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NUTRITIONAL ASPECTS OF AIDS

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INTRODUCTION

In 1982, physicians in the southwest region of Uganda, bordering on Zaire and Rwanda, noted an increasing number of patients presenting with extreme weight loss, associated with malaise, fever, itchy maculopapular rash, oral candidiasis, and prolonged diarrhea. The illness was called "Slim Disease" by

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the local people because of the marked wasting (114). The typical patient, according to reports from the Ugandan Minister of Health, had experienced a six month prodrome with malaise and intermittent fever, usually treated unsuccessfully with aspirin, chloroquine, or chloramphenicol. Anorexia then developed, and in the next six months intermittent diarrhea and weight loss began. Western and traditional medicine failed to alter the disease progression, and ultimately the patients presented in a debilitated terminal state. Serwadda et al (114) described 29 patients that were identified in the field and studied in some detail. Approximately two thirds had weight loss greater than 20% of usual body weight accompanied by chronic diarrhea, and nearly two fifths had lymphadenopathy. Patients with diarrhea and weight loss of 10 kg or more were seropositive for HIV and anergic on skin testing. They concluded that "Slim Disease" was truly a new syndrome in Uganda. "Slim Disease" was associated with HIV-1 infection and "not unlike Acquired Immune Deficiency syndrome (AIDS)" in its clinical and epidemiological features. None the less, the syndrome was distinguished from AIDS and AIDS-Related Complex (ARC) by the extreme weight loss and diarrhea characteristic of "Slim Disease" patients. It is now obvious that these intestinal and nutritional manifestations are the major clinical presentations of AIDS in Africa (10), and the symptoms of "Slim Disease" described by Serwadda et al have been incorporated by the World Health Organization (WHO) into the clinical case definition of AIDS in Africa (25, 134).

At about the same time, clinicians in Brussels and Paris identified AIDS in African patients in Europe, most of whom were originally from Zaire or Rwanda (13, 22, 23). A search for AIDS in Central Africa was therefore initiated in late 1983, and reports of confirmed HIV infections soon were forthcoming (103, 106). Similar to the situation in Uganda, oral candidiasis, diarrhea, and weight loss were the most common signs of illness in these patients. By 1986, it was fully recognized that an enteropathic AIDS syndrome, manifested by wasting, chronic diarrhea, and recurrent fever, was a common presenting clinical triad in AIDS patients in Central and East Africa (10) and in other developing countries such as Haiti (89). In one study in Kinshasa, Zaire, for example, 98 of 243 (40%) of AIDS patients presented with persistent diarrhea (26). In contrast, *Pneumocystis carinii* pneumonia (PcP) was not a frequent diagnosis in this setting (129a, 106, 131).

In the Western world, the AIDS epidemic was ushered in by reports of an unusually high incidence of PcP or Kaposi's sarcoma (KS) in previously healthy homosexual men (16, 17). In 1986, Blaser & Cohn (12) reviewed 359 published cases of AIDS (excluding papers reporting patients with particular manifestations associated with AIDS) and 87 cases from the Colorado registry. Approximately 50% of these patients had documented PcP, in contrast to a relative paucity of this type of pneumonia among Africans with AIDS and patients native to the tropics but living in Western countries. While diagnostic

inadequacies certainly existed in Third World countries, which would lead to underestimating the incidence of PcP in Africa, it was deemed unlikely that they could account for all of the differences observed.

It is difficult to directly compare the incidence of intestinal disease among Western and African or Haitian AIDS patients, as few published series report the cumulative incidence of various system manifestations in patients. Many authors simply state that diarrhea is a common complication of AIDS (3, 31, 35, 52, 55, 74, 110, 118) and then review a selected group of patients with diarrhea without elaborating the universe from which they were selected. However, in one autopsy series from Los Angeles of 216 cases that satisfy the Centers for Disease Control (CDC) case definition of AIDS, the autopsy diagnoses and cumulative infectious disease experience, as abstracted from clinical records, are presented (72). These 216 AIDS patients had 242 episodes of respiratory infection compared to 113 episodes of intestinal infection. In 147 cases opportunistic infections (OI) of the respiratory system were considered to be the immediate cause of death, but only in 15 cases were gastrointestinal illness similarly classified. Thus, although rather common, intestinal infections generally had far less severe manifestations than respiratory tract infections in these patients.

Chronic infectious, inflammatory, or neoplastic diseases result in persistent tissue catabolism leading to wasting. A classic example is tuberculosis, a disease known as "consumption" because of the clinical wasting that occurs during its course (68). The many different OI and malignancies associated with AIDS are no exception, and weight loss greater than 10 kg (or greater than 10% of body weight) is now included in the case definition for AIDS used by the CDC and by WHO for developing countries. When a disease also targets the intestinal tract, these effects may be even more striking. Multiple mechanisms of catabolism and wasting may help explain the severe wasting seen in "Slim Disease."

INTESTINAL TRACT MANIFESTATIONS IN AIDS PATIENTS

Although many factors are involved in the pathogenesis of the relentless weight loss and dramatic changes in body composition associated with AIDS (75, 79), it has become clear during the past 3–4 years that HIV infection itself has a major impact on the structure and function of the entire alimentary tract (50). In addition, OI contribute significantly both through systemic effects on appetite and metabolic rate and also locally in the gut. These mechanisms have previously been discussed in the *Annual Review of Nutrition* (70). HIV itself has been found in the intestinal mucosa and may directly lead to intestinal symptoms and influence nutritional status.

Table 1 Gastrointestinal symptoms in AIDS[a]

Symptom	Etiological agents
Oral	*Candida* sp.
	Aphthous ulcers (CMV, HSV, HIV)
	HSV
	Kaposi's sarcoma
Dysphagia/odynophagia	*Candida* sp.
	CMV
	HSV
	Kaposi's sarcoma
Dyspepsia	CMV
Diarrhea/malabsorption	AIDS enteropathy
	Cryptosporidium sp.
	Microsporidium sp.
	Isospora belli
	MAI
	CMV
	Giardia lamblia
	Strongyloides stercoralis
	Salmonella sp. *Shigella* sp.
	Clostridium difficile
	HSV
	CMV
	Neisseria gonorrhoeae
Gastrointestinal bleeding	Lymphoma
	Kaposi's sarcoma
	Candida sp.

