Lessons from Pharmacokinetics in the Design of New Nutrition Formulas for Critically Ill Patients

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Severe injury causes alterations in protein metabolism [1], including net muscle protein breakdown, increased transfer of amino acids (AAs) from the peripheral to the splanchnic area, intense use of AAs for gluconeogenesis and consequently a marked increase in nitrogen loss, leading to a negative nitrogen balance [2]. When persistent and/or very severe, this process is responsible for protein wasting and in turn for morbidity and mortality.

Nutritional supply must therefore form an integral part of therapeutic strategy in critically ill intensive care unit (ICU) patients. But the qualitative intake of nitrogen has to match the requirements of such patients, which are specific and different from those of healthy subjects [1]. The specificity of their requirements arises from a number of factors, some of which are summarized in table 1.

However, because historically the technical aspects were mastered before knowledge of the physiopathological alterations became fully known [3], the specific AA needs of ICU patients unfortunately long went unrecognized, and recommended requirements were merely adapted from those set for healthy subjects. Most products tailored for enteral use supply nitrogen in the form of high nutritional value proteins, and most solutions for parenteral nutrition (PN) provide a mixture of free AAs that reproduce the composition of these high-quality reference proteins (egg and cow milk proteins), namely \( \approx 45\% \) essential AAs (EAAs) and a ratio of EAAs to total nitrogen of \( \approx 3.1 \text{ mg/g}. \)

It is clear that current formulas are unlikely to meet ICU patients' requirements fully [4]. The key questions that must be addressed are the following: (1) How do we determine the AA requirements of critically ill...
patients? (2) Are there distinct disease-related qualitative requirements? (3) Should the requirements be fully individualized?

Isotope-based studies have yielded many important results [5]. However, these methods are difficult to implement for the non-EAAs (NEAAs), giving uncertain results that are possible for only one AA at a time, all other AA intakes remaining constant. Owing to overlapping and competition for cell transport and metabolism, it is likely that requirements for any given NEAA or EAA depends on the provision of a number of other AAs. For example, providing extra leucine (LEU) at pharmacological dosages (which is reasonable since this AA promotes protein synthesis at the translational step [6]) may modify valine (VAL) and isoleucine behavior (and therefore requirements) since these three AAs compete strongly for cell uptake and metabolism [7].

Another way to assess AA requirements is to use variations in AA concentrations in plasma [8], because AAs must pass into the bloodstream after oral, enteral or parenteral administration before any further cell metabolism or incorporation into proteins can take place. Although the plasma pool of AAs is quantitatively very small compared with its intracellular free pool, and almost insignificant compared with the AAs incorporated into the protein pool, the blood compartment may play a key role in controlling AA availability for protein synthesis [6] and for specific functions such as nitric oxide synthesis in the case of arginine (ARG) [9]. We have recently discussed the characteristics, regulation and metabolic significance of plasma AA levels [7].

Plasma AA concentrations at any particular time reflect an equilibrium between their rate of entry (Ra) into plasma and their rate of exit (Rd) from it. Ra sums AA intake and AAs released by tissues, and Rd sums AA oxidation,
metabolism and incorporation into proteins and, to a minor extent, loss in urine, feces, etc. [7].

Thus hyperaminoacidemia in a patient in stable metabolic conditions results from an overload of one or several AAs. Conversely a hypoaminoacidemia reflects a shortage of one or several AAs because their rate of utilization exceeds the rate of de novo synthesis plus protein catabolism, with an insufficient intake of the given AA(s).

Merely looking at AA levels in the post-absorptive state, although it simplifies the problem (i.e. in this case Ra = AAs arising from protein catabolism + de novo synthesis), cannot predict the effects of feeding, and so is of limited usefulness and may even lead to erroneous conclusions [3]. To estimate whether intake matches requirements it is necessary to measure the plasma AA level both at the basal state (i.e. post-absorptively) and at various times during AA administration.

We [10, 11] and others [12–14] have found that during continuous enteral [11], oral [13] or parenteral [10, 12, 14] administration of AAs there is a first sharp increase in AA levels and then a plateau lasting several hours. The level of the plateau, which reflects the balance between Ra and Rd, appears to be related to the rate of perfusion of each AA for any given subject [8].

