

**ENERGY EXPENDITURE AND WASTING IN HUMAN IMMUNODEFICIENCY VIRUS INFECTION**

DEREK C. MACALLAN, PH.D., M.R.C.P., CAROLE NOBLE, B.Sc., S.R.D., CHRISTINE BALDWIN, B.Sc., S.R.D., SUSAN A. JEBB, PH.D., S.R.D., ANDREW M. PRENTICE, PH.D., W. ANDREW COWARD, PH.D., MALCOLM B. SAWYER, A.I.S.T., TOM J. MCMANUS, F.R.C.O.G., AND GEORGE E. GRIFFIN, PH.D., F.R.C.P.

**Abstract Background.** Increased expenditure of energy at rest has been considered a contributing factor to the negative energy balance and weight loss that occur in patients with human immunodeficiency virus (HIV) infection. However, the true determinant of energy balance is not resting but total energy expenditure. We sought to determine the contribution of total energy expenditure to weight changes in patients with HIV-associated wasting.

**Methods.** We performed 51 assessments of energy metabolism in 27 men with HIV infection at different stages of disease, including periods of both rapid and slow weight loss. Resting energy expenditure was measured by indirect calorimetry, total energy expenditure by the doubly-labeled-water technique, and energy intake by recording the weight of food consumed. The results were compared with the rate of weight loss or gain.

**Results.** The mean ( $\pm$ SD) total energy expended by

the HIV-infected men was  $2750 \pm 670$  kcal per day, no more than that expended by normal men. There was a significant positive relation between total energy expenditure and the rate of weight change ( $r = 0.61$ ,  $P < 0.001$ ); thus, during rapid weight loss, total energy expenditure was reduced to  $2180 \pm 580$  kcal per day ( $P = 0.009$ ), primarily because of reduced physical activity. During rapid weight loss, the negative energy balance ( $-850 \pm 580$  kcal per day) was primarily the result of the reduction in energy intake, to  $1330 \pm 610$  kcal per day; intake correlated strongly with the rate of weight change ( $r = 0.84$ ,  $P < 0.001$ ).

**Conclusions.** In patients with HIV infection, total energy expenditure is reduced during episodes of weight loss. Reduced energy intake, not elevated energy expenditure, is the prime determinant of weight loss in HIV-associated wasting. (N Engl J Med 1995;333:83-8.)

WASTING is a major complication of human immunodeficiency virus (HIV) infection, and it makes an important contribution to both the morbidity and the mortality of the disease.<sup>1</sup> Weight loss in patients with HIV infection tends to be periodic, occurring particularly in relation to episodes of secondary infection or gastrointestinal disease.<sup>2</sup> Many factors are likely to be involved in the pathogenesis of wasting.<sup>1</sup> For example, the intake of energy may be compromised by anorexia due to disease or the side effects of drug treatment, by upper gastrointestinal disease<sup>3</sup> and enteropathy, or by gastrointestinal infection that interferes with the absorption of nutrients. In addition, intermediary metabolism is deranged: the oxidation of carbohydrates is suppressed and sensitivity to insulin increased,<sup>4</sup> plasma triglyceride concentrations are increased,<sup>5</sup> and the turnover of protein may be accelerated.<sup>6,7</sup> The net result appears to be that ingested substrates are redirected into fat rather than lean tissue.<sup>8,9</sup>

Whatever the underlying metabolic mechanisms, weight loss must ultimately be the consequence of a negative energy balance. Energy balance equals energy intake minus energy expenditure, but the relative importance of these factors in the energy deficit associated with HIV-related wasting is not known. Several studies have shown increased resting energy expenditure in HIV infection.<sup>1</sup> Despite this, during rapid weight loss in the presence of secondary infection, the

intake of energy rather than its expenditure appeared to be critical in determining energy balance and weight loss.<sup>3</sup>

The true determinant of energy balance, however, is not resting but total energy expenditure; the difference arises primarily from the cost of the energy used in activity. Total energy expenditure is harder to measure than resting energy expenditure, because it requires an extended period of measurement and a method of measurement that does not interfere with usual activity. The doubly-labeled-water technique is a unique tool for the measurement of total energy expenditure in free-living subjects that does not interfere with habitual daily activity.<sup>10-12</sup> In this study, we measured energy metabolism in a group of men with HIV infection at different stages of their disease. Our primary aim was to identify the relative contribution of changes in energy expenditure and intake to the pathogenesis of HIV-related weight loss.

