Therapeutic Considerations of L-Glutamine: A Review of the Literature

by Alan L. Miller, ND

Abstract

The most abundant amino acid in the bloodstream, L-glutamine fulfills a number of biochemical needs. It operates as a nitrogen shuttle, taking up excess ammonia and forming urea. It can contribute to the production of other amino acids, glucose, nucleotides, protein, and glutathione. Glutamine is primarily formed and stored in skeletal muscle and lungs, and is the principal metabolic fuel for small intestine enterocytes, lymphocytes, macrophages, and fibroblasts. Supplemental use of glutamine, either in oral, enteral, or parenteral form, increases intestinal villous height, stimulates gut mucosal cellular proliferation, and maintains mucosal integrity. It also prevents intestinal hyperpermeability and bacterial translocation, which may be involved in sepsis and the development of multiple organ failure. L-glutamine use has been found to be of great importance in the treatment of trauma and surgery patients, and has been shown to decrease the incidence of infection in these patients. Cancer patients often develop muscle glutamine depletion, due to uptake by tumors and chronic protein catabolism. Glutamine may be helpful in offsetting this depletion; however, it may also stimulate the growth of some tumors. The use of glutamine with cancer chemotherapy and radiotherapy seems to prevent gut and oral toxic side-effects, and may even increase the effectiveness of some chemotherapy drugs.
Altern Med Rev 1999;4:239-248.

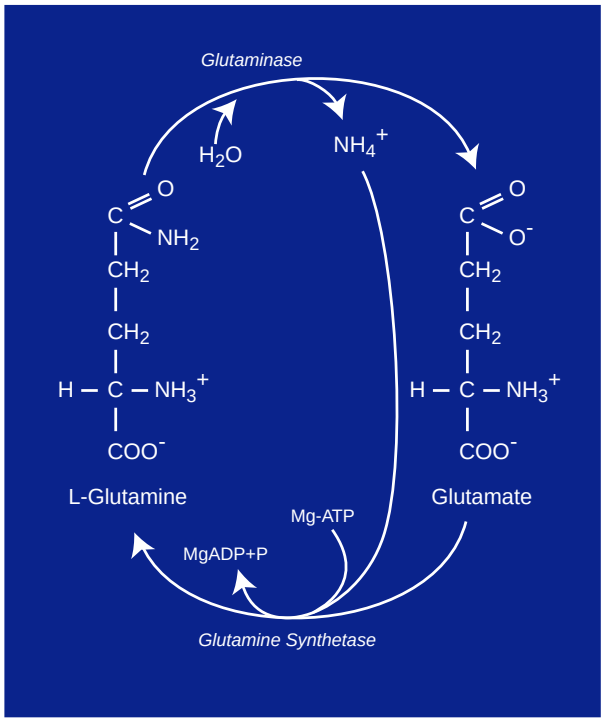
Introduction

L-glutamine is the most prevalent amino acid in the bloodstream, accounting for 30-35 percent of the amino acid nitrogen in the plasma. Because glutamine contains two ammonia groups, one from its precursor, glutamate, and the other from free ammonia in the bloodstream, one of glutamine's roles is as a "nitrogen shuttle," which helps protect the body from high levels of ammonia. Thus, glutamine can act as a buffer, accepting excess ammonia, then releasing it when needed to form other amino acids, amino sugars, nucleotides, and urea. This capacity to accept and donate nitrogen makes glutamine the major vehicle for nitrogen transfer between tissues.

Glutamine is considered a non-essential amino acid, as human cells can readily synthesize it via activity of the enzyme glutamine synthetase (see Figure 1), which is found in high concentration in skeletal muscle, liver, brain, and stomach tissue. Because of the body's capacity to synthesize this amino acid, and because of the relative amount of glutamine in the body

Alan L. Miller, N.D.—Technical Advisor, Thorne Research, Inc.; Senior Editor, Alternative Medicine Review.
Correspondence address: P.O. Box 25, Dover, ID 83825. alan@thorne.com

Figure 1. Glutamate-Glutamine Interconversion.