This finding prompted us [15] to construct a one-compartment model with first-order elimination kinetics [16], to study the relationship between the increase in plasma AA level (pAAI) and the rate of perfusion for a given AA (AAx):

\[
\frac{(AA_{xt3} - AA_{xt0})}{f} = \text{rate of perfusion}
\]

Where AAxt3 is the pAAI of a given AA after 3-hour perfusion and AAxt0 the pAAI of the same AA at the post-absorptive state. There is a consensus [16, 17] that nutrition must be interrupted 3 h before the start of the test infusion, this wash-out period representing a compromise between too-short and too-long fasting.

We tested this model in healthy subjects receiving a new AA solution (AFD 10%, B. Braun) for PN [10]. The plasma concentrations of the infused AAs were closely \( r^2 = 0.92 \) correlated to their infusion rate (fig. 1). In addition, as expected, the steady state was reached within 3 h on AA infusion (except for glycine and lysine: 6 h). Renal reabsorption was over 99% for most of the AAs.

Our hypothesis and its related model were also tested in an interventional study in ICU patients [18] to determine whether a qualitative manipulation of AA intake could improve the nutritional status of patients. Surgical patients received total PN for two consecutive 5-day periods. The patients were randomized into 2 groups. The control group received the same standard AA solution for the full 10 days. The experimental group received the standard solution during the first 5 days, but was switched to a more individualized solution during the last 5 days. The composition of the second solution was determined from the dynamic test described above, i.e. choosing a solution...
available on the market that provided less of the AAs found to be oversupplied and more of those found to be undersupplied. AAs were defined as oversupplied or undersupplied when outside the 95% confidence interval (above or below the curve, respectively). Thus the selected solution provided (per gram of nitrogen) less of the AAs given in excess and more of those that were short.

During the second 5-day period (the test was performed again on day 8), imbalances persisted in the control group but were almost abolished in the experimental group. In addition, the mean of 5-day nitrogen balance was significantly higher during the second period in the experimental group than in the control group: 4.5 ± 0.8 vs. 0.2 ± 0.7 g nitrogen/day (p < 0.01). These findings suggest that the relationship between rate of infusion and plasma AA variations may offer a rational basis for choosing the most appropriate AA mixture for catabolic patients.

In our study on ICU patients [18], the relationship between (Aaxt3 – AAx0) and rate of perfusion was less close (r^2 = 0.45–0.88 with no relationship in 1 patient) than in our study on healthy subjects [10], and varied from one patient to another. This emphasizes the fact that the behavior of perfused AAs is patient-specific, and argues for setting intake rates on a patient-by-patient basis, or at least according to pathology (see below).

Notably, in 5 of 12 patients, the alanine (ALA) increase was appreciably lower than predicted from its rate of perfusion, which was very high. This evidently reflects a very high utilization of this AA in gluconeogenesis. The search for a relationship between this observation and overproduction of

![Fig. 1. Relation between the rate of infusion of amino acids and their plasma variations at steady-state (t3h–t0) in healthy volunteers. —— = Linear regression; ---- = 95% confidence interval. Reproduced from Bérard et al. [10] with permission.](image-url)
hormones (e.g. glucagon) and mediators (e.g. tumor necrosis factor-α (TNFα), interleukin-6) in the concerned patients would be useful and deserves future study. Also of major interest was the observation on day 3 that all but one of the patients analyzed displayed abnormally high variations in levels of lysine (LYS), which was apparently infused in too high amounts for our population of catabolic patients. This was accompanied by a surprisingly high enrichment of plasma ARG; although on the contrary data from the literature [19] would have led us to expect that standard solutions would undersupply this AA. This may be because LYS and ARG share a common transport system, called CAT [9]. Therefore, oversupplying LYS may be responsible for a decrease in ARG uptake and further metabolism with an accumulation of both AAs in plasma. Decreasing LYS intake in the experimental group also normalized ARG levels [18].

A study of particular interest is that of Lerebours et al. [20]. Gastroenterological patients (mainly with Crohn's disease) received the same AA solution in two cross-over periods over 16 or 24 h. Plotting the plasma variations of each AA against the infusion rate showed a clear-cut relationship between the two parameters (NB: in this study AA_t0 was obtained after 7.5 h withdrawal of the perfusion and sample at steady state after 15.5 h of perfusion). Increasing the perfusion rate 1.5-fold (i.e. the same amount over 16 h instead of over 24 h) resulted in 2.5-, 4.5-, 2.0-, and 2.2-fold increases in proline (PRO), ALA, VAL and LEU, respectively. Increases for most of the other AAs were proportional to the increases in infusion rate. This suggests that PRO, ALA, VAL and LEU intakes are excessive compared with intake of other AAs in these patients. However, urinary elimination of AAs did not differ between the two rates of perfusion, indicating that the imbalance remained in the homeostatic range. Evidently then, a standard AA solution undersupplies ALA in ICU patients [18] but oversupplies it in gastrointestinal patients [20].

