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Series Editor: Adrianne Bendich

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Victor R. Preedy
Vinood B. Patel *Editors*

Glutamine in Clinical Nutrition

Humana Press

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Adrianne Bendich, Ph.D., FACN, FASN, Series Editor

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Preface

Glutamine was originally considered a nonessential amino acid due the fact that it can be synthesized from glutamate. Glutamine is also the most abundant amino acid and a major contributor to whole body nitrogen metabolism in man. However, over several decades, evidence has supported the notion that glutamine is "conditionally essential" and thus important in human health. For example, glutamine protects the intestinal tract, skeletal muscle, and neuronal tissue against metabolic stress. Some of the earlier studies showed that reduced intracellular glutamine in muscle was associated with loss of lean tissue or wasting. This led to the development of nutritional support regimens in which glutamine was administered by enteral or parental routes. However, this is rather a simplistic notion of glutamine's role and potential in disease. It is now known that glutamine has an almost ubiquitous function and is important in maintaining the cellular milieu of virtually every organ in the human body. Thus, its supplementation not only modulates skeletal muscle mass in postsurgical stress but also improves lymphocyte count, enhances outcome scores, and ameliorates the peroxidation of lipids as just a few examples. However, more recent studies have suggested that the administration of glutamine conjugated, or co-administered, with substrates provides greater efficacy that glutamine alone. Furthermore the efficacy of conjugated glutamine is enhanced when administered in complex cocktails that may contain other nutraceuticals. The science of glutamine is thus complex, and finding all the relevant information in a single source has hitherto been problematic. This is however addressed in *Glutamine in Clinical Nutrition*.

It has five major sections:

Section 1: Basic Processes at the Cellular Level and in Animal Models
Section 2: Glutamine Use in Critically Ill Patients and Their Diagnosis
Section 3: Glutamine in Normal Metabolism and Under Surgical Stress
Section 4: Clinical Aspects of Glutamine in the Intestine
Section 5: Clinical Aspects of Glutamine in Certain Patient Populations

Coverage includes glutamine structure and function, amino acid transporters, glutamine transaminases, one-carbon metabolism, uptake and immunomodulation, the pituitary gland, thyroid-stimulating hormone release, the TCA cycle, *mammary tissue*, cancer cells, metabolic imaging, endotoxemia, metabolic stress, major surgery, intensive care, *multiple trauma*, sepsis, dipeptides, insulin sensitivity, critically ill children, liver cirrhosis, *ammonia*, *encephalopathy*, the glutamine-glutamate-alpha-ketoglutarate axis, glutamine cycling, metabolic syndrome, glucagon-like peptide-1, presurgery, malnutrition, diabetic foot ulcers, epithelial tight junction, colitis, *Helicobacter pylori* infection,

intestinal hypoxic injury, dipeptides, intestinal microcirculation, manganese toxicity, epilepsy, glutamine synthetase deficiency, plasma antioxidants, HIV, ischemia reperfusion injury, cancer immunosuppression, exercise, cancer cachexia, skeletal muscle, myostatin, and many other areas. Finally there is a chapter on "Web-Based Resources and Suggested Readings."

Contributors are authors of international and national standing, leaders in the field, and trendsetters. Emerging fields of science and important discoveries are also incorporated in *Glutamine in Clinical Nutrition*.

This book is designed for nutritionists and dietitians, public health scientists, doctors, epidemiologists, health care professionals of various disciplines, policy makers, and marketing and economic strategists. It is designed for teachers and lecturers, undergraduates and graduates, researchers and professors.

The Editors

London, UK

Rajkumar Rajendram
Victor R. Preedy
Vinood B. Patel

Series Editor Page

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes (1) a synthesis of the state of the science; (2) timely, in-depth reviews by the leading researchers and clinicians in their respective fields; (3) extensive, up-to-date fully annotated reference lists; (4) a detailed index; (5) relevant tables and figures; (6) identification of paradigm shifts and the consequences; (7) virtually no overlap of information between chapters, but targeted, interchapter referrals; (8) suggestions of areas for future research; and (9) balanced, data-driven answers to patient as well as health professionals questions that are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter and in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research and practice oriented, have the opportunity to develop a primary objective for their book; define the scope and focus; and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

Glutamine in Clinical Nutrition, edited by Rajkumar Rajendram, Victor Preedy, and Vinood Patel, is a very welcome addition to the Nutrition and Health Series and fully exemplifies the series' goals. Although glutamine is not an essential amino acid and can be synthesized de novo, it is the most abundant amino acid in the human body. Glutamine has numerous valuable metabolic functions: nitrogen transport, maintenance of the cellular redox state, serves as a metabolic intermediate and can be used as a source of energy, and is a required component of glutathione, the major intracellular antioxidant. Its central role in human physiology and metabolism in healthy individuals and its critical importance during the stresses of injury, inflammation, chronic diseases, and fetal development make it sufficiently important to warrant this 40 chapter, comprehensive volume. This book is designed as a resource for nutritionists and dietitians, public health scientists, physicians, epidemiologists, and health care professionals of various disciplines who interact with clients, patients, and/or family members. This important volume provides objective, relevant information for teachers and lecturers, advanced undergraduates and graduates, researchers and professors who require extensive, up-to-date literature reviews, instructive tables and figures, and excellent references on major aspects of glutamine related to human health and disease.

The volume contains in-depth chapters that review the cellular and genetic aspects of glutamine's actions. Relevant animal models are described that help us to better understand the tissue and organs

that are most affected by glutamine metabolism; both healthy and clinically relevant models are reviewed. The majority of the volume examines the importance of glutamine in patients as glutamine is considered a conditionally essential amino acid when the body is under the severe stress of sepsis, cancer, premature birth, and immunosuppression, as examples. It must be noted that this is the first volume to be published for health professionals and advanced students that examines the biochemistry, clinical nutrition, and therapeutic aspects of glutamine.

The editors of this volume are experts in their respective fields and represent the medical profession as well as the academic research community. Dr. Rajkumar Rajendram is an intensive care physician, anesthetist, and perioperative physician. He was trained in general medicine and intensive care in Oxford, and he attained membership in the Royal College of Physicians (MRCP) in 2004. Dr. Rajendram then trained in anesthesia and intensive care in the Central School of Anesthesia, London Deanery and became a Fellow of the Royal College of Anaesthetists (FRCA) in 2009. He is one of the first intensivists to become a Fellow of the Faculty of Intensive Care Medicine (FFICM). Dr. Rajendram recognized that nutritional support was a fundamental aspect of critical care and, as a visiting research Fellow in the Nutritional Sciences Research Division of King's College London, he has published over 50 textbook chapters, review articles, peer-reviewed papers, and abstracts. Professor Victor Preedy is a senior member of King's College London where he is a Professor of Nutritional Biochemistry and Professor of Clinical Biochemistry at King's College Hospital. He is also Director of the Genomics Centre and a member of the School of Medicine. He is a member of the Royal College of Pathologists, a Fellow of the Society of Biology, the Royal College of Pathologists, the Royal Society for the Promotion of Health, the Royal Institute of Public Health, the Royal Society for Public Health, and in 2012 a Fellow of the Royal Society of Chemistry. Dr. Patel is a Senior Lecturer in Clinical Biochemistry at the University of Westminster and honorary Fellow at King's College London. Dr. Patel obtained his degree in Pharmacology from the University of Portsmouth, his Ph.D. in protein metabolism from King's College London, and completed postdoctoral research at Wake Forest University School of Medicine. Dr. Patel is a recognized leader in alcohol research and was involved in several NIH-funded biomedical grants related to alcoholic liver disease. Dr. Patel has edited biomedical books in the area of nutrition and health and disease prevention and has published over 160 articles.

The volume is organized into five major sections. *Section One*, containing ten related chapters, discusses the basic biochemical processes that involve glutamine at the cellular level and the physiological functions as well as certain pathophysiological functions that have been identified using animal models. The first chapter provides a broad-based perspective on the functions of glutamine and its importance in serving as a major source of molecules used in the synthesis of other amino acids, proteins, and other complex molecules within the human body. Glutamine is a critical nutrient for all rapidly proliferating cells and growing tissues, including cancerous tissues. In addition to providing building blocks for immune and other proliferating cells, glutamine contributes to the maintenance of redox balance by providing reducing equivalents that are also necessary for the synthesis of fatty acids. The chapter also explores the potential uses of glutamine supplementation in cases where its synthesis is insufficient to maintain muscle mass. Tables and figures included describe major metabolic cycles and the importance of glutamine as a source of nitrogen. The second chapter describes the molecules, at the cellular level, that are involved in the transport of glutamine in and out of cells. The authors focus mainly on the description of the functional properties of the physiologically important and Na+-dependent glutamine transporters belonging to the solute carrier 1 and SLC38 families. The chapter includes excellent figures and detailed descriptions of the regulation and the functional properties of the Sodium-Coupled Neutral Amino Acid Transporters (SNATs) of the SLC38 gene family that control influx and efflux of glutamine from cells.

