Glutamine: commercially essential or conditionally essential? A critical appraisal of the human data[1,2]

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ABSTRACT   Glutamine is a nonessential amino acid that can be synthesized from glutamate and glutamic acid by glutamate–ammonia ligase. Glutamine is an important fuel source for the small intestine. It was proposed that glutamine is necessary for the maintenance of normal intestinal morphology and function in the absence of luminal nutrients. However, intestinal morphologic and functional changes related to enteral fasting and parenteral nutrition are less significant in humans than in animal models and may not be clinically significant. Therefore, it is unclear whether glutamine is necessary for the preservation of normal intestinal morphology and function in humans during parenteral nutrition. It was suggested that both glutamine-supplemented parenteral nutrition and enteral diets may prevent bacterial translocation via the preservation and augmentation of small-bowel villus morphology, intestinal permeability, and intestinal immune function. However, it is unclear whether clinically relevant bacterial translocation even occurs in humans, much less whether there is any value in the prevention of such occurrences. Results of the therapeutic use of glutamine in humans at nonphysiologic doses indicate limited efficacy. Although glutamine is generally recognized to be safe on the basis of relatively small studies, side effects in patients receiving home parenteral nutrition and in those with liver-function abnormalities have been described. Therefore, on the basis of currently available clinical data, it is inappropriate to recommend glutamine for therapeutic use in any condition.   *Am J Clin Nutr* 2001;74:25–32.

INTRODUCTION

Glutamine is classified as a nonessential amino acid because it can be synthesized from glutamate and glutamic acid by the enzyme glutamate–ammonia ligase. Glutamine is the preferred fuel for the small intestine of rats (1) and is extracted from the splanchnic circulation in significant amounts by the human jejunum, albeit less so than in rats (2, 3). A significant number of the carbon fragments from exogenous glutamine oxidation enter the glucose pool, consistent with the nonessential status of this amino acid (4). Glutamine stimulates in vitro crypt cell proliferation in the ileum and colon and therefore, presumably, the jejunum as well (5). Splanchnic extraction in humans is similar regardless of whether glutamine is provided enterally or parenterally; therefore, I will not differentiate between studies in which parenteral or enteral glutamine was used (6). It remains unclear, however, whether glutamine is the preferred fuel for the small intestine of humans. Recent data suggest that glutamate, rather than glutamine, may be the preferred fuel for catabolic rats, that glutamate is more efficiently metabolized by the intestine, and that glutamate results in greater mucosal protein synthesis than does glutamine (7). For the purposes of this review, I focused primarily on investigations in humans.

There are 2 issues: *1*) Does glutamine deficiency develop in humans in the absence of glutamine during total parenteral nutrition (TPN), during systemic injury, or during critical illness, and what are the pathologic findings? and *2*) Can such pathologic changes be prevented or corrected with glutamine supplementation? Investigations using animal models clearly showed that in most but not all cases (8–17), intestinal villus hypoplasia increases intestinal macromolecule permeability and intestinal immunologic dysfunction and decreases intestinal mucus gel secretion when the animals are provided glutamine-free TPN as an exclusive means of nutritional support or when systemic injury is induced.

DOES GLUTAMINE DEFICIENCY OCCUR IN HUMANS?

There is little confirmatory evidence of glutamine deficiency in humans and of a role for either glutamine replacement therapy or pharmacologic doses of glutamine. Glutamine is one of the most common plasma amino acids and its concentration often decreases postoperatively (18, 19), during sepsis (20), and after multiple trauma (21) or major burns (22), just as do the concentrations of many other amino acids, electrolytes, minerals, and trace elements. Decreased blood concentrations of glutamine do not necessarily indicate a deficient state, as is the case with other nutrients, although a decrease in serum glutamine concentrations does correlate with a decrease in duodenal mucosal glutamine concentrations (23). Intracellular glutamine concentrations do generally decrease in catabolic, critically ill patients and the subsequent increase in endogenous glutamine synthesis cannot completely offset the increased loss of glutamine from the

intracellular compartment (specifically skeletal muscle). However, the clinical significance (clear effects on diagnostic modalities, treatment interventions, or outcome) of these observations has not been shown. In addition, the loss of amino acids from skeletal muscle is not specific to glutamine.

