PROCEEDINGS OF THE NUTRITION SOCIETY
A Scientific Meeting was held at Lady Spencer-Churchill College, Oxford Polytechnic, Oxford on 26–28 July 1989

Symposium on 'New substrates in clinical nutrition'

Dipeptides in clinical nutrition

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Few areas of medical research and development have been the scene of such substantial and valuable progress as has the recent surge of research in parenteral nutrition (Cuthbertson, 1982). Short-chain peptides might be considered as 'brand new candidates'. Their potential use is based on the assumption that 'tailored' amino acid solutions will increase the benefits of intravenous nutrition for specific patient groups. Undoubtedly, this new approach has introduced a new dimension, though the explosion of new information about extraintestinal peptide assimilation is only a prelude, before intravenous use of di- and tripeptides in common clinical practice (Fürst, 1985*a*; Adibi, 1987).

'Liquours thus injected into veins, without preparation and digestion will make odd commotions in the blood, disturb nature and cause strange symptoms in the body, yet they have other thoughts of liquours, that are preferred of such things as have passed the digestion of the stomach' (Wren, 1665; Cuthbertson, 1982). This immemorial advice from Sir C. Wren would seem to be the first hint that enzymic digests are useful for parenteral nutrition. In 1913 Henriques & Anderson maintained nitrogen equilibrium in a goat by means of intravenously injected enzymic hydrolysate; the preparation contained about 150–200 g N/l in the form of peptides. The therapeutical implication followed 24 years later when Elman (1937) reported beneficial effects with an acid hydrolysate of casein in patients unable to take protein by mouth. In the middle of the 1960s Wretlind produced the first appropriate enzymic hydrolysate of casein consisting of (/l) about 670 g free amino acids and 330 g low-molecular-weight peptides. This preparation was widely and successfully used until the 1970s, when a large number of crystalline amino acid preparations appeared on the market (for references, see Fürst, 1985*a*).

Wretlind (1972, 1981) repeatedly emphasized that a suitable intravenous preparation should conform to that of a protein of high biological value, thus it should include all essential and non-essential amino acids found in such protein. The major unsettled inquiry, how to prepare and formulate such a 'complete, well-balanced' amino acid solution is, thus, to be solved. In this context it is notable that free tyrosine and free

cystine are poorly soluble while free glutamine and free cysteine are unstable during sterilization procedures and storage. The absence of these amino acids in currently available amino acid solutions creates a great problem, since tyrosine is proved to be an essential amino acid in chronic uraemia and together with cystine is considered to be essential in childhood. The indispensibility of these amino acids has also been claimed in liver cirrhosis. Profound intramuscular depletion is characteristic of catabolic conditions, and its extent seems unrelated to the magnitude of trauma or the dietary regimen (for references, see Fürst, 1985*a*). Thus, glutamine, tyrosine, and cystine should be mandatory components of intravenous amino acid solutions.

The possibility of substituting the currently available amino acid solutions with highly soluble and stable glutamine, cystine and tyrosine containing short-chain peptides recently became feasible (Fürst, 1985*a*; Adibi, 1987; Adibi *et al.* 1987), thus providing the opportunity to supply these amino acids by the intravenous route. In the last 7 years we have been engaged in studies designed to evaluate the potential role of the previously-stated approach. Our basic research plan attempted to combine peptide synthesis and characterization with investigations aimed at examining in vivo uptake and subsequent utilization. These investigations have been combined with trials to evaluate the nutritional benefit of the peptides, first in suitable animal models, resembling relevant pathological conditions, and successively to appraise their value in human nutrition.

PEPTIDE SYNTHESIS AND CHARACTERIZATION

In earlier studies we utilized chemical methods in aqueous phase. The procedure as well as the progress of purification have been described in detail (Stehle *et al.* 1982*a*; Stehle & Fürst, 1985). More recently we applied biotechnological methods. The purity of the synthesized final products approached 100% and the structures could be fully confirmed by field-desorption mass spectrometry and proton magnetic resonance spectroscopy (Stehle *et al.* 1982*a*,*b*; Groeger *et al.* 1988–9). Great attention was paid to examining the stability of the synthetic peptides during storage and heat-sterilization, especially bearing in mind the known instability of free glutamine (Meister, 1956; Stehle *et al.* 1984; Stehle & Fürst, 1987). No liberation of ammonia or formation of pyroglutamic acid, glutamic acid or L-alanyl-L-glutamic acid was observed (Stehle & Fürst, 1987).

The use of immobilized biocatalysts facilitates the development of rational and economical methods (Groeger *et al.* 1988–9; Stehle *et al.* 1990). Clear advantages of this novel approach are high (stereo)specificity of the reaction. The major benefit, however, is the economical low-price production of the desired short-chain peptides. Indeed, these factors might be the prerequisite for a rational industrial production of the peptides.

