The Inefficiency of Total Parenteral Nutrition to Stimulate Protein Synthesis in Moderately Malnourished Patients

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The acute whole-body and peripheral tissue protein response to total parenteral nutrition (TPN) was evaluated before surgery in moderately malnourished patients with stable disease. A primed constant infusion of (U-^{14}C) tyrosine was used in combination with simultaneous measurements of the leg exchange of amino acids, glucose, glycerol, and free fatty acids (FFA). Energy expenditure was measured by indirect calorimetry. Sixteen patients with stable disease and in need of nutritional support were randomized to receive TPN at rates either corresponding to resting requirements (nonprotein calories at 120% of REE with 0.2 g of N/kg/d) or at increased rates (200% of REE with 0.33 g of N/kg/d). Energy expenditure was not affected by the low rate of TPN, but increased with the high rate, with a thermic effect corresponding to 16% of basal levels. Tyrosine flux and incorporation rate into whole-body proteins (protein synthesis) were not altered by the low TPN rate, but increased with the high rate. Estimates of protein breakdown decreased, and tyrosine oxidation increased significantly with both rates of TPN. Protein synthesis was stimulated at the high dose rate only. However, a positive whole-body tyrosine balance (net protein synthesis) measured by the ^{14}C tyrosine technique was associated with a continued negative tyrosine balance across the skeletal muscle compartment in the leg. The results demonstrate that TPN given at rates corresponding to resting needs of 0.2 g of N/kg/day is insufficient to promote protein synthesis in the majority of body proteins. Skeletal muscles may remain in negative protein balance even at high TPN loads. Our results reflect the difficulties of expanding lean body mass through intravenous nutrition in moderately malnourished patients—even those with stable disease.

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WE HAVE OBSERVED THAT a considerable number of patients receiving intravenous nutrition or nasogastric tube-feeding remain in negative amino acid balance, even while in the fed state.[1] This has been particularly obvious whenever the amino acid balance has been measured across peripheral tissues.[2] Such an inefficient therapy may be due to either the underlying disease or an inadequate treatment. We have speculated that a lack in the overall initiation of whole body protein synthesis in response to clinical nutrition may, in part, be explained by the recent medical practice of decreasing both calorie and protein prescriptions, particularly with regard to intravenous (I.V.) nutrition. Our theory is that this recent practice may lead to a situation in which changes in plasma levels of substrates and hormones will be too small to effectively trigger an overall initiation of the whole body protein synthesis. Therefore, in order to test this theory, we have measured whole body protein kinetics by infusing patients with stable disease with (U-^{14}C) tyrosine in combination with simultaneous measurements of flux of amino acids across the leg. In the patients with a nitrogen intake of 0.2 or 0.33 g of N/kg/day respectively, total parenteral nutrition (TPN) was given at rates corresponding to either 1.2 or 2.0 times the resting requirements of nonprotein calories. The results demonstrate that I.V. nutrition at rates close to those of resting needs improves overall protein balance by inhibiting protein breakdown only, whereas much higher infusion rates are needed to induce net whole-body protein synthesis, although protein balance in skeletal muscles may remain negative even in the presence of a net whole-body protein synthesis.

Material and Methods

Patients

Sixteen patients (four women and 12 men) with varying diagnoses and nutritional status, but with stable dis-

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TABLE 1. *Nutritonal Status in the Two Groups of Patients Randomized to Receive Different Levels of TPN. (mean ± SEM)*

	Nutritional Therapy	
	120% of REE 0.2 g of N/kg	200% REE 0.33 g of N/kg
Age (years)	67 ± 3	69 ± 3
Body weight (kg)	62.4 ± 2.7	65.3 ± 4.5
Arm muscle circumference (cm)	23.3 ± 0.9	23.2 ± 1.3
S-albumin (g/l)	31.3 ± 1.6	34.6 ± 1.4
Total body potassium (mmol)	2847 ± 163	2870 ± 295

(REE = resting energy expenditure).

ease, were studied in a surgical ward. Mean values of age and nutritional variables are presented in Table 1. All but two patients were studied before surgery. In the two patients studied before surgery, the measurements were made during stable conditions, 10 days and 5 weeks after surgery, respectively. All patients had normal serum liver tests and serum creatinine. No patients with cancer disease were included in this study. All patients were judged on clinical grounds as candidates for nutritional support, and all had lost between 5–10% of body weight, with no significant difference between the two groups. All received a regular hospital diet of their own choice. Their intake included approximately 1100–1300 Kcal of nonprotein calories and 40–45 g of protein per day. The diagnoses were: angina abdominalis (two), gastric and duodenal ulcer (five), status post vascular reconstruction (one), aortic aneurysm (two), intermittent claudication (one), chronic pancreatitis (one), diverticulitis (one), chronic cholecystitis (one), oesophagitis (two). This study was approved by the Ethical Committee and the Isotopic Committee, Sahlgrenska Hospital. Informed consent was obtained from all patients.

