

- “Cachexia may well represent the devastating flip side of the tremendous achievements of modern medicine, as the incidence of cachexia is also a function of survival of chronic illness.”
- “Many diseases – which rapidly led to death only a few years ago – are now better controlled by new therapies. Even if we cannot cure and eradicate these diseases, their natural history has significantly increased by months and years. Although these new therapeutic strategies represent a remarkable advantage over the previous standards of care, ***it is impossible to ignore the fact that many more patients are now facing the nutritional and metabolic consequences of prolonged immunological and hormonal challenges due to both the illness process itself and the aggressive therapies.***”

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Clinical & Performance Program, Vol. 8

**Nutrition and
Critical Care**

Luc Cynober
Frederick A. Moore

Baracos VE. Overview on
metabolic adaptation to
stress, pp. 1-13.

“An understanding of the
nature of stress is
fundamental to the rational
design of nutrient mixtures to
feed patients whose
homeostasis has been altered
by one or more stressors.”

“All stresses may be
presumed to be associated
with characteristic
modifications in the
metabolism of lipids,
carbohydrates, amino acids,
and micronutrients.”

KARGER



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Using the Organic Acids Test – Part 3
Dr. Jeff Moss

Clinical Nutrition (2004) 23, 1256-1266

ELSEVIER

REVIEW

Acute and "chronic" phase reaction—a mother of disease

Stig Bengmark

Department of Surgery and Liver Institute, UCL, London, UK

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Clinical Nutrition

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KEYWORDS
Acute phase response;
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Cellular membranes;
Endothelial cells;
Abdominal obesity;
Insulin resistance;
Growth hormones;
Free fatty acids;
Alzheimer disease;
Parkinson disease;
Neurodegenerative diseases;
Atherosclerosis;
Coronary-vascular diseases;
Cancer;
Breast cancer;
Colorectal cancer;
Prostatic cancer;
Diabetes;
Crimson;
Fatty liver;
Gallbladder disease;
Chronic renal disease;

Summary The world is in diseases. Almost half of the mortality is due to these chronic diseases. And they are these diseases are associated consumption of calorie-conc also under consumption of a function of the innate immune changes induced in response the subsequent development chronic diseases. The endo importance, and the function the function of the underlying cells; their ability to obtain nutrients and antioxidants and to eliminate waste products. The abdominal adipocytes seem to play a key role, as they have the ability to in stressful situations release much of proinflammatory cytokines, PA-1 and free fatty acids compared to elsewhere in the body. The load on the liver of these various substances in often of greater magnitude than the liver can handle. Some of the most common chronic diseases and their potential association with more and "chronic" phase response, and more metabolic syndrome are discussed separately. The need for studies with lifestyle modifications is especially emphasized.
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Bengmark S. Acute and "chronic" phase reaction – a mother of disease, *Clin Nutr*, Vol. 23, pp. 1256-66, 2004

E-mail address: S.bengmark@ucl.ac.uk (S. Bengmark).

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doi:10.1016/j.cnu.2004.07.016

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Considerations for the Catabolic Patient