IN VIVO UTILIZATION OF INTRAVENOUS DIPEPTIDES: ANIMAL STUDIES

There is convincing evidence for an extraintestinal assimilation of di- and tripeptides. Following parenteral injection they are rapidly cleared from plasma without being accumulated in tissues and without appreciable loss in urine (Adibi *et al.* 1977; Amberger *et al.* 1985; Fürst, 1985*a*; Stehle *et al.* 1988*a*). This rapid clearance does not appear to be affected by bilateral nephrectomy or enterectomy (Adibi & Krzysik, 1977). The results from isotope studies with Ala[U^{14}C]Gln in rat and dog indicate that the peptide is easily

Table 1. *Kinetic values for L-alanyl-L-glutamine (Ala-Gln) and glycyl-L-tyrosine (Gly-Tyr)*

(Mean values and standard deviations)

	Ala-Gln (*n* 10)		Gly-Tyr (*n* 11)	
	Mean	SD	Mean	SD
r^2	0·975	0·024	0·975	0·028
K^{el} (/min)	0·185	0·024	0·203	0·019
$t_{½}$ (min)	3·80	0·50	3·44	0·32
V (l)	10·52	2·43	13·08	2·34
V^1 (l/kg)	0·140	0·028	0·176	0·032
Cl (l/min)	1·92	0·36	2·65	0·48

r^2, coefficients of determination; K^{el}, elimination rate constants; $t_{½}$, elimination half-lives; V, distribution volumes; V^1, coefficient of distribution; Cl, plasma clearance.

available and the constituent amino acids are rapidly used for protein synthesis, preferentially in muscle tissue (Stehle *et al.* 1989*a*). Data derived from studies with continuous total parenteral nutrition (TPN) in rats offer firm evidence that parenterally administered alanyl-glutamine provides free glutamine, especially for maintenance of the intracellular glutamine pool in muscle (Albers *et al.* 1984).

Importantly, infusion of alanyl-glutamine abolished the net efflux of glutamine and involved a net influx of alanine over the canine hindlimb similarly to the effect with equimolar amounts of free alanine and free glutamine (Roth *et al.* 1988). These results demonstrate that parenteral supply of alanyl-glutamine reduces muscle release of glutamine in postoperative anaesthetized dogs.

IN VIVO UTILIZATION OF INTRAVENOUS DIPEPTIDES: HUMAN STUDIES

Considering the results obtained in traumatized rats, it should be borne in mind that the intracellular muscle free amino acid pool of this animal is probably less suitable for the investigation of amino acid metabolism, due to the great differences in their distribution in human and rat muscle (Fürst, 1985*b*). Therefore, human studies are pertinent to evaluate efficacy and safety in healthy volunteers and successively to appraise whether intravenous provision of short-chain peptides favourably influences overall nitrogen economy or is associated with other clinical benefit.

KINETIC STUDIES

To examine in vivo kinetics of L-alanyl-L-glutamine and glycyl-L-tyrosine, peptide bolus doses of 30 mg/kg and 6 mg/kg were given within 5 s to ten and eleven volunteers, (aged 23–32 years) respectively (Albers *et al.* 1988). During a period of 30 min, blood samples were drawn on eighteen occasions for automated high-performance liquid chromatographic (HPLC) determination of plasma free amino acid and peptide concentrations (Graser *et al.* 1985). Elimination half-lives ($t_{½}$) were calculated from the elimination

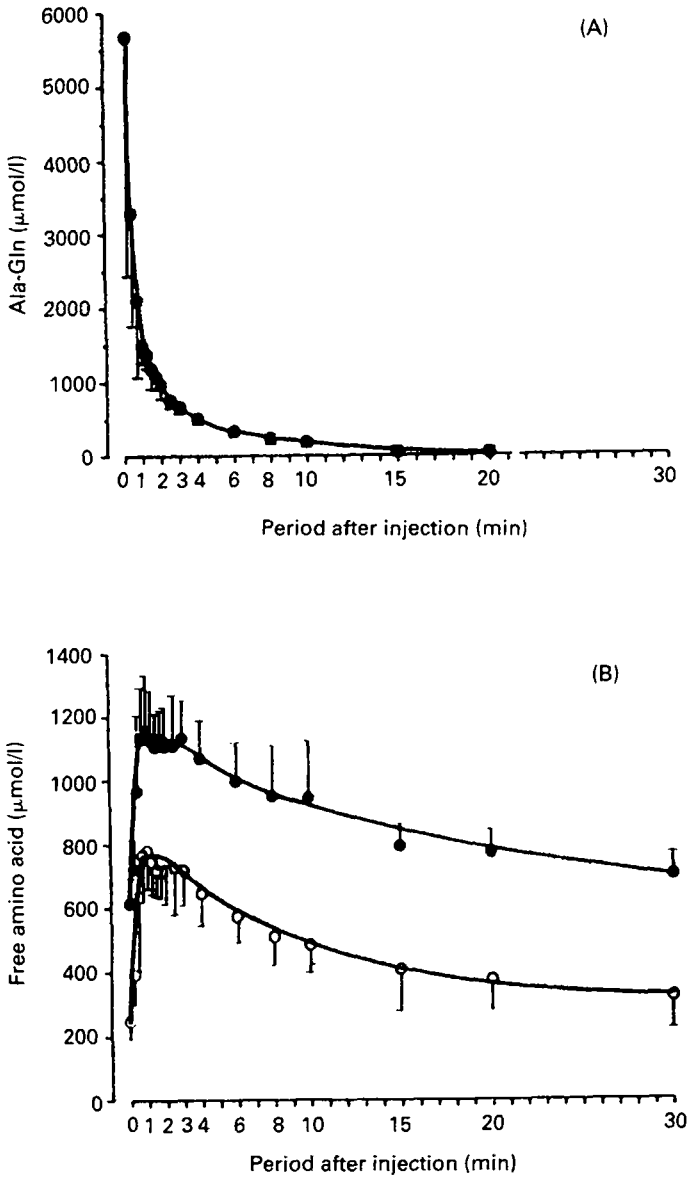

Fig. 1. Time-courses of plasma disappearance of (A) L-alanyl-L-glutamine and (B) liberation of alanine (○) and glutamine (●) after a single injection of L-alanyl-L-glutamine in ten healthy subjects. The eighteen sampling times are indicated. (Adapted from Albers *et al.* 1988.) Points are means and standard deviations represented by vertical bars.

