Influence of Whole Body Protein Turnover Rate on Resting Energy Expenditure in Patients with Cancer


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ABSTRACT

Whole body protein turnover and resting energy expenditure are measured simultaneously in weight stable and weight losing patients with lung (n = 22) or colorectal cancer (n = 38). These results were compared with those from weight stable and weight losing non-cancer controls (n = 22). Rates of whole body protein turnover were calculated from the plateau isotopic enrichment of urinary ammonia and urea following a primed, continuous, 24-h infusion of $^{15}$N-glycine. Resting energy expenditure was measured by indirect calorimetry.

All groups of cancer patients had significantly elevated rates of whole body protein turnover ($P < 0.05$) and synthesized, on average, 1.9 g/kg/day more protein compared with weight stable non-cancer controls. In contrast, the resting energy expenditure of cancer patients and controls was similar. Moreover, there was no correlation between individual rates of whole body protein turnover. Thus, although cancer patients had rates of whole body protein turnover which were 50–70% greater than controls, this did not result in a measurable increase in resting energy expenditure. The assumption that elevation of whole body protein turnover or resting energy expenditure causes weight loss in cancer patients must be an oversimplification.

An acute phase protein response was observed in the majority of cancer patients. Although the presence of such an inflammatory response did not correlate with the rate of whole body protein turnover, the role of inflammatory mediators in the pathogenesis of disturbed protein metabolism in cancer patients merits further investigation.

INTRODUCTION

The majority of hospitalized cancer patients are undernourished (1). Furthermore, between 10 and 20% of individuals with malignant disease die as a result of the severe wasting characterized by cancer cachexia (2, 3). Weight loss is caused by a negative energy balance. In cancer patients this could be the result of a decreased food intake, an increased energy expenditure, or a combination of these two. When anorexia is present a decreased food intake is probably the major cause of weight loss (4). However, neither the incidence nor the possible mechanisms of an increased energy expenditure in cancer patients are known (5).

Whole body protein turnover has been estimated to account for between 10 and 20% of basal energy expenditure in man (6). A reduction in the rate of protein turnover is thought to be one of the main methods of energy conservation during periods of reduced food intake (7). It has been suggested that this adaptive mechanism might be impaired in patients with malignant disease (8) and this possibility is supported by observations that in some cancer patients the rate of whole body protein turnover is elevated above normal (9–11). Thus the energy expenditure of the cancer-bearing host might be abnormally high, a situation which could either initiate or worsen a negative energy balance.

However, not all workers have shown that whole body protein turnover is increased in patients with cancer (12, 13). These contradictory results might be explained by the small size and heterogeneity of the groups of patients examined. In addition, few studies have investigated whole body protein turnover and resting energy expenditure measurements made in the same individuals. Thus, the aim of this study was to determine whether rates of whole body protein turnover were increased in patients with cancer and if so whether they are associated with an increased resting energy expenditure and hence weight loss. We have measured whole body protein turnover and resting energy expenditure simultaneously in both weight stable and weight losing patients who had either colorectal or non-small cell bronchial cancer. These results are compared with those from both weight stable and weight losing non-cancer patients.

One possible cause of an increased rate of whole body turnover in cancer patients might be the production of inflammatory mediators in response to neoplasia. The acute phase protein response is a characteristic alteration in the serum concentration of certain circulatory proteins which usually accompanies the body's inflammatory response to injury (14). Such an acute phase protein response can be demonstrated in the majority of individuals with progressive neoplasia (15, 16). Furthermore, in patients with trauma or sepsis there is often a marked acute phase response (14) and whole body protein turnover is increased (17). We have compared the rates of whole body protein turnover in cancer patients with and without an acute phase protein response in order to determine whether an abnormal protein metabolism in patients with cancer is associated with an inflammatory response.

PATIENTS AND METHODS

The percentage weight change from preillness stable weight was used to divide patients into weight stable (±5% weight loss) or weight losing groups (>5% weight loss). This arbitrary division was used to separate those in energy balance from those with a negative energy balance.

