Soluble Receptors for Tumor Necrosis Factor Are Markers for Clinical Course But Not for Major Metabolic Changes in Human Immunodeficiency Virus Infection

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Tumor necrosis factor alpha (TNF) is a potential mediator of the metabolic changes in human immunodeficiency virus type 1 (HIV) infection. Soluble TNF receptor types I and II (sTNFR-I and -II) presumably reflect TNF activity. To examine the relationship between sTNFRs and host metabolism, resting energy expenditure (REE), body composition, and transferrin, albumin, triglyceride, retinol-binding protein, and sTNFR concentrations were measured in 12 asymptomatic and 18 symptomatic HIV-infected male subjects and 15 male control subjects. sTNFRs were increased in parallel with disease severity. REE was elevated approximately 8% in HIV-infected subjects ($P = .005$). REE correlated positively with fat free mass (FFM) and the presence of HIV infection, but not with sTNFRs. Inverse correlations existed between sTNFR-I or -II and albumin concentration ($r = -.48$, $P = .007$, and $r = -.49$, $P = .006$, respectively), between sTNFR-II and transferrin concentration ($r = =.53$, $P = .003$), and between ln(sTNFR-II) and percent body fat ($r = -.37$, $P < .05$), but not between sTNFRs and triglyceride or retinol-binding protein. Thus, sTNFRs are markers for clinical course but not for major metabolic changes in HIV infection.

INFECTION WITH human immunodeficiency virus type 1 (HIV) is associated with several changes of host metabolism.[1-7] These changes, alone or in combination with decreased nutrient intake and intestinal malabsorption, are thought to contribute to the profound wasting that invariably accompanies progressive HIV disease and is strongly correlated with the timing of death.[1-9] Metabolic alterations found in HIV infection include an increase of resting energy expenditure (REE), already present early in the course of the disease, a higher rate of fat oxidation, hypertriglyceridemia associated with a decreased cholesterol concentration, increased de novo hepatic lipogenesis, and a decreased rate of protein synthesis.[1-7] The pathophysiologic mechanisms responsible for these metabolic disturbances are still poorly understood.

The cytokine tumor necrosis factor alpha (TNF) has been implicated as a key mediator of cachexia. Indirect evidence for the involvement of TNF is derived from the observation that in animals and humans, TNF administration induces anorexia, weight loss, and metabolic alterations similar to those found in acute infections.[1,10-14] Moreover, anti-TNF antibodies were shown to attenuate cachexia, and a chimeric TNF receptor-Fc protein was reported to prevent cachexia and runting in mice.[15,16] However, precise correlates between endogenous TNF activity and the clinical syndrome of wasting have proved elusive. In a chronic disease like HIV infection, TNF probably acts mainly at the local tissue level in a paracrine fashion rather than systemically, and circulating TNF concentrations are usually not detectable in HIV-infected subjects.[1,2,5,6,17,18]

The biological responses of TNF are initiated after interaction with two distinct membrane receptors, types I and II. Soluble forms of the extracellular domain of these receptors (soluble TNF receptor types I and II [sTNFR-I and -II]) are shed by proteolytic cleavage of the membrane receptor and have been found in human serum, urine, and other body fluids.[18-20] Because TNF administration induces increased shedding of the receptors, sTNFRs may be considered a reflection of TNF activity.[21] Previously, we have found that in HIV infection serum concentrations of sTNFRs (1) are increased in parallel with clinical stage and (2) are better predictors of progression to symptomatic disease than the $CD4^+$ lymphocyte count or the β_2-microglobulin concentration.[17,22] These observations indicate that the TNF system is activated in HIV infection, even though TNF itself is usually not detectable in the circulation of HIV-infected subjects.

In the present study, we sought to determine the relationship between metabolic and nutritional alterations found in HIV infection and the TNF system. Serum concentrations of sTNFRs were used as parameters for activation of the TNF system.

SUBJECTS AND METHODS

Subjects

Thirty HIV-infected men entered the study. Twelve participants were asymptomatic (Centers for Disease Control stage II or III), and 18 were symptomatic (stage IV).[23] For at least 2 months before the study, all subjects were clinically stable without diarrhea, clinically active opportunistic infections, progressive Kaposi's sarcoma, or fever (>37.8°C). Patients with known endocrinologic disorders (eg, diabetes mellitus or thyroid disease), malignancy other than Kaposi's sarcoma, or a history of intravenous drug use were excluded. The control group consisted of 15 healthy men, who were matched for smoking habits.[24]

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The study protocol was approved by the Medical Ethics Committee of the Academic Medical Center. All participants gave informed consent.

