Fuels For Intestinal Cells

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The mucosa lining the small and large intestine needs fuel to maintain energy metabolism, to express genes, to allow growth during the process of rapid cell turnover, and for nutrient transport and absorption. Not all potential fuels provide equal support for all of these needs. Thus, the "proper" fuel depends, in part, on the endpoint measured, for example oxygen uptake and consumption, carbon dioxide or lactate production, gene expression or growth, or nutrient transport and absorption. Moreover, the status of the whole organism can affect the need for various energy substrates. Factors that can affect the use of a substrate include feeding pattern (fasted or fed), diet composition, site of nutrient presentation (luminal vs. vascular, small bowel vs. colon, jejunum vs. ileum), stage of development (suckling, lactation, old age), or presence of pathology (e.g., malnutrition, sepsis, infection, bowel resection, diabetes). Most of the conditions studied have involved the small intestinal mucosa, as it is more responsive to changes in experimental and natural variables, and more specific markers are available as surrogate endpoints for cellular function.

NATURALISTIC DELIVERY OF SUBSTRATES TO THE SMALL INTESTINAL MUCOSA

The simultaneous delivery of substrates from lumen and blood, as well as the vertical gradient of cell differentiation, creates a unique anatomic route for the provision of nutrients. When amino acids are provided intraluminally, the outer two thirds of the villus are preferentially fed, whereas the lower one third receives the major portion of intravenous amino acids (1). Most of the luminal amino acids (and glucose) traverse the enterocyte and are absorbed intact. However, although amino acids in the extracellular pool are not the direct precursor for enterocyte protein synthesis, they pass through an intracellular pool that is in equilibrium with the cellular protein (2). In vivo, in the rat, when glutamine is provided both intraluminally and intravenously, the amount of glutamine utilized is the sum of what is extracted from each delivery route (3), although that from the lumen is more oxidized to lactate (3) or carbon dioxide (4).

Glucose is not a major oxidative fuel for the small intestine, and most is absorbed intact, when provided in the presence of the major amino acids oxidized by the
FIG. 1. Fuel oxidation in human small intestine. The three dietary amino acids that provide most of the oxidative substrate are glutamine (gln), glutamate (glut), and aspartate (asp). Most of these are provided in the lumen, although some glutamine released from muscle is provided arterially. Blood glucose serves as another source of alanine carbon. Other end products of amino acid metabolism include lactate, NH$_4^+$, and CO$_2$. α-KG, α-ketoglutarate; AcCoA, acetylCoA; ala, alanine; cit, citrulline; OxAc, oxaloacetate; pro, proline; pyr, pyruvate.

mucosa, namely glutamine, glutamate, and aspartate. Of the total carbon dioxide produced by rat small intestine, 80% is derived from these three amino acids (5). About two thirds of the glutamine and nearly all of the aspartate are metabolized in the rat jejunum, whereas nearly all intraluminal glucose is recovered intact (4). However, the proportion of glucose to lactate varies from approximately 33% to 100%, depending on the site of infusion, nutritional status of the animal, presence or absence of other substrates, and perfusion conditions (4). Arterial glucose is metabolized to carbon dioxide three times better than intraluminal glucose, but still much less than arterial glutamine (6). Some glycolysis does occur, however, so that the major source of the carbons in portal vein alanine is luminal glucose (5) (Fig. 1).

FACTORS AFFECTING THE UTILIZATION OF SUBSTRATES BY THE SMALL INTESTINE

Feeding has a marked effect on the utilization of mixed substrates. During fasting, in the rat, ketones are the major fuel oxidized to carbon dioxide by jejunal enterocytes (7). After feeding, however, amino acids (glutamine, glutamate, and aspartate) provide 77% of the carbon dioxide. Major differences are seen in fuel oxidation in the small and large intestine (Table 1). In the rat, a gradient of resting oxygen uptake is found that decreases from duodenum to ileum, presumably reflecting oxidation of endogenous substrates (8). However, a similar gradient is not present in the guinea
pig (8). Butyrate is oxidized in the rat colon to carbon dioxide at a rate 10 times that of glutamine and 50 times that of glucose, and a very shallow gradient is seen, with the lowest oxidation in the ascending colon and the highest in the descending colon (9).