Signs & Symptoms	Consider	Treatment Plan	Monitor	Supplementation
Signs & Symptoms: - Feeling "lousy" - Fatigue - Cravings - Depression/anxiety - Poor quality sleep - Poor digestion/absorption/leaky gut - Chronic pain/infection	Optimize pH	Optimize fluid and electrolyte balance	Morning urinary pH -pH paper	Potassium bicarbonate -K Alkaline (Moss) Magnesium -Magnesium Glycinate (Vital Nutrients)
Clinical Findings: - High % body fat - Low bone density - High fasting insulin - Heavy metal burden - Calcium to phosphorus ratio 3:1 - High normal globulin - Cholesterol (220-280) - High LDL, low HDL - High triglycerides - Low normal serum potassium, high normal serum sodium - High normal BUN with normal creatinine - Low urinary sulfate - Genomic variations	Optimize muscle mass (reduce sarcopenia) and amino acid levels	Pay special attention to protein and amino acids	Body composition: -Bioelectric impedance scale Grip strength: -dynamometer	Amino acids -Custom Amino Base (Metabolic Maint.) Protein powders/bars -UltraLean products (Biogenesis) -Paleo products (DFH)
	Reducing inflammation	Reduce inflammation Address food allergies	Inflammatory biomarkers: -HS-CRP -Fibrinogen levels -WBC -Differential	Anti-inflammatory agents -Inflametric (Olympian) -D-Flame (Protocols) -Pain Guard (Perque) Fish Oils -Ultra Pure Fish oil (Vital Nutrients) Food allergy blends -AllerGzymes (DFH)
	Improving insulin sensitivity	Watch carbohydrate/protein ratio	Fasting glucose Fasting insulin Cravings	Metabolic Synergy (DFH)
	Optimize dietary carbohydrate/protein ratios	Replete protein deficiencies and reduce carbohydrate intake along with improvements in dietary quality	Diet diary Optimal protein intake -1.0 – 1.2 g/kg body weight	Protein powders/bars -Paleo products (DFH) -UltraLean (Biogenesis)
	Optimize GI function	Dietary changes, supplementation of digestive aids	Patient signs and symptoms	Betaine HCl (Vital Nutrients) Digestzymes (DFH) Intestinal Repair Complex (Biogenesis)
	Optimize micronutrient deficiencies/imbalances	Supplementation of multis Possible emphasis on vitamin D, iodine, and zinc	Serum 25 OH vitamin D Fatigue/serum thyroid indicators Zinc taste test	Multi Nutrients (Vital Nutr) Vitamin D (Vital Nutr) Iosol (Moss) Zinc Supreme (DFH)

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Using the Organic Acids Test – Part 3
Dr. Jeff Moss

NEURO-SIGNALS

Invited Review

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Biological Mechanism of Antidepressant Effect of Omega-3 Fatty Acids: How Does Fish Oil Act as a 'Mind-Body Interface'?

Kuan-Pin Su

Department of General Psychiatry and Mind-Body Interface Laboratory (MBI-LAB), China Medical University and Hospital, Taichung, Taiwan; Stress, Psychiatry and Immunology Laboratory (SPI-Lab), Institute of Psychiatry, King's College London, London, UK

Key Words
Major depressive disorder · Depression · Docosahexaenoic acid · Arachidonic acid · Prostaglandins · Thromboxanes · Leukotrienes · Cyclo-oxygenase 2 · Cyclo-oxygenase 1

Abstract
The unsatisfactory results of monoamine-based antidepressant therapy and the high occurrence of somatic symptoms and physical illness in patients with depression imply that the serotonin hypothesis is insufficient to approach the aetiology of depression. Depressive disorders with somatic presentation are the most common form of depression. Somatization, the bodily symptoms without organic explanation, is similar to cytokine-induced sickness behaviour. Based on recent evidence, omega-3 polyunsaturated fatty acids (n-3 PUFAs, or n-3 fatty acids) are enlightening a promising path to discover the unsolved of depression, sickness behaviour and to link the connection of mind and body. The PUFAs are classified into n-3 (or omega-3) and n-6 (or omega-6) groups. Docosahexaenoic acid and arachidonic acid, the major bioactive components of n-3 PUFAs, are not efficiently synthesized in humans and should therefore be obtained directly from the diet, particularly by consuming fish. Docosahexaenoic acid deficiency is associated with dysfunctions of neuronal membrane stability and transmission

prostaglandin E₂ synthesis, which might be linked to the somatic manifestations and physical comorbidity in depression. The role of n-3 PUFAs in immunity and mood function supports the promising hypothesis of psychoneuroimmunology of depression and provides an excellent interface between 'mind' and 'body'. This review is to provide an overview of the evidence about the role of n-3 PUFAs in depression and its common comorbid physical conditions and to propose mechanisms by which they may modulate molecular and cellular functions.

Introduction
Major depressive disorder (MDD) is a serious psychiatric illness with a high lifetime prevalence rate [1]. However, the current treatment for this high burden disease is not satisfactory. Less than 50% of patients achieve full remission with optimized medication treatment [2] despite that more than 40 antidepressants with mechanisms related to serotonin, noradrenaline and/or dopamine

Su KP. Biological mechanism of antidepressant effect of omega-3 fatty acids: How does fish oil act as a 'mind-body interface'? *Neurosignals*, Vol. 17, pp. 144-152, 2009

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Table 1. Overlapping of symptoms of acute sickness behaviour associated with IFN- α therapy and the somatic symptoms in MDD

