basic science, diagnosis, and treatment of weight loss and wasting. Finally, to pass recommendations intended to streamline research and provide more conclusive research in all aspects of AIDS-related wasting in an attempt to implement a standard of care for all patients infected with HIV.
Foreword by Donald P. Kotler, M.D.

Assisting members of TAG in developing a white paper on nutrition in HIV infection has been an unusual experience, one that has caused me to consider factors beyond the narrow application of the scientific method to a medical problem. The "audience" that will read this report on nutrition is different from usual, and will include people from all strata in the health care system. This review is a unique opportunity to elucidate the adverse effects of malnutrition in HIV infection and to formulate a plan for improving our knowledge base and ability to intervene successfully. This paper could be a turning point in the application of nutritional therapies in HIV-associated malnutrition.

The overall rationale for considering nutrition in HIV infection is that malnutrition contributes to the problems of the HIV-infected individual in ways that are independent of immune depletion. While immune depletion cannot be reversed at the present time, malnutrition may be reversible using current therapies, and treatment may have clinical benefits irrespective of the course of immune deficiency. While this thesis concentrates upon chronic treatment rather than cure, it is consistent with current realities.

There have been steady advances in understanding the extent and composition of weight loss in HIV infection, its relevant pathogenic mechanisms, and the potential benefits of nutritional therapies. Importantly, there is a growing realization that malnutrition is associated with adverse clinical outcomes. The point should have been obvious from the beginning, since starvation in the absence of any other disease causes severe morbidity and even mortality. The development of malnutrition in an illness is generally felt to be secondary to the underlying pathologic process, and that improvement is possible only by addressing the underlying disease. However, successful treatment of opportunistic infections and primary antiretroviral therapy in HIV infection have not been accompanied by a diminution of the problem; in fact, the prevalence of unexplained wasting has increased as other disease complications have been successfully treated.

Despite the advances in knowledge, the nutritional care of most HIV-infected individuals is poor. Unfortunately, this disease is not alone in its neglect of proper nutrition by many caregivers. Several components are necessary for a successful nutritional program including basic science, clinical investigations and trials, access and advocacy for nutritional therapy, and appropriate health care policies. There are major deficiencies in all of these areas.

The major deficits in basic and clinical science involve confounding factors. The development of malnutrition is multifactorial and its key pathogenic features vary during disease progression. Demographic factors influence nutritional status in an uncertain manner. The relationship to viral activity also is uncertain. Most clinical tools in clinical nutrition are inaccurate or difficult to apply. Clinical trials of nutritional therapies have been as limited in infection as in other chronic diseases. Nutrition trials have been a very low priority for formal clinical trials networks. Despite the complex and multifactorial nature of malnutrition in HIV infection, treatment strategies have not been tailored to specific pathogenic mechanisms. Most studies are small, phase 2 trials, which only establish the presence or absence of a biologic effect. Their design and implementation have been slow so that results typically follow rather than precede and direct the establishment of standard clinical practice. Few trials can be termed definitive, very few
are comparative in design, and almost none have analyzed cost vs. benefit or long term clinical outcomes.

Clinical application of nutritional therapies is random and arbitrary. There is no advocacy for proper nutrition. There are no generally accepted standards of nutritional care for HIV-infection. There often is little patient sophistication on nutritional issues and little emphasis on nutrition education by most health care providers. Many clinicians have noted an increased use of alternative, nutritional therapies by patients. In many cases, their application also is random and arbitrary, and have uncertain and undocumented risks plus definite costs.

These problems have profound implications for the formulation and implementation of health care policy, including reimbursement. We must admit that health policy decisions have clinical outcomes. Third party payers are forced to make choices in an information vacuum. The lack of information may lead to irrational or even stupid policies. Without an appropriate structure for expanding the knowledge base, the situation is not likely to improve. The academic infrastructure for clinical investigation is eroding. Studies are becoming increasingly expensive to perform. The impetus for cost cutting may lead to further loss of our ability to provide nutritional support under any circumstances. Given these problems, one might question whether the development of proper nutritional management of HIV infection even is possible. I believe that successful nutritional therapy is possible in HIV infection. Many patients have benefitted greatly from nutritional therapies. The general level of studies in the literature is improving in quality. Presently, a strong case can be made for nutritional management of HIV-infected individuals. The current task is to optimize the results of our efforts and to ensure that all patients receive proper consideration and access to nutritional therapies. Allowing the marketplace to dictate the development and application of nutritional or other medical therapies is hazardous, and may lead to fewer expenditures without consideration of outcome or even long term costs. Scientists' ability to effect change in the practice of medicine is limited, as our audience consists mainly of other scientists.

The role of translating and interpreting the literature for the nonscientist and for the policy maker has been assumed by AIDS activists, such as TAG. This is their third such attempt, the first two concerning Kaposi's sarcoma and lymphoma. The authors have done a credible job. I am envious that they seem to have learned the topic much faster than I did. They saw their job as not to applaud the advances in the field so much as to highlight the major remaining deficiencies in knowledge and uncertainties in treatment. Moreover, they formulated a set of specific recommendations to foster further advances in the field. They do not provide a wish list of specific studies, but rather an integrated mechanism through which "experts" can design studies to address the most important basic science and clinical questions.

I have had the opportunity to know many AIDS activists since 1981. While many were seen during serious or terminal illnesses, I had the opportunity to get to know several patients in depth, and came to appreciate their motivations in self-help.

There has been an evolution in activists' modus operandi. Initially, they simply tried to be noticed, for example, by baring a chest in the face of a (terrified) state bureaucrat in order to demonstrate the normal placement of a Hickman catheter, by publicly denouncing a specific FDA staff member during an Advisory Board meeting, by defying the laws governing interstate commerce in order to deliver an unproven therapy to New
York City, and other activities. The second wave of AIDS activism showed them as urban guerillas complete with phone zaps, death faxes, buyers’ clubs, and bag men (the bag contained money to cover bail for those arrested during demonstrations). While this behavior brought notice and respect (fear), it did not bring substantial changes to the medical care of AIDS patients.

AIDS activism has matured and diversified. While all activist groups are united in their goal to influence the evolution of health care to make it more effective and accessible for patients, the means to this end differs considerably among the groups. With maturation has come the appreciation, especially among members of TAG, that the fundamental laws of biology apply in HIV infection, and that substantial improvements in treatment outcome will require an expansion of the usable knowledge base.

The recommendations are reasonable and could lead to studies which, define the natural history of nutritional status in HIV infection, identify and characterize the pathogenic mechanisms, definitive clinical trials, including estimations of costs and clinical outcomes in addition to nutritional endpoints, and extrapolation of the results in the continuing development of health care financing policy. With sufficient support and perseverance, we can make the nutritional management of AIDS a model for the therapy of chronic disease.
Executive Summary

We reviewed the current state of basic and clinical research on, and diagnosis and medical management of, HIV-associated wasting and malnutrition.

HIV-associated wasting syndrome is a multifactorial complication of HIV disease, involving complex interactions among HIV, the opportunistic infections and cancers, chronic inflammatory activation of the immune system, gastrointestinal organ injury and endocrine and immune system dysregulation. Much remains to be elucidated regarding the pathogenesis, differential diagnosis and optimal therapeutic treatment of HIV-associated wasting and malnutrition.

**Basic Research on HIV Wasting Syndrome.** Emerging evidence indicates that weight loss, and particularly loss of body protein (lean body mass or body cell mass) contributes to shortened survival in people with HIV disease. While the entire metabolic system appears dysregulated in the course of HIV disease, particularly when acute OIs occur, it appears that excess breakdown (catabolism) of protein is synonymous to wasting syndrome.

We recommend significant increases in basic research on the etiology, pathogenesis and natural history of HIV-associated wasting syndrome, with larger, prospective epidemiologic studies and collection of useful clinical tissue samples.

**Diagnosis.** Current diagnostic techniques do not adequately discriminate between loss of body weight in general and loss of lean body mass in particular. New assays, such as bioelectrical impedance analysis (BIA), may provide a clearer picture of lean body mass (non-fat mass) depletion.

Currently there is no consensus for the differential diagnosis of patients presenting with HIV-associated weight loss. Some doctors recommend a conservative approach, with no invasive diagnostic techniques and empirical use of antidiarrheal medications. We disagree with this outdated approach. Many pathologies often casually lumped together under the term "AIDS enteropathy" turn out to be, upon proper diagnosis, treatable opportunistic infections. Others remain untreatable, but proper diagnosis remains helpful in optimizing symptom management and in rapid enrollment of clinical trials.

We recommend the convening of a consensus panel on optimizing differential diagnosis of HIV-associated wasting conditions, and improvements in our understanding of how to use newer techniques such as BIA.

**Treatments for HIV-associated Wasting Syndrome.** Treating HIV-associated wasting conditions is critically dependent on proper diagnosis and an appropriate nutritional regimen. Treatments range from antiemetics to appetite stimulants, anti-infectives, anti-diarrheals, endocrine and metabolic treatments such as growth hormone and anabolic steroids, to cytokine modulators. Most studies of treatments for HIV-associated wasting and related conditions have suffered from inadequate sample size, and there remains no standard of care for many aspects of HIV-related wasting.

We call for intensified clinical research efforts in this under-studied area, and the development of an evolving standard of care. Particular attention needs to be devoted to discovering safe, effective treatments for several asyet untreatable infections, such as
cryptosporidiosis and microsporidiosis. These studies will require new collaborative efforts among NIH, the pharmaceutical industry, academic researchers and the HIV community.

Public Education & Information. There is a paucity of information available to care providers, clinicians and people with HIV, about the diagnosis and management of HIV-associated wasting syndrome. We recommend new efforts to develop and disseminate guidelines to optimize diagnosis and treatment in this understudied area.
Recommendations

PATHOGENESIS & BASIC RESEARCH

1. The National Institutes of Health (NIH) Office of AIDS Research (OAR) should convene an expert panel to review current research on HIV-associated wasting syndrome and develop a cross-NIH research plan to ensure that there is a coherent, coordinated research agenda covering epidemiology, natural history, diagnosis, treatment and public education.

2. NIH should expand the knowledge base for research on HIV-associated wasting syndrome by increasing funding for basic, investigator-initiated research project grants (R01s) and for targeted research programs (requests for application, RFAs). Current funding for research on HIV-associated wasting is inadequate. Hitherto, limited funding and inadequate peer review have been major obstacles to furthering basic research on HIV wasting syndrome.

3. The National Institute of Diabetes, Digestive Diseases & Kidney (NIDDK) and/or the National Institute of Allergy & Infectious Diseases (NIAID) should encourage multidisciplinary collaborations among epidemiologists, infectious disease specialists, immunologists and gastroenterologists to develop expert consortia to conduct multidisciplinary studies of the epidemiology, pathogenesis and treatment of HIV-associated wasting syndrome.

4. NIDDK and/or NIAID should encourage multidisciplinary collaborations among epidemiologists, infectious disease specialists, immunologists and gastroenterologists to conduct multidisciplinary studies of the epidemiology, pathogenesis and treatment of HIV-associated wasting syndrome.

5. NIH should fund more research on those opportunistic complications which may contribute to wasting, such as cryptosporidiosis, and microsporidiosis. Targeted drug-discovery efforts (e.g., by the NCI Developmental Therapeutics Program, DTP) should be developed to screen potential lead compounds. This resource should be made available to academia and industry.

6. NIH should fund more research on endocrine, metabolic and immunological regulatory systems which contribute to HIV-associated wasting. If insufficient R01s make it through peer review, special RFAs should be considered.

EPIDEMIOLOGY, NATURAL HISTORY & DIAGNOSIS

7. The current CDC definition of the HIV wasting syndrome needs to be critically assessed in light of newly-emerging data on loss of lean body mass and its correlation with malnutrition. The Public Health Service (PHS) should convene an expert panel to examine the adequacy of the current CDC definition and to consider adding lean body mass indices as diagnostic indicators for wasting.

8. NIDDK and/or NIAID should conduct a large, prospective, longitudinal natural history study of people with HIV infection, gathering clinical and laboratory data and clinical samples and specimens for a tissue bank, to generate new
hypotheses about the pathogenesis of HIV associated wasting. This natural history could be piggy-backed aboard existing cohorts if available, or developed de novo; it should be developed with expertise from AIDS gastroenterologists, infectious disease specialists and epidemiologists.

9. More data are needed on possible differences in the incidence, progression, diagnosis or treatment of HIV wasting syndrome in different populations-e.g., based on class, access to health care, experience of site, access to insurance, by sex, among injecting drug users, prisoners, and children.

10. Further research should be conducted to refine, validate and standardize the use of lean body mass (LBM) diagnostics, such as bioelectrical impedance analysis (BIA), to define LBM levels and to optimize the use of such diagnostics.

11. An expert committee should meet to develop standard clinical guidelines for the monitoring of wasting in early, middle and late-stage HIV disease, for differential diagnosis. Gaps in this clinical standard should provide a research agenda for improving our diagnostic capabilities.

CLINICAL TRIALS

12. Presently, most studies of HIV wasting are preliminary, pilot studies with small sample size and low statistical power, which may not provide definitive data. Many of these studies are sponsored by industry, and are unreliable for a number of reasons. NIH and industry need to sponsor many more largescale, multi-center, clinical endpoint studies for treatments intended to alleviate HIV-associated wasting.

13. The lack of sufficient support from the large clinical research networks (e.g., ACTG, CPCRA) has prevented many large-scale, well-designed, randomized, multi-center studies of wasting treatments from taking place. We recommend that NIDDK, in collaboration with NIAID (and possibly NICHD), form an AIDS Wasting Consortium (AWC), modeled after the NCI AIDS Malignancy Consortium. Through the AWC, NIDDK would fund a core group of highly committed researchers to conduct pilot studies, and design and coordinate randomized studies, of wasting treatments. NIDDK would fund core activities, laboratories and clinical costs, and NIAID would provide access to its clinical sites and laboratory expertise. We propose first-year funding for the AWC at $4M (see current AMC budget) with growth to $10 M/Y within two years. The OAR should work with NIDDK and NIAID to ensure that the AWC is coordinated within the newly coordinated clinical trials structure proposed by the AIDS Research Program Evaluation Working Group (the Levine Committee, March 1996).

14. The impact of commonly-used, approved and experimental treatments for AIDS and HIV disease upon appetite, weight, and metabolism should receive more emphasis in clinical trials. Drugs which have serious negative impact on appetite, weight or metabolism should have warnings inserted upon their FDA-approved labeling.
15. Pharmacokinetic studies should examine the impact of malabsorption on the ability of people with wasting to achieve therapeutic drug levels of their many oral medications.

PUBLIC EDUCATION AND INFORMATION

16. OAR, working with NIAID and NIDDK, should develop a public education program for physicians, people with HIV, care providers and community-based organizations about the need for aggressive monitoring, early diagnosis, rapid treatment and continued follow-up of all patients at risk for HIV-associated wasting syndrome. 10 The Wasting Report 1996
Epidemiology

In 1987, the United States Centers for Disease Control (CDC) revised the surveillance case definition of AIDS to include HIV wasting syndrome as an AIDS-indicator condition. Since the revision, HIV wasting syndrome has become the second most frequently reported AIDS-related clinical condition in the United States (Weinroth 1995).

The CDC defines the AIDS wasting syndrome as profound involuntary weight loss greater than 10% of baseline body weight plus either chronic diarrhea (at least two loose stools per day for greater than 30 days) or chronic weakness and documented fever for greater than 30 days, intermittent or constant in the absence of concurrent illness or condition other than HIV infection that could explain the findings (for example, cancer, tuberculosis, cryptosporidiosis, or other specific enteritis).

National AIDS surveillance data were published in 1993 by Bernard Nahlen of the CDC (Nahlen 1993), who reviewed records of 147,225 individuals with AIDS reported to the CDC from 1 September 1987 to 31 August 1991. The frequency of HIV wasting syndrome and its association with demographic and exposure category variables and with other AIDS-indicator diseases was assessed.

A total of 10,525 (7.1%) had wasting syndrome as the only AIDS-indicator condition, and 15,726 (10.7%) had wasting syndrome plus at least one other AIDS-indicator condition. Patients with wasting syndrome as the only AIDS diagnosis were more likely to be female, black and/or Hispanic (Nahlen 1993).

**TABLE 1: CHARACTERISTICS OF ADULT/ADOLESCENT AIDS PATIENTS, 1 SEPTEMBER 1987-31 AUGUST 1991:**

<table>
<thead>
<tr>
<th></th>
<th>Total #</th>
<th>HIV Wasting (%)</th>
<th>HIV Wasting Plus O.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>Only</td>
</tr>
<tr>
<td>Male</td>
<td>130,852</td>
<td>82.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Female</td>
<td>16,373</td>
<td>79.2</td>
<td>10.2</td>
</tr>
<tr>
<td>White</td>
<td>77,811</td>
<td>83.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Black</td>
<td>43,384</td>
<td>81.2</td>
<td>7.7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>24,447</td>
<td>80.0</td>
<td>11.3</td>
</tr>
<tr>
<td>Asian/Other</td>
<td>1,503</td>
<td>87.4</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Suttmann and colleagues (Suttmann 1995) evaluated 100 HIV-positive individuals for nutritional, clinical, and immunological parameters. In addition, 39 patients with AIDS were followed for a mean of 343 days. The results were alarming; 63% of the HIV-positive patients showed evidence of malnutrition, and 21% suffered from wasting. Of the 39 AIDS patients, reduced body cell mass was observed in 32. Patients with body cell mass greater than 30% of body weight had significantly prolonged survival.

