Enhanced generation of interleukins 1β and 6 may contribute to the cachexia of chronic disease

Tommy Cederholm, Bengt Wretlind, Kjell Hellström, Birger Andersson, Lennart Engström, Kerstin Brismar, Annika Scheynius, Jan Forslid, and Jan Palmblad

ABSTRACT The cachexia of disease may be promoted by proinflammatory cytokines, e.g., interleukin (IL) 1β, tumor necrosis factor α (TNF-α), and IL-6. These, as well as some antiinflammatory cytokines, e.g., IL-1 receptor antagonist (IL-1ra), IL-10, and transforming growth factor β1 (TGF-β1), were analyzed in serum (IL-6, IL-1ra, IL-10, TGF-β1) and stimulated blood monocytes (IL-1β, TNFα, IL-6) obtained from elderly patients with protein-energy malnutrition (PEM). Twenty-one uninfected malnourished patients aged 75 ± 1 y (i ± SD), with a body mass index (BMI; in kg/m²) of 17.2 ± 0.5 and various noncancer disorders, and 22 healthy matched control subjects aged 72 ± 1 y, with a BMI of 25.4 ± 0.7 (significantly different from patients, P < 0.001), were included. Fifteen patients and their corresponding control subjects were reexamined 3 mo later. Isolated monocytes were stimulated with lipopolysaccharide (LPS) and concentrations of IL-1β, TNF-α, and IL-6 were determined. Serum concentrations of IL-6, IL-1ra, IL-10, TGF-β1, and acute-phase reactants were analyzed. Serum concentrations of orosomucoid and IL-6 were higher in the malnourished subjects than in the control subjects (1.14 ± 0.1 compared with 0.8 ± 0.3 g/L, P < 0.001; and 5 ng/L compared with undetectable concentrations, P < 0.01, respectively). Higher generation of IL-1β (2.7-fold; P < 0.05) and IL-6 (3.7-fold; P < 0.05) was found in monocytes from patients with PEM relative to the control subjects when monocytes were stimulated with 0.1 µg LPS/mL. Monocyte TNF generation and serum concentrations of IL-10, IL-1ra, and TGF-β1 did not differ. Similar results were obtained at follow-up. IL-1ra was negatively correlated with delayed cutaneous hypersensitivity (r = −0.34, P < 0.05). We conclude that enhanced generation of proinflammatory cytokines such as IL-6 and IL-1β in malnourished patients may contribute to the PEM often encountered in chronic nonmalignant disorders. Am J Clin Nutr 1997;65:876–82.

KEY WORDS Chronic disease, protein-energy malnutrition, cachexia, inflammation, insulin-like growth factor I, interleukin 1β, interleukin 6, tumor necrosis factor α, interleukin 1 receptor antagonist, interleukin 10, transforming growth factor β1

INTRODUCTION

Chronic illness is often associated with reduced appetite, low food intake, and increased energy expenditure, which may result in protein-energy malnutrition (PEM) (1). In a previous study of noncancer patients admitted for acute disease we found elevated serum concentrations of orosomucoid in subjects with PEM (2). The observed acute-phase response could not be explained by clinical or other laboratory findings of traditional inflammatory or infectious disorders. At a 9-mo follow-up those patients who recovered from PEM had normalized serum orosomucoid concentrations, whereas those who remained malnourished had high, sustained concentrations of the acute-phase reactant. These findings point to the existence of unidentified, clinically unrecognized inflammatory reactions in PEM.

The production of acute-phase proteins is under the control of macrophage-derived cytokines, e.g., interleukin (IL) 1β, tumor necrosis factor α (TNF-α) and IL-6 (3). These substances mediate not only inflammatory and immune reactions, but also the development of cachexia (4). The balance between them and antiinflammatory cytokines, such as IL-1 receptor antagonist (IL-1ra), IL-10, and transforming growth factor β1 (TGF-β1) is probably pivotal for the fine-tuning and resolution of inflammation.