[a] CMV = Cytomegalovirus; HSV = Herpes Simplex virus; MAI = *Mycobacterium avium intracellulare*.

Gastrointestinal Symptoms in AIDS

One way to organize the myriad of intestinal manifestations in AIDS is to classify them by principal symptoms (Table 1)

ORAL DISEASES One of the causes of diminished food intake in patients with AIDS is the oral pathology associated with the illness. Often painful conditions affect swallowing and impair taste and diminish appetite. Oral candidiasis is found commonly in patients with AIDS, and more than 50% of HIV-infected individuals with oral thrush will go on to develop full-blown AIDS within two years (73). In fact, one of the clues to the AIDS epidemic in Africa was a marked increase in the incidence of oral candidiasis in adults (114). Infection is characterized by extensive but otherwise typical plaques of greyish-white exudate that may spread throughout the oral cavity. Treatment with an oral antifungal such as ketoconazole is usually successful.

Aphthous ulceration is another common problem of unknown cause;

although HIV, cytomegalovirus (CMV), and herpes simplex virus (HSV) have been isolated from these ulcers, the significance of these isolations is unclear. In contrast, hairy leukoplakia is found only in AIDS patients and has been associated with Epstein-Barr virus (EBV) and human papillomavirus infection (113). Eighty percent of patients with hairy leukoplakia will have developed full-blown AIDS within one year. The condition is usually asymptomatic and no specific treatment is required.

Oral KS is commonly found on the palate and is usually indicative of more extensive involvement of the gastrointestinal tract (113). Intestinal KS can also occur in the absence of skin involvement (49).

DYSPHAGIA AND ODYNOPHAGIA Difficulty with swallowing and painful swallowing generally indicate esophageal candidiasis (5). The dysphagia may be so severe that even liquids are difficult to tolerate. Infection is almost invariably invasive, and systemic antifungal therapy is usually necessary. In addition, CMV and HSV can cause esophageal symptoms (18, 124, 132). Around 20% of patients with AIDS will experience esophageal symptoms at some time during the illness.

DYSPEPSIA Symptoms of gastritis, duodenitis, and peptic ulceration may occur. In the AIDS patient, these manifestations may be due to CMV, which can cause multiple, shallow ulcers throughout the stomach and duodenum (64, 132). These lesions are apparent at endoscopy, and the virus can be isolated from biopsy material. Treatment of CMV gastrointestinal disease is now possible with ganciclovir (64, 124).

DIARRHEA Diarrhea is one of the most devastating clinical problems in AIDS and obviously has a major impact on nutritional status (27–28, 83, 118, 121). Several patterns of diarrheal disease are evident in AIDS patients. A secretory-like high-volume watery diarrhea is commonly observed in patients infected with *Cryptosporidium parvum* but also occurs in patients infected with CMV, *Mycobacterium avium-intracellularae* (MAI), and *Microsporidium* sp. Other patients with these infections, as well as patients infected with *Giardia lamblia, Isospora belli,* and *Strongyloides stercoralis* may present with malabsorption and steatorrhea. In addition, AIDS patients can develop invasive colonic disease with bloody diarrhea associated with CMV, *Salmonella* sp, *Shigella* sp., and, on occasion, *Entamoeba histolytica.*

ANO-RECTAL SYMPTOMS Rectal pain or discomfort, tenesmus, and a bloody mucopurulent rectal discharge are common findings in patients with rectal HSV infection. These findings are not diagnostic, of course, and should

be thoroughly investigated, since they may also be due to more easily treated infections by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

GASTROINTESTINAL BLEEDING Bleeding from the upper gastrointestinal tract is a relatively uncommon symptom in AIDS. In a recent survey, gastrointestinal bleeding occurred in approximately 3% of nearly 500 patients (9). Hematemesis and/or melena was attributed to a variety of conditions (including gastric and duodenal lymphoma, *Candida* infections, HSV and CMV esophagitis, and MAI duodenitis) and to a variety of non-AIDS-related lesions. Bleeding may also occur from KS and distal gut lymphomas (11). A thorough work-up is essential in order to identify the cause and select the appropriate treatment.

Gastrointestinal Infections in AIDS

Opportunistic organisms constitute the most clinically significant and nutritionally important group of alimentary infections seen in HIV patients. Other enteric pathogens that are not opportunistic in the true sense of the word may also cause illness in AIDS patients. Some studies have attempted to assess the prevalence of these infections in patients with HIV infection and are summarized in Table 2.

Table 2 Prevalence of gastrointestinal infections in patients with HIV infection and diarrhea[a]

Pathogen	Prevalence (%)
Viruses	
CMV	7–45
HSV	4–18
Bacteria	
Salmonella sp.	5–25
Shigella sp.	1–5
Campylobacter sp.	9–11
MAI	5–12
Chlamydia trachomatis	11
Vibrio parahaemolyticus	4
Clostridium difficile	7
Protozoa	
Cryptosporidum sp.	15–16
Giardia lamblia	4–15
Entamoeba histolytica	11–25
Isospora belli	2
No infective agent isolated	15–45

[a]Adapted from References 28, 83, 118.