Another important function of glutamine is to serve as a precursor for the neurotransmitter glutamate in the glutamate-glutamine cycle in the mammalian brain. This cycle is illustrated in the included figures that describe the brain cells and enzymes involved in this cycle. Chapter 3 examines the

glutamine-glutamate cycle in depth. In the central nervous system, glutamate is locally converted from glutamine, which is absorbed into the neurons and acts as a neurotransmitter. Glutamate is an important excitatory amino acid neurotransmitter in the brain. The authors of Chap. 3 describe the recent laboratory animal studies on the function of glutamine and glutamate as extracellular signal mediators in the autocrine and/or paracrine system of the endocrine tissues. Glutamine and glutamate have been shown to play a dual role as excitatory neurotransmitters in the central nervous system as well as extracellular signaling molecules in endocrine tissues such as the adrenal gland, pancreas, and testis and in the pituitary gland. Specific models of in vitro and in vivo signaling of thyroid-stimulating hormone release from the pituitary gland provide a new avenue for exploring the role of glutamine in pituitary gland functions. Chapter 4 describes the central role of glutamine in the metabolism of cells of the immune system. Glutamine, in addition to glucose, is used as an energy source by immune cells especially when stimulated by antigens that trigger cellular proliferation. The cell culture studies that are reviewed clearly indicate the important roles of glutamine as an energy source as well as a precursor of the antioxidant, glutathione, to protect immune and surrounding cells from oxidative damage.

The fifth chapter examines the roles of the glutamine transaminases. The authors describe and include important figures to help the reader to visualize several glutaminase pathways and suggest that the glutaminase II pathway can provide metabolically critical molecules to epithelial cells in several tissues, including the brain (choroid plexus), prostate, bladder, and pancreas. Recent interest has focused on the glutaminase II pathway as it is found in a number of human cancer tissues; the presence of the glutaminase II pathway may be of fundamental importance in cancer biology. Given all of the metabolic pathways that involve glutamine, it is not surprising that the importance of glutamine for cancer cells is an area of intense research. Chapter 6 examines a glucose-independent, glutamine-driven tricarboxylic acid cycle that serves as an alternative energy-generating pathway for the survival and growth of tumor cells despite hypoxic and nutrient-deprived microenvironments. Cell culture studies have documented that glutamine is a viable alternative source of energy for glucose-deprived cancer cells. New studies are looking at drug candidates that can disrupt cancer cell use of glutamine as an energy source. Chapter 7 describes the role of glutamine in the multiple metabolic pathways of breast tumor cells. Glutamine metabolism differs significantly in basal compared to luminal breast cancer cells in that basal breast cancer cells require exogenous glutamine while luminal breast cancer cells are independent of exogenous glutamine. The chapter describes the metabolic differences between these two tumor cell types and suggests that these differences present therapeutic opportunities. Chapter 8 provides an historic perspective of the research to find cancer drug candidates. Because glutamine is so central to normal cell function, there has been limited success in finding a drug candidate that provides an acceptable risk:benefit ratio; however, research continues. Chapter 9 expands upon the role of glutamine in cancer cells by exploring the diagnostic potential of this activity to find active sites of cancer cell metabolism. The authors indicate that since the 1950s, glutamine has been recognized as an important tumor nutrient that contributes to key metabolic processes in proliferating cancer cells. Glutamine participates in bioenergetics, supports cell defenses against oxidative stress, complements glucose metabolism, and is an obligate nitrogen donor for nucleotide and amino acid synthesis. Glutamine also influences a number of signaling pathways that contribute to tumor growth. The chapter reviews the mechanisms involved in using glutamine plus positron emission tomography (PET) imaging to describe the metabolic activities of cancer cells.

The final chapter in the first section reviews the alterations in glutamine metabolisms that occur during sepsis and septic shock that are seen in patients and can be best studied using animal models and cell cultures. Chapter 10 describes the cellular responses to bacterial infections in animal models exposed to endotoxins that can lead to sepsis, septic shock, and to multiple organ dysfunction syndrome. We learn that endotoxemia markedly modifies glutamine metabolism in tissues with a decrease of intestinal glutamine uptake and metabolism, and a decrease in oxygen consumption. In skeletal muscle, endotoxemia increases endogenous glutamine synthesis and release resulting in a decrease in the muscle glutamine content. In lungs, endotoxemia results in a decrease of glutamine uptake with

increased endogenous glutamine synthesis and release. Supplementation with glutamine in its free form or in its dipeptide form resulted in a decrease in intestinal permeability and bacterial translocation and decreased intestinal inflammation. In the lung, glutamine supplementation attenuated pulmonary inflammation and injury. The results of these studies have led to preliminary studies in patients with septic shock that are reviewed in the next section.

Section Two contains eight chapters that review the use of glutamine in critically ill patients and in the diagnosis of the status of certain critically ill patients. The first chapter in this section, Chap. 11, examines the normal rate of glutamine turnover and the effects of critical illness on the turnover of glutamine. The total pool of free glutamine in the human body turns over every 24 h. The extracellular glutamine pool is approximately 2 g and it has a rapid turnover; the intracellular glutamine pool contains more than 50 g and turns over more slowly. The author stresses the need for monitoring serum glutamine levels in critically ill patients especially when glutamine is provided either via the enteral or parenteral routes. Chapter 12 describes in detailed tables and figures the clinical studies using glutamine in the intensive care setting in surgical and critically ill patients. Although the laboratory animal data appear promising, current clinical data are not consistent and this may be due to the heterogeneity of the patient populations and their disease states, the lack of studies using pretreatment as used in laboratory animal studies, and differing doses and duration of treatments. Related to this chapter is the analysis of the use of glutamine in critically ill and less critically ill patients in intensive care units. Chapter 13 reviews the clinical studies that have examined the potential for glutamine supplementation to improve the outcomes of patients with multiple traumas. As with other chapters, these authors recommend the initiation of more well-controlled studies that can help to clarify the levels of benefit.

Chapter 14 reviews the immune responses to sepsis and the use of glutamine containing enteral and parenteral preparations. The authors note that glutamine is of value to immune responses to infections, yet the patient intervention data are inconsistent.

Chapter 15 examines the potential roll of glutamine in preserving insulin sensitivity in critically ill patients. The authors explain that hyperglycemia is a key metabolic feature associated with the stress response in critically ill patients. The stress response causes an exaggerated production of catecholamines and cortisol that combined with the presence of inflammatory cytokines results in insulin resistance. Stress hyperglycemia has been linked to poor outcomes, and the authors review the clinical studies that control high glucose levels using supplemental glutamine in the form of a dipeptide. They review the positive clinical data on the use of glutamine-enriched total parenteral nutrition in critically ill adult patients. Chapter 16 focuses on an in-depth review of the clinical data on the use of glutamine supplementation in critically ill adult patients in order to develop a rationale for glutamine use in critically ill children. In critically ill adults, plasma glutamine levels decrease quickly and significantly, remaining low for up to 21 days, and are associated with increased morbidity and mortality. Data have consistently shown benefits of glutamine supplementation in this patient population, and these studies have resulted in the American Society of Parenteral and Enteral Nutrition (ASPEN) and the European Society of Enteral and Parenteral Nutrition (ESPEN) recommending that 0.3–0.5 g of glutamine/kg bw be added to parenteral nutrition in critically ill adults. The authors review the limited studies with preterm and very low birth weight infants who have been given glutamine and the studies in limited numbers of children with severe infections and illnesses and indicate that the findings are inconsistent. Differing routes of administration, dose, degree of illness, and cause of childhood illnesses may be some of the reasons for the inconsistent findings. Further clinical studies that are randomized and double blind, of sufficiently long duration, and with a physiologically efficacious dose of glutamine for preterm infants are recommended as a first step in developing criteria for use in this patient population that is known to be at significant risk for sepsis and septic shock.

As mentioned above, in critically ill patients, glutamine is often given enterally and it is metabolized mainly in the liver as a source of energy. Glutamine is also metabolized to glutamate and ammonia by the liver type of the mitochondrial enzyme glutaminase. It is critical to determine the

level of liver function especially in patients with liver cirrhosis. Chapter 17 describes a diagnostic test, the oral glutamine challenge, which is used to monitor liver function. The high protein meal that is used in this test induces an increase in blood ammonia in patients with cirrhosis but not in healthy controls or liver transplant patients. When the blood ammonia levels increase, it is transported to the central nervous system where ammonia may promote toxic effects including hepatic encephalopathy. Of interest, the oral glutamine test is also used in drug development to assess the effect of new drugs on liver function. The final chapter in this section, Chap. 18, discusses the biochemical reactions that result in ammonia formation in patients with hepatic encephalopathy, the effects on brain and other tissues, and the potential for glutamine supplementation to reduce certain of the adverse effects in these critically ill patients.