## METHODS

### Subjects

We studied 27 men 28 to 62 years of age (median, 35) recruited from two HIV clinics in London. All tested positive for antibodies to HIV by the enzyme-linked immunosorbent assay and the Western blot assay. At the time of each study, a clinical history and physical examination were performed, and the stage of HIV infection was determined according to the criteria of the Centers for Disease Control and Prevention<sup>13</sup>; height, weight, and skin-fold thickness at four sites were measured to estimate lean body mass,<sup>14</sup> and complete blood counts and CD4 cell counts were performed. The men received nutritional counseling and support and antiretroviral treatment throughout the study period according to our standard protocols.

Total energy expenditure was not measured in a control group, because extensive data on normal subjects have been published. For purposes of comparison, however, resting energy expenditure was measured in 14 normal men 26 to 33 years of age who were well, had stable weight, and were at low risk for HIV infection. The study protocol was approved by the ethics committee of the Wandsworth

From the Division of Infectious Diseases, St. George's Hospital Medical School, London (D.C.M., C.N., G.E.G.); the Department of Genitourinary Medicine, King's Healthcare, London (C.B., T.J.M.); and the Dunn Clinical Nutrition Centre, Cambridge (S.A.J., A.M.P., W.A.C., M.B.S.) — all in the United Kingdom. Address reprint requests to Dr. Macallan at the Division of Infectious Diseases, St. George's Hospital Medical School, London SW17 0RE, United Kingdom.

Supported by the Medical Research Council of the United Kingdom. Dr. Macallan was the recipient of a Medical Research Council Training Fellowship.

District Health Authority, and all the men gave written informed consent.

### Study Protocol

To assess the men with HIV infection during periods of stable weight, weight loss, and weight gain, we asked them to weigh themselves regularly on digital electronic scales throughout the study period. Nine men were studied once, 13 twice, 4 three times, and 1 four times. The rate of weight change at the time of each study of each man was calculated from a plot of the weights recorded before, during, and after the study; each measurement was based on a median of 6 measurements (range, 2 to 36) obtained over a period of 3 months (range, 0.5 to 11). The men were divided into the following four groups, according to the type of weight change measured: rapid weight loss ( $\geq 3$  kg lost per month), slow weight loss ( $< 3$  kg lost per month),<sup>2</sup> stable weight, and weight gain (at least 0.25 kg gained per month).

### Measurement of Energy Balance

Resting energy expenditure was measured by indirect calorimetry with a ventilated hood and a metabolic monitor (Deltatrac, Datex Instrumentarium, Helsinki, Finland). The value obtained for each man was compared with a predicted value calculated from Schofield's equations for normal men<sup>15</sup> and with values in the normal subjects. Total energy expenditure was calculated from the difference between the elimination rate of deuterium, which is lost from the body in water, and that of oxygen-18, which is lost in both water and carbon dioxide. This difference yields a measure of the mean rate of production of carbon dioxide and hence a measure of energy expenditure when standard calorimetric equations are used.<sup>10</sup> To obtain these measurements, the men received a weighed oral dose of approximately 100 g of pyrogen-free water containing 174 mg of oxygen-18 and 70 mg of deuterium per kilogram of body weight. Urine samples were collected before the dose, four hours after the dose, and then daily for 14 days. The levels of the isotopes of deuterium and oxygen-18 in the urine samples were analyzed in duplicate by mass spectrometry (Aqua Sira, Fisons Instruments, Middlewich, Cheshire, United Kingdom). The rate of production of carbon dioxide was calculated from the difference between the elimination-rate constants for deuterium and oxygen-18; the resulting value was multiplied by the heat equivalent of carbon dioxide, assuming a respiratory quotient of 0.85, to give total energy expenditure.<sup>10,12,16</sup> The measurement had an average coefficient of variation of 2.9 percent.<sup>16</sup>

Energy intake was assessed prospectively by recording the weight of the food consumed over a seven-day period; when this was not possible, a seven-day food diary or the man's recall of food consumed during the preceding 24 hours was used. The energy content of the ingested food was calculated from standard tables.<sup>17</sup>

### Statistical Analysis

To compare men of different body sizes, the data were expressed in terms of body mass. Lean body mass was used as the denominator for resting energy expenditure and body weight as the denominator for total energy expenditure, because these gave the closest relations. The line derived by plotting resting energy expenditure against lean body mass intersected the x axis at  $-12.7$  kg; that value was therefore added to the denominator to avoid a mathematical artifact as described elsewhere.<sup>18</sup> No such correction was needed for body weight, because when total energy expenditure was plotted against weight, the intercept did not differ significantly from zero.