Nutritional Status

The arm circumference and triceps skinfold were measured at the midpoint of the left arm. The arm muscle circumference was calculated as described by Haider and Haider.[3] The measurements were compared with Swedish reference values for arm anthropometric measures.[4] Serum albumin was analysed according to the standard procedure of our hospital (bromcresol green). Total body potassium (TBK) was measured in a whole-body counter.[5] Values for body weight and total body potassium were compared to predicted normal values accounting for age and sex. These values are referred to as body weight index and total body potassium index.

Whole Body Tyrosine Kinetics

The patients were studied at rest in bed. Tyrosine kinetics were measured on Day 1 (see below) after an overnight fast (12 hours) and during TPN infusion on Day 2. After infusions and measurements (7 hours) on Day 1, the patients were allowed to eat freely until 8 p.m. After this time, water intake only was allowed. On the morning of Day 2 after the 12-hour fast, the second infusion was given. The parenteral nutrition solutions (see below) were infused together with the isotope for 6 hours, as they were during Day 1.

During the fasted and fed states (Days 1 and 2, respectively), whole-body protein kinetics were measured at steady state conditions after a primed constant infusion of L-(U-^{14}C) tyrosine (0.6 uCi/kg body weight) in each individual.

On Day 1, (^{14}C) tyrosine was administered intravenously in 500 ml of normal saline (for the first 10 minutes), using a monoexponentially primed infusion followed by a constant infusion (80 ml/hr) during 6 hours in which an infusion pump (IVAC) (Stockholm, Sweden) was used.[6] The same pump was used for all isotopic infusions. To determine specific radioactivity of whole blood tyrosine, radial arterial blood samples were drawn before infusion and at 4, 5, and 6 hours after the start of infusion. In samples taken at 4, 5, and 6 hours after infusion, plateau values were calculated from the mean specific radioactivity according to our previous investigations of the change in time course rise in specific activity.[6] Whole blood samples were immediately precipitated by 10% trichloraocetic acid (final concentration), and tyrosine was enzymatically converted to tyramine[7] and analyzed fluormoetrically, as described in Waalkes and Underfriend's report.[8] The radioactivity was measured by liquid scintillation beta counter. Measurement of specific radioactivity in expired carbon dioxide and the determination of the oxidation rate of tyrosine were measured in a ventilated hood system[9] during the last 30 minutes of infusion.[6]

The oxygen consumption and carbon dioxide production were measured during the last 30 minutes of the infusion periods.[9] The energy expenditure was calculated from measurements of respiratory gas exchanges, according to Lusk et al.[10]

On Day 2, before the I.V. nutrition infusions were given, the resting oxygen consumption and carbon dioxide production were measured during a 30 minute period. The residual $^{14}CO_2$ in expired gases was quantified and accounted for as blank values in subsequent calculations of tyrosine oxidation. The isotope was added to the amino acid solution (0.8 uCi/kg body weight) and was infused (as on Day 1), using a monoexponentially primed constant infusion rate. The constant infusion rate was determined by the calculated prescription of the nitrogen need (see below) by means of the IVAC infusion pump that had been used for ^{14}C-tyrosine infusions of Day 1. The oxygen consumption, car-

bon dioxide production, and tyrosine oxidation were again measured during the last 30 minutes after the 6-hour infusion.