Thus a number of factors may affect the relationship between rate of perfusion and pAAI enrichment. These factors may include the type of pathology (depleted vs. hypermetabolic) [21], and the level of concomitant energy administration [8, 21]. Notably, the rate of plasma clearance after total parenteral nutrition (TPN) cessation also depends on the underlying pathology [17, 18].

Such a direct relationship between the rate of infusion and the patients' needs cannot be established for all AAs when they are provided by the oral or enteral route [13]. This is because, using this route of administration, the first absorption stage in the splanchnic area totally modifies the pattern of AAs appearing in the general circulation.

For example, a large proportion of glutamate (GLU) is extracted and metabolized in the gut [22], and a large proportion of glutamine (GLN) is metabolized by both the intestine and the liver [23]. Therefore, even though GLU + GLN represent ≈ 20% of total AAs in ingested proteins, they form only a small minimal proportion of the AAs appearing in the general circulation.
Conversely, branched-chain AAs (BCAAs) also represent ≈ 20% of AAs in ingested proteins, but make up 40% of total AAs appearing in the general circulation, because BCAAs are only poorly metabolized in enterocytes and not at all in hepatocytes [24]. However, the kinetics of AAs appearing in the general circulation are particularly interesting because it is clear that there is a relationship between plasma enrichment of AAs and protein synthesis (especially in muscle) in the postprandial state [1, 6]. Recent studies [25, 26], strongly suggest that sarcopenia in elderly subjects may result from an abnormally high postprandial sequestration of AAs in the splanchnic area (twice that in young subjects). Providing 80% of the daily ration of proteins in a single meal affords similar protein synthesis in elderly and young adults [27]. This suggests that splanchnic sequestration of AAs is a saturable process. This may explain why a very high intake of GLN (>30 g/day) by the enteral route is required to obtain a beneficial effect in critically ill patients, whereas lower intakes have no effect [28, 29].

Monitoring variations in plasma AAs during continuous enteral nutrition may also help to evaluate the efficacy of the form of nitrogen intake. For example, we demonstrated that when nitrogen was provided in the form of a peptide-based diet, LEU plasma levels and LEU enrichment (LEUt3–LEUt0), were associated with a higher insulin secretion [11].

Finally, the new and interesting concept of slow/fast proteins [30] is also relevant here: ingestion of fast proteins (e.g. lactalbumin) leads to a faster and higher increase in plasma LEU than that of slow proteins (e.g. casein), but this is a transient effect and the areas under the curves of pAAI after some hours, the amount of proteins oxidized and the protein turnover are equivalent, regardless of the type of protein. Since these proteins affect protein synthesis and protein catabolism differently, this concept may nevertheless have important applications in feeding ICU patients according to their underlying type of catabolism (decreased protein synthesis or increased protein catabolism).

In conclusion, kinetic measurements of plasma AAs following parenteral or enteral administration of AAs throw light on patients' qualitative requirements. These determinations can be used to define more closely adapted solutions for critical care patients and could be useful for individualized patient monitoring. In addition, these findings justify pharmacy facilities, the cost-effectiveness of which versus marketed ready-to-use bags is currently a subject of discussion.

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**Discussion**

*Dr. Baracos:* In the study by Bérard et al., did the amino acid infusion contain all 20 amino acids used in protein synthesis and any other amino compounds of interest, or was it a subset?

*Dr. Cynober:* Which one, on healthy subjects [1] or patients in the intensive care unit (ICU) [2]?

*Dr. Baracos:* Both, particularly in the ICU patients. I would say that it is perfect or has been nicely done.

*Dr. Cynober:* The product used in the ICU patient study was really a standard product, at that time it was most popular in France. The name is Vinténe®, containing 20 g of amino acids and all standard amino acids but no cysteine, no glutamine, and very low amounts of tyrosine. It was really a standard solution mimicking the composition of the most efficient proteins such as egg or milk protein.

*Dr. Baracos:* I would like to see that done with all the amino compounds of potential interest. I find this approach enormously helpful. I guess the difficulty that I have with the present discussion on mono amino acid therapy is that if you are giving glutamine or arginine or leucine, or whatever it is you may chose to supplement, what you might expect to be the outcome of that supplementation is only as good as your concept of what is likely to be the first limiting amino acid. If you are supplementing something which actually is in fact the second limiting amino acid or if there are two concurrent, or 3 or 4, I don't know how many concurrent amino acids which are limiting to an important degree, you supplement one of those, you can expect to see exactly nothing. I think the approach that you described could be quite useful, especially in those situations where you believe the amino acid requirements to be highly deviated from the normal condition but you do not have a clue as to where to start. So we very much look forward to seeing more work of this kind in different patient populations.