Study Protocol

The study was performed under standardized conditions in a quiet, temperature-controlled room (22°C). Subjects were in the postabsorptive state (12 to 14 hours) and confined to bed in the supine position. On the day of study, subjects came to the Metabolic Ward at 8 AM by car or public transportation (strenuous exercise like running or cycling was not permitted). After an equilibration period of 2 hours spent lying in bed, indirect calorimetry was performed, body composition was measured, and blood samples were taken for determination of total white blood cell count, hemoglobin, albumin, transferrin, retinol-binding protein, glucose, triglyceride, hormones, TNF, and sTNFR-I and -II. Urine was collected during the study (4 hours) and analyzed for nitrogen content.

Serum samples for determination of sTNFR-I and -II were coded and stored at −70°C until analyzed. They were assayed in one batch by a technician who was unaware of the clinical and HIV status of the subjects.

$CD4^+$ lymphocyte counts from HIV-seropositive subjects were obtained from medical records. The $CD4^+$ lymphocyte count at the last visit before the study, while subjects were clinically stable, was obtained (median time between $CD4^+$ count and study, 2 months; range, ≤1 week to 6 months).

Indirect calorimetry. To determine REE and substrate oxidation rates, indirect calorimetry was performed using a ventilated hood with a mass flow meter, a zirconium oxygen sensor, and an infrared-absorption carbon dioxide analyzer (model 2900, Computerized Energy Measurement System; Sensor Medics, Anaheim, CA) as described previously.[2,3] Oxygen consumption and carbon dioxide production were measured continuously for at least 30 minutes. During these measurements, subjects were asked to close their eyes but not sleep, and the room was semidarkened. To allow for adaptation to the hood, results of the first 10 minutes were discarded.

Body composition was measured with a bioelectric-impedance analyzer (BIA 109; Akern, Florence, Italy) as described previously.[2,3]

Assays

Total white blood cell count and hemoglobin concentration were determined using a STK S analyzer (Coulter, Luton, UK). $CD4^+$ lymphocytes were counted by direct staining with monoclonal antibodies and a flow cytometry system. Albumin, triglyceride, and glucose concentrations were quantified by a SMAC-II Technicon Autoanalyzer (Tarrytown, NY). A radial immunodiffusion technique was used to determine concentrations of transferrin and retinol-binding protein (Behring Diagnostics, La Jolla, CA).

Hormones. Plasma insulin was determined by an in-house radioimmunoassay (RIA), glucagon by a commercial RIA (Daiichi Radioisotope Laboratories, Tokyo, Japan), cortisol by fluorescence polarization immunoassay on TDx (Abbott Laboratories, North Chicago, IL), and plasma catecholamines by radioenzymatic assay. Thyrotropin level was measured by a third-generation assay with a detection limit of 0.01 mU/L (TSH-IMCA; Behring, Germany), and thyroxine and triiodothyronine were determined by in-house RIAs.

TNF and sTNFR concentrations. TNF concentration was determined by an enzyme-linked immunosorbent assay (antibodies kindly donated by Dr W.A. Buurman; detection limit, 30 pg/mL).[25] Concentrations of sTNFR-I and -II were determined by enzyme-bound immunological assays (antibodies kindly donated by Dr H. Gallati, Hoffmann-LaRoche, Pharmaceutical Research–New Technologies, Basel, Switzerland).[17,22] Quality-control samples (four levels, samples of a previous study[17]) were measured for each assay. From the results of quality-control samples, an assay was accepted, refused, or corrected if all quality-control results had a constant deviation.

Urinary nitrogen content was determined by the micro-Kjeldahl technique.

Calculations

REE and substrate oxidation rates were calculated from oxygen consumption, carbon dioxide production, and urinary nitrogen excretion, according to published methods.[2,3,26]

Statistical Analysis

Data are expressed as the mean ± SD or as the median and range. Statistical analysis was performed using the Epi Info software package (Epi Info Version 5.01; Centers for Disease Control, Epidemiology Program Office, Atlanta, GA) and the Statistical Analysis System software package (SAS 6.03; SAS Institute, Cary, NC). Comparisons between groups were made with an unpaired Student's *t* test or Mann-Whitney tests, as appropriate for each variable depending on its distribution.

