

CASE ILLUSTRATIONS

CASE ILLUSTRATION 4.1 —

METABOLIC FRAGILITY FROM INSUFFICIENT GLU & GLN

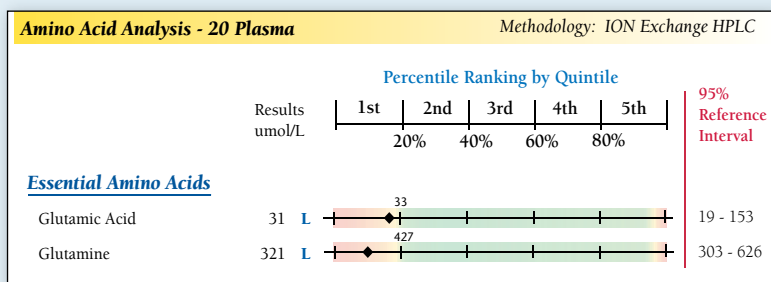
History: Four years prior to the testing date, this 30-year-old clinician had recurrent urinary tract infections for several months, treated with antibiotics. She says, “Then suddenly my body just broke down. My immune system just collapsed and I had infections everywhere: lungs, ears, nose, bladder, etc. I got allergic to everything I ate.”

Current diagnosis and symptoms: Interstitial cystitis, frequent upper respiratory infections, constipation and bloating.

The amino acid profile was measured on a plasma specimen. The results show concurrent low Glu and Gln. Although neither amino acid is below the 95th percentile ranges, the dependent nature of this pair makes the results quite unusual. The physiological state might be described as one of metabolic fragility because of difficulty in responding to systemic pH and ammonia production shifts.

She reports that her bladder and general body pain is much worse in the morning, a time when systemic pH is under stress from cortisol-stimulated organic acid and ammonia formation.

The most common amino acid-based treatment in such cases is to use customized free-form essential amino acid mixtures formulated as described in this chapter. Such low glutamic acid and glutamine patterns are very frequently accompanied by multiple imbalances in utilization of EAA. ❖

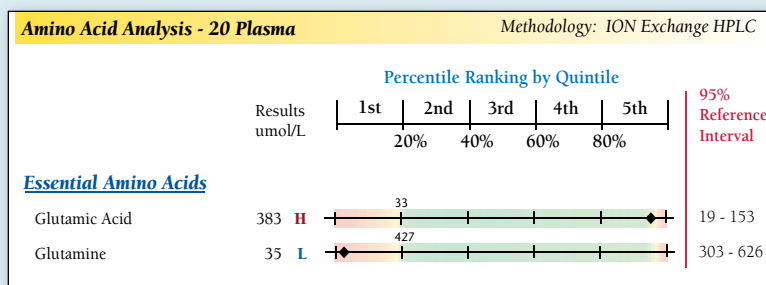


CASE ILLUSTRATION 4.2 —

HIGH GLU/GLN RATIO IN A PATIENT WITH AUTISM

A routine amino acid profile was ordered along with other metabolic testing on a severely autistic 3-year-old girl. Her plasma glutamate was very elevated, 383 μ M (19–153), while glutamine was only 35 μ M (303–626).

Extreme elevations of multiple organic acids were found in urine, consistent with acidemia and calcium was very high in erythrocytes, indicating difficulty maintaining the membrane calcium pumping system. Her plasma fatty acid profile showed an extremely high AA/EPA ratio that is associated with the pro-inflammatory state and her urine contained very high quinolinate and kynurenate levels, indicating interferon- γ -stimulated macrophage inflammatory response. Since her urinary p-hydroxybenzoate was very elevated, one area of suspected etiology is a severe overgrowth of bacteria or parasites producing an inflammatory response in the gut.