*Dr. Breuillé:* I have a small comment about Dr. Baracos proposal. I think it is true that there is a risk of losing some effect when you have secondary limiting amino acids, but it probably is worth a try. My other comment is that, with this kinetic study, it is in fact necessary to see the amino acids that are going to accumulate or not. We know that some amino acids accumulate easily or not at all. For instance amino acids like threonine or valine accumulate very easily in the blood, and others like tyrosine or cysteine do not. So my question is, is there a risk of missing some amino acids?

*Dr. Cynober:* I didn't answer Dr. Baracos, it was more a comment. I don't claim that these solutions, especially for the parenteral route, are totally inadequate for patients, especially those in the ICU with major stress. Of course then we can discuss a number of issues, for instance the reliability of the compartment that we are exploring, but it
is exactly the same problem of what is the best precursor pool when you are working with stable isotope, etc. Of course if we improve the alanine intake there is a risk that other amino acids become more limiting but it is not certain, we have to verify that. Remember that in the data I presented when we provided more alanine we corrected the imbalance and there was no new imbalance or almost no new imbalance appearing in patients, and the nitrogen balance was improved in that group. Now the second part of your comment/question, when you say that threonine accumulates, or tyrosine accumulates, to which study are you referring?

Dr. Breuillé: We know that some amino acids are very well controlled in their concentration in the blood, for instance for cysteine it is very difficult to see a large increase in this amino acid. It is true that it is even more pronounced if you look at the supplementation by the enteral route, and so it is very difficult to extrapolate the enteral administration.

Dr. Cynober: All amino acid increases are very well controlled for the simple reason that high amounts of most amino acids may induce brain disorders and the organism makes very big efforts to control the concentration of amino acids in fixed concentrations. It is my opinion, and if you look at the range of variation of amino acids in physiology and pathology, it is almost the same for most amino acids.

Dr. Zazzo: Some clarity about the critically ill patients in St. Antoine Hospital. We know that the amino acid profiles are different in liver disease, acute liver disease especially, and renal failure. I think these patients were not in renal failure, had no organ failure, but probably you must accept this kind of patient on the rationale of this prospective study.

Dr. Cynober: In that study patients with renal and hepatic failure were not included, and during the study those patients where excluded from the protocol. I mentioned that organ failure modifies the requirement of amino acids. Another thing related to this aspect is the problem of lysine. From a survey of the literature, I am certain that lysine is given in excess in ICU patients. But note that if we are afraid of the possibility of arginine giving rise to nitric oxide, perhaps it is a good thing to provide some patients large amounts of lysine. Furthermore, we have heard that it would be alright for ICU patients to have 50% essential amino acids. I don't share this view because essential amino acids are not used in large amounts in such situations and they recycle very well. I think that the true problem of availability is the amount of nonessential amino acids in this situation.

Dr. Nitenberg: I have two short questions. Maybe I missed something in the methodology of the Bérard studies [1, 2]. I don’t know how to use the plasma concentrations of amino acids. Finally you show that you have a decrease in alanine, for example, in very severe patients, but did you measure what the uptake of alanine was in this situation, and what about excretion, because if uptake is improved it is very different from the situation in which there is a high excretion of amino acids. In one of your slides, at day 8, you show that suddenly the nitrogen balance was negative in the control group compared to the positive balance on day 3. Did the situation of these patients change to explain that? Finally, if you suggest that there is a shortage in alanine, do you suggest that the dipeptide alanyl-glutamine is perfectly suited for critically ill patients?

Dr. Cynober: It makes sense to come to such a conclusion. First, you said a decrease in alanine. There was no decrease in alanine, there was an increase which was lower than expected from the rate of perfusion. That is quite different because of course due to the activation of transporter controlled by the hormones, by cytokines and other mediators, there is a relationship between the use of this amino acid and further use in the tissues. As an example, if by using a pharmacological method or, in a model of perfused rat liver for example, you block alanine utilization in gluconeogenesis with the stimulation of glucagon, you will immediately see an increase in free alanine in the liver.
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Then there is a control, which is called trans inhibition control, which causes the increase in intracellular alanine to exert a feedback on the cellular transport of alanine, and the uptake of alanine will immediately be decreased. In other words there is the same type of concept as developed by Newsholme et al. [3] some years ago about the control of the pathway. I think it is important to understand the mathematical manipulation well in that circumstance. Concerning your other question, it is not a negative nitrogen balance, it is a null balance, i.e. not different from zero, and I am not certain that this balance was significantly different from the two balances during the first period. Perhaps you were very impressed by the fact that from day 0 to day 5 it was up and down for the control group after that. It is true nitrogen, it is not derived from urea, and so I am confident with this parameter.