WHAT HAPPENS TO THE BODY WITHOUT GLUTAMINE?

We studied a group of 8 normal volunteers provided with standard TPN as an exclusive source of nutrition for 2 wk (24). Despite a statistically significant decrease in jejunal villus height and an increase in intestinal macromolecule permeability (although the 2 observations themselves were not correlated), no subject developed signs or symptoms of diarrhea or malabsorption. The morphologic and functional changes occurred in the absence of a change in glutamine status, as determined by the plasma glutamine concentration. These observations cast doubt on the theory that glutamine deficiency is solely responsible for the intestinal morphologic and functional changes that occur in humans during TPN. More importantly, however, despite the decrease in jejunal villus height during TPN in the healthy volunteers we studied, there was no evidence of inflammation microscopically and villus height and architecture remained normal. These data are a reminder that it is important to recognize the difference between statistical significance and clinical significance. Furthermore, even the microvilli and intercellular tight junctions remained normal, although intracellular edema did develop. It is possible that the intracellular edema was related to an expanded extracellular compartment, although this was not investigated; it was not related to the increased macromolecule permeability. One might conclude that "if it ain't broke, it can't be fixed."

Our observations are consistent with other human investigations. For example, van der Hulst et al (25) studied a heterogeneous group of ill, hospitalized patients who required TPN. After 10–14 d of either standard or glutamine-supplemented TPN, duodenal villus height decreased significantly and intestinal permeability increased significantly in the group that received standard, glutamine-free TPN. However, as in our study, villus height remained normal. If one removes the single outlier from the permeability data of van der Hulst et al, no obvious difference appears to have occurred in intestinal permeability, although the clinical relevance of increased intestinal permeability still remains to be realized. In critically ill patients there is no evidence that intestinal villus morphology changes acutely and there is little evidence that intestinal permeability increases as a result of critical illness alone (26).

Several investigators also reported that bacteria translocate from the gut lumen to mesenteric lymph nodes during TPN. It was hypothesized that this could relate in part to abnormalities in intestinal morphology and permeability (27–30), although the results of all studies do not support this concept and data for humans are scarce (31). Whether bacterial translocation even occurs in humans and, if it does, whether it is clinically significant must be addressed before a solution to the problem is developed.

The incidence of documented bacterial translocation of viable bacteria from the gut lumen to either mesenteric lymph nodes or to the systemic circulation during either TPN or surgery is ≈10% (32, 33). Sedman et al (33) studied 267 general surgical patients (gastrointestinal malignancy, inflammatory bowel disease, and biliary obstruction) and found that in 21 of 23 patients in whom had mesenteric lymph node cultures were positive for bacteria, blood cultures were negative for bacteria; in the 2 patients who showed evidence of bacterial translocation in blood cultures positive for bacteria, the organisms differed between blood and lymph nodes. Similarly, of 7 patients who had serosal cultures positive for bacteria, none had blood cultures positive for bacteria. Patients who had evidence of bacterial translocation had more postoperative septic episodes, but the organisms were different in all but 2 cases. This indicated that the risk of sepsis was, in general, independent of bacterial translocation. Preliminary studies indicate that the severity of trauma and hypovolemic shock play a role in the development of bacterial translocation rather than does the route of nutrient intake (32). Regardless, bacterial translocation has not been conclusively shown to be of clinical significance in humans (33, 34). In addition, even allowing that bacterial translocation does occur in humans to a clinically significant degree, there is no evidence to support a role for TPN-associated villus hypoplasia because Sedman et al (33) found that villus height was similar in patients with and without documented bacterial translocation. Furthermore, bacterial translocation in humans was not shown to be associated with increased mortality (33).

The intestinal immune system likely plays an important role in the prevention of bacterial translocation. Our work (35) and that of van der Hulst et al (36) showed that in humans, unlike in animal models (37), TPN is not associated with intestinal immune dysfunction, which is defined as a decrease in intestinal immunoglobulin secretion or gut-associated lymphoid tissue. Therefore, bacterial translocation, even if it did occur somehow in association with TPN use, would be unrelated to a breakdown in the intestinal immune barrier. Similarly, as previously discussed, our studies indicated that TPN was not associated with any ultrastructural abnormalities such as the disruption of intercellular tight junctions that could open a pathway for the paracellular transport of bacteria. The absence of these abnormalities in humans casts doubt on the theory that glutamine supplementation can prevent, or even reduce, the incidence of bacterial translocation in humans.