Groups were compared by analysis of variance with a post hoc Scheffé's test; when data from more than one study of a single man ap-

peared in a group, a single mean value was used. Linear regression was used to compare measurements of energy with the rate of weight change.

## RESULTS

### Subjects and Clinical Details

Fifty-one studies were performed over periods of up to two years in 27 men with HIV infection. Of these studies, 14 were performed when the men were largely asymptomatic (i.e., with stage II disease), 1 when fever and lymphadenopathy were present (stage III disease) and 36 after the occurrence of an AIDS-defining secondary infection, cancer, or unexplained weight loss (stage IV disease)<sup>13</sup> (Table 1).

Seven measurements were made in six men during episodes of rapid weight loss ( $\geq 3$  kg per month). Four of these measurements were made during proved secondary infections, three involving cytomegalovirus (two cases of colitis and one of pneumonitis) and one involving gastrointestinal cryptosporidiosis. Of the other three measurements made during episodes of rapid weight loss, one was made in a man with an acute febrile illness (no pathogen was isolated) and an allergic drug reaction, and two were made in men with pathogen-negative diarrhea. The seven men studied during episodes of weight gain had all been treated recently for opportunistic infections: cytomegalovirus infection in four and cerebral toxoplasmosis, pulmonary tuberculosis, and *Pneumocystis carinii* pneumonia in the other three; one man was gaining weight despite persistent cryptosporidial diarrhea.

### Resting Energy Expenditure

Resting energy expenditure, as corrected for body mass, was higher by 9.6 percent in the HIV-infected men than in the normal men ( $P=0.002$ ), and the mean

Table 1. Clinical and Anthropometric Measurements and Resting Energy Expenditure in Men with HIV Infection.\*

VARIABLE	NORMAL MEN	MEN WITH HIV INFECTION†		
		ALL	STAGE II	STAGE IV
No. of men	12	27	9	19
No. of studies	12	51	14	36
CD4 cells/mm <sup>3</sup> — median (range)	Not done	20 (0–480)	250 (20–480)	10 (0–167)‡
Weight — kg	73.3 ± 5.4	65.2 ± 11.1§	68.2 ± 10.1	64.2 ± 11.4¶
Lean body mass — kg	61.4 ± 5.1	55.3 ± 8.0	56.9 ± 7.1	54.8 ± 8.4**
Resting energy expenditure — kcal/day				
Absolute no.	1670 ± 150	1700 ± 250	1700 ± 260	1710 ± 250
Per kilogram of lean body mass	27.3 ± 2.0	30.9 ± 3.1††	29.8 ± 1.9	31.4 ± 3.3††
Corrected for lean body mass (per kg + 12.7)	22.8 ± 1.5	25.0 ± 2.3‡‡	24.3 ± 1.8	25.4 ± 2.5‡‡
Percentage of predicted value	94 ± 6	104 ± 10§§	100 ± 9	105 ± 10§§

\*Plus-minus values are means ± SD. Resting energy expenditure is expressed as an absolute value and in terms of lean body mass, as measured anthropometrically; the most valid group comparisons may be made with the values corrected for lean body mass (see the Methods section). Except as otherwise noted, P values are for the comparison with normal men by analysis of variance.

†One man was initially classified as having stage III disease; he was studied then and after his disease progressed to stage IV. Another man who was first studied when he had stage II disease and again when he had stage IV disease is included in both groups.

‡‡P < 0.001 for the comparison with men with stage II infection. There were no other significant differences between these groups.

§P = 0.017.

¶P = 0.031.

||P = 0.014.

\*\*P = 0.037.

††P < 0.001.

‡‡P = 0.002.

§§P = 0.003.

Table 2. Resting and Total Energy Expenditure and Energy Intake in Men with HIV Infection, According to Change in Weight.\*