Section Three contains six chapters that examine the interactions between glutamine and insulin. The first chapter in this section, Chap. 19, provides an overview of the molecular interactions required to affect insulin secretion. The chapter describes how the glutamine-glutamate-α-ketoglutarate axis regulates amino acid and glucose-stimulated insulin secretion based on studies of mouse models of congenital hyperinsulinism and studies of human islet cells. The importance of glutamine-stimulated insulin secretion is examined using several knock-out mouse models and cell culture studies that are explained in detail in the excellent figures in this chapter. Chapter 20 reviews the multifactorial nature of the metabolic syndrome and the role of glutamine and glutamate in its development and adverse health effects, especially cardiovascular disease. The authors indicate that the metabolic syndrome is a complex disorder that can include highly related diseases such as type 2 diabetes, dyslipidemias, central obesity, arterial hypertension, nonalcoholic fatty liver disease (NAFLD), prothrombotic and proinflammatory states, and polycystic ovarian syndrome. The pathogenesis of the metabolic syndrome is linked to insulin resistance. The first link between the metabolic syndrome and glutamine/glutamate is the finding of significantly higher concentrations of serum glutamate in obese patients compared to normal weight, age and sex-matched individuals. Newer data linking genetic mutations resulting in enzyme changes has shown that an enzyme, glutamate decarboxylase 1, acts as an autoantigen in insulin-dependent diabetes. Excellent tables and figures help to illustrate the candidate genes and their interactions in the development and progression of the metabolic syndrome. The next chapter (Chap. 21) examines the functions of glutamine that are related to insulin and glucose responses to food intake. Low serum glutamine concentrations have been documented in individuals with impaired fasting glucose and impaired glucose tolerance and in type 2 diabetes patients. Large cohort studies have reported that low circulating glutamine levels predict type 2 diabetes incidence. The chapter reviews the clinical studies that found a beneficial reduction in gastric emptying when glutamine was given as a supplement with a meal.

The next three chapters examine the potential for glutamine to improve the overall metabolic status of patients undergoing surgery. Chapter 22 describes the unique circumstances of repair of the congenital defect, cleft lip, and the surgery's effects on glycemic control. The authors describe their blinded clinical study in age and defect-matched boys who were given glutamine parenterally prior to and during surgery or placebo and the supplemented group was found to have significantly better glycemic control and less stress responses following surgery. The authors of Chap. 23 also report on the results of their blinded intervention study in a cohort of moderately malnourished adults who are scheduled for gastric surgery. Three groups were identified prospectively. One group got parenteral glutamine in the postoperative period; another got parenteral glutamine both preoperatively and postoperatively. The third group got no additional glutamine. The authors report that the group that had both doses of glutamine had a trend of fewer admissions to intensive care and reduced duration of parenteral nutrition following surgery. The incidence of hyperglycemia was lowest in this supplemented group. Chapter 24 describes the serious adverse effects of diabetes that can result in diabetic foot ulcers. Ulcers affecting the lower limbs of diabetics are among the most frequent and costly clinical complications of the disease. The authors describe recent studies using a glutamine-containing supplement in diabetic patients with foot ulcer wounds and found enhanced healing and greater

collagen formation. These preliminary studies add to the need for further data on glutamine use in patients undergoing surgical procedures and wound healing.

Section Four includes five chapters that provide the reader with basic information on the role of glutamine in maintaining the integrity of the intestinal wall, a review of the models used to examine the effects of a breach in the intestinal wall, and the importance of glutamine. We learn that enterocytes prefer glutamine as a source of energy, but these cells lack the capacity to synthesize glutamine. Glutamine is essential in maintaining gastrointestinal structure and barrier function. In vitro studies using cell monolayers demonstrated a direct influence of glutamine on tight junction integrity in the intestinal epithelium. Chapter 25 includes useful figures that describe cellular and laboratory studies that show the importance of glutamine in the intestine. The next, related chapter (Chap. 26) examines the importance of glutamine in animal models of colitis. The author explains that inflammatory bowel disease (IBD) is an idiopathic chronic condition of the gastrointestinal tract characterized by intermittent periods of inflammation and remission. The pathogenesis of IBD includes interactions between genetic, enteric microbiota, environmental, and immunological factors. The anti-inflammatory and immunoenhancing functions of glutamine have led to its use in animal models of this complex disease. Although benefits have been seen in animal models, there have not been consistent improvements in clinical trials.

There is a unique chapter that explores the effects of *Helicobacter pylori* infection in the GI tract and the potential for adverse effects in infected patients if they are treated with glutamine. Chapter 27 examines the interplay between the effects of *H. pylori* on the GI tract's metabolism, the finding that *H. pylori* can use glutamine as an energy source and that glutamine supplementation in *H. pylori* models actually enhanced inflammation, most likely by enhancing the production of ammonia. Obviously, in vitro and laboratory animal models were of great value in determining the potential for harm in supplementing patients with glutamine as a therapy for *H. pylori* infection.

As indicated above, preterm infants are at risk for glutamine and other amino acid deficiencies as the placenta is no longer supplying amino acids and the stressed preterm infant may not be able to synthesize sufficient glutamine and/or arginine. The next chapter examines the serious effects of intestinal dysfunction and the role of glutamine and arginine in the preterm infant and term infant. Chapter 28 reviews the laboratory animal studies that suggest a potential use of arginine, glutamine, and arginyl-glutamine (Arg-Gln) dipeptide to prevent and treat small intestinal hypoxic injury in pediatric patients especially in neonates. The final chapter (Chap. 29) reviews the effects of sepsis on glutamine metabolism and the use of glutamine by intestinal cells as a source of energy. Intestinal microcirculatory dysfunction is a key factor in the development of sepsis. Proposed mechanisms by which glutamine beneficially affects intestinal microcirculation include maintenance of functional capillary density, microvascular integrity, enhancement of leukocyte rolling, and adherence to intestinal microcirculation. Glutamine also influences the expression of adhesion molecules, and production of cytokines, the reduction of oxidation stress and nitric oxide-related mechanisms, heat shock proteins, and other effectors. The authors agree with other chapter authors that glutamine should be examined as a therapeutic strategy for patients with sepsis under controlled conditions.

The last section in the volume, *Section Five*, includes 11 chapters that examine a number of clinical conditions, most of which either have been shown to benefit from glutamine supplementation or are a consequence of disruption in glutamine metabolism. The first three chapters examine the importance of glutamine in the human brain and the adverse consequences to disruption in normal glutamine levels. The first chapter (Chap. 30) describes the interactions between glutamine and manganese. Manganese is an essential mineral and is found in the active site of several metalloenzymes including glutamine synthetase. However, chronic exposure to high levels of manganese can be toxic and result in a neurological disorder, referred to as manganism. The authors explain that exposure to high levels may be from consumption of well water containing high levels of the metal, exposure to a fuel additive used in some unleaded gasolines, exposure to organic manganese-containing pesticides, occupational exposure of miners, battery manufacturers, automotive repair technicians, and others.

Manganism is characterized by neuropsychiatric symptoms resembling those observed in idiopathic Parkinson's disease including hypokinesia, rigidity and tremor, postural instability, dystonia and bradykinesia, micrographia, mask-like facial expression, and speech disturbances. Manganese competes with glutamine for entry into brain cells. Manganese toxicity is associated with the disruption of glutamine and glutamate transport in astrocytes and can result in glutamine-mediated neurotoxicity. Chapter 31 reviews the importance of glutamine in the glutamine-glutamate-GABA cycle in the brain, which controls the balance between the excitatory and inhibitory nerve transmission. This chapter focuses on the association between the disruption of the cycle and resultant seizures or epilepsy. Epileptic seizures result from abnormal, excessive neuronal activity in the brain that may be due to the imbalance between excitability and inhibition in neurotransmission. There are data that suggest that in the epileptic brain, there is a lower than normal concentration of glutamine that appears to be linked to decreased functioning of glutamine synthetase. It is not clear at present whether glutamine supplementation would be of help in epilepsy. Chapter 32 describes the consequences of a unique congenital genetic defect that results in the lack of the enzyme glutamine synthetase that is often associated with fetal and early neonatal death. One case is described in an infant who suffered from neonatal onset severe epileptic encephalopathy and was entered into a clinical case study. Fortunately, when glutamine supplementation was provided, it resulted in relatively beneficial effects on patient alertness and reduced several but not all of the adverse brain effects.

Chapter 33 describes the oxidative damage associated with HIV infection and their current drug treatments. The link with glutamine is through glutamate as this amino acid is required for glutathione synthesis. Glutathione is a major antioxidant and treated HIV patients have significantly lower glutathione levels than non-HIV infected individuals. Glutathione (L-y-glutamyl-l-cysteinyl-glycine) is the major intracellular water-soluble antioxidant involved in metabolic processes and cell viability. Glutamine supplementation significantly increased glutathione concentrations in a clinical study with treated HIV patients, and the authors found that glutamine supplementation not only increased glutamate levels but also contributed to increasing cysteine and glycine through alterations in their metabolism.

Two chapters examine the impact of glutamine status on the oxidative tissue damage that is a consequence of ischemia/reperfusion injury. Chapter 34 reviews the model systems that strongly suggest that end-stage renal disease patients who are candidates for kidney transplant should be given glutamine supplementation prior to surgery. The models predict that supplementation results in an increase in glutathione levels that would be of value during the expected ischemia/reperfusion associated with kidney transplant. Also, as it is well accepted that the kidney that is to be transplanted is exposed to ischemia when removed from the donor, followed by reperfusion when it is transplanted. Thus, the kidney may also benefit by being bathed with a solution containing glutamine. Chapter 35 expands upon the data discussed in the previous chapter and describes the effects of ischemia/reperfusion (I/R) injury and its consequences in other tissues and organs. Intestinal I/R injury occurs in a variety of clinical settings. Intestinal ischemia/reperfusion can result from many causes including major trauma, hemorrhage, small bowel transplantation, superior mesenteric artery and vein thrombosis, acute pancreatitis, sepsis, cardiopulmonary bypass, and burn injuries. The injury leads to the generation of inflammatory factors, release of cytotoxic substances, activation of pathologic enzymes, and activation of immune cells in the intestine. These changes can result in intestinal mucosal injury, enhanced intestinal permeability, and inflammation, leading to gut dysfunction or even multiple organ dysfunction syndrome. The chapter includes discussions of injury to the liver, heart, brain, and kidney. Animal model research is critical to achieving the maximum beneficial effect of glutamine as the delivery route, dose, and timing need to be optimized for each organ system and each patient population.