**IMPACT OF WASTING ON SURVIVAL**

There appears to be a direct relationship between the loss of body weight and disease progression and survival. Kotler and colleagues' (Kotler 1989b) retrospective analysis demonstrated a significant correlation between the degree of wasting and death. Body cell mass depletion (discussed below) was measured in patients dying with wasting in
the absence of formal nutritional support. According to Kotler, the extrapolated body cell mass at death was 54% of normal, which corresponded to a body weight at death of 66% of ideal.

Body weight, however, was demonstrated to be a poor indicator of malnutrition. In Kotler's analysis, body weight was within the normal range (91% of ideal) in a majority of patients with severe body cell mass depletion (Kotler 1989b). Body fat content had no direct relationship to survival.

In addition to AIDS, wasting is correlated with reduced survival in other diseases. Patients with tuberculosis, cancer, and inhabitants of the Warsaw ghetto during World War II provide evidence for a clear relationship between depletion in lean body mass and death. Much like Kotler's 1989 report, these studies have shown that death is imminent once severe weight loss occurs (Guenter 1993, Suttman 1995, Graham 1993). Weight loss and loss of body cell mass are risk factors for death (Guenter 1993, Suttman 1995, Graham 1993). These reports demonstrate that, although wasting can be linked to fever, thrush, diarrhea, and other AIDS manifestations, wasting may contribute to death independently of the clinical complications which give rise to it, such as opportunistic infections.

DIFFERENCES IN BODY COMPOSITION BETWEEN WOMEN AND MEN

A number of studies at the Eleventh International Conference on AIDS specifically highlight the differences in body composition between women and men. The importance of these data are two-fold. First, these studies shed more conclusive light on the hypothesis that wasting manifests itself differently in men and women. Second, these studies suggest that the etiology and pathogenesis of wasting, at least endocrine involvement, may also be inherently different between men and women.

In a study of 189 (125 HIV-positive men and women; 64 HIV-negative controls) volunteers, Raghaven and colleagues (Raghaven 1996) reported that both HIV-positive men and women have significantly lower weight, fat, and body cell mass that HIV-negative controls. Moreover, HIV-positive women had a more significant loss in body fat than HIV-positive men. These findings are duplicated by Engelson and colleagues (Engelson 1996b) who report that in a study of 279 clinically ill AIDS patients, HIV-positive women lose disproportionately more fat than HIV-positive men. A study by Muurahainen and colleagues (Muurahainen 1996) has also demonstrated that a significant difference in body composition can be found among white and nonwhite women. Data from this study concludes that HIV-positive nonwhite women with CD4 counts greater than 200 cells displayed significant depletion in body cell mass in the presence of normal body mass indexes (weight adjusted for height). Early body cell mass depletion was not seen in white women. The researchers from all these three studies all conclude that additional research in necessary to corroborate these significant findings and to determine factors contributing to malnutrition and wasting in HIV-positive women.

Both Engelson (Engelson 1996c) and Raghaven (Raghaven 1996) speculate that significant differences in the underlying etiology of wasting contributes to the significant body composition differences between HIV-positive men and women. As depleted lean body mass in HIV-positive men may be a direct result of low testosterone, the significant loss of fat in women may be due to depleted levels of estrogen and progesterone in HIV.
positive women. Again, further research in the etiology and pathogenesis of wasting in HIV-positive women are essential in further understanding these potential etiological differences and provide clues to appropriate treatments.
The Anatomy and Physiology of Nutrition

To better understand the multifactorial process by which wasting syndrome can occur, it is important to define the rather complicated process that nutrients (the food we eat and the liquids we drink) play in maintaining life. The digestive tract, endocrine system, and immune system are all important organ systems that can become dysfunctional in HIV-positive individuals. Many possible complications that can occur in people with AIDS-related wasting are cited in this report. The following overview is intended to provide readers with a basic understanding of the anatomy and physiology of nutrition.

THE DIGESTIVE SYSTEM

The digestive system controls the processes by which nutrients are absorbed into the bloodstream for distribution throughout the body. This system is comprised of the mouth, pharynx, esophagus, stomach, small intestine (the duodenum, jejunum and ileum), the large intestine (cecum and colon), and the rectum. From most of these organs, specific enzymes are produced to metabolize nutrients into usable sources of energy. For example, pepsin, an enzyme produced by the stomach, breaks down large proteins into smaller proteins called peptides. Once partially-digested food has entered the duodenum, the pancreas secretes a number of enzymes which continue breaking down proteins into peptides and subsequently into amino acids and splitting fats into monoglycerides and fatty acids. Further down the digestive tract, small intestinal enzymes further break down food and complete the digestive process.

The small intestine is the most crucial point in the digestive process for nutrient absorption. This organ consists of three divisions: the duodenum, the jejunum, and the ileum. Each division of the small intestine subserves an essential role in the digestive and absorptive process. The duodenum is the uppermost division and is the part to which the end of the stomach attaches. It is about 10 inches long and is shaped roughly like the letter "C." In the duodenum and upper part of the jejunum, Brunner's glands produce mucus, which aid in protecting the walls of the small intestine and mixing nutrients with digestive enzymes. The remainder of the small intestine from the termination of the duodenum is named jejunum and ileum. The jejunal portion continues for approximately the next eight feet, where it becomes the ileum.

The jejunum and ileum are the most important divisions of the small intestine controlling absorption. The lining of the jejunum and ileum consists of folds and villi-finger-like projections responsible for absorbing nutrients. Both divisions are rich in absorptive cells, mucosa-associated lymphoid tissue (MALT)-more specifically, gut-associated lymphoid tissues (GALT). These mucosal and GI lymphoid tissues may contain up to 40% of the body's T lymphocytes, compartmentalized away from the bloodstream, focusing on meeting pathogenic challenges which may enter the digestive tract.

HIV/AIDS associated infections and pathology can affect each of these divisions of the small intestine, all of which may contribute to the wasting syndrome. These disease processes will be discussed below in the section on pathogenesis and etiology.

Once food has been digested, villus epithelial cells absorb the major products of digestion: simple sugars, fatty acids, and amino acids (table 1). Also absorbed are water, minerals and vitamins. Most digested substances enter the capillaries of the villi and are collected in a system of veins that converge on the portal vein, which carries blood from
the intestines to the liver, where absorbed nutrients are processed further. Absorbed fats enter the lymphatic system.

**TABLE 2: SUMMARY OF THE CHEMICAL DIGESTION OF FOOD**

<table>
<thead>
<tr>
<th>DIGESTIVE ENZYMES/FUNCTION</th>
<th>ACTS ON THIS FOOD</th>
<th>RESULTING IN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saliva (Mouth)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>Starch (polysaccharide)</td>
<td>Maltose (a double sugar)</td>
</tr>
<tr>
<td><strong>Gastric Juice (Stomach)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease (pepsin)+</td>
<td>Proteins</td>
<td>Proteoses and peptones (partially digested proteins)</td>
</tr>
<tr>
<td>hydrochloric acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase</td>
<td>Emulsified fats (butter, cream, etc.)</td>
<td>Fatty acids and glycerol*</td>
</tr>
<tr>
<td><strong>Bile</strong></td>
<td>Large fat droplets (unemulsified fats)</td>
<td>Small fat droplets or emulsified fats</td>
</tr>
<tr>
<td><strong>Pancreatic Juice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease (trypsin)</td>
<td>Proteins (either intact or partially digested)</td>
<td>Proteoses, peptides, and amino acids*</td>
</tr>
<tr>
<td>Lipase (steapsin)</td>
<td>Bile-emulsified fats</td>
<td>Fatty acids and glycerol*</td>
</tr>
<tr>
<td>Amylase (amylopsin)</td>
<td>Starch</td>
<td>Maltose</td>
</tr>
<tr>
<td><strong>Intestinal Juices</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptidases</td>
<td>Peptides</td>
<td>Amino acids*</td>
</tr>
<tr>
<td>Sucrase</td>
<td>Saccharose (cane sugar)</td>
<td>Glucose and fructose*</td>
</tr>
<tr>
<td>Lactase</td>
<td>Lactose (milk sugar)</td>
<td>Glucose and Galactose*</td>
</tr>
<tr>
<td>Maltase</td>
<td>Maltose (malt sugar)</td>
<td>Glucose*</td>
</tr>
</tbody>
</table>

*Substances are end products of digestion or, in other words, completely digested ready for absorption.

**THE LIVER**

The liver is a chemical factory that metabolizes nutrients absorbed by the small intestines, processing them further before releasing them into general circulation. Liver cells serve many functions. First of all, liver cells chemically alter potentially toxic substances and render them harmless. Secondly, liver cells convert amino acids, sugars, and fats into energy sources. Once nutrients have been processed fully by the liver, they are released into the general circulation of blood.

Clearly, each organ of the digestive tract plays an important part in metabolizing nutrients. For severely immune compromised individuals, including those with HIV infection, many opportunistic infections (OIs) and possibly HIV itself—can drastically alter the process by which the food we eat is digested. Thus, properly diagnosing and treating opportunistic infections (OIs) is crucial to ensure adequate digestion and absorption of vital nutrients. These complications are discussed in the following chapter on the etiology and pathogenesis of wasting.

**HORMONES & THE ENDOCRINE SYSTEM**
Once food has been converted into useful nutrients, certain hormones play key roles in determining how the body will utilize them in the body. Hormones produced by endocrine glands are major regulators of metabolism, growth and development, reproduction, and the stress response. Endocrine organs secrete hormones which move through the blood, bind to receptors on target cells, and stimulate cell and tissue activity, affecting the cell's growth and maturation, activity, metabolism, reproduction and death. Several of these hormones are altered significantly during HIV infection. As discussed in the etiology and pathogenesis chapter of this report, endocrine hormone abnormalities can be the result of infection, tumors, stress, and malnutrition.

The first hormones of concern are certain adrenal hormones, produced the adrenal glands, located over the kidneys. The adrenal gland has two distinct sections-the adrenal medulla and the adrenal cortex. The adrenal medulla produces the hormone epinephrine (adrenaline), which mobilizes glycogen and increases oxygen consumption when needed. The adrenal cortex produces cortisol (a glucocorticosteroid), belonging to a class of steroids derived from cholesterol. Its primary role in metabolism is to promote synthesis of carbohydrates. Cortisol is also a naturally-occurring anti-inflammatory agent. It is most often produced by the adrenal cortex at times of physical stress, both physical (the immune response to illness, surgery, etc.) and psychological (anxiety and depression). When activated, this hormone has a profound influence on carbohydrate and protein metabolism and on the specialized functions of the cells of many tissues.

The pancreas produces both insulin and glucagon. The primary role of insulin is to decrease blood levels of glucose. The primary role of glucagon is to increase blood glucose. Insulin deficiency (diabetes mellitus) an may lead to production of high levels of organic acids by the liver because of faulty metabolism of fat.

Testosterone-produced by the testes in men-is a sex hormone which plays a large role in proper nutrient metabolism. By stimulating protein anabolism, testosterone promotes growth of skeletal muscles (responsible for greater muscular development and strength in males) and promotes growth of bone. Testicular function is regulated by another endocrine gland situated deep inside the brain, the pituitary gland, which releases luteinizing hormone, which signals the testes to produce testosterone.

Another very important hormone produced by the pituitary gland is growth hormone (somatotrophin). The principal action of growth hormone is to promote bodily growth indirectly by accelerating amino acid transport into cells. With the faster entrance of amino acid into cells, anabolism of amino acids to form tissue protein also accelerates. This in turn, tends to promote cellular growth. In addition to its stimulating effect on protein anabolism, growth hormone also influences fat metabolism.

METABOLISM

Foods are first digested, then absorbed (as either simple sugars, fatty acids, or amino acids), and finally metabolized. Intermediary metabolism, as the term is usually defined, means the chemical changes absorbed foods undergo within the body cells. More simply, metabolism is the body's utilization of foods. Described below are metabolic processes in healthy human beings. In people with HIV/AIDS, metabolism is often altered, sometimes drastically.
The body metabolizes simple sugars, fatty acids, and amino acids to supply itself with energy and make complex compounds (by way of synthesis) that it needs. It consists of two main processes, namely catabolism and anabolism. Each of these, in turn, consists of numerous chemical reactions. Catabolism is the process of breaking down nutrients to supply cells with energy in a form they can use for doing their work. Anabolism is the process by which cells synthesize complex compounds (e.g., cytokines, hormones, structural proteins, etc.). Catabolism supplies the energy that does the work of anabolism and all other kinds of cellular work.

Simple Sugar Metabolism

As described above, most simple sugars are digested and absorbed in the body as glucose. All body cells catabolize glucose, by way of an oxidation process, for their needed energy supply. Glucose is the preferred energy fuel of human cells—preferred to fatty acids and amino acids, that is. Therefore, cells get their energy first from glucose—so long as enough of it continues to enter them—then next from fatty acids, and last from amino acids. Glucose is also used by the body to synthesize larger carbohydrate molecules known as glycogen (starch). When glucose runs low, a process known as gluconeogenesis, which takes place in the liver, makes new glucose from glycogen and amino acids. If blood glucose remains high after catabolism, the excess glucose is converted to fat and to glycogen, again by the liver.

Fat Metabolism

Body cells both catabolize and anabolize fatty acids (glycerol and triglycerides). Fat constitutes a more concentrated energy food than simple sugars. Fatty acid catabolism, like simple sugar catabolism, consists of two main processes, each of which, in turn, consists of a series of chemical reactions. The first process takes place in the liver where fat is converted to either fatty acids or glycerol by a process known as hydrolysis. Then, through a process known as ketogenesis, fatty acids are converted to acetoacetic acid and transported to tissue cells for the final step of catabolism (oxidation via the citric acid cycle). Glycerol, which also derives from fat, is transported to tissue cells and oxidized via the citric acid cycle. Fat anabolism (fat deposition or lipogenesis) consists of the storage of fats mainly in adipose (fat) tissues. Fat stored in the fat depots constitute the body’s largest reserve energy source.

Protein and Amino Acid Metabolism

In amino acid (protein) metabolism, anabolism is primary and catabolism is secondary. In simple sugar and fat metabolism, the opposite is true. Amino acids are primarily tissue-building foods. Simple sugars and fats are primarily energy-supplying foods. The cellular process called protein synthesis (protein anabolism) produces many substances—muscle protein, enzymes, antibodies, and some secretions, to name a few. Protein anabolism plays a major role in the growth and reproduction both of cells and of the body as a whole. Protein anabolism is also the chief process of tissue repair. It accomplishes the healing of wounds, the formation of scar tissue, and the replacement of cells destroyed—especially during infections like HIV. Protein catabolism, like the catabolism of fats, consists of two process. First, liver cells carry on deamination, a process that converts amino acids to keto acids and ammonia. Then keto acids may be changed to glucose by liver cells (gluconeogenesis), or liver and tissue cells may oxidize them (citric acid cycle) or convert them to fat (lipogenesis). Amino acids may be
essential or nonessential; essential amino acids are usually protected while nonessential amino acids are burned like glucose. Various hormones also influence the rates of protein catabolism and anabolism.

Usually a state of protein balance exists in the normal healthy adult body—that is, the rate of protein anabolism equals the rate of protein catabolism. Nitrogen is a constant proportion of protein and is easy to measure; 99% of the body's nitrogen is in protein. When the body is in protein balance, it is also in a state of nitrogen balance; nitrogen taken into the body (via protein foods) equals the amount of nitrogen in protein catabolic waste products excreted in the urine, feces, and sweat. When protein catabolism exceeds protein anabolism, as has been shown in AIDS/HIV, the individual is then said to be in a state of negative nitrogen balance, or in a state of tissue wasting—because more of his/her tissue proteins are being catabolized (broken down) than are being replaced by protein synthesis.

**Metabolic Rates and the Theory Behind Calories**

The term metabolic rate means the amount of energy produced by the body in a given time by catabolism. It represents energy expended or used for accomplishing various kinds of work.

The total metabolic rate is defined using two direct determinants: First is the basal metabolic rate—the energy used to do the work of maintaining life under the basal conditions (i.e., is awake but resting, in a postabsorptive state [12 to 18 hours after the last meal], and is in a comfortably warm environment). The basal metabolic rate accounts for 70% of the total metabolic rate. Second is the energy used to do all kinds of skeletal muscle work—from the simplest activity such as feeding oneself or sitting up in bed to the most strenuous kind of physical labor or exercise. Very often—as a result of HIV and OIs—the immune system places a heavy burden on all three determinants of the total metabolic rate.

**Energy Balance and its Relationship to Body Weight**

When we say that the body maintains a state of energy balance, we mean that its energy input equals its energy output. Energy input per day equals the total kilocalories (Kc) in the food ingested and adequately absorbed per day. Energy output equals the total metabolic rate expressed in kilocalories. Body weight remains constant when the body maintains energy balance—when the total calories in the food ingested equals the total metabolic rate. Body weight decreases when energy output—which includes fighting infections—exceeds energy input. This is explained in detail in our discussion of energy expenditure and HIV infection in the etiology and pathogenesis chapter of this report.

**CYTOKINES AND THE IMMUNE SYSTEM**

When reviewing the discussion of wasting syndrome in this report and elsewhere, a fair amount of emphasis is placed on the role of the immune system—more specifically the immune response to infections—and its relation to wasting.

There are several distinct populations of lymphoid cells—produced by lymphoid tissues—that can be identified by specific cell-surface markers. One class of lymphocytes, thymus
derived or T cells, mediates the cellular response, while another class of lymphocytes, B cells, mediate the humoral (antibody) immune response.