Significant species differences occur in utilization of fuels by the small intestinal mucosa (Table 2) (4,10–15). The use of ketones, glutamine, glucose, and arginine differs considerably in different species. Arginine is an essential amino acid in the cat and to a lesser degree in the dog (14), and the use of glutamine differs in rats and pigs (11,15). The rat differs from the human in its use of ketones and glucose (4,10), and the dog extracts much more glucose than the rat, and more glucose than glutamine (12), suggesting that glutamine may be much less important for dog than for rat intestine. The rat has been found to develop mucosal atrophy of the small intestine during short-term (3-day) fasting, and many studies have been performed to determine the optimal conditions for parenteral feeding that would restore small intestinal mucosal mass. However, very limited data examine instead of document a similar phenomenon in humans, and the available data support only a limited loss of mucosal tissue, even after prolonged total parenteral nutrition (16).

### TABLE 1. Relative importance of potential gut fuels

<table>
<thead>
<tr>
<th>Fuel</th>
<th>Lumen</th>
<th>Blood</th>
</tr>
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<tbody>
<tr>
<td>Glutamine</td>
<td>Major: 80% of total</td>
<td>Major: 20% of total</td>
</tr>
<tr>
<td>Glutamic acid, aspartic acid</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Glucose</td>
<td>Low (small bowel)</td>
<td>Major (fasting rat)</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>High (colon)</td>
<td>Moderate (fasting human)</td>
</tr>
<tr>
<td>Ketones</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Polyamines</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td>Nucleotides</td>
<td>??</td>
<td>??</td>
</tr>
</tbody>
</table>

Arg, arginine.

### TABLE 2. Species differences in small bowel utilization of fuels

<table>
<thead>
<tr>
<th>Species</th>
<th>Observation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>Glycolysis from glucose &gt; human</td>
<td>4</td>
</tr>
<tr>
<td>Rat</td>
<td>Ketone use &gt; human during fasting</td>
<td>10</td>
</tr>
<tr>
<td>Rat</td>
<td>Glutamine use &gt; pig</td>
<td>11</td>
</tr>
<tr>
<td>Dog</td>
<td>Glucose extraction &gt; human</td>
<td>12</td>
</tr>
<tr>
<td>Cat, dog</td>
<td>Arg is essential amino acid</td>
<td>13</td>
</tr>
<tr>
<td>Pig, weaning</td>
<td>Arg production &gt; arg metabolism</td>
<td>14</td>
</tr>
<tr>
<td>Pig, birth</td>
<td>Glutamine, glucose as fuels &gt;</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>glutamine for amino acid synthesis</td>
<td></td>
</tr>
</tbody>
</table>
METHODOLOGIC ISSUES

The mucosal cell in the intestine exists in a special milieu between the lumen and the lamina propria, supplied from both sides by nutrients. In addition, the cells comprising the mucosa are moving along a vertical axis from undifferentiated crypt cells to mature villous cells; in some species a horizontal functional gradient is seen from duodenum to ileum, or from ascending to descending colon. The various preparations used to study fuel utilization in the intestinal mucosa inevitably disrupt this complex hierarchy, including isolated segments in vivo, in vitro segments perfused vascularly or luminally, everted sacs, cross-sectional rings, and isolated enterocytes or colonocytes.

The problems seen with studies of these systems include loss of polarization in isolated cells, loss of vascular supply in rings and sacs, use of single substrates in the absence of other major fuels, and loss of vertical and horizontal gradients. It is not surprising, therefore, that even in a single species (rat), the rate of oxygen uptake has varied by at least three- to fourfold (even up to 400-fold), depending on the preparation used (17). If oxygenation varies, so does the extent of glycolysis (lactate production) (18). Adenosine triphosphate (ATP) production was compared with carbon dioxide production in rat enterocytes, and was found to occur mainly from glucose through the anaerobic pathway (19), and glycolytic flux was six to seven times higher in jejunal cells than in ileal cells. In isolated cells, however, the glucose absorbed into and removed from the enterocyte cannot be distinguished, and both apical and basolateral surfaces of the cell are exposed to the nutrient, rather than just the one surface. The rate of oxidation of some nutrients is greater in isolated cells than in the intact organ, especially in the case of the colonocyte where cell viability is not so compromised by isolation. Thus, many studies reflect more the potential of the isolated cell for fuel metabolism than the function of the intact organ.