The purpose of the current study was to evaluate production of cytokines in monocytes and serum cytokine concentrations in samples obtained from chronically ill noncancer patients with PEM. Moreover, we related these data to changes in the nutritional status of the subjects during an observation period of 3 mo.

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SUBJECTS AND METHODS

Case-control subjects

Twenty-one depleted (see below) patients aged 75 ± 1 y (x ± SD) and 22 age-matched (72 ± 1 y) apparently healthy, well-nourished control subjects were included. Fourteen patients were enrolled at the time of discharge from the Department of Medicine, Stockholm Söder Hospital. They had been admitted 1–2 wk earlier because of exacerbation of their underlying disease; the rest of the patients were recruited from the outpatient clinic. The subjects were selected for being able to cooperate. None of the patients suffered from malignant disease. Five had chronic obstructive airway disease, 11 suffered from more than one major disease (6 of whom had chronic obstructive lung disease), and the rest had various other diagnoses (chronic ischemic heart disorders, aortic aneurysm, and Parkinson disease). Six had had gastric resection because of ulcer. Within the preceding 2 mo, 12 of the patients had suffered from pneumonia, bronchitis, or urinary tract infections that had been treated with antibiotics. None displayed uremia, hepatic failure, rheumatoid arthritis, or diabetes mellitus, and none were taking medication known to activate the immune system. The control subjects were voluntarily recruited from a local association of retired citizens. Informed consent was obtained before subjects entered the investigation. The study was approved by the local ethics committee.

Prospective cohort study design

All patients were told that they were undernourished. They received written and verbal information about the importance of improving their nutritional status. During this study the patients lived at home and ate their usual diet. Ten patients were prescribed an oral supplement providing 1.7 MJ (400 kcal) and 40 g protein/d (two 200-ML packages of Fortimel; Nutricia, Zoetermeer, Netherlands). Consent to participate in the random supplement administration was obtained from 14 of the 21 patients. Four patients died shortly after inclusion, one was later excluded because of severe herpes zoster, and one declined follow-up. Three months after the start of the study, the remaining 15 patients (8 of whom had been prescribed the supplement) and their corresponding control subjects were reexamined. By repeated telephone calls, the supplemented patients were encouraged to take the prescribed supplement.

Nutritional assessment, IGF-I analysis, and
dynamometric measurements

Nutritional status was determined as described by Cedermol et al (5), by assessing body mass index (BMI; weight in kg/height² in m); 6, triceps skinfold thickness (TSF; using a Harpenden caliper from British Indicators Ltd, Luton, United Kingdom; 7), arm muscle circumference (AMC; 7), serum albumin (Kodak Ektachem 700XR; Kodak Company, Rochester, NY), and delayed cutaneous hypersensitivity reaction [DCH; by means of injections of extracts from Candida, purified protein derivative of tuberculin (PPD), and mumps; 8]. For DCH the size of the largest induration was measured 48–72 h later and expressed as the sum of the largest diameter and the largest perpendicular diameter (8). In general, the malnourished patients had at least three subnormal nutritional variables (Table 1). Serum concentrations of the anabolic peptide hormone insulin-like growth factor 1 (IGF-I) were analyzed by radioimmunoassay technique after serum had been acid-ethanol extracted and precipitated in the cold (9). Muscle function was measured by a Harpenden hand-grip dynamometer and by peak expiratory flow using a Wright Peak flow meter (Nycomed AB, Stockholm). Serum concentrations of orosomucoid (BNA; Swedish Hocbi AB, Stockholm) were analyzed to detect an ongoing acute-phase reaction (reference value < 1.1 g/L).

Monocyte separation and cytokine analyses

EDTA-anticoagulated blood and serum were obtained from each subject. Platelets were removed by centrifugation at 200 × g for 10 min at 20 °C. The cell pellet was retained.