Glutamate is converted to L-Glutamine via the enzyme *glutamine synthetase*, utilizing ammonia, magnesium, and ATP. L-Glutamine is hydrolyzed to glutamate by the enzyme *glutaminase*.

compared to other amino acids, it has long been thought that glutamine was not a necessary component of the diet. In fact, approximately five to ten grams per day of glutamine is consumed in the diet, and under normal circumstances dietary intake and synthesis of glutamine is adequate and balanced with demand. In situations where a particular tissue is in greater need of glutamine, inter-organ transfer of glutamine usually makes up for increased site-specific requirements. However, under certain pathological circumstances the body's tissues need more glutamine than the overall amount supplied by diet and *de novo* synthesis. During catabolic stress, for instance, intracellular glutamine levels can drop more than 50 percent, and plasma concentration falls 30 percent.[1] It is under these circumstances that supplemental glutamine becomes necessary.[2]

Skeletal muscle contains the greatest intracellular concentration of glutamine, comprising up to 60 percent of total body glutamine stores, and is considered the primary storage depot of glutamine, and thus the primary exporter of glutamine to other tissues. In times of metabolic stress, glutamine is released into circulation, where it is transported to the tissue in need. Intracellular skeletal muscle glutamine concentration is affected by various insults, including injury, sepsis, prolonged stress, starvation, and the use of glucocorticoids. Besides skeletal muscle, the lungs are the next largest producer of glutamine.

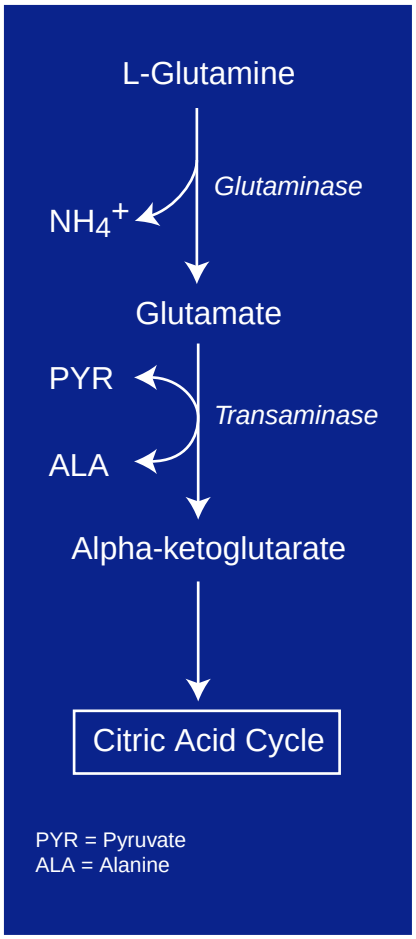
Glutamine can be converted to other amino acids, to glucose in the liver, and contributes to nucleotide, amino sugar, and protein biosynthesis. Glutamine is one of the three amino acids involved in glutathione synthesis. Glutathione, an important intracellular antioxidant and hepatic detoxifier, is comprised of glutamic acid, cysteine, and glycine.

Glutamine, Wound Healing, and Immune Cells

Fibroblasts, lymphocytes, and macrophages use glutamine as a metabolic fuel, as well as using it for nucleotide synthesis, which regulates cellular proliferation. Glutamine depletion can slow fibroblast growth, while adequate glutamine can stimulate growth and cellular proliferation *in vitro*. The dependence on glutamine in fibroblasts makes this nutrient a vital component of the healing response in wounds.[2]

In vitro lymphocyte research reveals these cells do not demonstrate any glutamine synthetase activity and are dependent on preformed glutamine. Lymphocytes respond to glutamine supplementation by proliferating, as well as producing more lymphocyte-derived cytokines *in vitro*.[3,4] The gastrointestinal tract is continuously exposed to the exterior environment of the body via food, liquid, and

Figure 2. L-Glutamine Catabolism.



In the mitochondria of enterocytes, L-glutamine is converted to alpha-ketoglutarate, which is utilized for the ATP production in the citric acid cycle.

swallowed salivary and mucus secretions, and therefore contains a large number of immune cells along its length. Glutamine's positive effects on the GI tract appear to stem from its ability to "feed" immune cells as well as mucosal cells.

Commercial total parenteral nutrition (TPN) solutions, commonly used in trauma and surgical patients, do not contain glutamine. This can result in atrophy of the gut mucosa, decreased gut-associated lymphoid tissue (GALT), and increased intestinal permeability. A study investigating the effects of glutamine-enriched TPN versus standard TPN in mice showed normalization of GALT activity, compared with GALT atrophy in standard TPN.[5] Other studies also point toward enhancement of gut immune activity with glutamine supplementation, but a defined mechanism has yet to be elucidated.[6-8] Enhancement of GALT activity could have profound effects on systemic immunity by strengthening gut immunity and reducing gut permeability.

