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# Role of Cytokines in AIDS Wasting

HERNAN R. CHANG, MD,* ABDUL G. DULLOO, PHD,† AND BRUCE R. BISTRIAN, MD, PHD*

*From the *Laboratory of Nutrition/Infection, Cancer Research Institute, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA; and the †Department of Physiology, Centre Médical Universitaire, University of Geneva Medical School, Geneva, Switzerland*

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ABSTRACT

There is now a large literature implicating cytokines in the development of wasting and cachexia commonly observed in a variety of pathophysiologic conditions. In the acquired immunodeficiency syndrome (AIDS), cytokines elicited by primary and secondary infections seem to exert subtle and sustained effects on behavioral, hormonal, and metabolic axes, and their combined effects on appetite and metabolism have been postulated to drive wasting. However, correlations of increased blood levels of a particular cytokine with wasting in AIDS have not been consistent observations, perhaps because cytokines act principally as paracrine and autocrine hormones, as well as indirectly by activating other systems. A better understanding of the mechanisms underlying the catabolic effects of cytokines is clearly needed if more efficacious strategies are to be developed for the prevention and treatment of wasting in AIDS. In this review we first examine the interacting factors contributing to the AIDS wasting syndrome. We then analyze the complex and overlapping role of cytokines in the pathophysiology of this condition, and put forward a number of hypotheses to explain some of the most important features of this syndrome. *Nutrition* 1998;14:853–863.


Key words: cytokines, wasting, cachexia, malnutrition, HIV, AIDS

## INTRODUCTION

There are close interrelationships between malnutrition and infection. Malnutrition enhances susceptibility to infections, exacerbates their harmful effects, and influences their outcome. Infections also can produce malnutrition: the wasting syndrome and cachexia are common complications of infections, and they play an important role in the morbidity and mortality of the AIDS. Indeed, although wasting is not universally observed in AIDS patients, the wasting syndrome in a human immunodeficiency virus (HIV)-seropositive individual is generally utilized to establish the diagnosis of AIDS[1] and is defined by a decrease in body mass greater than 10% in the absence of concomitant opportunistic infections, malignancies, and other identifiable causes of weight loss.[1] Independent of the causes of wasting, AIDS patients who experience weight loss beyond a certain percentage of ideal body weight are at greater risk of death, thereby establishing a link between survival and the extent of body cell mass depletion.[2–5] Consequently, reversing wasting should improve the life expectancy and quality of life.[6] However, this has proved to be difficult and the outcome of nutritional supplementation is poor, with the tendency for weight gain to be fat and water and not lean tissue.

## CONTRIBUTING FACTORS FOR MALNUTRITION IN AIDS

The causes of malnutrition leading to wasting in AIDS are believed to be a combination of several factors, which, as shown in Table I, can be classified under three main categories: 1) reduced nutrient intake, 2) malabsorption, and 3) metabolic disturbances.

### *Reduced Nutrient Intake*

Of the factors that may underlie the reduction in nutrient intake in HIV patients, anorexia is usually the most prominent. It is primarily the result of the cytokine responses to the infection per se, but it can also be caused or exacerbated (as an unwanted side effect) by certain medications employed in HIV patients receiving multidrug therapy for concomitant medical problems. A diminished ability to ingest nutrients can also be observed in HIV patients suffering from some central nervous system (CNS) processes such as dementia or tumors. Furthermore, the almost universal presence of inflammatory processes, infections, or both, involving the digestive tract of AIDS patients producing gingivitis, stomatitis, esophagitis, or enteritis, often impair the ability to ingest, in large part due to pain preventing intake or aggravated by food intake, as well as absorb nutrients. The net effect is that all

Correspondence to: Bruce R. Bistrian, MD, PhD or Hernan R. Chang, MD, Laboratory of Nutrition/Infection, Cancer Research Institute, Department of Medicine, Beth Israel Deaconess Medical Center, West Campus, Harvard Medical School, Boston, MA 02215-5310, USA. E-mail: bbistria@west.bidmc.harvard.edu




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TABLE I.

CONTRIBUTING FACTORS FOR MALNUTRITION IN HIV DISEASE

| |
|---|
| Reduced nutrient intake |
| Anorexia without apparent cause |
| Anorexia due to opportunistic infections and malignancy |
| Anorexia due to medication |
| Inability to take nutrients (dementia, CNS processes) |
| Inflammatory, infectious, or malignant GI processes |
| Malabsorption |
| Opportunistic infections |
| Malignancy |
| HIV enteropathy |
| Metabolic abnormalities |
| Cytokine-mediated abnormalities (multicausal) |
| Changes in energy expenditure |
| Increased muscle proteolysis |
| Inefficient protein synthesis |
| Futile cycling? |

CNS, central nervous system; GI, gastrointestinal; HIV, human immunodeficiency virus.

these factors contribute to a deficit of energy and nutrient supply to meet the body's needs.