WHAT IS THE ROLE OF GLUTAMINE REPLACEMENT?

Several studies showed improved nitrogen balance with glutamine supplementation, although treatment and control formulas were not always isonitrogenous and improved outcome was not necessarily associated with the improvement in nitrogen balance. Glutamine supplementation may, however, be unable to replete intramuscular glutamine in critically ill patients, suggesting that the depletion of skeletal muscle glutamine during systemic illness may be a normally occurring adaptive response of the body (38). Regardless, it was suggested that the glutamine requirement may also be met by ingestion or infusion of other amino and keto acids such as glutamic acid, aspartic acid, arginine, asparagine, and oxaloacetate, which may act as glutamine homologues (glutamine precursors and derivatives) (39). Conversely, a preliminary study showed that the substitution of glutamine for an equivalent amount of other amino acids does not lead to enhanced visceral protein synthesis (40, 41). Data from rodent models indicate that the greater the amount of exogenous glutamine provided, the greater the intestinal glutaminase expression and glutamine metabolism (42). In other words, the

more glutamine that is provided, the more readily it is metabolized.

Studies with glutamine replacement therapy have not achieved much clinical success. Hulsewe et al (43) found that glutamine-supplemented TPN failed to prevent the increase in intestinal permeability or blunt the decrease in duodenal villus height observed in malnourished preoperative patients. Tremel et al (44) studied 12 patients hospitalized in the intensive care unit; 6 of the patients received glutamine-supplemented TPN and the other 6 patients received standard TPN for 9 d. Greater D-xylose absorption was observed in the glutamine-supplemented group on the basis of elevated serum and urine D-xylose concentrations. However, because no baseline studies were performed, it is impossible to ascertain whether D-xylose absorption was different between these patients before TPN began, especially considering the small number of patients included in the study.

We found that intestinal macromolecule permeability was significantly greater with a standard enteral formula than with a glutamine-supplemented formula in healthy volunteers who were enterally refed after 2 wk of TPN, although the clinical significance of intestinal macromolecule permeability must be addressed before definitive, clinically important conclusions can be made (24). Finally, Anderson et al (45) compared the effects of glutamine (1 g/m^2 4 times/d, but more during preparative radiation and chemotherapy) and glycine in a group of bone-marrow-transplant patients. No difference in the numbers or types of infections was seen between groups.

There are no data indicating that glutamine-free TPN is associated with clinically significant abnormalities, including bacterial translocation and sepsis. Until a specific state of glutamine deficiency can be conclusively recognized in humans, glutamine replacement appears to have little purpose. Administration of pharmacologic doses to obtain a neutraceutical effect is a separate issue and is discussed below.

THERAPEUTIC USE OF GLUTAMINE IN PHARMACOLOGIC DOSES

Short-bowel syndrome

It has been hypothesized that glutamine supplements may help promote bowel adaptation after massive resection and that the absence of dietary glutamine (including that provided parenterally) may lead to a suboptimal adaptive response. Although many studies have been carried out in rodents, few have been undertaken in humans Additionally, most of the studies in humans included patients with long-standing short-bowel syndrome, in whom the adaptation period was long past. A single case report describes the unsuccessful use of parenteral glutamine to treat new-onset short-bowel syndrome from gastroschisis and necrotizing enterocolitis in a child (46). In a preliminary study, Bouteloup et al (47) evaluated the daily ingestion of 50 g glutamine in 8 patients with ileostomies who had 140 m of small bowel resected. Slight but statistically significantly increased nitrogen absorption and increased nitrogen balance were found in the glutamine-supplemented group. However, improved nitrogen balance was expected given that the subjects consumed perhaps as much as 75% more protein during the experimental period than during the baseline period; water and electrolyte losses were unaffected. Byrne et al (48) reported on the unblinded treatment of 6 adult patients with short-bowel syndrome in whom the com-

bination of growth hormone, oral or intravenous glutamine, and a high-fiber diet resulted in greater water, nitrogen, sodium, and energy absorption and lower stool weights compared with baseline; there was no control group. It was unclear what the specific contributions of glutamine, fiber, and growth hormone were. It was also unclear whether simple dietary measures—such as an increase in the amount of soluble dietary fiber, fluid, and electrolyte consumed (including the use of oral rehydration solutions) and increased carbohydrate and protein intakes—would have been similarly effective in patients with an intact colon.

