

Organic Acids Part 2

Dr. Jeff Moss

Using organic acids to resolve chief complaints and improve quality of life in chronically ill patients

Part II

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Journal of Work Exposes Medical Students to System's Ills - NYTimes.com Page 1 of 2

The New York Times

September 9, 2009

Summer of Work Exposes Medical Students to System's Ills

By STEVE DODD

SEATTLE — This summer, medical students from the University of Washington took a long look under the hood of the health care system that can almost be reliably, and many surprised to compare how well with their own skills, ages and their students' experience.

Summer of work exposes medical students to system's ills, The New York Times, September 9, 2009

The students learned not only to deliver better and safer care, but also to better understand the system's problems and how to fix them. In a series of hands-on experiences, the students learned to work with patients with chronic conditions — diabetes, hypertension, obesity, depression — that left many questioning how much any one physician could really accomplish.

"I often wondered what we were actually doing to help people," Mr. Dodd said.

"...a tidal wave of chronic illness..."

For 11 years, the University of Washington School of Medicine has dispatched its rising second-year students across the Northwest to provide primary care in rural and underserved areas. The resulting program, a difficult, but a recent number of students took part this year — 107 from a class of 200.

The school has a reputation for producing some of the nation's best doctors, nurses, dentists and other health care professionals. The school has a long history of training students to work in underserved areas, and the program is one of several others, along with two others, designed to help students learn to practice in areas with a shortage of primary care doctors.

This year, the students set out on a mission to understand the health care system's problems and how to fix them. The students were sent to work in rural and underserved areas, but few students returned thinking there was little to be done.

http://www.nytimes.com/2009/09/09/us/politics/09med.html?_r=1&ft=health&ft=... 9/9/2009

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- "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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**Nestlé Nutrition Workshop Series
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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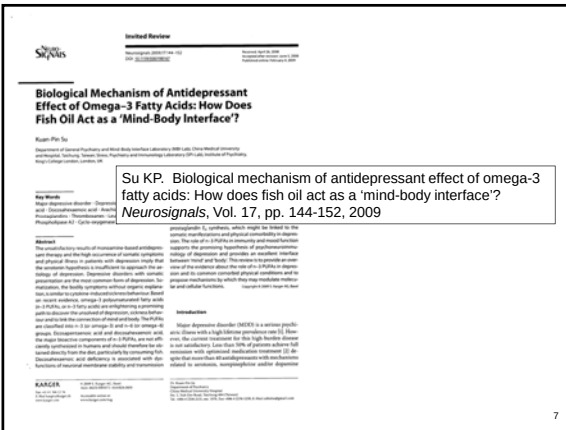


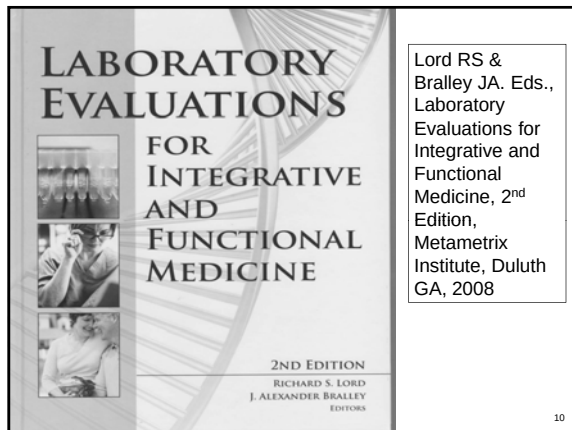
Table 1. Overlapping of symptoms of acute sickness behaviour associated with IFN- α therapy and the somatic symptoms in MDD