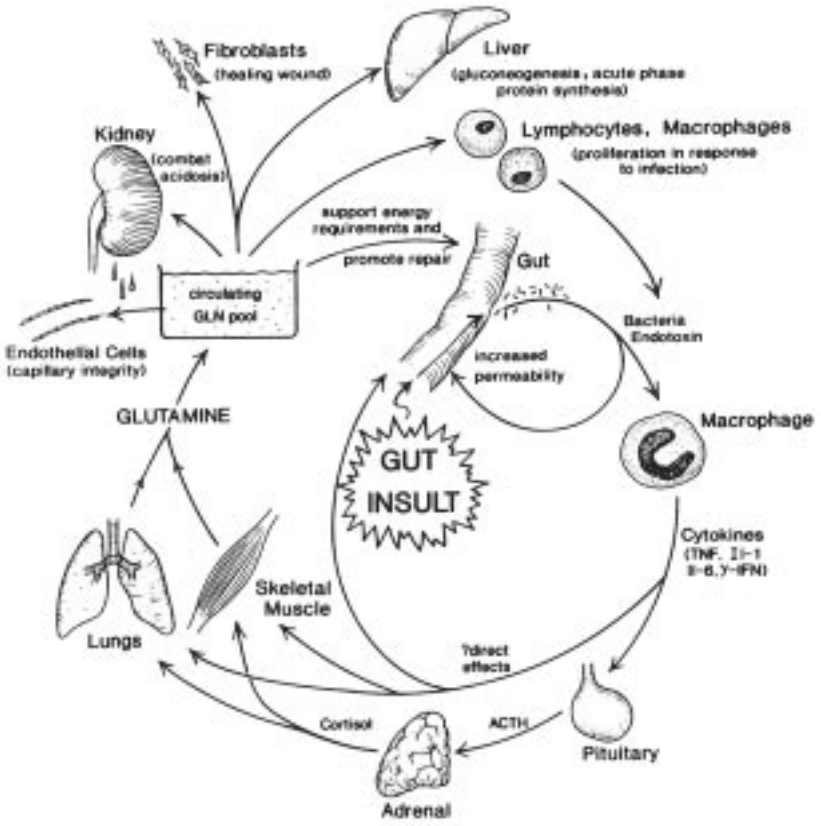
Plasma glutamine levels have been found to be decreased in endurance athletes who overtrain. This is defined as training too often and at such high intensity that muscles do not fully recover between workouts. These athletes tend to have a higher incidence of infectious diseases and allergies, and have been noted to have swollen lymph nodes and experience slower wound healing. They also have reduced markers of immune function compared to athletes not overtraining. It has been suggested that decreased plasma glutamine probably stems from a loss of glutamine stores from skeletal muscle while exercising, which are not given the chance to rebuild before the next workout. This may reduce the long-term availability of glutamine for immune cells and fibroblasts. Low-intensity exercise does not seem to be associated with glutamine depletion from skeletal muscle or a deleterious effect on the immune system.[9-12] Athletes undergoing a strenuous workout schedule may be able to reduce the risk of infections by supplementing with glutamine. The percentage of athletes free of infection one week after a strenuous event was significantly larger (81%) in a group who supplemented with glutamine, compared to a placebo group (49%).

Glutamine and the Gastrointestinal Tract

The gastrointestinal tract is by far the greatest user of glutamine in the body. The small intestine accounts for the largest uptake of glutamine of any organ, absorbing this amino acid from the lumen of the gut as well as from the bloodstream. Epithelial cells lining the small intestine (enterocytes) use glutamine as their principal metabolic fuel. Glutamine is converted in the mitochondria of intestinal cells to glutamate, then alpha ketoglutarate, which is utilized in the tricarboxylic acid

Figure 3. Inter-Organ Glutamine Flow Following Gut Insult.

From Souba WW.[2] Used with permission.



After a gut insult, increased permeability causes bacterial translocation. Leukocyte migration and cytokine release cause a further increased permeability, which triggers the hypothalmic-pituitary-adrenal (HPA) axis to induce a release of glutamine from skeletal muscle and lungs into the circulating glutamine pool. It is subsequently taken up by the gut to be utilized for repair of the damaged intestinal barrier.

(TCA, Krebs) cycle for ATP production (see Figure 2). Colonocytes also utilize glutamine; however, they prefer short-chain fatty acids as their primary fuel. Since enterocytes have little glutamine synthetase activity (see Figure 1) and a great amount of glutaminase, which metabolizes glutamine, they are also dependent on a supply of pre-formed glutamine.