*Malabsorption*

In addition to reduced nutrient intake, intestinal malabsorption (due to intestinal dysfunction and inflammation) can also be an important contributory factor to malnutrition in AIDS cases.[7–11] However, a causal link between abnormal malabsorption tests and wasting is not clear. In HIV-infected children, although postnatal gain in weight and lean body mass were found to be lower than in an HIV-negative comparison group,[12] an earlier study by the same group[13] found that lactose malabsorption was not associated with higher rates of diarrhea or growth failure. This underlies the fact that carbohydrate malabsorption in HIV-infected children is not the only factor responsible for growth failure. Moreover, fat malabsorption is generally more clearly related to development of malnutrition. In fact, malabsorption, particularly of fat but also certain minerals and vitamins, is common in patients with protracted diarrhea, and patients with HIV infection are prone to develop a variety of enteric infectious processes that cause diarrhea. These include those due to protozoan, viral, bacterial, and fungal pathogens (see Table II), as well as neoplasm (lymphoma, Kaposi sarcoma) and disseminated infectious processes. The role of several additional enteric pathogens (including enteroaggregative *Escherichia coli*) in the pathogenesis of diarrhea and malabsorption has not been adequately studied and certainly deserves more attention.[14,15] Furthermore, the paucity of food in the intestine over long periods of time, in conjunction with protein-energy malnutrition, may provoke structural changes and functional intestinal atrophy. The resulting decline in digestive functions could further impair absorption of both macronutrients (fat, protein, and carbohydrates) and micronutrients (vitamins and minerals). Thus, absorptive dysfunction compounds the problem of reduced nutrient intake and often aggravates anorexia through abdominal symptoms. In fact, in many if not most malabsorption syndromes, it is generally the reduction in oral intake induced by symptoms related to malabsorption (cramps, bloating, pain, and diarrhea) that is responsible for most of the energy gap between intake and total expenditure.

*Metabolic Abnormalities*

Like many pathophysiologic conditions such as sepsis and cancer, a hypermetabolic state, characterized by an increase in resting energy expenditure (REE) and disturbances in the metabolism of protein (muscle proteolysis) and fat (hypertriacyglycerolemia), has also been implicated in the AIDS wasting syndrome. In fact, an earlier notion that hypermetabolism is the major driving force behind wasting in AIDS has been particularly attractive because it provided an explanation for the excessive loss of muscle, and the difficulty of reversing the wasting syndrome (with nutritional therapy most often resulting in gain in body fat and water, with marginal or no gain in lean tissue). These metabolic abnormalities have been associated with futile cycling, such as that occurring when fatty acids are being mobilized at an accelerated rate from adipose tissue, and then reesterified into triacylglycerol for storage again in fat,[16] as well as the wasteful use of substrates underlying the conversion of glucose into fatty acids, before being stored as fat (i.e., de novo lipogenesis).[17]

The contribution of these metabolic pathways to the hypermetabolic state is, however, unclear and hypertriacylglycerolemia in the HIV patients does not correlate with wasting.[18–21] Moreover, although an increase in REE has been reported in all stages of HIV infection,[22–27] the notion that hypermetabolism is the primary factor underlying wasting in AIDS has been challenged by more recent studies in patients with HIV indicating that the increase in REE per se is not sufficient to cause wasting.[25] First, REE is increased even in asymptomatic HIV-infected patients with normal CD4 cell counts, but such individuals can usually sustain their weight and lean body mass for prolonged periods. Second, in patients who were actively losing weight or had stable weight, REE was about 10% higher than normal, but their total energy expenditure (TEE) was found to be no greater than that predicted for healthy individuals. These apparent discrepancies between increased REE coexisting with normal or low TEE have been reconciled with data indicating that the increased REE is largely compensated by energy saved as a result of reduced physical activity, and it is loss of appetite leading to decreased intake, coupled with malabsorption, that primarily drives wasting in AIDS.

To what extent such reduction in physical activity is the result

TABLE II.

GASTROINTESTINAL OPPORTUNISTIC INFECTIONS IN AIDS

| | |
|---|---|
| Esophageal disorders | *Candida albicans*, cytomegalovirus, herpes simplex virus, HIV |
| Diarrhea | |
| Protozoal | *Cryptosporidum, Microsporidia (Enterocytozoon bieneusi, Encephalitozoon intestinalis), Isospora belli, Giardia lamblia, Entamoeba hystolytica, Blastocystis hominis* |
| Viral | Cytomegalovirus infection (esophagitis, gastritis, duodenitis, colitis), enteric viruses (adenovirus, rotavirus, coronavirus), herpes simplex virus |
| Bacterial | *Myobacterium avium* intracellulare, *Salmonella, Shigella, Campylobacter, Clostridium difficile, M. tuberculosis, Bartonella, Escherichia coli* |
| Fungal | Coccidiodomycosis, histoplasmosis |
| Others | Idiopathic (HIV?) |

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

of lethargy and fatigue from the illness per se or that of a normal adaptive physiologic response to save energy is unknown. However, it is clear that the decrease in physical activity will alter the quality of life, which may further deteriorate because a drastic reduction in locomotor activities might lead not only to muscle atrophy and consequential functional impairments, but can also contribute to the failure to rebuild lean body mass during realimentation. Furthermore, an increase in REE during active weight loss is by no means trivial, because this is counterproductive to the adaptive reduction in REE that is the normal response in order to buffer the energy deficit and hence contributes to exacerbate the negative energy balance even further.