Calculation of Tyrosine Flux and Protein Dynamics

Whole-body tyrosine flux, oxidation, and incorporation into proteins (protein synthesis) were calculated as described by James et al.[7] Assuming the mass fraction of tyrosine in protein to be 3%, protein synthesis was derived from the difference between whole body tyrosine flux and oxidation of tyrosine.[7] Assumptions and limitations of this method and other methods for measurement of whole body protein kinetics have been discussed in detail in the report of Waterlow et al.[11]

I.V. Nutrition

Results of energy expenditure, as measured during Day 1, were used to calculate the individuals' resting needs for TPN on Day 2. Seven patients were randomized according to nutritional state[12] to receive nonprotein calories at a level corresponding to 120% of their resting energy expenditure (REE) and 0.2 g of nitrogen per kg body weight (Table 1). The remaining nine patients were randomized to receive nonprotein calories at a level of 200% of their REE and 0.33 g of nitrogen per kg body weight. Half of the nonprotein calories were given in the form of 30% D-glucose solution and half as a soybean oil fat emulsion (Intralipid 20%*). The crystalline amino acid solution was Vamin N†. Vitamins, minerals, and trace elements were given according to recommendations for hospitalized patients. All three solutions (glucose, lipids, and amino acids) were infused simultaneously into a central vein using IVAC pumps.

Substrate Exchange Across the Leg

Arterial (A radialis) and venous (V femoralis) blood samples were drawn simultaneously 6 hours after the start of the infusion at steady state. The whole blood samples were analyzed for free amino acids, which were separated by HPLC-technique with a precolumn derivatization procedure.[13,14] Plasma samples were analyzed for glucose, and glycerol by kits from Boehringer Mannheim, West Germany. Free fatty acids (FFA) were measured by an enzymatic colorimetric test (NEFA)™ (Wako Chemical Company, Osaka, Japan). Leg blood flow was measured by a strain-gauge plethysmograph.[1,2] All these measurements were performed both during fasting (Day 1) and I.V. nutrition (Day 2). The leg exchange of amino acids and energy substrates were calculated as the arterio-venous difference multiplied by the leg blood flow.[1,2]

TABLE 2. *Energy Expenditure, Respiratory Quotient, and Energy Expenditure in Percentages of Predicted Expenditure According to Harris-Benedict (mean ± SEM)*

		Nutritional Therapy	
		120% of REE 0.2 g of N/kg	200% of REE 0.33 g of N/kg
Energy expenditure (Kcal/24 hrs)	Fasting	1129 ± 78	1095 ± 56
	TPN	1148 ± 92	1274 ± 67‡
Respiratory quotient	Fasting	0.79 ± 0.03	0.79 ± 0.01
	TPN	0.82 ± 0.01†	0.84 ± 0.01‡
Energy expenditure in % of that predicted*	Fasting	85 ± 3	83 ± 5
	TPN	87 ± 5	97 ± 5‡

* Calculated from Harris-Benedict formula.
† Fasted *vs.* TPN $p < 0.05$.
‡ Fasted *vs.* TPN $p < 0.01$.

Statistical Analysis

Paired comparisons were obtained from each patient between the fasted and the fed states, and were evaluated using Student's t test for paired observations. The comparison in the fed state between 120 and 200% intakes was performed by the nonparametric Mann-Whitney u-test. Correlations were calculated using the least square method. A parametric group comparison test was used to test whether the leg balance of amino acids or substrates differed significantly from zero balance; $p < 0.05$ was chosen as the significant level.[15]

Results

Thirty-two infusions were performed in 16 patients, who were randomized into two comparable groups with regard to age and nutritional status. Thus we obtained two groups ($n = 7$, $n = 9$) that did not differ significantly in their overall nutritional state (Table 1), energy expenditure (Table 2), and tyrosine flux (Table 3). Although the patients are a heterogeneous group with a variety of diseases, the normal fasting protein breakdown data and its comparatively small standard error in Fig 1 indicates that the patients rather suffered from moderate malnutrition than catabolism (Fig 1). Over a period of 6 months, the mean body weight loss was 7.5 ± 2 kg. The body weight index for the total patient material was 0.87 ± 0.03, and the total body potassium index was 0.98 ± 0.02, suggesting that body fat represented the major part of the weight loss. The arm muscle circumference and triceps skinfold were 93 ± 2% and 78 ± 9% of the predicted normal values.

* Intralipid 20%® contains per liter: 200 g of soybean oil, 12 g of lecithin, 22.5 g of glycerol.

† The L-amino acid solution used for infusion contained in grams per liter: gly 2.1, asp 4.1, glu 9.0, ala 3.0, arg 3.3, cystein-cystin 1.4, his 2.4, ile, 3.9, leu 5.3, lys 3.9, met 1.9, phe 5.5, pro 8.1, ser 7.5, thr 3.0, trp 1.0, tyr 0.5, val 4.3.