Intestinal Morphology

The small intestine mucosa is comprised of a single cell thickness of mostly columnar epithelial cells, with endocrine cells, mucin cells, and Paneth cells interspersed between them. The absorptive capacity of the small intestine is greatly increased by the presence of villi, with corresponding crypts between them. The most mature cells occupy the tip of the villi, while immature cells are at the base of the villi, in the crypts. The immature cells proliferate and migrate to the tip, where they mature, then are reabsorbed or sloughed off into the lumen. The entire process takes only three to six days. This high rate of proliferation and turnover is usually well-regulated by nutrient availability, gastrin, growth hormone, bacterial flora, and neuro-regulatory activity. However, the presence of food passing through the gastrointestinal tract seems to be the primary stimulus for regulation of this proliferative response, as it can affect all of the aforementioned regulatory systems.[13] After seven days of fasting, even with the use of TPN, gut mass can be reduced by as much as 50 percent.[14,15]

Glutamine and Intestinal Permeability

Most of the research on glutamine and its connection to intestinal permeability has been conducted in conjunction with the use of TPN. Commercially-available TPN solutions do not contain glutamine, which can result in small intestine mucosal villous atrophy. In an animal study, glutaminase infusion

significantly decreased glutamine concentration in the bloodstream, accompanied by diarrhea, villous atrophy, mucosal ulceration, and intestinal necrosis.[16] This study emphasizes the importance of glutamine to the integrity of the small intestine, and specifically the need for glutamine uptake from the bloodstream as well as the intestinal lumen. Mucosal atrophy also occurred in animals fasted while on TPN. Addition of glutamine to the TPN solution reversed the mucosal atrophy.[17] Others have noted similar results of decreased villous atrophy, increased jejunal weight, and decreased intestinal permeability with the use of glutamine-enriched TPN solutions.[18-22]

One potential consequence of increased intestinal permeability is microbial translocation. Trauma, infection, starvation, chemotherapy, and other stressors are all associated with a derangement of normal intestinal permeability. Bacteria, fungi, and their toxins can subsequently translocate across the mucosal barrier into the bloodstream and react with the reticuloendothelial system. Cytokines produced from this reaction stimulate the hypothalamic-pituitary-adrenal axis, resulting in cortisol release from the adrenals.[2,23] Cortisol increases glutaminase activity in intestinal enterocytes, stimulating increased breakdown and utilization of glutamine in the small intestine. Cortisol also causes increased proteolysis in other tissues, and a release of glutamine from skeletal muscle (see Figure 3). Although this adaptation response provides metabolic assistance to help heal hyperpermeable gut tissue, severe damage to the mucosa or other tissue utilizing glutamine for healing, or prolonged stress can deplete skeletal muscle glutamine and consequently deprive enterocytes (which are using more glutamine in their stressed state) of their vital supply of glutamine.[2,23] In numerous animal studies, the addition of glutamine or glutamine dipeptides (stable dipeptides of glutamine with alanine or glycine) in experimentally-induced intestinal hyperpermeability improves gut barrier function, as well as immune activity in the gut.[24-29]

Another consequence of skeletal muscle glutamine depletion is the subsequent depletion of the glutamine-containing tri-peptide antioxidant glutathione, which may lead to oxidative damage of the muscle.[30] It is known that glutathione production occurs in the liver; however, supplemental glutamine has been shown to increase gut glutathione production threefold.[31] Although no studies have proven it, oral glutamine supplementation might increase intestinal glutathione synthetase activity, which can improve antioxidant activity in the gut, as well as augment NK cell activity.

Glutamine and Trauma

Increased intestinal permeability has been associated with trauma from burns,[32] surgery,[33,34] hemorrhagic shock,[35] and other physical trauma.[36] Injury of any tissue besides the intestines shunts glutamine away from the blood and into the tissues, making less glutamine available for the gut. Glucocorticoid release in acute stress, including surgery, infection, trauma, burns, sepsis, or other severe illness, causes accelerated protein breakdown. These patients can quickly lose significant amounts of protein, much of it from skeletal muscle, in an attempt to provide adequate amounts of glutamine for tissue healing and maintenance of gut integrity. As glutamine is depleted, wound healing is impaired, intestinal permeability increases, and the risk of microbial translocation, sepsis, and multiple organ failure increases significantly.[37,38]

The loss of skeletal muscle glutamine after surgery was illustrated in a group of 19 patients undergoing total hip replacement surgery. Skeletal muscle and plasma glutamine concentration was significantly decreased after surgery, compared to control groups (no

surgery) on either bedrest or fasting for four days.[39] Glutamine supplementation can attenuate this surgery-induced glutamine depletion. In a study of glutamine and elective abdominal surgery, a glutamine-containing TPN solution (0.285 g glutamine/kg/24 hrs) was given to patients for three days following surgery. Skeletal muscle glutamine levels declined 25 percent, compared to a 40-percent loss in the control TPN group.[40]