As reviewed in earlier chapters, cancer cells utilize glutamine as an energy source and for the synthesis of molecules that have adverse effects on many tissues and organs within the body. The next two chapters look at some of these adverse effects to determine the potential for balancing the risk/benefits of glutamine supplementation for cancer patients. Chapter 36 describes in detail the mechanisms by which tumor cells downregulate immune cells through the synthesis of cytokines and

altering receptors so that immune cells that would kill tumor cells can no longer function. In cell culture and laboratory animal studies, depletion of glutamine from culture media benefits immune cells and reduces the function of tumor cells. Yet, the potential to reduce systemic glutamine levels has not proven to be efficacious, and the more favorable targeting of intracellular glutamine is considered a more viable research focus. Chapter 37, in contrast, reviews the potential for glutamine supplementation to improve the muscle functions of patients with cancer cachexia so that they can benefit physically and emotionally from an exercise program. We learn that cachexia is characterized by involuntary body weight loss due to the cancer's production of cytokines that result in deep lean body mass loss and decreased fat stores and accounts for over 20 % of all cancer deaths. In the hypercatabolic state seen in cancer patients, where a negative nitrogen balance and increased muscle breakdown occur, glutamine demand increases, resulting in a significant reduction in plasma levels. The authors review the biochemical changes associated with cancer cachexia and conclude that in the cancer catabolic state, glutamine nutritional supplementation and exercise as adjuvant therapy can improve patient response, quality of life, and survival.

Two chapters continue the examination of the role of glutamine in muscle under varying physiological and pathological conditions. Chapter 38 reviews the effects of exercise as well as certain disease states on muscle use of glutamine. Muscle glutamine metabolism can be altered in a number of catabolic conditions, including cancer, sepsis, diabetes, and/or prolonged or exhausting physical exercise. Serious muscle damage and catabolism lead to the activation of local and acute inflammatory response. These processes increase the cell consumption of glutamine, promoting the imbalance of the synthesis and degradation of this amino acid. The reduction of glutamine and the increased inflammatory response increase protein breakdown, which can reduce the cell antioxidant concentrations and promote immunosuppression. The authors note that in athletes, glutamine supplementation may not prevent the inflammatory response and muscle damage or enhance performance, but may help the recovery of cells, including skeletal muscle. Chapter 39 discusses the substance that causes muscle wasting and how glutamine can affect this process. Myostatin is the negative regulator of muscle mass and its overexpression results in muscle atrophy. The authors explain that high myostatin circulating levels have been associated with weight loss in patients with AIDS, in the sarcopenia of aging, in atrophy due to muscle denervation or disuse, as well as in cancer patients as discussed above. Cell culture and laboratory animal studies suggest that glutamine supplementation can reduce levels of myostatin in a number of model systems. As with many of the clinically relevant outcomes discussed throughout this important volume, the preclinical findings consistently point to the potential for glutamine supplementation to either reduce the adverse effect or, in some instances, improve clinical outcomes. The final chapter in this comprehensive, clinically relevant volume provides a wealth of information on web-based resources and suggested readings for the health provider interested in the myriad of data concerning glutamine's role in human physiology and pathology.

The above description of the contents of the 40 chapters in this volume attest to the depth of information currently available concerning the central role of glutamine in maintaining the health of the individual as well as providing benefits as a supplement for certain patient populations. Each chapter includes Key Points, Keywords, and complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. Key features of this comprehensive volume includes over 200 detailed tables and informative figures, an extensive, detailed index, and more than 1,800 up-to-date references that provide the reader with excellent sources of worthwhile information.

In conclusion, *Glutamine in Clinical Nutrition*, edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, provides health professionals in many areas of research and practice with the most up-to-date, well-referenced volume on the importance of glutamine in maintaining the overall health of the individual as well as serving as a critical source of energy and precursor of other amino acids and glutathione that are especially critical in the disease conditions discussed in the chapters. This unique volume will serve the reader as the benchmark in this complex area of interrelationships between nonessential and conditionally essential amino acid functions and the unique role of

glutamine specifically in the synthesis of brain neurotransmitters, collagen formation, insulin and glucose modulation, and the functioning of all organ systems that are involved in the maintenance of the body's metabolic integrity. Moreover, the physiological, genetic, and pathological interactions between plasma levels of glutamine, glutamate, and related nonessential amino acids that are synthesized through glutamine metabolism are clearly delineated in clear and useful tables and figures so that students as well as practitioners can better understand the complexities of these interactions. Unique chapters examine the effects of glutamine status that can be significantly altered by the effects of genetic mutations. Chapters review the consequences of these mutations from prepregnancy, during fetal development, in the neonate and infancy. The editors are applauded for their efforts to develop the most authoritative and unique resource on the role of glutamine in health and disease to date, and this excellent text is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., F.A.C.N., F.A.S.N.
Series Editor

About the Series Editor

Dr. Adrianne Bendich Ph.D., F.A.S.N., F.A.C.N. has served as the "Nutrition and Health" Series Editor for over 15 years and has provided leadership and guidance to more than 120 volume editors that have developed the 60+ well-respected and highly recommended volumes in the Series.

In addition to "**Glutamine in Clinical Nutrition,**" **edited by Rajkumar Rajendram M.D., Victor Preedy Ph.D., and Vinood Patel Ph.D., major new editions** in 2012–2014 include:

1. **Handbook of Clinical Nutrition and Aging, Third Edition**, edited by Connie W. Bales Ph.D., R.D., Julie L. Locher Ph.D., M.S.P.H., and Edward Saltzman, M.D., 2014
2. **Nutrition and Oral Medicine, Second Edition**, edited by Dr. Riva Touger-Decker, Dr. Connie C. Mobley, and Dr. Joel B. Epstein, 2014
3. **Fructose, High Fructose Corn Syrup, Sucrose and Health**, edited by Dr. James M. Rippe, 2014
4. **Nutrition in Kidney Disease, Second Edition**, edited by Dr. Laura D. Byham-Gray, Dr. Jerrilynn D. Burrowes, and Dr. Glenn M. Chertow, 2014
5. **Handbook of Food Fortification and Health, volume I** edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, and Dr. Vinood B. Patel, 2013
6. **Handbook of Food Fortification and Health, volume II** edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, and Dr. Vinood B. Patel, 2013
7. **Diet Quality: An Evidence-Based Approach**, **volume I** edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013
8. **Diet Quality: An Evidence-Based Approach**, **volume II** edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013

9. **The Handbook of Clinical Nutrition and Stroke**, edited by Mandy L. Corrigan, MPH, RD, Arlene A. Escuro, MS, RD, and Donald F. Kirby, M.D., FACP, FACN, FACG, 2013
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18. **Nutritional Health, Strategies for Disease Prevention, Third Edition**, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr., 2012
19. **Chocolate in Health and Nutrition**, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
20. **Iron Physiology and Pathophysiology in Humans**, edited by Dr. Gregory J. Anderson and Dr. Gordon D. McLaren, 2012

Earlier books included **Vitamin D, Second Edition** edited by Dr. Michael Holick; "**Dietary Components and Immune Function**" edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi, and Dr. Victor R. Preedy; "**Bioactive Compounds and Cancer**" edited by Dr. John A. Milner and Dr. Donato F. Romagnolo; "**Modern Dietary Fat Intakes in Disease Promotion**" edited by Dr. Fabien De Meester, Dr. Sherma Zibadi, and Dr. Ronald Ross Watson; "**Iron Deficiency and Overload**" edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; "**Nutrition Guide for Physician**s" edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple, and Dr. Mary Struble; "**Nutrition and Metabolism**" edited by Dr. Christos Mantzoros; and "**Fluid and Electrolytes in Pediatrics**" edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include "**Handbook of Drug-Nutrient Interactions**" edited by Dr. Joseph Boullata and Dr. Vincent Armenti; "**Probiotics in Pediatric Medicine**" edited by Dr. Sonia Michail and Dr. Philip Sherman; "**Handbook of Nutrition and Pregnancy**" edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch, and Dr. Elliot Philipson; "**Nutrition and Rheumatic Disease**" edited by Dr. Laura Coleman; "**Nutrition and Kidney Disease**" edited by Dr. Laura Byham-Grey, Dr. Jerrilynn Burrowes, and Dr. Glenn Chertow; "**Nutrition and Health in Developing Countries**" edited by Dr. Richard Semba and Dr. Martin Bloem; "**Calcium in Human Health**" edited by Dr. Robert Heaney and Dr. Connie Weaver; and "**Nutrition and Bone Health**" edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.