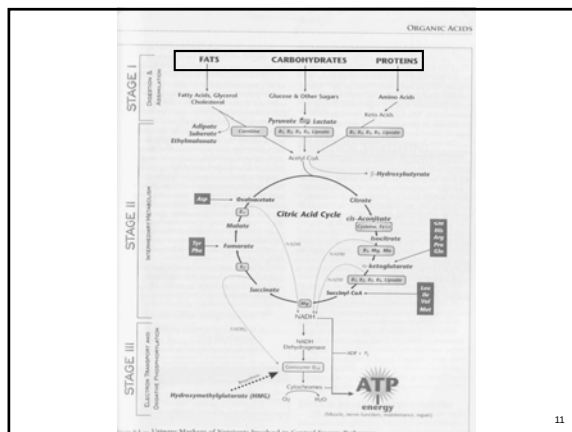
Symptoms	Prevalence in IFN- α therapy ^a , %	Prevalence in MDD ^b , %
Fatigue/asthenia	39-90	73
Headache	27-67	33 ^c
Gastrointestinal symptoms	50 ^c -1	34-47 ^f
Psychomotor slowing	40 ^c	59-65 ^f
Insomnia	20-39 ^d	63
Irritability	35 ^d	50
Arthralgia	9-36	31 ^e
Musculoskeletal pain	26-32	62-80 ^{e,2}
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.

Organic acids

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Pyruvate and lactate as major indicators of catabolic physiology and overall severity of chronic illness

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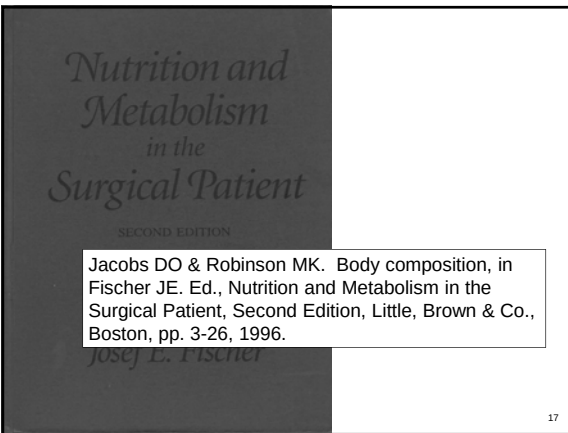
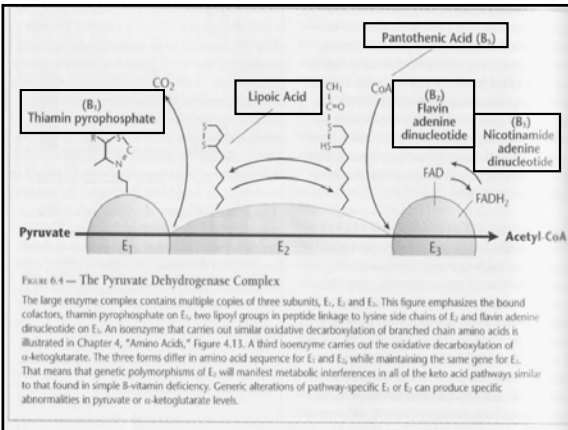


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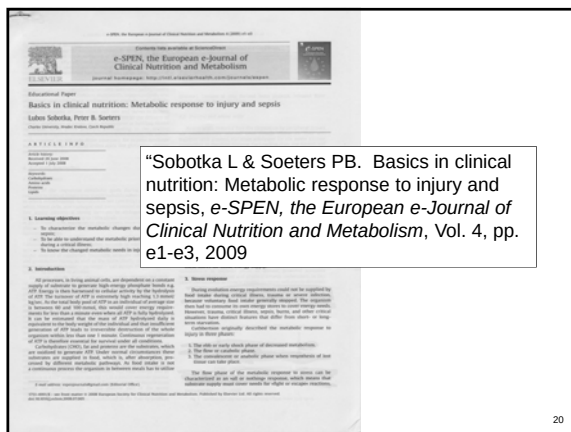
- "...within the first 24 hours of illness, glycogen stores are rapidly depleted, and thus muscle amino acids, glycerol, lactate, and pyruvate released from the periphery are used as precursors for accelerated hepatic gluconeogenesis."
- "The magnitude of increase in glucose production is proportional to the extent of illness."
- "The glucose produced is used by the central nervous system, which specifically requires carbohydrate to meet its energy needs, although its rate of utilization is relatively normal."
- "The remainder of the glucose is used for reparative processes in wounds or in other injured tissues."