TABLE 3. *Tyrosine Kinetics in the Fasting and Fed State (means, SEM)*

		Nutritional Therapy	
		120% of REE 0.2 g of N/kg	200% of REE 0.33 g of N/kg
Tyrosine flux (nmol/min/kg)	Fasting	488 ± 61	488 ± 31
	TPN	475 ± 60	625 ± 34†‡
Tyrosine oxidation (nmol/min/kg)	Fasting	29 ± 6	32 ± 4
	TPN	37 ± 6*	61 ± 7†§
Tryosine incorporation into protein (nmol/min/kg)	Fasting	459 ± 57	456 ± 28
	TPN	448 ± 57	564 ± 28†‡

* Fasted *vs.* TPN, $p < 0.05$.
† Fasted *vs.* TPN, $p < 0.01$.
‡ 120% *vs.* 200%, $p < 0.05$.
§ 120% *vs.* 200%, $p < 0.01$.

TABLE 5. *Arterial concentrations of Nonprotein Substrates (mean ± SEM)*

		Nutritional Therapy	
		120% of REE 0.2 g of N/kg	200% of REE 0.33 g of N/kg
Glucose (mmol/l)	Fasting	5.0 ± 0.1	4.7 ± 0.2
	TPN	7.4 ± 0.4†	7.7 ± 0.7†
Lactate (mmol/l)	Fasting	0.56 ± 0.05	0.57 ± 0.04
	TPN	0.60 ± 0.05	0.82 ± 0.08†§
Glycerol (mmol/l)	Fasting	122 ± 8	125 ± 22
	TPN	124 ± 16	166 ± 23†
FFA (mmol/l)	Fasting	580 ± 50	520 ± 50
	TPN	380 ± 60*	300 ± 40†

* Fasted *vs.* TPN, $p < 0.05$.
† Fasted *vs.* TPN, $p < 0.01$.
‡ 120% *vs.* 200%, $p < 0.05$.
§ 120% *vs/* 200%, $p < 0.025$.

Energy Expenditure

The energy expenditure was not affected by the low rate of TPN, but increased ($p < 0.01$) with the high rate. The respiratory quotient (RQ) increased with both therapies, compared with the fasting RQ ($p < 0.05$). The measured energy expenditure during fasting was significantly lower than that predicted from the Harris-Benedict equation, but approached the predicted levels with the high rate of TPN. These findings agree with our earlier results in hospitalized patients.[9]

Tyrosine Flux, Oxidation and Flux into Protein

Tyrosine flux and protein synthesis were not affected at all by the lower rate of I.V. nutrition (120% of REE and 0.2 g of N/kg), but were significantly increased ($p < 0.01$) by the higher rate of infusion (200% of REE and 0.33 g of N/kg), when compared with the fasted state. Tyrosine oxidation increased significantly with both rates of TPN. In comparisons of the two groups of patients, tyrosine flux, oxidation, and protein synthesis were equal in the fasted state. Calculations of whole-body protein flux, oxidation, and synthesis are presented in Table 3. Protein breakdown decreased significantly in response to the two TPN rates (Fig 1). Estimates of protein breakdown were calculated as described by Waterlow et al.[11] and represent minimum values, since de novo synthesis of tyrosine from phenylalanine was not accounted for.[16]

TABLE 4. *Arterial Concentrations and Balances of Tyrosine and Total Amino Acids Measured Across the Leg in the Fasted and Fed State (mean ± SEM)*

		Nutritional Therapy	
		120% of REE 0.2 g of N/kg	20% of REE 0.33 g of N/kg
Arterial concentration of tyrosine (μmol/l)	Fasting	46 ± 5	44 ± 7
	TPN	52 ± 4	46 ± 5
Balance of tyrosine (nmol/100 g/min)	Fasting	−28 ± 17	−32 ± 13
	TPN	−22 ± 35	−28 ± 13
Arterial concentration of total amino acids (μmol/l)	Fasting	1885 ± 117	1807 ± 143
	TPN	2576 ± 129*	2878 ± 266*
Balance of total amino acids (nmol/100 g/min)	Fasting	−535 ± 534	−726 ± 204
	TPN	−103 ± 649	−186 ± 511†

* Fasted *vs.* TPN, $p < 0.01$.
† Fasted *vs.* TPN $p < 0.05$ with a "sign test for few observations."