*Synopsis*

The most likely scenario in the development of the wasting in HIV-infected patients can be summarized as follows:

- Despite increased REE in response to HIV-infection, the patients can maintain their weight often for long periods of time, most probably through reductions in the amount of energy they expend on physical activity. This "compensation," however, may still be deleterious because it interferes with lifestyle and increases the susceptibility to muscle atrophy, and consequential functional impairment.
- Subsequent weight loss is primarily caused by poor appetite, malabsorption, or both, generally triggered by secondary infections.[22,25] Furthermore, the persisting hypermetabolic state is counterproductive to the adaptive down-regulation of resting metabolism that normally occurs in uncomplicated starvation, thereby exacerbating the wasting process.
- The rate of weight loss and the severity of wasting is likely to be dependent upon the type, severity, and outcome of the secondary infection. AIDS patients with malnutrition due principally to malabsorptive symptoms seem to restore body weight and lean body mass when recovering from secondary opportunistic infection or when receiving nutritional support,[28,29] similar to what has been observed in non-HIV individuals recuperating from starvation, anorexia nervosa, and other clinical conditions, although both body fat and lean tissue are being recovered, fat is being restored at a disproportionately faster rate relative to lean tissue repletion.[30–34] However, when protein energy malnutrition is largely a reflection of systemic illness and inflammation, the recovery of lean tissue seems to be even poorer or delayed, such that body weight repletion is more as fat than body protein, similar to patients with sepsis, presumably related to inefficient protein anabolism.[33]

It is against this background presentation of the interacting factors contributing to malnutrition and functional impairment in HIV-infected patients—namely anorexia, malabsorption, hypermetabolism, lethargy, and impaired fat and protein metabolism—that the role of cytokines in the AIDS wasting syndrome is discussed in the following sections.

## CYTOKINES IN WASTING AND CACHEXIA OF AIDS

*Historical Perspective*

In the 1980s, Beutler and Cerami[35] isolated a 17-kDa protein while searching for a mediator to account for the metabolic changes (particularly hypertriacylglycerolemia) observed in animals infected with the protozoan parasite *Trypanosoma cruzi* (Chagas' disease agent). This protein was termed *cachectin*, as it was supposed to mediate the wasting and hypertriacylglycerolemia found in those experimental animals.[35] Cachectin was subsequently found to reduce the activity of lipoprotein lipase (LPL) (potentially accounting for lower triacylglycerol turnover in vivo) and to promote lipolysis in vitro.[36] In addition, purified cachectin was able to produce anorexia, weight loss, and fever when injected into experimental animals. Subsequently, when the cachectin DNA sequence was isolated, it become apparent that its DNA sequence was identical to that coding for tumor necrosis factor (TNF).[36] TNF had been previously isolated from the serum of animals injected with bacterial endotoxins and was able to produce necrosis of transplanted tumors in animals.[37] Furthermore, administration of purified or recombinant TNF to experimental animals provokes very similar metabolic and hemodynamic changes to those observed during bacterial sepsis that could be blocked by the use of specific antisera or monoclonal antibodies.[38,39] Administration of recombinant TNF to humans suggested that this cytokine could play an important role in the early activation of the hemostatic mechanism in septicemia.[40] Recent experimental studies with knockout mice (for the 55-kDa TNF receptor) have confirmed the importance of TNF in the pathophysiology of endotoxic shock.[41,42]

It is now well established that TNF and other cytokines (e.g., interleukins, interferons) are a group of hormonelike polypeptide mediators released by various cell types having pleiotropic actions on many cell types, and they play a regulatory role in normal and abnormal homeostasis and in host defense mechanisms (inflammatory and immune responses). Cytokines share some general characteristics in their mode of action: different cytokines can have a similar effect on several target cells (redundancy); they can activate the secretion of other cytokines (producing a "cascade"); and they can also initiate their own secretion (autocrine), act in a paracrine fashion on neighboring cells, or act on distant cells as hormones. In addition to their pleiotropic actions on many body systems, they could potentially contribute to the wasting and cachexia of AIDS by their ability to induce anorexia, alter energy expenditure, increase muscle proteolysis and net protein breakdown, and initiate various abnormalities of lipid metabolism.

*Cytokines in HIV Infection*

A role for TNF in AIDS wasting syndrome was postulated in earlier studies indicating that TNF serum levels were elevated in patients with AIDS.[43] However, subsequent studies failed to show high-serum TNF levels in most AIDS patients, and no correlation appeared to exist between serum TNF levels and the magnitude of weight loss in AIDS patients.[44–48] At least in some studies the choice of the methods to determine TNF activity (immunoassay versus bioassay) might account for the differences observed. Pentoxifylline, a xanthine that inhibits the production of TNF by decreasing activity of the transcription factor NF-kB, has been used to highlight indirectly the possible importance of TNF in the hypertriacylglycerolemia observed in AIDS patients. Administration of pentoxifylline was shown to reduce the triacylglycerol levels in AIDS patients, although this reduction was only marginally significant ($P = 0.06$) and the study was open label (nonblinded).[49] More importantly, pentoxifylline does not alter other aspects of AIDS wasting, emphasizing the fact that AIDS wasting is not entirely TNF dependent.