A glutamine dipeptide (alanyl-glutamine) was utilized in a study of nitrogen economy in major abdominal surgery patients. Control patients (on standard TPN) lost approximately 36 grams of protein daily, compared to a loss of 14 grams daily in the dipeptide-supplemented TPN group. This amounted to a savings of over 600 grams of protein over the four-day post-operative period. The circulating lymphocyte count remained stable in the supplemented group, versus a 20-percent loss in the control group. Supplemented patients also had improved markers of glutathione levels, and were in the hospital 6.2 days fewer after surgery. The authors estimate the daily requirement of exogenous glutamine in surgical patients to be 12 grams per day, with 25 grams per day needed in severe trauma or infection.[41]

Maintenance of immune function and gut barrier function following trauma is vitally important, as infection is a major cause of morbidity and mortality in severe trauma cases. It is thought that these infections often are a result of gut hyperpermeability and bacterial translocation to systemic circulation. A recent study illustrates the need for glutamine supplementation in these patients. Sixty patients with multiple trauma were given glutamine-containing enteral nutrition for at least five days following their injuries, with dramatic results. Incidence of pneumonia was 17 percent in the glutamine group, compared to 45 percent in the control group ($p<0.02$). Bacteremia occurred in seven percent of the glutamine group and 42 percent of the control group, and only one patient (3%) in the glutamine group had sepsis, compared to eight of the controls (26%). The researchers noted the majority of bacteremia and sepsis cases in the control group involved gram-negative bacteria, while none of the bacteremia and sepsis cases in the glutamine group involved these organisms, which lead them to believe glutamine may have prevented bacterial translocation from the gut.[36] It was also suggested enteral glutamine dosing provided better protection than TPN in trauma patients, with a lower incidence of infections. This has been confirmed by other studies.[42,43]

Glutamine and Cancer

One area of glutamine research which has recently garnered much attention is the effect of glutamine on cancer therapy regimens. Numerous clinical studies have been conducted utilizing glutamine in conjunction with radiation and chemotherapy, with promising results.

In addition to glutamine being the principal metabolic fuel for the rapidly proliferating cells of the intestines and immune system, glutamine is also the main fuel for most rapidly growing tumors, which have high glutaminase activity, similar to small intestine enterocytes. Tumor growth can deplete skeletal muscle glutamine and glutathione, providing less fuel for enterocytes and creating a catabolic, cachectic state. It is suggested the tumor can become a "glutamine trap," further enhancing systemic glutamine loss.[44] Researchers investigated the consumption of glutamine by colonic tumors and noted these tumors did not extract glutamine at a greater rate than normal intestinal tissue, regardless of the tumor size, type, differentiation, classification, or vascularization.[45] Regardless of the speed of uptake, the mass of the tumor could potentially rob glutamine from all healthy tissue.

There has been some concern about supplementing cancer patients with glutamine, as it was hypothesized that supplementation may increase tumor growth. *In vitro* cell culture studies do, in fact, show a dependence on glutamine and increased cellular growth with the addition of glutamine.[46-49] This has not been proven to be the case *in vivo*.[50-52] In fact, an animal study demonstrated the opposite finding — glutamine supplementation reduced tumor growth. In this study, tumor growth was reduced by 40 percent, and a 30-percent increase in NK activity was noted as well. The authors stated, "These data indicate that oral glutamine supplementation, through support of host glutamine stores and glutathione production, may decrease tumor growth by enhancing NK cell activity."[54] In a study of fibrosarcoma in rats, Klimberg et al found glutamine supplementation of an enteral diet increased muscle glutamine by 60 percent without stimulating tumor growth or tumor glutamine utilization.[52] A cell culture study using stimulated neutrophils and tumor cells which were incubated with glutamine demonstrated inhibition of glutamine uptake by malignant cells due to the anti-tumor activity of the stimulated neutrophils.[53] These findings suggest glutamine might stimulate some tumor cell types but not others, or it may stimulate cell growth, while at the same time increasing cellular anti-tumor immune function via increased NK cell activity or neutrophil activation.

The rapidly growing cells of the intestinal tract are easily killed by radiation and chemotherapy. Glutamine supplementation in rats subjected to abdominal radiation prevented the expected gut mucosal ulceration and increased permeability. A significant decrease in mortality (zero versus 45% in controls) was also noted after eight days.[55] In a study of patients undergoing radiation and chemotherapy (cisplatinum and 5-fluorouracil) for esophageal cancer, glutamine supplementation (30 g/day) prevented the increase in gut permeability seen with controls. Glutamine supplementation also prevented the significant reduction in lymphocyte count seen in the control group.[56]

Severe oral mucositis is common in bone marrow transplantation, a severe yet potentially lifesaving treatment which includes whole body irradiation and chemotherapy. Oral glutamine (one gram four times per day) was administered to patients having bone marrow transplantation, and a significant reduction in oral pain and mucosal inflammation was observed.[57]

