Effect of Systemic Hyperinsulinemia in Cancer Patients

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ABSTRACT

Data defining the isolated effect of insulin on whole body protein and glucose metabolism in cancer patients are limited. Ten normal volunteers (controls), age 55 ± 3 years (mean ± SEM); 8 cancer patients, age 61 ± 3 years, weight loss 2 ± 1% (CANWL); and 8 cancer patients, age 55 ± 2 years, weight loss 18 ± 2% (CAWL), were studied in the postabsorptive state. Whole body leucine kinetics were determined during a baseline and then a study period during which insulin was infused at 1.0 milliunits/kg/min to achieve a high physiological level of 71 ± 6, 83 ± 5, and 64 ± 5 microunits/ml in controls, CANWL, and CAWL, respectively. Whole body net balance equals protein synthesis minus protein breakdown. Glucose disposal (mg/kg/min) is the rate of D30 infusion at steady state.

Glucose disposal of CANWL and CAWL during the study period was significantly (P < 0.05, analysis of variance) less than controls (3.91 ± 0.6 in CANWL, 3.66 ± 1.0 in CAWL, and 5.87 ± 0.6 mg/kg/min in controls), suggesting resistance to insulin with respect to carbohydrate metabolism. Hyperinsulinemia, under euglycemic and near basal amino acid conditions, significantly reversed the negative postabsorptive leucine net balance (P < 0.05, analysis of variance) by decreasing protein breakdown in controls as well as weight-stable and weight-losing cancer patients, suggesting that cancer patients are not resistant to the anticiabatic effect of insulin with respect to whole body protein metabolism.

INTRODUCTION

The syndrome of cancer cachexia is characterized by severe weakness, debilitation, and generalized host wasting (1). This malnourished state is associated with decreased survival (2), and in up to one-half of cancer patients cancer cachexia has been implicated as the sole cause of death (3). The etiology of this syndrome is multifactorial in nature, and while decreased nutrient intake is partly responsible, a major contribution comes from the well described abnormalities in host intermediary metabolism of carbohydrate, protein, and fat (4). Reports documenting abnormal peripheral glucose disposal (5), gluconeogenesis (6), and whole body glucose turnover (7) confirm alterations in carbohydrate metabolism in these patients. Abnormalities of protein metabolism have been reported at the whole body level (8, 9) as well as in skeletal muscle (9) and liver proteins (9). Fat metabolism is also modified as evidenced by abnormal host lipid stores (10), and free fatty acid and glycerol turnover rates (11, 12). The cachectic cancer patient ineffectively utilizes nutrients and furthermore seems to be unable to adapt to the malnourished state as normal humans do by conserving lean body mass (13). With the advent of TPN, the ability to provide adequate nutrient intake in debilitated cancer patients was made possible. However, nutritional support to improve the clinical outcome in this group of patients has not been associated with a survival benefit (4, 14). Part of the explanation for the lack of success with standard nutritional support may lie in the failure of the current nutritional regimens to completely reverse the abnormalities of intermediary metabolism.

A well documented abnormality of metabolism in cancer patients is resistance to insulin with respect to carbohydrate metabolism (15, 16). These studies documented decreased uptake of glucose in peripheral tissues and in the whole body under the influence of insulin. However, data examining the response of cancer patients to insulin with respect to protein metabolism are limited. This is potentially important for 2 reasons. (a) Resistance to the well described anticiabatic actions of insulin (17, 18) could be a partial etiology for the increased catabolism of protein stores, which has been previously documented in cancer patients (8, 9). (b) Resistance to insulin with regard to protein metabolism could be responsible for lack of demonstrable survival benefit in patients supported by TPN. The present study was undertaken to examine the isolated effects of hyperinsulinemia under euglycemic conditions with near basal amino acid levels on protein and glucose metabolism in weight-stable and weight-losing cancer patients.

MATERIALS AND METHODS

Subjects. Cancer patients were selected based on a histological diagnosis of cancer, with or without the presence of weight loss at the time of presentation. These patients were selected from the Surgical Service of the Memorial Sloan-Kettering Cancer Center. All were preoperative surgical patients studied before any surgical, radio-, or nutritional therapy except one patient who was studied 6 months after the last dose of a chemotherapy regimen. Cancer patients were divided into 2 groups based on weight loss greater or less than 10% of premorbid weight during the 6 months before diagnosis.

