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Protein Sparing and Protein Replacement in Acutely Injured Patients During TPN With and Without Amino Acid Supply

G. Iapichino, L. Gattinoni, M. Solca, D. Radrizzani, M. Zucchetti, M. Langer and S. Vesconi

Istituto di Anestesiologia e Rianimazione, Università di Milano, I-20122 Milano, Italy

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Abstract. The metabolic effects of TPN were studied in a selected group of trauma patients. Nineteen patients were randomly divided into two groups: the first was treated with glucose and insulin, the second with glucose, insulin and amino acids. Each patient in both groups received TPN isocaloric with respect to daily energy output and the treatment lasted five days. Each group was further divided into two subsets (severe or moderate catabolism) according to fasting energy output with respect to the expected energy expenditure. During the acute flow phase, both in moderate as well as in severe catabolism, glucose and insulin were effective for protein sparing; the maximum protein sparing effect was reached when giving a caloric intake equal to 130% of daily energy output. Glucose, insulin and amino acids were effective in replacement of nitrogen losses. In moderately catabolic patients nitrogen balance was significantly better than in severely catabolic patients. This study shows that early and short-term TPN is effective in controlling the flow phase of trauma. Glucose and insulin appear to be the determinants of the protein sparing effect when given in amounts equal to those needed; amino acids provided protein replacement when given in amounts equal to about 20% of energy output. Energy supply higher than 120 – 130% of daily energy output does not increase protein sparing and protein replacement, the only effect being a further increase in metabolism, which is possibly dangerous in critically ill patients.

Key words: Trauma – Protein sparing – Glucose – Insulin – Amino acids

Introduction

Early total parenteral nutrition (TPN) has been used in critically ill patients to control the catabolic phase following trauma and to replace nitrogen loss. However, only a few reports [8, 14, 15, 19, 22] deal with the use of TPN to supply the nutritional and energy requirements of patients.

The value of TPN when energy is supplied according to measured energy output is still questioned, for this has been shown, in some investigations, to have a nitrogen sparing effect [14, 15, 19, 11] whilst in others this has not been found [8]. This discrepancy might arise from the differences in the nutritional state of the patients before injury, the severity of the reaction to trauma, and the timing of TPN. Moreover, the protocols and the nutritional treatment were quite dissimilar both in terms of total energy supply and insulin and amino acid administration. The aim of this work was to study the possibilities of early TPN during the first six days after trauma, with or without amino acids, to control the reaction to trauma and to replace nitrogen losses in a relatively homogeneous group of patients.

Material and Methods

Patient Selection

Nineteen critically ill patients admitted to hospital immediately after trauma were studied. Their sex, age, body weight and diagnoses are listed in Table 1. Sixteen patients were artificially ventilated because of flail chest, postoperative cardio-respiratory insufficiency and/or coma, for periods ranging from four to eight days. Every patient was in good nutritional condition and within ± 10% of an ideal body weight [5]. Four additional non-injured, normocatabolic, protein depleted patients were included as controls (Table 1).

None of the subjects, injured or control, had a previous history of dialysis or chronic liver disease, all

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Table 1. Characteristics and diagnoses of the patients