Animal studies with methotrexate chemotherapy have demonstrated that glutathione given with methotrexate increased tumor methotrexate concentration and tumoricidal activity. This combination also reduced the incidence of methotrexate-induced side-effects of gut toxicity and sepsis, and improved survival rates.[58-63] The mechanism is unclear, but may involve methotrexate conjugation by glutamine, reducing the metabolism of methotrexate, or possibly increased glutathione synthesis and subsequent cellular protection promoted by glutamine supplementation.[64]

Discussion

Although glutamine is formed in the body from *de novo* synthesis, and is part of an everyday diet, bodily stores can be overwhelmed by injury, burns, surgery, overtraining, or cancer. Enterocytes, fibroblasts, lymphocytes, and macrophages use glutamine as a metabolic fuel, and the functioning of these cells can be significantly affected with glutamine depletion. Glutamine supplementation via oral, enteral, or parenteral routes increases skeletal muscle glutamine stores and has been shown to improve gut permeability and mucosal morphology, as well as markers of immune function.

Glutamine supplementation is necessary in trauma and surgical patients, and in the critically ill to prevent gut mucosal atrophy, infection, and to reduce gut permeability, sepsis, and possibly multiple organ failure. More

intense study still needs to be conducted to confirm the latter.

Cancer can cause a great loss of glutamine from skeletal muscle, reducing the amount available for normal metabolism by enterocytes. It appears glutamine supplementation can ameliorate loss of glutamine stores and improve gut and immune function, but this information should be balanced with the possibility it might also increase the growth of some tumors.

Standard cancer chemotherapy and radiotherapy regimens can be very damaging to normal tissue. It now appears the use of glutamine in these patients can prevent many toxic side-effects, increase tumor concentration of methotrexate, and increase tumoricidal action. More research is required to determine the mechanisms of the protective and cytotoxic actions of glutamine.

References

1. Askanazi J, Carpenter YA, Michelsen CB, et al. Muscle and plasma amino acids following injury: Influence of intercurrent infection. *Ann Surg* 1980;192:78-85.
2. Souba WW. *Glutamine Physiology, Biochemistry, and Nutrition in Critical Illness*. Austin, TX: R.G. Landes Co.; 1992.
3. Rohde T, MacLean DA, Klarlund Pedersen B. Glutamine, lymphocyte proliferation and cytokine production. *Scand J Immunol* 1996;44:648-650.
4. Ardawi MS. Glutamine and glucose metabolism in human peripheral lymphocytes. *Metabolism* 1988;37:99-103.
5. Li J, King BK, Janu PG, et al. Glycyl-L-glutamine-enriched total parenteral nutrition maintains small intestine gut-associated lymphoid tissue and upper respiratory tract immunity. *JPEN J Parenter Enteral Nutr* 1998;22:31-36.
6. O'Riordain MG, De Beaux A, Fearon KC. Effect of glutamine on immune function in the surgical patient. *Nutrition* 1996;12:S82-S84.
7. van der Hulst RR, von Meyenfeldt MF, Tiebosch A, et al. Glutamine and intestinal immune cells in humans. *JPEN J Parenter Enteral Nutr* 1997;21:310-315.
8. Gismondo MR, Drago L, Fassina MC, et al. Immunostimulating effect of oral glutamine. *Dig Dis Sci* 1998;43:1752-1754.
9. Parry-Billings M, Blomstrand E, McAndrew N, Newsholme EA. A communicational link between skeletal muscle, brain, and cells of the immune system. *Int J Sports Med* 1990;11:S122-S123.
10. Walsh NP, Blannin AK, Robson PJ, Gleeson M. Glutamine, exercise and immune function. Links and possible mechanisms. *Sports Med* 1998;26:177-191.
11. Rowbottom DG, Keast D, Morton AR. The emerging role of glutamine as an indicator of exercise stress and overtraining. *Sports Med* 1996;21:80-97.
12. Newsholme EA. Biochemical mechanisms to explain immunosuppression in well-trained and overtrained athletes. *Int J Sports Med* 1994;15:S142-S147.
13. Wilmore DW. Metabolic support of the gastrointestinal tract. Potential gut protection during intensive cytotoxic therapy. *Cancer* 1997;79:1794-1803.
14. Souba WW, Strebel F, Bull J, et al. Interorgan glutamine metabolism in the tumor-bearing rat. *J Surg Res* 1988;44:720-726.
15. Souba WW. The gut as a nitrogen-processing organ in the metabolic response to critical illness. *Nutr Support Services* 1988;8:15-22.
16. Bakerville A, Hambleton P, Benbough JE. Pathological features of glutaminase toxicity. *Br J Exp Pathol* 1980;61:12-18.
17. O'Dwyer ST, Smith RJ, Hwang TL, Wilmore DW. Maintenance of small bowel mucosa with glutamine-enriched parenteral nutrition. *JPEN J Parent Enteral Nutr* 1989;13:579-585.
18. Hwang TL, O'Dwyer ST, Smith RJ, et al. Preservation of small bowel mucosa using glutamine-enriched parenteral nutrition. *Surg Forum* 1987;38:56.
19. Grant J. Use of L-glutamine in total parenteral nutrition. *J Surg* 1988;44:506-513.
20. Barber AE, Jones WG, Minei JP, et al. Glutamine or fiber supplementation of a defined formula diet. Impact on bacterial translocation, tissue composition, and response to endotoxin. *JPEN J Parent Enteral Nutr* 1990;14:335-343.

