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Dr. Young: It is presumptuous of me and certainly very difficult to try to overview and integrate the information we’ve been presented with during the course of the last two days. I think we’d all agree that we’ve been given a mass of interesting and exciting information that we shall need to ponder and try to decide where it fits into the future design of enteral products, particularly with respect to their nitrogen components. Yesterday Dr. Robert Dobbie raised the issue of the clinical relevance of the basic science that began our workshop discussion; Dr. Freedman indicated that the pancreas was the site of the soul, and Dr. Reeds said his heart was in the gut, so we’ll begin at the gut.

Dr. Reeds gave us a very nice presentation indicating how the gut modifies the profile of amino acids that are presented to the portal circulation. And he made various observations that are important and worth thinking about. One in particular related to the fact that glutamine, glutamate, and cystine are extensively taken up and utilized by the intestinal mucosa. Another observation he made that I find very interesting is the important extent to which amino acid catabolism contributes towards meeting the energy needs of the mucosa. I’d like to ask Dr. Reeds to try to indicate to us what the clinical relevance of this might be with respect to the improved formulation of the amino acid component of enteral feeds.

We then heard about the regulation of splanchnic protein metabolism from our colleague, Dr. Tessari, and one observation that I found particularly interesting was the prandial stimulation of albumen synthesis, and the extent to which that accounted for a significant utilization of the amino acids that are absorbed. We heard this afternoon from Dr. Bergström that cytokines downregulate albumen synthesis, and I wonder whether – under conditions of disease where cytokine levels are high and therefore albumen synthesis is low – this accounts for the reduced level of efficiency with which ingested protein is utilized.
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In Dr. Grimble’s excellent presentation, we heard that the peptide transporter PepT1 is fairly resistant to the stresses and strains that occur in disease states – in contrast to the downregulation of the amino acid transporter system – and this presumably has clinical implications with respect to the design of the protein, peptide and amino acid components of enteral feeds.

We heard from Alan Jackson about the significant nitrogen flux within the intestinal tract, and he raised the question of what the significance of this might be in diseases of the large bowel. I guess that’s not known at the moment, but this is an area that we need to explore further, particularly with respect to how one might optimize the maintenance of the nitrogen economy of the host.

We heard about fast and slow proteins from Dr. Beaufrère. It’s beautiful physiology, but I’m just trying to think through what the clinical implications of those observations might be. The one that I found particularly interesting was the issue that Dr. Millward raised, related to the impact on appetite regulation of the type of protein ingested. The whole area of the impact of the dietary amino acid profile on CNS function is something we need to think more about.

Dr. Millward’s presentation of the postprandial utilization concept is, I think, an extremely important new development for the better evaluation of the consequences of enteral feeding, at least from a protein metabolic standpoint. His postprandial utilization model is a relatively clinically friendly model, and I can see ways in which he might make it even more friendly, perhaps using bolus rather than infusion approaches, but at least this offers us an opportunity to begin to address the question of what the amino acid requirements are under particular specific pathophysiological conditions.

And finally, I’m still trying to understand the whole issue of sulfur amino acid relations, and it seems to me that there is a lot there to think about. I was intrigued by the presentations related to that particular topic. We don’t really know what the optimum methionine/cysteine ratio should be in the normal individual but it appears that this ratio may have to change to effectively maintain sulfur amino acid economy in the sick patient.

Dr. Fürst: The second day was clearly related to clinical applications. Consequently it is no problem to place the papers in a clinical context and see practical applications. I would once again like to emphasize that basic science research is the prerequisite for understanding the regulation of many systems, so it is an extremely important basis for our clinical work, even if it is not necessarily always directly applicable to the clinical context. Selye, the father of stress, said, ‘Our facts must be correct. Our theories need not be if they help us to discover important new facts’ – and that is just what we are doing with basic research. We make a lot of mistakes; we consider them and go further and find new facts and new research theories. For example the branched-chain amino acid approach, especially implicating leucine, tried in the mid 1970s and claimed in the 1980s, was not successful. Nevertheless, it takes its place as an important tool in helping our understanding of metabolism, but not in the clinical context.
Now I would like to bring up some other points. One is the question of study design. As Dr. Silk pointed out, there have recently been many poorly conducted studies. One may legitimately ask, why. It is one of the most important tasks for the future to ensure that the performance and endpoints of a study are appropriate. In this context I have great difficulty in accepting the suggestion that an enteral feeding regimen that provides perhaps only 50% of the prescribed energy and protein should be accepted as a realistic baseline. Indeed, such a regimen will certainly ruin the validity of the results obtained.