This case has multiple metabolic disturbances that can be affecting systemic pH and brain chemistry. Her situation is exacerbated by the loss of control over conversion of glutamate to glutamine. There is the possibility of genetic impairment of hepatic glutamine synthetase, but correction of potential dependent metabolic issues could be undertaken before attempting to confirm such diagnosis. ❖

TABLE 6.1 — SUMMARY OF ABNORMALITIES FOR ORGANIC ACIDS IN URINE

Name		Potential Intervention	Metabolic Pathway
Fatty Acid Oxidation			
Adipate	H	L-Carnitine, 500–1000 mg TID;	Fatty acid oxidation
Suberate	H	L-Lysine (if low), 500 mg TID; B ₂ , 100mg BID	
Ethylmalonate	H	See text for other interventions in genetic disorders	
Carbohydrate Metabolism			
Pyruvate	H	B ₁ , up to 100mg TID with B complex support; For concurrent H Lactate: lipoic acid, 500mg TID	Aerobic/anaerobic energy production
Lactate	H	Coenzyme Q ₁₀ , 50 mg TID	
β-Hydroxybutyrate	H	Chromium picolinate, 200 µg BID	Balance of fat and CHO metab.
Energy Production (Citric Acid Cycle)			
Citrate	H	Arginine, 1–3 gm/day	Citric Acid Cycle Intermediates
	L	Aspartic acid, 500 mg	
Cis-aconitate	H	Cysteine, 1000 mg BID; Check for iron deficiency	
Isocitrate	H	Lipoic acid, 25 mg/kg/day Magnesium, 400 mg; manganese, 20 mg	
α-Ketoglutarate	L	α-KG, 300 mg; arginine, 1000 mg; glutamine, 1–5 g	
	H	B-complex, 1 TID; lipoic acid 100 mg	
Succinate	L	Isoleucine, 1000 mg TID; valine, 1000 mg TID	
	H	CoQ ₁₀ , 50 mg TID, Magnesium, 500 mg	
Fumarate	L	Tyrosine, 1000 mg BID; phenylalanine, 500 mg BID	
Malate	H	CoQ ₁₀ , 50 mg TID, B ₃ , 100 mg TID	
Hyoxymethylglutarate	LH	CoQ ₁₀ , 50 mg TID	(L) Substrate-limited CoQ ₁₀ synthesis (H) HMG-CoA reductase inhibition
B-Complex Vitamin Markers			
α-Ketoisovalerate	H	B-complex, 1 TID; lipoic acid 100 mg	Valine catabolism
α-Ketoisocaproate	H		Leucine catabolism
α-Keto-β-methylvalerate	H		Isoleucine catabolism
Xanthurenate	H	Vitamin B ₆ , 100 mg/d	Tryptophan catabolism (hepatic)
β-Hydroxyisovalerate	H	Biotin, 5 mg/day; Magnesium, 100 mg BID	Isoleucine catabolism
Methylmalonate or Propionate	H	B ₁₂ , 1000 µg TID	Valine or odd-chain fatty acid catabolism
Formiminoglutamate	H	Folic acid, 400 µg/d	Histidine catabolism
Neurotransmitter Metabolism			
Vanilmandelate	LH	Tyrosine, 1000 mg BID-TID, between meals and phenylalanine hydroxylase cofactors as needed	(L) Tyrosine-limited or (H) Tyrosine-depleting epinephrine & norepinephrine catabolism
Homovanillate	LH	Contraindicated for patients taking MAO inhibitors	(L) Tyrosine-limited or (H) Tyrosine-depleting DOPA catabolism
5-Hydroxyindolacetate	LH	5-hydroxytryptophan, 50–100 mg TID; magnesium, 300 mg; vitamin B ₆ , 100 mg (5-HTP may be contraindicated with SSRI's)	(L) Tryptophan-limited or (H) Tryptophan-depleting Serotonin catabolism
Kynurenate	H	B ₆ , 100 mg; magnesium, 300 mg	Inflammation-stimulated macrophage and astrocyte kynurenine pathway activity
Quinolate	H	Magnesium, 300 mg	

Table 6.1 continued on following page...

