Increased Whole-Body Protein Turnover in Sick Children with Newly Diagnosed Leukemia or Lymphoma

C. Lawrence Kien and Bruce M. Camitta

ABSTRACT

Using a single dose, $[^{15}N]$glycine turnover technique, whole body rates of protein synthesis and breakdown were assessed in six healthy children and in eight children with newly diagnosed leukemia (DeWys, W. D. Cancer Res., 42: 721s–726s, 1982) or lymphoma (Baracos, V., Rodemann, H. P., Dinarello, C. A., and Goldberg, A. L. N. Engl. J. Med., 308: 553–558, 1983). Based on excretion of $[^{15}N]$ as urinary ammonia, synthesis (g protein per kg body weight per day) was significantly (p < 0.025) higher in the cancer patients [5.4 ± 1.5 (S.D.)] compared to the controls (3.6 ± 0.9); breakdown was also higher (p < 0.02) in the patients (5.5 ± 1.8) compared to the controls (3.1 ± 1.1). When only the seven patients with leukemia were considered, there also were significant increases in synthesis (5.4 ± 1.6, p < 0.05) and breakdown (5.4 ± 1.9, p < 0.025) compared to controls. Increases in both synthesis and breakdown were also observed in the patients when the protein turnover data were expressed as a function of the rate of creatinine excretion or the calculated lean body mass. We conclude that whole body protein turnover is increased in sick children at the time of diagnosis with some forms of newly diagnosed cancer.

INTRODUCTION

Anorexia, nausea, gastrointestinal dysfunction, and increased energy metabolism may singly or in combination result in negative energy balance and secondarily in protein malnutrition (7, 33). The effects of PEM on ultimate clinical outcome in various forms of neoplasia remain controversial (3). Nevertheless, in individual cancer patients a means must be found to reverse cachexia in order to prevent premature death from the complications of malnutrition.

Since continual synthesis of proteins in all tissues accounts for a major proportion of resting energy requirements (21), increased rates of protein synthesis in neoplastic as well as in normal cells could result in elevated energy requirements in the cancer patient (33). Using nitrogen or amino acid tracer techniques, several investigators have assessed WBPT in patients with cancer (5, 17, 18, 26, 28). Three studies suggested that cancer per se or the relative tumor burden may be associated with increased WBPT (5, 17, 26). Another study (18) demonstrated normal WBPT in untreated patients. The type of cancer, the extent of metastases, complications such as infection and effects of previous surgery, and methodological differences all could interact to affect the measured level of WBPT in an individual patient or type of cancer. Cancer patients who have undergone body compositional changes because of inadequate energy intake, as well as those who are ingesting low protein intakes, may have abnormally low rates of body protein turnover (12, 35). Furthermore, chemotherapy also could affect protein turnover (17, 18). Thus, the rates of synthesis of various body proteins may be increased or decreased, depending on the balance of the effects of cancer, chemotherapy, and secondarily, nutritional status. Unusually low (normal or subnormal) rates of protein turnover could result in more favorable energy balance. However, one might postulate that low rates of protein turnover could result in decreased intercellular recycling of amino acids, which would impair the responses to metabolic stress when increased synthesis of protein in certain tissues may be beneficial (e.g., toxicity from chemotherapy) (1, 31). In the present paper, we describe our initial studies, which suggest that WBPT is increased in pediatric patients at the time of initial diagnosis of leukemia or lymphoma. Further studies are obviously necessary as we continue to explore whether these changes in WBPT are a consequence of cancer per se, steroid treatment, or stress in general.

MATERIALS AND METHODS

Subjects. Newly diagnosed patients with acute lymphocytic leukemia, acute myelocytic leukemia, or non-Hodgkin's lymphoma admitted to Milwaukee Children's Hospital from January to December 1981, were recruited for this study. The results on 8 patients in whom informed consent was obtained and urine collections were complete form the basis for this report. All patients had a history of fever, and 6 had fever during the study. Two of the patients had documented infection: Patient 7 (Staphylococcus aureus bacteremia but not clinical sepsis) and Patient 10 (oticis media with perforation). Three of the patients had documented recent weight loss prior to the study, and 7 had a history of decreased appetite. Five exhibited hepatosplenomegaly. There were 2 patients with serum albumin concentrations less than 3.0 g/dl, and 6 with a level below 3.8 g/dl (lower limit of normal for children in this age group at our hospital). None of the patients had evidence of significant compensated or uncompensated metabolic acidosis; venous pH ranged from 7.37 (CO$_2$: 30.1 mEq/liter) to 7.46, and CO$_2$ from 20.1 (pH 7.48) to 30.1 mEq/liter. Except for Patients 9 and 14, all of them received one oral dose of prednisone during the 12- to 15-hr nitrogen turnover study.