The control group consisted of 10 normal, healthy, weight-stable volunteers within 15% of their ideal body weight (19). Both cancer patients and controls were studied in the postabsorptive state after a 10–12-h overnight fast. Informed written consent was obtained before any testing, and all studies were carried out in the Adult Day Hospital of the Memorial Sloan-Kettering Cancer Center at rest in the supine position under an Institutional Review Board-approved protocol. These subjects had no history of systemic illness, hypertension, ischemic heart disease, or diabetes mellitus. None was taking medication known to alter protein or glucose metabolism. Subjects consumed their usual diet for the 3 days before study. A 24-h urine collection was completed before study that was analyzed for total creatinine. Demographic and nutritional indices of the cancer patients and volunteers are listed in Tables 1 and 2.

Isotopes and Infusates. 1-[1-14C]Leucine (50 μCi/mm) and [4-14C]-HCO3 (250 μCi/mm) were obtained from Dupont (Boston, MA). 1-[1-14C]Leucine was diluted in normal saline to a final concentration of 0.56 μCi/ml. [4-14C]HCO3 was also diluted in normal saline to a final concentration of 0.9 μCi/ml. All tracers were filtered through a 0.2-μm sterilizing filter (Acrodisc; Gelman Sciences, Ann Arbor, MI) before infusion. The insulin infusate was composed of 100 ml of sterile normal saline, 2 ml of the subject’s plasma, and 31 units of regular Humulin (Lilly and Co., Indianapolis, IN) for a final concentration of 77 μU/ml. Insulin was infused at 0.56 nCi/ml. [1-14C]HCO3 was also diluted in normal saline to a final concentration of 0.9 μCi/ml. All tracers were filtered through a 0.2-μm sterilizing filter (Acrodisc; Gelman Sciences, Ann Arbor, MI) before infusion. The insulin infusate was composed of 100 ml of sterile normal saline, 2 ml of the subject’s plasma, and 31 units of regular Humulin (Lilly and Co., Indianapolis, IN) for a final concentration of 300 milliunits/ml. The amino acid infusate was 10% Trasvalos without electrolytes (Travenol Laboratories, Deerfield, IL), which contains (in mg/100 ml) 730 leucine, 600 isoleucine, 580 lysine, 580 valine, 560...
phénylalanine, 480 histidine, 420 threonine, 400 methionine, 180 tryptophan, 2070 alanine, 1150 arginine, 1030 glycine, 680 proline, 500 serine, and 40 tyrosine. The exogenous glucose infusion was 30% dextrose (Abbott Laboratories, North Chicago, IL).

Experimental Protocol. The experiment was divided into 2 parts: the basal postabsorptive state, which consisted of a 120-min equilibrium period (−165 to −45 min) and a subsequent sampling period of 45 min (−45 to 0 min) immediately followed by a euglycemic, hyperinsulinemic, near basal amino acid period consisting of another 120-min equilibrium period (0−120 min) followed by a second sampling period of 45 min (120−165 min) (Fig 1). During the study period, a 10% amino acid solution was administered to achieve near basal leucine levels (euleucinemia) because of the putative regulatory effect of leucine on protein turnover (20).

On the morning of study, 2 18-gauge catheters (Deseret, Sandy, UT) were inserted into peripheral forearm veins in one arm for infusion of tracers, glucose, insulin, and amino acids. After documentation of adequate collateral hand blood flow, the radial artery of the same arm was cannulated with a 20-gauge catheter (Deseret) under local anesthesia for sampling of arterial blood. In the opposite arm, a 2-in 18-gauge polyethylene catheter was inserted retrograde in a deep antecubital vein to sample the venous effluent of the forearm muscle bed. Reasonable assurance that a deep vein was cannulated was obtained by the inability to palpate the tip of the catheter after placement.

At −165 min, a primed continuous infusion of L-1-(14C)-leucine (bolus 16 μCi, continuous infusion 0.16 μCi/min) was started. In addition, 14C-labeled sodium bicarbonate was given as a bolus of 3.6 μCi to prime the bicarbonate pool (21). After the 2-h equilibration period, arterial blood was drawn at 1-h intervals for glucose, physiological amino acid, and insulin concentrations, as well as for the determination of L-1-[1-14C]leucine and 14C-labeled KIC specific activities. Expired gas was collected in Douglas bags using a Rudolph mask for 5 min twice during the sampling period for determination of total CO2 production. The specific activity of expired 14CO2 was determined 4 times during the sampling period by the amount of radioactivity collected in a hyamine solution designed to trap 1 mmol of carbon dioxide (22).