Lung Cancer Patients. Twenty patients with histologically proven, inoperable, non-small cell bronchial carcinoma who were either untreated or who had not undergone antineoplastic therapy within the previous 2 months underwent standard staging procedures. Investigations included clinical examination, chest X-ray, bone scan, and hepatic ultrasound or isotope scan. Nine were shown to have stage 2 disease and 11 stage 3 disease according to the WHO classification. Eight were weight stable and 12 were weight losing. Of the weight stable group 5 had stage 2 disease and 3 had stage 3 disease. In the weight losing group there were 4 with stage 2 disease and 8 with stage 3 disease.

Colon Cancer Patients. Thirty-eight patients with newly diagnosed colorectal carcinoma were all studied prior to laparotomy when histological confirmation and staging according to Dukes' classification was carried out. Sixteen patients had stage B disease, 11 stage C, and 10 stage D. Seventeen were weight stable and 21 weight losing. Of the
seventeen stable patients, 10 were stage B, 4 stage C, and 3 stage D. Of the 21 weight losing patients, 7 were stage B, 7 stage C, and 7 stage D.

Non-Cancer Patients. Twenty-two patients with various nonneoplastic diseases who had been admitted to a surgical ward for routine investigations were used as a control group. Eight were weight stable, and 14 were weight losing. The diagnosis of the weight stable individuals were 4 benign polyp of the colon, 2 duodenal ulcer disease, one cholelithiasis, and one benign stricture of the large intestine. The diagnoses of the 14 weight losing individuals were 6 duodenal ulcer, 2 cholelithiasis, 2 benign strictures of small intestine, 2 spastic bowel syndrome, 2 benign polyp of colon, and one cecal diverticulum.

All patients were of performance status 2 or better (WHO Performance Score), had normal adrenal and thyroid function tests and were clinically judged to be free of other metabolic or endocrine disorders. None were pyrexial, had clinical or radiological evidence of infection, were receiving steroids, or were severely anemic.

All patients had a normal serum urea and creatinine and although some patients with hepatic metastases had abnormal liver function tests, none had a bilirubin concentration outside the normal range (3–18 μmol/liter).

The study was approved by the local ethical committee. All patients were informed of the purpose and procedure of the study and all gave informed consent.

Measurement of Whole Body Protein Turnover. Whole body protein turnover was measured by a standard and well described method (18, 19). A primed continuous 24-h infusion of [15N]glycine was administered and the isotopic enrichment of urinary ammonia and urea was measured in urine collected during the second half of the infusion (12–24 h). This collection has been shown to concur with plateau isotopic enrichment of urinary ammonia and urea (20).

Enrichment of a sample taken at 24 h was compared with that from the 12–24-h collection to ensure that isotopic equilibrium had been achieved. No significant difference was determined between the 15N enrichment of the integrated 12–24-h sample and that of the sample taken at 24 h for either urea or ammonia.

Rates of whole body protein turnover were calculated using the stochastic model of Picou and Taylor-Roberts (21). The basic assumption of this model is that in the steady state and at isotopic equilibrium the proportion of isotope excreted in the chosen end product of nitrogen metabolism (ammonia or urea) is equal to the proportion of the nitrogen turnover excreted in that same end product. Nitrogen turnover was calculated using the formula Q = d/E, where Q is nitrogen turnover, D the quantity of isotope infused, and E the isotopic enrichment of the chosen urinary end product.

The assumptions of the stochastic model mean that in the steady stage Q is equal to the rate of protein synthesis (S) plus the rate of nitrogen excretion (E). This also equals the rate of protein breakdown (B) plus the rate of nitrogen intake (I). Thus Q = I + B = S + E. Since this study was performed with patients in the fasting state, the rate of protein turnover is equal to the rate of protein breakdown. Rates of whole body protein synthesis were calculated by subtracting 24-h urinary nitrogen excretion from Q.