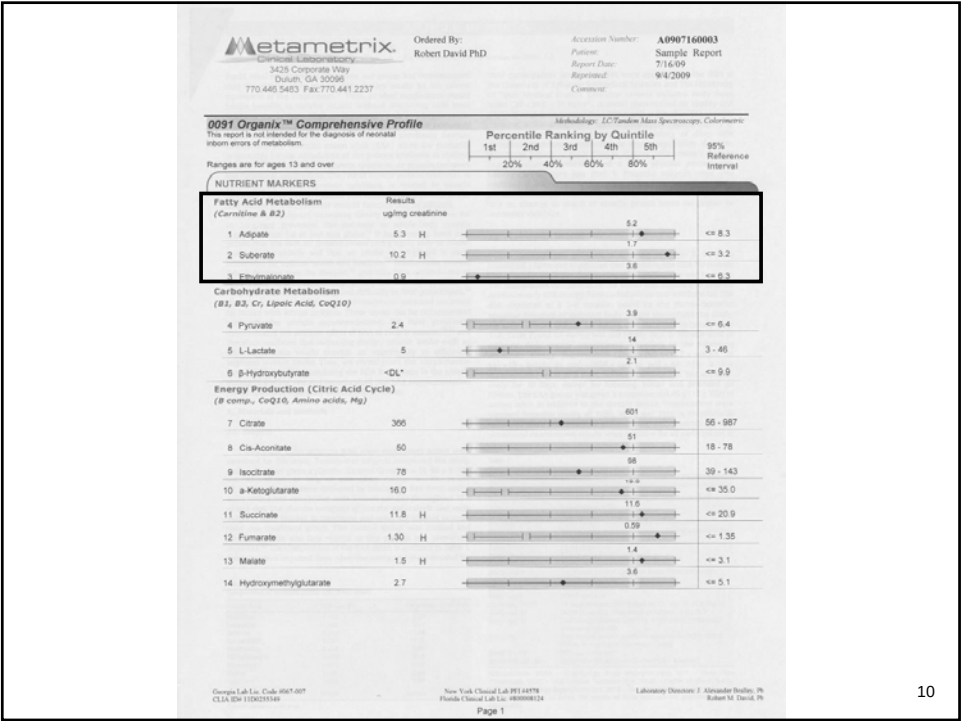
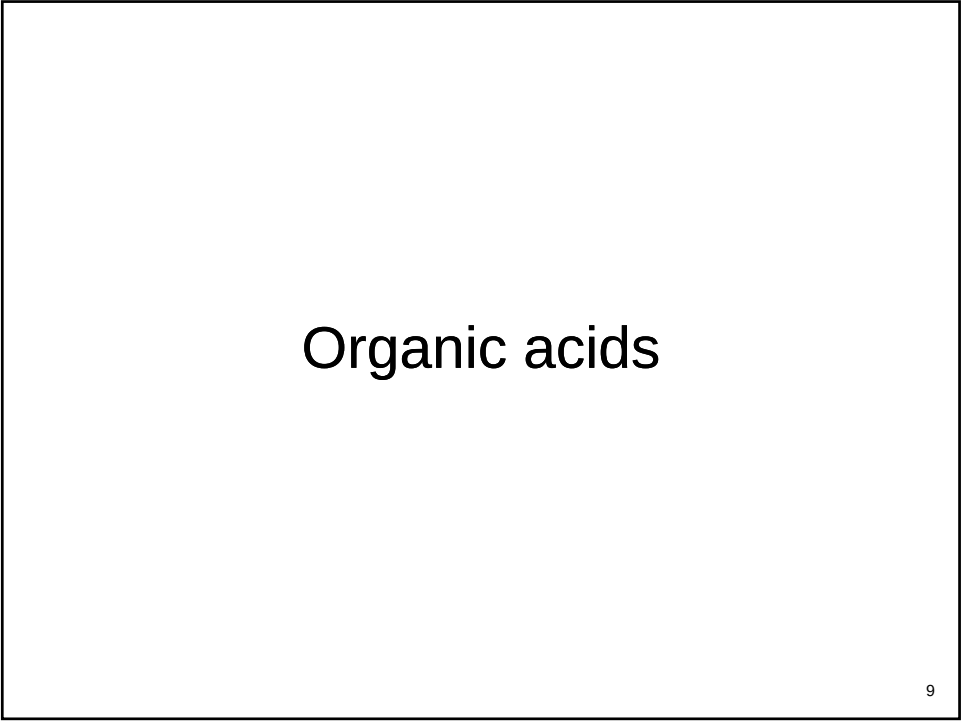
Symptoms	Prevalence in IFN- α therapy ^a , %	Prevalence in MDD ^b , %
Fatigue/asthenia	39–90	73
Headache	27–67	33 ^c
Gastrointestinal symptoms	50 ^{c, 1}	34–47 ^f
Psychomotor slowing	40 ^c	59–65 ^f
Insomnia	20–39 ^d	63
Irritability	35 ^d	50
Arthralgia	9–36	31 ^e
Musculoskeletal pain	26–32	62–80 ^{g, 2}
Abdominal pain	15–20	21 ^e
Anorexia	13–19	40
Anxiety	13–18 ^d	57
Poor concentration	14 ^d	51