More recently, 2 placebo-controlled studies using similar treatment regimens were conducted. Scolapio et al (49) studied 8 patients with short-bowel syndrome (2 with an intact colon) with a mean residual small-bowel length of 71 cm who required home TPN for 13 y. Treatment consisted of growth hormone (0.14 mg$\cdot$kg$^{-1}\cdot$d^{-1}), glutamine (oral, 0.63 mg$\cdot$kg$^{-1}\cdot$d^{-1}), and a complex-carbohydrate diet. These investigators found no decrease in stool volume (except in patients with residual colon, which is expected because of the increased absorption of the metabolic products of the complex-carbohydrate diet) or in nitrogen or magnesium losses and no improvement in D-xylose absorption. In addition, no changes in the morphology of the small intestine were observed. Significantly increased body weights— resulting from fluid retention, peripheral edema, and sodium and potassium absorption—were noted. Szkudlarek et al (50) studied 8 patients with short-bowel syndrome (4 with no colon and 2 with a small amount of colon) with an average residual small-bowel length of 104 cm who had received home TPN for an average of 7 y. Treatment consisted of growth hormone and glutamine (oral and parenteral) or placebo for 28 d. The patients maintained their usual diets. There were no improvements in energy, fat, carbohydrate, or nitrogen absorption and the stool volume did not change. Body weight, lean body mass, and sodium absorption all increased, which was most likely related to the use of growth hormone. Significant side effects, including fluid retention, peripheral edema, and carpal tunnel syndrome were observed in the group treated with growth hormone. Glutamine-supplemented TPN (without growth hormone) does appear to prevent fluid retention and expansion of the extracellular fluid compartment in both bone-marrow-transplant patients and in patients undergoing radiation treatment and high-dose chemotherapy (51, 52); therefore, it is possible that these effects could have been negated by the growth hormone. In preliminary studies, other investigators found no increases in body weight or lean body mass with glutamine supplementation in otherwise well-nourished patients with short-bowel syndrome (53).

Acute pancreatitis and inflammatory bowel disease

A recent study compared the use of glutamine-supplemented TPN (0.3 g$\cdot$kg$^{-1}\cdot$d^{-1}) and standard TPN in a group of 52 patients hospitalized with acute pancreatitis or inflammatory bowel disease (54). A shorter length of stay was found in the patients with pancreatitis who received the glutamine-supplemented TPN but not in the patients with inflammatory bowel disease. Because the glutamine-supplemented TPN was more expensive, overall costs were similar between groups. No differences in infectious complications with glutamine supplementation were noted.

Five studies (one open-labeled) of glutamine supplementation were performed in patients with Crohn disease. None of the 5 studies ($n = 16$, with a placebo group; $n = 38$, with a placebo group; $n = 13$, with a crossover design; $n = 18$; and $n = 9$)

showed a benefit of glutamine supplementation on disease activity, intestinal permeability, or nutritional indexes at doses of 21 g/d, 21 g/d, 15 g/d, 42% compared with 4% of amino acid intake, and 12 g/d, respectively (55–59). However, in the preliminary open-labeled study of Zoli et al (57), a significant decrease in intestinal permeability was described. However, the pretreatment ratio of lactulose to mannitol in these patients was far greater than was reported in any other study of which I am aware. In addition, Den Hond et al (58) found no change in intestinal permeability in a much larger study. It was suggested that both glutamine-stimulated T cell function and the metabolism of glutamine to nitric oxide might actually increase intestinal inflammation. In fact, Shinozaki et al (60) observed significantly increased colonic inflammation in a rodent model of ulcerative colitis in which rats were fed a diet supplemented with 24% glutamine, although those animals that received a lesser amount of glutamine had the least inflammation. Consistent with these results in rodents, the pediatric Crohn disease activity index actually improved more so in the control group than in the glutamine-supplemented group in one study (59).