Dr. Bendich is President of Consultants in Consumer Healthcare LLC and is the editor of ten books including "**Preventive Nutrition: The Comprehensive Guide for Health Professionals, Fourth Edition**" coedited with Dr. Richard Deckelbaum (www.springer.com/series/7659). Dr. Bendich serves on the Editorial Boards of the *Journal of Nutrition in Gerontology and Geriatrics*, and *Antioxidants*, and has served as Associate Editor for *Nutrition* the International Journal; served on the Editorial Board of the *Journal of Women's Health and Gender-based Medicine* and served on the Board of Directors of the American College of Nutrition.

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Dr. Bendich received the Roche Research Award, is a *Tribute to Women and Industry* Awardee, and was a recipient of the Burroughs Wellcome Visiting Professorship in Basic Medical Sciences. Dr. Bendich was given the Council for Responsible Nutrition (CRN) Apple Award in recognition of her many contributions to the scientific understanding of dietary supplements. In 2012, she was recognized for her contributions to the field of clinical nutrition by the American Society for Nutrition and was elected a Fellow of ASN. Dr. Bendich is an Adjunct Professor at Rutgers University. She is listed in Who's Who in American Women.

About the Volume Editors

Dr. Rajkumar Rajendram is an intensivist, anesthetist, and perioperative physician. He graduated in 2001 with a distinction from Guy's, King's and St. Thomas Medical School, in London. As an undergraduate he was awarded several prizes, merits, and distinctions in preclinical and clinical subjects. This was followed by training in general medicine and intensive care in Oxford, during which period he attained membership of the Royal College of Physicians (MRCP) in 2004. Dr. Rajendram went on to train in anesthesia and intensive care in the Central School of Anaesthesia, London Deanery and became a fellow of the Royal College of Anaesthetists (FRCA) in 2009. He has completed advanced training in intensive care in Oxford and was one of the first intensivists to become a fellow of the faculty of intensive care medicine (FFICM) by examination. He coauthored the Oxford Case Histories in Cardiology which was published by the Oxford University Press in 2011. He is currently preparing the text for the Oxford Case Histories in Intensive Care. His unique training and experience has been tailored for a career in intensive care with a subspecialty interest in perioperative medicine.

Dr. Rajendram recognizes that nutritional support is a fundamental aspect of critical care. He has therefore devoted significant time and effort into nutritional science research. As a visiting research fellow in the Nutritional Sciences Research Division of King's College London, he has published over 50 textbook chapters, review articles, peer-reviewed papers, and abstracts from his work.

Victor R. Preedy B.Sc., Ph.D., D.Sc., F.S.B., F.R.S.H., F.R.I.P.H.H., F.R.S.P.H., F.R.C.Path., F.R.S.C. is a senior member of King's College London (Professor of Nutritional Biochemistry) and King's College Hospital (Professor of Clinical Biochemistry; Hon.). He is attached to both the Diabetes and Nutritional Sciences Division and the Department of Nutrition and Dietetics. He is also Director of the Genomics Centre and a member of the School of Medicine. Professor Preedy graduated in 1974 with an Honours Degree in Biology and Physiology with Pharmacology. He gained his University of London Ph.D. in 1981. In 1992, he received his Membership of the Royal College of Pathologists and in 1993 he gained his second doctoral degree, for his contribution to the science of protein metabolism in health and disease. Professor Preedy was elected as a Fellow of the Institute of Biology in 1995 and to the Royal College of Pathologists in 2000. Since then he has been elected as a Fellow to the Royal Society for the Promotion of Health (2004) and the Royal Institute of Public Health and Hygiene (2004). In 2009, Professor Preedy became a Fellow of the Royal Society for Public Health and in 2012 a Fellow of the Royal Society of Chemistry. In his career Professor Preedy worked at the National Heart Hospital (part of Imperial College London) and the MRC Centre at Northwick Park Hospital. He has collaborated with research groups in Finland, Japan, Australia, the USA, and Germany. He is a leading expert on biomedical sciences and has a longstanding interest in how nutrition and diet affects well-being and health. He has lectured nationally and internationally. To his credit, Professor Preedy has published over 500 articles, which include peer-reviewed manuscripts based on original research, reviews, and numerous books and volumes.

Dr. Vinood B. Patel is currently a Senior Lecturer in Clinical Biochemistry at the University of Westminster and honorary fellow at King's College London. He presently directs studies on metabolic pathways involved in liver disease, particularly related to mitochondrial energy regulation and cell death. In addition, research is being undertaken to study the role of nutrients, phytochemicals, and fatty acids in the development of fatty liver disease and iron homeostatic regulation. Another area includes identifying new biomarkers that can be used for diagnosis and prognosis of liver disease. Dr. Patel graduated from the University of Portsmouth with a degree in Pharmacology and completed his Ph.D. in protein metabolism from King's College London in 1997. His postdoctoral work was carried out at Wake Forest University Baptist Medical School studying structural-functional alterations to mitochondrial ribosomes, where he developed novel techniques to characterize their biophysical properties. Dr. Patel is a nationally and internationally recognized alcohol researcher and was involved in several NIH-funded biomedical grants related to alcoholic liver disease. Dr. Patel has edited biomedical books in the area of nutrition and health prevention, autism, and biomarkers and has published over 160 articles.

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Part I
Basic Processes at the Cellular Level and in Animal Models

Chapter 1
Glutamine Structure and Function: A Starter Pack

Peter B. Soeters

Key Points

- The main function of glutamine is to support cell proliferation in all situations where proliferation is enhanced (inflammatory states, growth). Another important function is to produce NADPH in the first steps of glutamine breakdown, which serves to maintain the redox state.
- Glutamine is an anaplerotic substrate. Its breakdown yields glutamic acid and subsequently α-oxoglutarate, which replenishes intermediates of the Krebs-cycle that can branch off at several sites and deliver building stones for cells and matrix.
- In addition to the utilization of the carbon skeleton, the two nitrogen atoms are also utilized for the synthesis of purines and pyrimidines. Other important products are proline, aspartic acid and other nonessential amino acids.
- When cell proliferation and wound healing are required, glutamine is furnished by increased synthesis in peripheral tissues (mainly muscle). Precursors are glucose and glutamic acid, derived from carbon skeletons and amino groups of amino acids and synthesized in the liver. Branched chain amino acids in peripheral tissues supply amino groups for glutamine synthesis.
- The net release of glutamine from peripheral tissues is in principle the best indicator of an adequate supply of glutamine, but has not consistently been measured and related to outcome.
- In severe liver failure peripheral release of glutamine fails to be metabolized by these organs, leading to pathologically elevated levels.
- Especially parenterally administered glutamine(peptide) enriched amino acid mixtures have beneficial effects on infections and bowel integrity in inflammatory states of long duration. In view of the maximal production rate of approximately 30 g/24 h in sepsis, dosages administered above this level are pharmacological and may be deleterious in patients with primary or secondary liver failure.

Keywords Glutamine metabolism • Anaplerosis • Cataplerosis • Redox status • Cell proliferation • Glutamine production • Inflammatory activity • Glutamine administration • Glutamine status

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Abbreviations

ICW	Intracellular water
AIDS	Acquired immunodeficiency syndrome
NIDDM	Non-insulin-dependent diabetes mellitus
Rd	Rate of disposal
Ra	Rate of disappearance
NADPH	Reduced nicotinamide adenine diphosphate
NH_3	Ammonia

Introduction

The important role of glutamine in metabolism has been appreciated since more than 40 years [1–4]. In the early seventies the focus was mainly on glutamine utilization in the intestine (in cell cultures, in vivo and in the isolated vascularly perfused rat intestine), showing that glutamine is taken up by the intestine in far higher quantities than other amino acids. Its carbon is partly incorporated in tissue insoluble material, CO_2, citrulline, proline, and organic acids (lactic acid and citric acid). The nitrogen appeared largely in citrulline, alanine, ammonia, and proline. Nitrogen appearing in cell components (tissue insoluble material, e.g., protein, nucleotides) was not specified. The proximal small intestine accounted for most of the glutamine uptake and consequently for most of the ammonia release. Decades earlier, ammonia was proposed to cause hepatic encephalopathy, and systemic hyperammonemia was mainly ascribed to ammonia generated in the colon by bacterial degradation of urea and amino acids. This ammonia could escape hepatic detoxification by shunting of portal blood around the liver through collaterals (varices) formed as a consequence of portal hypertension due to liver cirrhosis or presinusoidal inhibition of portal flow. Consequently patients with hepatic failure and encephalopathy were treated with antibiotics and protein restriction. In the eighties, it became clear that ammonia formation largely occurs in the jejunum due to glutamine breakdown, which is not directly influenced by antibiotics. At the same time also immunocytes were found to metabolize substantial amounts of glutamine in vitro [4]. To acquire maximal proliferation rates in culture all cell types require, apart from other components in the medium in lower concentrations, glutamine and glucose, which in the absence of other oxidizable substrate were found to be partly oxidized but also to deliver the components earlier described.

In other studies incubations with whole muscle led to a catabolic state delivering amino acids into the medium but especially glutamine and alanine in larger quantities than their presence in muscle protein [5]. This implies that these two amino acids must have been newly produced. Later experiments in vivo demonstrated that glutamine and alanine production in muscle was greatly enhanced after any stressful event (trauma, endotoxin challenge, cecal ligation and puncture, burns) and this was found even earlier in vivo when measuring net arteriovenous release of amino acids across extremities in septic patients [6]. These findings led to the hypothesis that in stressful or/and malnourished states glutamine is lacking and that supplementation of glutamine improves the response to stress/trauma, etc. [7, 8] Benefit was considered to be especially achievable in the intestine.