GLUCOSE METABOLISM

Although a large amount of free glucose is ingested or made available from starch metabolism, rather little is metabolized in vivo by aerobic glycolysis in the mammalian small intestinal mucosa (6). About 50% to 60% of the glucose that is metabolized results in lactate through the glycolytic pathway, and the amount of this glycolysis increases as the oxygen tension decreases. Such glycolysis products appear as lactate secreted into the portal vein. Alanine synthesis by glycolysis accounts for only 3% of the absorbed glucose (5). Although starvation reduces the metabolism of glucose in the mucosa, glucose metabolism is unchanged by the presence of ketone bodies. As noted above (19), in isolated rat small and large bowel mucosal cells, maximal utilization rates are similar for glucose and for glutamine (10). Ketone bodies are much less readily oxidized. When glucose and glutamine were present together, no increase in oxygen consumption was noted (10,20,21). However, when glucose, glutamine or both were added to acetoacetate, an increased
oxygen consumption was noted (10). These data confirm the potential of the enterocyte and colonocyte for glucose oxidation, but the degree to which this occurs in vivo varies greatly according to the experimental conditions.

AMINO ACID METABOLISM

The available data suggest that amino acids (mostly glutamine, glutamate, and aspartate) account for the major energy source of the small intestine. The measured oxygen consumption from those three amino acids by human intestinal jejunum accounts for approximately 80% of the predicted consumption (5) (Table 3). Glutamate is metabolized to a much greater extent than most other amino acids (86% vs. 10% to 35% for leucine, lysine, phenylalanine, and threonine), but all are incorporated rather equally into mucosal protein (22). Dietary, not vascular, amino acids appear to be preferred for protein synthesis, at least in the pig (23). A recurring issue is whether glutamine is a preferred fuel for the enterocyte. The classic study by Windmueller and Spaeth (24) showed that oxidation of luminal glutamate (79%) was even greater than for glutamine (59%) in the intact rat small intestine. The utilization of glutamine by the intestine requires its deamidation to glutamate when delivered arterially (25,26). It seems likely, however, that most of the glutamate (or glutamine) used preferentially by the enterocyte is derived from the lumen. More than 90% of enteral glutamine is catabolized (27), but enteral glutamate is oxidized in humans even better than glutamine (28). The catabolism of enteral glutamine in pigs exceeds the rate of uptake of arterial glutamine fivefold (29). Finally, enteral glutamate is the major source of glutamate in glutathione, not the glutamate that is metabolized within the mucosa (30).

Thus, glutamine may be only a precursor for glutamate, especially when delivered lumenally, where the capacity for uptake of glutamine is greatest. In humans, 54% of glutamine nitrogen and 78% of the carbon skeleton (28) is extracted on first pass, showing that glutamine is converted to glutamate in the process. The extraction rates from the lumen equal those from the blood, but glutamine accounts for only 7% of total intestinal protein synthesis (28). Glutamine, therefore, seems to be used more extensively for energy metabolism than for protein synthesis. The calculated rates of glutamine synthesis far exceed those for plasma glutamine turnover, which is

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$O_2$ consumption (mmol/d)</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>12,000</td>
</tr>
<tr>
<td>Splanchnic bed</td>
<td>1,800</td>
</tr>
<tr>
<td>Jejunum [Gln (lumen + blood) + Glut &amp; Asp (lumen)]</td>
<td>450–550</td>
</tr>
</tbody>
</table>

consistent with the compartmentalization of glutamine in the splanchnic bed where it is metabolized and utilized (27,28).