Glutamine supplementation was also studied in patients with pouchitis after an ileal-anal anastomosis; the results were only slightly more encouraging. Glutamine suppositories (1 g/d for 21 d) were used in a nonblinded trial of 11 patients who had chronic pouchitis (61). Six of the 10 patients who completed the trials had no recurrence of their symptoms, although the follow-up period was not described.

Critical care

Although it has been hypothesized that glutamine is the preferred fuel for the small intestine of humans, enteral glutamine supplementation does not improve the fractional protein synthesis rate of intestinal mucosa in a hypercatabolic model in healthy humans (62). Several investigators reported that either parenteral or enteral glutamine supplementation improved the ability of the body to combat infection and described fewer infectious complications and a shorter hospital stay in patients who required TPN, although the data are controversial. Griffiths et al (63) reported that short-term ($\bar{x}$: 5 d) glutamine-supplemented TPN improved the survival of critically ill patients at 6 mo, although survival at 20 d was identical to that of the control subjects. Decreased total hospital and intensive care unit costs were found in the group that received the glutamine-supplemented TPN, although this may have been related to the fact that those who received glutamine and died, died faster than did the control subjects (8.5 compared with 13.5 d survival). Fewer patients in the glutamine group ($n = 15$) than in the control group ($n = 22$) died from multiorgan failure, although the statistical analysis of this difference was not reported. There was a trend toward a decreased length of stay in the hospital in a control group of patients that survived (22.5 compared with 37.5 d), including those who were in the intensive care unit (10 compared with 13.5 d), although these differences were not statistically significant. Considering the number of correlations evaluated in this study and the absence of the Bonferroni correction factor, it is difficult to conclude that the reason why survival was higher at 6 mo was solely related to the short-term glutamine supplement, especially considering that patients were at home for virtually 5 mo, at which time their diets and other variables were uncontrolled for.

Houdijk et al (64) found a significantly decreased incidence of pneumonia, bacteremia, and sepsis within the first 2 wk of injury

in a group of severe, multitrauma patients who received a glutamine-supplemented formula (30.5 g glutamine per 100 g protein) or a standard formula (3.5 g glutamine per 100 g protein) for ≥5 d, beginning within the first 48 h of injury. Although several patients in the standard-fed group developed gram-negative sepsis, it is unclear whether this occurred because of bacterial translocation through the gut wall and prevention of bacterial translocation. Jones et al (65) compared a glutamine-supplemented enteral formula with a standard formula supplemented with glycine in a group of critically ill patients. Both groups had similar lengths of hospital stay and rates of mortality and 6-mo mortality, although hospitalization costs were lower in the glutamine-supplemented group. More patients in the control group required TPN, which obviously had an effect on overall costs and suggests that the patients in that group may have been sicker than the patients who received the glutamine-supplemented formula; the median World Health Organization premorbid health score at admission was 10 in the glutamine group and 5 in the control group, although this differences was not statistically significant. Despite this, there were no significant differences in infectious complications between the groups. No indexes of nutritional status or gastrointestinal function were measured. In another study, a trend toward a decreased incidence of sepsis was observed in preterm neonates who received glutamine supplements enterally, although the clinical course was unaffected (54).

Bone marrow transplantation

Although glutamine-supplemented TPN was shown to improve in vitro neutrophil bactericidal function in pediatric burn patients (66) and to decrease the number of stool and throat cultures positive for bacteria in adult bone-marrow-transplant patients (67), it was not shown to reduce the number of clinically significant infections. However, note that the bone-marrow-transplant patients who received glutamine-supplemented TPN had a 1-wk shorter hospital stay, although it is unclear whether this was related to fewer throat and stool cultures positive for bacteria, less severe negative nitrogen balance, or a direct effect of glutamine on some unmeasured index. Schloerb and Amare (51) also found that bone-marrow-transplant patients who received glutamine-supplemented TPN had shorter hospital stays than did those who received standard TPN, although there was no significant difference in the incidence of infection between the 2 groups. In a follow-up study of 66 bone-marrow-transplant patients (43 with hematologic malignancies and 23 with solid tumors), Schloerb and Skikne (68) no longer found a decreased length of hospital stay associated with glutamine supplementation and found no differences in the incidence of sepsis, mucositis, diarrhea, graft versus host disease, mortality, or blood cultures positive for bacteria between patients who received a combination of oral and parenteral glutamine supplementation and similar patients who received an equal amount of glycine supplementation (placebo).