IMPACT OF INTESTINAL INFECTION ON GUT FUNCTION AND NUTRITIONAL STATUS Intestinal disease contributes to under-nutrition in AIDS by (*a*) reduction of food intake, (*b*) diminished absorption, and (*c*) increased nutrient losses. Oral intake can be impaired because of local disease in the oral cavity or esophagus, and the mechanisms for such impairment are, in general, clear-cut. Decreased food intake can also be secondary to anorexia, which is controlled by the central nervous system in response to small peptide mediators (cytokines) produced during inflammatory responses. Although the mechanisms by which many of the bacterial and some viral enteropathogens produce diarrhea have been the subject of intensive study and are now well characterized in many cases, relatively little is known about the pathogenesis of diarrhea that is caused by opportunistic protozoa such as *Cryptosporidium, Microsporidium,* and *Isospora belli,* atypical mycobacteria such as MAI, and certain viruses including CMV and HIV. Some of these microorganisms appear to affect gut function and structure in more than one way, thus precluding a straightforward classification by pathogenic mechanisms. Nevertheless it is useful to broadly classify pathogens into those that predominantly increase losses from the gut and those that have a primary and major inhibiting effect on absorptive mechanisms, while recognizing that in some instances overlap occurs and any assignment is oversimplication.

Increased losses from the gastrointestinal tract Net losses of water, electrolytes, protein, and cellular constituents from the intestinal tract occur in many disease processes. These secretions take place when the net accumulation of fluid in the small bowel exceeds its absorptive capacity and when compensation by the colon is inadequate to maintain net positive balance. A classic example is provided by cholera, in which crypt cell chloride secretion is enhanced and villus cell sodium absorption is diminished by the action of cholera toxin. These events are mediated by the intracellular accumulation of cyclic AMP owing to activation of adenylate cyclase by cholera toxin, and they result in a marked net accumulation of fluid in the gut lumen. Another common mechanism is exudative diarrhea, which is characteristically associated with intestinal inflammation and ulceration and leads to loss of blood and protein and the sloughing of intestinal epithelial cells. A classic example is the bloody diarrhea caused by invasive microorganisms such as *Shigellae* and *Salmonellae*. These infections tend to be severe and systemic in AIDS patients (69).

Secretory diarrheas: Probably the most frequent cause of watery secretory diarrhea in AIDS is the opportunistic pathogen *Cryptosporidium parvum*. This protozoan was known to be an enteropathogen in animals for many decades and was shown to cause human infection as recently as 1976 (99). Since then it has emerged as an important cause of self-limited diarrhea in

immunocompetent children and as a frequent cause of chronic secretory diarrhea in patients with AIDS (24, 30, 92, 97). As described in industrialized countries cryptosporidiosis is characterized by high-volume watery diarrhea that ranges from 1 to 25 liter/day (97). In Africa, however, this is not the most common presentation; more typical is a chronic, waxing and waning, small volume diarrhea (26). During the initial phase of the illness, fever, malaise, and, occasionally, abdominal pain are present. To date, the mechanism(s) by which this organism produces diarrhea has evaded us. The parasite is known to be locally invasive. It remains closely associated with the intestinal epithelium and resides in a unique niche as an intracellular but extracytoplasmic pathogen within the lipid bilayer of the apical gut cell membrane (90). This process results in disruption of surface microvilli, and it reduces the surface area available for intestinal absorption. During severe infection the entire intestinal tract can be affected, including both small and large bowel absorptive functions. In the small intestine, partial villous atrophy has been associated with cryptosporidial infection. A diagnosis is now generally made by detection of oocysts in feces by light microscopy using a modified acid fast stain or by auramine-rhodamine staining and fluorescence microscopy (15). The parasite can be seen in mucosal biopsies from the small or large intestine.

Treatment of *C. parvum* has proven elusive. Although a claim has been made about the effectiveness of spiramycin (107), this is disputed. In a few patients, remission but not cure has been achieved by oral administration of hyperimmune bovine colostrum (128). Encouraging therapeutic responses have been obtained during treatment with azidothymidine (AZT) (20, 27), which is reported to eradicate this organism from the intestine. Many patients, however, do not respond to any therapeutic approach, and supportive therapy with intravenous fluids and nutritional supplements may be life saving.

An identical syndrome of chronic watery diarrhea and weight loss, which is clinically indistinguishable from that seen with cryptosporidiosis, occurs with two related coccidial enteropathogens, *Microsporidium* sp. (92) and *Isospora belli* (30, 32, 92, 119). Infection may be associated with fever, abdominal pain, and severe dehydration. *Isospora* has been found in 15% of AIDS patients from Haiti (32) and can be diagnosed by light microscopy of stool; a modified acid fast stain or Giemsa can be used to demonstrate the oocyst stage (126). *Isospora belli* infection can usually be successfully treated with trimethoprim-sulfamethoxazole, but the recurrence rate is high and may require chronic suppression with the same drug. Metronidazole is an effective alternative treatment. *Microsporidium* has been found much less commonly but is easily missed by light microscopy and usually requires pathologic study of biopsy material for diagnosis. Although both *Cryptosporidium parvum* and *Isospora belli* produce morphological abnormalities of the small intestine, it

seems unlikely that this pathogenetic mechanism alone could explain the high volume diarrhea. As yet no secretory toxins have been identified, but the search continues. It is possible that these organisms exert their effect on the gut through activation of local neuroendocrine secretory pathways. High volume watery diarrhea is also associated with MAI infection of the intestine.

Exudative diarrheas: CMV is an important OI in AIDS patients, and may produce severe inflammatory and ulcerative damage throughout the gut. In the US and Europe CMV colitis is found in approximately 10% of AIDS patients with diarrhea (85). Patients with CMV colitis generally have fever, severe diarrhea (often with bleeding), and sometimes abdominal pain with marked abdominal tenderness. They are usually wasted and appear extremely unwell. Endoscopic examination of the colon can reveal deep ulceration like that found in Crohn's disease; milder forms may be indistinguishable from ulcerative colitis (4). Like other forms of inflammatory bowel disease, CMV colitis may be complicated by toxic dilatation of the colon.

CMV colitis almost certainly is the result of replication of the virus in intestinal epithelial cells. Diagnosis is made by detection of intracellular viral inclusions in biopsy material. Since many adults are already seropositive, including most AIDS patients, serology is not a reliable tool for diagnosis. Antibody titers may be low even in the presence of severe disseminated disease. Treatment with intravenous ganciclovir results in clinical improvement in at least 75% of patients (18, 64).