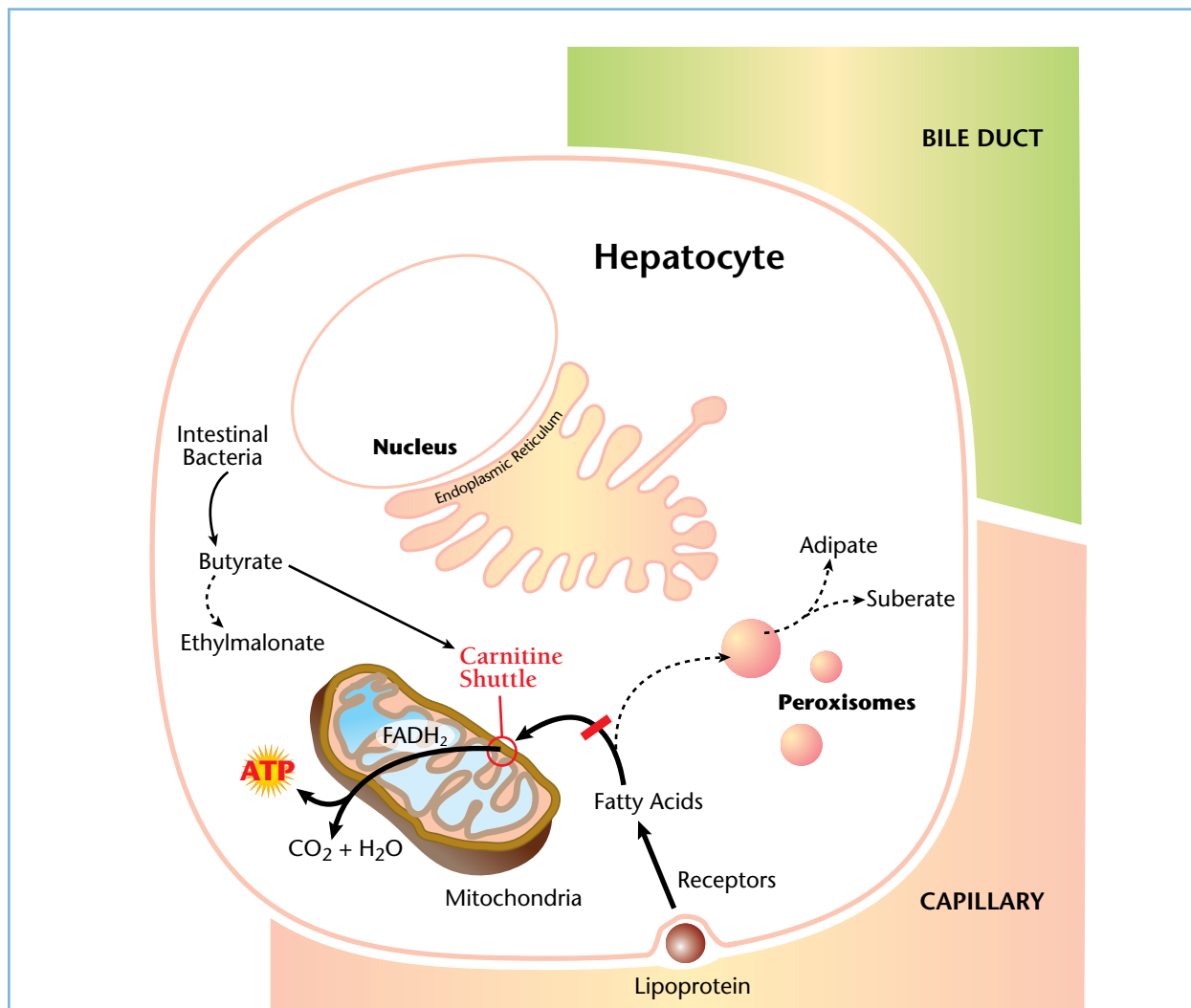


FIGURE 6.2 — Mitochondrial Fatty Acid Metabolism Markers

In all tissues except brain, most ATP generation is derived from oxidation of fatty acids. The process is initiated by entry of the fatty acid into the matrix of mitochondria. The rate limiting step for entry is the formation of fatty acyl carnitine by one of three enzyme systems that operate on medium, long or very long chain fatty acids. Even a slight interruption of this dynamic pathway causes increased amounts of fatty acids to be processed via omega oxidation occurring in peroxisomes. The lower efficiency of peroxisomal processing allows intermediates to escape and be lost when the blood is filtered in the kidneys. Adipate and suberate are biochemical markers that reflect the degree to which mitochondrial entry is impaired due to insufficiency of carnitine or other genotrophic factors. See Figure 5.4 (Fatty Acids) for carnitine shuttle details.

of fatty acyl-carnitine, and this reaction is governed by carnitine concentration. The extreme importance of fatty acid oxidation to provide cellular energy is indicated by the redundancy of systems. Both β - and ω -oxidation systems are contained in peroxisomes. When the mitochondrial system fails to meet demands, peroxisomes can take over to a limited degree, but lack of the

double membrane containment of the mitochondrion means that the system is less efficient because substrates may escape and be lost as renal excretory products. Examples of human mitochondrial β -oxidation deficiency are well known to produce infant death, though some individuals exhibit normal development for a few weeks or months.³⁶ As usual, the severe manifestations of such

THE STOMACH