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- "Injured tissue abounds with inflammatory cells, erythrocytes, and fibroblasts."
- "Cells populating such tissue undergo anaerobic metabolism and produce large quantities of lactate."
- "The lactate is then transported back to the liver for resynthesis of glucose that can then be reused by tissues undergoing repair (the Cori cycle)."

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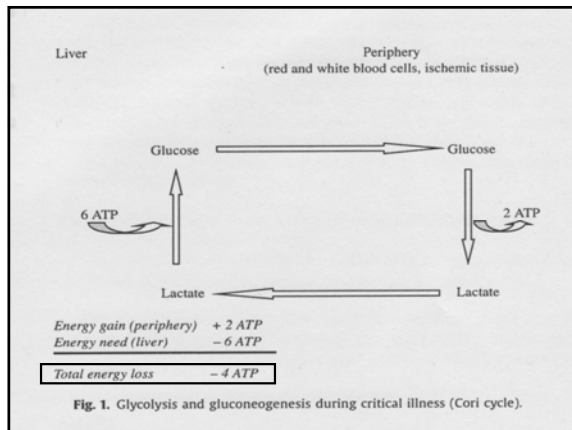
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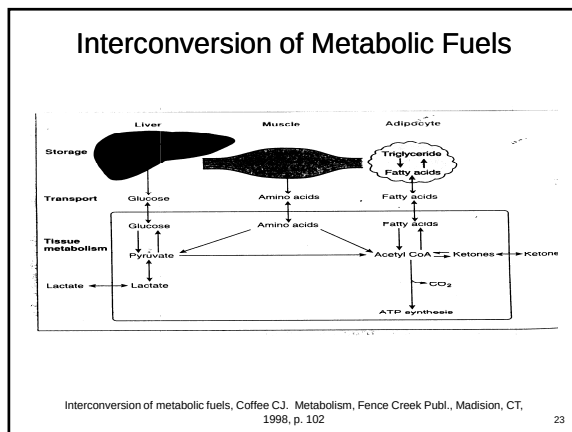
- "Quantitatively, lactate is the most important precursor of gluconeogenesis."
- "As this substrate is the result of anaerobic glucose metabolism, the glucose carbons circulate between peripheral tissues and liver (Cori cycle)."
- "Under normal conditions about 150 g of lactate is metabolized in the liver, but this amount can increase greatly in stress conditions."
- "The total energy loss in this cycle is 4 ATP molecules."

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Lactic Acidosis (Print) - eMedicine Critical Care Page 1 of 37

eMedicine
eMedicine.net

Lactic Acidosis

Author: Gunnerson KJ & Sharma S. Department of Internal Medicine, University of Virginia, Charlottesville, Virginia

Introduction

Background

By the turn of the 20th century, many physicians recognized that their patients who are critically ill could exhibit lactic acidosis. Lactic acidosis is a condition in which the blood is acidotic due to an accumulation of lactic acid. It is a common complication of many critical illnesses, and it is often associated with a high mortality rate. The pathogenesis of lactic acidosis is complex, and it can be caused by a variety of factors, including hypoxia, shock, and liver failure. The diagnosis of lactic acidosis is based on a blood lactate level greater than 4 mmol/L. The treatment of lactic acidosis is supportive, and it involves addressing the underlying cause of the acidosis. In some cases, dialysis may be required to remove the excess lactic acid from the blood.