Other important nonopportunistic enteropathogens that cause infectious colitis, such as *Salmonella* and *Shigella* sp., should always be considered in the differential diagnosis because they are treatable causes of this clinical entity. Effects on host nutritional status are largely due to losses of blood, protein, and intestinal cells from the gastrointestinal tract, although the systemic effects of fever, when present, are also contributory. Although *Entamoeba histolytica* is another important invasive enteropathogen commonly found in feces of homosexual men, the majority of isolates are now believed to be nonpathogenic, as judged by zymodeme analysis (1, 2). If this is truly a marker for clinical virulence, then strains from AIDS and ARC patients and male homosexuals without AIDS are unable to cause invasive amebic colitis.

Intestinal malabsorption: Malabsorption of a variety of nutrients, including fat, carbohydrate, vitamin B_{12}, folic acid, and possibly zinc and thiamine, is described in AIDS patients in association with certain intestinal infections (1, 38, 45, 62, 117, 118). Although few studies have systematically analyzed etiological agents and nutrient absorption, a number of organisms are able to produce such abnormalities. For example, partial or subtotal villus atrophy occurs with *Cryptosporidium, Isospora,* and *Giardia* infections. Villus archi-

tecture abnormalities are also know to occur in *Strongyloides*. The propensity of this helminth to disseminate in immunosuppressed individuals frequently leads to a fatal hyperinfection syndrome. Nevertheless, clinical symptomatic infection with or without hyperinfection is extremely uncommon in AIDS (87). MAI also produces villus shortening, steatorrhea, and a Whipple's disease-like disorder (53, 111, 130). Patients present with profuse diarrhea and weight loss, usually accompanied by fever and severe malaise. The small intestine affected by MAI, and similar in appearance to one infected with Whipple's disease, has "foamy" macrophages filled with acid-fast organisms. The diagnosis can be made by culturing MAI from feces, but treatment (even quadruple therapy with the antituberculous drugs ansamycin (rifabutin), clofazimine, cycloserine, and amikacin) is disappointing (54).

AIDS ENTEROPATHY Many AIDS patients with diarrhea and malabsorption do not have an obvious infective cause for their symptoms. In part this may be due to the difficulty in making certain diagnoses (e.g. *Microsporidia*) or the failure to search for enteric viruses. Possibly, however, the HIV virus itself, in the absence of OI, can cause intestinal damage and diarrhea. The recent demonstration of HIV-1 in the small and large intestinal mucosa of patients with AIDS strengthens the view that HIV may have a primary effect on intestinal function (46, 86, 98). HIV has been detected by co-culture techniques, by in situ hybridization with an HIV-1 specific probe, and by immunocytochemistry with antibody to gp41. Perhaps reflecting its neurotropism, the virus was present in the lamina propria, primarily in macrophages but also in enterochromafin cells at the base of crypts.

Several studies have investigated absorptive function in patients with HIV infection but in whom no other bacterial or parasitic infections are present (74, 91, 129). These studies confirm that partial villus atrophy occurs in HIV infection. This condition can be directly attributed either to HIV or to an as yet unidentified enteropathogen. Reduced activity of the brush border disaccharidase enzymes and impaired absorption of fat and D-xylose have also been demonstrated. In one study there was good correlation between the degree of fat malabsorption and the morphological changes in the small bowel mucosa (91). Apparently, reduction in serum concentrations of folic acid, vitamin B_{12}, and zinc also occurs in HIV-infected patients in the absence of other enteropathogens (129).

Thus HIV infection alone appears to cause an enteropathy with functional sequelae. The mechanisms involved are unclear, but the presence of many activated T cells in the lamina propria may be sufficient to play a causative role (88). The presence of HIV-1 in enterochromaffin cells also raises the possibility that release of mediators such as serotonin from these cells could directly modify intestinal absorptive and secretory processes.

Noninfectious Gastrointestinal Problems in AIDS

MALIGNANCY Kaposi's sarcoma is an extremely common associated feature of AIDS and occurs in the intestinal tract of 40% of patients at presentation and more than 70% of patients at autopsy (133). Lesions can be found commonly in the mouth but have been detected throughout the intestinal tract. This tumor produces dysphagia in the esophagus; in the lower gastointestinal tract it can cause diarrhea and, at times, a protein-losing enteropathy (11, 49). Massive hemorrhage, intestinal obstruction, and malabsorption have been reported. Diagnosis is usually made endoscopically, and biopsy is generally unnecessary. A variety of chemotherapeutic agents have been used to treat Kaposi's sarcoma including vinblastine, actinomycin D, bleomycin, cyclophosphamide, adriamycin, and α-interferon.

Non-Hodgkin's lymphoma occurs in the intestinal tract of AIDS patients but is much less common than Kaposi's sarcoma. Like the anal carcinomas that are now thought to be due to human papillomavirus infection (48), non-Hodgkin's lymphoma does not have a significant impact on nutritional status.

NUTRITIONAL ASPECTS OF AIDS AND THE WASTING SYNDROME

As in other chronic infectious or inflammatory diseases, wasting is a common manifestation in AIDS patients. The preceding discussion has already highlighted the infectious enteropathies that may occur in AIDS patients and contribute to development of adult protein-energy malnutrition (PEM). But it should be emphasized that any associated infection in AIDS patients, whether opportunisitic or not, will adversely affect nutritional status, as we would expect in patients without underlying HIV infections. The critical questions to ask are (*a*) what are the mechanisms involved in wasting in AIDS patients, (*b*) what are the clinical consequences, (*c*) is nutritional rehabilitation possible, and (*d*) are other measures available to modulate the wasting process? As a prelude, we review studies that evaluate the malnutrition associated with AIDS patients.