Arterial Concentrations and Leg Exchange of Amino Acids and Substrates

Table 4 shows the arterial concentration and balance of tyrosine, and the total amino acids during fasting and with the two rates of nutritional therapy. The arterial concentration of tyrosine was not affected by either of the nutritional therapies, but the concentration of phenylalanine increased three- to fourfold with TPN ($p < 0.01$, results not shown). The arterial concentration of total amino acids increased as a response to both nutritional therapies ($p < 0.01$). There was no improved balance of tyrosine across the leg with either of the nutritional therapies. The balance of total amino acids improved significantly ($p < 0.01$) with the high TPN rate.

Arterial concentrations of glucose, lactate, glycerol, and FFA were the same in the fasted state between the groups. Arterial levels of glucose and FFA changed significantly with the low rate of TPN and in addition lactate and glycerol changed on the high rate of TPN (Table 5).

The peripheral blood flow, balance of glucose, lactate, glycerol, FFA, and arterial concentrations of insulin are

presented in Table 6. With the low rate of TPN there were no improvements in substrate balance. The only positive balance obtained was that of glucose with the high rate of TPN ($p < 0.01$). The arterial insulin concentration increased from 4 to 19 μU/ml ($p < 0.05$) with the low level of TPN and from 5 to 42 μU/ml ($p < 0.01$) with the high rate of TPN. The insulin response was higher with the high rate, compared with the low rate of TPN ($p < 0.05$). When compared between the therapy groups, the glucose balance improved significantly with the high level as opposed to the low level of TPN ($p < 0.05$).

TABLE 6. *Blood Flow and Balance of Glucose, Lactate, Glycerol, and Free Fatty Acids and Arterial Concentration of Insulin in the Fasting and Fed States (mean ± SEM)*

		Nutritional Therapy	
		120% of REE 0.2 g of N/kg	20% of REE 0.33 g of N/kg
Blood flow (ml/100 g/min)	Fasting	3.0 ± 0.8	3.2 ± 0.5
	TPN	3.0 ± 0.5	4.1 ± 0.6*
Glucose balance (nmol/100 g/min)	Fasting	−98 ± 104	210 ± 165
	TPN	−160 ± 509	1690 ± 53†§
Lactate balance (nmol/10 g/min)	Fasting	−549 ± 204	−607 ± 86
	TPN	−319 ± 66	−608 ± 84‡
Glycerol balance (nmol/100 g/min)	Fasting	−140 ± 43	−246 ± 71
	TPN	−102 ± 30	−80 ± 106
Free fatty acid balance (nmol/100 g/min)	Fasting	−268 ± 410	−835 ± 249
	TPN	74 ± 364	−224 ± 189*
Insulin arterial concentration (μU/ml)	Fasting	4 ± 1	5 ± 1
	TPN	19 ± 6*	43 ± 10†‡

* Fasted *vs.* TPN, $p < 0.05$
† Fasted *vs.* TPN, $p < 0.01$.
‡ 120% *vs.* 200%, $p < 0.05$.
§ 120% *vs.* 200%, $p < 0.025$.

Discussion

This study has examined alterations in whole-body protein dynamics, compared with simultaneous measurements of amino acid balances across peripheral tissues in moderately malnourished patients who were candidates for I.V. nutrition. The two objectives of the study were to evaluate whether information obtained with the primed constant infusion of labeled tyrosine reflects similar net changes in tyrosine flux as obtained from measurements of the arteriovenous balances; and whether the TPN infusion given at rates close to the resting needs of an individual can turn on net whole-body protein synthesis.

The results demonstrate that information obtained by the frequently used primed constant infusion of amino acids cannot necessarily be extrapolated to reflect directional changes in protein synthesis or breakdown in peripheral tissues, such as skeletal muscles. Therefore, results from whole-body turnover measurements may rather represent net alterations occurring predominantly in one or several compartments only.