Patient	Sex	Age	B.W.	Diagnosis
Severe catabolism				
Group 1				
1	M	43	64	Mp + thoracic + head T
2	M	36	66	Mp + thoracic + abdominal organs T, laparatomy
3	F	45	70	Mp + thoracic + head + abdominal organs T, laparatomy
Group 2				
1	M	43	73	Mp + thoracic T
2	M	18	66	Mp + thoracic + head T
3	M	35	75	Mp + thoracic T, fat embolism
4	F	16	50	Mp + abdominal organs T, laparatomy
5	F	55	56	Mp + thoracic + head + abdominal organs T, laparatomy
6	M	30	88	Mp + thoracic + head + abdominal organs T, laparatomy
7	M	55	61	Colon infarction, peritonitis, hemicolectomy
8	M	65	69	Abdominal sepsis with multiple fistulas after head + abdominal organs T, laparatomy
Moderate catabolism				
Group 1				
1	M	41	61	Mp T, fat embolism
2	M	65	69	Mp + thoracic + head T
3	F	17	44	Mp + thoracic + head + abdominal organs T, laparatomy
4	M	77	63	Cardiac arrest during cholecystectomy, post-anoxic encephalopaty
Group 2				
1	M	57	89	Mp + thoracic T
2	M	50	59	Mp + abdominal organs T, pancreatitis
3	M	24	65	Mp + thoracic + head + abdominal organs T, laparatomy
4	F	75	55	Gangrenous bowel, laparatomy, peritonitis
Control				
Group 1				
1	F	56	45	Malabsorption
2	M	38	51	Malabsorption
3	F	36	60	Neoplasia, cachexia
4	M	58	50	Neoplasia, cachexia

Mp = multiple fractures; T = trauma

had gastro-intestinal failure for at least one week, but no renal or hepatic insufficiency.

Balance Measurements

Blood samples were withdrawn daily at 8 a.m. for routine blood analysis. Urine samples were collected daily using 10 N HCl as the preservative, and urinary

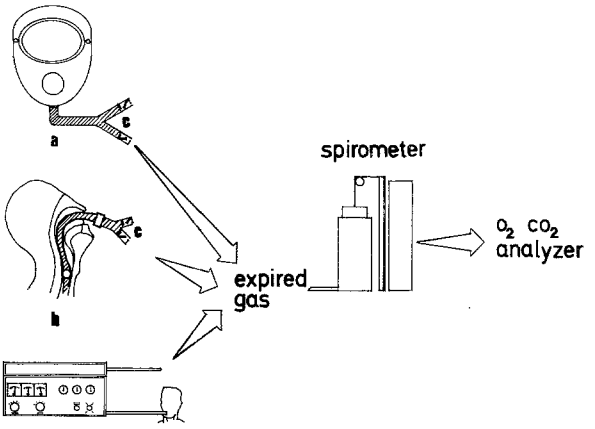

Fig. 1. Methodology of indirect calorimetry. *a* = air tight head canopy, *b* = intubated spontaneously breathing patient, *c* = Y and one way low resistance valves. Expired gases collection and analysis system. This system was connected directly to the expiratory line of the C system in spontaneously breathing patients or of the ventilator in mechanically ventilated patients

nitrogen loss was calculated as the sum of urea, creatinine, ammonium uric acid and α-amino nitrogen, determined by standard methods [16]. Drainage losses were analyzed for urea content. Body nitrogen output (N_0) was computed from the measured urinary nitrogen losses corrected for changes in the urea-nitrogen pool (total body water was assumed to be 50 to 60% of body weight, taking into account sex and body build) and from the measured urea nitrogen in the drainage losses plus an estimated insensible nitrogen loss through the skin and gastro-intestinal tract (15 mg/kg/day [4]). Daily nitrogen balance (NB) was calculated as the difference of nitrogen input (N_i) and N_0. The daily resting energy expenditure (i.e. energy output: E_0) was established by indirect calorimetry. Expired gases were collected in a spirometer from patients spontaneously breathing room air by means of an airtight head canopy (extubated patients) or suitable connection (intubated patients) (Fig. 1).

Before collection of gases we continuously monitored the F_{ECO_2} and when a steady state was achieved we began the collection. In patients treated by mechanical ventilation (Servo Ventilator 900 Mod. B) the expired gases were collected from the expiratory line and were analyzed for O_2 and CO_2 concentration using the Beckman OM11 and LB2 Gas analyzers. The O_2 analyzer was calibrated with an oxygen fraction similar to that inspired by the patient ($F_{IO_2} \leqslant 40\%$).