Healthy children served as controls. In 6 of the 9 children studied, the coefficient of variation in daily creatinine excretion was less than 20%, indicating complete urine collections (10); the results in these 6 children are presented below. Besides assessing the comparability of urine creatinine excretion rate on 2 consecutive days, we also assessed the

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[Additional text not included in the natural representation.]
qualitative shape of the isotope excretion curve (urine ammonia) to exclude major problems in urine collection.

**Experimental Design.** Rate of whole-body protein synthesis (S) and rate of whole body protein breakdown (B) were assessed, using a modification of previously described methods (8, 35). All cancer patients were studied in the Chemotherapy Unit of Milwaukee Children's Hospital, and all control subjects were studied at home. A single dose of [15N]glycine (1.0 mg [15N] per kg body weight) (Kor, Inc., Cambridge, Mass.) was administered at approximately 4:30 p.m., followed by the subject's ad libitum evening meal. By beginning the studies at this time it was possible to complete the [15N] turnover study prior to any other chemotherapy except for one dose of prednisone. Children at the time of diagnosis with these cancers (acute lymphocytic leukemia, acute myelocytic leukemia, and lymphoma) are generally ill with systemic signs of these, such as fever. Since the nutritional needs of such children will be a consequence of the entire clinical and metabolic condition, we chose not to exclude from our study the majority of patients who have fever, as well as those with overt evidence of infection. Each voided urine was collected in a separate container and kept refrigerated (controls), frozen (controls), or on ice (patients) prior to transfer to the laboratory freezer. A second 24-hr urine specimen was collected to complete the assessment of average daily creatinine excretion. Food intake of nitrogen and energy was assessed by weighing food offered to the subjects and that offered but not eaten. In this study, we wished to compare WBPT in these patients who normally eat meals to controls similarly fed. Moreover, there was no practical or clinically acceptable way to feed both patients and controls continuously.

**[15N] Turnover Based on Urine Ammonia Enrichment.** The study was originally designed to estimate whole body nitrogen turnover using measurements of [15N] enrichment of urinary ammonia (34, 35). The single-dose, stochastic method has been previously described in detail (35). The model consists of a 2-pool system: a protein pool and a metabolic nitrogen pool (35). Rate of whole body nitrogen flux ($Q$) is defined as the flow of ammonia nitrogen into and out of the metabolic nitrogen pool. The basic assumption is that the proportion of isotopic excreted in an end product ($M$) of nitrogen metabolism (such as ammonia) is the same as the proportion of $Q$ excreted in the same end product. Thus, we assume \( em = d = E_m/Q \) and \( Q = E_m - d = em \), where \( E_m \) equals the rate of excretion of unlabelled nitrogen in the particular end product, \( d \) is the single dose of [15N], and \( em \) is the cumulative excretion of [15N] until the time when the [15N] enrichment of $M$ has decreased to a low, quasi-plateau level. Note that $em$ is really equal to the product of the [15N] enrichment ($s$) of the urine end product and $E_m$, thus, \( Q = d/s \).

Chart 1 depicts a typical change in [15N] excretion with time after a single dose of [15N]. Our subjects were asked to void frequently (every 3 to 4 hr when awake) during the 15 hr following the [15N]glycine dose. The [15N] enrichment of the ammonia in each urine sample voided during this period was measured. In all subjects we observed an initial rapid rise and then fall in [15N] enrichment, followed by a quasi-plateau (Chart 1). As previously reported by others (35), this quasi-plateau usually occurred within 9 to 18 hr after the single dose. Thus, the qualitative aspects of isotope excretion in the cancer patients were not different from that described in subjects without cancer (35).