VARIABLE	RAPID WEIGHT LOSS (≥3 kg/mo)	SLOW WEIGHT LOSS (<3 kg/mo)	STABLE WEIGHT	WEIGHT GAIN (>0.25 kg/mo)	P VALUE†
No. of men	6	15	12	7	—
No. of studies	7	21	16	7	—
CD4 cells/mm <sup>3</sup> — median (range)	10 (0–20)‡	20 (0–250)‡	125 (10–480)	10 (0–167)	<0.001
Weight — kg	64.4±12.5	65.3±10.7	70.5±10.8	59.7±5.5	0.19
Energy expenditure — kcal/day					
Resting	1680±330	1660±220	1750±230	1790±203	0.58
Total	2180±580§	2720±600	3250±510	2750±640	0.007
Activity-related	500±300‡	1050±470	1490±400	960±490	<0.001
Physical-activity level¶	1.3±0.1‡	1.6±0.2	1.9±0.2	1.5±0.2**	<0.001
Energy intake — kcal/day	1330±610‡  ††	2220±510‡‡	2770±460	3300±850	<0.001
Energy balance — kcal/day	−850±580§§	−520±520¶¶	−480±590	+480±320	<0.001

\*Plus-minus values are means ±SD.

†Obtained by an analysis of variance using the F test.

‡P&lt;0.001 for the comparison with men with stable weight. In this and the following footnotes, the P values were obtained by an analysis of variance using the post hoc Scheffé's test.

§P=0.009 for the comparison with men with stable weight.

¶Denotes the ratio of total energy expenditure to resting energy expenditure.

\*\*P=0.035 for the comparison with men with stable weight.

‡‡P=0.006 for the comparison with men with weight gain.

||P=0.005 for the comparison with men with weight gain.

|||P=0.027 for the comparison with men with slow weight loss.

†††P&lt;0.001 for the comparison with men with weight gain.

§§P=0.002 for the comparison with men with weight gain.

|||P=0.01 for the comparison with men with stable weight.

(±SD) energy expenditure was 3.6±10.1 percent higher than the values predicted by Schofield's equations<sup>15</sup> (P=0.007 by the paired Student's t-test) (Table 1). However, there was no significant relation between resting energy expenditure and the rate of weight change (Table 2).

### Total Energy Expenditure and Energy Intake

Total energy expenditure in the HIV-infected men ranged from 1340 to 4040 kcal per day (mean, 2750±670). Total energy expenditure was not measured in the normal men in this study, but mean values of 3420±740 kcal per day have been obtained in normal men 30 to 39 years of age.<sup>19</sup> There was thus no evidence to suggest that total energy expenditure was increased in the men with HIV infection.

When it was expressed per unit of weight to allow

comparisons between groups, total energy expenditure was significantly reduced in the HIV-infected men studied during rapid weight loss (Table 3). There was a positive relation between total energy expenditure and the rate of weight change (Fig. 1A). The men who were losing weight rapidly had the lowest total energy expenditure, whereas those with stable weight or weight gain had higher values. This finding is contrary to what would be expected if an increased expenditure of energy were responsible for the negative energy balance in these subjects.

The reduction in total energy expenditure during weight loss could be attributed primarily to the part of the expenditure that was related to activity. This was demonstrated in terms of both a reduction in the absolute amount of energy attributed to activity (the difference between total and resting energy expenditure)

Table 3. Expenditure, Intake, and Balance of Energy per Kilogram of Total Body Weight in Men with HIV Infection, According to Change in Weight.\*

VARIABLE	RAPID WEIGHT LOSS (≥3 kg/mo)	SLOW WEIGHT LOSS (<3 kg/mo)	STABLE WEIGHT	WEIGHT GAIN (>0.25 kg/mo)	P VALUE†
No. of men	6	15	12	7	—
No. of studies	7	21	16	7	—
Energy expenditure per kilogram — (kcal/day)					
Resting‡	26.2±3.4	25.7±2.5§	25.0±1.8	30.1±2.8¶	0.001
Total	33.4±4.0¶	41.5±5.4	46.3±5.4	46.1±9.0	<0.001
Activity-related	7.2±3.7**††	15.8±5.6	21.2±5.4	16.0±7.4	<0.001
Energy intake per kilogram — kcal/day	20.1±8.2**‡‡§§	34.0±5.4‡‡	39.5±6.2	55.1±11.8¶¶	<0.001
Energy balance per kilogram — kcal/day	−13.3±8.7‡‡	−8.1±7.6¶¶	−6.6±8.0	+8.0±5.2	<0.001

\*Plus-minus values are means ±SD.

†Obtained by an analysis of variance using the F test.

‡Shown for comparison only, because differences between groups may arise from differences in weight, as discussed in the Methods section.

§P=0.006 for the comparison with men with weight gain. This and the following P values were obtained by an analysis of variance using the post hoc Scheffé's test.

¶P=0.002 for the comparison with men with stable weight.

\*\*P&lt;0.001 for the comparison with men with stable weight.

‡‡P&lt;0.001 for the comparison with men with weight gain.