Standard medical treatments focusing on the gastrointestinal tract most often involve treating stomach issues. Proton pump inhibitors, histamine-2 (H_2) receptor antagonists and other types of antacid drugs are among the most frequently prescribed medications. The use of these medications can generate other risk factors originating from altered GI function, including bacterial overgrowth,^{13,14} interstitial nephritis¹⁵ and hip fracture.¹⁶ By frequency of medical treatment and by scope of effects, the stomach becomes primary for evaluating gastrointestinal function. The primary function of the stomach is receiving and retaining food for the secretion of gastric acid to initiate the digestive process.

Gastric secretion of hydrochloric acid (HCl) is essential for proper assimilation of elements such as calcium and zinc, digestion of protein (proteolytic activity of pepsin requires a pH of less than 5) and for adequate sterilization of stomach contents. Low pH is

also required for proper release of vitamin B_{12} from food sources. When stimulated, the parietal cells of the stomach secrete an isotonic solution containing enough HCl to make the gastric fluid pH less than 1 (see Figure 7.1). At this extreme acidity, the hydrogen ion concentration of gastric fluid is about 3 million times greater than that of arterial blood. It takes a tremendous amount of cellular energy to maintain this gradient because of the high activity of membrane pumps utilizing ATP. Perhaps it is not surprising that problems of intestinal absorption are often due to inadequate secretion of HCl.¹⁷ Depletion of B-complex vitamins may be the precipitating event leading to reduced energy production in cells of the gastric pits. Patients over 50 years of age, who are particularly prone to inadequate secretion of HCl (hypochlorhydria) and intrinsic factor because of degenerative gastric disorders (e.g., atrophic gastritis), are frequently deficient in vitamin B_{12} .¹⁸

Symptoms of inadequate stomach acid are similar to those of excess acid and are frequently mistaken.