Rates of REE were compared by analysis of covariance to correct for differences in REE attributable to differences in fat-free mass (FFM).[27] For both HIV-infected groups, the same correction factor emerged. Therefore, for comparison of rates of REE between healthy control and HIV-infected subjects, results of the two HIV-infected groups were pooled.

To determine whether multiple factors accounted for differences in REE, stepwise multiple regression analysis was performed after logarithmic transformation of the variables, with the exception of FFM. This analysis examines the relation between each potential explanatory variable and the outcome variable of interest, ie, REE, ignoring all other variables, starting with the single variable that has the strongest association with the dependent variable and entering it into the model; subsequently, other variables are found among those not yet in the model that, when added to the model so far obtained, explain the largest amount of the remaining variability.[28] A categorical variable was created for HIV status (HIV-seronegative = 0 and HIV-seropositive = 1).

Pearson correlation coefficients were calculated between sTNFR-I and -II and between TNF and sTNFR-I or -II, combining the data of all subjects. Using only the data of HIV-seropositive groups, Pearson correlation coefficients were calculated between sTNFR-I and -II, between sTNFR-I and FFM, TNF, transferrin, retinol-binding protein, albumin, and triglyceride, respectively, and between sTNFR-II and these parameters. Furthermore, the correlation coefficient between both sTNFRs (after logistic transformation) and body fat mass expressed as percent body weight was calculated. In addition, stepwise multiple regression analysis was performed to examine whether an association was dependent on other variables.

Significance level was set at P less than .05.

RESULTS

Clinical characteristics of the subjects are listed in Table 1. Symptomatic HIV-infected subjects were slightly older as compared with the asymptomatic group, and they weighed less than control subjects. Zidovudine use was highest in the symptomatic group associated with lower hemoglobin concentrations (8.1 ± 1.0 *v* 9.1 ± 0.5 mmol/L, $P = .002$, and *v*

Table 1. Physical Characteristics, Smoking Habits, Zidovudine Use, and CD4+ Counts

Parameter	Group (I) Control	(II) Asymptomatic HIV+	(III) Symptomatic HIV+	P Value I v II	I v III	II v III
No. of subjects	15	12	18			
Age (yr)						
Median	37	35	41			.04
Range	27-60	30-48	31-61			
Weight (kg)	77.1 ± 7.6	73.4 ± 12.3	70.3 ± 6.8		.01	
BMI (kg/m²)	23.2 ± 2.1	23.0 ± 3.6	21.8 ± 2.0			
FFM (kg)	61.9 ± 6.1	58.0 ± 8.1	57.7 ± 6.5			
Body fat (%)	19.7 ± 3.8	20.5 ± 5.8	18.0 ± 4.0			
Smokers						
No.	9	11	11			
%	60	91.7	61.1			
ZDV users						
No.	0	2	14	—	—	.001
%	0	16.7	77.8			
CD4+ (cells/μL)						
Median	—	450	175	—	—	.002
Range		20-900	10-500			

NOTE. Data are the mean ± SD unless otherwise indicated. Only significant differences are shown (unpaired Student's *t* test or Mann-Whitney test).

Abbreviation: ZDV, zidovudine.

9.1 ± 0.9 mmol/L, $P = .008$, control and asymptomatic subjects, respectively) and lower total white blood cell counts ($3.0 \pm 1.5 \times 10^9$/L *v* $5.7 \pm 1.3 \times 10^9$/L, $P = .00004$, and *v* $5.0 \pm 1.9 \times 10^9$/L, $P = .004$, control and asymptomatic subjects, respectively). Median CD4+ lymphocyte counts were significantly lower in the symptomatic group as compared with asymptomatic subjects.

REE and substrate oxidation rates in the three study groups are listed in Table 2. Whole-body REE was not significantly different in HIV-infected subjects as compared with healthy control subjects or in asymptomatic as compared with symptomatic HIV-infected subjects. When REE was expressed per kilogram FFM, significant differences were found between control subjects and both HIV-infected groups ($P = .02$ and $P = .001$, control subjects *v* asymptomatic and symptomatic subjects, respectively), but not between asymptomatic and symptomatic HIV-infected subjects. Analysis of covariance showed that the rate of REE was elevated approximately 8% in HIV-infected subjects as compared with healthy control subjects ($P = .005$). In symptomatic subjects, lower rates of glucose oxidation and higher rates of fat oxidation were found as compared with rates in asymptomatic subjects. No differences in substrate oxidation rates were found between healthy controls and HIV-infected subjects.