21. Li J, Langkamp-Henken B, Suzuki K, Stahlgren LH. Glutamine prevents parenteral nutrition-induced increases in intestinal permeability. *JPEN J Parent Enteral Nutr* 1994;18:303-307.
22. Khan J, Iiboshi Y, Cui L, et al. Alanyl-glutamine-supplemented parenteral nutrition increased luminal mucus gel and decreased permeability in the rat small intestine. *JPEN J Parent Enteral Nutr*1999;23:24-31.
23. Wilmore DW, Smith RJ, O'Dwyer ST, et al. The gut: a central organ after surgical stress. *Surgery* 1988;104:917-923.
24. Souba WW, Klimberg VS, Hautamaki RD, et al. Oral glutamine reduces bacterial translocation following abdominal radiation. *J Surg Res* 1990;48:1-5.
25. Gianotti L, Alexander JW, Gennari R, et al. Oral glutamine decreases bacterial translocation and improves survival in experimental gut-origin sepsis. *JPEN J Parenter Enteral Nutr* 1995;19:69-74.
26. Bai MX, Jiang ZM, Liu YW, et al. Effects of alanyl-glutamine on gut barrier function. *Nutrition* 1996;12:793-796.
27. Pangrahi P, Gewolb IH, Bamford P, Horvath K. Role of glutamine in bacterial transcytosis and epithelial cell injury. *JPEN J Parenter Enteral Nutr* 1997;21:75-80.
28. Chun H, Sasaki M, Fujiyama Y, Bamba T. Effect of glutamine on intestinal permeability and bacterial translocation after abdominal radiation injury in rats. *J Gastroenterol* 1997;32:189-195.
29. Foitzik T, Stufler M, Hotz HG, et al. Glutamine stabilizes intestinal permeability and reduces pancreatic infection in acute experimental pancreatitis. *J Gastrointest Surg* 1997;1:40-47.
30. Hammarqvist F, Luo J, Corgreave I, et al. Skeletal muscle glutathione is depleted in critically ill patients. *Crit Care Med* 1997;25:78-84.
31. Cao Y, Feng Z, Hoos A, Klimberg S. Glutamine enhances gut glutathione production. *JPEN J Parenter Enteral Nutr* 1998;22:224-227.
32. Ziegler TR, Smith RJ, O'Dwyer ST, et al. Increased intestinal permeability associated with infection in burn patients. *Arch Surg* 1988;123:1313-1319.
33. Roumen RM, van der Vliet JA, Wevers RA, Goris RJ. Intestinal permeability is increased after major vascular surgery. *J Vasc Surg* 1993;17:734-737.
34. Vinnars E, Bergstrom J, Furst P. Influence of the postoperative state on the intracellular free amino acids in human muscle tissue. *Ann Surg* 1975;182:665-671.
35. Roumen RM, Hendriks T, Wevers RA, Goris JA. Intestinal permeability after severe trauma and hemorrhagic shock is increased without relation to septic complications. *Arch Surg* 1993;128:453-457.
36. Houdijk AP, Rijnsburger ER, Jansen J, et al. Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet* 1998;352:772-776.
37. Biolo G, Toigo G, Ciocchi B, et al. Metabolic response to injury and sepsis: changes in protein metabolism. *Nutrition* 1997;13:S52-S57.
38. Wilmore DW. Catabolic illness: strategies for enhancing recovery. *N Engl J Med* 1991;325:695-702.
39. Askanazi J, Elwyn DH, Kinney JM, et al. Muscle and plasma amino acids after injury: The role of inactivity. *Ann Surg* 1978;188:797-803.
40. Wernerman J, Hammarkvist F, Rustom M, Vinnars E. Glutamine and ornithine-alpha-ketoglutarate but not branched-chain amino acids reduce the loss of muscle glutamine after surgical trauma. *Metabolism* 1989;38:S63-S66.
41. Morlion BJ, Stehle P, Wachter P, et al. Total parenteral nutrition with glutamine dipeptide after major abdominal surgery. *Ann Surg* 1998;227:302-308.
42. Moore FA, Moore EE, Jones TN, et al. TEN versus TPN following major abdominal trauma—reduced septic morbidity. *J Trauma* 1989;29:916-923.
43. Kudsk KA, Croce MA, Fabian TC, et al. Enteral versus parenteral feeding. *Ann Surg* 192;215:503-511.
44. Klimberg VS, McClellan JL. Glutamine, cancer, and its therapy. *Am J Surg* 1996;172:418-424.
45. van der Hulst RR, von Meyenfeldt MF, Deutz NE, Soeters PB. Glutamine extraction by the gut is reduced in patients with depleted gastrointestinal cancer. *Ann Surg* 1997;225:112-121.