$\dot{V}O_2$ and $\dot{V}CO_2$ were measured daily four or five times; the mean values were taken as the average resting gas exchange for each 24-h period. The following formulae were used:

Table 2. Schedule of treatment in injured patients

Day	Basal	1	2	3	4	5
(E_i/basal E_0) 10^2	–	40	70	90	120	150
Group 1 (pts = 7; M 4, S 3) glucose	–	+	+	+	+	+
Group 2 (pts = 12; M 4, S 8) glucose	–	+	+	+	+	+
amino acid	–	–	–	+	+	+

(E_i/basal E_0) 10^2 = Energy intake (E_i) as a percentage of E_0 measured during the basal period; M = moderate catabolism; S = severe catabolism

Group 1 Patients receiving glucose (plus insulin when necessary to maintain normoglycemia) throughout the study period.

Group 2 Patients receiving glucose (plus insulin as in Group 1) and amino acids. Daily amino acids intake was constant and accounted for 18 – 20% of basal E_0

$$\dot{V}O_2STPD = \dot{V}_E \left(F_{IO_2} \frac{1 - F_{EO_2} - F_{ECO_2}}{1 - F_{IO_2} - F_{ICO_2}} - F_{EO_2} \right)$$

$$\dot{V}CO_2STPD =$$

$$= \dot{V}_E \left[F_{ECO_2} - \left(F_{ICO_2} \cdot \frac{1 - F_{EO_2} - F_{ECO_2}}{1 - F_{IO_2} - F_{ICO_2}} \right) \right]$$

$\dot{V}_E$ = Expired ventilation in l/min

$F_{I,E}$ = Fractional concentration of O_2 and CO_2 in inspired and expired gases

The daily resting protein, non-protein and total caloric expenditure, expressed in kilocalories, were calculated from standard formulae [6]. When the non-protein RQ was more than 1, calorimetric factors were derived according to Elwyn et al. [7]. Body weight was recorded at the beginning and the end of the study.

Experimental Procedure

During the 24 – 36 h after injury (basal period) the blood volume was restored, the acid-base balance and hemodynamic status were corrected and glucose was administered in an amount not exceeding 50 g/day.

Following this period the injured patients were randomly assigned to two groups: *Group 1* received glucose and insulin for five days in increasing amounts; *Group 2* received glucose and insulin for five days with added amino-acids during the last three days. The control patients (C) formed Group 3 and were treated as the Group 1 patients. The injured patients in each group were further divided into two subsets: severely catabolic (S) and moderately catabolic (M).

We considered as severely catabolic those patients in whom E_0, measured during the day before the treatment (basal fasting period: Table 2), was 23% above the predicted E_0 computed according to the Harris Benedict formula [6] and as moderately catabolic the patients in whom E_0 of the fasting period was greater than predicted, but was less than 23% [1].

The schedule of treatment for each group is summarized in Table 2. After the study period, TPN was withdrawn for 24 h in six patients of Group 1, three for each subset of severity. Glucose was provided in concentrated water solutions, and was insulin also given subcutaneously every 4 – 6 h when necessary to maintain a blood sugar between 1 – 1.5 g/l (in the control group insulin was not necessary); proteins were provided as crystalline l-amino-acid solutions [2]. Electrolytes, minerals and vitamins were provided according to standard criteria.

Informed consent was obtained in each subject investigated.

Statistical Analysis

Regression analysis by the least square method and Student's Test were used. Values are expressed as mean ± Standard Deviation.

Results

According to the ratio between measured and predicted E_0 during the first 24 – 36 h after injury, 11 patients were severely catabolic and eight moderately catabolic. E_0 in kcal/kg nitrogen loss and blood glucose, recorded in these patients and in four non-catabolic controls, are listed in Table 3.