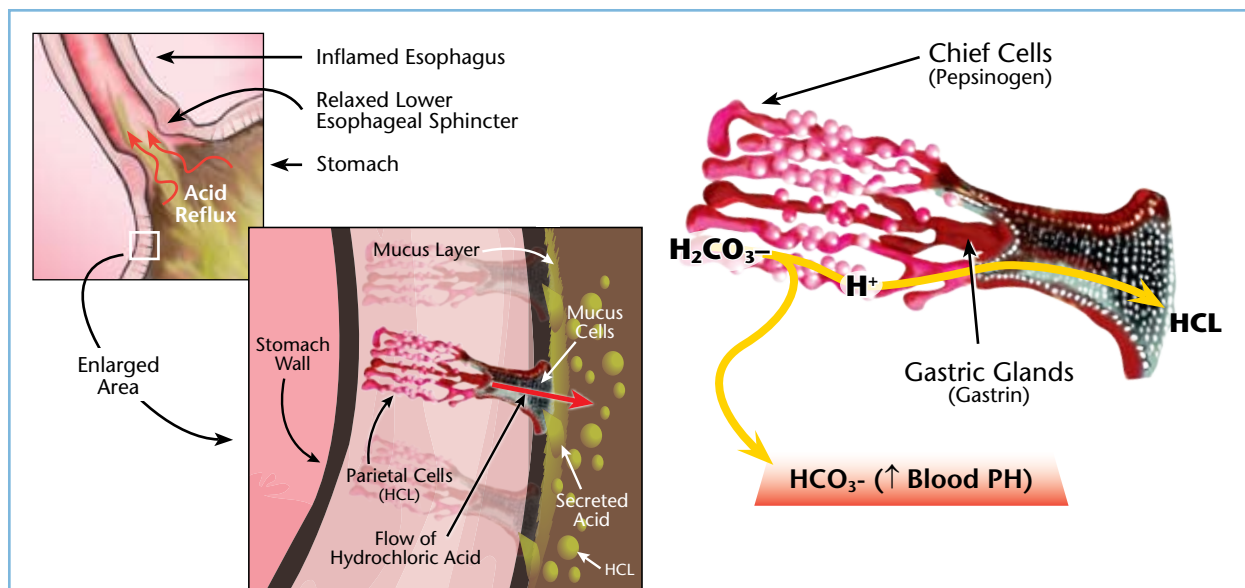


FIGURE 7.1 — The Gastric Pit

Overloading the stomach and failure of the lower esophageal sphincter to close cause reverse flow of stomach acid into the unprotected lining of the esophagus. Failure of the pyloric valve to close causes premature emptying and maldigestion. Protein digestion is interrupted and elemental absorption is impaired when food is not adequately acidified. Blocking of stomach acid secretion by pharmaceutical agents designed to prevent heartburn and to treat stomach ulcers can easily cause such interruption of digestion. Laboratory profiles of amino acids and essential elements frequently show low levels of essential amino acids and essential trace elements, respectively, that are warning signs of the long term effects of insufficiency of these critical nutrient factors. See Chapter 3, “Nutrient and Toxic Elements” and Chapter 4, “Amino Acids” for discussion and illustration of those abnormalities.

enzyme preparations. Therefore, unlike chymotrypsin, it is not affected by oral pancreatic enzyme replacement therapy (see Figure 7.3).³⁷ Elastase is also not affected by previous gastrointestinal surgery, gastric dysmotility or mucosal disease of the small intestine. Fecal elastase is a simple, non-invasive, relatively inexpensive and accurate functional test for patients with suspected pancreatic exocrine insufficiency and/or chronic pancreatitis, and is superior to the fecal chymotrypsin determination and the more complicated pancreolauryl test for pancreatic cholesterol hydrolase enzyme activity.^{37, 38, 44}

Pancreatic exocrine dysfunction has been described frequently in both insulin- and non-insulin-dependent diabetes patients and is often considered a complication of diabetes. However, diabetes secondary to chronic pan-

creatitis (often caused by biliary microlithiasis) may also be much more common than was previously believed. Approximately 20 to 40% of chronic pancreatitis patients will develop secondary diabetes, whereas diabetes can impair pancreatic exocrine function at least as often.⁴⁵ Pancreatic elastase has been advocated as a screening test for pancreatic insufficiency, chronic pancreatitis, biliary microlithiasis and elevated risk of the development of diabetes. Undiagnosed and untreated pancreatic insufficiency can also result in malabsorption of proteins, fats and, ultimately, the entire spectrum of fat-soluble vitamins.⁴⁶⁻⁵⁰ Reduced pancreatic elastase, combined with elevations in fecal protein, meat and vegetable fibers, are clinical indications for supplemental pancreatic enzyme and betaine hydrochloride supplementation.