### TABLE 1

Anthropometric and biochemical variables in malnourished patients (PEM) and control subjects

<table>
<thead>
<tr>
<th>All subjects at entry</th>
<th>Reexamined subjects</th>
<th>3 mo later</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At entry</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 21)</td>
<td>(n = 15)</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>Controls</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>17.4 ± 0.7¹</td>
<td>25.5 ± 1.1²</td>
</tr>
<tr>
<td>Women</td>
<td>17.4 ± 0.7</td>
<td>24.2 ± 0.9²</td>
</tr>
<tr>
<td>Men</td>
<td>17.1 ± 0.5</td>
<td>25.5 ± 1.2²</td>
</tr>
<tr>
<td>Triceps skinfold thickness (mm)</td>
<td>8.2 ± 1.0</td>
<td>22.3 ± 1.5²</td>
</tr>
<tr>
<td>Women</td>
<td>8.2 ± 1.0</td>
<td>21.4 ± 2.0²</td>
</tr>
<tr>
<td>Men</td>
<td>6.2 ± 0.6</td>
<td>11.0 ± 0.8²</td>
</tr>
<tr>
<td>Arm muscle circumference (cm)</td>
<td>19.5 ± 0.6</td>
<td>22.9 ± 0.7²</td>
</tr>
<tr>
<td>Women</td>
<td>19.4 ± 0.6</td>
<td>22.2 ± 0.6³</td>
</tr>
<tr>
<td>Men</td>
<td>19.6 ± 0.4</td>
<td>27.2 ± 0.7²</td>
</tr>
<tr>
<td>Delayed skin hypersensitivity (mm)</td>
<td>14.6 ± 3.3</td>
<td>28.5 ± 3.0²</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>35.2 ± 1.2</td>
<td>39.3 ± 0.6³</td>
</tr>
<tr>
<td>Serum insulin-like growth factor I (µg/L)</td>
<td>85.9 ± 7.5</td>
<td>123.1 ± 8.6³</td>
</tr>
<tr>
<td>Serum orosomucoid (g/L)</td>
<td>1.14 ± 0.06</td>
<td>0.78 ± 0.04³</td>
</tr>
</tbody>
</table>

¹ ± SEM.
² Significantly different from PEM subjects (t test): ² P > 0.001, ¹ P < 0.01, ³ P < 0.05.
³ Significantly different from value at entry, P < 0.05 (t test).
Platelet-free plasma, prepared by centrifugation of the plateletrich plasma at 1000 × g for 10 min at 15 °C, was added to the cell pellet. This reconstituted blood was mixed 1:10 with 4.5% dextran T-500 (Apoteksbolaget, Stockholm) and allowed to sit for 45 min for sediment to form. The leucocyte-rich plasma was carefully layered onto a NycoPrep 1.068 gradient (Nycomed Pharma AS, Oslo) in a siliconized tube and centrifuged at 425 × g for 15 min at 15 °C. The monocyte-rich band was then washed twice in a siliconized tube with calcium- and magnesium-free Hanks balanced salt solution (HBSS; Gibco, Paisley, United Kingdom). The cells were counted and diluted to 10⁶ cells/L in a growth medium consisting of HBSS with penicillin (100,000 U/L), streptomycin (100 mg/L), HEPES (1 mol/L), and 2% autologous serum.

Monocytes comprised > 70% of the cells as determined by flow cytometry (FACSCan; Becton Dickinson, Erembodegem-Aalst, Belgium). All media and tubes used for monocyte preparation were free from endotoxin as tested by COATEST endotoxin (Chromogenix AB, Mölndal, Sweden). The monocytes were incubated with Escherichia coli 055:B5 lipopolysaccharide (LPS; Difco Laboratory, Detroit) at 0.1, 1, or 10 μg/L at 37 °C in 5% CO₂. After 24 h, the experiment was stopped by freezing (−20 °C). Concentrations of IL-1β, IL-6, and TNF-α in the combined freeze-thawed cell supernates and cell lysates were analyzed with a commercial enzyme-linked immunosorbent assay (ELISA; Medgenix Diagnostics, Fleurus, Belgium). Serum IL-6 analyses were performed with a chemiluminescence-augmented ELISA technique as described previously (10). The limit for detection was 1 ng/L. Serum concentrations of IL-1α, IL-10, and TGF-β1 were determined by commercial ELISA kits (R & D Systems, Minneapolis; Medgenix Diagnostics, Fleurus, Belgium; and Predicta, Genzyme Corporation, Cambridge, MA).