I would also like to raise the question of bioavailability. When discussing new substrates, one should emphasize that it is not always possible to correct a deficiency with supplementary measures. Taurine deficiency occurs in numerous clinical situations, taurine supplementation might not be desirable because this substance is not taken up. So we should look for new products well suited to our purpose. We should not be lazy and accept old preparations; we should look at the data obtained from basic research and produce new preparations that will have a positive impact on our clinical efforts.

Finally, I would like to consider the influence of intestinal blood flow. This is a very important factor in the study of substrate handling in the intestine. It was not really considered in the models that were presented on the first day, but it should have been. At this point I would like to ask one of my teachers, Dr. Kinney, who perhaps has the greatest experience in connecting basic science with clinical practice, to tell us his ideas about these two days.

**Dr. Kinney:** First I’ve found the two days extremely informative. However, I was a little surprised that, while we have heard a great deal about the cells and their function in relation to the intestinal tract, the perfusion of those cells did not seem to be part of the discussion. I think it’s generally accepted that with a protein meal, one can expect that it will be followed by an increase in intestinal blood flow, but I have to ask, do we have any information about the relation between either peptides or free amino acids in relation to their influence on intestinal blood flow? I was also interested in Dr. Barbul’s discussion of possible arginine supplementation and the fact that’s it’s a source of nitric oxide – this may seem a little off the subject but I think it may be related: in muscle it has been shown that insulin can be a vasodilator; in fact some people are even referring to it as a vasoactive peptide. It has also been shown that insulin seems to induce the production of nitric oxide in the endothelium of muscle. This kind of thing needs to be thought about if we’re to embark on arginine-supplemented peptides for parenteral nutrition. The kinds of patient we are most interested in treating this way may well turn out to be those with major insulin resistance, which adds another complicating factor to the whole problem of blood flow to the intestine.

**Dr. Young:** Would anyone in the audience like to make a comment before we finish?

**Dr. Reeds:** I certainly would. I did make some comments about the regulation of portal blood flow, and those were largely that we didn’t quite know what
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regulated it. However, it’s interesting that, as far as we can tell, it is in some way related to delivery of nutrients from either side of the gut. We’ve found that there’s a very good relation between total food intake (but we can’t really identify whether any one of the components of this is of particular importance) and blood flow. That would be fine if it wasn’t for the fact that when we did our parenteral nutrition studies (and I think we may be the first people to have measured portal blood flow under parenteral nutrition) it was 10% lower than if we gave the equivalent nutrition enterally; and both values were higher than the blood flow after an overnight fast. I could happily spend the next 5 years just investigating that question.

I see the results that we’ve been getting as clinically significant at three levels. The first is that if, as we believe at this stage, these reflect obligatory inherent aspects of gut metabolism, the design of enteral formulas should take that into account, and in particular consider very seriously the glutamate and aspartate needs of gut metabolism itself. The second area of clinical significance relates to the fact that glutamic acid is substantially neurotoxic, because it’s the major excitatory neurotransmitter within the central nervous system; it is crucial that the gut handles glutamate properly and protects the body from absorption. The third area relates to the conundrum of parenteral versus enteral nutrition, because we have this very interesting and very key relation between glutamine, proline, and arginine. I find it no accident that there’s strong evidence that glutamine and arginine have as yet unknown effects on the immune system, and that one can interchange arginine and proline at will, which opens up some very interesting thoughts about the clinical significance of this pathway for wound healing. So this is what I see as the clinical significance of our findings.