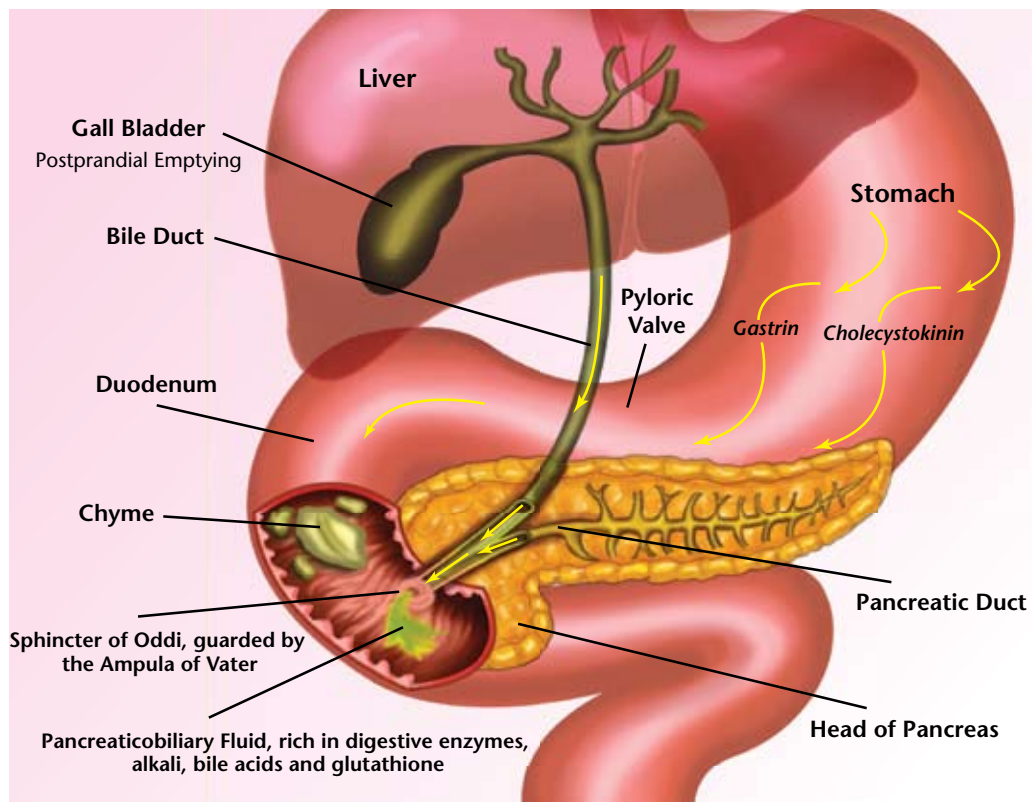


FIGURE 7.2 — The Pancreaticobiliary System

In order to retain food for adequate generation and mixing of stomach acid, the pyloric valve must remain closed until small (~ 4 cc) boluses of chyme that require pH neutralization by alkaline pancreatic fluid and fat emulsion by biliary flow. The joining of biliary fluid with pancreatic fluid just before entry into the mid-duodenum helps to protect the pancreas from un-neutralized stomach acid and it assures the co-mixing of both fluid types with the chyme. The frequency of allergic reactions to foods such as nuts and milk derives, in part, from the strong requirement of those foods with high fat content and content of proteins that are difficult to digest. The undigested food proteins pass into the small intestine where they can gain entry to the intestinal blood supply, requiring processing by the immune system (see below under “The Immune Barrier”).