Glutamine has been considered an essential amino acid for the intestine, and this view has received support from its trophic effects in experimental animals. Partial reversal of the atrophy induced by total parenteral nutrition (TPN) has been shown with 2% glutamine in rats with transplanted small intestine (31), and complete reversal with 1% glutamine in suckling pigs (32). However, glucose produced nearly as much reversal. In a study on rats, the addition of intravenous lipid to parenteral amino acids was necessary to achieve 75% to 85% reversal of small bowel atrophy induced by TPN (33). Moreover, neither glutamate nor aspartate has been used as control for glutamine, so the specificity of the response to glutamine is more apparent than real. It seems likely that any three of those major sources of amino acid oxidation in the small intestine should be capable of supporting growth in that organ. Thus, it is not clear that glutamine is uniquely important in restoring mucosal mass. It is worth remembering also that the atrophy seen in animals occurs much less strikingly in humans, if at all (16).

In humans, glutamine has been considered by some to be conditionally essential. However, approximately 60% of glutamine production represents de novo synthesis (34,35). The carbon skeleton for glutamine, α-ketoglutarate, is a Krebs cycle intermediate and can be made from carbohydrate, fat, or amino acids. Moreover, glutamine metabolism is higher in lymphocytes than it is in enterocytes (331 vs. 230 μmol/h/g dry weight) (36), and glutamine has effects on immune function as well as on correction of acidosis and neurotransmission. Thus, its clinical benefits, if indeed confirmed, may result from actions other than as a unique fuel for the intestine.

**SHORT CHAIN FATTY ACIDS**

Starches and dietary fiber not absorbed in the small intestine enter the colon of nonruminants, where colonic bacteria convert the carbohydrate to short chain fatty acids (SCFA). Absorption of these nutrients allows the colon to salvage considerable energy that would otherwise be lost in the stool. SCFA, especially butyrate, supply the substrate for 5% to 30% of the basal metabolic rate of the intact organism (37,38). The highest figures have been obtained in herbivores, such as rabbits. The wide variation in part may be related to differences in methodology used. More energy from short chain fatty acids could be available in nonruminants if dietary fiber could be digested in the small intestine. In humans, in developed countries, short chain fatty acids provide approximately 6% to 10% of energy requirements in the body (38).

Butyrate, the preferred large intestinal fuel, accounts for approximately 80% of the total oxygen consumption (39). Its oxidation exceeds that of glutamine and glucose 10 and 70 times, respectively (40). It is absorbed in the proximal and distal colon by passive diffusion and in the proximal colon by active transport mechanisms that are linked to various ion exchange transporters (41). It is possible that the
regulation of fluid and electrolyte fluxes demonstrated in the presence of butyrate is related to an energy-generated effect, but this fuel effect has not been well substantiated. Butyrate also has many effects that may not be related to its role as a fuel. These include protection against neoplasia, regulation of colonic motility and blood flow, and a possible effect on colonic healing in various colitides.

Short chain fatty acids and ammonia are both bacterial metabolites that are used by the colon, but they have opposite effects on glucose metabolism by colonocytes. When both are present, more glycolysis occurs in pig colonocytes. Acetate is preferentially oxidized, and butyrate produces ketones (42). Ammonia decreases butyrate (not acetate) utilization, and increases glycolysis from glucose. In germ-free animals (i.e., in the absence of colonic microflora), the capacity to oxidize butyrate was increased (43). Thus, it may be difficult to assess the use of butyrate in the colon in vitro in the absence of other luminal colonic contents.

OTHER FUELS

Only a fraction of a percent of oleic acid is metabolized to carbon dioxide by rat small intestinal explants (44). Gut bacteria produce large amounts of polyamines, and polyamine-deficient diets in rats cause gut hypoplasia of the small and large bowel (45). Moreover, 30% of arterial putrescine is metabolized to succinate, and up to 70% in fasted rats (46). It is not clear, however, if these compounds are quantitatively significant sources of energy for the intestinal mucosa. Glutamine and pyrimidine metabolism are linked biochemically through the enzyme carbamoyl phosphate synthetase II in the production of endogenous pyrimidines (45). However, it is not known whether dietary nucleic acids are necessary over and above de novo pyrimidine synthesis, or whether parenteral nucleotides have any effect on enterocytes.