Characteristics of Malnutrition in AIDS Patients

Determination of body composition, which requires sophisticated methods or machinery, is essential in understanding the nature of a wasting process. For example, determination of body cell mass is desirable but usually requires whole body counting of ^{40}K, which is simple but depends on the availability of a four pi whole body liquid scintillation counter. Nearly all (>97%) body potassium is in nonadipose cells, and a constant proportion of potassium

(0.018%) is the radioactive isotope ^{40}K. Thus, measurement of total body ^{40}K (which may be detected with an accuracy of ±4% with the whole body counter) can be used to calculate total body potassium, and from these measurements one can extrapolate body cell mass (105). Body cell mass can also be determined by measuring intracellular water volume, since fat is relatively water poor. One method employs isotope dilution, for example using $^{3}H_2O$ to estimate total body water and $^{35}SO_4$ to estimate extracellular water. Intracellular water volume is then calculated as the difference between the two measures (104). Body fat content can be estimated by underwater weighing. Alternatively, simple anthropometry can be used to measure skinfold thickness and limb circumference, which are related to fat content by standard equations. Energy balance is usually determined by directly measuring O_2 consumption and CO_2 production and calculating the metabolic expenditures.

These methods have been used to evaluate a limited number of malnourished patients with clinical AIDS who were being treated for some acute complication of the disease (79). Depletion of body cell mass was present in all subjects. While the degree of depletion paralleled weight loss (-18%), body cell mass was even more severely affected (-32%). Assessment of lean tissue losses based on weight loss thus significantly underestimated the real losses. Total body potassium normalized for height (TBK/Ht) was significantly lower in subjects with diarrhea (62 ± 9% of ideal) than in those without diarrhea (74 ± 9% of ideal). In addition to depletion of lean body mass, body fat content was also diminished, although the values in patients were not significantly different from those obtained in healthy male homosexuals. Fat depletion was more marked in female than in male AIDS patients. This finding is noteworthy because women normally have a higher body fat content than males. The relatively greater depletion of fat than of potassium in the women AIDS patients resembled the body composition pattern seen in patients with eating disorders and wasting. Indeed, the small number of women AIDS patients in this study had severe oral and/or esophageal candidiasis and great difficulty in eating; therefore, starvation was an important aspect in their clinical picture. In contrast, the body composition pattern in the men is consistent with the metabolic changes due to infection or inflammation. Intracellular water content was diminished, but extracellular water, expressed as a percent of body weight, was increased in all of the AIDS patients compared to normal values. The relative increase in total body water explains why lean body mass diminished more than body weight in the group. The key message in these data is that the severity of the nutritional deficiency in AIDS patients will often be underestimated by simple anthropometric measures and body weight.

Another important observation in this study is that depleted body cell mass

is not an invariable consequence of AIDS. Two patients in the group with a history of *Pneumocystis carinii* pneumonia or cutaneous KS had completely normal total body potassium. In addition, the changes in fat content were variable, and some patients had normal or elevated body fat associated with severe lean body mass losses. A relative increase in protein catabolism over catabolism of fat is common in sepsis, surgery, or trauma (70). This kind of response differs from the findings in simple starvation, in which adaptive mechanisms utilize fat for energy needs first, as fat is the largest store of energy in the body (14).

In a few patients studied in serial fashion, Kotler et al (79) found a good correlation between body cell mass and length of survival following the measurement. Short survival was also associated with diarrhea, a common symptom in patients with marked total body potassium depletion, and this group of subjects experienced a course of relentless clinical deterioration.

Kotler et al (78) subsequently studied the relationship of body cell mass and survival time in a group of 32 subjects who were evaluated within 100 days of death by means of TBK/Ht determination, normalized for age and sex. The study revealed progressive depletion of body cell mass until death, and the regression line predicted death at a value of TBK/Ht of 54% of normal. Post-mortem examinations were performed on seven patients, and TBK/Ht data closely fit the calculated regression line in five of these patients. One of the remaining two patients had a very low TBK/Ht (27% of normal) and had received only intravenous dextrose and water for the last three months of life. The second patient had an unexpected high TBK/Ht (77%) associated with systemic MAI infection with marked organomegaly and enlarged lymph nodes packed with mycobacteria. Presumably the tissue load of organisms contributed to the measured TBK. While body weight paralleled the TBK/Ht measurements, at 100 days before death the regression line for weight was at 90% of normal, which would not predict the subsequent course, whereas the TBK/Ht was already decreased to 71% of normal. As noted earlier, a relative increase in total body water occurs together with depletion of body cell mass. In contrast, the calculated body fat content showed no correlation with survival time ($r = -0.11$) and varied considerably from normal or increased to markedly diminished in individual patients.

Kotler et al (78) remarked that the degree of weight loss at death was similar to that noted in humans undergoing lethal starvation, for example individuals dying during the seige of Leningrad or during the Warsaw ghetto uprising in World War II. They suggest that AIDS should be considered as a chronic, progressive debilitating process rather than solely as an "aggressive overwhelming illness," since the therapeutic approaches to the former, such as nutritional rehabilitation, may offer significant benefit to the patient.

Indeed, clinically stable AIDS patients with established losses in body cell

mass can maintain body composition for prolonged periods. Thus, in a group of five AIDS patients, five seronegative homosexual males, and six seronegative heterosexual males serially studied by Kotler et al (76) over a six-week period, no differences in dietary intake of protein, fat, or carbohydrate were detected and no change in TBK/Ht or intracellular water volume was found, even though the patients had evidence of malabsorption of carbohydrate and fat. One explanation may be that resting metabolic rate (RMR) determinations revealed a significant 16% decrease in metabolic expenditure in AIDS patients. Thus hypometabolism appeared to largely compensate for nutrient losses associated with intestinal malabsorption. Kotler et al (76) rightly considered AIDS to be a paradigm for malnutrition in clinical disease, as AIDS wasting syndrome involves multiple mechanisms and different potential therapeutic opportunities.