Nitrogen Sparing Effects

Nitrogen losses as a function of "daily E_i/E_0" [3] in all severely catabolic patients, when receiving solely

1 Kinney [18] has stated that the range of E_0 increase after trauma is between 0 and 40% above the predicted value, and we initially divided injured patients in to two subsets: severely and moderately catabolic, using the mean values of Kinney's range (20%). However, when we applied the discriminant function analysis to our data we found that this point was 23%

2 Isopuramin Plus^R (Stholl S.pA., Modena, Italy); composition (g/100 ml): 1.56 g N,l-Tryptophan 0,32,l-Isoleucine 0,70,l-Phenylalanine 1,01,l-Valine 0,67,l-Threonine 0,75,l-Arginine 1,17,l-Lysine HCl 2,45,l-Leucine 1,06,l-Histidine 0,51,l-Methionine 0,72,l-Gycine 0,64

3 In the schedule treatment (Table 2) E_i was planned as an increasing percentage of E_0 of the basal period. However, in the results the "daily E_i/E_0" ratio refers to the amount of energy actually utilized (i.e. energy given – energy lost in the urine) divided by the E_0 measured on the same day, which changed during the course of treatment (Table 4).

Table 3. Metabolic findings of the patients during basal fasting period

	(E_0/E_0 predicted) 10^2	E_0 (kcal/kg)	N_0 g/day	Glycemia g/l
Severe catabolism	+38.53±12.27	33.97±4.62	18.72±5.92	1.28±0.46
Moderate catabolism	+ 8.24±12.68	25.09±2.49	10.75±3.44	1.20±0.17
Control	− 3.17±7.25	22.45±4.51	6.25±3.02	0.77±0.12

E_0 = energy output; N_0 = nitrogen loss

glucose and insulin (i.e. five days of treatment for three patients of Group 1 and the first two days of treatment in eight patients of Group 2) are shown in Fig. 2.

Figure 3 shows nitrogen loss as a function of E_i/E_0 in the moderately catabolic patients when receiving glucose and insulin alone (five days of treatment in the four patients of Group 1 and the first two days of treatment in the four patients of Group 2). Figure 4 shows nitrogen loss as a function of E_i/E_0 of four control patients who received only glucose.

In all patients nitrogen loss was negatively correlated with E_i/E_0. A plateau was reached at E_i values between 100−120% of E_0. No further consistent decrease of nitrogen loss was found with greater values of E_i.

The plateau value of nitrogen loss in severely catabolic patients (E_i about 120% of E_0) was similar to that of control patients in basal conditions (0.18 versus 0.16 g nitrogen/kg) whilst at the same plateau point less nitrogen was lost by the moderately catabolic patients (0.12 versus 0.16 g nitrogen/kg).

At an E_i of about 120% of E_0 (i.e. plateau point of nitrogen loss) the nitrogen spared was 44% (S), 35% (M) and 48% (C) of nitrogen loss before the glucose and insulin treatment.

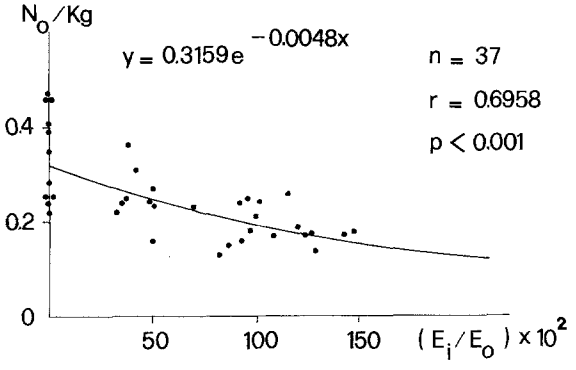

Fig. 2. Daily nitrogen losses (N_0, as g/kg) during TPN with glucose and insulin in severely catabolic patients. Energy intake (E_i) is expressed as a percentage of the same day energy output (E_0)

In the patients where TPN was totally withdrawn after glucose and insulin treatment the nitrogen loss suddenly increased, reaching the pre-treatment values (Table 5).