rate-constants (K^{el}) of the descending slope of the individual plasma log concentration *v.* time curves, fitted by the method of least squares. Distribution volumes (V) of the peptides were determined by dividing the total given dose of the injected peptide by its concentration at time zero, extrapolated from the best-fitting line. Plasma clearance (Cl)

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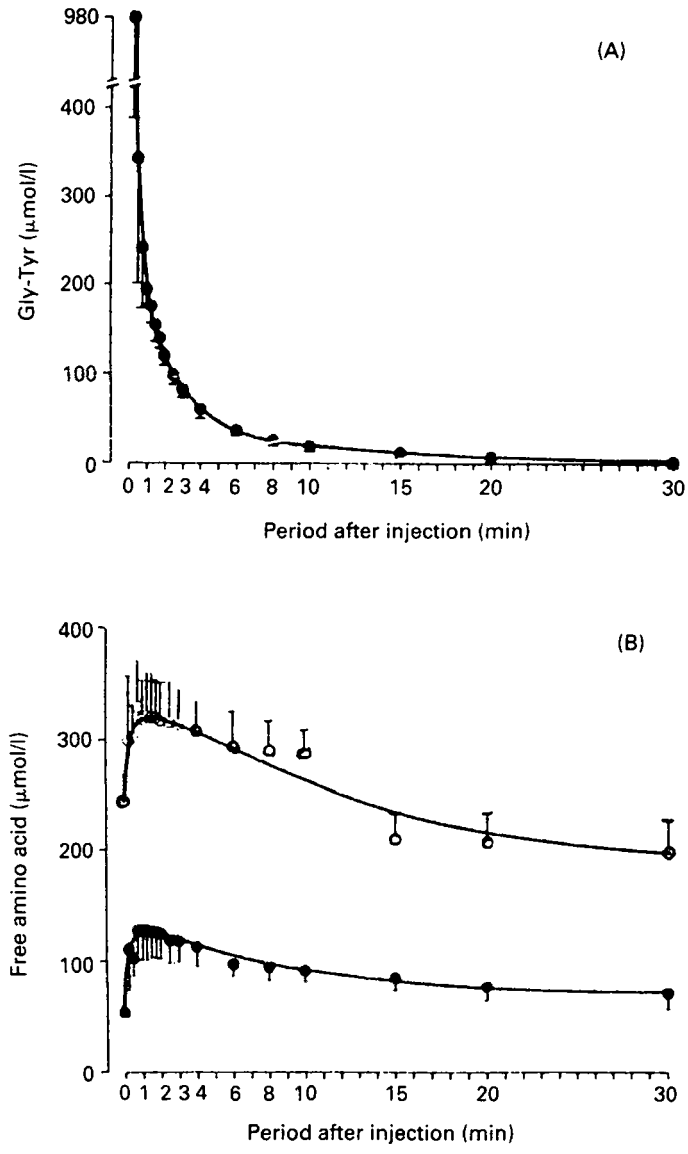

Fig. 2. Time-courses of plasma disappearance of (A) glycyl-L-tyrosine and (B) liberation of glycine (○) and tyrosine (●) after a single injection of glycyl-L-tyrosine in eleven healthy subjects. The eighteen sampling times are indicated. (Adapted from Albers *et al.* 1988.) Points are means and standard deviations represented by vertical bars.

was calculated by multiplying the distribution volume by the respective K^{el} (Gladtke & von Hattingberg, 1977). Kinetic values are given in Table 1.

The mean plots of plasma concentrations of peptides *v.* time after the intravenous bolus injections are shown in Figs. 1 and 2 respectively. At 30 min after the bolus injection no peptides could be detected. The plasma disappearance rates expressed as $t_{½}$

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Table 2. *Composition of amino acid–peptide solutions (g/l)*

	Peptide solution	Control solution
L-arginine	2·52	2·52
L-aspartic acid	3·13	3·13
L-cysteine	1·07	1·07
L-glutamic acid	6·86	6·86
L-histidine	1·83	1·83
L-isoleucine	2·97	2·97
L-leucine	4·04	4·04
L-lysine	2·97	2·97
L-methionine	1·45	1·45
L-phenylalanine	4·19	4·19
L-proline	6·17	6·17
L-serine	5·72	5·72
L-threonine	2·29	2·29
L-tryptophan	0·76	0·76
L-valine	3·28	3·28
L-alanine	2·29	2·29
Glycine	1·60	1·60
L-tyrosine	0·38	0·38
L-alanyl-L-glutamine	13·26	
L-alanine	5·44*	16·44
L-glutamine	8·92*	
Glycyl-L-tyrosine	2·64	
Glycine	0·83†	1·69
L-tyrosine	2·01†	
Total AA (peptides)	69·42	71·65
Total nitrogen	10·04	10·13

* Acquired from L-alanyl-L-glutamine.
† Acquired from glycyl-L-tyrosine.

revealed 3·8 and 3·4 min with coefficients of determination (r^2) of 0·98. As shown in Table 1 the distribution volumes (V) and the coefficients of distribution (V^1) showed only little interindividual variation (Table 1).