These findings have been confirmed in a recent study in England of 13 HIV seropositive subjects, 10 of whom were CDC stage IV, and 9 healthy males from no known risk group (M. Foskett and G. Griffin, personal communication). No significant difference was found in dietary intake of protein or energy, even though the HIV-positive group had a significantly lower body mass index, mid-arm muscle circumference, and grip strength measured with a hand dynamometer. Fat absorption, measured by the ^{14}C-triolein breath test, was at the limit of the normal range. Two of three subjects who were followed prospectively over a period of several months, and who remained clinically well, were able to maintain weight and nutritional status. The third subject lost 3 kg at the onset of an episode of *P. carinii* pneumonia and continued to lose weight thereafter, even with resolution of the infection and constant nutrient intake achieved by supplementation with commercial complete liquid diet and carbohydrate.

Mechanisms of Malnutrition and Wasting in AIDS

In addition to the obvious potential relationship of wasting to impaired dietary intake due to oral and esophageal lesions and/or anorexia, and effects of intestinal malabsorption with or without clinical diarrhea, malnutrition can also be due to the metabolic effects of infection and inflammation mediated by peptide products of mononuclear cells, collectively termed cytokines (70). These mediators, including interleukins 1 beta and 6 (IL-1β and IL-6) and cachectin/tumor necrosis factor alpha (C/TNFα), link the immune and metabolic responses to infection, activate immune responses, and provide the energy and substrate requirements for the diverse anabolic events turned on by the stress. Since the host almost always responds by curtailing dietary intake, catabolism of stored nutrients is necessary to provide energy and substrates for the increased protein synthesis requirements of the normal host immune response. Absolute losses of protein, fat, and carbohydrate from the body

occur in all infected patients, and in part convalescence is determined by the time needed to replenish lost nutrients.

The recent report of elevated C/TNFα levels in AIDS patients (81) is consistent with the idea that cytokines may be involved in the pathogenesis of the wasting syndrome in these patients. Indeed, this molecule was identified first by its inhibition of the synthesis of lipoprotein lipase (LPL), an enzyme involved in clearance of triglyceride from serum. A clearance defect was thought to be the cause of marked hypertriglyceridemia observed in a study of animals with *Trypanosoma brucei* infection (8). C/TNFα also is a transcriptional inhibitor of the synthesis of enzymes involved in lipid synthesis; this process leads to depletion of fat from adipose tissue and weight loss (93). When C/TNFα levels were determined in humans with HIV infection, elevated levels were observed in none of 8 asymptomatic patients, 2 of 13 patients with lymphadenopathy, 5 of 9 patients with ARC, and all 9 patients with clinical AIDS (81). The mean serum level of C/TNFα progressively increased across the clinical spectrum of HIV infection, with the highest levels found in patients with ARC or AIDS plus secondary infections and weight loss. When the assays were repeated in seven patients with elevated C/TNFα, the levels remained above normal but varied considerably over time, in part dependent on the presence or absence of secondary infections. Although it is tempting to speculate that elevated C/TNFα levels are the cause of the cachexia in AIDS, increases in circulating cytokine may simply be a response to the multiple infections experienced by these patients. The critical question posed by Beutler (7), does C/TNFα "cause disease, combat disease, or merely serve as an indicator?" remains to be answered.

Whether cause or effect, blood monocytes isolated from AIDS patients release large amounts of C/TNFα into the culture medium (82, 135). These cells spontaneously produce C/TNFα in vitro, and they are hypersensitive to lipopolysaccharide (LPS) or interferon-γ (IFN-γ) stimulation. This heightened production of cytokines is under investigation and probably involves regulatory influences on the cells in vivo. For example, THP-1 cells, a human monocyte cell line, do not constitutively produce C/TNFα or IL-1β, and neither mRNA nor product is made when LPS is added (95). In vitro responses from cells chronically infected with HIV are no different, even when LPS or LPS plus IFN-γ are added. However, these cells show a 2–7-fold increase in C/TNFα production and a 2.5–13-fold increase in release of IL-1β when they are acutely infected with HIV and exposed to LPS or LPS plus IFN-γ. Increases in mRNA for the two cytokines were also observed and indicate that regulation is at the transcriptional level. The cells also exhibited phenotypic changes indicating that the retrovirus induced differentiation of monocyte precursors, which primes these cells to respond to a second signal, such as LPS. This in turn up-regulates cytokine genes and increases cytokine

production. Lau & Livesey (82) suggest that high circulating levels of acid labile IFN-α may serve the same function in vivo in AIDS patients. Normal human blood monocytes could be induced to manufacture C/TNFα by exposure to AIDS sera or to IFN-α; the effects of such exposure could be abrogated by addition of antibody to IFN-α but not to IFN-γ.

Lipid studies have been performed in 32 patients with AIDS (including 26 with OI, 1 with KS, and five with both OI and KS) as well as in 8 seropositive subjects without OI, and 9 heterosexual and 8 homosexual male controls (57). These data document that hypertriglyceridemia is commonly present in AIDS patients; none of the above patients had diabetes, renal failure or the nephrotic syndrome, active hepatitis, or cirrhosis, and none were receiving steroids or estrogens that might account for the finding. Serum triglyceride levels in clinically well HIV-positive subjects were intermediate between the AIDS patients and the controls. Fifty percent of the AIDS patients or the healthy seropositive subjects had triglyceride levels above 190 mg/dl, but no difference was noted in cholesterol levels among the three groups. Lean body mass, measured as TBK/Ht, was reduced significantly in the AIDS patients as expected. These data at first seem to support the role of cytokines in the pathogenesis of the wasting syndrome in AIDS. However, there was no evident relationship between body cell mass and serum triglycerides (r = -0.178), even when data from AIDS patients with and without reduction in TBK below 76% of ideal were analyzed separately. There were also no significant differences in triglyceride levels between patients with wasting (245 $\pm$ 39 mg/dl) and better nourished subjects (217 $\pm$ 37 mg/dl).

Grunfeld & Palladino (58) have reviewed the effects of C/TNFα on metabolism in infected animals. They suggest that the effects of this peptide may differ in vitro and in vivo and from species to species. For example, there is ample confirmation of the effects of C/TNFα in cultured mouse fibroblasts, in which the mediator inhibits incorporation of labeled acetate into triglyceride, decreases LPL levels and activity, and stimulates lipolysis without affecting insulin receptors or insulin-stimulated glucose transport (65, 93, 102, 108). These same effects are also caused by other cytokines working through distinct surface receptors (58); however, they are not observed when fat cells from other species were employed (66, 67, 109).