The Effects of Nitrogen Replacement

The key index of replacement of protein wastage is the nitrogen balance, not nitrogen loss. When comparing Group 1 and Group 2 patients during the last three days of TPN, where the only difference was the composition of TPN, and not the total energy intake, nitrogen balance was significantly better in Group 2 patients despite higher nitrogen loss (Table 6).

The severity of trauma appears to be an important factor in determining the utilization of amino acid supply; nitrogen balance was actually significantly better in moderately than in severely catabolic patients in Group 2 (Table 6), being the E_i substantially equal either with the respect to daily E_0 either in composition (caloric to nitrogen ratio) in both subsets. The composition of TPN supplied during the last three days of the study did not differ significantly between Groups 1 and 2 (Table 7).

Nitrogen equilibrium was reached in Group 2 patients (severe and moderate) when total (glucose and amino acid) E_i was some 30% higher than daily E_0 i.e. a glucose intake about 100−120% of daily E_0. Absolute amounts of calories as well as nitrogen are listed in Table 8. Mean caloric intakes (48 and 38 kcal/kg) are about 130% of the treatment days' E_0 but about 150% of the basal fasting day E_0 (34 and 25 kcal/kg: Table 3).

Insulin Requirement

Insulin, independently of nitrogen intake, was always required in injured patients to maintain normoglycemia; the mean amounts required (when E_i glucose was $\geqslant$70% E_0) were 1 IU for every 3.99 ± 1.66 g of glucose (S) and 6.59 ± 1.26 (M), $p < 0.001$. Normo-

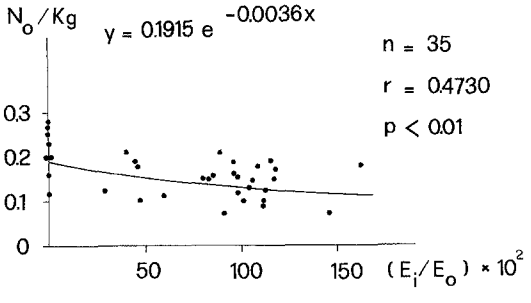

Fig. 3. Daily nitrogen losses (N_0, as g/kg) during TPN with glucose and insulin in moderately catabolic patients. Energy intake (E_i) is expressed as a percentage of the same day energy output (E_0)

Table 4. Daily energy output (E_0) as kcal/kg, and really given energy intake (E_i) as glucose with or without amino acid, as a percentage of E_0 measured during the basal period (E_i/basal E_0) 10^2, throughout the study period

Severe catabolism				Moderate catabolism			
(E_i/basal E_0) 10^2	E_0	(E_i/basal E_0) 10^2	E_0	(E_i/basal E_0) 10^2	E_0	(E_i/basal E_0) 10^2	E_0
0	33.9	119	44.1	0	25.1	120	29.4
	±4.6	120	46.6		±2.5	127	32.7
11	26.3	121	38.0	29	22.1	129	30.5
22	23.6	122	41.5	46	25.3	133	32.3
43	30.4	124	36.7	49	29.3	134	27.3
44	35.3	125	26.3	50	28.8	134	31.6
48	34.4	130	35.2	54	33.1	139	34.4
51	28.8	133	33.6	62	30.3	141	33.7
57	38.3	141	35.9	88	29.3	142	31.4
57	38.9	148	40.6	93	23.5	143	19.8
80	41.0	152	40.7	96	23.7	145	38.1
86	35.9	153	45.0	98	27.7	146	36.2
89	38.5	160	45.8	99	27.3	150	28.3
91	23.7	165	41.5	100	33.3	157	37.6
93	40.8	165	39.8	102	23.7	171	24.4
100	40.2	167	30.7	102	29.8	173	28.5
102	42.1	171	28.0	110	23.7	180	19.9
102	33.2	173	41.2	110	25.4	198	46.6
104	42.6	190	42.8	110	26.7	205	35.3
106	38.1	192	45.6	119	29.5		
108	33.4	193	56.6				
114	35.9	213	29.9				
115	38.7	236	32.0				
118	26.3	237	29.0				
119	35.9						

glycemia was maintained in control patients without insulin.