In addition, our results demonstrate that TPN at infusion rates close to resting needs with 0.2 g of N/kg/day, which is often prescribed in clinical practice, is insufficient to stimulate net whole-body protein synthesis. Our lowest nitrogen intake of 0.2 g of N/kg/day should then be compared to the recommended intake of 0.13 g of N/kg/day for oral diets.[17] Because TPN was given only at two different rates, with a fixed relationship between nonprotein calories and nitrogen, it was not possible to decide precisely where the inflection point was located for net protein accretion and how nonprotein calories *versus* amino acids promote protein synthesis in our groups of patients. (An investigation of the independent relationship between protein synthesis and nonprotein calories or protein would demand an unrealistically large number of patient-investigations). With the inspection of individual results in additional experiments, it is likely that the breakpoint would be somewhere between 1.7–2 times the resting requirements of nonprotein calories and at a nitrogen infusion of 0.25–0.30 g of N/kg/day. In a recent study, with increasing amounts of N^{15} glycine and oral intakes, protein balance was achieved at a daily oral nitrogen intake of approximately 0.8 g of protein/kg/day (N 0.13 g of N/kg/day).[18] Above this level, protein synthesis was stimulated proportionally—more so than protein breakdown—up to an intake of 0.3 g of N/kg/day. Our results agree with those from healthy well-nourished subjects[18,19] and patients following surgery,[20] but are not quite comparable to the results of normal individuals starved for 10 days and then given I.V. refeeding. Such volunteers have positive amino acid balance across the forearm.[21] The less efficient response in our patients may be a combined effect of malnutrition and constant infusion of I.V. nutrition. Constant infusion of I.V. nutrition alters arterial peak levels of both substrates and hormones markedly less than does oral bolus eating.[22] The stimulation of protein synthesis in the present study was associated with a thermic effect of approximately 16%, which agrees in magnitude with our previous experiments on constant TPN infusion at increasing rates.[23]

We have recently reported that the increase in arterial concentrations of amino acids is a more potent factor of stimulating amino acid uptake in peripheral tissues (across the leg) than insulin.[14] In addition, being at rest during the infusion is probably not the factor causing leg efflux of amino acids, since exercise aggravates amino acid efflux both immediately after and for several hours after exercise (own unpublished results). However, in the present study, we were able to demonstrate a stimu-

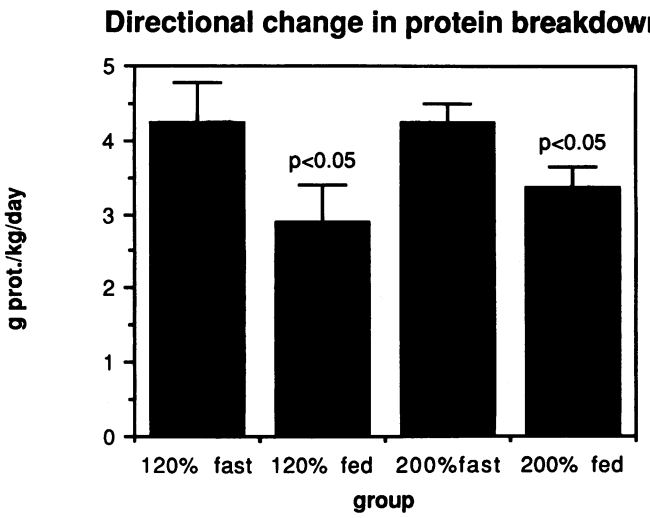

FIG. 1. Estimates of protein breakdown (g/kg/day) during fasting state and in response to low (120%) and high (200%) TPN infusion rates. The values are calculated as described by Waterlow et al.,[11] on the assumption that de novo synthesis of tyrosine from phenylalanine is unchanged from the fasted to the fed state. It should be emphasized, however, that the significant decrease in breakdown would be even more pronounced with regard to "true rates," since tyrosine de novo synthesis is increased in the fed state.[16] Bars indicate SEM.

lation in net whole-body tyrosine incorporation into proteins (protein synthesis) without any change in the arterial concentration of tyrosine. This lack of increase in the arterial concentration of tyrosine was concomitant with an unchanged balance of tyrosine across the leg, even with a high infusion rate. These results support the conclusion that protein synthesis is stimulated differently in peripheral tissues than it is in other tissues, such as visceral organs. In this respect, we regard the results obtained from the constant infusion tracer methods to represent primarily the synthesis of visceral proteins. It is not likely that the lack of statistically significant alterations in the balance of total amino acids, lactate, glycerol, and FFA with the low TPN rate are due only to an insensitive methodology, since the balance of glucose, FFA (Table 6), and amino acids (Table 4) were clearly improved when measured with the high TPN rate. We found it more likely that constant infusion of I.V. nutrition as it is used in medical practice gives increments too small in arterial levels of amino acids and insulin to switch the flux of many substrates from one direction to the opposite, as compared with the bolus intake of ordinary food.[23]