¶¶P=0.002 for the comparison with men with weight gain.

|||P=0.007 for the comparison with men with weight gain.

†††P=0.031 for the comparison with men with slow weight loss.

§§P=0.005 for the comparison with men with slow weight loss.

|||P=0.006 for the comparison with men with stable weight.

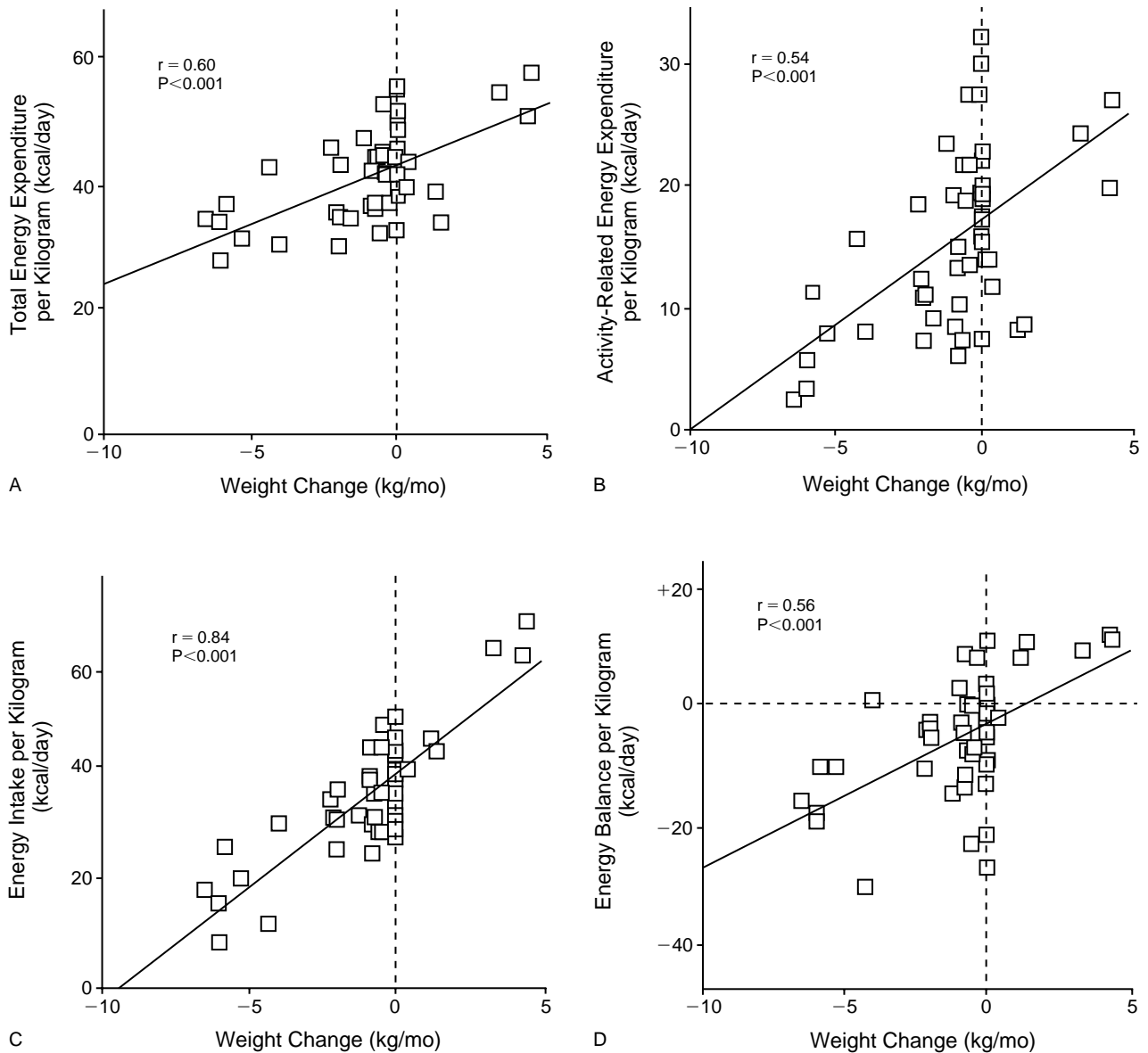


Figure 1. Relation between Measures of Energy Metabolism and the Rate of Change in Weight in Men with HIV Infection.