The rate of whole-body nitrogen flux ($Q$) was calculated from the average enrichment (atoms % excess) of urinary ammonia during the period (flux period) from the time the [15N] was administered until the inflection point when the quasi-plateau in enrichment occurred. This inflection point was determined by inspection. The mean flux period was 15.6 hr in the controls and 13.3 hr in the patients. To the extent that the flux period in the controls related to less frequent voiding and a longer sleeping period, the average enrichment of the ammonia may have been artifactualy slightly lower than it would have been had the flux period been more precisely defined by more frequent sampling. This error would imply that, from the basal $Q$ was artificially higher, not lower in the controls. This error, then, would weaken, not strengthen, our conclusions. At any rate, such small differences in timing would probably not affect the results very much (35).
either source was reacted in a Rittenberg tube with hypobromite to produce molecular nitrogen (36). Using the methods described previously (30), 15N enrichment was assessed by optical emission spectroscopy (Model NOI-5, V.E.B., Statron, DDR; Packer-Becker B.V., Groningen, The Netherlands). Using isotope ratio mass spectrometry (23), the 15N enrichments of ammonium sulfate (or chloride) standards were determined in another laboratory. The 15N enrichment of 8 of these standards was measured along with unknown and control samples on each day that optical emission spectroscopy was performed. One criterion for adequate instrumentation was a linear relationship by inspection and by regression between 15N abundance, determined each time by emission spectroscopy and previously by mass spectrometry. An acceptable equation had a correlation coefficient of greater than 0.99, without evidence of obvious outliers. The range of enrichment encompassed by these standards included all enrichments measured on pooled samples for determination of nitrogen flux. We found the following coefficients of variation (CV) for measurements of 15N abundance (atoms %) on 2 discharge tubes containing the same gas sample: 0.368 (CV = 0.7%); 0.375 (CV = 0.2%); 0.390 (CV = 0.3%); 0.414 (CV = 0.6%); 0.453 (CV = 0.6%); 0.458 (CV = 0.9%); 0.503 (CV = 0.0%); 0.654 (CV = 1.8%); urine urea (CV = 2.4%); and urine ammonia (CV = 0.7%). Our instrument was accurate in predicting the measured (mass spectrometric) determinations of 15N abundance (predicted - observed/observed): unenriched urine urea (+0.008) and unenriched urine ammonia (−0.011).

Total nitrogen content of urine was assessed using Kjeldahl digestion and an automated colorimetric method (25). Ammonia was measured using a modification of the Berthelot reaction (6). Urea nitrogen and creatinine were measured using autoanalyzer methods (16). Lean body mass was calculated from creatinine excretion, as was suggested by Waterlow et al. (35), using previously published data relating urine creatinine excretion to lean body mass (total body potassium measurements) in healthy children (10).

Anthropometry and Statistics. Arm fat area and arm muscle area were calculated, and percentiles were estimated (11). The 2-sample t test, the Wilcoxon test, and linear and rank correlation were assessed (4).

RESULTS

Table 1 indicates that there were no significant differences between the control group and the patient group with respect to various nutritional indices. The ages of the subjects in the control and cancer groups were, respectively, 10.8 ± 4.1 (S.D.) and 7.9 ± 4.3 years (p > 0.05) (Table 2). There was no correlation between individual rates of protein turnover and age.

Protein Turnover Based on 15N Excretion as Urine Ammonia. The results for S and B (g protein per kg per day) in the control subjects are quite similar to the values reported previously (3.9 ± 0.9 and 3.4 ± 0.7, respectively) in similarly aged children studied with a repeated-dose 15N turnover model (Table 2) (22). Table 2 and Chart 2 indicate the 50 to 79% increase in S and B in the cancer patients. Four and 6, respectively, of the patients showed higher rates of S and B than any of the control subjects. When Patient 11 with lymphoma was excluded from the statistical analysis, we still found that the means for S (5.4 ± 1.6) and B (5.4 ± 1.9) were still significantly higher in the leukemia patients, compared to the controls (t test, p values: S, p < 0.05; B, p < 0.025). Synthesis and breakdown also were significantly increased in the cancer patients when the calculations were based on the values for nitrogen excretion and nitrogen intake for the entire 24-hr period after the glycine was administered.