The hypothesis was supported by low plasma and tissue levels of glutamine, found in critically ill patients and considered to indicate glutamine deficiency [9]. Basic research and clinical application of modulated nutritional formulas have simultaneously been undertaken before metabolism had been clearly defined and shortages confirmed. Still today modulated feeds are administered without full knowledge of their metabolism. In several publications, the benefit of the supplementation of glutamine has been postulated to result from different mechanisms without apparent

Table 1.1 Proposed roles of glutamine in stressed states (infection, trauma, inflammation, growth)

Proposed roles of glutamine in stress/trauma/infection
Adapted from Wischmeyer [10]
Tissue protection
Enhanced heat shock protein expression
Antiapoptotic effect
Fuel source for epithelial cells
Anti-inflammatory
Attenuation of NF-κB/stress kinase activation
Enhanced peroxisome proliferator-activated receptor-γ activation
Attenuation of cytokine expression
Preservation of tissue metabolic function in stress states
Preservation of ATP levels following sepsis and ischemia/reperfusion
Preservation of mitochondrial function
Antioxidant/attenuation of inducible nitric oxide synthase expression
Enhanced glutathione levels following stress
Attenuation of iNOS synthase activation in sepsis and ischemia/reperfusion
Reduction of oxidant stress

connection and without trying to outline the central role of glutamine in intermediate metabolism (Table 1.1) [10]. In this chapter we describe the role of glutamine in intermediary metabolism in health and disease, the likelihood that its production may be deficient and how to assess this, and situations in which supplementation with glutamine may be beneficial, how much should be supplemented, and in what manner.

Glutamine as a Universal Precursor in Intermediary Metabolism

In this section we describe the central role, played by glutamine, in intermediary metabolism, delivering carbon skeletons and nitrogen containing molecules to support the synthesis of cells and matrix in trauma and disease.

Glutamine (Fig. 1.1) is readily transported into cells and deamidated in several tissues (intestine, spleen, immune cells, kidney) to yield glutamate and NH_3. Glutamate in turn is either transformed to α-ketoglutarate by means of its dehydrogenase or transaminated to equally yield α-ketoglutarate, which serves as an intermediate in the Krebs cycle. In this way, glutamine and glutamic acid (together with glucose) serve as anaplerotic substrates, replenishing Krebs-cycle intermediates in proliferating tissues (Fig. 1.2). In these tissues, the intermediates are only partly regenerated as would happen when the Krebs cycle would exclusively operate to oxidize acetyl-coA, because intermediates branch off at several sites to provide substances supporting cell proliferation in the immune response, wound repair, and growth, and to maintain redox balance. This is called cataplerosis (Fig. 1.3).

In starvation combined with stress (disease, trauma, infection) peripheral tissues (predominantly muscle) become catabolic, implying that protein synthesis is lower than degradation (Fig. 1.4). The resulting amino acids are released in the circulation. A large proportion of these amino acids is taken up by the liver, producing substantial amounts of glucose, glutamic acid, acute phase proteins, and other products in lower quantities (Figs. 1.5 and 1.6). Glucose and glutamic acid are in turn released into the circulation, and are, besides fatty acids, which largely function as fuel, the only substances taken up in peripheral tissues, (skin, adipose tissue, bone but predominantly muscle) in stressed conditions. There they donate their carbon skeletons and amino groups to form glutamine, glycine, alanine,

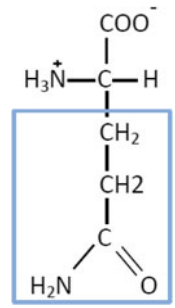

Fig. 1.1 Structure formula of glutamine. The formula shows the ionization at neutral pH (7.0). The part of the molecule inside the *blue box* shows the "R-group" responsible for the specific properties of the amino acid. The part outside the box is common to all amino acids (adapted from Lehninger. Principles of Biochemistry. D.L. Nelson, M.M.Cox. Publisher W.H. Freeman and Company. New York, USA, 2005)

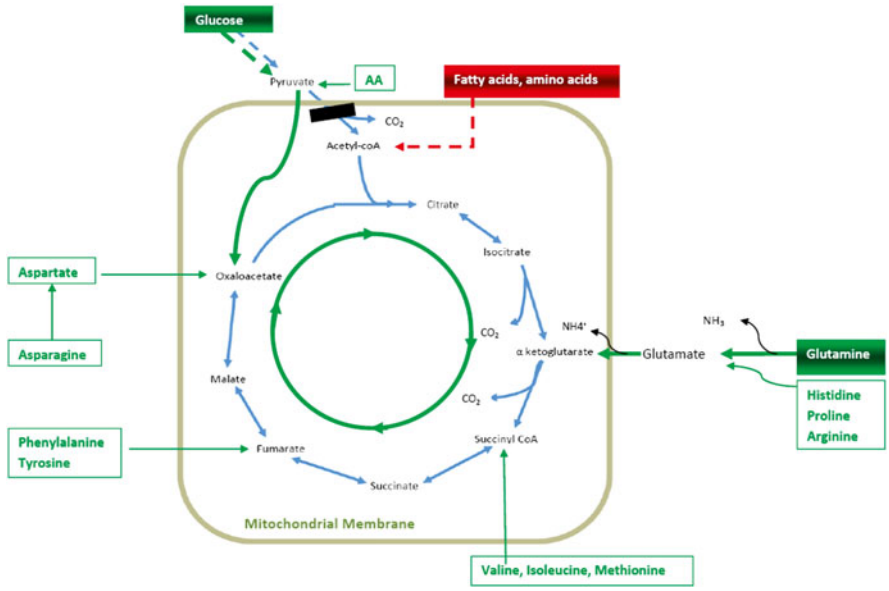

Fig. 1.2 Proliferating cells/growing tissues. *Anaplerosis.* Anaplerosis in activated immune cells and cells in growing tissues. Glutamine, glutamate, and glucose are the main anaplerotic substrates in activated/proliferating cells. Other amino acids probably have a minor role in anaplerosis and are preferentially used in protein synthesis. Complete oxidation of glucose and glutamine is inhibited. Acetyl-coA introduced in the TCA cycle is largely derived from fatty acids and ketone bodies and little from amino acids. Glutamine and glucose furnish little acetyl-coA (see block at pyruvate dehydrogenase step)

and proline in far higher amounts than the quantities present in muscle protein and released after net protein degradation [11]. Which carbon skeleton and which nitrogen ends up where is not exactly specified in vivo in humans but may be estimated on a stoichiometric basis. The amino group of glutamate and branched chain amino acids supplies most of the amino-nitrogen of glycine, alanine, and proline. Glutamine is produced partly from amidation of glutamic acid by ammonia derived from purine metabolism or/and taken up from the circulation, partly from transamination and subsequent amidation of glucose derived α-oxoglutarate. Alanine, produced in muscle after transamination of glucose derived pyruvate and the amino group of glutamic acid, is the major gluconeogenic amino

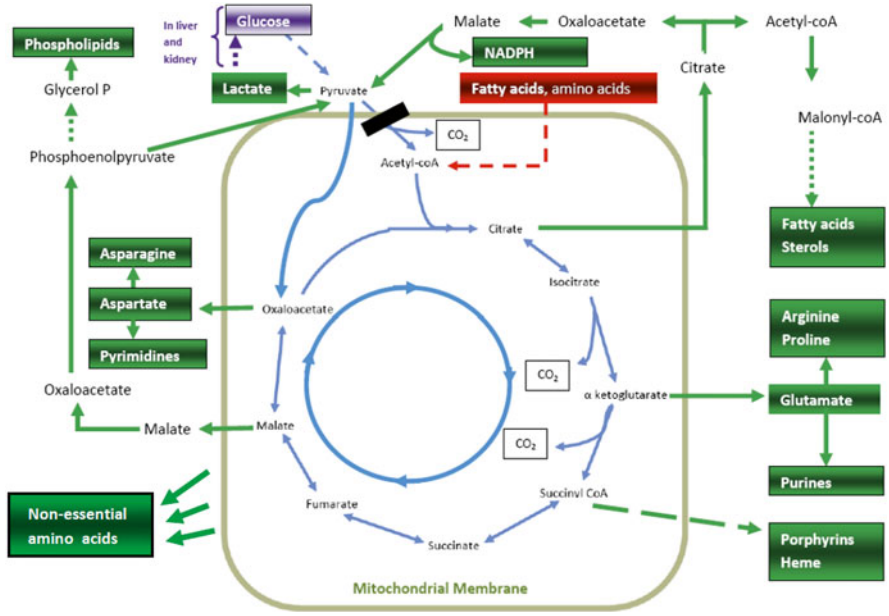

Fig. 1.3 Proliferating cells/growing tissues. *Cataplerosis.* Cataplerosis in activated immune cells and cells in growing tissues. Cataplerosis furnishes acetyl-coA for FA and sterol synthesis, NADPH in the malate-pyruvate cycle, glutamate for the synthesis of purines, aspartate for pyrimidines. Pyruvate is partly transaminated with glutamic acid to yield alanine (not shown). It is not exactly known how many and which intermediates are cataplerotically transaminated with glutamic acid to yield other non-essential amino acids. Glycolysis furnishes lactate. Lactate and alanine are exported and can serve as precursors of gluconeogenesis in liver and kidney