Measurement of Resting Energy Expenditure. Measurements of resting energy expenditure were made using an indirect calorimeter with a rigid canopy (22), a sensitive paramagnetic oxygen analyzer (Taylor Servomex Ltd., Crawborough, Sussex, United Kingdom) and an IR rigid canopy (22), a sensitive paramagnetic oxygen analyzer (Taylor Servomex Ltd., Crawborough, Sussex, United Kingdom) and an IR rigid canopy (22), a sensitive paramagnetic oxygen analyzer (Taylor Servomex Ltd., Crawborough, Sussex, United Kingdom), and an IR oxygen analyzer (Grubb Parsons, Ltd., Walkergate, Newcastle-upon-Tyne, United Kingdom). The system provides measurements of VO2 and VCO2 for which the repeatability is ±5% (SEM; 95% confidence limits). The equipment was calibrated frequently using oxygen pure nitrogen, 0.8% carbon dioxide, and air of known barometric pressure. The 80 estimates of VO2 and VCO2 collected during each calorimetry run of 40 min were processed on line by a microprocessor and converted to mean energy production using the formulae of Weir (23).

Resting energy expenditure is expressed in relation to the patients' lean body mass. Lean body mass was derived from the measurement of total body water. Tritiated saline (4 MBq) was injected i.v., and serum samples were obtained 3 and 4 h after injection. During the period of equilibration all urine passed was collected to measure the loss of tritium in urine. Lean body mass was derived from the volume of body water assuming that lean tissue contains 73% water (24).

Experimental Design. Whole body protein turnover and resting energy expenditure were measured during the same 24-h period. On the day prior to study patients ate a standard hospital diet. After an overnight fast, patients remained in bed from the time of waking. The baseline enrichment of 15N in ammonia and urea was obtained from a urine sample taken at 8 a.m. At 9 a.m., a primed, constant 24-h infusion of [15N]glycine was commenced. At this time, the patient's head was positioned in the canopy of the indirect calorimeter. Following a 30-min acclimatization run there was a 10-min break. A 40-min calorimetry run was then undertaken.

During the 24-h infusion patients were allowed free access to water but not to food. The mean priming dose of [15N]glycine was 0.3 mg 15N/kg (99 continuous 24-h infusions at the mean rate of 0.28 mg 15N•kg•24 h•1). The [15N]glycine was dissolved in NaCl (150 mm) and sterilized by microfiltration. During the infusion, urine was collected in 2 consecutive 12-h periods. A further sample was obtained at the end of the 24-h infusion.

Analytical Methods. Urine samples were prepared for mass spectroscopy using a sodium/potassium cationic ion-exchange resin (25). The resin ammonia complex was treated with alkaline hypobromite to liberate molecular nitrogen and 15N abundance measured using a double collector mass spectrometer (V.G. Micromass 602B; V. G. Quadrupoles, Cheshire, United Kingdom) with a precision of 0.0008 atom % excess. All urine was collected in storage cans containing 20 ml of HCl (6 mmol-1) and 8 mg of chlorhexidine gluconate (ICI Ltd., Macclesfield, Cheshire, United Kingdom). Total urinary nitrogen was measured by the microkjeldahl method (26).

Assessment of Acute Phase Protein Status. Serum C-reactive protein was measured in all patients as a marker for the presence of an acute phase protein response (14). Serum taken at the time of the protein turnover study was stored at −80°C until analysis. C-reactive protein was measured by a standard radial immunodiffusion technique using antiserum and standards obtained from Behringwerke AG (Marburg, Lahn, West Germany). The limit of detection of this assay is a C-reactive protein concentration of 5 mg/liter or less. An undetectable concentration of C-reactive protein was considered to indicate that there was no acute phase protein. A concentration of >10 mg/liter was designated as a positive acute phase response (15, 16).

Statistical Analysis. Results were tested for significance by a one way analysis of variance. Individual experimental groups were compared with non-cancer controls using the method described by Dunnett (27).

RESULTS

Of the weight losing patients, those with lung cancer had lost significantly more weight (21%; P < 0.05) than either the colon cancer (14%) or the non-cancer (14%) patients (Table 1). The mean duration of weight loss was similar for all groups. The serum albumin concentration was within the normal range for all patients except for the weight losing lung cancer patients where the concentration (32 ± 2 g/liter) was significantly less than that of the weight stable lung cancer patients (37 ± 1 g/liter; P < 0.05).

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<th>Table I Patient characteristics</th>
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<td>Noncancerous Lung cancer Colon cancer</td>
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<td>Wt (kg)</td>
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<td>% wt loss</td>
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<td>Duration of wt loss (mo)</td>
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<td>Albumin (g/liter)</td>
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* WS, weight stable; WL, weight losing.