Concentrations of metabolic parameters are shown in Table 3. No significant differences were noted, except for a lower albumin concentration in symptomatic subjects as compared with control subjects. Although there was a trend for triglyceride levels to be elevated in HIV-seropositive subjects, this did not achieve significance, possibly due to the small number of individuals studied. Concentrations of sTNFRs differed significantly between each group (Table

Table 2. REE and Substrate Oxidation Rates

Parameter	Group (I) Control	(II) Asymptomatic HIV+	(III) Symptomatic HIV+	P Value I v II	I v III	II v III
No. of subjects	15	12	18			
REE (mJ/d)*	7,554 ± 571	7,931 ± 797	7,745 ± 845			
REE/kg FFM (mJ/d)*	123 ± 9	136 ± 17	134 ± 9	.02	.001	
G_{ox} (mg/kg FFM/d)	1.3 ± 1.2	2.1 ± 1.0	0.9 ± 0.9			.003
F_{ox} (mg/kg FFM/d)	1.4 ± 0.6	1.2 ± 0.5	1.8 ± 0.7			.01
P_{ox} (mg/kg FFM/d)	1.0 ± 0.2	0.9 ± 0.3	0.9 ± 0.4			

NOTE. Data are the mean ± SD. Only significant differences are shown (Student's unpaired *t* test).

Abbreviations: G_{ox}, glucose oxidation rate; F_{ox}, fat oxidation rate; P_{ox}, protein oxidation rate.

*To convert kJ to kcal, multiply by 0.2381.

Table 3. Concentrations of Glucose, Albumin, Transferrin, Retinol-Binding Protein, Triglyceride, and sTNFR-I and -II

Parameter	Group (I) Control	(II) Asymptomatic HIV+	(III) Symptomatic HIV+	P Value I v II	I v III	II v III
No. of subjects	15	12	18			
Glucose (mmol/L)*	5.0 ± 0.6	5.2 ± 0.5	5.1 ± 0.6			
Albumin (g/L)	43.7 ± 2.8	42.4 ± 2.6	41.1 ± 4.1		.04	
Transferrin (g/L)	2.42 ± 0.39	2.57 ± 0.49	2.40 ± 0.33			
RBP (mg/L)	46.3 ± 4.5	43.5 ± 14.1	43.6 ± 18.9			
Triglyceride (mmol/L)*	0.91 ± 0.32	1.32 ± 0.57	1.37 ± 0.77			
sTNFR-I (ng/mL)	0.72 ± 0.31	0.99 ± 0.19	1.47 ± 0.40	.02	.00003	.001
sTNFR-II (ng/mL)	1.40 ± 1.28	3.22 ± 1.34	5.13 ± 1.83	.002	.00001	.005

NOTE. Data are the mean ± SD. Only significant differences are shown (Student's unpaired *t* test).

Abbreviation: RBP, retinol-binding protein.

*Multiplication factors for conversion of glucose and triglyceride concentrations from mmol/L to mg/dL: 18.01 and 88.57, respectively.

3). The lowest concentrations were found in healthy controls and the highest in symptomatic HIV-infected subjects. TNF was just above the detection limit in 40% of control subjects and approximately 60% of HIV-infected subjects. There were no significant differences in median TNF concentrations between the three groups (data not shown).

There were no differences in plasma concentrations of glucagon, catecholamines, or cortisol (Table 4). Insulin concentration was slightly higher in both HIV-infected groups as compared with control subjects, but this difference reached significance only in the group of asymptomatic carriers (Table 4). Plasma concentrations of thyroid hormones did not differ between groups; none of the subjects was suffering from hyperthyroidism (data not shown).

Stepwise multiple regression analysis was used to analyze biologically plausible parameters that explained significant amounts of the variability of REE.