Gunnerson KJ & Sharma S. Lactic acidosis, eMedicine Critical Care, Medscape.com.

http://emedicine.medscape.com/article/1477077/print 2/4/2005

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Pathophysiological classification of lactic acidosis	
HYPOXIC	NON-HYPOXIC
Ischemia	Delayed Clearance
Shock, severe anemia, cardiac arrest	Renal or hepatic dysfunction
Global Hypoxia	→ Pyruvate Dehydrogenase Dysfunction
Carbon monoxide poisoning	→ Sepsis, thiamine deficiency, catecholamine excess, alcoholic and diabetic ketoacidosis
Respiratory Failure	Uncoupling of Oxidative Phosphorylation
Severe asthma, COPD, asphyxia	→ Cyanide, salicylates, methanol & ethylene glycol metabolites, anti-retroviral drugs, valproic acid, biguanides, INH
Regional Hypoperfusion	Accelerated Aerobic Glycolysis
Limb or mesenteric ischemia	→ Increased effort, sepsis, seizures, large fructose loads, malignancies

Pathophysiologic classification of lactic acidosis.

- "...hyperlactemia in patients with sepsis is a marker of the severity of stress response."
- Hyperlactemia may possibly develop as a byproduct of overall acceleration in glycolysis in severe sepsis."
- "This may well be an adaptive host mechanism designed to provide efficient generation of energy in response to severe stress."

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Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Page 1 of 7

MEDLINE Abstract

Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients.
Crit Care. 2006; 10(1):R22. (2006, 1-06-00062).

Gunnerson KJ, Bass W, Ho D, Nelson JS.
 Virginia Commonwealth University, Respiratory Engineering Branch Center Laboratory, Department of Anesthesiology/Critical Care Medicine, College of Virginia/Virginia Commonwealth University, 1000 East Broad Street, Richmond, VA 23298, USA.

INTRODUCTION: Acid-base abnormalities are common in the intensive care unit (ICU). Differences in outcome exist between respiratory and metabolic acidosis in similar pH ranges. Some forms of metabolic acidosis (for example, lactic acidosis) have been associated with poor outcomes, whereas others (for example, hyperchloremic acidosis) have been associated with better outcomes. The authors designed this study to determine the nature and clinical significance of metabolic acidosis in critically ill patients. **METHODS:** An observational, cohort study of critically ill patients was performed in a tertiary care hospital.

RESULTS: A total of 1,000 patients were enrolled in the study. The study was conducted from January 2001 to April 2003. All patients had a pH < 7.35 and a bicarbonate < 22 mEq/L. The study was designed to evaluate the outcome of patients with metabolic acidosis (lactate > 4 mmol/L) compared to patients with non-lactate metabolic acidosis (lactate < 4 mmol/L).

CONCLUSIONS: In this study, patients with metabolic acidosis (lactate > 4 mmol/L) had a higher mortality rate compared to patients with non-lactate metabolic acidosis (lactate < 4 mmol/L).

Gunnerson KJ et al. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients, *Crit Care*, Vol. 10, No. p. R22, 2006

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- “In critically ill patients in which a measurement of lactate level was ordered, lactate and strong anion gap were strong independent predictors of mortality when they were the major source of metabolic acidosis.”
- “Overall, patients with metabolic acidosis were nearly twice as likely to die as patients without metabolic acidosis.”

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REVIEW

Biology of Cachexia
*Michael J. Finkale**

Almost half of all cancer patients show a syndrome of cachexia, characterized by loss of adipose tissue and skeletal muscle mass. Such patients have a decreased survival time, compared with the survival times among patients without weight loss, and loss of total body protein leads to substantial impairment of respiratory muscle function. This weight-change can be fully explained by the accompanying anorectic and catabolic hypermetabolism alone in some wasting cancers. Despite a falling caloric intake, patients with cachexia frequently show an increased expenditure as a result of increases in resting energy expenditure, thermogenesis of brown fat, and thermogenesis of skeletal muscle. In addition, there is an increase in peripheral and whole-body fatty acid cycling, and glucose flux of cytosolic, including serum secreted lactate (1 and 2, interferon- γ , and leukotriene) have been proposed as mediators of the cachexia. However, the results of a study by Tisdale and colleagues (3) show that the loss of mass of the cachexic