Panel A shows total energy expenditure, Panel B activity-related energy expenditure, Panel C energy intake from a record of the weight of food consumed, and Panel D the energy balance (intake minus expenditure). All values are expressed per kilogram of total body weight to normalize for body mass.

(Fig. 1B) and a reduced level of physical activity (the ratio of total to resting energy expenditure) in the men losing weight (Table 2).

#### Energy Intake

Complete records of energy intake were obtained for 49 of the 51 studies. One set of records was unusable because the patient had HIV dementia, and one was inadequate; these studies were conducted in the slow-weight-loss and weight-gain groups, respectively. Of the 49 complete records, 38 were based on a seven-day record of the weight of food consumed, 9 on food diaries, and 2 on 24-hour recall. Energy intake was very closely associated with the rate of weight loss (Tables 2

and 3); the relation was positive, with a steeper slope than for total energy expenditure ( $r=0.84$ ,  $P<0.001$ ) (Fig. 1C), so that the reduction in intake in HIV-infected men when they were losing weight exceeded the reduction in total energy expenditure. As a consequence, the calculated energy balance (the difference between expenditure and intake) was negative during weight loss and positive during weight gain, as would be expected from basic thermodynamic considerations (Fig. 1D).

#### DISCUSSION

The results of this study indicate that total energy expenditure is not excessively high in men with HIV in-

fection. Indeed, the values in HIV-infected men with stable weights were similar to or lower than those in normal men.<sup>19,20</sup> Furthermore, when total energy expenditure was related to the rate of weight change, men who were losing weight had lower values for energy expenditure. Thus, increased energy expenditure was not the primary cause of weight loss in these HIV-infected men. The negative energy balance during weight loss must therefore have arisen from a reduction in energy intake. This supposition was confirmed by direct measurement of energy intake, the reduction in which exceeded the reduction in total energy expenditure and was therefore sufficient to account for the expected energy deficit. The men whose weight remained stable were those who could maintain an adequate energy intake, as we reported previously.<sup>21</sup>

In physiologic terms, episodes of rapid weight loss are often associated with secondary infections,<sup>2</sup> which may cause an increase in resting energy expenditure,<sup>3</sup> although no such increase was demonstrated in this study. Episodes of acute infection are also characterized by reduced activity, as is reflected by the large reduction in activity-related energy expenditure during weight loss. Some measurements of total energy expenditure and physical-activity level were very low, representing periods of severe debility or hospitalization. Fatigue and lethargy, very common symptoms in patients with HIV infection, may play a protective part by reducing the consumption of body tissue during episodes of illness, though perhaps at the same time reducing the activity-related stimulation of muscle-protein synthesis. Alterations in diet-induced thermogenesis, the other component of total energy expenditure, may occur but are unlikely to be quantitatively important.

Profound anorexia was common during secondary infections. The anorectic effect of infection is well recognized, but its mechanisms are poorly understood. Cytokines such as tumor necrosis factor may play a part, particularly in hypothalamic centers regulating food intake. Although plasma concentrations of tumor necrosis factor are not consistently increased in patients with HIV infection,<sup>1,5,22</sup> we found raised concentrations in another cohort of men drawn from the same population of HIV-infected men as that studied here.<sup>6</sup>

The contribution of malabsorption to energy balance is difficult to measure. A quantitatively important degree of malabsorption should have been evident as a shift in the curve for energy balance (Fig. 1D), such that when the patient's weight was stable there would be a positive intercept, representing unused energy intake; no such effect was found. Similarly, there was no discrepancy between the negative energy balance measured in the group with slow weight loss, the group most likely to have gastrointestinal disease,<sup>2</sup> and that predicted from the rate of weight change measured. However, care needs to be taken in evaluating data on energy balance, because they represent the small differences between two measured values and because errors in reporting food intake are common.

The finding that total energy expenditure in HIV-infected men is not excessively high and is not increased during weight loss shows that the primary contributor to altered energy balance and thus to weight loss in HIV infection is decreased food intake. However, the prevention of weight loss or the promotion of weight gain and the recovery of body tissue, particularly skeletal muscle, after weight loss may require more than merely adequate energy intake, because energy supplied in the presence of active secondary infection may be preferentially deposited as fat rather than lean tissue.<sup>9</sup> Thus, other interventions — for example, the administration of anabolic agents such as growth hormone — may be beneficial, but HIV-associated wasting can only be managed effectively in the presence of an adequate energy supply.

We are indebted to the nursing staff of McEntee ward, St. George's Hospital, who facilitated this study, and to the men who willingly participated in this investigation.

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