This regression analysis, adjusted for smoking habits using the data of all subjects, led to the following equation: REE = 801 + 16(FFM) + 2.3(HIV status × FFM). Neither sTNFR-I nor sTNFR-II contributed to this equation. Determination of the residual sum of squares in this regression analysis showed that FFM contributed 32% of the variability of REE ($P = .0001$) and HIV status × FFM contributed 13% ($P = .003$). Since the influence of FFM on REE was similar in both HIV-seropositive groups, the data of these groups were combined to examine whether other variables influencing REE could be recognized. Except for FFM, no other variable was found. In particular, no significant association between sTNFRs and REE was found.

Correlation Analysis

A positive correlation existed between sTNFR-I and -II (all subjects, $r = .87$, $P = .0001$; HIV-seropositive subjects, $r = .77$, $P = .0001$). Combining only the data of HIV-seropositive groups, inverse correlations were found between sTNFR-II and transferrin concentration ($r = -.53, P = .003$), sTNFR-II and albumin concentration ($r = -.49, P = .006$), and sTNFR-I and albumin concentration ($r = -.48, P = .007$). No correlation existed between sTNFR-I and transferrin concentration ($r = -.25$, $P = .19$) or between sTNFR-I or -II and retinol-binding protein or triglyceride concentration (data not shown). A weak but significant positive correlation was found between TNF level and sTNFR-I ($r = .38, P = .04$), but not between TNF and sTNFR-II ($r = .22, P = .24$).

Body fat mass expressed as percent body weight correlated negatively with ln(sTNFR-II) ($r = -.37, P < .05$), but no correlation was found between this parameter and sTNFR-I or between sTNFR-I or -II and FFM. In a stepwise multiple regression analysis, the association between body fat mass expressed as percent body weight and sTNFR-II was found to be independent of transferrin or albumin concentration. Transferrin concentration emerged as an independent variable, but albumin concentration was found to depend on transferrin concentration (data not shown).

Table 4. Concentrations of Insulin and Catabolic Hormones

Parameter	Control	Asymptomatic HIV+	Symptomatic HIV+
No. of subjects	15	12	18
Insulin (mU/L)			
Median	3	6	5
Range	1-6	1-14	1-14
Glucagon (ng/L)	99 ± 27	108 ± 36	108 ± 19
Cortisol (μmol/L)	0.34 ± 0.10	0.39 ± 0.13	0.33 ± 0.09
Adrenalin (ng/L)			
Median	17	31	20
Range	8-125	5-409	5-180
Noradrenalin (ng/L)	160 ± 66	168 ± 105	154 ± 111

NOTE. Data are the mean ± SD unless otherwise indicated. No significant differences were found between the three groups, except for slightly higher median insulin concentrations in asymptomatic carriers *v* control subjects (Student's unpaired *t* test, $P = .02$).

DISCUSSION

In the present study, correlations between host metabolism and the TNF system were evaluated in HIV infection. As previously reported by us and others,[1-7] an increased rate of REE of approximately 8% was found in both asymptomatic and symptomatic HIV-infected subjects. In accordance with our previous observations, sTNFRs were increased in parallel with severity of clinical stage.[17,22] REE was related to FFM and the presence of HIV infection. There was no dose-response relationship between REE and sTNFRs in HIV infection. sTNFRs correlated with some parameters of nutritional status, ie, percent body fat and transferrin and albumin concentration, but not with triglyceride or retinol-binding protein concentration.

The whole-body rate of REE depends on the metabolically active body mass, estimated by FFM.[27] To compare rates of REE in patient and control groups, we used analysis of covariance to correct for differences of absolute FFM.[3,27] However, FFM contains not only the metabolically active body mass but also extracellular fluid and mineral mass. In a cross-sectional study in malnourished patients with symptomatic HIV infection (more than half of whom were concurrently suffering from an opportunistic infection), depletion of body cell mass with a higher percentage of body weight as water, corresponding to overhydration of the extracellular space, and hypoalbuminemia has been reported.[29] Although it cannot be excluded that some of the symptomatic patients in our study had an increased water space, it does not seem likely. None of the subjects had overt edema, and only one subject had moderate hypoalbuminemia (albumin concentration, 31 g/L). Furthermore, bioelectric-impedance analysis has been found to be accurate for measuring body composition in clinically stable HIV-infected subjects.[30]