Interleukin-1 (IL-1) shares many of the characteristics of TNF and can also produce anorexia, hypertriacylglycerolemia, and stimulate hepatic fatty acid synthesis.[50,51] In addition, IL-1 reduces LPL activity and produces lipolysis.[19,50] Moreover, both TNF and IL-1 can promote HIV-1 replication in in vitro cellular systems, which has led to the suggestion that cytokines may be important for the progression of HIV infection to AIDS. Thus, TNF production is linked to HIV infection and the potential role of TNF in this setting is a source of this enhanced production.[52,53] Naturally occurring cytokine antagonists such as the soluble form of the p55 (type I) TNF receptor (TNFsRp55) and the IL-1$\beta$ receptor antagonist (IL-1Ra) are produced in the body to counteract the potentially harmful effects of excessive TNF and IL-1

production, respectively.[54,55] Enhanced plasma levels of soluble TNF receptors have been reported to be correlated with rapid progression toward AIDS in HIV-1 infected patients.[56] Moreover, a study suggested that enhanced TNFsRp55 and TNFsRp75 (type II) were predictive of worsening nutritional status in HIV patients.[57] A more recent study showed that high serum levels of IL-1$\beta$, TNF, and IL-8 together with an excess of the natural inhibitors IL-1Ra and TNFsRp55 were seen in asymptomatic HIV-1-positive African women but not in African women with AIDS or in HIV-negative controls.[46] This study suggests that cytokine antagonists may play a role in modulating cytokine-associated symptoms in the early phases of HIV infection.[46] Alternatively, because most of the AIDS patients in that study were at the endstage of their disease and therefore likely to have significant protein-energy malnutrition, it might only reflect the inability or reduced ability to synthesize new proteins, including cytokines. On the other hand, another study has found no correlation between elevated soluble TNF receptor types I and II levels and metabolic disturbances in HIV infections.[58]

Other studies have shown increased serum/plasma levels of IL-1, TNF, IL-6, and interferon-$\gamma$ in some populations of HIV-infected patients.[47,48,58,59] IL-6, an important mediator of the acute-phase response, reduces LPL activity in vitro and in vivo and promotes fatty acid synthesis.[60,61] In contrast to TNF and IL-1, IL-6 serum levels are consistently raised in AIDS and IL-6 has been implicated in the development of cachexia in inflammatory and neoplastic processes.[47,48,59,62–64] Serum levels of IL-6 in HIV-infected patients are high when compared with non-infected normal subjects.[65] The levels of IL-6 appear to increase according to the stage of HIV disease and appear to be higher in terminal stages of the disease.[65,66] However, no data has been provided yet to link IL-6 blood levels directly with the development of wasting and cachexia in AIDS patients.

A major problem with studies regarding cytokines and circulating soluble receptors in the bloodstream of patients with HIV is that cytokines principally act in an autocrine and paracrine manner, thus making blood levels not necessarily relevant for a proper interpretation of their effects on tissues, organs, or body systems. Moreover, cytokines are rapidly internalized by cells and they can activate the release of other substances. With respect to cytokine actions, it is therefore more adequate to think in terms of effects on tissues, organs, or systems rather than trying to simply correlate a complex clinical syndrome such as wasting with elevated circulating cytokine levels. For instance, IL-6 has been more consistently found in the blood of HIV patients, and this is probably due to its longer half-life in serum as well as related to its major role in the acute-phase response as compared with IL-1 and TNF, which are rapidly cleared from the bloodstream.

### *Cytokines and Altered Energy Balance*

The role of some cytokines such as TNF, IL-1, IL-2, IL-6, and interferon-$\gamma$ in controlling food intake, energy expenditure, or both, have been underscored by many experimental studies.[67–73] These studies have demonstrated that exogenous administration of those cytokines may mimic the hypermetabolism and anorexia associated with infection. In addition, pretreatment with specific anticytokine antibodies blocked the anorectic and thermogenic effects to the exogenous administration of cytokines as well as those of cytokine-secreting tumors. Furthermore, other studies utilizing techniques of intracerebroventricular microinjection have demonstrated the anorexigenic effects of several substances that can be induced by cytokines. Those substances include platelet-activating factor, several chemokines/intercrines such as IL-8, platelet factor-4, interferon-inducible protein-10, monocyte chemotactic protein-1/monocyte chemotactic and activating factor (MCP-1/MCAF), regulated-upon-activation of normal T cell expressed and presumably secreted (RANTES), as well as $\beta$2-microglobulin, a marker for immune activation.[74–76] These findings suggest an interaction (and perhaps redundancy or synergistic action) of several immunomodulators that are released during inflammatory and immune processes to induce anorexia.