Radiation and chemotherapy

Oral glutamine supplements have been studied in patients who undergoing radiation therapy for prostate cancer and in patients with chemotherapy-associated mucositis (45, 69–76). Richards et al (69) reported preliminary results that glutamine supplementation had no effect on the frequency of bowel movements or stool volume or consistency, although significant improvements were seen in ileocolonic morphology as assessed by light microscopy. However, the severity and duration of radi-

ation-induced mucositis improved in patients with head and neck cancers, although the need for analgesic medication did not decrease. This finding questions the significance of the clinical effect (70). Anderson et al (45) found that despite an improvement in mucositis with glutamine supplementation in a group of autologous, but not allogenic, bone-marrow-transplant patients, the need for opiate medication actually increased in the glutamine-supplemented group. Glutamine-supplemented TPN also has no effect on chemotherapy-associated toxicity (77).

Bozzetti et al (71) found no effect of glutamine supplementation on chemotherapy-associated diarrhea in a study of 65 breast cancer patients. Oral glutamine supplementation failed to prevent the development of mucositis in patients with metastatic gastrointestinal cancers who received 5-fluorouracil (72, 73), although a study with parenteral glutamine (14–22 g/d) decreased the incidence of asymptomatic gastroduodenal mucositis (74). Canovas et al (75) reported the preliminary results for 27 bone-marrow-transplant patients who received high-dose chemotherapy. There was a similar incidence of anorexia, stomatitis, dysphagia, nausea, vomiting, and diarrhea in those who had received 20 g glutamine/d and in control subjects. Similar results were reported by Jebb et al (76) although, these investigators also found no decreased length of hospital stay in the glutamine group. The only study that suggested a benefit of glutamine supplementation on the severity or duration of mucositis was open-labeled (78).

Postoperative patients

Few data support the hypothesis that glutamine supplementation is associated with a decreased risk of infection in general surgical patients. Diggory et al (79) found mesenteric lymph node cultures positive for bacteria postoperatively in 1 of 10 patients who received standard TPN, in 0 of 10 patients who received glutamine-supplemented TPN, and in 3 of 38 patients who received no TPN before surgery. A decreased length of hospital stay was observed after major surgery in 2 studies of patients who received glutamine supplementation. In the first study, Jiang et al (80) found that when nitrogen balance improved with glutamine supplementation, the postoperative increase in intestinal permeability was lower and the length of hospital stay was shorter in a variety of patients with gastrointestinal cancers or biliary obstruction (among other pathologic conditions) who received TPN preoperatively for <1 wk. Although this patient group was heterogeneous and the indications for short-term TPN, and for TPN of any duration, were obscure, the data are intriguing. In the second study, the length of hospital stay was shorter but there was no decrease in infections or bacterial translocation after glutamine supplementation; nitrogen balance was not determined (81). In the largest study of parenteral glutamine supplementation conducted thus far, Powell-Tuck et al (82) studied glutamine-supplemented TPN in 168 hospitalized patients who required TPN, although most patients were studied preoperatively. No differences in septic complications, TPN duration, length of hospital stay, quality-of-life scores, overall mortality, mortality at 6 mo, mortality in intensive care unit patients, or cause of death were seen between patients who received standard TPN and those who received glutamine-supplemented TPN in this placebo-controlled trial.

The potential mechanism for glutamine's effect on immunologic function (which could explain the decreased length of hospitalization) was evaluated in 2 small studies only. Aosasa et al (83) evaluated the effect of oral glutamine supplementation on the in vitro stimulation of mesenteric blood mononuclear cells in a group of colorectal cancer patients. They found that patients who received glutamine supplementation had lower tumor necrosis factor α concentrations in their mesenteric blood than did control subjects, although there were no differences in peripheral blood or in interleukin between the 2 groups. The authors concluded that supplemental glutamine prevented the activation of mesenteric mononuclear cells, which presumably blunted a systemic inflammatory response as might occur during sepsis. Unfortunately, other cytokines were not investigated and the findings of Aosasa et al appeared to be unique to mesenteric blood; mucosal cytokine production was not examined. Furthermore, the clinical significance of these observations, including effects on systemic inflammatory responses in relevant clinical situations and progression to multiorgan failure, is unknown. In the second study, performed in intensive care unit patients, the total lymphocyte count was actually greater in the control group than in the glutamine-supplemented group, although the ratio of CD4$^+$ to CD8$^+$ was higher in the glutamine-supplemented group (84).