Lymphocytes (i.e., CD4 and CD8 T cells and B cells) and other immune cells (macrophages, neutrophils, etc.) produce chemicals called cytokines-soluble proteins which act as intercellular messengers between other immune cells. Tumor necrosis factor (TNF) is a potent cytokine with many effects on immune and metabolic processes. TNF has two forms, TNF-alpha (also known as "cachectin") and TNF-beta (also known as "lymphotixin"). TNF is mainly produced by monocytes and macrophages but is also produced in NK cells, B and T-lymphocytes, and cells of the brain, liver and skin (Tracey 1993). TNF may be released by cells after exposure to bacteria, viruses, parasites, or tumors. Other cytokines that mediate an inflammatory response are interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon-alpha (IFN-a).

In the presence of an acute infection, these cytokines induce an inflammatory response. The inflammatory response is initiated by cytokines to "rid" the body of infection. The inflammatory response to cytokines increases lipogenesis, glucogenesis, cholesterol synthesis, and inhibits protein synthesis. In other words, inflammation increases production of fats, sugars and cholesterol, and decreases production of protein in muscle.

BRINGING IT ALL TOGETHER: THE ANATOMY & PHYSIOLOGY OF MALNUTRITION

As discussed above, metabolism is the term used to describe chemical alteration of nutrients within the body. Simple nutrients, such as glucose, can be synthesized into larger molecules, such as glycogen (starch), and vice versa. Similarly, large molecules, such as proteins, can be degraded to smaller molecules, such as amino acids, then converted to other nutrients or burned for energy. The enzymatic reactions of metabolism each effect one chemical change, and many changes are required for synthesis, degradation and conversion. For this reason, arrays of enzymes are linked and form cycles. A cycle is a metabolic pathway in which substance A reacts with molecule B to form molecule C, which then through a series of reactions, regenerates B so that more A can be processed. Most enzymes in a pathway can catalyze a reaction in either direction. A few key enzymes work only in one direction and determine the overall direction of the metabolic pathway. These enzymes can be activated or inactivated by the signals that regulate metabolism (i.e., cytokines and hormones).

There are several layers of control of metabolism during normal or abnormal situations. Under normal circumstances, metabolic stability is needed since the body requires a continuous source of fuel, both glucose and fatty acids, while intake (absorption) occurs intermittently through the day. After a meal, there is too much energy available for use, and the energy must be stored. Hours after a meal and before the next meal, there is no readily available supply of energy, which must be retrieved from storage. Such variations in metabolism are not seen in people who are fed constantly by intravenous infusion. The major metabolic regulators under normal circumstances include insulin and glucagon, which have opposite effects. Insulin promotes the disposal of glucose and stimulates the synthesis of glycogen (starch), triglycerides (fats), and proteins. Glucagon promotes the breakdown of these molecules and the production of glucose. As would be expected, insulin levels rise after a meal, while glucagon levels fall, and the reverse happens in the postabsorptive state. Epinephrine (adrenaline) also can switch metabolism rapidly, providing glucose and fatty acids for a "fight or flight" reaction.
Metabolic Derangements and Illness: A Model for AIDS-related Wasting

Starvation and cachexia are the two major examples of abnormal situations leading to metabolic alterations. Starvation can be defined as a deprivation of food, either voluntary or involuntary, that leads to weight loss. Classic studies of the adaptation to prolonged starvation have elucidated the complex but integrated physiology and biochemical changes that occur. During long-term starvation, the body must adapt to nutrient deprivation. Ultimately, most of the energy requirements of the body are derived from stored fat; approximately 80-90% of calories required. Protein catabolism accounts for the remaining 20% of caloric needs. Metabolic alterations occur over time to decrease the body's need for glucose. Skeletal muscle increasingly utilize free fatty acids. The brain, however, cannot use free fatty acids as an energy source since these substances do not readily cross the blood-brain barrier. Through a process known as ketogenesis, free fatty acids are broken down into ketones which can then be used readily by the brain.

Illness and injury produce different effects on metabolism, and can lead to cachexia when chronic. With chronic inflammation, the most significant feature of metabolism is the negative nitrogen balance and depletion of body protein.

The Response to Infection

The response to injury and infection has been described since antiquity. The cardinal signs of inflammation—rubor (redness), color (heat), dolor (pain), and tumor (swelling)—were first described by Cornelius Celsius sometime in the first century A.D. These early observations on inflammation have been broadened by observations over the last two centuries to include the multitude of endocrine and metabolic responses of the patient with serious illness. When symptoms of inflammation are associated with a known infection, alterations of physiologic and metabolic parameters are expected within a certain time and a predictable magnitude. The metabolic changes associated with illness can be described by way of the acute phase response.

The acute phase response (cachexia) involves accelerated mobilization of first fatty acids and then protein (amino acids) from tissue. The metabolic alterations associated with cachexia can be viewed as an integral part of the body's defense. A key feature of the chronic phase response is the use of protein from skeletal tissue necessary for maintaining glucose levels (gluconeogenesis), repair, and survival. This use of proteins helps aid in the removal of harmful enzymes secondary to catabolism. This is important since these enzymes could lead to harmful chemical reactions that perpetuate tissue injury and could lead to fatal, mutliorgan failure. In addition, since the metabolic changes are promoted by changes in the directions of metabolic pathways, simply providing amino acids and energy as food does not alter the process substantially. Thus, the effects of cachexia cannot be reversed simply by feeding. Moreover, while the acute phase response may be life-saving in the short run, it will inevitably lead to severe protein depletion if prolonged.

Cachexia involves more than just alterations in protein metabolism. It also includes changes in energy expenditure and in behaviors including appetite. The mediators of the cachetic response are specific cytokines, the same molecules that direct the immune response to injury or infection, and hormones. It was initially postulated that a single
cytokine was responsible for the metabolic alterations, but later studies showed that several cytokines have cachectin-like effects and that each cytokine has multiple cellular effects. Thus, the same factors that coordinate the immune response also coordinate the metabolic alterations necessary to fuel the immune and inflammatory response.

In response to inflammation and the physical and psychological stress associated with injury or infection, cortisol, epinephrine, and glucagon production increases to counter inflammation and stress. Much like specific cytokine production, these hormones can also produce cachetic-like effects.
Etiology and Pathogenesis

The wasting syndrome can be divided into two categories: acute weight loss, which often rebounds after an OIs is brought under control, and chronic weight loss, which is more difficult to reverse.

In early HIV infection, the process of wasting is thought to be a result of altered metabolism—by way of endocrine abnormalities and cytokine production—since many studies indicate normal caloric intake in asymptomatic HIV-infected patients (Dworkin 1990, Grunfeld 1992b, Hommes 1990, Kotler 1990, Melchior 1991).

OIs and malignancies, which occur in late-stage HIV disease, are thought to be the most significant cause of weight loss and wasting (Grunfeld 1992b). These often result in reduced caloric intake, malabsorption and possible metabolic derangement. In end-stage disease, the cause of wasting and malnutrition can be multifactorial and complicated by one or more OIs.

Primary HIV infection, OIs, malignancies, pre-existing gastrointestinal disease and treatment side effects can all contribute to AIDS-related wasting. HIV-related wasting can be broken down into two categories: altered metabolism and decreased nutrient intake, with most individuals in late-stage disease suffering from a combination of both.

ANOREXIA & MALABSORPTION

Anorexia

Anorexia is described as diminished appetite—an indifference to or aversion to food. The resulting malnutrition can be life-threatening. Although anorexia is not a prominent feature of early HIV disease, it can be quite serious in late-stage disease. Caloric intake correlates strongly with weight change in patients with AIDS (Grunfeld 1992b).

Though anorexia can be multifactorial, it can be diagnosed and treated with complete accuracy. Anorexia can be caused by OIs, cytokine dysregulation, endocrine tissue destruction, depression, and toxicities or side effects from AIDS therapies. Anorexia may also occur secondary to nutrient malabsorption since unabsorbed nutrients in the lower intestine have an inhibitory effect on food intake.

Many AIDS complications can cause hepatomegaly or splenomegaly—enlargement of the liver or spleen, respectively. These enlargements can exert pressure on the intestines resulting in early satiety (a feeling of fullness after ingesting small amounts of food). Kaposi’s sarcoma (KS) of the upper or lower GI tract may also cause early satiety.

Oropharyngeal Complications and Anorexia

OIs of the oral cavity (mouth) and the pharynx (throat) can significantly influence an individual's diet. Many HIV-infected individuals suffer from oropharyngeal complications, such as candidiasis (thrush), Kaposi’s sarcoma, or aphthous ulcers. In late-stage HIV disease, these complications can be quite severe, causing great pain and blockage. Eating often becomes an unpleasant task because of the altered taste of food and the painful ulcerations in the mouth.
Oral thrush (candidiasis) is an infection caused by the fungus Candida albicans. It often occurs relatively early in HIV disease, and can also be induced by certain antibiotics or steroids. Candidiasis is usually diagnosed by visual examination, culture, or smear, and treated with Nizoral, Nystatin, Clotrimazole troches (Myclex), Fluconazole (Diflucan) or other antifungals. However, drug-resistant candidiasis has recently become more common among HIV-infected persons.

Kaposi's sarcoma (KS) is a cancerous-like lesion caused by the uncontrolled growth of blood vessels (angiogenesis) which can occur on the skin (cutaneous lesions) as well as internally (visceral lesions). Oral KS lesions are most often found on the gums and hard palate (roof of the mouth). They are dark in color, and although usually flat and non-painful, may become raised, ulcerated, and painful. If lesions in the oral cavity become extensive, mechanical difficulty with eating, gum disease, and tooth loss may become a problem. Local therapy for oral KS, including intralesional Velban (Vinblastine) and radiation, can cause much discomfort and create an aversion to food. The Velban-injected lesions are often painfully sore for a week, and the primary complication resulting from radiating oral KS is mucositis (ulceration and dryness of the mouth, burning sensations, less saliva, swelling, and change in taste).

Viral Infections (CMV, HPV, Oral Hairy Leukoplakia, Herpes Infections). The signs and symptoms of these various viral infections vary considerably. Oral hairy leukoplakia (OHL) and HPV (oral warts) can both occur relatively early in HIV infection and tend not to be associated with pain. CMV and herpes infection (usually herpes simplex) can both cause ulceration of the oral cavity or esophagus, making eating difficult. Treatment for OHL, which is caused by Epstein-Barr virus (EBV) is high-dose acyclovir (Zovirax). Oral warts can be treated with acid or lasers. Oropharyngeal CMV can be treated with systemic ganciclovir (Cytovene) or foscarnet, while oral herpes may be treated with acyclovir, famciclovir or penciclovir.

Aphthous Ulcers of the mouth are prevalent in HIV disease. Their origin is unknown but it is theorized that cytokines as well as certain drugs (e.g. ddC) may play a role in their formation. These ulcers can be quite large, usually occurring on the palate, sides of the tongue and walls of the mouth. They are also extremely painful, making chewing, drinking and swallowing almost impossible. Thalidomide has been reported to be an effective treatment for aphthous ulcers.

Other Factors Affecting Dietary Intake

All too often, the psychological and social factors, physical disabilities, pain and lethargy associated with HIV-infection are overlooked as important causes of inadequate food intake. Moreover, medications used to treat depression and pain (opiates) can cause anorexia. Social factors which are linked with inadequate food intake include, physical and social isolation, poor knowledge of dietary recommendations, and poverty. Inability to physically feed oneself or procure food can seriously affect food intake.

Malabsorption and Diarrhea

Intestinal nutrient malabsorption in AIDS patients was an early observation and remains a serious problem in many cases. When present, small intestinal injury may be severe and associated with significant functional impairment (i.e., dysregulation of enzyme or mucous production and inadequate absorption). Moreover, complications of the
gastrointestinal tract can manifest themselves in either a clinically silent or overt manner. Impairment of the small intestine is more specifically characterized as villus atrophy (emaciation) and crypt hyperplasia (cell overgrowth).

The most common infections causing villus and crypt abnormalities of the small intestine are protozoa and bacterial infections. In a study of 250 HIV-infected individuals referred for GI evaluation, enteric pathogens were identified in 83% of the 141 AIDS patients with diarrhea (Kotler 1994). HIV—which has not officially been categorized as an enteric pathogen—has also shown to be a possible pathogen, causing small intestine injury and malabsorption.

**Intestinal Parasites**

Infection by intestinal parasites triggers diarrhea and malabsorption in persons with AIDS by causing emaciation of the villus. Villus atrophy occurs because of excessive losses of enterocytes and crypt hyperplasia. Kotler and colleagues note that not only do villus atrophy and crypt hyperplasia interfere with the production of digestive enzymes produced by the small intestine, but they also interfere with proper absorption of nutrients (Kotler 1993a).

**Cryptosporidiosis:** The protozoan Cryptosporidium parvum, which may cause massive secretory diarrhea, is the most commonly identified parasite in people with AIDS. Kotler has observed several different pathologies associated with cryptosporidiosis, including disease of the bile ducts, small intestine, and large intestine. Cryptosporidium infection of the small intestine causes malabsorption and wasting while large intestine disease is more commonly associated with symptoms of colitis (Kotler 1995a). According to Kotler, disease of the large intestine may reflect a reactivation of a previous cryptosporidium infection, whereas infection of the small intestine is often a newly-acquired disease.

C. parvum may be transmitted from person to person, animal to person, or acquired by drinking contaminated water. In people with healthy immune systems, cryptosporidiosis can cause acute, but limited diarrhea. In patients with AIDS, however, infection with cryptosporidiosis can result in a protracted enteropathy and is often accompanied by profuse, watery diarrhea. Currently, there are no satisfactory treatments for cryptosporidiosis.

**Microsporidiosis:** Another common parasitic family that can infect the small intestines are microsporidia (mainly Enterocytozoon bieneusi). Other members of the microsporidia family-Encephalitozoon hellem and cuniculi, and Septata intestinalis-can produce disseminated infections. E. bieneusi infection of the small intestine was first reported in 1985 (Desportes 1985). This condition has been increasingly recognized worldwide and may be responsible for a significant percentage of cases of diarrhea and severe malabsorption in AIDS. However, Rabeneck and colleagues, who conducted a controlled case study, were unable to demonstrate an association between E. bieneusi infection and diarrhea. Of 106 HIV-positive men, half with and half without diarrhea, E. bieneusi was detected with equal frequency in duodenal biopsies of men from each group (Rabeneck 1993).

**Isosporiasis:** Isospora belli is a parasite most commonly found in tropical and subtropical climates. Isospora belli commonly affects the small intestine and can cause villus atrophy and malabsorption.
Other parasites common in persons with HIV especially gay men include, Giardia lamblia and Entamoeba. While many of these infections can be treated effectively, chronic disease left unchecked may lead to intense malabsorption and nutritional deficits.

**Bacterial/Mycobacterial Infections**

The role of bacterial infections in causing malabsorption is not entirely understood. Significant bacterial infections in HIV disease include Salmonella, Shigella, Campylobacter, and Clostridium difficile. According to Kotler and colleagues, malabsorption is caused by bacteria that produce lesions and enterocyte injury (Kotler 1995b). These infections are most evident in the ileum, thus promoting bile salt malabsorption, which promotes ion and water secretion in the colon, leading to diarrhea (Hofmann 1976). However, Smith and colleagues (Smith 1988) offer the hypothesis that bacterial overgrowth can cause diarrhea since depletion of CD4 cells leads to altered Immunoglobulin A (IgA) production. Altered IgA production combined with impaired gastric acid secretion may lead to bacterial overgrowth. Not only can bacterial overgrowth cause malabsorption, but it can also lead to chronic mucosal inflammation via the immune response to these infections (Weinroth 1995).

Unlike parasitic infections that cause villus atrophy and bacterial infections that affect the ileum, enteric infection with Mycobacterium avium complex (MAC) affects the gut-associated lymphoid tissue (GALT). According to Roth and colleagues, GALT is infiltrated by MAC-infected macrophages, which produces a physical blockage, thus malabsorption. (Roth 1993).

**HIV in the Gastrointestinal Tract: Is It an Enteric Pathogen?**

The hypothesis that HIV infects cells of the small intestine is known as 'AIDS enteropathy.' 'AIDS enteropathy' is a catch-all phrase used to explain symptoms without an identifiable cause. Simply put, a patient who reports diarrhea and/or small intestine damage and upon evaluation is found not to have any identifiable disease-causing pathogen or etiological agent is often diagnosed with 'AIDS enteropathy.' Any HIV-positive patient who presents with diarrhea and/or progressive weight loss should be evaluated fully to determine the underlying cause(s) for diarrhea and weight loss. The importance of a full clinical evaluation of HIV-positive patients who report diarrhea and/or weight loss is described in greater detail following this chapter.


Two studies by Ullrich and colleagues have attempted to test these hypotheses further. Patients in whom p24 antigen was detected in the gastrointestinal mucosa exhibited a profound deficiency in the brush-border cell enzyme, lactase (Ullrich 1989). A study
published three years later by Ullrich and colleagues (Ullrich 1992) set out to determine whether the presence of HIV in the gastrointestinal mucosa actually alters cellular function. This study was also designed to measure whether or not AZT would improve gastrointestinal cellular function. 33 HIV-positive patients were studied. All patients were asymptomatic and reported no history of enteric pathogens. Twelve patients were receiving AZT therapy upon entering the study. Ullrich reported a trend that AZT-treated patients were less likely to have p24 antigen in the gastrointestinal mucosa. However these data were not statistically significant. Patients not taking AZT who were found to be p24 antigen positive were more likely to lactase deficient than patients receiving AZT. These data were statistically significant. Overall, p24 antigen-positive patients had lower lactase activity than p24 antigen-negative patients, suggesting that the presence of p24 antigen causes a cellular maturational defect as measured by lactase activity. Moreover, lower crypt mitotic (reproduction) rates were reported in the p24-positive antigen groups (Ullrich 1992). These data hint, but do not prove, the occurrence of HIV-associated gut enteropathy. The Ullrich study, which set out to answer both etiological and treatment-related questions, was too small to answer them. Moreover, these data have not yet been duplicated by any other study.