The patterns of the constituent free amino acid concentrations in plasma after a bolus injection are included in Figs. 1 and 2. Peptide disappearance was accompanied by a prompt and considerable increase in the concentrations of alanine, glutamine, glycine and tyrosine. The increments over the basal values between 1 and 3 min were equimolar for alanine 414·8 mmol/l (SD 34·6) and glutamine 442·0 mmol/l (SD 34·9) and for glycine 72·4 mmol/l (SD 5·2) and tyrosine 67·4 mmol/l (SD 5·5).

CONSTANT INTRAVENOUS INFUSION OF ALA-GLN

In a subsequent study, a commercial amino acid solution was continuously infused over 4 h in six apparently healthy volunteers (23–32 years) at an infusion rate of 96 mg amino acids/kg per h (Albers *et al.* 1989). Three subjects received a supplement of 24 mg

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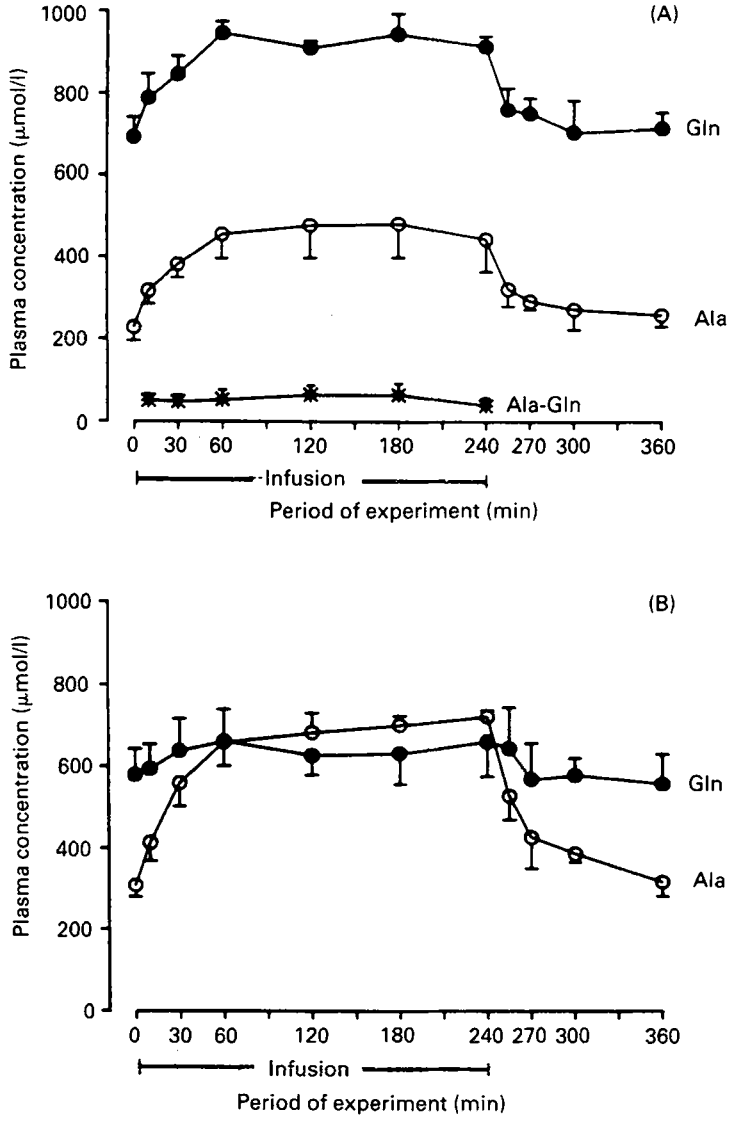

Fig. 3. Plasma concentrations of alanine (○), glutamine (●) and Ala-Gln (*) before, during and after infusion of a commercial amino acid solution supplemented with L-alanyl-L-glutamine (A) and alanine and glycine (B). For composition, see Table 2. The eleven sampling times are indicated. (Adapted from Albers *et al.* 1989.) Points are means and standard deviations represented by vertical bars.

L-alanyl-L-glutamine and 5 mg glycyl-L-tyrosine/kg per h; the other three subjects served as controls. They received instead of the dipeptides an isonitrogenous supplement of 29 mg free alanine and 3 mg free tyrosine/kg per h. N was infused at a rate of 18 mg N/kg per h corresponding to a total supply of 38·4 (SD 3·3) g amino acids or amino acids and