*What are mechanisms (and mediators) by which anorexia and hypermetabolism are produced?* Several neurotransmitters, amino acids, peptides, and cytokines can potentially influence food intake during starvation and infectious processes. In addition, some neurotransmitters function during normal regulation of food behavior. Prominent among them are corticotropin-releasing hormone (CRH), neuropeptide Y (NPY), cholecystokinin (CCK), norepinephrine, acetylcholine, serotonin, dopamine, glutamate, $\gamma$-aminobutyric acid, and others.[77–79] The paraventricular nuclei (PVN) and the hypothalamus appear to be important areas for the control of compensatory feeding behavior in response to changes in energy homeostasis.[80] CRH and NPY appear to play a prominent role in the responses to starvation. Increases of NPY in the PVN area produce hunger together with activation of the hypothalamic-pituitary-adrenal (HPA) axis.[81] Increases of CRH produce a reduction in messenger RNA (mRNA) for NPY together with anorexia and activation of the HPA axis, as well as increased thermogenesis, lipolysis, hyperglycemia, and inhibition of expected insulin secretion.[79,80,82] The paradoxical activation of the HPA axis (together with the secretion of glucocorticoids) during the secretion of both substances, CRH and NPY, which have opposite effects on feeding behavior, might be explained by the fact that when the HPA axis is activated, it is done so in the setting of different orchestrated responses.[83,84]

Several cytokines, such as TNF, IL-1, and IL-6, as well as other mediators of inflammation, which were initially and collectively called "tissue corticotropin-releasing factor," can activate the HPA axis during inflammatory states.[85,86] Activation of the HPA axis by cytokines leads to the secretion of glucocorticoids, an action believed to participate in the negative feedback control of the immune response.[85,86] During inflammatory states TNF is secreted first and promotes the cellular secretion of IL-1; and the release of both cytokines leads to the secretion of IL-6, which in turn acts in conjunction with glucocorticoids to elicit the production of many mediators of the acute-phase response by the liver.[62,85,87] TNF, IL-1, and IL-6 act in a synergistic manner, whereas glucocorticoids down-regulate the secretion of those cytokines[63,87–89] and other inflammatory mediators including nitric oxide, platelet activating factor, and prostanoids.[90–92] TNF, IL-1, and IL-6 also participate in the stimulation of the HPA axis during endotoxin administration.[93] Noteworthy, anti–IL-6 antibodies can almost completely block the stimulation of the HPA axis by endotoxin.[93]

*As these cytokines do not appear to cross the blood-brain barrier in significant amounts, how can these cytokines be acting at the CNS level?* One explanation is that TNF, IL-1, and IL-6, produced peripherally, can act on CRH neurons through the activation of other cells such as astrocytes or microglial cells in the brain or cells in the area postrema, which are not protected by the blood-brain barrier, to secrete cytokines or other substances. Alternatively, activated endothelial cells, phagocytic cells, or activated T cells migrating through the blood-brain barrier can initiate further cellular production of cytokines to act on CRH-producing neurons. To gain an insight into these mechanisms we performed a study in which transgenic mice expressing high levels of soluble TNF-R1 fusion protein (and therefore having blunted circulating TNF levels) showed reduced thermogenesis and blunted mRNA expression for TNF, IL-1, IL-6, and CRH in the brain in response to a parenteral challenge (D. Arsenijevic, I. Garcia, H. R. Chang,

and A. G. Dulloo, unpublished observations). These results support the hypothesis that local production of TNF, IL-1, and IL-6 in the brain may mediate the increased brain production of CRH to produce anorexia and hypermetabolism during endotoxin administration. Furthermore, that study demonstrates that TNF is necessary for eliciting the increased production of CRH and that TNF is indeed needed as an amplifier of the inflammation cascade through up-regulation of IL-1 and IL-6 production. This finding is in agreement with other data showing that CNS administration of antibodies to neutralize IL-1$\beta$, IL-6, or TNF inhibits the thermogenic and anorectic responses to peripherally injected endotoxin in the rat.[94] Further systems such as the noradrenergic system may be activated during inflammatory stress.[95] The overall effect should be the enhancement of CRH production, which carries the previously mentioned effects including anorexia, lipolysis, and increased thermogenesis and therefore weight loss.

Systemic administration of IL-1 also stimulates the expression of CRH mRNA in the PVN together with dose-dependent activation of the HPA axis and sustained suppression of food intake.[96,97] This effect of IL-1 is partially reversed by CRH antisera administration.[98] IL-1 receptors have been demonstrated in hypothalamic structures.[99,100] Almost identical effects on CRH release and food intake have been reported for TNF, IL-6, IL-2, and interferon-$\gamma$,[100] suggesting that sustained and moderate increases in the levels of those cytokines (which act synergistically) can potentially increase CRH, thereby blocking the normal compensatory hypothalamic response to weight loss (i.e., increased appetite and reduced thermogenesis). And indeed, elevated levels of several cytokines, including IL-1 and IL-6, have been reported in the cerebrospinal fluid of AIDS patients.[101] Thus, local production of cytokines within the CNS can contribute to the wasting syndrome and cachexia observed in HIV infection and AIDS through chronic release of CRH.