Many researchers who reported isolating HIV from gastrointestinal mucosa have provided evidence that lymphoid tissue of the small intestine (GALT) is a major reservoir for HIV infection (Fox 1989; Kotler 1991 a, Reka 1993, Reka 1994, Renee 1988). Thus far, two reports demonstrate a correlation between HIV infection of lamina propria lymphoid tissue and malabsorption. Both of these reports cite inflammation - due to the presence of HIV in GALT-as a cause of obstruction of the intestinal canal, mucosal and enzyme-secreting crypts, and damage to villi. MacDonald and colleagues have reported evidence that normal activation of mucosal T cells of these lymphoid tissues in response to HIV infection can alter intestinal function (MacDonald 1988). Clemmens and colleagues report that proliferation of the epithelial cells of the villus is drastically altered due to an overabundance of cytokine production (Clemmens 1995).

Liver Abnormalities

Autopsy studies have shown that hepatic (liver function) alterations are present in most patients dying of AIDS (Weinroth 1995). The liver is frequently affected by OIs such as MAC and CMV (Glascow 1985). Viral hepatitis is also common in individuals with HIV infection and can seriously damage the liver. No specific hepatic abnormality has been attributed solely to HIV infection, nor is there a specific hepatic finding commonly seen in patients with AIDS (Weinroth 1995). Drugs and therapies used to treat HIV disease can have serious effects on liver function due to their hepatic toxicities.

Vitamin and Mineral Deficiencies

Vitamin and mineral concentrations are abnormal in individuals with wasting syndrome. These include low levels of vitamin B-12, vitamin A, vitamin C, folate, carotene, and zinc (Coodley 1993). These deficiencies may result from decreased dietary intake or malabsorption (Weinroth 1995). Studies to evaluate the clinical importance of such deficiencies and replacement therapy are in their infancy.
METABOLIC ABNORMALITIES

Changes in metabolism are common in HIV infected persons. This section focuses on the clinical significance of metabolic abnormalities and their impact on malnutrition in early, middle, and late stages of HIV. Healthy metabolic processes are discussed in the Anatomy & Physiology chapter of this report.

Protein and Amino Acid Metabolism

Protein is composed of linear chains of amino acids. There are twenty naturally-occurring amino acids necessary for life; of these humans can synthesize twelve—the so-called "non-essential" amino acids—while eight must be ingested in the diet, and are therefore known as "essential".

Studies of protein metabolism in AIDS are conflicting. In the absence of secondary infection, both the synthesis and the breakdown of protein are decreased in patients with AIDS (Stein 1990). Patients with AIDS-related weight loss suffer from a greater depletion of protein in proportion to their total body weight (Kotler 1990b). This decrease in protein synthesis may make it difficult to maintain lean muscle mass, or to regain it after periods of rapid weight loss.

According to Stein and colleagues (Stein 1990), protein breakdown and negative nitrogen balance (a marker of muscle breakdown) occurs frequently during AIDS associated OIs. These data were duplicated in a later study by Grunfeld and colleagues (Grunfeld 1993a), which reported that patients with AIDS and active OI(s) were anorectic and did not show adequate conservation of protein, thus showing decreased nitrogen balance. In the same study, Grunfeld and colleagues (Grunfeld 1993a) reported no accelerated loss of nitrogen in the urine of most asymptomatic HIV-positive patients—indicating that nitrogen-releasing amino acids were being metabolized efficiently to build muscle. However, these data are extremely limited based on the small sample size studied and still require confirmation. Of major importance is the fact that both studies demonstrated significant decreases in nitrogen balance and increased protein catabolism in HIV-infected patients with secondary infections. To this end, protein metabolism in AIDS, especially in its early stages, should be studied more extensively.

Other studies have also attempted to define mediators of increased protein catabolism in HIV/AIDS. According to Beutler and colleagues, when media from endotoxin stimulated macrophages are applied to muscle in vitro, the rate of muscle degradation is accelerated. The cytokines or combination of cytokines released from macrophages capable of accelerating muscle protein degradation were not known (Beutler 1985a), but are now believed to include the inflammatory mediators tumor necrosis factor (TNF), interleukin1 (IL-1) and possibly other cytokines TNF, in animal models, induces protein catabolism (Strieter 1988).

Fat Metabolism

Altered fat metabolism is common in HIV infection. Dysfunctions in fat metabolism, known as hypertriglyceridemia, have not been linked to lean body mass depletion (muscle wasting). Grunfeld and colleagues were the first to note hypertriglyceridemia in asymptomatic and symptomatic HIV-positive patients. Symptomatic HIV-positive patients presented with higher serum triglyceride levels when compared with HIVnegative
controls. Asymptomatic HIV-positive patients showed intermediate triglyceride levels, ranging between the symptomatic patients and HIV-negative controls. Fifty percent of the symptomatic group had abnormally elevated triglyceride concentrations, as did 50% of the asymptomatic group. However, no correlation was observed between either the high levels of triglycerides and body cell mass depletion (Grunfeld 1989). Nonetheless, elevated triglycerides indicate immune activation and are a bad prognostic marker.

**Carbohydrate Metabolism**

Hommes and colleagues reported that glucose metabolism appears to be altered in HIV-infected patients (Hommes 1991). However, whether or not this finding correlates with muscle wasting has yet to be determined.

**The Inflammatory Response to HIV and OIs**

HIV/AIDS is a chronic inflammatory disease. Inflammation, which is mediated by the immune response to HIV and OIs, causes muscle mass to be catabolized (broken down) in response to the body's demand for energy. Instead of sequentially using glucose and then fat-as typically seen in nutrient-starved, healthy people-energy production becomes progressively protein based (i.e., utilizing amino acids readily available from muscle).

**Hypermetabolism**

Extensive reports document metabolic disorders which occur during infection and cancer. Hypermetabolism, demonstrated by high resting energy expenditure (REE), increases in basal metabolic rate, and negative nitrogen balance, has been reported in many wasted patients with sepsis (Beisel 1975), cancer (Brennan 1977), and burns (Wilmore 1974). Patients with HIV and AIDS are hypermetabolic (Grunfeld 1992b, Melchior 1991, Hommes 1991). Hommes and colleagues found that an increase in resting energy expenditure is found in asymptomatic patients early in the course of HIV infection when CD4+ counts are normal (Hommes 1991). Melchior and colleagues demonstrated that resting energy expenditure is further increased later in HIV infection and may increase even further in the presence of acute opportunistic infections (Melchior 1991).

Do increases in resting energy expenditure correlate with wasting? Not necessarily, claims Grunfeld and colleagues. In one particular study, average weight was stable in patients with HIV infection or AIDS when secondary infections were not present. However, when patients with AIDS had active secondary infections, they demonstrated striking weight loss, averaging five percent of body weight in 28 days. There was no significant correlation, however, between weight loss and the increase in resting energy expenditure in individual patients (Grunfeld 1992b).

Although several studies have shown increased resting energy expenditure (REE) in HIV infection (Grunfeld 1992 a, Melchior 1991), reduced energy (caloric) intake, and not elevated energy expenditure, is the prime determinant of weight loss in HIV-associated wasting (Grunfeld 1992b). Recent data from Macallan and colleagues (Macallan 1995) suggests that in patients with HIV infection, total energy expenditure (TEE) is reduced during episodes of weight loss. The true determinant of energy balance is not REE but TEE. Other studies demonstrate that although REE is increased during episodes of weight loss, increased REE is not a constant feature of HIV infection (Suttmann 1993).
Increases in REE in early disease are adequately compensated for by modest increases in caloric intake, thus avoiding weight loss. However, if TEE continues to decrease and REE continues to increase, physical activity may become limited (thus halting exercise required for skeletal muscle growth) and energy intake may be reduced (Donald Kotler, personal communication).

Cytokines and the Cachectin Hypothesis

The body's response to infection has been well studied, however, the complexities of cytokine production during infection are not completely understood. In cancer patients, numerous derangements take place in cytokine and hormonal function that directly affect nutrition and often cause cancer cachexia. Cytokines are produced in a programmed sequence in an attempt, sometimes futile, to battle invading infection or cancer. Immune cells produce cytokines in the course of the inflammatory and anti-infective response. Cytokine infusions in humans reproduce the classic symptoms associated with infections. These include some that are prominent in AIDS: fever, myalgias, nausea, anorexia, fatigue, lethargy, diarrhea, anemia, tachycardia, and confusion (Grunfeld 1991).

No single cytokine is the sole cause of the anorexia and cachexia associated with HIV disease. Nevertheless, multiple cytokines may contribute. Numerous animal studies implicate cytokines as potent mediators of anorexia and wasting; confirmatory human studies have yet to be done.

Does TNF Cause Wasting?

Because of the metabolic abnormalities (discussed above) that occur in chronic infections and AIDS, there has been a fair amount of research attempting to implicate the immune system's response to infection as the cause of metabolic abnormalities. Beutler and colleagues, citing data that weight loss is associated hypertriglyceridemia, attempted to find a host factor-dubbed "cachectin"-that mediates the rapid depletion of fat tissues (Buetler 1987). Media from macrophages—which contain multiple cytokines—was found to induce wasting when given to rats. The media from macrophages was also tested on fat cells in vitro, and was found to decrease fatty acid synthesis and increase the breakdown of stored triglycerides. The factor in question was found to be identical to the cytokine, tumor necrosis factor (TNF).

Tumor Necrosis Factor (TNF) and Other Cytokines

Soon after Beutler's report, a series of studies found high levels of TNF in people with AIDS (Lahdevirta 1988, Beutler 1989, Tracey 1988). Thus, TNF was implicated further as the cause of wasting. Moreover, Grunfeld and colleagues reported in 1991 that several other cytokines were also responsible for inducing hypertriglyceridemia, and possibly wasting: interleukin-1 (IL-1) as well as the interferons alpha, beta, and gamma promote increased catabolism of fat, in vitro (Grunfeld 1991).

To test the above mentioned hypothesis, Grunfeld and colleagues administered cytokines to animals. TNF was not found to have any effect directly on fat or muscle tissue. Although it was reported that TNF and IL-1 rapidly increase plasma triglycerides, they did not slow the clearance of triglycerides from the circulation. However, from these data, an intricate metabolic theory known as futile cycling was cited (Grunfeld 1991).
In healthy individuals there is a metabolic cycling process by which triglycerides from fat tissue are transported to the liver, oxidized, and converted into carbohydrates (glucose) when total energy expenditure (TEE) is increased and extra energy is needed. In turn, glucose can then be used to build or restore lost protein from muscles. When TNF was administered to animals this important function of metabolism was altered; fat tissue was broken down, oxidized by the liver, and converted back into fat tissue. From these data, Grunfeld concluded that futile cycling wastes energy and could theoretically contribute to the wasting syndrome in laboratory animals (Grunfeld 1991). However, given the data that conclude that hypertriglyceridemia does not contribute to wasting per se, it appears that people with AIDS compensate for futile cycling of fatty tissue.

Measuring and studying TNF and other cytokine levels in human subjects has been problematic. Once removed from the body, serum levels of TNF have a half-life of six minutes before it proceeds to break down. No consensus exists on the best method for quantifying TNF levels. Little is known about the relationship between the regulation of the secretion of TNF and its receptors in HIV infection. While numerous studies have found that plasma free TNF levels are significantly elevated in patients with symptomatic disease, there is little evidence of elevated free TNF in asymptomatic HIV-infected individuals (Lahdevirta 1988, Hober 1989, Krishnan 1990, Kalinkovich 1992). It is possible that measurements of serum TNF are not representative of activity of the TNF system and that TNF receptors and inhibitors are better markers. TNF in the blood is rapidly bound to nearby cells, and tends to act locally rather than systematically in vivo, making plasma TNF measurement difficult to carry out.

Cytokines have been implicated in causing anorexia. Two models, using TNF, have defined how cytokines can induce anorexia. Feingold and colleagues have reported that TNF decreases gastric production of enzymes and food movement throughout the gut. This results in retention of food in the stomach and small intestine (Feingold 1990). Fantino and colleagues (Fantino 1993) have reported elevated TNF levels in the central nervous system, which has been correlated with decreased appetite. Animal studies have also implicated other cytokines-gamma interferon and IL-1-in causing anorexia (Mori 1991). As discussed above, anorexia in itself has been found to be a leading cause of weight loss and wasting in HIV infection.

**Endocrine Function**

Data from a study conducted by Coodley and colleagues suggests that endocrine function in HIV wasting syndrome differs from that of HIV-infected patients without wasting. In this study, endocrine function was analyzed in sixty-six HIV-seropositive patients, fourteen of whom met the clinical definition of wasting. Thyroid, gonadal and adrenal function tests were performed on all patients. Total and free testosterone levels were significantly lower in the patients with wasting compared with the patients without wasting. Prolactin levels were significantly higher, and cortisol levels were higher (with borderline significance) in patients with wasting compared to patients with similar CD4 counts without wasting and were inversely related to weight loss (Coodley 1994).

**Testosterone**

Various reports have described altered testosterone levels in HIV-positive men. Testosterone promotes the growth and maintenance of muscle tissue. In a study by
Dobs and colleagues (Dobs 1988), 45% of the patients with AIDS had free testosterone levels below the normal range, as did 29% of the patients with AIDS-related complex (ARC) and 25% of the asymptomatic HIV-positive patients. Several other reports confirmed these findings. Coodley and colleagues found that testosterone was frequently lowered in advanced HIV infection (Coodley 1994). Several etiologies for decreased testosterone values have been suggested, including primary testicular dysfunction, drug side effects (particularly from ketoconazole and ganciclovir), hypothalmic abnormalities (perhaps stemming from severe illness), and elevations in cortisol levels (produced by the adrenal glands in the "stress response" to infection). Coodley directly correlated testosterone deficiencies with wasting, but could not determine whether it was the result of or a cause of wasting.

Because testosterone is an anabolic steroid, it has been suggested by a number of researchers that testosterone replacement therapy-and anabolic steroids, in general—could aid in restoring muscle nitrogen balances and recovering muscle protein loss. Data on testosterone and anabolic steroid therapies are discussed in the next chapter on treatments.

**Human Growth Hormone**

Little data are available on alterations in human growth hormone (HGH) in HIV infection or the relationship between endogenous HGH levels and wasting. Lieberman and colleagues have shown that low levels of insulinlike growth factor (IGF), a precursor to HGH, may be present and contribute to lower HGH levels. Although plasma growth hormone levels were normal in studied patients with wasting syndrome, some degree of growth hormone resistance was reported (Lieberman 1994).
DRUG SIDE EFFECTS

Nutritional Intake

Little attention has been paid to the adverse effects drugs have on nutritional intake. The anorexia, altered taste sensation, abdominal pain, vomiting, diarrhea, nausea and GI ulcerations associated with some drugs used for treating HIV disease must be considered. Eliminating the offending drug(s) may be difficult for many HIV-infected patients who are dependent on them. It makes sense to consider all drugs in a treatment regimen and weigh the benefits against the risks. If discontinuation of a certain drug is not possible and no second line therapy is available, then dose scheduling, delivery method and other drug manipulations— as well as dietary modifications—may be helpful. Drug combinations should also be evaluated to reduce their adverse side effects. Finally, clinical trials should pay more attention to anorexia and other GI complications as adverse events.

Metabolic and Hormonal Side Effects

In clinical trials designed to test the efficacy of drugs for HIV disease, little data have been collected about wasting and malnutrition as adverse events. Numerous medications used in the treatment of HIV disease result in hormonal or metabolic disturbances. For example, AZT can produce muscle wasting or myopathy. The use of IV pentamidine for Pneumocystis carinii infections is associated with pancreatic islet cell toxicity resulting in transient hypoglycemia due to increased insulin secretion. This can be followed by islet cell death and the development of permanent diabetes mellitus (Stahl-Bayliss 1986; Waskin 1988). Likewise, Megestrol acetate (Megace) may induce diabetes mellitus (Grimspoon 1993). Lowered levels of testosterone have also been associated with the use of Megace (Engelson 1995, Wagner 1995). Megace is thought to enhance lipogenic enzymes, leading to the addition of fat mass rather than lean body mass. ddl (Videx) can induce pancreatitis—a possible life threatening side effect. Amylase—a starch-splitting enzyme—is produced by the pancreas and the salivary glands to aid digestion of food. An increase in amylase serum levels may indicate pancreatitis.