There were 50 to 150% increases in S or B in the cancer patients when the rates were expressed as a function of body...
Increased Protein Turnover in Children with Cancer

Table 2

<table>
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<tr>
<th>Diagnosis</th>
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<th>B (g protein/kg/day)</th>
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Mean ± S.D. 10.8 ± 4.1 3.6 ± 0.9 3.1 ± 1.1

Cancer patients

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<th>Diagnosis</th>
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<th>B (g protein/kg/day)</th>
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Mean ± S.D. 7.9 ± 4.3 5.4 ± 1.5 5.5 ± 1.8

a ALL, acute lymphoblastic leukemia; AML, acute myelocytic leukemia; HL, acute histiocytic lymphoma.
b Controls versus patients: 2-sample t test, p < 0.025; Wilcoxon test, p = 0.05.
c Controls versus patients: f test, p < 0.02; Wilcoxon test, p = 0.02.

Increased protein turnover in children with cancer was significantly higher in the cancer group (4.7 ± 1.5) compared to the healthy control group (2.5 ± 1.0) (p < 0.01 by t test, and p < 0.01 by Wilcoxon test). A 112% increase in B was observed in the cancer group (4.7 ± 1.5 g protein per kg per day) compared to the controls (2.5 ± 1.0 g protein per kg per day) (p < 0.005 by t test, and p < 0.01 by Wilcoxon test).

We did not observe a statistically significant correlation between individual rates of synthesis (or breakdown) measured with the 2 end product methods.

Of more interest were the results obtained by averaging for each subject, nitrogen flux using each of the end products, and then calculating S and B from this "end product average" (Chart 3) (8). The rate of synthesis was significantly higher in the cancer group (7.1 ± 1.4) than in the controls (4.2 ± 0.8) (t test, p < 0.001; Wilcoxon test, p < 0.01; 7 of the 8 cancer patients had higher rates than any of the controls (Chart 3). The rate of breakdown was 100% higher in the cancer patients (7.2 ± 1.1) than in the controls (3.6 ± 1.4) (t test, p < 0.001; Wilcoxon test, p < 0.01) (Chart 3). All cancer patients had higher breakdown rates than the highest control value (5.2) (range, 6.0 to 9.4). The interindividual variation in S and B within each of the 2 groups was lower with the end-product average calculation.

Interrelationships among Ammonia Nitrogen Excretion, Urea Nitrogen Excretion, and Protein Turnover (Calculated from 15N Excretion as Urine Ammonia). The rate of ammonia excretion (g nitrogen per kg per day) was significantly increased in the cancer patients (0.013 ± 0.005) compared to the controls (0.006 ± 0.000) (p < 0.001 by t test; p < 0.01 by Wilcoxon test), and the percentage of total nitrogen excretion as ammonia nitrogen was significantly (p < 0.01 by Wilcoxon test) increased in the cancer group (8.5 ± 6.3%) compared to the controls (3.0 ± 0.8%). However, there were no significant differences between the amounts of urinary nitrogen excreted as ammonia and urea (p > 0.05).

Protein Turnover Calculated from 15N Excretion as Urea or Both Urea and Ammonia. Based on the 15N enrichment of excreted urine urea nitrogen, S (g protein per kg per day) was significantly increased (17%) in the cancer group (4.7 ± 1.5), compared to the healthy control group (2.5 ± 1.0) (p < 0.01 by t test, and p < 0.01 by Wilcoxon test). A 112% increase in B was observed in the cancer group (4.7 ± 1.5 g protein per kg per day) compared to the controls (2.5 ± 1.0 g protein per kg per day) (p < 0.005 by t test, and p < 0.01 by Wilcoxon test).

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the groups in the rate of urea nitrogen excretion expressed either per unit body weight or as a percentage of the total nitrogen excretion.

When studies in controls and patients were considered together, there were several types of correlations seen between the rate of ammonia excretion and indices of protein turnover: (a) there were significant rank correlations between the rate of ammonia nitrogen excretion (g nitrogen per kg per day) and S (g protein per kg per day) \( R = 0.55, p < 0.05 \), B (g protein per kg per day) \( R = 0.77, p < 0.005 \), and \( B - S \) \( R = 0.64, p < 0.02 \); (b) the percentage of total nitrogen excretion as ammonia nitrogen was significantly correlated (ranks) with S \( R = 0.68, p < 0.01 \) and with \( B \) \( R = 0.80, p < 0.001 \). Among the cancer patients only, there was no correlation of ammonia excretion with S or B, suggesting that the above series of correlations between ammonia excretion and protein turnover were due largely to differences between controls and patients.