† Mean ± SEM.
Whole Body Protein Synthesis Rates. The rates of whole body protein kinetics and urinary nitrogen excretion of weight stable and weight losing lung cancer, colon and non-cancer patients are shown in Table 2. When the isotopic enrichment of urinary ammonia was used to calculate rates of protein synthesis the mean rate in all groups of cancer patients was at least 75% greater than that of weight stable non-cancer controls ($P < 0.05$). However, although the mean rate of protein synthesis in weight losing non-cancer patients was greater than that of weight stable controls this difference was not statistically significant ($0.1 < P > 0.05$). Weight stable and weight losing lung cancer patients had slightly, but not significantly, higher mean rates of protein synthesis compared with weight stable and weight losing colon cancer patients (31 and 16%, respectively). Protein synthesis rates based on the isotopic enrichment of urinary urea were between 25 and 52% greater than those calculated from the isotopic enrichment of urinary ammonia. However, the overall pattern of results was similar to that obtained with ammonia.

Whole Body Protein Degradation Rates. The rates of protein degradation (equivalent to protein turnover; for an explanation see “Patients and Methods”) were all greater than the corresponding rates of protein synthesis since measurements were made with patients in the postabsorptive state (Table 2). The mean rates of protein degradation, based on the isotopic enrichment of urinary ammonia, for all groups of cancer patients were more than 60% greater than those of the weight stable non-cancer controls ($P < 0.05$). However, although the mean rate of protein degradation in weight losing non-cancer patients was greater than that of weight stable controls this difference was not statistically significant ($0.1 < P > 0.05$). Protein degradation was slightly but not significantly higher in weight stable and weight losing lung cancer patients compared with weight stable and weight losing colon cancer patients (27 and 18%, respectively). The mean rates of protein degradation were 16–30% higher when calculated from the isotopic enrichment of urinary urea, but the pattern of results was similar to that obtained with urinary ammonia. Rates of urinary nitrogen excretion were similar in all groups (Table 2).

Resting Energy Expenditure. Table 3 shows the rates of resting energy expenditure and whole body protein turnover expressed with reference to the patients’ lean body mass. There were no significant differences between the rates of resting energy expenditure of the weight stable non-cancer controls and any of the groups examined. The mean rate of whole body protein turnover was significantly greater in lung cancer patients ($P < 0.05$) but not in colon cancer patients or weight losing non-cancer patients when compared with the weight stable controls. There was no correlation between individual rates of whole body protein turnover and rates of resting energy expenditure (Fig. 1). Moreover, there was no correlation between individual rates of protein turnover and the severity of patients’ weight loss (Fig. 2).

Whole Body Protein Kinetics and Stage of Disease. The rates of whole body protein synthesis and degradation of the cancer patients and their stage of disease are shown in Table 4. Although mean rates of whole body protein synthesis and degradation tended to be higher in the colon cancer patients with stage C or D compared with B disease this trend was not statistically significant. Irrespective of stage of disease, patients with bronchial carcinoma had rates of protein synthesis and degradation similar to those of patients with advanced colon cancer (i.e., stage D).

Acute Phase Protein Response. An acute phase protein response was not detected in any of the non-cancer patients. In contrast, an acute phase protein response was detected in the majority of cancer patients (41 of 58). However, there were no statistically significant differences in the rates of whole body protein synthesis or turnover between those with or without an acute phase protein reaction (Table 5).

DISCUSSION

We have demonstrated that patients with lung or colon cancer, whether weight stable or weight losing, tend to have an elevated rate of whole body protein turnover. When whole body protein turnover was expressed with reference to total body weight, patients with either lung or colorectal cancer had turnover rates which were 50–70% higher compared with weight stable non-cancer controls ($P < 0.05$). These elevated rates of whole body protein turnover were not related to altered body composition since the rate of turnover was increased in both weight stable and weight losing cancer patients. When whole body protein turnover was expressed with reference to lean body mass the mean rate in patients with lung cancer was significantly greater than that of weight stable non-cancer controls ($P < 0.05$). However, although the mean rate in colon cancer patients was approximately 50% higher than weight stable non-cancer controls, this difference was not quite significant ($0.1 < P > 0.05$). This suggests that there was a greater elevation of protein turnover in lung cancer patients when compared with colon cancer patients.