The following table provides some hormonal and metabolic side effects of drugs used in HIV disease.
TABLE 3: HORMONAL AND METABOLIC SIDE EFFECTS OF DRUGS USED FOR HIV DISEASE.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Hormonal or Metabolic Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Didanosine</td>
<td>Pancreatic inflammation</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Decreased ionized calcium / Hypocalcaemia, Nephrogenic diabetes insipidus</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Reduced adrenal testicular steroidogenesis / Hypoadrenalism, Reduced 1,25-dihydroxy vitamin D formation / Hypogonadism</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>Diabetes mellitus, Reduced testosterone levels</td>
</tr>
<tr>
<td>Opiates</td>
<td>Increased cortisol metabolism</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Pancreatic islet cell destruction, Hypo/Hyperglycemia, Renal magnesium wasting / Hypomagnesaemia, Hypocalcaemia</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Increased cortisol catabolism</td>
</tr>
<tr>
<td>Suramin</td>
<td>Impaired adrenal glucocorticoid synthesis; degenerative pathological changes of the adrenal cortex</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Interference with renal potassium secretion</td>
</tr>
</tbody>
</table>

Table adapted from Grinspoon & Bilezikian (1993).
Diagnosis & Monitoring

Presently, the CDC criterion for a diagnosis of HIV related wasting is the loss of 10% of body weight plus either chronic diarrhea (two or more loose stools daily for more than 30 days) or chronic weakness and fever for greater than 30 days. There are currently no standard clinical criteria for monitoring nutritional status in HIV infection. Many researchers believe the criteria for wasting are in need of serious revision (Donald Kotler, personal communication). Data from numerous studies indicate that simple body composition studies through the use of bioelectrical impedance are feasible and reliable as indicators of nutritional status (Ott 1993, Sluys 1993).

BODY WEIGHT AS AN INDICATOR OF WASTING

Wasting in HIV infection is a combination of weight loss and loss of lean body mass (LBM) accompanied by malnutrition and malabsorption. Unintentional weight loss in the HIV-infected individual is now widely accepted as the final stage in the wasting syndrome. During HIV infection, some individuals undergo a slow transformation from lean body mass (non-fat tissue) to fat mass. In early disease, this may be the first evidence of the wasting syndrome. This transformation is not evident merely by observing body weight, which may remain constant or even increase during the gradual shift (Ott 1993). Thus, body weight is not a reasonable marker of malnutrition (Suttman 1991, Ott 1993, Kotler 1990c).

Excess body fat and excess extracellular water, may mask significant body cell mass depletion and is most likely to be seen in seriously ill patients (Kotler 1985). Thus, simply measuring changes in body weight does not measure body composition. The loss of muscle and perhaps organ tissue may remain unnoticed unless more detailed measurements are carried out. Bioelectrical impedance analysis (discussed below) has shown to be a highly accurate measurement of lean body mass.

Numerous studies cited in this report use body weight as an indicator for wasting and do not record data on lean body mass or body cell mass (LBM or BCM), making evaluations or comparisons of the data difficult.

It is important to differentiate between mere loss in weight and loss of protein stores (in lean tissue) that occur during HIV infection. When acute weight loss is halted by treating an 01, an individual may regain lost weight by adding fat rather than rebuilding lean tissue. The body needs lean tissue both in the form of skeletal muscle and visceral (organ) mass to maintain health and a responsive, functional immune system. Kotler and colleagues (Kotler 1989) provided data indicating that maintaining body mass can prolong life. Simply taking in more nutrients and gaining weight does not automatically produce recovery from wasting.

LEAN BODY MASS (LBM) & BODY CELL MASS (BCM)

Body cell mass (BCM) is defined as the amount of intercellular mass (the protoplasm or functional part of the cell) versus the amount of extracellular fluid found in the body (extracellular fluid and other body compartments, such as bones and ligaments, are not metabolically active). Lean body mass (LBM) which contains the body cell mass, is defined as the amount of non-fat tissue and is the nitrogen containing part of the body. It is the metabolically active tissue responsible for many functions including effective
immunity (Hemsfield 1991). HIV-infected individuals have depleted body cell mass; a higher percentage of body weight is water, corresponding to an overhydration of the extracellular space (Melchior 1991). Individuals whose lean body mass is preserved have a greater survival and recover more successfully from Ols (Ott 1993). Preservation of BCM is also associated with a greater quality of life, as indicated by better psychological state and energy levels (Kotler 1989a).

"GOLD STANDARD" TOOLS FOR MEASURING BODY COMPOSITION AND NUTRITION

There are several methods available to primary care providers and investigators to measure for malnutrition. Body weight, which may be acceptable as an initial screen for assessing nutritional status, is ineffective as a tool to decipher changes in lean tissue. Measuring nutritional status can be determined using the "gold standard" methods described here.

Muscle protein reserve can be estimated from the serum total protein, albumin, and transferring levels. These levels can typically be found in a screening profile assessment, commonly utilized by most primary care physicians treating HIV-positive patients. However, these serum levels, especially albumin, are highly sensitive and may not necessarily reflect clinical malnutrition.

Somatic (skeletal) protein reserve is estimated by collecting a 24-hour urine specimen and quantitating the total amount of creatinine present. This value is then compared to the amount of creatinine excreted by a control; a well-nourished and non-HIV-infected individual of the same weight and height. This comparison is referred to as the creatinine/height index.

Fat reserve is determined per anthropometric measurement of the patient's triceps skinfold. A nitrogen balance determination is used to evaluate the dynamic relationship between nitrogen utilization and nitrogen loss.

Graham and colleagues (Graham 1994) identified several lab values which appeared to predict HIV-associated wasting. Early predictors included, high B-2-microglobulin levels, fatigue and anemia. Interferon-alpha appears to stimulate B-2-microglobulin, which is a non-specific marker for generalized immune activation. 6 -2-microglobulin is part of the HLA class I protein on the surface of activated cells. During inflammation, B-2 -microglobulin particles are rapidly turned over and their levels increase in the blood.) Later predictors included a clinical diagnosis of AIDS and/or Candida (thrush) infection. Zangerle and colleagues (Zangerle 1994) found that BCM correlated inversely with urinary neopterin (another non-specific marker for immune activation). In contrast to the study by Graham, Zangerle failed to correlate B-2-microglobulin with BCM. Thus, measuring B-2-microglobulin levels has not yet been shown to be predicative of malnutrition or wasting.
TABLE 5: TOOLS AND VALUES OF TYPICAL NUTRITIONAL ASSAYS IN HIV.

<table>
<thead>
<tr>
<th>Clinical/Lab</th>
<th>Extent of Malnutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters</td>
<td>Mild</td>
</tr>
<tr>
<td>Albumin, gm/dL</td>
<td>2.8-3.2</td>
</tr>
<tr>
<td>Transferring, mg/dL</td>
<td>150 – 200</td>
</tr>
<tr>
<td>Creatinine/height index (%), actual/ideal X 100</td>
<td>60 – 80</td>
</tr>
<tr>
<td>Ideal body weight, %</td>
<td>80 – 90</td>
</tr>
<tr>
<td>Usual body weight, %</td>
<td>85 – 95</td>
</tr>
<tr>
<td>Weight loss/unit time</td>
<td>&lt;5%/month</td>
</tr>
<tr>
<td></td>
<td>&lt;7.5%/3 mo</td>
</tr>
<tr>
<td></td>
<td>&lt;10%/6 mo</td>
</tr>
</tbody>
</table>

Normal Anthropometric Measurements

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triceps skinfold, (mm)</td>
<td>12.5</td>
<td>16.5</td>
</tr>
<tr>
<td>Mid-arm circumference</td>
<td>29.3</td>
<td>28.5</td>
</tr>
</tbody>
</table>

While these diagnostic tools have certainly inabled primary care physicians to more specifically assess potential metabolic disorders, they are highly variable and do not accurately measure body composition (Kotler 1994c).

BIOELECTRICAL IMPEDANCE ANALYSIS (BIA)

Bioelectrical impedance analysis is a simple method to perform compartmental analysis of body weight. The device measure the electrical impedance of the body. Body weight is made up of fat, muscle, and water. BIA compartmentalizes and determines the mass value of all three. It is used to measure body cell mass in conducting nutritional evaluations for various chronic diseases. The data are analyzed by computer, taking into consideration variables such as height, weight, sex and age. A number of researchers have used BIA to assess BCM, LBM and ECM in HIV-infected individuals (Suttmann 1994, Ott 1993, Sluys 1993). According to Kotler, BIA is able to predict body cell mass and fat free mass within 5%. This variability is much lower than variability seen using "gold standard" tests (Donald Kotler, personal communication). BIA is simple to administer to patients, similar to an electrocardiogram. It is economical and non-invasive and can be administered at the bedside for patients who are not ambulatory.

EVALUATION OF THE DIGESTIVE TRACT AND GUT

There has been a fair amount of controversy surrounding what constitutes an appropriate evaluation of the digestive tract and gut. In 1990, Johanson and Sonnenberg published a cost-benefit analysis of running diagnostic tests on HIV-positive patients with diarrhea, which discouraged aggressively evaluating patients. Their conclusion was that a minimal evaluation should be performed in AIDS patients with diarrhea, and that a full evaluation should only be performed when patients do not respond to standard antidiarrheal therapy (Johanson 1990).
According to Douglas Simon (Simon 1992), many gastroenterologists have used the Johanson and Sonnenberg report to justify not being aggressive in evaluating AIDS-associated diarrhea. Diarrhea that is not immediately linked to a distinct pathogen in the stool sample is often diagnosed as AIDS enteropathy—a generalized term signifying an unknown cause. Given the many pathogens linked to diarrhea and malabsorption, which wouldn't typically make themselves known upon stool sample, this conservative diagnostic approach is inexcusable.

Problems with Sonnenberg and Johanson’s report are five-fold. First, the data and conclusions generated by the authors are based on a review of medical literature published between the years 1984 and 1987. HIV-positive patients with diarrhea were not studied, per se, in this particular study. Second, the authors seem to believe that 70% of patients with AIDS and cryptosporidiosis respond to diphenoxylate (Lomotil). In the many studies of agents to treat cryptosporidiosis, a chronic disease for which there is no standard treatment, none has reported a 70% response rate. Third, microsporidiosis was not an officially-recognized opportunistic infection at the time of those reports analyzed by the Sonnenberg and Johanson. It is only in recent years that microsporidiosis has been linked to diarrhea and malabsorption, for which diagnostic tools are now available. Fourth, in the time a patient is found to have diarrhea by an unknown pathogen, started on antidiarrheal therapy, and found to be unresponsive, valuable time has been lost in replenishing lost nutrients. Treating diarrhea and malabsorption aggressively, by way of antimicrobial therapy and possibly nutritional supplementation, can make a considerable difference in preventing or halting weight loss and wasting. Fifth, there are several clinical trials open and enrolling patients with identifiable pathogens causing diarrhea and malabsorption. An overlooked diagnosis will prevent many patients from enrolling in trials that may potentially offer positive results from experimental treatments.

According the Douglas Simon, Director of Gastroenterology at Bronx Municipal Hospital Center in New York, a complete evaluation is done if there is any degree of diarrhea along with weight loss, malabsorption, fever, abdominal pain, nausea, vomiting, or blood in stool. The evaluation begins with stool studies, which look for the presence of parasites or ova; both cryptosporidiosis and microsporidiosis are readily identifiable through these tests. Diagnostic techniques for identifying cryptosporidium particles (oocysts) in feces include variations of modified acid-fast stain, fluorescent auramin-rhodamine stain, ELISA antigen capture methods, indirect immunofluorescent assay (IFA) and monoclonal antibody tests. E. bieneusi, the leading microsporidium found to cause disease in HIV-positive patients, is now readily diagnosed by the examination of stool samples using one of three staining techniques. The disseminated species of microsporidia may be diagnosed by similar techniques in stool, urine, or nasal washings.

If a patient is found to have an identifiable pathogen, he/she is then treated. If treatment results in reduced diarrhea, patients are observed for possible relapse. If diarrhea persists, stool studies are repeated. Persistent pathogens are retreated; new pathogens are treated accordingly. A study by Kotler and colleagues (Kotler 1993a) suggests that the D-xylene absorption test can be used to identify patients with chronic unremitting diarrhea and malabsorption who may eventually become progressively malnourished. For patients in whom no identifiable pathogen is found upon stool studies, as well as those who do not respond to treatment is the presence of a known pathogen, a further gastrointestinal (GI) workup is performed.
THE GI WORKUP

The GI workup is most commonly performed by way of endoscopy. Two forms of endoscopy are available; either using a flexible sigmoidoscopy or colonoscopy with biopsy and/or and upper endoscopy with duodenal aspirate and biopsy. An electron microscope is used on biopsied tissue to determine the presence of microscopic pathogens. Biopsy may be critical, given the variety of intestinal parasites that can infect humans.

Deciding which endoscopy to use depends on the symptoms involved. Symptoms specific the upper half of the GI tract (malabsorption, periumbilical pain, large volume diarrhea, blooded stools) will often require upper endoscopy. Symptoms specific to the lower-half of the GI tract (no malabsorption, lower abdominal pain, small volume diarrhea, and/or blood in stool samples) requires flexible sigmoidoscopy.
Treatments for HIV Wasting Syndrome

As with the monitoring and diagnosis of wasting syndrome, a standard-of-care for the treatment of wasting syndrome does not yet exist. Once a thorough workup has been completed, and the patient's overall condition evaluated, a treatment regimen and nutritional program should be initiated immediately. Among the kinds of interventions which should be considered are treatments for inadequate food intake, malabsorption and diarrhea (anti-emetics and appetite stimulants), treatments for enteric pathogens (anti-infectives), appetite supplements (including oral, parenteral and enteral nutrition), endocrine and anabolic agents, and possibly cytokine modulators. These approaches must be tailored to an individual's medical condition, combined with an appropriate nutritional regime.

TREATMENTS FOR INADEQUATE FOOD INTAKE

The use of antiemetics may be helpful if nausea and vomiting (emesis) are causing appetite suppression. Appetite suppression can be treated with appetite stimulants.

Antiemetics

There are a number of antiemetics approved for the treatment of emesis (nausea and vomiting). Antiemetics, while widely used, have not been studied for safety and adverse events in patients with HIV/AIDS. Antiemetics interfere with the medullary centers (the vomiting center and chemoreceptor trigger zone) in the body that induce vomiting. Many compounds used to treat HIV, as well as a number of Ols themselves, can trigger these zones. The most common drugs used in clinical practice to control emesis in HIV-positive people include: granisetron (Kytril), hydroxyzine (Atarax, Marax, Vistaril), metoclopramide (Clopra, Reglan), ondansetron (Zofran), prochlorperazine (Compazine), promethazine (Mepergan, Phenergan, Prometh), thiethylperazine (Torecan), and trimethobenzapine (Tigan).

Appetite Stimulants

The only two treatments approved by the FDA for the treatment of AIDS-related wasting syndrome are appetite stimulants; Megace brand megestrol acetate and Marinol brand dronabinol.

MEGESTROL ACETATE

Megestrol acetate is a synthetic progestational agent originally approved as a treatment for inoperable breast cancer. It was also found to be effective as an appetite stimulant and as a treatment for weight loss in patients receiving chemotherapy for breast cancer (Schmoll 1991, Tchekmeydian 1987). The mechanism of appetite stimulation is unclear. Megestrol acetate also appears to increase fat synthesis and may alter testosterone and cortisol synthesis.

Approval of megestrol acetate was based on data from two twelve-week placebo-controlled studies conducted in patients with AIDS wasting. In a preliminary, open-label, pilot study, 21 of 22 patients who were administered 320 mg/day of megestrol acetate gained weight, with a mean increase of 7.3 kg. The median time to peak weight gain was 14 weeks (Von Roenn 1988).
In the first randomized, placebo-controlled study conducted by Von Roenn and colleagues, 270 patients were enrolled. All patients enrolled were evaluable for safety data and 195 patients were evaluable for efficacy data. All patients were randomized to receive megestrol acetate (either 100, 400, or 800 mg/day) or placebo. A five to seven pound weight gain was observed in the megestrol acetate group, and a two-pound weight loss was observed in the placebo group. At 12 weeks of therapy, however, the only statistically significant difference reported was between the 800 mg megestrol acetate group and placebo. While there was a trend towards increased mortality in the megestrol acetate group—20 of the 183 (7%) patients on megestrol acetate and 2 of the 86 (2%) patients on placebo died—the difference was not statistically significant (Von Roenn 1994).

In a second randomized study, conducted by Oster and colleagues, of 100 patients receiving 800 mg/day or placebo, a mean weight gain of 4.16 kg was noted at 12 weeks on megestrol acetate, compared with a loss of 0.61 kg in the placebo group. Body mass index increased by 1.36 kg in the treated group, versus a decrease of 0.21 in the placebo group. Non-responders tended to have more wasting and lower CD4 cell counts at baseline, but this was not statistically significant. Despite the overall weight gain, lean body mass declined in both groups (0.28 kg in the treatment group versus 0.34 kg in the placebo group), with a concomitant increase in fat mass in the treatment group. In these trials, the treatment group given 800 mg ingested 700-750 more calories per day compared to the placebo group at 8-12 weeks (Oster 1994).

Megestrol acetate, a drug originally studied in women with breast cancer, has been studied in very few HIV positive women. At the time of its FDA approval, megestrol acetate had only been studied in ten women. In all ten women, breakthrough bleeding not associated with regular menstrual cycles was reported (Von Roenn 1994, Oster 1994). A dose-ranging clinical trial of Megace in HIV-positive women with significant weight loss is currently being conducted.

One explanation for the rate at which fat mass accrues—accounting for the majority of body weight gained—is the speculation that megestrol acetate induces hypogonadism. That is, it decreases testosterone production in men (Wagner 1995, Engelson 1995). According to Kotler, however, it is still not known whether the failure to gain much lean body mass represents a megestrol acetate-induced hypogonadic state or the presence of underlying secondary infections. Nor is it known whether deposition of fat is beneficial in the long run (Kotler 1995c). To test the hypothesis that megestrol acetate fails to induce lean body mass increases because of its hypogonadic effects, the AIDS Clinical Trials Group is currently finalizing a protocol (ACTG 313) to study megestrol acetate alone and in combination with testosterone.