### Endotoxin and autoantibody assessment

Serum concentrations of endotoxins were analyzed by a chromogenic Limulus amoebocyte lysate test (COATEST endotoxin). The occurrence of autoantibodies was evaluated in 18 patients and 16 control subjects with indirect immunofluorescence using HEp-2 cells (Immuno Concepts Inc, Sacramento, CA) and acetone-fixed rat liver, gastric, and kidney tissue sections prepared in-house as antigen substrate (11).

### Statistics

Data are presented as means ± SEMs, unless otherwise indicated. Because the cytokine concentrations in monocyte suspensions showed large variations, these data were log-transformed during the statistical procedures to homogenize the variances. Student’s t test, the Mann-Whitney U test, chi-square test, and Fisher’s exact test were used when appropriate in comparison between unpaired groups. In the evaluation of changes during the observation period, Wilcoxon’s signed-rank test, the two-sample sign test, and repeated-measures analysis of variance (ANOVA) were performed. Pearson’s correlation coefficient was determined in correlation analyses. The calculations were performed by using BMDP-SOLO statistical software (SPSS Inc, Chicago).

### RESULTS

All patients were severely malnourished at entry to the study (Table 1). The malnutrition was mainly of the marasmic type as evidenced by low anthropometric values and relative skin hypersensitivity anergy. Serum concentrations of IGF-I in patients were lower than in control subjects (Table 1). IGF-I showed weak but significant correlations with AMC (r = 0.33, P = 0.04) and DCH (r = 0.4, P = 0.02), but not with BMI, TSF, or serum albumin. In contrast with the findings in the control subjects, serum orosomucoid was slightly elevated in the patients (Table 1). IL-6 was detected in the serum of 17 depleted subjects, whereas none of the control subjects had measurable amounts of IL-6 in their serum (Figure 1). A significant correlation between patient serum concentrations of orosomucoid and IL-6 was noted (r = 0.54, P < 0.05). IGF-I did not correlate with any of the two acute-phase markers.

Concentrations of IL-1β, IL-6, and TNF-α in monocyte suspensions stimulated with LPS at various concentrations showed a linear dose-response pattern (Figure 2). Monocytes from malnourished subjects produced more cytokines than did monocytes from the control subjects. After log-transformation of the data, t tests revealed significant differences between patients and control subjects for IL-1β and IL-6 after stimulation with LPS at the lowest concentration, 0.1 μg/L (Figure 2). TNF production did not differ significantly between groups. In this study serum IGF-I concentrations did not correlate with monocyte generation (0.1 μg LPS/L) of IL-1β or IL-6 (r = −0.3, P = 0.1).

![FIGURE 1. Serum interleukin 6 (IL-6) concentrations in subjects with protein-energy malnutrition (PEM; ⬤) and in well-nourished control subjects (○). The horizontal lines denote the mean values. The horizontal dotted line indicates the lowest level detectable by the enzyme-linked immunosorbent assay technique used. †, deceased.](image-url)
CYTOKINE ACTIVITY IN CACHECTIC ELDERLY PATIENTS

![Graph showing cytokine activity](https://academic.oup.com/ajcn/article/65/3/876/4655322)

**FIGURE 2.** Interleukin (IL) 1β, tumor necrosis factor α (TNF-α), and IL-6 expression in suspended monocytes stimulated by lipopolysaccharide (LPS) at various concentrations, from patients with protein-energy malnutrition (●) and well-nourished control subjects (○). Data are given as median values with the 25th (lower lines) and 75th (upper lines) percentiles. For statistical evaluation by Student's t test we transformed the cytokine data to log values to achieve a normalized distribution. This procedure was not possible for data obtained at the LPS concentration of 0.1 μg/L after 3 mo because several of the values were zero. In these cases, Fisher's exact test was used to evaluate detectable compared with nondetectable cytokine concentrations in the two groups. * P < 0.05.