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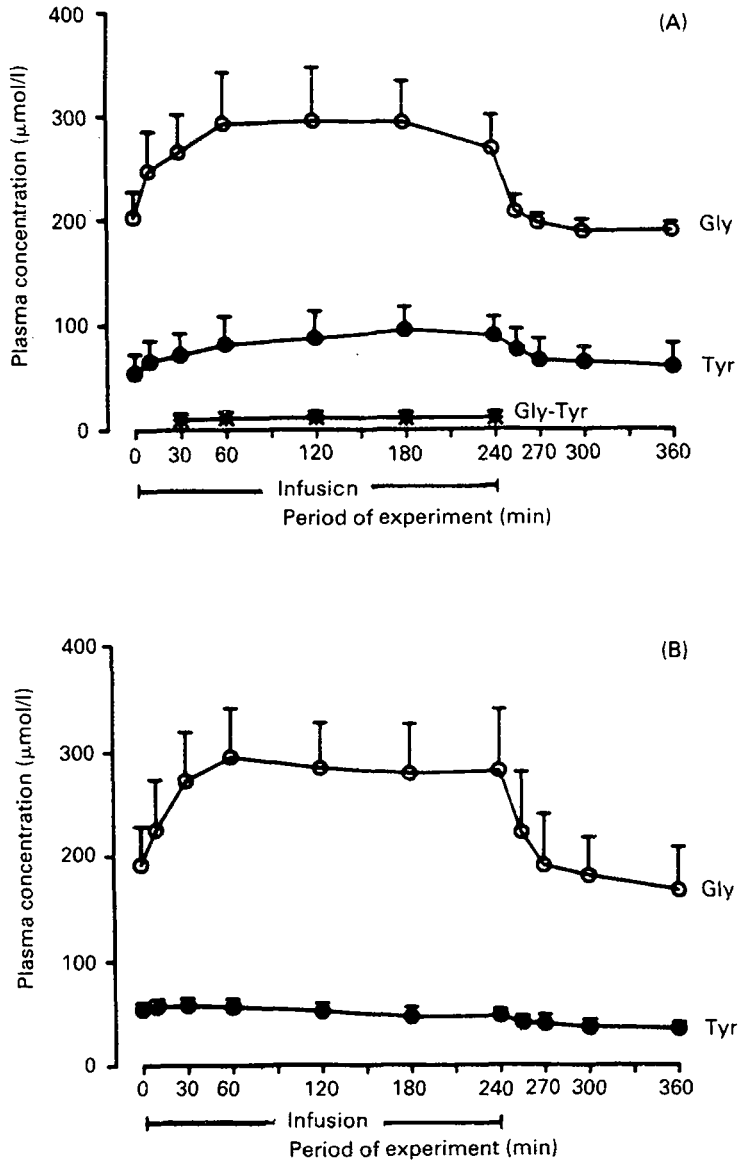

Fig. 4. Plasma concentrations of glycine (○), tyrosine (●) and Gly-Tyr (*) before, during and after infusion of a commercial amino acid solution supplemented with glycyl-L-tyrosine (A) and alanine and glycine (B). For composition, see Table 2. The eleven sampling times are indicated. (Adapted from Albers *et al.* 1989.) Points are means and standard deviations represented by vertical bars.

dipeptides over the 4 h. The composition of the solutions are given in Table 2. Repeated venous blood samples were drawn on eleven occasions, before, during and after the infusion for the HPLC determination of plasma free amino acids and peptides (Graser *et al.* 1985).

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Continuous infusion of the solutions was not accompanied by any side effects and the volunteers reported no complaints. Infusion of the peptide-supplemented solution resulted in a prompt increase in alanine, glutamine, glycine and tyrosine concentrations (Figs. 3 and 4). The concentrations attained an apparent steady-state after 60 min. The increments over the basal values between 60 and 240 min were: alanine 255·1 (SD 57·8) mmol/l, glutamine 232·8 (SD 22·1) μmol/l, glycine 86·5 (SD 10·0) μmol/l and tyrosine 34·3 (SD 2·8) μmol/l. During the entire infusion period, only trace amounts of the dipeptides could be measured in plasma, the values being just at the detection limit. In the 6 h urine collection dipeptides were not detectable. Since none of the dipeptides was detected in the urine, the results suggested a 'nearly quantitative' hydrolysis of the infused peptides, and indeed indicate subsequent utilization of the constituent free amino acids.

Infusion of the alanine- and glycine-supplemented control solution resulted in an increase of the concentration of these amino acids, the time-course being similar to that seen during infusion of the peptide solution (Figs. 3 and 4). The increments for alanine and glycine over the basal values during the apparent steady-state between 60 and 240 min were 381·0 (SD 1·0) μmol/l and 95·0 (SD 6·6) μmol/l. Throughout the infusion of the control solution no appreciable changes in free glutamine concentrations were observed but free tyrosine levels revealed a steady decrease. Compared with the initial concentration the final value of tyrosine was diminished by 34·1 (SD 2·7)%.

The occurrence of equimolar increments of alanine, glutamine, glycine and tyrosine (Albers *et al.* 1988) as well as the prompt liberation of these amino acids (Albers *et al.* 1989) suggests extracellular hydrolysis of the infused dipeptides. Intracellular cleavage of dipeptides has been repeatedly demonstrated after enteral supply of the peptides, preferentially at the site of the renal or intestinal brush border (Ganapathy *et al.* 1987). This interpretation of intracellular hydrolysis after intravenous provision of the peptides would require an equimolar efflux–reabsorption from tissues or organs of the liberated amino acids, a difficult proposition to accept given the heterogeneity of the various transport systems and intermediary metabolism of the constituent amino acids. Considerable hydrolase activity in plasma (Krzysik & Adibi, 1979; Adibi & Morse, 1982; Adibi, 1987; Stehle *et al.* 1988*b*) as well as the recent report describing hepatic assimilation of dipeptides by enzymes located on the liver sinusoidal plasma membranes (Lochs *et al.* 1986) also highly support an extracellular hydrolysis. Accordingly, Hundal & Rennie (1988) were able to identify a dipeptide hydrolase from plasma membrane in skeletal muscle.