Upon completion of the baseline measurements, a primed continuous infusion of insulin (bolus = 400 milliunits/m2, continuous infusion of 1 milliunit/kg/min) and a continuous infusion of 10% Trasavol amino acid solution without electrolytes were started. The rate of amino acid infusion was 0.011 ml/kg/min (the rate of leucine infusion was 0.65 μmol/kg/min). These infusion rates were selected to achieve and maintain a high physiological insulin concentration of approximately 80 microunits/ml and euleucinemia based upon our own data (23) and the work of others (24). Euglycemia was maintained with a 30% dextrose infusion. The arterial glucose was measured at the bedside at 5- to 10-min intervals, and the dextrose infusion rate was adjusted accordingly. Endogenous glucose production under the influence of insulin at this level has been demonstrated to be completely suppressed in similar control and cancer patients (25) during the equilibration period, therefore the rate of exogenous glucose infusion to maintain euglycemia at steady state was used to determine the rate of whole body glucose uptake.

After a 2-h euglycemic, hyperinsulinemic, euleucinemic equilibration period, arterial and expired gas samples were collected at 15-min intervals for 45 min for determination of the same parameters as in the baseline period. At the termination of the study period, the isotope, amino acid, and insulin infusions were discontinued, and the glucose infusion was maintained for 30−45 min to avoid rebound hypoglycemia.

Analytical Methods. Arterial blood samples were obtained and allocated into appropriate tubes (Becton Dickinson, Rutherford, NJ) and immediately placed on ice. Arterial blood for immunoreactive insulin determination was collected in plain tubes, centrifuged, and immediately frozen for subsequent analysis by radioimmunoassay (Autopak, Micromedics, Horsham, PA). Arterial blood for immunoreactive glucagon determination was collected into Na-EDTA tubes with 1000 kallikrein inhibitor units of aprotinin (Trasylol; FBA Pharmaceutical, New York, NY), centrifuged, and frozen for later analysis by standard radioimmunoassay (26) (Diabetic Core Center, Philadelphia, PA). A sub aliquot of arterial blood was used for determination of glucose concentrations at the bedside (Glucose Analyzer 2; Beckman Instruments, Fullerton, CA). The rest of the blood was collected into tubes containing sodium heparin. After centrifugation, an aliquot of plasma was immediately deproteinized using 50 μl of 50% sulfosalicylic acid/ml of plasma and then frozen at −80°C until extraction of KIC (27) and subsequent determination of the plasma concentration and specific activity. The KIC was separated from 3 ml of plasma and the plasma concentration determined by high performance liquid chromatography using an internal standard (Series 4 Perkin-Elmer, Stamford, CT) with fraction collection. Immediately after collection of the KIC peak, 500 μl were used to determine radioactivity using a liquid scintillation counter (Minaxi Tricarb; Packard Instrument Co., Chicago, IL), and 200 μl of the remaining collected peak were re-injected for determination of the concentration used in the calculation of the specific activities. The remaining plasma was used for determination of amino acid profiles using ion exchange chromatography and post column ninhydrin derivatization (Pickering Laboratories, Mountainview, CA). The average percent recovery of KIC was 85% in known standards made in the laboratory.

The percent CO2 in expired air was determined by gas analysis (Medical Gas Analyzer 1100; Perkin-Elmer, Stamford, CT). The volume of expired air in the Douglas bag was determined by the evacuation time with a calibrated pump. Hydroxide of 10X Hyamine (1 ml) in absolute ethanol (2 ml) with phenolphthalein indicator was used to collect 1 mmol of CO2 for liquid scintillation counting (22).

Procedures. Skinfold were measured at 4 classic sites (biceps, triceps, subscapular, and iliac crest) using skinfold calipers (Lange Calipers, Cambridge, MD). By using regression equations that relate skinfold measurements to underwater weight (28), the percent total body fat was estimated. Skinfold measurements were performed by a single investigator to minimize variability.

Calculations. In all calculations, the values from each period were averaged to provide one value per period per subject.