No clinical signs of ongoing infection could be identified in the patients by case history, physical examination, urinalysis, frequent chest X-ray, or microbiological examinations. None had fever at the time of blood sampling and peripheral leucocyte counts were the same as in control subjects (6.5 ± 0.6 and 5.9 ± 0.5 × 10⁹/L, respectively, NS). Endotoxin concentrations in serum were not increased and did not differ between patients and control subjects, being 1.3 ± 0.5 and 1.2 ± 0.4 ng/L, respectively. Low, but detectable, titers of antinuclear or other autoantibodies or both were found in 50% of patients (median 1:25, range 1:25–1:400) and in 81% of control subjects (median 1:100, range 1:25–1:100) (P = 0.06).

Patient serum concentrations of IL-1ra, IL-10, and TGF-β1 were not significantly different from those of control subjects (Table 2). Serum IL-1ra was negatively correlated with DCH (r = −0.34, P < 0.05), whereas the other immunosuppressive cytokines were not.

Shortly after the start of the study four patients died. Serum concentrations of IL-6 were higher in these four patients than in the other subjects in the group (Figure 1). According to the anthropometric measurements, the surviving patients appeared to remain malnourished at reexamination 3 mo later (Table 1). A slight but nonsignificant increase in serum IGF-I was observed and serum concentrations of the anabolic peptide were no longer significantly lower than in the reexamined control subjects (Table 1). Serum orosomucoid concentrations remained unchanged (Table 1). IL-6 in serum decreased (P < 0.05, Figure 1), but still more patients than control subjects (P < 0.05) had detectable serum IL-6 concentrations. The two acute-phase proteins did not correlate significantly (r = 0.28). Cytokine production from monocytes showed, once again, linear dose-response curves. As observed at entry into the study, significantly more IL-1β and IL-6 were produced in cell suspensions stimulated with LPS at 0.1 μg/L (Figure 2). The decline in serum IL-6 did not correlate with weight changes.

Eight of the 15 patients who were reexamined had been prescribed oral supplementation. The supplemented patients had slightly increased (P < 0.05) body weights (median 1.3 kg, 3%) and TSF (1 mm). Otherwise, no changes were observed. Weights of the seven unsupplemented patients did not change (median 0.3 kg, 0.5%). Supplemented and unsupplemented patients did not differ in the cytokine-generating capacity of their monocytes (data not shown). Neither was there a difference in serum concentrations of orosomucoid or IL-6 (Table 3). As stated above, there was a slight decrease in serum IL-6 during the observation period, but repeated-measures ANOVA did not show this decline to be associated with the supplementation (Table 3). However, the small number of patients urges cautious interpretation of these results.

We decided to define “clinical improvement” as an increase of > 5% in at least four of six nutritional and dynamometric variables (BMI, TSF, AMC, DCH, hand-grip strength, and PEF). This criterion was fulfilled by four patients. IGF-I concentrations increased to normal in all four patients (from 89.8 ± 22.7 to 141 ± 23.8 μg/L, P = 0.07, sign test). In three of them there was a simultaneous drop in serum orosomucoid as well as in serum IL-6 concentrations. Moreover, three of the four “clinically improved” patients had received the supplement. Eight patients were prescribed the supplement, which leaves five that did not meet the criterion for “clinical improvement”. Serum IGF-I concentrations tended to be elevated (but not normalized) in seven of the supplemented subjects (P = 0.06). Serum concentrations of IGF-I in the supplemented group at the start and reexamination were 85.9 ± 18.3 and 103.3 ± 18.4 μg/L, respectively (NS). In contrast, only two of the seven unsupplemented patients had increased serum IGF-I concentrations at reexamination.
TABLE 2
Interleukin 1 receptor antagonist (IL-1ra), IL-10, and transforming growth factor β1 (TGF-β1) in serum from malnourished patients (PEM) and control subjects