An interesting observation is the steadily decreasing tyrosine concentration during infusion of the control solution (Fig. 4). It is tempting to speculate that infusion of an almost tyrosine-free amino acid solution results in a depletion of this amino acid. However, it is difficult to conceive that such a specific depletion could occur within the short infusion period of 4 h, especially since some tyrosine should have been converted from the ample amount of phenylalanine available. A possible explanation for the steadily decreasing tyrosine concentration may rest in competitive inhibition of tyrosine efflux due to the excessive supply of amino acids infused which share the L-transport system (Christensen & Kilberg, 1987). In fact, these amino acids have been given in concentrations of not less than 14 mmol/l approaching the K_m value of the L-transport system in muscle of 20 mmol/l (Salter *et al.* 1986). It is assumed that in the other tissues the transport systems are much more sensitive. Nevertheless, the considerable fall in

Table 3. *Composition of peptide-supplemented amino acid solution (g/l)*

Constituent	
L-arginine	6·98
L-glutamic acid	11·03
L-histidine	1·73
L-isoleucine	2·10
L-leucine	2·85
L-lysine	3·38
L-methionine	2·70
L-phenylalanine	2·03
L-proline	7·05
L-serine	7·05
L-threonine	2·70
L-tryptophan	1·05
L-valine	2·33
L-alanine	12·98
Glycine	7·80
L-cysteine (acetyl-cysteine)	0·39 (0·52)
L-tyrosine (N-acetyl-L-tyrosine)	0·92 (1·13)
L-alanyl-L-glutamine*	20·00
Glycyl-L-tyrosine†	4·00
Total amino acids (peptides)	99.07
Total nitrogen	15·87

* Corresponding to 8·20 g L-alanine and 13·46 g L-glutamine.
† Corresponding to 1·24 g glycine and 3·05 g L-tyrosine.

plasma tyrosine concentration could be fully compensated by infusion of glycyl-L-tyrosine as a tyrosine source.

These results emphasize that the infused peptides are readily hydrolysed in healthy man. The impressively short elimination $t_{½}$ values and exceptionally high clearance rates of the peptides as well as the rapid availability of the constituent free amino acids suggest efficient assimilation of the peptides. The results indicate that synthetic L-alanyl-L-glutamine and glycyl-L-tyrosine can be applied safely and efficiently as a source of free glutamine and tyrosine in the frame of parenteral nutrition.

CATABOLIC PATIENTS

As emphasized previously in the present compilation profound intracellular glutamine depletion is characteristic of injury (Vinnars *et al.* 1975; Askanazi *et al.* 1980*b*; Milewsky *et al.* 1982) and other hypercatabolic conditions (Askanazi *et al.* 1980*a*; Roth *et al.* 1982; Muhlbacher *et al.* 1984). Two recent observations suggest that glutamine is involved in regulation of muscle protein balance: the striking direct correlation between muscle glutamine and the rate of protein synthesis (Jepson *et al.* 1988) and the positive effect of glutamine on protein anabolic processes in vitro (Rennie *et al.* 1986; MacLennan *et al.* 1987). If maintenance of intracellular glutamine pool promotes conservation of muscle protein (Rennie *et al.* 1986; MacLennan *et al.* 1987; Jepson *et al.* 1988) there is an obvious indication for glutamine supplements in the parenteral nutrition of patients with

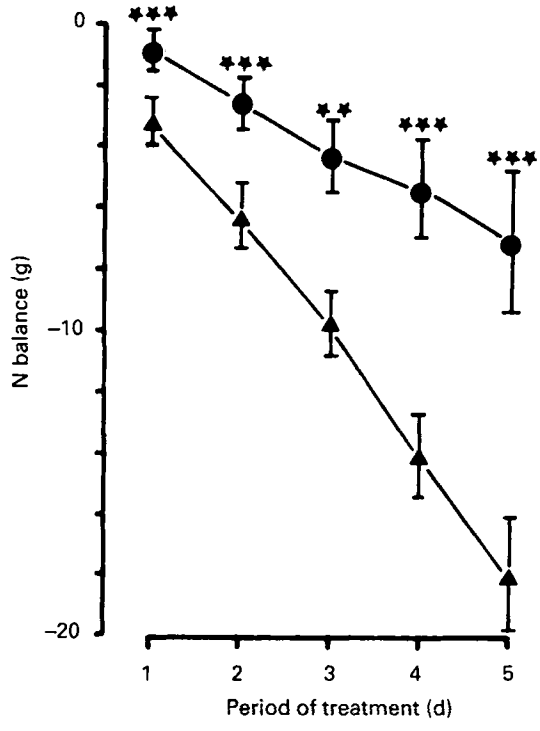

Fig. 5. Cumulative nitrogen balance in patients receiving L-alanyl-L-glutamine-supplemented total parenteral nutrition (TPN) (●) or conventional control solution (▲). Points are means with their standard errors represented by vertical bars. *** $P<0{\cdot}001$, ** $P<0{\cdot}01$.

injury and infection, though instability prevents its addition to existing preparations. This drawback can be overcome by use of synthetic glutamine-containing dipeptides.