^a [46], unless otherwise specified; ^b [99], unless otherwise specified; ^c [100]; ^d [101]; ^e [102]; ^f [103]; ^g [104].

¹ Nausea, vomiting, bowel problems.

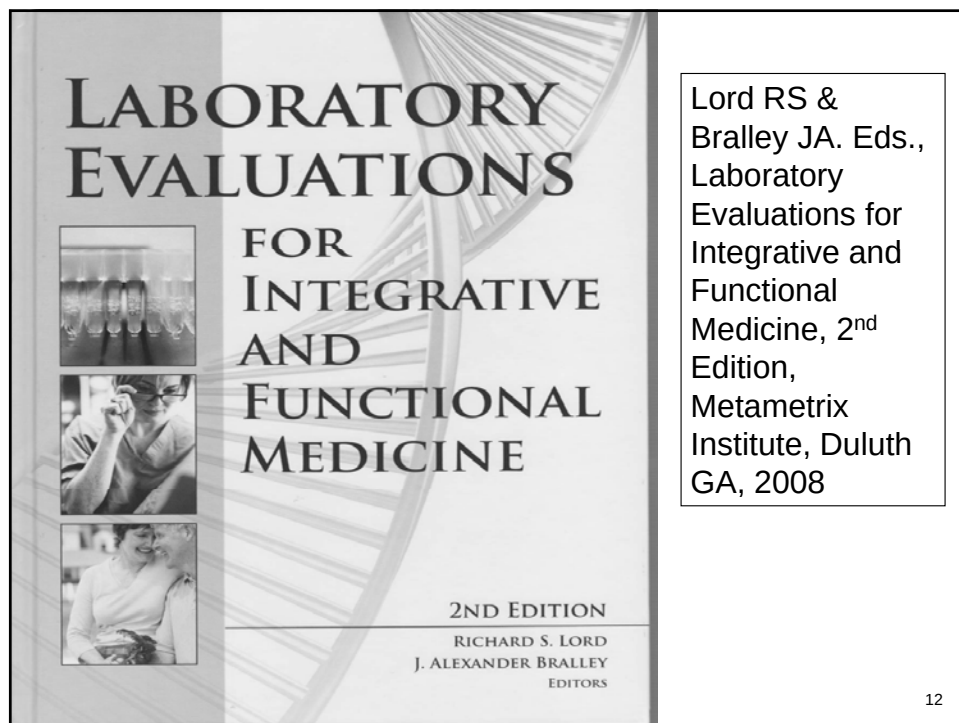
² Result from depressed inpatient population.

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Fatty acid metabolism: Carnitine