<table>
<thead>
<tr>
<th></th>
<th>PEM (n = 20)</th>
<th>Controls (n = 21)</th>
<th>PEM (n = 14)</th>
<th>Controls (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1ra (ng/L)</td>
<td>443 ± 146/1</td>
<td>238 ± 68</td>
<td>221 ± 52</td>
<td>356 ± 107</td>
</tr>
<tr>
<td>IL-10 (ng/L)</td>
<td>2.4 (0.4–4.3)/2</td>
<td>3.2 (0.5–3.9)</td>
<td>1.9 (1.1–3.7)</td>
<td>2.7 (0.5–4.2)</td>
</tr>
<tr>
<td>TGF-β1 (μg/L)</td>
<td>58.2 ± 7.1</td>
<td>50.2 ± 2.7</td>
<td>50.7 ± 4.8</td>
<td>49.9 ± 3.8</td>
</tr>
</tbody>
</table>

1 ± SEM. No significant differences were noted.
2 Presented as median values (25th–75th percentile) because of skewed distributions.

DISCUSSION

Although the malnourished patients had no clinical evidence of infection, either at entry or at reexamination, they had higher serum concentrations of orosomucoid and IL-6 than did the control subjects. In parallel, monocytes from the patients produced more IL-1β and IL-6 than did cells from the control subjects when challenged by endotoxin at concentrations found during serious infections. These observations support the concept that PEM during disease is associated with an activation of the inflammatory system (3, 12) and corroborate our previous report (2). It is likely that the illnesses of the patients and the concurrent inflammation triggered the PEM. Because serum endotoxin concentrations were not increased, gram-negative infections or bacterial translocation in the gut (13) seem unlikely to have been the initiators of the inflammatory processes. Neither were there any signs of increased reactivity against endogenous antigens, which might have become expressed during the PEM process. It is conceivable that the stimuli for inflammatory activity vary according to the underlying disorder. The individual response to inflammatory stimuli may also vary.

A growing body of evidence indicates that cytokines, such as IL-1β, TNF-α, and IL-6, are involved in the pathogenesis of the cachexia often observed in acutely and chronically ill patients. These peptides, secreted mainly by macrophages when challenged by various antigens, may interfere with the nutritional balance through several mechanisms. Reduced appetite and weight loss are observed in animals administered IL-1β and TNF-α (14, 15) or inoculated with IL-6-producing tumors (16) and these effects are attenuated by anticytokine antibody therapy (14, 16, 17). In fact, the anorectic feature of TNF gave rise to its other common name, cachectin (18). Protein metabolism is also altered because these cytokines induce muscle protein catabolism (15, 19) and change liver metabolism causing acute-phase protein production (15, 19, 20). Moreover, energy expenditure is increased by IL-1β (21). The redundancy of the three cytokines makes it feasible to consider them as an entity. Because serum analyses of IL-6 seem to be more reliable than corresponding tests of IL-1β and TNF-α, we chose to perform serum analyses of IL-6 only.

Reports of cytokine concentrations and activity in noncancer-induced PEM in humans are not consistent. In support of our findings, elevated serum concentrations of proinflammatory cytokines, i.e., TNF-α, have been observed in depleted patients with congestive heart failure (22, 23) and with chronic obstructive pulmonary disorder (24). Chronic hypoxia has been suggested to promote enhanced monocyte secretion of IL-1β and IL-6 (25). Because many of the patients in the current study suffered from pulmonary diseases, one may speculate that hypoxia is one possible mechanism contributing to the activation of the immune system. In patients with rheumatoid arthritis low body cell mass and increased resting energy expenditure have been associated with augmented TNF-α and IL-1β production (26). In contrast, other reports have shown impaired or unaffected production and action of IL-1β (or associated substances) during PEM (27–30). Such variations may be due to differences in patient selection.