The availability of recombinant C/TNFα permitted studies to be carried out in vivo. Although rC/TNFα given intravenously to rats did lead to a rapid and sustained increase in serum triglycerides (39, 42) owing to an increase in very low density lipoprotein (19, 40, 80), this change resulted from an increase in hepatic lipogenesis that paralleled the change in serum triglycerides (56). Alteration in lipid synthesis was not found in other organs, not even in adipose tissue. Administration of IFN-α or IL-1β also stimulated lipogenesis in the liver (41) with a time course similar to that of C/TNFα, which suggests

that IFNα and IL-1β act directly and not by inducing C/TNFα. In addition, no increase in the tissue content of the lipogenic enzymes acetyl-CoA carboxylase or fatty acid synthetase could be found, but rather an increase in citrate, an allosteric activator of acetyl-CoA-carboxylase in liver, was detected (59).

Thus, Grunfeld and colleagues believe that C/TNFα in vivo leads to higher triglyceride levels because it enhances hepatic lipogenesis and not because it inhibits LPL. Whereas in vivo administration of C/TNFα to mice, rats, and guinea pigs inhibits LPL synthesis in epididymal fat cells (but not in other adipose tissues in the same species), there is a period during which triglyceride is already increasing but no change in LPL activity is detectable (59). In addition there is no change in clearance of triglyceride rich-lipoproteins (42, 80). The response of humans has yet to be defined.

While the results do implicate C/TNFα in the pathogenesis of cachexia, it is difficult to determine whether or not C/TNFα alone is responsible. Crude C/TNFα containing culture media supernatants from stimulated macrophages cause sustained weight loss when administered to mice, but the purified cytokine results in acute anorexia and weight loss that is not sustained with repeated injections of the same dose (60, 67, 101, 120, 122, 125). This tachyphylaxis is not due to an altered clearance of the cytokine or to a humoral immune response (47). In contrast, tumors that have been genetically engineered to continuously secrete C/TNFα lead to chronic anorexia, weight loss, and ultimately death when transplanted into nude mice (100). The effects can be abrogated by antibody to C/TNFα (116) and are not caused by the non-C/TNFα secreting parent tumor. One explanation for the difference in response may be that other metabolically active factors are produced by these tumors and synergistically interact with C/TNFα in the host to produce cachexia. This possibility is consistent with experiments showing that C/TNFα enhances muscle proteolysis in vivo (44), whereas recombinant C/TNFα does not cause proteolysis of muscle in vitro (94). IL-1β is a distinct cytokine with the same range of biological activities as C/TNFα; it is one of the major mediators of the immunologic and metabolic response to infection (33). In many situations, IL-1β and C/TNFα interact synergistically, and C/TNFα can act as an inducer of IL-1β as well (34). Thus, in view of the elevated C/TNFα levels reported in AIDS patients, it is not surprising that IL-1β is also present in serum or in culture supernates from monocyte cultures from AIDS patients (6, 37, 84, 112). One study showed spontaneous hyperproduction of IL-Iβ by in vitro cultured monocytes from a subset of patients (84). These subjects tended to have more severe disease, as manifested by more OI, higher fever, and lower absolute T4 counts and T4:T8 ratios; these clinical and laboratory differences were not statistically significant, however. Prospective studies will need to evaluate the role of either IL-1β or C/TNFα in the catabolic events occurring in AIDS patients.

Another cytokine of metabolic importance is IL-6, which previously was known as hepatocyte-stimulating factor, B cell–stimulating factor-2, hybridoma plasmacytoma growth factor, or interferon beta-2. IL-6 production is stimulated in humans when peripheral blood mononuclear cells are exposed to HIV but not if they are first exposed to HIV neutralizing antibody (96). Adherent mononuclear cells were even more responsive to HIV and produced considerably more IL-6 than did the unseparated peripheral blood cells. Neither T cells nor non-T cell nonadherent cells responded to the virus in vitro. Early increases in IL-6 mRNA were detected within 2 h of addition of HIV to the IL-6 producing cells, and maximum levels were attained by 4 h. The mechanisms of activation are not clear, but HIV inactivated with β-propiolactone also induces IL-6 message and results in increased IL-6 secretion. Thus, retrovirus infection of the IL-6–producing cell may not be required, and a signal at the cell surface conveyed by HIV binding may be sufficient. Since IL-1β is a potent inducer of IL-6 (29), it is possible that the signal for IL-6 production may be IL-1β itself. More recently, it has been shown that administration of recombinant human C/TNFα to patients induces the production of IL-6 within minutes; peak production occurs 2–3 h after a bolus of C/TNFα is administered (63). IL-6 overproduction by HIV patients, either as a result of IL-1β of C/TNFα activity, may be responsible for the chronic polyclonal B cell activation seen in AIDS and in the development of B cell malignancy. Potentially, it may also induce some of the metabolic alterations that rearrange biosynthetic priorities in the liver in favor of production of acute phase proteins while production of albumin and transferrin is discontinued, a hallmark of protein-energy malnutrition.

Management of Wasting in AIDS Patients

Whether or not antiviral therapy for HIV or treatment of HIV-related infections affects nutritional status is not known at present. This subject may be considered under several headings, namely, how nutritional status is affected by antiviral therapy directed at HIV, how it is affected by treating HIV-related opportunistic infections, and how it is affected by supplemental nutritional support. Although AIDS patients strongly favor nutritional support and consume considerable amounts of vitamin, mineral, and other nutritional supplements, this is uncontrolled and little data is available on the efficacy of such measures (123).