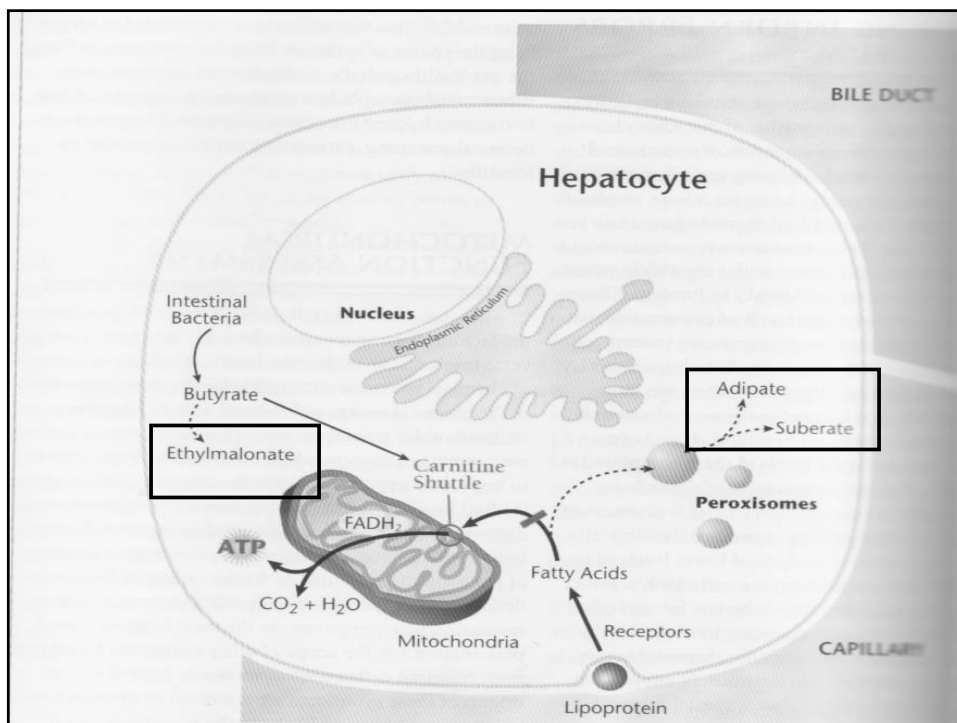
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Adipate Suberate

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Fatty acid metabolism: Basic information

- “Fatty acid metabolism by mitochondrial β -oxidation is the dominant energy-yielding pathway in most tissues.”
- “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 the system is less efficient because substrates may escape and be lost as renal secretory products.”

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Adipate and suberate

- “Adipate (adipic acid) and suberate (suberic acid) are six- and eight-carbon-long dicarboxylic acids, respectively.”
- “Low carnitine availability or impaired enzyme activity can slow fatty acid oxidation by decreasing the transport of fatty acids into the mitochondria...”
- “Need for extra carnitine may be indicated when urinary levels of adipate and suberate are elevated.”

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Adipate and suberate

- “Carnitine can be synthesized from the essential amino acid, L-lysine.”
- “However, limitations of available lysine due to dietary deficiency or digestive impairment or genetic polymorphism of the required enzymes can cause carnitine requirements to exceed biosynthetic capacity.”
- “Therefore, carnitine is a conditionally essential dietary component.”

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Carnitine and Stress

“Loss of carnitine in muscles can result from chronic overuse of lipids by the mitochondria.”

Bahl JJ & Bressler R. The pharmacology of carnitine, Ann Rev Pharmacol Toxicol, Vol. 27, pp. 257-77, 1987.

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Carnitine and Hyperinsulinemia

“The regulation of carnitine dependent transfer of fatty acids seems to depend mainly on the rate-limiting activity of carnitine palmitoyltransferase I (CPT-I) and its regulation by malonyl-CoA.”

Bremer J. The role of carnitine in cell metabolism, in Carnitine Today, DeSimone C & Famularo G eds., Chapman & Hall, New York, 1997, pp. 1-37.

19

Carnitine and Hyperinsulinemia

“The muscle isoform of CPT I is highly sensitive to allosteric inhibition by malonyl CoA, the precursor of fatty acid synthesis.”

Kelley DE & Goodpaster BH. Skeletal muscle triglyceride. An aspect of regional adiposity and insulin resistance, Diabetes Care, 24(5):933-41, 2001.

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Carnitine and Hyperinsulinemia

“It is tempting to speculate that in the preobese state a higher than normal content of malonyl-CoA in liver and muscle, possibly caused by hyperinsulinemia, predisposes to a reduced capacity for fatty acid oxidation and accumulation of fatty acyl-CoA.”

McGarry JD. Glucose-fatty acid interactions in health and disease, Am J Clin Nutr, 67(3S):500S-504S, 1998.

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Carnitine and Hyperinsulinemia

Stress accompanied by obesity lessens the positive impact of carnitine in two ways:

1. Higher levels of gluconeogenesis during stress increases lipolysis, causing depletion of endogenous carnitine stores.
2. Obesity and hyperinsulinemia increases levels of the fatty acid precursor malonyl CoA, which inhibits CPT-I, without which carnitine cannot function.