Whole Body Leucine Kinetics. Whole body leucine flux was calculated using a stochastic model for protein metabolism. This analysis

Table 1 Demographics

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Gender (M:F)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controla</td>
<td>53 ± 3</td>
<td>5:5</td>
</tr>
<tr>
<td>CANWLc</td>
<td>61 ± 3</td>
<td>6:2</td>
</tr>
</tbody>
</table>

* a n = 10.  b Mean ± SE.  * CANWL is the weight loss <10% (n = 8).  dCAWL is the weight loss ≥10% (n = 8).

Table 2 Nutritional indices

<table>
<thead>
<tr>
<th>% IBW (%)</th>
<th>Wt loss (%)</th>
<th>Albumin (mg/dl)</th>
<th>Cr/Ht* (mg/cm)</th>
<th>% fat (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controla</td>
<td>106 ± 3'</td>
<td>4.4 ± 0.1</td>
<td>6.8 ± 0.4</td>
<td>29 ± 2</td>
</tr>
<tr>
<td>CANWLc</td>
<td>103 ± 2</td>
<td>2 ± 1</td>
<td>4.3 ± 0.1</td>
<td>9.4 ± 1.1</td>
</tr>
<tr>
<td>CAWLd</td>
<td>100 ± 5</td>
<td>18 ± 2'</td>
<td>3.9 ± 0.2</td>
<td>6.2 ± 0.7</td>
</tr>
</tbody>
</table>

* a Cr/Ht, urinary creatinine excretion divided by the height.  b Mean ± SE.  c CANWL is the weight loss <10% (n = 8).  d CAWL is the weight loss ≥10% (n = 8).  * Significance versus that of control.
assumes near steady state conditions (29). Using this model, total leucine turnover or flux (Q) equals

\[ Q = R_d + Ox = R_a + I \]

where \( R_d \) equals the rate of leucine incorporation into protein, \( Ox \) equals the rate of leucine oxidation, \( R_a \) (endogenous leucine rate of appearance) equals the rate of leucine released from protein, and \( I \) equals the rate of exogenous leucine input (\( \mu \)mol/g/kg/min). The exogenous leucine infusion was determined from the rate of infusion of amino acids. The rate of leucine turnover (\( Q \)) is calculated as:

\[ Q = F/KIC SA \]

where \( F \) is the infusion rate of L-[l-14C]leucine (dpm/kg/min), and KIC SA (dpm/mol) is the specific activity of KIC in the plasma compartment under equilibrium conditions. KIC is the transaminated ketoacid of leucine, and measurement of its plasma specific activity is believed to be a more accurate assessment of the specific activity of leucine in the precursor pool for protein flux and oxidation (30, 31). By using L-[l-14C]-labeled KIC "reciprocal pool" kinetics, one accounts for the incomplete recovery of labeled 14C carbon dioxide from the bicarbonate pool (21).

The leucine oxidation rate (\( Ox \)) was calculated as:

\[ Ox = E/(K \times KIC \ SA) \]

where \( E \) equals the rate of appearance of 14CO2 in the expired air (dpm/min), and \( K \) represents a correction factor (0.81) that corrects for the incomplete recovery of labeled 14C carbon dioxide from the bicarbonate pool (21).

An estimate of the rate of leucine incorporation into protein (\( R_a \)) was calculated as:

\[ R_a = Q - Ox \]

The rate of leucine release into plasma space from protein degradation (\( R_d \)) was calculated as:

\[ R_d = Q - I \]

The net balance of leucine into or out of protein was calculated as the difference between the \( R_d \) and \( R_a \).

Statistics. All data are presented as mean ± SEM. Statistical analysis was performed by using an analysis of variance or a Student’s t test where appropriate. Statistical significance was defined as \( P < 0.05 \).

RESULTS

Demographics and Nutritional Indices. Cancer patients in both groups had a greater prevalence of males than females compared to control subjects. Those with weight loss <10% of premorbid weight were slightly but significantly older than controls, and tended to have localized disease. This group was comprised of lung and gastrointestinal diagnosis, whereas the group with weight loss greater than 10% of premorbid weight was solely comprised of gastrointestinal tumors (Table 1).

Neither group of cancer patients had statistically significant differences in any of the nutritional indices measured including serum albumin, creatinine/height ratio, or percent of ideal body weight (Table 2) when compared to controls or each other.

Hormonal Profile and Glucose Disposal. Baseline postabsorptive insulin concentrations in both cancer groups were within the normal range and were not significantly different from control levels. Euglycemia was maintained during the study period in each group with a coefficient of variation of the glucose clamps of 8 ± 1% in each group.