Another potential mechanism by which sustained production of cytokines could enhance the secretion of CRH is through reduction of the sensitivity of target tissues to the effects of glucocorticoids. For instance, a decreased affinity of glucocorticoid receptors for cortisol has been described in phagocytic cells from some AIDS patients.[102] In those AIDS patients, there were elevated levels of cortisol and corticotropin associated with signs of glucocorticoid deficiency including hyponatremia and postural hypotension pointing to a glucocorticoid-resistant condition.[102] By this mechanism, HPA axis activation would be resistant to the negative feedback mechanism provided by the secretion of glucocorticoids. Interestingly, IL-2 in combination with IL-4 has been described to produce resistance of T cells to the action of glucocorticoids by reducing the affinity of the glucocorticoid receptor for its ligand.[103] IL-4 is involved in antiinflammatory mechanisms together with other cytokines, such as IL-10 and IL-13, and they are able to augment the expression of IL-1Ra.[104–108]

Both insulin and glucocorticoids play an important role in the peripheral response to fasting and starvation. They also appear to play a role in the CNS regulation of energy balance by regulating NPY synthesis and release.[83] Thus, insulin, as opposed to its peripheral anabolic effects, promotes a state of negative energy balance (through anorexia and increased energy expenditure) by reducing NPY gene expression in the hypothalamus.[83] Fasting (which lowers insulin levels) increases hypothalamic NPY gene expression.[109] Glucocorticoids have opposing effects to insulin, thus promoting a state of positive energy balance with an increase of caloric intake.[83,110] Peripherally, glucocorticoids, as well as glucagon, catecholamines, and growth hormone, may induce insulin resistance when these hormones are present in enhanced levels and in the presence of stress or infections such as in sepsis.[111] Current data, however, suggest that glucagon and catecholamines are not highly elevated in AIDS, whereas elevated basal cortisol levels have been found frequently.[112,113] Administration of TNF to humans has been found to produce a hyperglycemic state without alterations in insulin levels, suggesting an insulin resistance-like state.[114] Moreover, infusion of TNF into experimental animals produces marked insulin resistance.[115] These findings may help to partly explain the hyperglycemia and the relative insulin resistance observed in several infectious processes. However, HIV infection is characterized by high rates of insulin clearance as well as an increased sensitivity of peripheral tissues to insulin.[112]

*Is there a role for leptin?* The newly described molecule leptin and its putative receptor also appear to play a role in maintaining normal weight. Leptin is the protein product of the *ob* gene and its circulating levels reflect energy stores in adipocytes, suggesting its role as an "adipostat."[116–118] The leptin receptor gene is highly expressed at the hypothalamic level.[119,120] Increased leptin levels produce anorexia and increased energy expenditure, possibly by reducing the release of NPY[119,121] at the hypothalamic level. Thus, reduced leptin levels induce hunger and reduced thermogenesis, pointing to a role for reduced levels of leptin in the adaptive changes to fasting/starvation. On the other hand increased leptin levels may be related to resistance to obesity (anorexia and enhanced thermogenesis), and may be acting on melanocyte-stimulating hormone and the melanocortin-4 receptor, in other regions of the brain.[112–124] Glucocorticoids and insulin have been demonstrated to up-regulate the production of leptin.[125–127] Cytokines, such as TNF and IL-1, and endotoxin, are able to stimulate leptin production[128] and anorexia is directly proportional to the increase of leptin pointing to a potential role of this molecule in the anorexia associated with infection.[128] However, a first study measuring leptin levels in patients with AIDS found that leptin levels were not increased relative to body fat in patients who were anorexic, were losing weight, or had a history of weight loss. Also, leptin levels were not elevated during secondary infection, suggesting a lack of a link between increased leptin levels and anorexia in AIDS.[129] Another study comparing the levels of leptin in HIV-infected men to age- and body-fat-matched uninfected individuals showed no differences in serum leptin levels and there was no correlation with lean body mass.[130] There was, however, correlation between leptin concentrations and percent body fat and body fat content, extending the notion that circulating leptin levels directly reflect adipose tissue mass, even in HIV-infected men with low body-fat content.[130]

### *Cytokines and Muscle Proteolysis*

A significant loss of lean body mass mainly due to muscle proteolysis has long been appreciated to be characteristic of wasting and cachexia in trauma and sepsis (as well as in AIDS, cancer, fasting, and acidosis). Well before the wealth of information that currently exists on cytokine pathophysiology, several investigators were searching for mediators, such as the so-called "muscle proteolysis factor," that could be responsible for the metabolic disturbances and wasting observed.[131] Theoretically the loss of lean body mass could be due to an increase in tissue protein degradation or a decrease in tissue protein synthesis or a combination of both. Accelerated protein breakdown in muscle is necessary to meet the needs of the anabolic response in liver, hemotopoietic, and wound tissue during stress and infection. On the other hand, in starvation (and in the absence of infection) there is increased appetite on refeeding, reduced energy expenditure, and relative preservation of muscle mass, but also no requirement for enhanced anabolism in those select tissues. In the wasting of AIDS and in the presence of cytokines there might be maintenance or declines in basal metabolic rate together with anorexia and muscle catabolism. What, therefore, would be the cause for muscle wast-