Protein Turnover in Relation to Nutritional or Clinical Indices. Among the 8 cancer patients there was a considerable variation in protein turnover rates (Table 2). However, in the small group of patients, we did not observe any significant trends between protein turnover rates (S or B) and the following indices of nutritional or clinical status: weight-for-height; muscle area or fat area percentile; serum albumin; peripheral blood blast count; presence of hepatosplenomegaly; type of leukemia; and presence of infection.

DISCUSSION

Rates of whole-body protein synthesis and breakdown were markedly increased in children at the time of diagnosis of leukemia or lymphoma. Since whole-body protein synthesis is an important determinant of resting energy expenditure (21, 37), one might question whether these patients may have had elevated resting energy expenditure, as has been reported in other cancer patients (33). This question is currently being explored in subsequent studies. It is important to consider that leukemia, a systemic disease, could have much different effects on WBPT than localized solid tumors.

Previous studies have shown increased WBPT in adults with non-oat cell bronchogenic carcinoma (17) and combined malnutrition and cancer (26). Others, studying patients with testicular carcinoma (18) and small-cell carcinoma of the lung (28), have found, respectively, normal or abnormally low rates of S and B. WBPT also has been quantitated in adults with colorectal carcinoma, using \([1-\text{14C}]\text{leucine} \) (5), and with the single-dose \([\text{15N}]\text{glycine} \) method (13). In the former study, it was shown that rates of S and B were correlated with the tumor burden, but no controls were reported (5). However, Glass et al. (13) studied patients just before and 12 weeks after resection of colorectal carcinoma and found no significant changes in either S or B, using analyses of \([14N] \) excretion in ammonia, urea, or the average of both end products. Comparing this study with that done previously by the same group in considerably younger, healthy subjects (8), one finds that S in the cancer patients was moderately higher (ammonia) or slightly lower (urea or end product average), and B was lower. As Glass et al. (13) point out, both methodological differences and differences in the severity of the cancer could have accounted for the differences in the 2 studies of cancer patients (5).

It is possible that associated infection, nonspecific stress, and/or corticosteroid treatment caused, in part, the metabolic response to the neoplasm which we observed. However, the significance of our observations may relate, in part, to insight that we may gain into optimal nutritional management. In this regard, energy and protein requirements of these sick patients will relate to all of these and other effects on protein metabolism, and not only to the effects of cancer per se. If energy expenditure as well as protein turnover is increased in these patients, then aggressive nutritional support may be necessary at the time of diagnosis to support protein synthesis and prevent malnutrition (21).

It may be useful in future studies to examine WBPT in other children, acutely ill and stressed with other noncancerous diseases, as additional controls for our studies. Of particular interest and relevance to this point is the recent observation by Baracos et al. (1) that human leukocytic pyrogen, isolated from monocytes, stimulated net skeletal muscle protein degradation in vitro. Perhaps, as they (1) suggest, endogenous pyrogen could be a common mediator for increased skeletal muscle, protein degradation in patients with fever, including those with sepsis, trauma, burns (2), and cancer. Moreover, it is possible that pyrogen could cause increased protein synthesis in the liver (1). We speculate, then, that increased rates of whole-body protein synthesis and breakdown found in our cancer patients may be caused, at least in part, by a "stress hormone" (1), leukocytic pyrogen. Thus, fever and increased WBPT may be caused by the same common mediator, although fever per se may have some effect on skeletal muscle proteolysis (1). Finally, as part of an ongoing study of leukemia, we will examine the relationship between the presence or absence of fever and the level of WBPT.

A major effect of glucocorticoids on muscle is decreased protein synthesis (34). Protein breakdown in skeletal muscle accounts for 20% of the rate of whole-body protein breakdown in burned children (2). In healthy adults, muscle protein synthesis accounts for approximately 50% of the total body rate of protein synthesis (15). Thus, the nonskeletal muscle protein turnover in children contributes to a significant extent to S and B. A review of the observed effects of glucocorticoids on liver protein turnover in animals (31) leads us to consider that glucocorticoid treatment could have caused a net increase in S or B in our patients. However, it is of interest that Motil et al. (24) could not detect effects of corticosteroids on WBPT in a small number of adolescents with Crohn’s disease. Clarification of this question of the effect of steroids may result from future studies of children prior to any treatment.