Dr. Déchelotte: I would like to make 3 different points. I am quite convinced that the pharmacokinetic approach may be helpful to design formulas, but I think when we make some pharmacokinetic calculations at best we would need to have several distinct and different infusion rates in order to check whether there are some linear pharmacokinetics or not. Probably our metabolic clearance of several amino acids is not linear. That could explain why in healthy subjects there is a very nice relationship between the infusion rate and concentration just because the metabolic clearance rate is supposed to be constant all the time for the people, and it is quite different in your patients in both studies, as you underlined, because some metabolic clearance of some distinct amino acids, such as valine, may be reduced in the case of valine or increased in the case of alanine. So I think before drawing definite conclusions about the ideal profile of the amino acid composition we need more information on the dose relationship, the infusion rate relationship to the whole pharmacokinetic approach.

Dr. Cynober: This is why the session is entitled 'towards the future'. I agree with you. Of course if you have increasing levels of perfusion you have additional information but by knowing the rate of perfusion you can calculate the rate of utilization of the whole body and you can calculate the central clearance, but note that it is exactly what Lerebours et al. [4] did, it was the same amount of amino acids at a different rate. We achieved exactly the same condition and we had the same linear regression. Also there is a classic paper, an American paper by Clowes et al. [5], which was published in Surgery almost 20 years ago. They made arteriovenous differences and made similar calculations, and made the same conclusions about the reliability between the rate of perfusion and tissue utilization of amino acids.

Dr. Déchelotte: Going on with the same point. The difference also in the Lerebours et al. study [4] was that during the night patients were fed cyclically or continuously, so they also received higher amounts of glucose and lipids during the night together with amino acids over 12 or 14h instead of 24h. Probably then there was some influence of energy intake on the metabolic clearance of amino acids. The second point is about this difference in kinetics between casein and whey proteins which was so elegantly shown by Boirie et al. [6]. Of course there was a difference in the acute effect on protein synthesis or protein degradation but, as you know, there was also a difference in the net leucine balance at the end and casein had a better global leucine balance than lactoserum because it has less influence on protein synthesis but a better beneficial effect on inhibition of protein degradation. This kinetic difference is mainly related to the gastric emptying profile of these proteins. I assume we should be cautious in extrapolating these data from healthy subjects to the situation of ICU patients where we know that there is a great incidence of gastroparesis. The difference in the profile of gastric emptying, degradation, absorption and influence on protein metabolism could be quite different for these two types of proteins.

Dr. Cynober: We have to rewrite this paper because I remember that the total balance was not different.
I feel that this type of approach may be very useful because we were discussing huge amounts of arginine, huge amounts of glutamine, and new products with huge amounts of both glutamine and arginine, nobody studied any competition. At the last ESPEN Congress in Glasgow several new products were displayed without any pharmacokinetics or clinical evaluation. On one hand we are discussing pharmacology and on the other we don’t make the studies which are required for such products. Could you imagine that a new non-steroidal anti-inflammatory agent is released on the market without any pharmacokinetic or pharmacological study? I think we have to take note of all these elements, which is probably not feasible, but of course the protein nature of the different diets used, some are based on animal proteins which are very rich in lysine and poor in arginine. If you use soy proteins it is the reverse and the difference is huge, and therefore you can have major interference in the metabolism. Again we discussed the problem of giving immune-enhancing diets to elderly subjects. Why to elderly subject, because there are some data which indicate that this probably has something to do with the splanchnic sequestration of amino acids and the specific metabolism of arginine into citrulline in this tissue. We need data about that. Of course I agree with your interpretation of the Boirie et al. [6] study.

Dr. Déchelotte: My last point was about splanchnic uptake in older patients. The data by Arnal et al. [7] were gained in healthy old people, not in ICU patients. I agree with you that there are very little data in these old ICU patients. We studied the splanchnic uptake of leucine in operated patients with a cross-perfusion of stable isotopes. They were middle-aged, about 50–55-year-old cancer patients, and the splanchnic uptake of leucine and glutamine was quite similar in these patients to that observed in healthy subjects.