The effect of L-alanyl-L-glutamine-supplemented TPN on post-operative N balance and muscle free intracellular glutamine concentrations was investigated in twelve patients undergoing elective resection of carcinoma of the colon or rectum (Karner *et al.* 1989; Stehle *et al.* 1989*b*). The patients were randomly allocated to a peptide treatment group or a control group and received isonitrogenous (0·23 g N/kg body-weight (BW) per d) and isoenergetic (166 kJ/kg BW per d) TPN via a central venous catheter over 5 d; the source of the non-protein energy (140 kJ/kg BW per d) was equally from glucose and a fat emulsion (Intralipid (Kabi-Vitrum, Sweden), 200 g/l).

The peptide group received TPN supplemented with the dipeptides L-alanyl-L-glutamine (280 mg/kg BW per d; 54 mg N/kg BW per d) and glycyl-L-tyrosine (50 mg/kg BW per d; 5·9 mg N/kg BW per d) (Table 3), while the control group received corresponding amounts of free alanine- and glycine-N. The infusion of the solutions was free of any side effects, and post-operative recovery was normal for each patient.

The daily N balance was significantly more positive with the glutamine dipeptide on each post-operative day. The mean daily N balance of −1·5 (SE 0·4) g with L-alanyl-L-glutamine was more positive than that of −3·6 (SE 0·2) g with the control solution ($P<0{\cdot}001$). The cumulative N balances on the fifth post-operative day (Fig. 5) were −7·1

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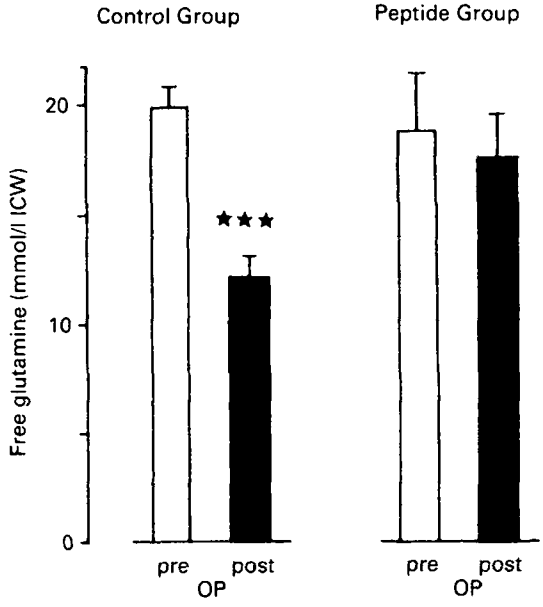

Fig. 6. Intracellular muscle free glutamine concentrations (mmol/l intracellular water, ICW) in patients before (□) and after (■) major uncomplicated abdominal operation (OP). One group received total parenteral nutrition (TPN) with conventional amino acid solution (n 6, control group), the other group was given TPN supplemented with L-alanyl-L-glutamine (n 6, peptide group). Values are means with their standard errors represented by vertical bars. Mean value was significantly different from pre-op value: *** $P<0{\cdot}001$.

(SE 2·2) and −18·1 (SE 1·7) g N, respectively ($P<0{\cdot}001$). The peptides were not detectable in plasma and muscle, and the plasma concentrations of the constituent amino acids did not differ between the treatment groups.

A percutaneous muscle biopsy (quadriceps femoris muscle) was performed (Bergström, 1962) and blood samples were obtained both during induction of anaesthesia and on the third post-operative day. Muscle free intracellular glutamine concentrations were similar preoperatively in the peptide and control group, 18·9 (SE 1·2) mmol/l intracellular water (ICW) and 19·7 (SE 0·9) mmol/l ICW respectively. Intracellular glutamine concentrations were maintained with TPN-containing L-alanyl-L-glutamine (17·5 (SE 1·0) mmol/l ICW), but were markedly decreased in patients receiving the control solution (12·0 (SE 0·6) mmol/l ICW; $P<0{\cdot}001$) (Fig. 6).

In preliminary studies, five patients with severe accidental injury were investigated in cooperation with Drs G. Guarnieri and G. Toigo, Trieste, Italy (Karner *et al.* 1989). On the day of admission, the patients were treated as necessary with fluid, electrolytes and whole-blood transfusions. After resuscitation, the necessary surgical procedures were performed. Thus, the nutritional therapy was not started until 2 or 3 d after the trauma. Two patients received TPN providing 310 mg amino acid-nitrogen and 165 kJ/kg BW per d. Three patients were given isonitrogenous and isoenergetic nutrition, but with 52

Table 4. *Average nitrogen balance over 5 d (post-injury days 3–7) and the individual cumulative N balances without (n 2) and with (n 3) L-alanyl-L-glutamine-supplemented total parenteral nutrition (TPN) in patients following severe accidental injury*

(Mean values with their standard errors)

	TPN without L-alanyl-L-glutamine				TPN with L-alanyl-L-glutamine					
Patients . . .	1		2		1		2		3	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
N balance (g N/d)	−15·3	2·0	−17·1	4·5	−4·8	0·8	−5·6	2·7	−9·7	4·8
Cumulative N balance (g N)	−76·3		−85·6		−24·2		−27·8		−48·5	

mg/kg BW per d of the amino acid-N provided as L-alanyl-L-glutamine-N. Muscle biopsies were performed and blood samples were obtained simultaneously 2–3 d after injury (i.e. at the commencement of the nutritional therapy) and on the fifth day of the treatment. Although the provision of about 20 g L-alanyl-L-glutamine (13 g glutamine) improved the daily and cumulative N balance (Table 4), it did not appreciably affect intracellular muscle glutamine concentrations.