Several investigators have suggested that whole body protein turnover increases with advancing stage of disease and percentage weight loss (9, 11, 28). In the present study both the lung and colon cancer patients with weight loss tended to have more advanced disease (see “Patients and Methods”). Furthermore, rates of whole body protein turnover tended to be higher in the colon cancer patients with either lymph node or hepatic metastasis (Table 4). However, rates of protein turnover did not increase with stage of disease in the lung cancer patients (Table 4). Moreover, there was no overall relationship between individual rates of whole body protein turnover and percentage

<table>
<thead>
<tr>
<th>Table 2 Whole body protein kinetics and urinary nitrogen excretion of cancer and non-cancer patients</th>
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<tr>
<td><strong>Enrichment</strong></td>
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<tr>
<td>Protein synthesis</td>
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<tr>
<td>(g protein/kg/day)</td>
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<td>Protein degradation</td>
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<td>(g protein/kg/day)</td>
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<td>Nitrogen excretion</td>
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* WS, weight stable; WL, weight losing.

| **Mean ± SEM.** |

| **Equivalent to protein turnover rates (see “Patients and Methods”).** |

2592
Table 3 Whole body protein turnover and resting energy expenditure of cancer and non-cancer patients

<table>
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<tr>
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<th>Noncancerous</th>
<th>Lung cancer</th>
<th>Colon cancer</th>
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<tr>
<td>Whole body protein turnover (g protein/kg lean body mass/day)</td>
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<tr>
<td>Enrichment of Ammonia</td>
<td>3.05 ± 0.29*</td>
<td>4.27 ± 0.55</td>
<td>5.80 ± 0.90</td>
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<td>4.29 ± 0.49</td>
<td>5.70 ± 0.64</td>
<td>7.10 ± 0.69</td>
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<tr>
<td>Resting energy expenditure (kJ/kg lean body mass/day)</td>
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<td></td>
<td>119 ± 5</td>
<td>118 ± 2</td>
<td>122 ± 7</td>
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<td>129 ± 5</td>
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<td>132 ± 8</td>
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* WS, weight stable; WL, weight losing.

Fig. 1. Whole body protein (P) turnover plotted against resting energy expenditure in cancer patients (•, weight stable; ○, weight losing) and non-cancer patients (□, weight stable; □, weight losing). Whole body protein turnover was calculated from isotopic enrichment of urinary urea and both variables are expressed with reference to the patient’s lean body mass (LBM). K, k; d, day.

Fig. 2. Whole body protein (P) turnover plotted against percentage weight loss. For symbols, see Fig. 1 legend. d, day.

Most previous studies have examined individuals in the postprandial state and have demonstrated an elevated rate of tracer flux in patients with advanced disease (9–11, 28, 29). We have demonstrated that postprandial patients with either colon or lung cancer have an elevated rate of protein turnover irrespective of stage of disease or degree of weight loss. Two studies have suggested that protein turnover is not elevated in the cancer host (12, 13). However, since both studies were performed with patients in the fed state, this may simply indicate that the rate of protein turnover responds to feeding by a smaller amount in cancer patients than in normal individuals (12).

It has been suggested that elevated whole body protein turnover may increase the cancer patient’s energy expenditure and thus initiate or worsen a negative energy balance (11). We were unable to demonstrate a significant difference between the rates of resting energy expenditure of cancer patients and that of the weight stable non-cancer controls (Table 3). Furthermore there was no correlation between the rates of whole body protein turnover and resting energy expenditure for any of the patient groups examined (Fig. 1). Thus, although patients with malignant disease had an elevated rate of whole body protein turnover, this was not associated with a detectable increase in their resting energy expenditure.

An elevated rate of whole body protein turnover was observed in all cancer patients, yet only a proportion lost weight. Therefore, the suggestion that cancer patients lose weight because of an increased rate of resting energy expenditure or whole body protein turnover (10) must be an oversimplification.