46. Kang YJ, Feng Y, Hatcher EL. Glutathione stimulates A549 cell proliferation in glutamine-deficient culture: the effect of glutamate supplementation. *J Cell Physiol* 1994;161:589-596.
47. Kang YJ. Buthionine sulfoximine spares intracellular glutamate: a possible mechanism for cell growth stimulation. *Cell Mol Biol Res* 1993;39:675-684.
48. Ollenschlager G, Simmel A, Roth E. Availability of glutamine from peptides and acetylglutamine for human tumor-cell cultures. *Metabolism* 1989;38:S40-S42.
49. Moyer MP, Armstrong A, Aust JB, et al. Effects of gastrin, glutamine, and somatostatin on the in vitro growth of normal and malignant human gastric mucosal cells. *Arch Surg* 1986;121:285-288.
50. Bartlett DL, Charland S, Torosian MH. Effect of glutamine on tumor and host growth. *Ann Surg Oncol* 1995;2:71-76.
51. Austgen TR, Dudrick PS, Sitren H, et al. The effects of glutamine-enriched total parenteral nutrition on tumor growth and host tissues. *Ann Surg* 1992;215:107-113.
52. Klimberg VS, Souba WW, Salloum RM, et al. Glutamine-enriched diets support muscle glutamine metabolism without stimulating tumor growth. *J Surg Res* 1990;48:319-323.
53. Learn DB, Thomas EL. Inhibition of tumor cell glutamine uptake by isolated neutrophils. *J Clin Invest* 1988;82:789-796.
54. Fahr MJ, Kornbluth J, Blossom S, et al. Harry M. Vars Research Award. Glutamine enhances immunoregulation of tumor growth. *JPEN J Parenter Enteral Nutr* 1994;18:471-476.
55. Klimberg VS, Souba WW, Dolson DJ, et al. Prophylactic glutamine protects the intestinal mucosa from radiation injury. *Cancer* 1990;66:62-68.
56. Yoshida S, Matsui M, Shirouzu Y, et al. Effects of glutamine supplements and radiochemotherapy on systemic immune and gut barrier function in patients with advanced esophageal cancer. *Ann Surg* 1998;227:485-491.
57. Anderson PM, Ramsay NKC, Shu XO, et al. Effect of low-dose oral glutamine on painful stomatitis during bone marrow transplantation. *Bone Marrow Transplant* 1998;22:339-344.
58. Griffiths RD. Outcome of critically ill patients after supplementation with glutamine. *Nutrition* 1997;13:752-754.
59. Klimberg VS, Nwokedi E, Hutchins L, et al. Glutamine facilitates chemotherapy while reducing toxicity. *JPEN J Parenter Enteral Nutr* 1992;16:83S-87S.
60. Fox AD, Kripke SA, De Paula J, et al. Effect of a glutamine-supplemented enteral diet on methotrexate-induced enterocolitis. *JPEN J Parenter Enteral Nutr* 1988;12:325-331.
61. Rouse K, Nwokedi E, Woodliff JE, et al. Glutamine enhances selectivity of chemotherapy through changes in glutathione metabolism. *Ann Surg* 1995;221:420-426.
62. Klimberg VS, Pappas AA, Nwokedi E, et al. Effect of supplemental dietary glutamine on methotrexate concentrations in tumors. *Arch Surg* 1992;127:1317-1320.
63. Rubio IT, Cao Y, Hutchins LF, et al. Effect of glutamine on methotrexate efficacy and toxicity. *Ann Surg* 1998;227:772-778; discussion 778-780.
64. Charland SL, Bartlett DL, Torosian MH. A significant methotrexate-glutamine pharmacokinetic interaction. *Nutrition* 1995;11:154-158.