INTRAMUSCULAR GLUTAMINE DEPLETION DURING CATABOLIC STRESS – A REAPPRAISAL

Recent studies have demonstrated that glutamine consumption by the intestinal tract is markedly increased during catabolism (Kapadia *et al.* 1982; Souba & Wilmore, 1983, 1985). In a 70 kg patient about 10–14 g glutamine/d is taken up by the gastrointestinal tract (Kapadia *et al.* 1982). Including the kidney uptake of about 4 g glutamine/d (Souba *et al.* 1985*a*) the total glutamine influx may thus be about 14–18 g/d. During stress, the reported value of muscle glutamine efflux varies in the range of 9–13 g/d depending on the severity of the catabolic stimulus (Kapadia *et al.* 1982; Souba & Wilmore, 1983, 1985). Thus, the estimated glutamine consumption appears to exceed the release by about 5 g/d. This value almost exactly matches the extent of muscle glutamine depletion in our surgical patients treated with conventional TPN over the 3 d period. Accordingly, in these patients, provision of about 12–13 g glutamine/d as the dipeptide L-alanyl-L-glutamine almost abolished the trauma-induced muscle glutamine depletion and greatly improved the N balance (Karner *et al.* 1989; Stehle *et al.* 1989*b*). These findings may indicate that the increased intestinal requirement of metabolic fuel is fully covered. In contrast, following severe accidental injury the same amount of L-alanyl-L-glutamine indeed improved N balance but the diminished muscle free intracellular glutamine pool was not influenced. This would suggest that in severely stressed patients the increased intestinal requirement of metabolic fuel is partly compensated but not covered.

According to the original hypothesis, the fate of intramuscular glutamine was to supply hepatic processes with carbon and N, and any deficit in glutamine could limit these processes during catabolic stress (Vinnars *et al.* 1975; Askanazi *et al.* 1980*a*,*b*). However, in the light of the present knowledge, a revision of the previously stated hypothesis is indicated. Thus, glutamine may primarily serve as an obligatory nutrient necessary for

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normal maintenance of the intestinal mucosa (Kapadia *et al.* 1982; Souba & Wilmore, 1983; Souba *et al.* 1985*b*). The reportedly increased intestinal requirement for metabolic fuel during catabolic stress might be matched by an enhanced demand for muscle glutamine and lead to intracellular glutamine depletion. This line of reasoning leads to the conclusion that the delivery of adequate amounts of glutamine is essential to maintain the integrity of mucosa, to preserve the muscle glutamine pool, and improve overall N economy during conditions of stress.

In conclusion, the present studies indicate that the increased intestinal requirement for metabolic fuel in post-operative patients can be well covered by the provision of 12–13 g glutamine/d. In contrast, following severe accidental injury, this estimated requirement may provide only part of the needed glutamine. Thus, while for patients suffering from major uncomplicated operative trauma a daily provision of 18–22 g L-alanyl-L-glutamine is recommended, a supply of 25–35 g L-alanyl-L-glutamine/d might be pertinent for patients after severe injury.

FUTURE ROLE FOR PEPTIDES IN PARENTERAL NUTRITION

The potential use of short-chain peptides as additional or alternative substrates for amino acids in the frame of parenteral nutrition has been recently reviewed (Adibi, 1987). As a main advantage, Adibi (1987) cites the low osmolarity of dipeptide-based parenteral solutions enabling them to meet the N requirement of patients with severe fluid restriction. Another approach is based on the premise that improvement of the quality of available amino acid solutions currently lacking glutamine, but also tyrosine and cystine, are major steps in solving the unsettled task of how to formulate and prepare a 'complete, well-balanced' amino acid solution (Wretlind, 1972, 1981). To come near to achieving this goal, a stable and highly soluble cystine-containing peptide has now been synthesized in our laboratory (Stehle *et al.* 1988*a*, 1990). The results of current animal studies (Stehle *et al* 1988*a*) underline the rapid and effective utilization of this synthetic peptide after intravenous bolus injection.

The very fast elimination of all synthetic peptides examined offers the advantage that substantial amounts can be provided without accumulation of these solutes in biological fluids. Thus the possible risk of undesirable pharmacological or physiological side effects, or both, are likely to be avoided.

The aim of this present study was to elaborate the nutritional potential of short-chain peptides and in catabolic conditions especially the needs for glutamine peptides. Indeed, only one peptide, L-alanyl-L-glutamine has been examined and the value of other glutamine-containing dipeptides remains to be evaluated.

It is certainly too premature to give a comprehensive recommendation about the nature and specification of the most favourable peptide or peptide groups. The potential utilization of a peptide by target tissues will most probably vary according to its structure and its biological effects (Adibi *et al.* 1987; Hundal & Rennie, 1988; Roth *et al.* 1988). Specific diseases may lead to certain amino acid deficiencies, antagonisms or imbalances in various organ tissues; these conditions might selectively cause a nutritional requirement for one or more specific peptides which are appropriate for use only in that specific condition to support the attenuated tissue.

These studies were supported by grants from BMWi (Industrielle Gemeinschaftsforschung, AIF no. 6668), and BMFT (Forschungsvorhaben no. 0319007A3).

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Printed in Great Britain