SUGGESTIONS FOR FUTURE RESEARCH

Studies should be carried out in a situation as close to that of the intact organ as possible, and in a species with intestinal physiology that reflects that of the human. These requirements are difficult to achieve in practice. Moreover, some nutrients (e.g., glutamine and butyrate) may have trophic or other functions that are not strictly related to their oxidative potential. Table 4 lists some of the recent controlled clinical studies that have been reported with glutamine supplementation, but using surrogate endpoints as diverse as intestinal permeability, nitrogen balance, mortality rates, and polymorphonuclear cell function. Only one study actually measured those variables (small bowel morphology, nutrient absorption) that might be considered direct endpoints for assessing the effect of glutamine as an intestinal fuel. The results of these experiments are not very supportive of a clinical deficiency in glutamine, or of a role for glutamine supplementation, even measuring a variety of endpoints unrelated to intestinal function. Future experiments should be designed to distinguish real nutritional endpoints from other effects, which, if reproducible, may reflect other...
### TABLE 4. Controlled clinical studies of glutamine (gin) supplementation (1992–99)

<table>
<thead>
<tr>
<th>Study design</th>
<th>Surrogate endpoint and result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM transplants ± gin/TPN</td>
<td>N balance, no</td>
<td>JPEN 1993;17:407</td>
</tr>
<tr>
<td>Burn patients ± gin/TPN</td>
<td>Bactericidal function of</td>
<td>JPEN 1994;18:128</td>
</tr>
<tr>
<td>16 trauma patients ± gin/EN</td>
<td>N balance, plasma gin</td>
<td>J Trauma 1996;40:97</td>
</tr>
<tr>
<td>17 postoperative patients ± gin/EN</td>
<td>Plasma gin</td>
<td>Am J Clin Nutr 1997;65:977</td>
</tr>
<tr>
<td>19 CABG patients ± ala-gln/TPN</td>
<td>Endotoxemia incidence</td>
<td>Acta Anesth Scand 1997;41:385</td>
</tr>
<tr>
<td>14 CD patients ± oral gin</td>
<td>Gut permeability unchanged</td>
<td>JPEN 1999;23:7</td>
</tr>
<tr>
<td>84 ICU patients ± gin/TPN</td>
<td>Lower mortality</td>
<td>Nutrition 1997;13:295</td>
</tr>
<tr>
<td>78 ICU patients ± gin/EN</td>
<td>Mortality same</td>
<td>Nutrition 1997;15:108</td>
</tr>
<tr>
<td>34 surgical patients ± ala-gln/TPN</td>
<td>Lower postoperative complications</td>
<td>Langenbecks Arch Chir 1998;115:605</td>
</tr>
<tr>
<td>14 pancreatitis patients ± gin/TPN</td>
<td>Lower IL-8 release from WBC, same IL-6, and TNF release</td>
<td>Nutrition 1998:14:261</td>
</tr>
<tr>
<td>65 chemotherapy patients ± oral gin</td>
<td>Diarrhea and clinical response same</td>
<td>Nutrition 1997;13:748</td>
</tr>
<tr>
<td>8 short bowel patients ± GH, gin crossover</td>
<td>Small bowel morphology same, micronutrient absorption same</td>
<td>Gastroenterology 1997;113:1074</td>
</tr>
</tbody>
</table>

ala, Alanine; BM, bone marrow; CABG, coronary artery bypass graft; CD, Crohn’s disease; EN, enteral nutrition; GH, growth hormone; ICU, intensive care unit; PMNs, polymorphonuclear leukocytes; TNF, tumor necrosis factor; TPN, total parenteral nutrition; WBC, white blood cells.

functions of the added nutrient. To do this, variables reflecting both nutritional utilization (e.g., substrate oxidation, carbon dioxide production, cell growth) and functional effects (immune response, cell differentiation) should be measured, and a clear distinction made between the two types of endpoint.

The uniqueness of a nutrient for an intestinal organ can be assessed only if it is compared with other compounds that are readily available and possibly also important in vivo. Thus, glutamine should be compared with glutamate or aspartate, and butyrate should be tested in the presence of other colonic luminal compounds such as acetate or ammonia. Moreover, attention should be given to whether the experimental model reflects a fasting or fed state. In interpreting published reports, be alert to the complexity of intestinal biology in the intact organism and make cautious applications of experimental results in small rodents and isolated cells, for example, to clinical situations in intact human organs.
REFERENCES


**DISCUSSION**

*Dr. Ghoos:* One thing about glutamine remains very intriguing: in maternal milk of all mammals, glutamine is the amino acid present in the highest concentration. Do you know of a reason why infants should need such a high intake of glutamine?