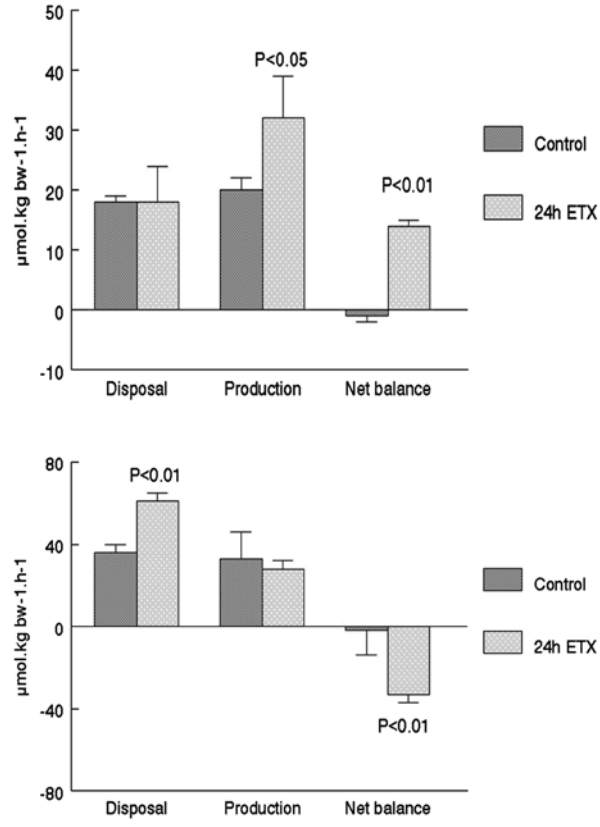

Fig. 1.4 Multicatheterized pig model of sepsis (after 24-h endotoxin infusion) [11]. *Upper panel*: Disposal (protein synthesis) and production (protein degradation) of phenylalanine in muscle of pigs 24 h after an endotoxin challenge. *Lower panel*: Disposal (protein synthesis) and production (protein degradation) of phenylalanine, corrected for oxidation in liver of pigs 24 h after an endotoxin challenge. The net balance represents the release of amino acids in the hindquarter and uptake in the liver. (Figure adapted from data in Bruins MJ et al, Clin Sci (Lond). 2003 Feb;104(2):127–41. PubMed PMID: 12546635 with permission [11])

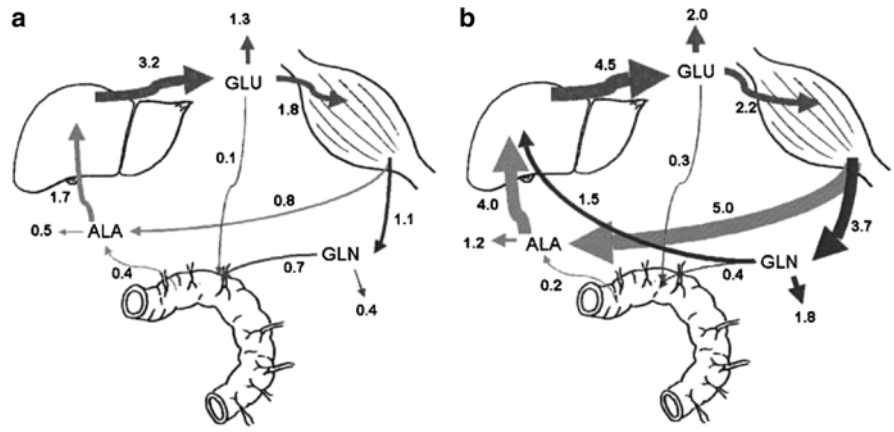

Fig. 1.5 Fluxes of glutamic acid, glutamine, and alanine between liver, muscle, and intestine [11]. Fluxes of glutamate (GLU), glutamine (GLN), and alanine (ALA) between liver, muscle, and portal-drained viscera after a 24-h infusion of (**a**) saline or (**b**) endotoxin. Release of other amino acids by muscle and intestine and uptake by liver are not shown. The release of glutamic acid by the liver should be emphasized, because it is utilized in peripheral tissues to furnish building blocks for rapidly proliferating cells (figures reproduced from Bruins MJ et al. Clin Sci (Lond). 2003 Feb;104(2): 127–41. PubMed PMID: 12546635 with permission [11])

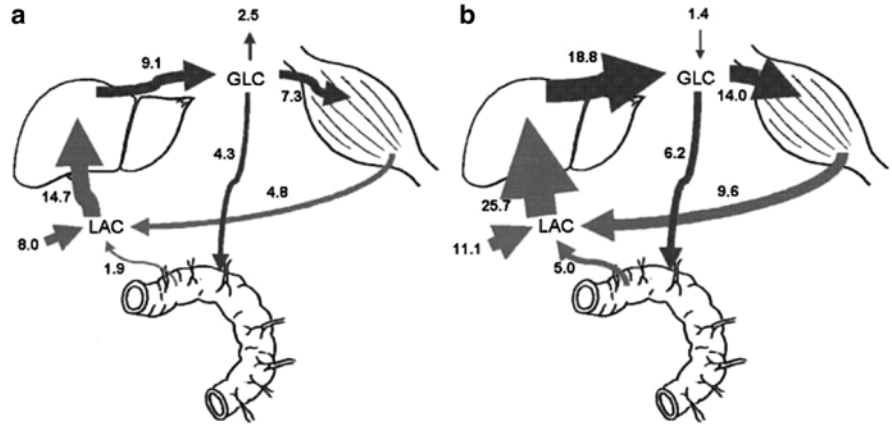

Fig. 1.6 Fluxes of glucose and lactate between liver, muscle and intestine [11]. Fluxes of glucose (GLC) and lactate (LAC) between liver, muscle and portal-drained viscera after a 24-h infusion of (A) saline or (B) endotoxin. Fluxes are given as μmol/minute/kg bodyweight (figures reproduced from Bruins MJ et al, Clin Sci (Lond). 2003 Feb;104(2): 127–41. PubMed PMID: 12546635 with permission [11])

acid in the liver, in addition producing urea or donating its amino group to α-oxoglutarate, forming glutamic acid. Another major substrate for hepatic glucose formation is lactate, accounting for less than 50 % of the products of glucose breakdown in peripheral tissues and in a variable rate in rapidly proliferating cells in the stress response (Cori cycling) (Fig. 1.6). The complex cycling of glucose and amino acids across several organs is an example of many of the metabolic processes in the body. It ensures continuous availability of necessary substrates and allows instantaneous regulation. Glucose and ammonia formation in the kidney with glutamine as substrate is part of this cycling and probably serves in the kidney to excrete superfluous nitrogen, to preserve anaplerotic substrate and to maintain acid base balance. Accelerated gluconeogenesis in liver and kidney is necessarily accompanied by

increased urea and ammonia production, respectively. Not only peripheral tissues are catabolic, but the anabolic synthesis of immune cells, wound cells, matrix, etc. does not match peripheral nitrogen losses, so that in stress situations there is net nitrogen loss in the whole body. Hepatic glutamic acid production in (stress-) starvation can be considered to be a nitrogen sparing mechanism, but hepatic amino acid induced gluconeogenesis inevitably is accompanied to some degree by urea formation, although this is very low in pure starvation, when, in contradistinction with stress starvation, gluconeogenesis largely occurs in the kidney, utilizing mainly glutamine and producing ammonia, which is partly excreted in the urine.

Altogether in stress situations muscle in collaboration with the liver releases high quantities of glutamine, glycine, proline, alanine, and lower quantities of the remaining 16 amino acids present in muscle protein [11]. These processes increase quantitatively when the inflammatory response or growth rates are stronger. Muscle catabolism therefore plays a useful adaptive role in host response and inhibiting this response may be deleterious but cannot or only modestly be accomplished by nutritional means. Supplementation with glutamine-enriched parenteral nutrition increases the total appearance in plasma although endogenous glutamine (and alanine) production in peripheral tissues continues [12]. Metabolism in the liver is complex because, in addition to its role in intermediary metabolism, the liver has an important immune function, producing immune cells and proteins, active in host response.

It is noteworthy that matrix (collagen), comprising at least a quart of the solids in peripheral tissues, contains high amounts of alanine, glycine, and proline and that it is synthesized during tissue formation and wound healing. The degree with which its catabolism in peripheral tissues contributes to the amino acid mix that is released in the circulation is probably modest, because turnover of collagen is low, possibly with the exception of a small more rapidly turning over pool [13].

In the tissues responsible for host response and growth, besides glucose (via pyruvate carboxylase), glutamine (via glutamic acid), and to a lesser degree other glucogenic amino acids are taken up as anaplerotic substrate (Fig. 1.2), furnishing the carbon for purines, pyrimidines, sterols, and fatty acid synthesis (Fig. 1.3). In addition both nitrogens of glutamine are built into pyrimidines (via aspartic acid) and purines. Furthermore glutamine yields substantial amounts of proline used in collagen synthesis especially in growing states and in (wound) healing. Glycine is produced in high quantities via 3-phosphoglycerate (branching off from glycolysis) via serine formation and also provides nitrogen for pyrimidine synthesis. Another role of the high production rate of glycine in peripheral tissues consists of, together with alanine-, glutamine-, and glutamine-derived proline, the synthesizing collagen, because these amino acids are present in collagen in far higher amounts than in myofibrillar protein.