The average protein intake of the cancer patients, although in an adequate range for healthy children, was lower than that of the controls. Thus, hyperalimentation was not the cause for increased S and B in these cancer patients (14, 23). Based on the anthropometric data, only 2 patients had evidence of PEM, consistent with our previous study, which showed a low incidence of PEM in leukemia patients (20). However, 6 of the 8 patients had hypoalbuminemia without other evidence of liver dysfunction. Thus, protein malnutrition may have been present in these patients who had high, not low, levels of protein turnover; this suggests a metabolic difference between these cancer patients and other nutritionally deprived experimental subjects, such as obese adults on zero protein intakes (12), and malnourished children.

* C. L. Kien, and B. M. Camitta, unpublished data.
ished infants with more severe depletion of body mass (35).

The interpretation of our present studies depends upon the adequacy of the models used to estimate WBPT, since the concept itself is basically defined by the methodology. We have used several modifications of a single-dose $^{15}$N glycine turnover model to estimate WBPT in these children. Our choice of this model was related to our desire to complete nitrogen turnover studies in children with untreated cancer, without the necessity of exposing the children to additional venipunctures. Garlick et al. (12) and Waterlow et al. (35) have clearly shown that the single-dose $^{15}$N glycine-urine ammonia method gives quite valid results relative to the effects of chronic nutritional changes. Only in regard to the effects of acute, overnight fasting (8) have these groups presented any evidence that their urine ammonia model may give disparate results, compared to a model with independent assumptions (e.g., $[1-^{14}$C] leucine). Our application of the model, of course, involved less controlled dietary conditions. The present study, though, was aimed at a comparison to normally fed, healthy children. Since any interpretation of this model depends on standardization of dietary conditions between groups, comparison of our sick patients to healthy controls mandated meal feeding, which also happens to be a usual and acceptable condition for the former group.

Our patients ingested less protein than did the controls. Previous human applications of $^{15}$N turnover models have generally suggested that lower protein intake will be associated with unchanged (14) or lower (12, 23) WBPT, except when the level of protein in the diet is very low (0.4 g/kg/day), in which case there may be a modest (15 to 30%) increase in $S$ or $B$ (29). Infusions (i.v.) of glycine and very high plasma glycine concentrations (7 mg/dl) may be associated with an increased contribution of glycine nitrogen to urinary ammonia nitrogen (27), but such high plasma glycine concentrations would not be found in healthy children.

Our patients were not acidemic, but the increased urinary ammonia excretion suggested that they were responding to increased acid production (acidosis). There was no intergroup difference in how the urine was handled that could explain these results. Increased urine flow in acidic subjects and increased urine hydrogen ion concentration per se may increase the renal ammonia production and the proportion which is subsequently excreted (32). Certainly, some of our cancer patients were being relatively overhydrated to induce a brisk diuresis. If our cancer patients were in a state of mild metabolic acidosis, glycine nitrogen would contribute more to ammonia production than in the normal state (32). Thus, $^{15}$N enrichment of urine ammonia could have been increased by a mechanism independent of protein turnover. On this basis, our protein turnover results in the cancer patients were under-, not overestimates.

After many of our studies were complete, Fern et al. (8), using the single-dose $^{15}$N glycine model, showed that the end product used, urea nitrogen or ammonia nitrogen, will markedly affect the conclusions concerning the response of WBPT to overnight fasting. We did not collect blood for determination of $^{15}$N enrichment of plasma urea. Nevertheless, we felt it would still be of interest to calculate our results, based on urine urea $^{15}$N excretion, even without a correction for $^{15}$N retained in plasma urea. $S$ and $B$ were higher in the patients, regardless of which end product was used.

In summary, using 3 variations of a single-dose $^{15}$N glycine nitrogen turnover technique, we have found markedly elevated rates of WBPT. Methodological validation of our present results would depend upon using a WBPT method with different assumptions. It also will be important to recruit a sufficient number of subjects to be able to determine whether the variations in protein turnover correlated with variations in clinical activity of the cancer, and/or other secondary clinical problems, such as infection. In addition, future studies might address a possible relationship between resting energy expenditure and WBPT.

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