During the study period, both groups of cancer patients had significantly decreased whole body glucose disposal when compared to controls, and there was no difference between CANWL and CAWL.

Arterial Amino Acid Concentrations, L-[l-14C]Leucine Infusion, and KIC Specific Activities. The baseline leucine levels in both groups of cancer patients were not significantly different from control levels, and euleucinemia with near basal amino acid levels was maintained during the study period in all groups (Table 4). Total arterial amino acids were not different during the baseline period in either of the cancer groups from the control group, and each groups’ total arterial amino acids increased by approximately 30% during the study period, mostly due to the large concentration of glycine and alanine in the amino acid solution (Table 4). Isotopic steady state was achieved for KIC during both the baseline and study period in all groups as depicted in Fig. 2. The average L-[l-14C]leucine infusion during the experiment was 13.3 ± 0.2, 13.8 ± 0.2 dpm/\( \mu \)mol in controls, CANWL, and CAWL, respectively (\( P = NS \)).

Baseline Leucine \( R_d \), Oxidation and \( R_d \), and Response to Euglycemic, Euleucinemic, Systemic Hyperinsulinemia. Baseline leucine \( R_d \) was 2.18 ± 0.06, 2.29 ± 0.17, and 2.41 ± 0.14 \( \mu \)mol/kg/min in C, CANWL, and CAWL, respectively, which were not significantly different from each other and in response to systemic hyperinsulinemia each significantly decreased (\( P < 0.05 \) analysis of variance) to 1.87 ± 0.10, 1.88 ± 0.15, and 2.05 ± 0.13 \( \mu \)mol/kg/min, respectively (Fig. 3a). Baseline oxidation of leucine was 0.34 ± 0.03, 0.31 ± 0.03, and 0.31 ± 0.04 \( \mu \)mol/kg/min in C, CANWL, and CAWL, respectively, which were also not different from each other and in response to systemic hyperinsulinemia significantly increased (\( P < 0.05 \)) to 0.51 ± 0.04, 0.54 ± 0.03, and 0.51 ± 0.05 \( \mu \)mol/kg/min, respectively (Fig. 3b).

Baseline leucine \( R_d \) was 1.84 ± 0.06, 1.98 ± 0.16, and 2.11 ± 0.15 \( \mu \)mol/kg/min in C, CANWL, and CAWL, respectively, and in response to systemic hyperinsulinemia did not significantly change 1.95 ± 0.08, 1.93 ± 0.14, and 2.13 ± 0.15 \( \mu \)mol/kg/min, respectively (Fig. 3c). The whole

| Table 4 | Arterial leucine, total arterial amino acid concentration, and KIC specific activity |
|-----------------|----------------|----------------|----------------|
|                 | Period         | Leucine (\( \mu \)mol/liter) | TAA (\( \mu \)mol/liter) | KIC SA (dpm/mol) |
| Control \( ^a \) | Baseline       | 116 ± 6\( ^b \) | 1521 ± 155 | 2638 ± 134 |
|                 | Study          | 111 ± 7       | 2084 ± 218\( ^c \) | 2386 ± 148 |
| CANWL \( ^e \)  | Baseline       | 130 ± 7       | 1722 ± 105 | 2446 ± 234 |
|                 | Study          | 131 ± 8       | 2276 ± 143\( ^d \) | 2245 ± 191 |
| CAWL \( ^c \)   | Baseline       | 123 ± 13      | 1693 ± 112 | 2573 ± 277 |
|                 | Study          | 118 ± 11      | 2221 ± 137\( ^f \) | 2327 ± 143 |

\( ^a \) TAA, total arterial amino acids; SA, specific activity.

\( ^b \) \( n = 10 \).

\( ^c \) Mean ± SE.

\( ^d \) Significance versus baseline.

\( ^e \) CANWL is weight loss <10% (\( n = 8 \)).

\( ^f \) CAWL is weight loss ≥10% (\( n = 8 \)).
Increased rate of whole body protein turnover, increased liver protein synthesis, and decreased muscle protein synthesis (37). Exogenous insulin in the same model has also been shown to decrease carcass weight loss in cachectic animals (38).

In patients with cancer, the existence of abnormal rates of whole body protein synthesis and degradation are not as well established. Most have reported these rates to be elevated compared to postabsorptive normal humans (39), starved normal humans (8), and malnourished benign disease patients (8). However, others have reported no difference compared to postabsorptive humans (40).