AIDS

Glutamine supplementation (4–8 g/d) failed to decrease intestinal permeability in patients with AIDS enteropathy (85). In a small, preliminary study, Den Hond et al (86) suggested that pretreatment with glutamine could prevent some of the increased permeability observed with the use of nonsteroidal antiinflammatory drugs, although the data were not consistent.

SAFETY ISSUES

Just because a substance is a nutrient, it cannot be assumed (in the absence of appropriate data) that its use is safe, especially in pharmacologic doses given to patients who are not deficient in the nutrient. One recalls the issues that surrounded L-tryptophan, among other nutrients (87). Most short-term studies of intravenously infused glutamine in healthy volunteers ($n = 14$) reported no safety concerns (26, 43, 66, 77, 88, 89). However, Hornsby-Lewis et al (39) found significantly elevated hepatic amino transferases in patients after 4 wk of glutamine-supplemented home TPN and were forced to stop their study. The etiology for this observation is unknown. One preliminary study suggested that orally administered glutamine may precipitate, or exacerbate, hepatic encephalopathy and reaction time and is associated with electroencephalographic changes in patients who have otherwise stable cirrhosis (89). In vitro studies showed significantly increased glutamine toxicity in peripheral lymphocytes from patients with Alzheimer dementia or Down syndrome than in peripheral lymphocytes from healthy control subjects; similar observations were made in otherwise healthy elderly subjects (90). This heightened sensitivity to exogenous glutamine suggests a potential role for impaired glutamine metabolism in dementia and therefore a potential worsening of dementia with glutamine supplementation. Further study of glutamine supplementation in these patient groups and in the elderly will be necessary before glutamine supplementation can be deemed safe in these populations.

Glutamine appears to be an essential amino acid for methylcholanthrene sarcoma growth in rats. However, 2 studies showed that supplementation with glutamine (91) or a glutamine precursor (92) does not stimulate tumor growth in animal models of fibrosarcomas and Yoshida ascites hepatoma. In addition, glutamine sup-

plementation does not enhance mammary tumor growth in rats (93). However, theoretical issues remain regarding the promotion of tumor growth by glutamine (94). At one time, antiglutamine chemotherapy was developed for treatment of solid tumors, but was abandoned because of significant toxicity, not because of lack of efficacy (95). Longer-term studies are necessary to determine whether glutamine promotes tumor growth in humans.

CONCLUSION

In an era of evidence-based medicine, it is important that both idealism and commercial interests not be permitted to bias inter- pretation of the available data. Glutamine well illustrates the potential pitfalls inherent in the extrapolation of animal data to humans (the "leap of faith" argument). However, a consistent finding in many, but not all, clinical studies is a relation between glutamine supplementation and a decreased length of hospitaliza- tion. This outcome measure can be affected by a multitude of fac- tors; however, glutamine supplementation did not appear to be associated with a decreased incidence of infection in the studies reviewed herein. One cannot assume that randomization automat- ically ensures an equal number of each of these factors in gluta- mine-supplemented and control groups. It is naive to believe that a decreased length of hospitalization is related solely to frequent, short-term glutamine supplementation. However, these data can- not be ignored. In addition, many placebo-controlled trials with glutamine used the amino acid glycine as the control, by conven- tion, although recent data suggest that glycine may have potential immunologic and so-called antioxidant properties of its own (96). Should these observations with glycine prove clinically meaning- ful, the studies described herein in which glutamine showed no benefit over that of the placebo glycine would be invalidated. Further study is clearly necessary to determine whether the observed decreased length of hospitalization after glutamine sup- plementation is simply a quirk or is related to some as yet uniden- tified quality of glutamine. Until such consistent, but nebulous, observations can be ascribed directly to glutamine on the basis of clinical trials that have both adequate power and adequate control groups, prudence is recommended before glutamine supplemen- tation is considered. In addition, limited data are available con- cerning the mechanism for any of glutamine's purported effects and whether these effects are the of altered cellular physiology, metabolic regulation, or regulation of gene expression. The pres- ence of passion does not replace the absence of data. ✤

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