Various amino acids have been used to explore protein dynamics in humans. Some of them may be less appropriate for this purpose than others.[11] It has been suggested that under many experimental circumstances, carboxylabeled leucine may be the most suitable amino acid.[11] The main limitation with tyrosine is that, because de novo synthesis of tyrosine from phenylalanine is not measured by the single infusion of (^{14}C) tyrosine, protein breakdown cannot be calculated precisely. This limitation may be overcome in future studies by the simultaneous infusion of deuterium, labeled phenylalanine.[24,25] In the present study, tyrosine was judged the most suitable marker for investigating how protein synthesis is turned on in response to low and high TPN infusion, and how such a response relates to flux across peripheral tissues. The advantage with tyrosine is that approximate plateau values are reached within 4–6 hours after a primed monoexponential infusion.[6] Others have shown that a theoretical advantage with leucine due to a more rapid appearance of $^{14}CO_2$ in expired carbon dioxide is not a real one and that, although absolute rates differed, the two amino acids gave qualitatively the same information on protein synthesis.[26] This kind of whole-body kinetic experiment should, however, not be expected to produce the absolute values discussed by Waterlow and colleagues.[11] Because the majority of leucine taken up is not used for protein synthesis, but is probably used for oxidation in skeletal muscles, leucine may be less appropriate than tyrosine for use in measurements of flux across the leg to reflect protein balance.[14,27,28] By contrast, tyrosine is not metabolized in the skeletal muscles. These aspects are illustrated by the fact that the leg exchange of tyrosine was unchanged in both fasted and fed state, whereas the efflux of total amino acids decreased. This decrease was significant with the high rate of TPN. Such results also show that the improved nitrogen economy across the leg was achieved by decreasing leg output of glutamine and alanine (results not shown), which is perhaps due to decreased branched chain oxidation.

It has been reported that postabsorptive de novo synthesis of tyrosine from phenylalanine is around 15% of the tyrosine flux in humans.[24] Feeding or infusions of phenylalanine, as used in this study, stimulate phenylalanine to tyrosine conversion to a significant extent, depending on the infusion rate of phenylalanine.[16] In contrast to tyrosine, the phenylalanine plasma concentration increased significantly with both rates of TPN. Therefore, it was not possible to calculate protein breakdown rate in absolute values. However, we know that protein breakdown decreased significantly even at a low TPN infusion rate, since the intake of tyrosine increased in all patients (by 41 nmol/kg/min, the infusion rate of tyrosine), though this did not increase tyrosine flux. If, however, we assume that de novo tyrosine synthesis is equal in the fasted and fed states, we will then have an estimate of minimum values for breakdown in comparison with the measured values of protein synthesis. We regard this approach as reasonable, since under no circumstances has phenylalanine to tyrosine conversion been reported to decrease in the fed state as com-

pared with the fasted state. Although the absolute values for breakdown cannot be regarded as correct, it can be shown in a mathematical plot how protein breakdown and balance will change depending on various absolute rates in de novo tyrosine synthesis in fasted and fed states (results not shown). The change will be a linear decrease in breakdown, resulting in constant improvements in protein balance with both low and high TPN infusions. Estimates of protein breakdown are presented in Figure 1.

In conclusion, this study demonstrates that changes in whole-body protein kinetics estimated by the primed constant infusion of ($U^{14}C$) tyrosine may represent net changes in only some or few compartments, rather than show the same directional changes in the majority of whole-body compartments. This was demonstrated by a net whole-body protein synthesis in combination with a simultaneous net outflow of tyrosine from skeletal muscles. The results in the present study may have important bearing on the formulation of TPN regimens to patients, although they represent kinetics that come after only 6 hours of TPN infusion. The results support the suggestion that standard prescriptions of TPN will hardly promote protein synthesis in the skeletal muscles in the majority of hospitalized malnourished patients and are, in a significant number of patients, perhaps inadequate to promote net protein synthesis at all. Improved nitrogen balance in such patients is then achieved by decreasing protein breakdown rates. Whether we would see similar results after a 10–15 day period of parenteral nutrition is not known at present, although the difficulties in expanding lean body mass by I.V. nutrition is well-recognized as reported by others.[28–30]

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