The rates of catabolism and synthesis in the present study were approximately 10% elevated in the weight-losing group compared to controls. Prior work has shown that a normal adaptation to a chronically starved state would be to decrease protein turnover and conserve nitrogen (8, 41), therefore no decrease in the rate of catabolism and synthesis in the face of weight loss probably represents a maladaptation in itself. Our body net balance of leucine reversed from a net negative value to positive during euglycemic, euleucinemic, hyperinsulinemia primarily by the $R_a$ decreasing below the $R_d$ in both cancer groups, as was also seen in controls (Fig. 4).

DISCUSSION

It is widely accepted that cancer patients have abnormalities of intermediary metabolism. This study has documented that preoperative cancer patients who display insulin resistance with respect to glucose metabolism are not resistant to the antictabolistic effect of insulin with respect to whole body protein metabolism.

In normal humans, insulin causes a decrease in hepatic endogenous glucose production and a stimulation of glucose uptake and storage (32). Resistance to insulin, with respect to both hepatic and peripheral glucose metabolism, can be seen in patients with adult onset diabetes mellitus (33), and this results in hepatic overproduction in the fasting state and decreased uptake of glucose in the fed state. Exogenous insulin administration has been shown to reverse these alterations and restore glucose processing in insulin-dependent and non-insulin-dependent diabetes (34). Although there are reports of glucose intolerance (5) and variable insulin sensitivity in cancer patients, there are little data on the nature and mechanism of this tissue insensitivity to insulin. Prior work from our laboratory in weight-losing cancer patients have documented that the endogenous glucose production is reduced to zero at the levels of serum insulin achieved in this study (25), therefore the rate of glucose infusion is probably a good measure of whole body glucose disposal in these controls and cancer patients. A state of insulin resistance with respect to glucose metabolism was demonstrated by the decreased rate of glucose infusion in both cancer groups under similar plasma insulin concentrations.

Clinically, the abnormalities of protein metabolism in cancer patients include decreased plasma proteins, and visceral organ and skeletal muscle atrophy (35). In the tumor-bearing rat, chronic protein malnutrition causes accelerated loss of carcass weight without effect on the growth of the tumor (36), whereas the normal non-tumor-bearing animal put under similar conditions of malnutrition would adapt and conserve nitrogen. This suggests that the tumor will continue to grow at the expense of the host, and is not under the same nutritional constraints as the host. Further investigations using this model with the addition of protein kinetic measurements found that there was an
laboratory has previously demonstrated increased rates of synthesis and degradation in cachectic cancer patients (8) as well as by others (9). Most of the patients in the present study who had significant weight loss were not cachectic subjectively or by the nutritional indices measured (Table 2), and this may explain the lack of difference observed between controls and cancer patients in the baseline state.

Insulin is a potent regulator of protein turnover. In vitro, insulin decreases protein breakdown and increases muscle protein synthesis (42). In normal humans, the in vivo study of insulin is more complicated. Systemic euglycemic insulin infusion invariably induces a dose-dependent reduction in plasma amino acid levels, with the branched chain amino acids being the most significantly affected (43). This decrease in plasma amino acid concentrations may cause intracellular depletion of substrate for protein synthesis, and therefore the full effect of insulin cannot be determined under these conditions. Prior studies using leucine kinetics (18, 24) maintained euleucinemia, near basal amino acid levels, and normal glucose concentrations and demonstrated that high physiological insulin markedly decreased whole body protein degradation without significantly affecting synthesis in normal humans, thus confirming that euleucinemia and near basal amino acids allow insulin to act fully as an antitobolite without affecting ongoing protein synthesis. The present study has documented that cancer patients who were resistant to the effect of insulin with respect to whole body glucose disposal were not resistant to the antitobolite effects of insulin on whole body protein turnover. This work defines a possible avenue of treatment that needs study in controlled trials to determine possible benefit for the pre- and/or postoperative cachectic cancer patient.

ACKNOWLEDGMENTS

The authors wish to acknowledge the expert technical support of Bruce Ng and Charles Ahrens and the direction of Nada Vydelingum, Ph.D. We would also like to thank Warren Heston, Ph.D.; Michael Burt, M.D., Ph.D.; and the members of the Surgical Metabolism Laboratory, from this country and abroad, whose advice and help made this study possible.

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