ing in AIDS? TNF and IL-1 have been shown to produce skeletal muscle catabolism in addition to their anorectic and net nitrogen loss effects,[132,133] but by different mechanisms. Moreover, administration of TNF and IL-1 to experimental animals have been found to produce weight loss, net nitrogen loss, skeletal muscle catabolism, and increased liver weight.[134,135] The effects were observed independent from and additive to those resulting from semistarvation.[134,135] Recent evidence strongly suggests that activation of the ubiquitin-proteasome pathway is responsible for muscle wasting in several catabolic states.[136] The activation or the suppression of the pathway is related to the rate of ubiquitin conjugation to proteins. Higher rates of ubiquitin conjugation result in enhanced muscle proteolysis. Glucocorticoids promote muscle proteolysis, an action that opposes the anabolic effects of insulin, by increasing mRNAs encoding ubiquitin and proteasomes subunits and therefore increasing ubiquitin-protein conjugates.[136] In the fasting state, muscle proteolysis may take place in the presence of glucocorticoids and when insulin levels are low. Glucocorticoids in combination with several cytokines such as TNF, IL-1, and IL-6 participate in stimulation of the ubiquitin-proteasome pathway producing muscle proteolysis.[137–139] In AIDS, all the requisite conditions for muscle proteolysis are present: increased basal levels of cortisol,[113] low circulating insulin levels,[113] and subtle release of several cytokines that may be acting synergistically.

Interference with TNF production by anti-TNF antibodies or by administration of pentoxifylline produces blockade of muscle proteolysis in vivo.[140,141] Pentoxifylline may be acting to block muscle proteolysis through inhibition of the proteasome-dependent activation of the transcription factor NF-kB, which is also needed for TNF production.[142] Blockade of IL-1 action by administering soluble IL-1Ra to experimental animals prevents muscle proteolysis in response to endotoxin.[143] Recently, a novel glycoprotein, able to produce muscle proteolysis in vitro, as opposed to TNF and IL-6, which are unable to do so and are only effective in vivo, has been described in rodents and in the urine of cachectic patients with certain cancers.[144] Whether this glycoprotein also is produced in AIDS patients with cachexia is unknown. Because cytokines such as TNF and IL-1 are not able to produce muscle proteolysis in vitro, their effects on muscle proteolysis may be indirect.[143,145,146]

### *Cytokines and Endocrine Abnormalities*

Several subtle endocrine alterations have been demonstrated in HIV patients that potentially may be related to cytokine production.[113] Thyroid hormone, adrenal, and gonadal homeostasis could be altered during HIV infection by cytokines. The euthyroid sick syndrome can be observed with severe caloric depletion and severe illnesses, and is characterized by impaired peripheral conversion of thyroxine to T3, resulting in high normal or normal circulating levels of thyroxine and lower levels of T3.[147] In addition, enhanced rT3 levels are present due to reduced clearance,[147] whereas thyrotropin (TSH) levels appear to be within normal limits. In AIDS patients with anorexia and weight loss, conversion of thyroxine to T3 is decreased (euthyroid sick syndrome) as well as the levels of insulin-like growth factor-I (IGF-I), whereas in stable HIV patients T3 levels are normal.[148,149] The reduction in T3 in those patients might be the consequence of an adaptive response to caloric deprivation, as is also observed during fasting and malnourished states. Maintenance of such low levels of T3 during nutritional rehabilitation may hamper the buildup of lean body mass. Infusion of IL-6 to patients with cancer and normal thyroid function has been shown to acutely decrease TSH and T3 and to enhance levels of rT3, but after several weeks of IL-6 administration only TSH was found to be elevated.[150] Similarly, infusion of TNF to normal persons produced acute decreases of TSH and T3 and increased rT3.[151] The clinical significance of such changes in thyroid function upon cytokine administration are not completely understood but suggest that the changes observed in AIDS patients may be due to the effects of cytokines.

In AIDS, increased basal levels of cortisol have been demonstrated,[113] and this might reflect the activation of the stress response. As a result of such cortisol levels, the cortisol response to provocative testing may be abnormal. Cytokines can directly stimulate the release of corticotropin (ACTH), CRH, and cortisol,[96–100,152] which might suggest their potential role for the mild cortisol elevations in HIV patients. The demonstration of glucocorticoid resistance in some HIV patients[102] may provide an additional explanation for cortisol elevations in the serum of some AIDS patients.

Data on gonadal function in AIDS has been gathered mostly from male patients. There are substantial data to indicate that HIV infection is accompanied by hypogonadism.[113] Hypogonadism in AIDS can be primary (testicular) or central in etiology, and may be due to the release of cytokines. For instance, administration of TNF to healthy men produces a rise in luteinizing hormone (LH) followed by a decrease in testosterone levels.[153] Moreover, IL-1 has been shown at high levels to block steroidogenesis by inhibiting the binding of LH to Leydig cells.[154] A particularly noteworthy relationship is that CRH, which is induced by cytokines, is also produced by Leydig cells of the testes and produces autocrine effects by inhibiting testosterone biosynthesis. Decreases in testosterone levels may make difficult any attempt to increase muscular mass. Indeed, administration to AIDS patients of megestrol acetate, which stimulates appetite, also lowers testosterone levels, and results in weight gain but mainly of fat mass.[155] Recent experimental data suggest that the appetite-stimulant effect of megestrol acetate involve stimulation of synthesis, transport, and release of neuropeptide Y in the hypothalamus.[156]

## CONCLUSIONS AND PROSPECTS

The nutritional status of an individual can be one of the major determining factors in resistance to infection. HIV infection, on the other hand, often produces malnutrition leading to wasting and cachexia. Wasting syndrome in AIDS is multifactorial: HIV infection of gastrointestinal tissue and lymphoid tissue particularly, anorexia, inadequate nutrient intake and malabsorption, and catabolic effects on intermediary metabolism play important roles along with similar effects of repeated secondary infections. Currently available preventive/therapeutic approaches for wasting in AIDS include baseline nutritional assessment[157] (Table III), early diagnosis of malnutrition and maintenance of adequate nutritional intake, early diagnosis/prevention of opportunistic infections, and appetite stimulants as well as anabolic hormonal therapy.[158–160] Adequate antiretroviral therapy might be considered during early stages of HIV infection as part of the wasting preventive measures, because successful treatment of the primary infection with HIV or secondary infections is the most potent of anabolic therapies.