*Dr. Alpers:* I do not know the answer to that. However, I showed how plasma glutamine rises more than other amino acids after feeding in humans, because the release of glutamine from the large muscle mass is greater than that of any other amino acid. To some extent then, what comes out in the milk will be a reflection of what is circulating in the bloodstream at the time the mother nurses. So I could easily say that the high glutamine concentration is a reflection of what is in the blood. I do not know whether those studies are done in fasted or fed mothers. I doubt very much if they fasted them, so they probably were fed. That still does not mean that some special need might not exist for glutamine in the newborn, but I do not know of one. I do not think it could be said a priori that the level in the milk was high because the newborn needed it.

*Dr. Ghoos:* Is glutamine a stimulator of immunologic function?
Dr. Alpers: Much literature is available on the uptake of glutamine by immune cells. It is definitely taken up by a variety of cells in the immune system, and to levels that are somewhere from 50% to 80% as high as in the intestine. The intestine is still the most active as far as I know. Because of that, many people have felt that the clinical benefits of glutamine may be related to alterations in immune function, and immune function has been examined in these studies. But again, that is starting with the assumption that glutamine is important. Immune cells definitely do use glutamine and I think they metabolize it to glutamate.

Dr. Brandtzæg: Again on the issue of glutamine and the immune system, I believe some interest is seen in this in sports medicine, in relationship to infections in elite competitors. Do you know anything about that?

Dr. Alpers: I suspect that most of those controlled studies—if they were indeed controlled—are in the vaults of the companies that promoted the idea. Do not misinterpret what I am saying: I am not saying that glutamine is necessarily bad or not a good fuel, but all the evidence so far is that for the intestine it is no better than glutamate. Is glutamate better than anything else? Again, the studies have not been done comparatively to the same degree. For example, the study I mentioned in the rat, where glutamine was compared with proline, serine, alanine, and so on, showed that those amino acids are not metabolized to the same extent as glutamate. When comparing something that is normally metabolized twice as much with something that is metabolized half as much, of course a difference is seen. A need is seen to go back to experiments comparing substrates that are equally metabolized.

Dr. Brandtzæg: My specific question was whether those experiments showed a reduced frequency of upper respiratory tract infections in elite competitors.

Dr. Alpers: The data on the use and function of glutamine in elite athletes are mixed and inconclusive. Amino acid patterns have been examined in a few studies following intense training. One study reported a persistent change in plasma amino acids (valine and threonine increased <10%, but significantly; glutamine and histidine decreased 20%) in athletes with chronic fatigue and infection (1). However, when these athletes received glutamine supplement for 3 weeks, only 6 of 10 returned to their training, and there was no control group. Another study found no difference in plasma glutamine concentration in overtrained swimmers with or without upper respiratory infections (2). Glutamine supplementation given to marathon runners and elite male rowers after intense training with low plasma glutamine (20%) increased the T-lymphocyte helper-to-suppressor ratio and decreased subsequent infection, but infections were detected by questionnaire alone (3). In marathon runners studied by the same group, plasma concentrations of glutamine, alanine, and branched chain amino acids, and T-lymphocytes were decreased in the first hour after the race, and returned to normal after 16 hours, but glutamine supplementation had no effect on lymphocyte distribution (4). Another group found that decreased plasma glutamine concentrations postexercise in marathon runners were not responsible for the decrease in killer T-cell activity (5).

Dr. Zoppi: Among the factors that are important for fuel oxidation in the small bowel, what is the role played by ions such as zinc and copper in humans for the metabolism of fuel?

Dr. Alpers: It is a very difficult question to answer. Zinc is important for all cells and for a variety of enzymes. I believe that zinc deficiency would be deleterious for a cell that was in less than optimal condition, but I do not have any specific information on this.

Dr. Bjarnason: If glutamine is a fuel for Krebs' cycle, then of course, if Krebs' cycle is fed with glutamine and go one circle, you end up with glutamine again, so I cannot see how it can be the main fuel by that mechanism?