Nutritional recovery may be counteracted by the presence of proinflammatory and catabolic cytokines. The poor nutritional outcome in eight of our patients who received oral supplementation may be related, at least in part, to sustained, enhanced cytokine activity. We reported previously on a group of elderly malnourished patients (some of whom are also in the present study) in whom the effect of oral supplementation was best in those who lacked signs of ongoing inflammatory activity (31). The decrease in serum IL-6 concentrations during the observation period probably reflects diminished activity in the underlying disease, but our data do not exclude other influences.

As expected, IGF-I concentrations in serum were low in our depleted patients (32). In experimental models, IGF-I activity is inhibited by the administration of proinflammatory cytokines (33). Thus, both low secretion of IGF-I and depressed response to the secreted peptide may impede anabolic processes in chronically ill patients. Increased serum concentrations of IL-6 are a well-established marker of inflammatory activity during infections (34) and postoperatively (35). Our finding of a positive correlation between IL-6 and orosomucoid is in line with other observations (36). Elevated concentrations of IL-6

TABLE 3
Serum orosomucoid and serum interleukin 6 in supplemented and unsupplemented patients at entry and after 3 mo

<table>
<thead>
<tr>
<th></th>
<th>Entry 3 mo</th>
<th>After 3 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum orosomucoid</td>
<td>g/L</td>
<td>ng/L</td>
</tr>
<tr>
<td>Supplemented</td>
<td>1.13 ± 0.09</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>Unsupplemented</td>
<td>1.11 ± 0.11</td>
<td>1.07 ± 0.11</td>
</tr>
</tbody>
</table>

1 ± SEM.
2 Significantly different from entry, P = 0.02 (repeated-measures ANOVA).
may also predict imminent death (37). Such observations were also corroborated by our investigation, although the IL-6 concentrations in our moribund patients were only moderately raised.

In most inflammatory disorders, enhanced generation of proinflammatory cytokines is balanced or counteracted by production of antiinflammatory cytokines, such as IL-1ra (38, 39), IL-10 (40), or TGF-β1 (41). IL-10 has been reported to depress the gene expression (42) and secretion of several proinflammatory cytokines (43) and to deactivate macrophages (44); TGF-β1 is regarded mainly as an immunosuppressive peptide with the ability to inhibit the growth of a variety of cell types (41). The close interaction between pro- and antiinflammatory cytokines is believed to contribute to the regulation and termination of the inflammatory response. Because serum concentrations of IL-1ra, IL-10, and TGF-β1 in our PEM patients were not significantly different from those of the control subjects, one might speculate whether this skewed cytokine profile was significant for the emergence and persistence of their low-grade inflammatory reaction and malnutrition. We also evaluated the hypothesis that alterations in IL-10, IL-1ra, or TGF-β1 activity are involved in the PEM-associated impairment of DCH (45). Correlation analyses showed a weak negative relation between serum concentration of IL-1ra and DCH at entry. Analyses of cytokine generation in monocytes or tissues may yield more clinically relevant data than the measurements of their serum concentrations.

The current study indicated that PEM in noncancerous patients was associated with significant changes in proinflammatory and cachexia-promoting cytokine production that remained during an observation period of 3 mo. We conclude that inflammation and its mediators may be important in the development of PEM in a variety of chronic disorders. Sustained inflammatory activity may also be partly responsible for the difficulties in treating PEM. Reduced host defense, secondary to emaciation (45), paves the way for infectious complications (46), which further contribute to depletion (47). A vicious cycle of PEM is easily established (Figure 3). Considering the many complications associated with PEM (2, 48), programs for combined actions to counteract the various components of this vicious cycle are urgently needed.

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