Cytokines play a complex and overlapping role in the development of wasting and cachexia in AIDS. They can exert behavioral, hormonal, and endocrine effects that can persist for long periods of time to produce wasting and cachexia. Multipronged therapeutic approaches are therefore required to counteract their effects on different body systems. Attempts have been made to modulate the release of certain cytokines such as TNF by pharmacologic means in AIDS patients, with the aim of arresting or reversing the wasting process. For instance, pentoxifylline has been found in pilot studies to decrease TNF serum levels as well as serum triacylglycerols in AIDS patients.[49,161] However, viral load was not altered and there was no benefit in terms of weight

TABLE III.

BASELINE NUTRITIONAL ASSESSMENT OF PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

| |
|---|
| Anthropometry |
| Height, sex, present weight (% of ideal body weight and % of usual body weight) |
| Premorbid or usual body weight (% of ideal body weight) |
| Ideal body weight |
| Weight loss (% of ideal body weight), duration (months) of weight loss |
| Biochemical |
| Serum albumin, cholesterol, triacylglycerols |
| Immune/HIV-related status |
| CD4+ and CD8+ T cells, white blood cell count, hematocrit, hemoglobin |

(Modified from Bell SJ, et al., Nutrition support and the human immunodeficiency virus (HIV). Parasitology 1993;107:553.)

gain.[49,161] Other pilot studies have failed to show any benefits of pentoxifylline administration to AIDS patients in terms of weight gain or effect on serum TNF levels.[162] Similar observations have been made in cancer patients with cachexia, where pentoxifylline failed to improve anorexia or cachexia.[163] Thalidomide, a drug with sedative effects that has been used for many years for the therapy of some reactive forms of leprosy (erythema nodosum leprosum), has been found to down-regulate TNF production in vitro.[164] Thalidomide has shown in pilot studies to promote weight gain in HIV patients with wasting.[165,166] Thalidomide administration produced a reduction in serum TNF levels in a pilot study of HIV patients with wasting and tuberculosis.[166] However, in a recent trial in which thalidomide was effective for the therapy of aphthous ulceration of the mouth, there were increases in TNF and soluble TNF receptor type II as well as viral load.[167] Thalidomide has potent antiinflammatory properties and has been successfully used for therapy of certain types of aphthous ulcerations in AIDS patients as well as for the treatment of graft-versus-host disease in allogeneic bone marrow transplantations.[168,169] An additional mechanism by which thalidomide might promote weight gain is by improving the absorption of nutrients through the gastrointestinal tract.

To date, no firm evidence has been provided to indicate that pharmacologic blockade or manipulation of cytokine production is useful in the prevention or therapy of wasting and cachexia in AIDS. In fact, sustained blockade of cytokine production may produce harmful effects as they are needed for a proper functioning and tuning of the immune system and blockade of a particular cytokine may in turn produce blockade of other cytokines, which may have unpredictable results. For instance, administration of pentoxifylline produced an increase in mycobacterial load in macrophages from AIDS patients with disseminated *Mycobacterium-avium*-intracellulare complex infection.[170] An alternative way of counteracting the effects of cytokines may include use of a cytokine with inhibitory actions on other cytokines or a drug or drugs that enhance the release of inhibitors, although these agents would be subject to the same concerns. For instance, epinephrine has been shown to increase the release of the antiinflammatory cytokine IL-10, which has been previously found to inhibit TNF.[171,172] However, it is difficult to see how this could be clinically applied, although oral or B-agonist therapy would be theoretically possible. Finally, the use of antiinflammatory cytokines might be possible.

Potentially new approaches for prevention/therapy of wasting and cachexia of AIDS may include drugs that selectively can modulate the release of mediators acting at the target tissues, organs, or systems. For example, selective inhibitors or antagonists of CRH that can go across the blood-brain barrier or agents that can down-regulate hypothalamic release of CRH may effectively combat anorexia. Also, specific inhibitors of the ubiquitin-proteasome pathway might be useful to arrest muscle catabolism. However, the most effective therapy for wasting induced by infectious agents is always the successful treatment of the infection rather than the body's cytokine response to infection. Ultimately the ideal nutritional solution to AIDS wasting will be successful antiretroviral therapy.

Further work in this area is greatly needed and hopefully the results of those studies will enhance our knowledge and help us to explore new therapeutic avenues for wasting and cachexia of AIDS.

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*(For an additional perspective, see Editorial Comments on page 867.)*