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Adipate and suberate

- “A secondary cause of elevated adipate and suberate is riboflavin insufficiency.”
- Once they are inside the mitochondria, fatty acids cannot undergo oxidative metabolism without riboflavin coenzymes.”

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Ethylmalonate

- “Ethylmalonate accumulation is traced to different pathways than the long-chain fatty acid oxidation origins of adipate and suberate.”
- “Although the exact origin is somewhat unclear, current evidence suggests that ethylmalonate is formed from butyrate.”
- “Patients with ethylmalonic aciduria also have elevated levels of butyryl-CoA (and isobutyryl-CoA from isoleucine catabolism).”

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Ethylmalonate

- “Circulating butyrate, a short-chain fatty acid with four carbons, may be derived from intestinal bacterial metabolism.”
- “Butyryl-CoA is normally carried by carnitine into oxidative pathways.”
- “Just as for the long-chain fatty acids, carnitine may be insufficient to clear butyrate or riboflavin may be insufficient to sustain FAD, causing slowing of the rate of oxidation.”
- “Under these conditions, free butyrate is available for other reactions, including carboxylation to form ethylmalonate.

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Ethylmalonate

- “Thus, urinary ethylmalonate elevation shares carnitine and riboflavin dependencies with adipate and suberate, but the precursor arises from different metabolic sources.”
- “This may explain why in evaluating large numbers of organic acid profiles some individuals have elevated adipate and suberate with normal ethylmalonate, whereas other show the opposite pattern.”

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Ethylmalonate

- “Patients with ethylmalonic acidurias should not be treated with medium-chain triglycerides that produce metabolic stress from the accumulation of medium fatty acyl-carnitines.”
- “Glycine (250 mg/kg/d) has been found to be a useful adjunct in addition to carnitine and vitamin B₂ in the treatment of these patients.”

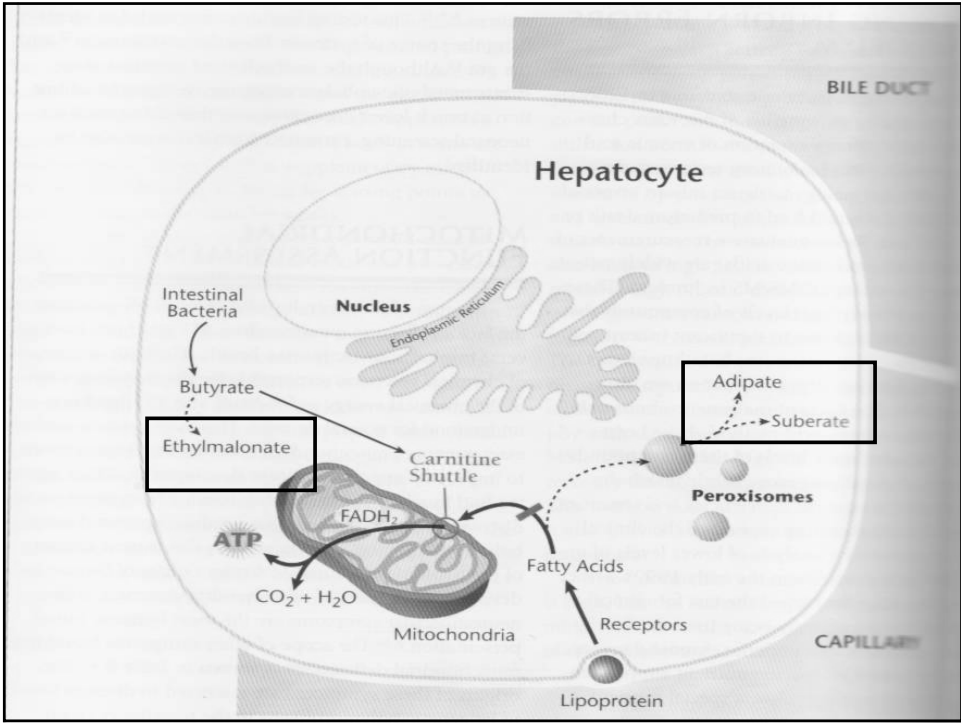
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Ethylmalonate

- “Ethylmalonate excretion may also be stimulated by isoleucine loading, indicating that it may be an intermediate produced in the isoleucine catabolic pathway.”

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Using the Organic Acids Test – Part 3
Dr. Jeff Moss



Considerations for the Catabolic Patient				
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Thank you!!

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