**DRONABINOL (MARINOL)**

Dronabinol is a synthetic form of one active ingredient found in marijuana-delta-9-tetrahydrocannabinol (THC). In cancer patients (Plasse 1991), increases in appetite were found in an open-label, dose-ranging study. However, patients continued to lose weight.

Approval of Dronabinol for the treatment of AIDS-related weight loss was based on two controlled studies. In the first study, conducted by Struwe and colleagues (Struwe 1993),
twelve patients were randomized to dronabinol or placebo. Only five completed the incredibly short, five-week study. The five patients who completed the study showed improvement in symptom distress and increased body fat, with minimal increases in appetite score and weight. However, based on the study design and the small patient population who completed the study, no statistically significant differences could be found between those who received dronabinol and those who received placebo.

A larger controlled trial in 139 patients has been completed and reported. In this study, Beal and colleagues (Beal 1993) enrolled 139 patients in a double-blind, placebo-controlled trial of dronabinol (2.5 mg bid) versus placebo for six weeks. At the end of six weeks, all patients were offered open-label drug. At the conclusion of the randomized study, 50 of the 72 dronabinol recipients and 38 of the 67 placebo recipients were evaluable. Appetite, measured on a visual analogue scale (a method by which patients self-report their appetite increase/decrease by use of a numerical scale) was significantly improved in the dronabinol group (p= 0.02). Mean weight change was +0.1 kg in the dronabinol group and -0.4 kg in the placebo group; these data were not statistically significant. At the end of the first month of the open-label extension of the study, there was no significant difference between patients originally randomized to receive either placebo or dronabinol.

TREATMENTS FOR OPPORTUNISTIC INFECTIONS AND DIARRHEA

Since wasting may result from specific disease complications such as OIs, effective OI treatment may arrest wasting, stabilize weight and even possibly replete lean body cell mass. Successfully treated patients-anyone who survived under the open-label compassionate use ganciclovir program-showed an increase in body weight, body cell mass as measured by total body potassium, body fat, and serum albumin, whereas untreated historic controls with CMV infection showed decreases in these parameters (Kotler 1989a). Treated patients showed an energy balance of more than 650 kilocalories/day greater than the untreated patients in the retrospective analysis.

Without a doubt, tremendous progress has been made in developing effective treatments for OIs, including some which cause malabsorption and diarrhea. Unfortunately, the two most significant malabsorption-associated parasitic infections-cryptosporidiosis and microsporidiosis-remain extremely difficult to treat, with no consistently effective standard treatments. A brief discussion of the treatments in development for microsporidiosis and cryptosporidiosis can be found in the next chapter.

Since secondary infections are a major cause of rapid wasting in AIDS, and successful treatment of infections in patients with AIDS can reverse or at least decelerate the wasting process, these therapeutic results give further support for a careful search for treatable infections in patients with AIDS and active weight loss.
### TABLE 6: CURRENT THERAPY FOR ENTERIC PATHOGENS IN PATIENTS WITH AIDS

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>ACUTE THERAPY</th>
<th>MAINTENANCE THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BACTERIAL / MYCOBACTERIAL INFECTIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella</td>
<td>Amoxicillin (1000 mg three times a day for 3 to 14 days) or TMP/SMX (1 double-strength tablet orally twice daily for 14 days); or ciprofloxacin (500 mg orally twice daily for 7 days)</td>
<td>If recurrences are frequent</td>
</tr>
<tr>
<td>Shigella</td>
<td>TMP/SMX (1 double-strength tablet orally twice daily for 5 to 15 days); or ampicillin (500 mg orally four times a day for 5 days); or ciprofloxacin (500 mg orally twice daily for 7 days)</td>
<td>If recurrences are frequent</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Erythromycin (250 to 500 mg orally four times a day for 7 days) or ciprofloxacin (500 mg orally twice daily for 7 days)</td>
<td>No</td>
</tr>
<tr>
<td>Clostridum difficile</td>
<td>Metronidazole (250 mg three times a day for 7 to 10 days) or vancomycin (125 mg orally four times a day 7 to 10 days)</td>
<td>No</td>
</tr>
<tr>
<td>Mycobacterium avium complex (MAC)</td>
<td>Clarithromycin (500 mg orally once a day) or Azithromycin (500 mg orally once a day); and ethambutol (15 mg/kg orally once a day); and Ciprofloxacin (500 to 750 orally twice daily); Rifampin (10 mg/kg orally once a day); or Rifabutin (300 to 450 orally once a day)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>PROTOZOAL INFECTIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giardia Lamblia</td>
<td>Metronidazole (250 mg three times a day for 5 days)</td>
<td>No</td>
</tr>
<tr>
<td>Entamoeba Histolytica</td>
<td>Metronidazole (750 mg three times a day for 10 days), then iodoquinol (650 mg three times a day for twenty days)</td>
<td>No</td>
</tr>
<tr>
<td>Isospora belli</td>
<td>TMP/SMX (160 mg of TMP and 800 mg of SMX three times a day for 10 days, followed by twice weekly therapy for 3 weeks)</td>
<td>TMP/SMX or pyrimethamine/ sulfadoxine</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>Undefined</td>
<td>Undefined</td>
</tr>
<tr>
<td>Microsporidium</td>
<td>Undefined</td>
<td>Undefined</td>
</tr>
<tr>
<td><strong>VIRAL INFECTIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Acyclovir (200 mg five times a day)</td>
<td>If recurrences are frequent</td>
</tr>
<tr>
<td>CMV</td>
<td>Ganciclovir (5 mg/kg body weight twice daily for 14 to 21 days) or Foscarnet (90 mg/kg twice daily)</td>
<td>Oral ganciclovir (1000 mg/day); or Foscarnet (90 mg/kg everyday)</td>
</tr>
</tbody>
</table>

Source: AIDS/HIV Treatment Directory, published by the American Foundation for AIDS Research (AmFAR)
TABLE 7: PROPHYLAXIS FOR ENTERIC PATHOGENS IN PATIENTS WITH AIDS. ADAPTED FROM THE UNITED STATES PUBUC HEALTH SERVICE/INFECTIOUS DISEASE SOCIETY OF AMERICAN GUIDELINES

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>INDICATION</th>
<th>FIRST CHOICE</th>
<th>SECOND CHOICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC</td>
<td>CD4 &lt; 75 cells</td>
<td>Rifabutin</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Recommended for consideration in all patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial</td>
<td>Neutropenia</td>
<td>G-CSF or GM-CSF</td>
<td>NONE</td>
</tr>
<tr>
<td>CMV</td>
<td>Advanced HIV</td>
<td>Oral Ganciclovir</td>
<td>NONE</td>
</tr>
<tr>
<td></td>
<td>Recommended only in select patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: AIDS/HIV Treatment Directory, published by the American Foundation for AIDS Research (AmFAR)

OCTREOTIDE ACETATE (SANDOSTATIN)

Octreotide acetate (Sandostatin), an approved hormonal agent similar to naturally occurring somatostatin, is approved for patients to reduce symptoms attributed to a rare form of intestinal cancer (metastatic carcinoid vasoactive intestinal peptide-secreting tumors). Octreotide is not an antibiotic, thus it will not eliminate diarrhea-causing pathogens from the intestinal tract. It is though to inhibit intestinal secretion and enhance electrolyte absorption. Data from clinical trials in patients with AIDS/HIV have been conflicting.

In 1995, Simon and colleagues (Simon 1995) published results from a randomized, double-blind, placebo-controlled trial of octreotide acetate in 129 HIV-positive patients with refractory diarrhea. Patients were randomized to receive octreotide acetate (100 micrograms subcutaneously three times daily) or placebo. No significant differences between the treatment group and control group were reported after three weeks on therapy.

Results from an open-label trial of octreotide acetate, published in 1991 (Cello 1991), did show a significant difference between patients with refractory diarrhea receiving octreotide acetate or placebo. A total of 51 HIV-positive patients with wasting received treatment with octreotide acetate at several different doses (50, 100, 250, and 500 micrograms subcutaneously three times a day). 21 of the 51 (41.2%) patients had a complete response, measured by a reduction in daily stool volume by 50%. 14 of the 21 (67%) had no identifiable pathogens at initial screening compared to 9 of the 30 (30%) nonresponders (p<0.01). Reduction in stool volume from baseline was associated with doses higher than 50 micrograms.

Results from the open-label trial conducted by Cello and colleagues are optimistic. Considering that a dose-related response to octreotide acetate is apparent in this open-label study, controlled studies examining higher doses of this compound are warranted.

Source: AIDS/HIV Treatment Directory, published by the American Foundation for AIDS Research (AmFAR)
**Nutritional Supplementation**

**ORAL NUTRITIONAL SUPPLEMENTS**

Specific oral nutritional supplements have also been postulated to have beneficial effects on HIV and the wasting syndrome. Recent analyses from the Multicenter AIDS Cohort Study (MACS) (Graham 1993) suggested that those individuals with higher levels of vitamins B1, B2, B6, and niacin have a survival advantage, while those supplemented with zinc had a higher mortality rate. However, the effect of nutritional supplementation in early stages of HIV infection is just beginning to be evaluated. In one preliminary study by Chlebowski and colleagues, 80 patients were randomized to receive standard oral supplementation or a formulation containing peptides, medium-chain triglycerides, fish oil, and fiber (2-3 cans per day). At the completion of the study, only 56 patients were evaluable. Of those patients evaluable, the majority had only consumed 1.5 cans a day; at least 0.5 to 1.5 cans below the protocol's selected dose. Patients randomized to receive the new formulation showed statistically significant increases in weight. However, much of the weight gained was fat mass-measured by tricep skin fold tests. More randomized studies using oral supplementation should be conducted to corroborate these data.

**ENTERAL AND PARENTERAL NUTRITION**

Enteral or parenteral supplementation may be an option for those patients with significant weight loss who are unable to meet caloric demands owing to anorexia or malabsorption. Few studies, however, have carefully examined the effect of alimentation (therapeutically administering nutrients) in AIDS.

Enteral alimentation may be useful if the absorptive function of the gastrointestinal tract remains intact. There may be absorption of elemental diets containing small peptides, branched chain amino acids, or medium chain triglycerides if GI tract function is only partially intact. Low-residue, lactose-free preparations may limit the amount of diarrhea resulting from enteral feedings. In a similar manner, gluten-free diets have been proposed but they has both been studied in detail. Enteral feeding by percutaneous endoscopic gastrostomy (PEG) tubes—a nutritional mixture administered through a tube placed directly into the stomach—was studied prospectively by Kotler (Kotler 1991 c) in eight patients with advanced GI infection. Amino acids were supplied as small peptides, and 40% of the lipid was in the form of medium chain triglycerides. Although weight gain did not reach statistical significance, there was a significant increase in body cell mass, fat content, and serum albumin concentrations. There was no change in CD4 count in this two month study.

In another study of enteral feeding via PEG tube, there was no significant weight gain noted in 14 patients (Cappel 1990). In this study, three patients developed cellulitis at the tube site, and one had gastrointestinal bleeding requiring transfusion. This approach should probably be reserved for selected patients who have no evidence of malabsorption.

Administration of total parenteral nutrition (TPN) has been studied in a few small uncontrolled series of AIDS patients in attempts to facilitate weight gain and replete body cell mass (Kotler 1984, Singer 1991, Singer 1992). Singer and colleagues (Singer 1992) reported a retrospective study of TPN in 22 patients with a more than 10% loss of body mass.
weight. Fifteen patients gained weight, and nine returned to previous activity. In an earlier study, eight of eight patients gained weight with a solution in which fat comprised 50% of nonprotein calories (Singer 1991). There was no associated increase in serum albumin, and in neither study were measurements of body cell mass performed.

Kotler and colleagues demonstrated weight gain in 12 patients with AIDS receiving intravenous TPN. Patients were administered therapy for a total of 14 weeks. In AIDS patients with wasting due to decreased food intake or severe malabsorption, treatment with TPN produced increases in body cell mass as well as body fat. Repletion of body cell mass occurred in all patients with altered intake and in 2/7 patients with CMV and MAC (Kotler 1990c).

In contrast, the North American Home Parenteral and Enteral Nutrition Registry reported that AIDS patients with severe and ineffectively treated systemic infection (including CMV and MAC) showed only gains in body fat with no increases in body cell mass after TPN administration (North American Home Parenteral and Enteral Nutrition Registry 1993). Although anorexia occurs in these infections, TPN does not reverse the loss of body cell mass. Preliminary data from other groups also suggest that fat rather than muscle is formed during enteral alimentation in unselected subjects (Kelson 1991). These short-term studies have not established improved survival or beneficial effects on absolute CD4 or CD8 cell numbers.

The issue of TPN in patients with AIDS is controversial, especially considering the costs of therapy, the risks of infection with long-term intravenous catheters, and the generally poor prognosis of the patients. At present, the use of TPN in AIDS patients must be evaluated on an individual basis, since controlled trials justifying its benefits have not been performed.

ENDOCRINE AND HORMONAL TREATMENT

HUMAN GROWTH HORMONE (RHGH, SEROSTIM)

Recombinant human growth hormone (rHGH), a drug marketed by three manufacturers to treat dwarfism and failure to thrive in children, has been studied for its anabolic properties. The recombinant versions of growth hormone, produced by Serono Laboratories (Serostim), Eli Lilly (Humatrope), and Genentech (Nutropin), all mimic naturally-occurring growth hormone. Both Serono and Genentech completed open-label studies of rHGH in HIV-positive people with wasting syndrome. Subsequently, Serono completed two efficacy trials, and filed a New Drug Application (NDA) with the FDA. Based on current data, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 8-7 against recommending approval for Serostim. A final decision whether or not to approve this drug is still pending by the FDA.

The development of growth hormone has shed a fair amount of light on the enormous possibility of using anabolic agents as life-saving treatment. It has, however, exemplified all that is wrong with drug development in AIDS: Inadequately designed trials, the limited scope of the Food and Drug Administration (FDA), and outrageous expense.

Recombinant human growth hormone was first studied in HIV-positive patients with wasting in a study by Mulligan and colleagues (Mulligan 1993). Six men with HIV-related weight loss (mean loss of 19%) were treated, open-label, with a constant metabolic diet
and growth hormone (0.1 mg/kg/day) for seven days. A mean body weight increase of 2.0 kg was observed in the HIV-positive men (compared with 1.6 kg increase in the control group). Significant increases in protein anabolism, nitrogen balance, and lipid metabolism were observed.

Results from two controlled trials using Serono's growth hormone have been completed. In the first study of 178 patients, a total of 90 patients were randomized to receive growth hormone. Statistically significant increases in body weight, lean body mass, and decreases in fat mass were reported by patients receiving growth hormone versus those receiving placebo after 12 weeks of therapy.

In the second pivotal confirmatory trial, Serono began enrolling patients into a placebo controlled trial of growth hormone, again in less than 200 patients, to study whether or not growth hormone would reverse weight loss. The FDA requested that Serono demonstrate significant increases in body weight in order to approve growth hormone. Growth hormone, a novel approach to reversing one of the greatest mortality risk factors in AIDS-muscle wasting-was being tested by a regulatory agency misguided by old science. Given the growing data illustrating depleted muscle mass to be independent of weight loss, Serono Laboratories chose not to challenge the FDA's definition of drug efficacy and hoped for the best.

Serono was defeated. The second study, which randomized patients in a 2:1 ratio to either growth hormone or placebo, used body weight as their primary endpoint. At 12 weeks, there was no significant difference between patients randomized to receive growth hormone or placebo in terms of weight gain. At baseline, patients had lost an average 10.5 kg of their ideal body weight. At 6 weeks, the median weight gain in the growth hormone group was 2.5 kg above baseline, whereas the median weight gain in the placebo group was 0.7 kg; these data were statistically significant. At week 12, however, the median weight gain decreased to 1.6 kg above baseline in the Serostim group and increased to 0.43 kg in the placebo group. The data at week 12 were not statistically significant. Lean body mass and fat mass parameters were not collected (Brietmeyer 1996).

The development of Serostim has been scrutinized heavily by community activists and clinicians. Serostim is very expensive. Under the cost recovery program allowed by the FDA for Serono's Treatment IND, Serostim costs $25.00 per milligram. At current doses that amounts to $150 per day, or $54,750 per year. Once the drug is FDA-approved, Treatment IND cost-recovery limitations will not apply, so the sky will be the limit for Serono-then and the willingness, or lack thereof, of third party payers and state AIDS Drug Assistance Programs (ADAPs) to cover its cost.

Regardless of whether FDA grants approval to Serono, there is a very real danger that third party payers will refuse to reimburse for Serostim because there is still so little information about how and for what period of time the drug should be used. Can lower doses be used for maintenance after a high-dose induction regimen? Should Serostim be combined with anabolic or appetite-enhancing approaches? Most importantly, it is still not known whether or not increasing lean body mass with rHGH will protect patients from opportunistic diseases, enhance immunity, slow down progression, or increase survival.
TESTOSTERONE

Because HIV-infected patients with wasting frequently have testicular atrophy and serum levels of total testosterone and free testosterone that are significantly lower than patients without wasting (hypogonadism), testosterone replacement therapy is currently being examined in clinical trials.

Testosterone has been used by many clinical practitioners to treat low testosterone levels (hypogonadism) in a broad spectrum of patients, including those with HIV. Unfortunately, very little data are available on testosterone replacement therapy in patients with HIV. Testosterone is commonly prescribed in long-acting ester form (cypionate or enanthate).