In addition to the production of nucleic acids, rapidly proliferating cells take up a normal amino acid mix for protein synthesis and cover their energy requirements to a limited degree by glycolysis, partial oxidation of glucose (6- to 5-carbon) in the pentose phosphate pathway and of glutamine in the step from α-oxoglutarate to succinyl-coA (5- to 4- carbon). Contrary to general belief more recent literature supports fatty acid oxidation as a main source of energy in rapidly proliferating cells (especially reported in cancer [14] and pregnancy [15]) whereas glucose oxidation via pyruvate - dehydrogenase and the formation of acetyl-coA oxidized in the Krebs cycle is substantially inhibited [16]. This is supported by a simple calculation that in stress starvation or in starving cancer patients a net loss of 14 g of nitrogen/24 hours, excreted in the urine, reflects a protein loss of approximately 87 g, yielding 45 g of glucose (nitrogen should be subtracted and not all amino acids are glucogenic), assuming that this nitrogen is largely derived from amino acids. Forty-five grams of glucose together with maximally 10 g of glycerol derived glucose would cover less than half of energy requirements of the brain, if fully oxidized, but even this is unlikely because of the role of glucose in proliferative pathways. These changes in metabolism constitute the hallmark of insulin resistance, inhibiting glucose oxidation and promoting Cori-cycling (glucose-pyruvate/lactate-glucose) and pentose phosphate pathway flux [17]. Therefore fatty acid oxidation must provide most of the energy (90 %) in stress starvation.

Importantly in the breakdown of glutamine NADPH is produced. Outside the mitochondrion, glucose yields NADPH in the first two steps of the pentose phosphate pathway and inside the mitochondrion in several pathways, the most important ones probably being the isocitrate-dehydrogenase pathway and the conversion of glutamine via glutamic acid to α-oxoglutarate. NADPH is crucial in maintaining redox balance (e.g., reducing oxidized glutathione and proteins), supporting fatty acid synthesis, cholesterol and other components and allowing an oxidative burst of macrophages in dealing with debris and microorganisms.

Why are even in vitro specifically glucose and glutamine necessary to allow rapid cell proliferation? [4, 18]

In vivo small bowel enterocytes rely to a substantial degree on glucose and glutamine to maintain their integrity [19]. Newsholme suggested that the specific need for glutamine and glucose in immune cells (probably all rapidly proliferating cells; see above) arises from the need to produce NADPH [20]. In addition, glutamine is very suitable for cell proliferation because it is abundantly present in the body and can function as an anaplerotic substrate for the Krebs cycle, delivering α-oxoglutarate. All subsequent intermediates can branch off and deliver other substrates for further processing to produce for instance nonessential amino acids. Glutamine is therefore a universal precursor of the carbon of many cell elements, and contains two nitrogen atoms, both of which can be utilized for the synthesis of the bases of nucleic acids and the amino nitrogen also playing an important role in transamination reactions.

The described trafficking of glutamine between organs plays another role. In the first step of the degradation of glutamine NH_3 is generated, which has toxic effects on the brain if it reaches the circulation in large amounts. The glutamine that is metabolized in tissues for other purposes (e.g., cycling) than its incorporation in protein, predominantly yields NH_3 in the first degradation step. These tissues are anatomically located in such a way that the NH_3 that is released is immediately scavenged. This applies to the intestine, producing substantial amounts of ammonia in the jejunum and via bacterial action in the colon, which is metabolized by the liver. The kidney also produces ammonia which is partly excreted in the urine and partly released in the systemic circulation, where it may reach the brain but to an even higher degree peripheral tissues (muscle, adipose tissue) where it may provide some of the amide-nitrogen for the synthesis of glutamine, binding toxic NH_3. After synthesis glutamine can be released in the systemic circulation, where glutamine serves as a non-toxic nitrogen carrier despite present in far higher concentrations than any other amino acid.

It has been suggested that supplementation with glutamine may increase glutathione synthesis (via glutamic acid). The evidence put forward is not very convincing. Even more, cysteine availability is more likely to be limiting than glutamic acid. It is more likely that its connection with glutathione consists of the important role of glutamine to produce NADPH in its breakdown which in turn promotes reduction of oxidized glutathione maintaining redox balance.

A fourth more specific role of glutamine may be as one of the osmolytes regulating cell homeostasis in hyper- and hypo-osmolar conditions. Cell swelling or shrinkage have been claimed to play a role in the regulation of protein synthesis [21]. The original correlation found between intracellular glutamine concentrations and protein synthesis has not consistently been confirmed in later research [22].

It may be concluded that in traumatized/diseased/growth conditions, glutamine has more specific roles as nontoxic nitrogen carrier, as anaplerotic substrate required for cell proliferation, as driver of NADPH production required for fatty acid synthesis and maintenance of redox balance, countering oxidative stress, and as an osmolyte. In view of its central place in intermediary metabolism, a shortage in glutamine availability would imply that flux in biosynthetic processes would be compromised. This will specifically be harmful in situations where rapid cell proliferation is required. The functions ascribed to glutamine (Table 1.1) are all resulting from this central role of glutamine in metabolism and not from separate unrelated metabolic pathways.

The Significance of Amino Acid Concentrations and Fluxes

Glutamine is by far the most abundant free amino acid in plasma and tissues in humans and varies in plasma in healthy man between 450 and 650 μmol/L. Plasma concentrations drop to 75 % of preoperative values after surgical trauma in non-depleted colorectal cancer patients to around 450 μmol/L and generally decrease in inflammatory states [23]. Plasma levels have been found to correlate more closely with disease severity than with malnutrition [24]. In tissues levels vary between 2 and 4 mmol/L intracellular water (ICW) in intestinal mucosa [23] and between 12 and 20 mmol/L intracellular water in muscle and liver (ICW) [9, 21, 25], whereas in pancreatitis patients with multiple organ failure, levels may drop as low as 5 mmol/L [26]. An exception exists in acute fulminant liver failure where very high levels have been found amounting to 1,000–3,000 μmol/L in plasma, which may be aggravated by renal failure [27, 28]. Apart from true liver failure, secondary liver failure may arise (shock, acute pulmonary hypertension and right heart failure) and eventual renal failure that may lead to failure to metabolize glutamine and other amino acids released by peripheral tissues in catabolic states. The liver and the kidney both metabolize glutamine and detoxify (liver) or excrete ammonia (kidney). Failure therefore leads to hyperaminoacidemia including high glutamine levels and hyperammonemia. In cerebral spinal fluid very high levels have been found in acute hepatic failure [27]. Recent data confirm the association between hyperglutaminemia and ICU mortality [29]. In this study low glutamine levels did not correlate with APACHE II score at admittance, but scrutiny of the detailed patient data is required to explain the discrepancy with an earlier study [24].

The steep concentration difference between plasma and tissue levels most likely is maintained by active Na^+/K^+-ATPase driven ion pump transport. This provides the drive for secondary transporters like the Na^+- glutamine co-transporter and other transporters and is partly responsible for the strong uphill gradient for many substances including amino acids and specifically glutamine. Intracellular glutamine concentrations may however also be influenced by glutamine delivery, intracellular production (from de novo synthesis or protein degradation), uptake (glutamine degradation and protein synthesis), and transport from inside to outside the cell. The fivefold difference between mucosal and muscle intracellular glutamine concentration shows that tissue-specific factors must also play a role. Different metabolic situations may exert specific effects on tissue amino acid concentrations via the mechanisms mentioned. Examples are sepsis [26], surgical trauma [30] or mono-organ failure [31].

A glutamine shortage can in principle be demonstrated by decreased release of glutamine and other amino acids (A–V concentration x leg or arm plasma flow x a factor extrapolating from this limb flow to total peripheral flow) from peripheral tissues (muscle, skin, bone) to tissues, requiring these amino acids and playing a crucial role in the response to trauma and disease (splanchnic tissues, immune system, wound) (Table 1.2). Clowes et al. reasoned that stable plasma amino acid concentrations prove that peripheral production balances central uptake [6]. He demonstrated in 1983 that septic cirrhotic patients with a low peripheral release of glutamine and other amino acids and thus metabolizing low quantities in their splanchnic tissues died of sepsis, while those with a high peripheral release survived [6].

Modern technology has allowed measuring the rate of appearance (Ra) in and disposal (Rd) from plasma of a certain substrate by the organism and it has been proposed that these measures might be an adequate measure for the supply of the substrate to the splanchnic and healing tissues. This is questionable because the relevant measure is the net release by peripheral tissues to the central tissues. Net release and uptake by organs are determined by the difference between Ra and Rd across an organ. Because both components can change in individual organs and total body Ra and Rd is determined by the sum of Ra's and Rd's of all organs, total Ra and Rd do not necessarily need to increase to nevertheless induce increased release from peripheral tissues and uptake by central tissues (Fig. 1.8). This means that the whole body Ra and the Rd of glutamine is not an adequate measure of the net release of glutamine from peripheral tissues to central tissues, active in host response.