Dr. Alpers: Glutamate is being generated from other substrates. If exogenous glutamate is
labeled, it is completely metabolized. If it is kept within the cell some of it might eventually end up as remade glutamate, but other substrates have come in to make glutamate as well. So, although it looks as though nothing has been accomplished, there should be an additive effect of metabolizing the exogenous glutamate together with other exogenous substrates.

**Dr. Parsons:** I have a question that has to do with other roles for glutamine and glutamate. First, I think that good evidence supports that glutaminase exists in the gastrointestinal tract and it can be upregulated, so therefore glutamine will go to glutamate, but what about the role of glutamate in the formation of citrulline and then arginine? In the rat with resected intestine, arginine becomes an essential amino acid. In newborn infants, where arginine is limited as it is used for the urea cycle, does glutamine play a role in citrulline production and reconversion back to arginine through the kidney?

**Dr. Alpers:** It might. In the newborn pig, the metabolism of arginine is different from later in life. If glutamate is available along with aspartate—and these data have been obtained in humans—more glutamate will be metabolized. If they are present in physiologic concentrations, wherein is much more glutamate than aspartate, both are metabolized 100%. If the same amount of aspartate as glutamate is put in, I think that it would still be 100% metabolized, because it goes through a similar mechanism inside the cell. But ordinarily, not nearly as much aspartate as glutamate is seen when proteins are broken down. So, I think they are both good fuels.

**Dr. Marini:** My question concerns the use of very long chain fatty acids (LCFA) soon after birth. A paper by Carlson showed that if LCFA was added, especially docosahexaenoic acid (DHA), the incidence of necrotizing enterocolitis can be reduced (6). I was impressed by this work. Although the infants appear to have a very much higher incidence of necrotizing enterocolitis than we do, nevertheless they were able to reduce that incidence by almost half.

**Dr. Alpers:** I do not have any experience with that. I think any substrate that the intestinal cell can handle has the potential to be useful, but to show that it is actually useful requires a lot of patients. Most of these studies are very small and it is not known what else has been going on. However, I do not think long chain fatty acids should be eliminated as a possible fuel for the intestine.

**Dr. Lentze:** I have a clinical question. You mentioned twice that TPN-related atrophy in the human might not exist. Can you be more explicit about that? For many years we have been teaching, and were taught ourselves, that a child on TPN needs fuel to feed the gut to avoid intestinal atrophy. I still think that is very important.

**Dr. Alpers:** No data in humans support this belief. One or two studies in just a few patients have tried to show morphologic changes in measurements in postoperative patients, but the changes were very small (7,8). One study did show a convincing change, although only in three patients with chronic pancreatitis who were probably protein malnourished (9). When these patients were treated with TPN, the villus height fell. However, no data are available for postoperative patients. I reviewed this subject in detail a few years ago (10). All the existing data had been taken from the rat, on the assumption that the rat was a similar model to humans. But, in fact it is not. This theory has been around for a long time, so if data were available to show atrophy of the human intestine with that kind of feeding, I think it would have come to light by now.

**Dr. Delvin:** If we study fuel intake in a wider sense than just glutamine or glutamate and look at other fuels, and also look at variables other than oxygen consumption, what is the effect of the different fuels on energy storage, and how would the energy be stored? In essence, what is the effect of the type of energy intake or fuel intake in terms of energy storage?
Dr. Alpers: Are you referring to energy storage within the enterocyte?

Dr. Delvin: Partly yes, and also what is being secreted through the basolateral membrane.

Dr. Alpers: I do not really know of a mechanism whereby the enterocytes store energy. They take in a tremendous amount of lipid, as you know, but that lipid is almost entirely secreted, mostly in the lymphatics, but some in the portal vein as well. A small amount is metabolized. The same is true of glucose—much of it goes through, but some is metabolized—and also for many amino acids. Amino acids in the portal vein increase after a meal, except for glutamate which is 100% metabolized. So not much is stored: in the intestine, a small amount may be held in short-term reserve for these cells that only live 3 days, in case of a little starvation. But even that is not necessarily true: I could imagine that if one were not getting anything in from the lumen, one would start breaking down from the liver and muscle, and substrates are then made available in the bloodstream for utilization by the intestine. In fact, animal experiments show that the intestine uses a greater proportion of those circulating substrates in the fasting state than does the rest of the body. So, the intestine is protected from starvation. I know of no storage pool. Do you know of any?