Dr. Berger: I am a bit confused about all those plasma levels and I need your help here. Of course we need pharmacokinetics, of course plasma is what we can get at, but our ICU patients are very unstable and their plasma levels, I know that from micronutrients, are just very difficult to assess regularly. Plasma levels reflect flow. You very nicely made the point that about 35–50% of enterally administered glutamine is likely metabolized into the gut. Not to have an increase in plasma level does not mean it does not work. What do you think about that, because of course we have to compare solutions which give the same amounts and if that was the point I fully agree, but not achieving the same plasma levels does not mean the solution is not working.

Dr. Cynober: Patients are unstable in the ICU but I studied burn patients for years and we can have a very reliable profile 2 or 3 days after burn injury. Again, and I agree with you, there are fluxes and there are concentrations. It is absolutely certain that the basal concentration or only the concentration under perfusion is of no interest. I am sure there are too many factors that can be involved in increase or decrease. That is why the difference in concentration and perfusion is mandatory. In that condition if you are able to saturate splanchnic sequestration of glutamine, you must see glutamine increasing the general circulation.

Dr. Moore: I used to be a disciple of Frank Cerra and read all his work. I really believed in it. We went through a phase, at least in the United States, of being very excited about altering the amino acid composition for these different solutions and thought that we were going to improve outcome. There were a number of trials done on branched chain amino acids suggesting that you could alter metabolic endpoints, improve protein synthesis, but we could never show an improved outcome. There was a small study from Spain [8] recently showing a decreased mortality. Similarly, in liver failure we can make people wake up in the ICU but not too many of them would walk out of the hospital as a result. With dialysis renal failure it is the same thing: we can decrease dialysis needs but at the end of the day there is the same number of dead patients. So my question to you is, is there a greater interest in Europe about this, and
then the second question is, if you had to tell me what the ideal amino acid solution is for my ICU patients what does it need to be supplemented with?

Dr. Cynober: I am very happy with that because it will allow me to discuss a specific problem and to demonstrate how a potentially very interesting concept has been killed, the concept of branched chain amino acids. Because I have not discussed two things: one is galenic which does not concern branched chain amino acids, and the other is the cost of the products. As you mentioned there has been a lot of work on the possible pharmacological effect of branched chain amino acids, and most of the results were disappointing. I will take the example I know the best, which is burn injury. In total there are six experimental and clinical studies involving supplementation of branched chain amino acids by the parenteral route. Branched chain amino acids in burn injury improve protein metabolism, improve nitrogen balance, decrease 3-methylhistidine excretion and so on, but only in one condition, when the solution is enriched with leucine. If you look at most of the products available on the market, due to the cost of amino acids they are actually enriched in valine, in isoleucine. Because the 3 amino acids compete very tightly for cell uptake and metabolism, when you are providing this so-called enriched solution of branched chain amino acid, what you are actually giving in percentage is a leucine-poor solution, and this explains why most of the studies failed to provide results. Again simple pharmacokinetic studies show that and the recent study I mentioned by Kimball and Jefferson [8] on the control of protein synthesis regulation is exactly in agreement: only leucine has such properties. Again, of course there is nothing to expect by providing 80% of the diet in the form of branched chain amino acids included in the total amount of nitrogen given it is totally imbalanced. That is why in the introduction I mentioned the concept, especially for parenteral nutrition, as being established long before we had most of the helpful physiopathological knowledge that we have now. Finally we are of the opinion that most experts say that all solutions are equivalent, nobody has shown any difference in manipulating the standard composition of amino acids. It is not a special European interest, it is an ignored field of research and I think that now is a good time to readdress this type of question.

Dr. Martindale: We have all these fluxes of amino acids. You haven't addressed the fact that we have 5 systems to absorb some of these amino acids: system Y, system B, system B0, system CAT2, etc. You showed CAT2 competing with lysine. So not only do we have the confusion of the individual amino acids but the 4 or 5 transporters for which they compete, and those are changed by diseases. We don't really know what happens to these transporters in critical illness, we don't know in sepsis, we don't know in trauma.

Dr. Cynober: Yes, it is perfectly true. It is the type of study we are performing, realistic studies with a pragmatic approach, and we have global results. At the tissue level I would like to mention the work by Souba and Pacitti [9]. For example Pacitti et al. [10] studied the N system of transport for glutamine in various tissues and with various results. But I fully agree that we have a lack of knowledge in this specific area.

References