The weight stable cancer patients had significantly higher rates of whole body protein turnover than the weight stable non-cancer controls (Table 2). This increase occurred in the absence of trauma or sepsis, the 2 main pathological states normally associated with increased whole body protein flux (17). The rate of protein synthesis in human tumors is approximately the same as that in the tissue of origin (30), and human neoplasms rarely exceed 1% of body mass (31). Thus, it is unlikely that the tumor itself could have caused the observed increase in whole body protein turnover. We decided therefore to investigate whether an inflammatory response by the host might be contributing to accelerated protein flux.

The majority of cancer patients in this study had a positive acute phase protein reaction (Table 5). Although the turnover rates in cancer patients with an acute phase protein response...
Protein kinetics are expressed with reference to the enrichment of ammonia.

Table 4 Whole body protein kinetics and stage of disease

<table>
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<th>Colon cancer</th>
<th>Lung cancer</th>
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<tr>
<td></td>
<td>Stage B</td>
<td>Stage C</td>
</tr>
<tr>
<td>Protein synthesis (g protein/kg/day)</td>
<td>2.97 ± 0.33*</td>
<td>3.11 ± 0.52</td>
</tr>
<tr>
<td>Protein degradation (g protein/kg/day)</td>
<td>3.41 ± 0.32</td>
<td>3.69 ± 0.54</td>
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* Mean ± SEM.

were 20% greater than in those with no response this difference was not significant. However, the possibility that the immune response of the host may participate in the production of some of the metabolic abnormalities of the cancer host is worthy of further investigation.

The rate of protein turnover has been shown to decrease during uncomplicated starvation (10, 32) and it has been proposed that this may be a mechanism of energy conservation. Since anorexia and the associated decreased food intake is a major cause of weight loss in cancer patients (4) it might be expected that protein turnover should decrease with increasing weight loss. The results of this study indicate that in patients with either lung or colorectal cancer there is no correlation between whole body protein turnover and weight loss (Fig. 2). That rates of whole body protein turnover were slightly, but not significantly, higher in weight losing non-cancer patients compared to weight stable controls further demonstrates the lack of a simple relationship between weight loss and whole body protein turnover in disease.

From stoichiometry it can be estimated that the minimum energy required for the synthesis of a gram of protein is about 3.6 kJ (6). Using the isotopic enrichment of urinary urea to calculate rates of protein synthesis, the mean rate of protein synthesis for all cancer patients was 4.6 g protein/kg/day compared with 2.7 g protein/kg/day for controls. This represents an increase of 1.9 g protein/kg/day. Since the mean weight of the patients was about 60 kg, the cancer patients were synthesizing an extra 114 g of protein/day. This extra protein synthesis would require the expenditure of 410 kJ which represents less than 8% of the patients mean resting energy expenditure. A change of this magnitude would be at the limit of detection of the method used to measure resting energy expenditure (see “Materials and Methods”). Moreover, resting energy expenditure can vary between normal individuals by up to 50% (33). Thus, if the above minimum estimates for the energy cost of protein synthesis are correct, we would probably not have detected the expected increase in resting energy expenditure.

That we were unable to detect a small rise in resting energy expenditure is one way to explain why the resting energy expenditure of the cancer patients was not measurably affected by an increased rate of whole body protein turnover. An alternative explanation could be that since resting energy expenditure is the sum of all energy dependent processes in the resting, postabsorptive individual, other energy requiring processes were reduced to compensate for the energy cost of increased protein turnover. It is also possible that although the patients with cancer had an elevated rate tracer flux, this might represent regional changes in protein turnover rather than a uniformly elevated rate of protein turnover in the whole body. It has been demonstrated that protein synthesis can be depressed in skeletal muscle and elevated in the liver of both patients and animals with cancer cachexia (12, 34). Furthermore, the efficiency of energy conversion and of protein synthesis may vary from one tissue to another. Thus, because whole body protein turnover and resting energy expenditure are measurements derived from all tissues of the body it would be wrong to assume that these 2 variables should necessarily change in parallel. It must also be stated that the exact relationship of kinetic parameters measured by tracer amino acid infusion to body protein metabolism remains unclear (35).

REFERENCES

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