Results of body composition studies in HIV-positive men receiving testosterone therapy have been reported (Engelson 1996a). All patients enrolled into the 12 week open-label study were treated with 400 mg doses, biweekly, of testosterone cypionate. Patients enrolled into the study were not underweight upon entry. The body composition measures analyzed included body weight, body cell mass, fat-free mass, and fat mass. As to be expected, testosterone concentrations rose as a result of replacement therapy. Mean average body weight increases of 0.9 kg were reported. This difference was not statistically significant. Significant differences were reported, however, when compared to baseline, in body cell mass (+1.2 kg, measured by BIA) and in fat free mass (+1.2 kg). The authors note that response to testosterone in this study was markedly different from the reported response to megestrol acetate, where more than two-third of the accrued weight was fat, as well as from studies of nutritional support, in which up to one-half of weight was gained as fat. The authors also rightfully conclude that, given the uncontrolled study design, the efficacy of testosterone therapy has not yet been demonstrated as a treatment for AIDS-related wasting. However, it is promising data, nonetheless.

The AIDS Clinical Trials Group (ACTG) is currently developing a study of testosterone for HIV-positive patients with wasting receiving megestrol acetate. The ACTG will examine whether or not concomitant testosterone therapy will reverse the hypogonadic effects of therapy with megestrol acetate. A testosterone transdermal system (testosterone delivered through a patch applied to the skin) is approved for the treatment of hypogonadism and is currently under investigation for the treatment of AIDS-related hypogonadism and wasting. Alza Pharmaceuticals, who produces a testosterone transdermal system applied to the scrotum (Testoderm), has already begun marketing its compound to HIV-positive patients with fatigue and decreased sex drive. No data have been reported whether or not HIV-positive patients who suffer from either of the above mentioned manifestations— as well as wasting—will benefit from the administration of low-dose testosterone via a transdermal system. A small trial in patients with low sex drive and a larger trial in patients with wasting are now underway.

ANABOLIC STEROIDS

Because testosterone carries both anabolic (muscle building) and androgenic (masculinizing) properties, anabolic steroids have long been considered a more adequate means of treating patients in catabolic states. Anabolic steroids are synthetic versions of the anabolic properties found in testosterone.
Since testosterone has been shown to restore nitrogen balance and weight in populations of hypogonadal men, it was assumed but never proved that anabolic agents in pharmacological doses could promote growth of muscle above the levels induced by normal testicular secretion. These assumptions were based on the belief that anabolic and androgenic actions are different, and a concerted effort was made to devise pure "anabolic" steroids that have no androgenic effects. Another assumption is that anabolic agents could be used to promote lean body mass increases without the masculinization adverse events of androgens.

There is no clear consensus in the medical literature that anabolic steroids consistently work as a way of building muscle mass. Even less is known about patients with HIV and wasting. What is assumed about anabolic steroids comes mainly from the lay press. Much of this is anecdotal and related to body builders using steroids in doses 10-100 times the medically therapeutic doses. Steroids have been implicated in causing everything from brain tumors to myocardial infarction to sterility (Vergel 1995).

There are many well-documented studies looking at the issue of utilizing more reasonable doses of steroids in healthy controls as well as physically impaired patients. Mild side effect reported include: virilization potentiation in women, gynecomastia in males, fluid retention and mildly increased blood pressure, impairment of gonadal function and potency, and increased liver function tests (associated with oral steroids).

Following is a chart, compiled by Nelson Vergel of the Program for Wellness Restoration (PoWeR), a national anabolic steroid advocacy group for people with AIDS/HIV and wasting (Vergel 1995). Compounds discussed, doses "recommended", and side effects reported do not come from clinical trials involving HIV-positive patients with wasting. Moreover, sound, scientific data demonstrating efficacy of these compounds in reversing AIDS-related wasting have not yet been reported.

**TABLE 8: ANECDOTAL SUMMARY OF AVAILABLE ANABOLIC STEROIDS & ASSOCIATED ADVERSE EVENTS.**

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>ANABOLIC</th>
<th>ANDROGENIC</th>
<th>REPORTED DOSES</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nandrolone (Deca Durabolin) Injectable</td>
<td>high</td>
<td>low</td>
<td>M: 100-200 mg/wk W: 25 mg/wk</td>
<td>Water retention</td>
</tr>
<tr>
<td>Methenolone (Primobolan Depot) Steroid Injectable</td>
<td>medium</td>
<td>very low</td>
<td>M: 100-30 mg/wk W: 25 mg/wk</td>
<td>No water retention; very gentle</td>
</tr>
<tr>
<td>Stanozolol (Winstrol) Injectable</td>
<td>medium to high</td>
<td>very low</td>
<td>M: 50 mg tiw W: 15 mg tiw</td>
<td>No water retention; slight virilization; pyrogenic</td>
</tr>
<tr>
<td>Stanozolol (Winstrol) Oral formulation</td>
<td>medium to high</td>
<td>very low</td>
<td>M: 6-10 X 2 mg/qd W: 1-4 X 2 mg/qd</td>
<td>Elevated liver enzymes</td>
</tr>
</tbody>
</table>
Oxandrolone (Oxandrin) Oral formulation

<table>
<thead>
<tr>
<th></th>
<th>low to medium</th>
<th>very low</th>
<th>M: 15-60 mg/qd</th>
<th>W: 5-20 mg/qd</th>
<th>Very gentle virtually no liver toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone Cypionate (Anadrol)</td>
<td>high</td>
<td>medium to high</td>
<td>M: 100 - 200 mg/wk</td>
<td>Water retention; potential balding; acne; gynecomastia; virilization in women</td>
<td></td>
</tr>
<tr>
<td>Testosterone Ethanthate</td>
<td>high</td>
<td>medium to high</td>
<td>M: 100 - 200 mg/wk</td>
<td>Virtually the same as Cypionate</td>
<td></td>
</tr>
</tbody>
</table>

Anabolic steroids are also being studied through the ACTG. Mulligan and colleagues will study nandrolone in HIV-positive women with wasting syndrome in ACTG 329. Oxandrolone, another anabolic agent, is currently approved and is being studied by Kotler and colleagues for the treatment of AIDS-related wasting. Currently, two controlled trials—one in HIV-positive men and one in HIV-positive women—are in the final stages of development and are due to begin enrolling this summer.

**CYTOKINE MODULATORS**

Since inflammatory cytokines have been implicated in the pathogenesis of HIV-associated wasting, it is reasonable to hypothesize that reducing levels of inflammatory cytokines, e.g., IL-1, IFN-alpha or TNF-alpha or TNF-beta, may ameliorate wasting, either by directly reducing inflammatory cytokine-mediated damage, or indirectly by reducing HIV replication. Serum TNF-alpha is elevated in patients with advanced HIV and OIs, but there is no clear correlation with the development of wasting. Despite several small studies, there is still no conclusive evidence that pharmacologic manipulation of cytokines can stabilize or reverse the wasting process.

**PENTOXIFYLLINE (TRENTAL)**

Pentoxifylline is a substituted methylxanthine derivative commonly used to treat the symptoms of intermittent claudication (leg pain while walking; usually the result of arterial disease of the limbs). It has been shown to decrease monocyte production of TNF-alpha mRNA through suppression of gene transcription (Doherty 1991). Pentoxifylline, at a dose of 400 mg t.i.d., significantly decreased serum TNF-alpha levels in a small study of 17 patients with HIV infection after 8 weeks of treatment (Dezube 1993). Most patients had CD4 counts below 100, but the presence or absence of the wasting syndrome was not noted. Fasting serum triglyceride levels declined by a mean of 25%. With all patients receiving concomitant antiretroviral therapy, HIVRNA levels appeared be stable as assessed by quantitative culture assay. Subsequent studies have confirmed the pentoxifylline-mediated decrease in serum TNF-alpha levels and the lack of antiviral effect (Dezube 1994; Landman 1992). In a small study of five patients with HIV wasting syndrome, there was no evidence of weight gain after 6 weeks of treatment (Landman 1992). In all these studies, pentoxifylline has been well tolerated; however, alterations of TNF-alpha levels may have an adverse effect of the natural history of OIs (Grunfeld 1992, Reyes-Teran 1994.) The addition of pentoxifylline to PBMCs from patients with
disseminated MAC was recently shown to increase colony counts 2.5-50-fold in five of six patients (Sathe 1994), presumably because inhibiting TNF reduced macrophages' ability to attack MAC particles.

**THALIDOMIDE**

Thalidomide was developed as a sedative by a German whiskey company in the late 1950s. It was quickly promoted and distributed worldwide, due to the assumption that it was much safer than many barbiturate sedatives.

The drug was never officially approved in the United States. It was distributed as an experimental drug through doctor's offices, and was often given to pregnant women suffering from morning sickness. In 1961, however, thalidomide was found to cause serious birth defects in children born to women who had taken the drug. As a result, the drug was withdrawn from the international market. In the United States, the thalidomide scandal went on to become the primary building block behind the 1962 Kefauver Amendments, which strengthened the FDA, giving it the power to deny approval if a drug sponsor failed to prove efficacy, as well as safety (over which FDA had oversight since 1938).

Like pentoxifylline, thalidomide decreases monocyte production of TNF-alpha by increasing degradation of TNF-alpha mRNA (Moreia 1993). Unlike pentoxifylline, which reduces TNF synthesis, thalidomide increases the breakdown of TNF. In vitro, thalidomide suppresses the activation of HIV in chronically infected monocytes and in PBMCs from HIV-infected patients. It ameliorates the syndrome of erythema nodosum leprosum (ENL) in lepromatous leprosy with associated decreases in serum TNF-alpha levels.

In a double-blind, placebo-controlled study conducted in Mexico by Reyes-Teran and colleague, 23 HIV infected patients with the wasting syndrome received thalidomide at a dose of 100 mg t.i.d. for 12 weeks. Significant weight gain and improved Karnofsky scores were noted in the group receiving thalidomide when compared with placebo. Rashes and somnolence were noted in the treatment group. There was no significant change in absolute CD4 count or viral load, as measured by PBMC end-point dilution cultures (Reyes-Teran 1994).

A second placebo-controlled, double-blind trial has examined the effect of thalidomide at a dose of 300 mg every day in 41 HIV-infected Thai patients with HIV and weight loss, 50% of whom had concomitant tuberculosis (Klausner 1994). After 21 days the thalidomide-treated patients had gained an average 4.5% of body weight compared with 0.9% in the control group (p<0.01). Twenty nine percent of thalidomide-treated patients developed rashes, and there was no significant change in absolute CD4 count, plasma viremia, or p24 antigen.

**THE PROSPECT OF COMBINATION THERAPY FOR THE TREATMENT OF WASTING**

Combination therapy with two of the more novel approaches to treating wasting-anabolic agents and cytokine modulators-could prove to be significant. This hypothesis has yet to be investigated due to the slow rate at which single therapeutic agents are still being developed and clinically tested for AIDS-related wasting syndrome.
According to Kotler, it is possible to assume that a combination of cytokine modulators (i.e., thalidomide), which have been shown in preliminary studies to inhibit protein catabolism, and anabolic agents (i.e., growth hormone), which have been shown in studies to increase protein synthesis, may prove to be very useful in reversing the metabolic dysfunction commonly found in HIV-positive patients with wasting (Donald Kotler, personal communication). A protocol to test this hypothesis is currently being developed.
CURRRENT OPINIONS ON AIDS-RELATED WASTING SYNDROME FROM PHYSICIANS, DIETITIANS, CLINICIANS & RESEARCHRES

Given the complexities and multifactorial nature of AIDS-related wasting, the authors of this reported solicited comments and insight from a broad range of physicians (primary care physicians, infectious disease specialists, gastroenterologists, and endocrinologists), registered dietitians, clinicians and researchers specializing in HIV-associated wasting. In researching the contents of this report, much insight was provided in various forms; telephone conversations, written correspondences, editorial comments, conference abstracts, and in-press manuscripts.

Specific comments from those providing insight are unattributed. The assurance of anonymity allowed those queried to discuss sensitive issues that they may not have otherwise.

Is the current definition of wasting, as provided by the CDC, an adequate determination?

Responses to this question varied greatly, depending on the area in which those interviewed specialized. The majority of clinicians, researchers, and some medical care providers (mostly gastroenterologists, infectious disease specialists, and endocrinologists) believed that alterations in metabolism and its affect on the shifting ratio of lean body mass to fat mass should be reflected in the definition. Wasting as defined by body composition analyses is not at all reflected in the current CDC definition. Many physicians caring for people with HIV and not involved in clinical research, believed the current CDC definition to be adequate in light of what is known in "the real world" about AIDS-related weight loss and wasting. These physicians believed that subjecting patients to diagnostic exams, especially where they are not readily available and perhaps costly, can be stressful to patients already undergoing intensive monitoring.

Is there a clear difference between weight loss and wasting?

The majority of those questioned or who provided comment on this particular question stated that a difference between weight loss and wasting is evident. Nevertheless, the level of response regarding data that differentiate between these two terms varied tremendously. Most physicians stated that differentiation is an important factor, provided that diagnostic assays used to determine a changing lean body mass/body fat ratio are widely recognized and accessible and that adequate treatments are available.

What is the pathogenesis of AIDS-related wasting?

Responses to this particular question were extensive, varied, and opinionated. Most believed that loss of appetite, diarrhea/malabsorption, and active opportunistic infections (OIs) are definitive manifestations that can lead to weight loss and wasting. When questioned about the possible mediators of metabolic dysfunction, there was a great amount of speculation and debate. Some researchers placed importance of one etiological theory over others. For some, inadequate nutritional intake/supplementation was the leading cause of progressive and chronic wasting. For others, endocrine dysfunction, hormonal disturbances, and anabolic deficiencies in HIV-infection were of particular importance and are being underestimated in AIDS-related wasting research and clinical care. Still, others argue that the chronic, inflammatory immune response, by
way of various cytokines (not TNF alone), is the root cause of metabolic derangement and should be studied more extensively. For the most part however, most individuals surveyed believed that wasting truly is multifactorial in nature and is the result of various complications in HIV-positive patients. The majority also agreed that different physiological alterations have greater influence in causing progressive weight loss at various stages of HIV-disease, usually as HIV-disease progresses.

**Are there distinct differences in the pathogenesis/etiology of wasting among men and women?**

Most of those queried reported a general concern, yet limited understanding regarding gender differences concerning malnutrition, body composition, and possible etiologies of wasting syndrome. A majority expressed that it was entirely possible and that reports of research conclusions have been limited. Some individuals, especially those conducting research or caring for large populations of HIV-positive women, reported that significant differences are evident and that research needs to investigate more closely the etiology and pathogenesis—especially the endocrine/metabolic dysfunction—of wasting in HIV-positive women.

**How should anorexia, malabsorption, and or weight loss be monitored and diagnosed in HIV-positive patients?**

Approximately three-quarters of those surveyed believe that guidelines, quite possibly from the United States Public Health Service, should be developed and widely recognized. There was a mixed response, however, in regards to the level of aggressiveness one should take in monitoring and diagnosing patients who report diarrhea or weight loss. In the case of diarrhea, stool samples are generally performed. In patients with an identifiable pathogen, a treatment—an indicated antibiotic and/or antidiarrheal—is prescribed. For patients who fail to respond to treatment, most doctors prescribe another treatment. Approximately one-quarter suggest enrolling in a clinical trial unless otherwise asked by a patient. Aggressive nutritional intervention was recommended by only one-quarter of those surveyed.

In the case of patients who have no identifiable pathogen in a stool sample, a second stool sample is collected and/or a referral is made for a GI workup (endoscopy). Most noted making a GI workup referral is largely dependent on the perceived rate and volume of diarrhea. For those patients with no identifiable pathogen upon stool assay and severe diarrhea (a term that ranged accordingly from 4 to 7 episodes a day), a GI workup referral was made. In most cases of patients with mild to moderate cases of diarrhea (which ranged from 1 to 5 episodes a day), an antidiarrheal agent was recommended and patients were asked to return if the diarrhea failed to subside. For those patients who still reported stable or progressive diarrhea after a recommended period (ranging from 1 to 3 weeks), a referral to a gastroenterologist was made.

As for anorexia and lack of appetite in people with HIV/AIDS, all those questioned were fully aware of the many possible manifestations of HIV/AIDS that can cause an aversion to food. However, most understood and disagreed that many physicians caring for people with HIV/AIDS easily excuse anorexia as an unavoidable manifestation in patients taking various treatments, are generally inactive, or for other vague reasons. A majority of those surveyed also reported making referrals to dietitians and/or nutritional programs for anorectic patients with perceived weight loss. Symptoms of oropharyngeal
complications were always investigated and, if present, treated accordingly. For patients with non-pathogenic anorexia, appetite stimulants, most often megestrol acetate, were prescribed.

Monitoring and diagnosing weight loss, in the absence of an O1, is largely dependent on resources available. Most individuals reported using an array of diagnostic tools to measure weight stabilization. Clinicians and researchers, as a whole, spoke highly of BIA technology and are requesting with increasing frequency, that it be the diagnostic tool of choice in treatment protocols for wasting. Many researchers and clinicians also concluded that if BIA is to be widely recognized, it will require validation in clinical trials. Medical care providers, both primary and specialized, reported using blood and urine values to diagnose weight loss. Most physicians reported ordering blood tests to measure specifically for metabolically-important blood values (i.e., testosterone, uric acid, glucose, cholesterol, HDL (high-density lipoproteins), LDL (low-density lipoproteins), etc.). Interestingly, a large percentage of those surveyed scrutinized an abnormal blood value and intervened only in the presence of weight loss. Body composition workups appear to be utilized minimally by physicians unaffiliated with research and/or immediate access to the appropriate diagnostic equipment.