Dr. Delvin: No. The question I really wanted to ask is whether the fact that different fuels might be given would result in the presence of different substrates, either extruded from the cell into the lymph pathway or remaining in the cell.

Dr. Alpers: It is hard to do such experiments in situ in the whole animal. I simply do not know of any data on that point.

Dr. Goulet: I agree with most of your comments, except maybe one. Do you not think that a place for glutamine may exist in the severely stressed patient? From my review of the literature, I believe this has been shown. In looking carefully at the provision of glutamine in severely stressed patients, it not only increases the nitrogen balance but it also decreases the rate of infection. Intensivists know that mortality in patients in the intensive care unit mainly results from multiple organ failure related to increased intestinal permeability and bacterial translocation. I do not believe glutamine has any value in normally nourished patients or in unstressed patients. I am somewhat interested in the data that seem to show that glutamine given to neonates in parenteral or to enteral nutrition solutions results in a decrease in the duration of ventilation, but not enough data are available to draw firm conclusions. However, I do believe glutamine is of value in the stressed patient.

Dr. Alpers: Let me reiterate my conclusions. I have nothing against glutamine or glutamate, but would like to propose the proper experiment that should be done. Accept that the clinical data are not terribly impressive: some studies appear to show an effect and others that do not. The properly controlled experiment would be to take glutamate, or some other amino acid that is also a good substrate for the intestine, and give it in equal amounts, in terms of oxidative substrate, to the added glutamine in the other limb of the experiment. What I think is happening now is that an easily oxidized substrate is being compared with a less easily oxidized substrate, and even then the difference shown is not terribly striking. In looking at nonoxidative outcomes, such as bacterial translocation, increased bacterial translocation has been observed in animal models that has been attributed to poor nutritional status. When this same endpoint (bacterial translocation) has been studied in humans, no relationship to poor nutritional status has been observed (11). So again, we have this difference in animals versus humans, preventing easy extrapolation to clinical conditions. In answering the question, "I give glutamine to my patients and I think they do better; should I stop giving glutamine?" I would say no, not if it works. But do not assume that glutamine is special or unique. It could well be that another substrate, given in an appropriate amount, would also be oxidized and would turn out to be just as good. That is the only concept that I am trying to get across.
Dr. Goulet: I agree, but we know that glutamine requirement increases in stressed patients with severe muscle catabolism. In the particular situation of the burned or otherwise traumatized patient, glutamine needs are not the same as in other patients. One could imagine that bowel physiology changes in that situation.

Dr. Alpers: Let me put this in another way. Of course, as most of the glutamine comes from muscle, in a situation such as you mentioned, if enough oxidized substrate is not given to the body, the usual amount of glutamine will not be released from muscle. So, it will look as though it is conditionally essential. But, from the kind of evidence I presented, I would just repeat that I know of no real evidence that glutamine is a conditionally essential amino acid.

Dr. Goulet: But one missing piece of the puzzle is glutamine synthesis during this situation.

Dr. Alpers: If not enough carbon backbone is given to the organism, it will not make as much; if enough is given it will. I am not trying to convince you, I am just trying to produce a little skepticism!

Dr. N. Wright: This may be a rat-specific phenomenon, but it is nonetheless interesting: if a 75% proximal resection is done and the rat is fed orally, an adaptation occurs in the ileal remnant. If that rat is isocalorically fed, that adaptation does not occur. So, food in the lumen is a stimulus to growth. This has been called "luminal nutrition," but I do not know what that means. Could you speculate on what luminal nutrition means—how absorption or mucosal work is translated into mucosal growth?

Dr. Alpers: This must mean that in the resected rat, for whatever reason, the amino acids supplied in the bloodstream do not penetrate high enough up the villus so that the bulk of the cells on a villus get sufficient substrate. On the other hand, in a normal rat, we showed a long time ago that amino acid precursors can be supplied all the way up the villus. Nobody has done this similar experiment in the resected animal, but I believe that it does not happen to the same degree. That is the best I can do.

REFERENCES