Discussion

The treatment of body protein loss after trauma by metabolic support has so far produced inconsistent results; difficulties of interpretation arise because of different experimental approaches.

Nitrogen loss and nitrogen balance during TPN are in fact the result of interactions of many variables, such as nutritional status, severity of trauma [24, 26] fluctuation in energy output during the catabolic phase [16], variations of energy intake with respect to energy output [15, 19], the specific effect of insulin [19, 25] and the amount and quality of amino-acid intake (branched chain amino acid [9–11] and lysine [12]. Hence it is important to select and classify a homogeneous population on the basis of the nutritional state and the constancy and severity of injury [20], and also to define the precise criteria for giving TPN.

Protein Sparing Effect

Glucose and insulin treatment in injured patients (Figs. 2 and 3) had a remarkable protein sparing effect during the catabolic phase. The same effect was

Table 5. Daily nitrogen loss (g/kg) before, at the end and after withdral of TPN with glucose and insulin

	Before TPN fast	Last TPN day	After TPN fast
Sever catabolism	0.38±0.14	0.19±0.04	0.32±0.11
Moderate catabolism	0.25±0.02	0.13±0.05	0.23±0.03

Table 6. Daily nitrogen loss (N_0: g/kg), nitrogen intake (N_i: g/kg) and balance (NB: g/kg) during 3rd, 4th and 5th days of TPN in Group 1 (glucose and insulin) and Group 2 (glucose, insulin and amino acids) patients

	Group 1		*Group 2*		
	N_0	NB	N_0	N_i	NB
Severe catabolism	0.19[a] ±0.04	−0.19[b] ±0.04	0.28[a] ±0.06	0.26 ±0.05	−0.02[b,d] ±0.08
Moderate catabolism	0.13 ±0.04	−0.13[c] ±0.04	0.17 ±0.06	0.23 ±0.07	+0.06[c,d] ±0.06

[a] $p < 0.001$
[b] $p < 0.001$
[c] $p < 0.001$
[d] $p < 0.01$

Table 7. Composition of TPN supplied during the last three days of the study period

	Group 1		*Group 2*		
	(E_i/E_0) 10^2	kcal/ kg	(E_i/E_0) 10^2	kcal/ kg	$kcal_{np}/gN_i$
Severe catabolism	123.22 ± 14.58	41.83 7.23	128.76 ± 28.56	47.57 ± 9.49	178.43 ± 42.65
Moderate catabolism	116.25 ± 17.88	33.87 ± 5.77	125.40 ± 132.07	37.49 ± 6.45	162.00 ± 77.53

Table 8. TPN composition when positive nitrogen balance was achieved

	(E_i/E_0) 10^2	E_i (kcal/kg)	N_i (g/kg)	NB (g/kg)
Severe catabolism	134.32 ± 28.71	48.07 ± 10.07[a]	0.28 ± 0.05	+ 0.04 ± 0.03
Moderate catabolism	128.49 ± 32.31	38.30 ± 6.44	0.23 ± 0.07	+ 0.07 ± 0.04

[a] $p < 0.05$

achieved in protein depleted patients with glucose alone (Fig. 4). Nitrogen loss decreased exponentially when increasing E_i/E_0 and reached a plateau at E_i equal to 120% of daily E_0. Greater quantities of E_i did not lower nitrogen loss further, consistently with our previous findings [15]. Nitrogen spared at the plateau was 44% of the basal fasting values in severely catabolic patients and 35% in moderately catabolic patients. Nitrogen loss at the plateau was in the range of the nitrogen loss of a normal non-catabolic fasting man. The treatment appears to be the unique factor in determining the protein sparing effect. The severity of the acute phase was in fact unchanged over the period of investigation as shown by a steady E_0 and the sudden return of nitrogen loss to pretreatment values 24 h after withdrawal of the TPN (Table 5).