IMPACT OF ANTIVIRAL THERAPY Antiviral agents such as AZT have given hope to many AIDS sufferers. AZT increases the life span of some patients with AIDS and reduces the number of opportunistic infections they experience (136). In one study, patients receiving AZT for 16 weeks had an average weight gain of 2.0 kg whereas those receiving placebo lost 1.3 kg ($p < .001$)

(43a). This finding suggests either that suppression of viral replication has a beneficial effect on body composition and nutritional status, perhaps by modulation of cytokine production from HIV-infected cells, or that improvement in immunological function decreases the prevalence of OI and accompanying nutritional deterioration.

IMPACT OF TREATING OPPORTUNISTIC INFECTIONS Evidence suggests that treating opportunistic infections (OI) improves nutritional status in AIDS. For example, patients with disseminated CMV infection who were treated with ganciclovir showed an increase in body weight, total body potassium, fat content, and serum albumin concentrations (75). Although energy balance was not measured directly, it was estimated that treatment of CMV altered the net energy balance from negative to positive and that the drug resulted in an approximate net gain to the body of more than 2,520 kJ/day.

NUTRITIONAL SUPPORT Few studies have carefully examined the effect of nutritional supplementation on nutritional status in AIDS. However, PEM resulting from AIDS is a major contributor to clinical debility in these patients (21). For this reason, controlled and uncontrolled dietary regimens have been used for some time, and although few regimens have been objectively evaluated, overall the impression is disappointing. However, little response can be expected if there is continuing opportunistic infection, and it is essential to first treat these infections as aggressively as possible. The Taskforce on Nutrition Support in AIDS has recently published (123) sensible dietary guidelines, and we strongly recommend their review by physicians and others involved in the care of AIDS patients. For example, the guidelines provide detailed information on how to help improve food tolerance by paying close attention to the acidity, temperature, texture, and seasonings of foods when eating is associated with impaired or painful swallowing or altered taste and/or anorexia. Low fat, low fiber, low residue, and low lactose diets are discussed, as well as the role of medium chain triglycerides, elemental diets, and enteral versus parenteral administration. The guidelines clearly state that an intake of 100% of the Recommended Dietary Allowance (RDA) for all micronutrients is prudent, but that no evidence is available to suggest that megadoses of any vitamin or mineral can alter the course of AIDS or improve nutritional status.

Kottler et al (77) recently reported on a small number of AIDS patients given home total parenteral nutrition (TPN). These patients had severe eating disorders and/or clinically significant small intestinal disease with clinical malabsorption. Six of 12 patients gained weight and showed an increase in body cell mass and body fat content. The other six patients had systemic OI, including CMV and MAI. While they also gained weight and increased body

fat content during TPN, no change in lean body mass was observed. In the group as a whole, clinical improvement paralleled the changes in body cell mass. In another study (43), a group of six less severely ill patients, with PEM but no active OI and no detectable malabsorption, were treated by percutaneous endoscopic gastrostomy feeding with a hydrolyzed protein solution. Enteral feeding resulted in some repletion of body cell mass, which was determined by changes in total body potassium, but the responses of body weight and fat content were variable. No change in $CD4^+$ cells was observed, however.

The adverse effects of protein energy and micronutrient malnutrition on immune function in humans have been extensively reviewed (51, 71). That malnutrition will adversely affect host defenses and increase the chance of opportunistic infection is commonly acknowledged. To document that nutritional repletion will improve host responses and reduce infectious complications is not a simple task, however (68), particularly in the case of HIV infection, which has such direct and severe effects on the immune system itself. Because diet and nutrition can be viewed as double-edged swords that can support the immune system or cause adverse effects, a sensible and balanced dietary approach, much like that advocated by the Taskforce (123), is appropriate. Unconventional approaches should be avoided until their benefit can be documented by carefully controlled clinical trials.

CONCLUSIONS

Intestinal disease and wasting are part of the clinical spectrum of HIV infection in humans. AIDS is a protean disease: several processes can occur simultaneously in these patients and can account for intestinal tract symptoms and weight loss. The causes need to be documented as thoroughly as possible in order to select appropriate therapies for individual patients. Further research is needed to refine the approaches to be taken and to define the etiology and pathogenesis of diarrhea and weight loss in the significant number of AIDS patients in whom no etiology or mechanism is apparent.

In addition to the direct effects of HIV virus and opportunistic pathogens or AIDS-associated tumors on the intestinal tract, altered endogenous metabolism is likely in these patients. This process is presumably under the influence of the cytokines regulating the immunologic and metabolic response to infection and inflammation; these cytokines include IL-1β, C/TNFα, IL-6, and perhaps still to be defined peptide mediators. Investigators in this area must relate in vitro events to in vivo events and must define cause and effect with respect to the cytokines. At present, considerable effort is being devoted to better understand the mechanisms and control of these host responses. This undertaking is important not only from a physiological point of view but because it may be possible in the future to modulate endogenous metabolism

in different disease states. For example, recent data have demonstrated that under certain in vitro or in vivo conditions, the alteration of 1,25-dihyroxy vitamin D_3 content or the addition of n-3 fatty acids to the diet modulates cytokine production, including IL-1β and C/TNFα, in humans (36, 127). Identification of dietary regimens that regulate cytokines in vivo is not imminent, but with careful work it may be possible in the future.

In the meantime, prudent dietary management of AIDS patients from the onset of infection, including nutritional education designed to minimize loss of lean body mass and prevent micronutrient deficiency, is an obvious and wise approach. Nutritional support should be oral whenever possible, enteral if oral intake is difficult, and only as a last resort, parenteral. A team approach, including a physician, nurse, and dietician, is useful in the care of AIDS patients. Patients should be discouraged from engaging in "mega" therapies with vitamins, minerals, or other dietary constituents because no objective information supports such unconventional therapy. A supportive and trusting relationship between the patient and the medical team is essential if these goals are to be accomplished. We anticipate that when the subject of nutrition and AIDS is again reviewed a few years from now, considerable advances in our knowledge of the pathophysiology of AIDS-related diarrhea and wasting syndrome will have taken place and many additional therapeutic strategies will be available to us.

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