**How should weight loss and wasting be treated?**

The inadequate treatments approved and lack of data on treatments used for other indications other than weight loss was a central concern to many of those questioned. All individuals report variable results using megestrol acetate or dronabinol in reversing weight loss. The physicians who measured efficacy of these compounds by BIA generally reported a less than favorable response. A majority of physicians reported administering TPN to patients with an active O1 and rapid weight loss who are either hospitalized or under home care surveillance.

**How should anti-diarrheals be used?**

Treatment strategies for patients reporting mild, moderate, or severe diarrhea were varied. Identifiable pathogens with an indicated treatment, found by stool sample and/or GI workup, were aggressively treated in most cases. Diarrhea resulting from an unknown etiology (AIDS enteropathy) upon stool analysis were either followed-up by an appropriate GI workup or treated with an antidiarrheal. The decision to refer patients to clinical trials was based primarily on the attending physician's or patient's knowledge of a particular trials existence.

**How should anabolics be used?**

Many reported prescribing an anabolic agent to treat wasting. Testosterone injections are commonly recommended by a number of those questioned, even in the presence of serum testosterone levels within normal reference ranges. The decision to administer other anabolic agents, mainly anabolic steroids, is based on a patient's knowledge of their existence. Most physicians report that anabolic steroids are a common prescription request by gay men with HIV. Many primary care physicians reported prescribing anabolic agents to patients who request them, despite the lack of data in HIV-positive patients from controlled trials. Among female patients, anabolics are discussed with little regard and are rarely prescribed.
GLOSSARY

**Acute:** refers to intense, short-term symptoms or illnesses that either resolve or evolve into longlasting, chronic disease manifestations.

**Adverse Event:** a toxic reaction to a medical therapy.

**AIDS (Acquired Immunodeficiency Syndrome):** the late stage of the illness triggered by infection with human immunodeficiency virus (HIV). According to the official definition published by the CDC, a person receives an AIDS diagnosis when he or she has a CD4 (helper T-cell) count of less than 200 and/or certain opportunistic infections common with advanced immune deficiency (see AIDS-defining illness).

**AIDS Clinical Trials Group (ACTG):** a network of medical centers around the country in which federally funded clinical trials are conducted to test the safety and effectiveness of experimental treatments for AIDS and HIV infection.

**Amoebiasis:** a parasitic intestinal infection caused by tiny unicellular microorganisms called amoebas. Symptoms include diarrhea.

**Amino Acid:** any of twenty nitrogen-containing acids that are the building blocks for proteins and required for human growth.

**Amphotericin B:** an intravenous drug for treatment of cryptococcal meningitis, candidiasis, histoplasmosis and coccidiomycosis and other fungal infections. Toxicities are severe and include fevers, chills, headache, anorexia, nausea, vomiting, diarrhea, kidney damage and neutropenia.

**Anabolic Steroid:** a synthetic steroid used to increase muscle mass and weight. Anabolic steroids are versions of the natural hormone testosterone but have fewer masculinizing effects. Anabolic steroids have been used to reverse AIDS-related wasting syndrome on an individual basis, but trial data are lacking.

**Androgen:** a masculinizing hormone.

**Anorexia:** the lack or loss of appetite that leads to significant decline in weight.

**Aphthous Ulcer:** a painful oral or esophageal sore of unknown cause that has a deep eroded base. Aphthous ulcers are common in people with HIV and are treated with corticosteroids. Thalidomide is an experimental alternative therapy.

**Asymptomatic:** without signs or symptoms of disease or illness.

**Atrophy:** a wasting or shrinking of cells, tissue, organs or muscle.

**Baseline:** the initial time point in a clinical trial, just before a volunteer starts to receive the experimental treatment being tested. At this reference point, measurable values such as CD4 count are recorded. Safety and efficacy of a drug are often determined by monitoring changes from the baseline values.
**Beta-2 (B-2) Microglobulin:** an immune system protein found in the blood. Elevated blood levels of this protein are associated with immune activation and are weakly predictive of worsening of the disease associated with HIV infection.

**Bioavailability:** the extent to which an oral medication is absorbed in the digestive tract and reaches the bloodstream.

**Biopsy:** removal of a small piece of tissue either surgically or with a small needle for microscopic examination to determine whether a patient has a particular disease.

**Cachexia:** a general weight loss and wasting occurring in the course of a chronic disease.

**Candida:** a group of yeast-like fungi, in particular Candida albicans, that infect the mouth as well as other mucous membranes in the esophagus, intestines, vagina, throat and lungs. Oral or recurrent vaginal candida infection is an early sign of immune system deterioration.

**Candidiasis:** an infection due to candida yeast. The symptoms of oral candidiasis (thrush) and vaginal candidiasis (formerly called monilia) include pain, itching, redness and white patches in their respective sites. Some common treatments are clotrimazole, nystatin, miconazole, and fluconazole.

**Carbohydrate:** an organic molecule made up solely of carbon, hydrogen and oxygen. Carbohydrates may be made up of only one or two components (mono- or disaccharides, also called "sugars") or be complex chains of repeating units (polysaccharides or "starches," also the "cellulose" in plant cell walls).

**Centers for Disease Control and Prevention (CDC):** the federal public health agency serving as the center for preventing, tracking controlling and investigating the epidemiology of AIDS and other diseases.

**Chronic:** refers to symptoms and diseases that last for an extended period of time without noticeable change.

**Clinical:** refers to physical signs and symptoms directly observable in the human body.

**Clinical Trial:** a study done to test an experimental medicine in human beings to see if it is safe and effective.

**CMV (Cytomegalovirus):** a herpes infection that causes serious illness in people with AIDS. CMV can develop in any part of the body but most often appears in the retina of the eye, the nervous system, the colon or the esophagus.

**Cohort:** a group of individuals with some characteristics in common that is the subject of a study of the epidemiology or natural course of a disease.

**Colitis:** inflammation of the colon, a condition that causes abdominal pain and diarrhea.

**Control Arm:** the group of participants in a clinical trial who receive standard treatment or a placebo, against which those receiving the experimental treatment are compared.
**Controlled Trial:** a clinical study in which one group of participants receives an experimental drug while another group receives either a placebo or an approved standard therapy. When participants do not know which group they are in, the trial is blinded. See also double-blind.

**Corticosteroid:** any steroid substance obtained from the cortex or outer portion of the adrenal gland or any synthetic substitute for such a steroid. Corticosteroids are immunosuppressive and include prednisone, corticosterone, cortisone and aldosterone.

**Cryptosporidiosis:** an opportunistic infection caused by the intestinal parasite Cryptosporidium parvum, a very common parasite in animals. Transmission occurs through ingestion of food or water contaminated with animal feces. The parasite grows in the intestines and bile ducts and causes severe, chronic diarrhea, especially in people with AIDS.

**Cytokine:** one of the proteins produced by white blood cells that act as chemical messengers between cells. Cytokines can stimulate or inhibit the growth and activity of various immune cells in response to the particular type of disease present. Examples of cytokines are the various interleukins and tumor necrosis factor.

**Double-Blind:** a kind of clinical study in which neither the participants nor the doctors know who is receiving the experimental drug and who is receiving the placebo or standard comparison treatments. This method is believed to achieve the most accuracy because either the doctors nor the patients can affect the observed results with their psychological biases.

**Drug-Drug Interaction:** the effects that occur when two or more drugs are used together. Such effects include changes of absorption in the digestive tract, changes in rate of the drugs' breakdown in the liver, new or enhanced side effects and changes in the drugs' activity.

**Dysphagia:** difficulty in swallowing.

**Efficacy:** strength, effectiveness. The ability of a drug to control or cure an illness. Efficacy should be distinguished from activity (see), which is limited to a drug's immediate effects on the microbe triggering the disease.

**Endocrine Gland:** one of the organs in the body that produces hormones.

**Endpoint:** a category of data used to compare the outcome in different arms of a clinical trial. Common endpoints are severe toxicity, disease progression or fall in such surrogate markers (see) as CD4 count, but sometimes death is used as an endpoint. Usually when an endpoint reaches a certain set magnitude of change from baseline, a trial participant is removed from the trial and receives an open-label therapy (either a standard treatment or experimental one being tested).

**Enteric:** pertaining to the intestines.

**Epidemiology:** the branch of medical science that studies the incidence, distribution and control of disease in a population.
FDA: the Food and Drug Administration, an agency of the United States Department of Health and Human Services that regulates the testing of experimental drugs and approves new medical products for marketing based on evidence of safety and efficacy.

Gastroenteritis: inflammation of the stomach and intestines, which can cause abdominal pain and diarrhea.

Gastrointestinal (GI) Tract: the organs that absorb and digest food, including the mouth, esophagus, stomach, small and large intestines, colon and rectum.

Hormone: an active chemical substance formed in one part of the body and carried in the blood to other parts of the body where it stimulates or suppresses cell and tissue activity.

Human Growth Hormone (HGH): a peptide hormone secreted by the anterior pituitary gland in the brain. HGH enhances tissue growth by stimulating protein formation. Recombinant, or genetically engineered, HGH is under investigation as a treatment to reverse AIDS-related wasting syndrome.

IL-1 (Interleukin-1): a cytokine that is released early in an immune system response by monocytes and macrophages. It stimulates T-cell proliferation and protein synthesis. Another effect of IL-1 is that it causes fever.

IL-2 (Interleukin-2): a cytokine secreted by CD4 cells to stimulate CD8 cytotoxic T-lymphocytes. IL-2 also increases the proliferation and maturation of the CD4 cells themselves. During HIV infection, IL-2 production gradually declines. Use of IL-2 therapy is under study as a way to raise CD4 cell counts and restore immune function.

IL-4 (Interleukin-4): a cytokine secreted by CD4 cells that promotes antibody production by stimulating B-cells to proliferate and mature.

IL-12 (Interleukin-12): a cytokine released by macrophage in response to infection that promotes the activation of cell-mediated immunity. Specifically, IL-12 triggers the maturation of CD4 cells, specific cytotoxic T-lymphocyte responses and an increase in the activity of NK cells. IL-12 is under study as an immunotherapy in HIV infection.

Interferon: one of a number of antiviral proteins that modulate the immune response. Interferon alpha (IFNa) is secreted by a virally infected cell and strengthens the defenses of nearby uninfected cells. A manufactured version of IFNa (trade names: Roferon, Intron A) is an FDA-approved treatment for KS, hepatitis B virus and hepatitis C virus. Interferon gamma is synthesized by immune system cells. It activates macrophages and helps orient the immune system to a mode that promotes cellular immunity. Interleukin: one of a large group of glycoproteins that act as cytokines. The interleukins are secreted by and affect many different cells in the immune system. See also IL-1, IL-2, IL-4, and IL-12.

In Vitro: refers to laboratory experiments conducted in cell cultures grown in an artificial environment, for example in a test tube or culture plate.
**In Vivo:** refers to studies conducted within humans or animals, in a living, natural environment.

**MAC (Mycobacterium Avium Complex):** a serious opportunistic infection caused by two similar bacteria (Mycobacterium avium and Mycobacterium intracellular) found in the soil and dust particles. In AIDS, MAC can spread through the bloodstream to infect lymph nodes, bone marrow, liver, spleen, spinal fluid, lungs and intestinal tract. Typical symptoms of MAC include night sweats, weight loss, fever, fatigue, diarrhea and enlarged spleen. MAC is usually found in people with CD4 counts below 100. MAC is also called MAI.

**Malabsorption:** inability of the intestines to absorb food, drug or any substance needed to maintain good health.

**Malaise:** a vague feeling of discomfort or uneasiness, often the result of infection or a drug’s side effects.

**Marinol (Dronabinol):** an appetite stimulant composed of THC, the active ingredient in marijuana.

**Megestrol Acetate (Megace):** an appetite stimulant approved for the treatment of weight loss in people with AIDS. Megestrol acetate is a synthetic version of the female hormone progesterone.

**Micronutrient:** a vitamin or mineral that the body must obtain from outside sources. Micronutrients are essential to the body in small amounts because they are either components of enzymes (the minerals) or act as coenzymes in managing chemical reactions. See also vitamin.

**Microsporidiosis:** an intestinal infection that causes diarrhea and wasting in people with HIV. It results from two different species of microsporidia, a protozoal parasite.

**Mucous Membrane:** moist layer of tissue lining the digestive, respiratory, urinary and reproductive tracts—all the body cavities with openings to the outside world except the ears.

**Neopterin:** a substance present in bodily fluids that is elevated when the immune system is activated. Serum neopterin levels are measured in some studies as an additional (or complementary) surrogate marker for HIV disease.

**NIAID (National Institute of Allergy and Infectious Diseases):** the federal agency that is responsible for a great deal of the government sponsored AIDS research. NIAID is a branch of the NIH.

**NIH (National Institutes of Health):** the federal agency responsible for overseeing government sponsored biomedical research. It is divided into 24 institutes and research centers.

**Open-Label Trial:** a study in which both researchers and participants know what drug a person is taking and at what dose.
**Opiate:** a natural or synthetic derivative of opium that has similar analgesic and sedative effects.

**Pancreatitis:** inflammation of the pancreas. Pancreatitis, an occasional side effect of ddl (see), can result in severe abdominal pain and death. Its onset can be predicted by rises in blood levels of the pancreatic enzyme amylase.

**Parallel Track:** a system for distributing certain experimental drugs to people who are unable to participate in ongoing clinical trials.

**Peptide:** two or more chemically linked amino acids.

**Phase I:** the earliest stage clinical trial for studying an experimental drug in humans. Phase I trials are generally comparatively small. They provide an initial evaluation of a drug's safety and pharmacokinetics—how the drug is absorbed, what tissues it reaches and how long it takes to leave the body. Such studies also usually test various doses of the drug (dose-ranging) to obtain an indication of the appropriate dose to use in later studies.

**Phase II:** a more advanced stage clinical trial that follows the Phase I trials. A phase II trial gathers preliminary information on whether an experimental drug works. Data often are based on laboratory assays that provide quick, but indirect measurements of a drug's effect on disease (see surrogate marker). Phase II trials often involve a hundred people or more who are randomly assigned to take either the experimental drug or a "control" (the standard treatment for the disease or no treatment at all). Usually the trial is double-blinded, which means no one knows who is getting the drug until the trial is completed and the results are analyzed.

**Phase III:** an advanced stage clinical trial that should conclusively show how well a drug works as compared to other treatments. Phase III trials are large, frequently multisite, tests. They should measure whether a new drug extends survival or otherwise improves the health of patients on treatment (clinical improvement) rather than just provide surrogate marker data. These studies generally last longer and are larger than phase II trials.

**Placebo:** a comparison substance (often a lookalike sugar pill) against which experimental drugs are sometimes compared. A placebo is an inactive substance. In placebo-controlled trials the control group takes placebo, while the test group takes an experimental drug. Many such studies are also double-blinded, which means that neither doctors nor patients know who is receiving drug or placebo.

**Protein:** large molecules made up of long sequences of amino acids. Some hormones, enzymes and cellular structures are proteins. Three-fourths of the dry weight of most cells consists of proteins.

**Randomized Trial:** a trial in which the participants are randomly assigned to receive one of the treatments under study or a placebo. See randomization.

**Refractory:** severe disease that is resistant to treatment.
**Steroid:** a member of a large family of structurally similar lipid substances. Steroid molecules have a basic skeleton consisting of four interconnected carbon rings. Different classes of steroids have different functions. All the sex hormones are steroids. Anabolic steroids increase muscle mass. Antiinflammatory steroids (or corticosteroids) can reduce swelling, pain and other manifestations of inflammation.

**Stomatitis:** inflammation of the mucous membranes in the mouth.

**Testosterone:** a naturally occurring male hormone. When administered as a drug it can cause gain in lean body mass, increased sex drive and possibly aggressive behavior. Many men with HIV have low testosterone levels.

**Thalidomide:** a drug that reduces levels of TNF It is being studied as a treatment for wasting and other complications of HIV, as well as a number of other diseases where TNF levels are a problem. Potential side effects include sedation, constipation, peripheral neuropathy and severe birth defects in the infants born to women who take the drug during pregnancy.

**TNF (Tumor Necrosis Factor Alpha, TNFa):** a cytokine produced by macrophages that helps activate T-cells. It also may stimulate HIV activity. TNF levels are very high in people with HIV, and the molecule is suspected to play a part in HIV-related wasting, neuropathy and dementia.

**TPN (Total Parenteral Nutrition):** a liquid food substitute infused directly into the blood designed to meet a person's entire nutritional needs. TPN provides an alternate nutritional route in cases of severe gastro-intestinal distress in which nutrient absorption is poor. It strengthens the body and relieves the digestive tract while therapy for the underlying condition progresses. TPN's high cost precludes its use as long-term therapy.

**Toxicity:** the harmful effects of a given drug that occur during therapy. The term is similar to side effect and adverse reaction.

**Vitamin:** organic molecules essential in small amounts for normal metabolism, growth and development of the body. See also micronutrient.

**Wasting Syndrome:** a condition characterized by loss of ten percent of normal weight without obvious cause. The weight loss is largely the result of depletion of the protein in lean body mass and represents a metabolic derangement frequent during AIDS.

**Zinc:** an essential mineral often depleted in persons with HIV. Zinc is a component of many enzymes. It is important in protecting cells against excess oxidation and helps immune cells mature and function. Ingesting high doses of zinc can be harmful because it interferes with the absorption of copper, another essential micronutrient.

Source: GMHC Treatment Issues
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