In accordance with our previous studies, REE was increased equally in asymptomatic and clinically stable symptomatic subjects.[2,3] Plasma concentrations of catabolic and thyroid hormones were not different from control values and were within normal limits. Thus, the increased REE cannot be explained by alterations of catabolic or thyroid hormones. Because the influence of FFM on REE was similar in the two HIV-infected groups, the data from these groups were pooled, and stepwise multiple regression analysis was performed to examine the correlation between different variables and REE. FFM was the only variable

found to influence REE. As reported previously, concentrations of sTNFRs were increased in HIV infection and increased in parallel with disease stage.[17,22] In contrast, the increase of REE was correlated with the presence of HIV infection but not with disease stage or serum concentrations of sTNFRs. Thus, although the presence of HIV infection is associated with hypermetabolism and with increased concentrations of sTNFRs, the existence of a causal relationship between the changes in REE and in sTNFRs is not supported by a dose-response relationship.

Some parameters of nutritional status were found to correlate with the concentrations of sTNFRs. A reduction of body cell mass with a relative increase of total body water and extracellular water volume, as well as an often less prominent reduction of body fat content, has been reported in acquired immunodeficiency syndrome patients.[1,8,29] In our study, no correlation was found between sTNFRs and FFM. A weak negative correlation was found between percent body fat and sTNFR-II, indicating that a decrease of body fat mass is associated with increased concentrations of sTNFR-II. Negative correlations existed between sTNFRs and albumin concentration, as well as between sTNFR-II and transferrin concentration, but no correlation was found with triglyceride or retinol-binding protein concentration. Thus, sTNFRs were not associated with major metabolic changes in HIV infection.

In a recent study, similar correlations between sTNFRs and albumin and transferrin concentrations were reported.[31] In contrast, we did not find a negative correlation between sTNFR-I and transferrin concentration. An explanation for this discrepancy might be that in the above-mentioned study the concentrations of sTNFR-I were higher than those of sTNFR-II, whereas in the present study, as well as in other studies in HIV-infected subjects, sTNFR-II was higher than sTNFR-I.[17,22,32]

The metabolic sequelae of TNF have predominantly been studied in the setting of short- or long-term TNF administration to laboratory animals or humans,[10-14,33] as well as after neutralizing the endogenous TNF response with antibodies or administration of a chimeric TNF receptor-Fc protein.[15,16] Although numerous studies have shown that TNF administration can mimic many of the metabolic alterations found in acute and chronic diseases, it is still unclear to what extent TNF is involved in the changes of host metabolism during disease processes in humans. Results of the present study indicate that in HIV infection, TNF activation, as reflected by elevated levels of sTNFRs, is present. However, although sTNFRs are good markers for the clinical course of HIV infection, they are not markers for major metabolic changes.

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REFERENCES

1. Grunfeld C, Feingold KR: Metabolic disturbances and wasting in the acquired immunodeficiency syndrome. N Engl J Med 327:329-337, 1992

2. Hommes MJT, Romijn JA, Godfried MH, et al: Increased resting energy expenditure in human immunodeficiency virus–infected men. Metabolism 39:1186-1190, 1990

3. Hommes MJT, Romijn JA, Endert E, et al: Resting energy expenditure and substrate oxidation in human immunodeficiency virus (HIV)-infected asymptomatic men: HIV affects host metabolism in the early asymptomatic stage. Am J Clin Nutr 54:311-315, 1991

4. Melchior JC, Salmon D, Rigaud D, et al: Resting energy expenditure is increased in stable, malnourished HIV-infected patients. Am J Clin Nutr 53:437-441, 1991

5. Grunfeld C, Pang M, Doerrler W, et al: Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. J Clin Endocrinol Metab 74:1045-1052, 1992

6. Hellerstein MK, Grunfeld C, Wu K, et al: Increased de novo hepatic lipogenesis in human immunodeficiency virus infection. J Clin Endocrinol Metab 76:559-565, 1993

7. Stein TP, Nutinsky C, Condoluci D, et al: Protein and energy substrate metabolism in AIDS patients. Metabolism 39:876-881, 1990

8. Kotler DP, Tierny AR, Wang J, et al: Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. Am J Clin Nutr 50:444-447, 1989

9. Chlebowski RT, Grosvenor MB, Bernhard NH, et al: Nutritional status, gastrointestinal dysfunction, and survival in patients with AIDS. Am J Gastroenterol 84:1288-1293, 1989