Elwin et al. [8] did not find a protein sparing effect by loading critically ill patients in the acute catabolic phase with glucose alone; it is possible that the larger amounts of glucose used in our study account for the differences. However, it is more conceivable that the key point is the use of insulin, with its important protein sparing effects [19, 25].

Exogenous insulin may correct the abnormally low serum insulin levels found during loading in severely injured patients [8], and enables better utilization of the glucose. We are unable to separate glucose and insulin effects since insulin was always added during the glucose infusion to maintain a steady blood glucose level. However, the differences in insulin needed between severely and moderately catabolic patients and the protein sparing effect of glucose alone in our non catabolic patients (without problem of synthesis and sensitivity to insulin) strongly suggest an insulin protein sparing action.

We do not known if the insulin acts by reducing muscular protein breakdown [21], through appropriate glucose utilization or by limiting urea production

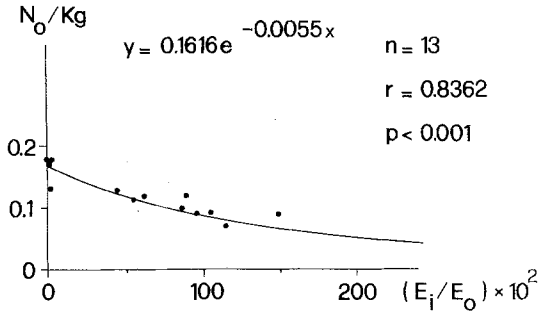

Fig. 4. Daily nitrogen losses (N_0, as g/kg) during TPN with glucose and insulin in control protein depleted patients. Energy intake (E_i) is expressed as a percentage of the same day energy output (E_0)

Protein Replacement Effects

The amount of amino acid used in our study is in line with the amount suggested to improve visceral protein synthesis [3]. TPN with amino acids resulted in an improved nitrogen balance, so suggesting a true protein replacement. Nitrogen loss as an index of protein sparing effect, during amino acid supply, is misleading because exogenous nitrogen also increases urea production. Our data show that the severity of trauma worsens nitrogen conservation so that it was impossible to reach a positive nitrogen balance in some of severely catabolic patients. When negative nitrogen balance was reversed (Table 8), regardless of catabolic class, the E_i as glucose was at least 100 – 120% of the daily E_0. Adding the amino-acid calories the total E_i, for nitrogen equilibrium reached 130% of daily E_0, i.e. 48 kcal/kg in severely catabolic patients and 38 kcal/kg in moderately catabolic patients. We believe that increasing glucose supply, i.e. with E_i higher than 130% of daily E_0, is useless, as blood glucose control is difficult to achieve and nitrogen sparing (Figs. 2 and 3) as well net protein utilization [21] are not likely to improve. Furthermore increasing E_i increases E_0 (Table 4), a further increase of E_i may cause metabolic rate (i.e. $\dot{V}O_2$ and $\dot{V}CO_2$) to rise to dangerous levels and to be hazardous in criti-

cally ill patients with poor cardiopulmonary reserves [1, 2, 13, 23].

In conclusion, the catabolic response in all injured patients is effectively reduced by early, short-term TPN; glucose and insulin appear to be responsible for the protein sparing effect of the treatment, while amino-acid infusion provides protein replacement. Severity of trauma reaction defines the absolute amount of calories, nitrogen and insulin to be administered to correct negative nitrogen balance. This is always possible if at least 100 – 120% of caloric requirements are given as carbohydrates plus about 20% as protein.

At higher caloric intake there is no consistent gain in protein sparing and replacement while the resulting hypermetabolism could be harmful to critically ill patients.

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Dr. G. Iapichino
c/o reparto Rianimazione "E. Vecla"
Ospedale Policlinico
via F. Sforza 33
I-20122 Milano, Italy