10. Tracey KJ, Cerami A: Tumor necrosis factor: An updated review of its biology. Crit Care Med 21:S415-S422, 1993

11. Spiegelman BM, Hotamisligil GS: Through thick and thin: Wasting, obesity, and TNFα. Cell 73:625-627, 1993

12. Fong Y, Moldawer LL, Marano M, et al: Cachectin/TNF or IL-1α induces cachexia with redistribution of body proteins. Am J Physiol 256:R659-R665, 1989

13. Warren RS, Starnes F, Gabrilove JL, et al: The acute metabolic effects of tumor necrosis factor administration in humans. Arch Surg 122:1396-1400, 1987

14. Van der Poll T, Romijn JA, Endert E, et al: Tumor necrosis factor mimics the metabolic response to acute infection in healthy humans. Am J Physiol 261:E457-E465, 1991

15. Sherry B, Gelin J, Fong Y, et al: Anticachectin/tumor necrosis factor antibodies attenuate development of cachexia in tumor models. FASEB J 3:1956-1962, 1989

16. Teng MN, Turksen K, Jacobs CA, et al: Prevention of runting and cachexia by a chimeric TNF receptor-Fc protein. Clin Immunol Immunopathol 62:215-222, 1993

17. Godfried MH, van der Poll T, Jansen J, et al: Soluble receptors for tumour necrosis factor: A putative marker of disease progression in HIV infection. AIDS 7:33-36, 1993

18. Gehr G, Braun T, Lesslauer W: Cytokines, receptors, and inhibitors. Clin Invest 70:64-69, 1992

19. Tartaglia LA, Goeddel DV: Two TNF receptors. Immunol Today 13:151-153, 1992

20. Engelmann H, Aderka D, Nophar Y, et al: Soluble and cell surface receptors for tumor necrosis factor, in van Furth R (ed): Mononuclear Phagocytes. Dordrecht, The Netherlands, Kluwer Academic, 1992, pp 359-365

21. Lantz M, Malik S, Slevin M, et al: Infusion of tumor necrosis factor (TNF) causes an increase in circulating TNF-binding protein in humans. Cytokine 2:402-406, 1990

22. Godfried MH, van der Poll T, Weverling GJ, et al: Soluble receptors for tumor necrosis factor as predictors of progression to AIDS in asymptomatic human immunodeficiency virus-1 infection. J Infect Dis 169:739-745, 1994

23. Centers for Disease Control: Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR 36:1S-14S, 1987

24. Perkins KA, Epstein LH, Marks BL, et al: The effect of nicotine on energy expenditure during light physical activity. N Engl J Med 320:898-903, 1989

25. Engelberts I, Moller A, Schoen GJM, et al: Evaluation of measurement of human TNF in plasma by ELISA. Lymphokine Cytokine Res 10:69-76, 1991

26. Ferrannini E: The theoretical bases of indirect calorimetry: A review. Metabolism 37:287-301, 1988

27. Ravussin E, Bogardus C: Relationship of genetics, age, and physical fitness to daily energy expenditure and fuel utilization. Am J Clin Nutr 49:968-975, 1989

28. Altman DG: Practical Statistics for Medical Research. London, UK, Chapman & Hall, 1991

29. Kotler DP, Wang J, Pierson RN: Body composition studies in patients with the acquired immunodeficiency syndrome. Am J Clin Nutr 42:1255-1265, 1985

30. Sluys TEMS, van der Ende ME, Swart GR, et al: Body composition in patients with acquired immunodeficiency syndrome: A validation study of bioelectric impedance analysis. JPEN 17:404-406, 1993

31. Süttmann U, Selberg O, Gallati H, et al: Tumour necrosis factor receptor levels are linked to the acute-phase response and malnutrition in human-immunodeficiency-virus–infected patients. Clin Sci 86:461-467, 1994

32. Aukrust P, Liabakk NB, Müller F, et al: Serum levels of tumor necrosis factor-α (TNFα) and soluble TNF receptors in human immunodeficiency virus type 1 infection—Correlations to clinical, immunologic, and virologic parameters. J Infect Dis 169:420-424, 1994

33. Tracey KJ, Wei H, Manogue KR, et al: Cachectin/tumor necrosis factor induces cachexia, anemia, and inflammation. J Exp Med 167:1211-1227, 1988