Tisdale MJ. Biology of cachexia, *J Nat Cancer Inst*, Vol. 89, No. 23, pp. 1763-73, December 3, 1997

studies suggest that the action at the cytoskeleton is important for the function of the sarcomere. In addition, catechol has been observed in some sarcomeric models even without a cytoskeleton involvement, suggesting that other factors may be involved. These probably include catecholamines, which act directly on skeletal muscle and adipose tissue and the presence of which has been associated with the clinical development of catechol. A polyunsaturated fatty acid, stromangiotoxin, also affects the action of such catecholamine factors and has been shown to stabilize the processes of sweating and cooling energy expenditure in patients with gangrenous cancer. Such a pharmacologic approach may provide new insights into the treatment of catechol. (J Natl Cancer Inst 1997;89:730-73)

The word "cachexia" is derived from the Greek "kakos" meaning "bad" and "hexis" meaning "condition." It occurs in a number of disease states, including cancer, acquired immunodeficiency syndrome (AIDS), major trauma, surgery, malnutrition, and severe sepsis. Cachexia is characterized by weight loss, wasting, depletion of lean adipose tissue and skeletal muscle mass. Weight loss in cancer patients differs from that found in simple starvation. During the first few days of starvation, glycogen stores are depleted by the liver and myofibrillar myosin. Despite loss of fat and muscle glycogen, there is no increased glycogen production by the liver, using gluconeogenic anhe acids released from catabolism of muscle. This early phase is replaced by long-term starvation by the use of fat as a fuel, in which the

single patients, through dietary counseling, failed to reverse the anorexia (20). Trials of intravenous nutrition in cachectic cancer patients also failed to show benefits in terms of increased median survival time or long-term weight gain (21). Although a distinction weight gain was observed, the weight was subsequently lost, suggesting the retention of water (22). Analysis of body composition indicated that patients receiving total parenteral nutrition temporarily maintained body fat stores, but there was no evidence for preservation of lean body mass. Thus, the cause of wasting in cancer cachexia is more complex than that in simple starvation.

reading were not taken seriously, it may be a contributing factor. In addition, the presence in *1* of extremely dissonant, synthetic harmonic appositions and the ability to see how these have been required to be the most important factors in the physical and psychological aspects of a person's quality of life (cf. *1*) are features of the *1* that are absent from early editions. *1* is together with a talented author who has been justifiably to be praised by the production of fiction by the talent that excite their efforts by writing on the hypothetical

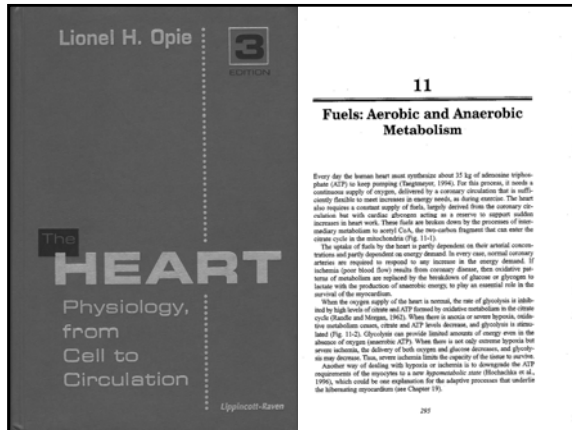
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- “Patients with progressive cancer have been shown to have an increased glucose synthesis not only from lactate, but also from alanine and glycerol.”
- “The Cori cycle normally accounts for 20% of glucose turnover, but it was shown to be increased to 50% in cachectic cancer patients, accounting for the disposal of 60% of the lactate produced.”

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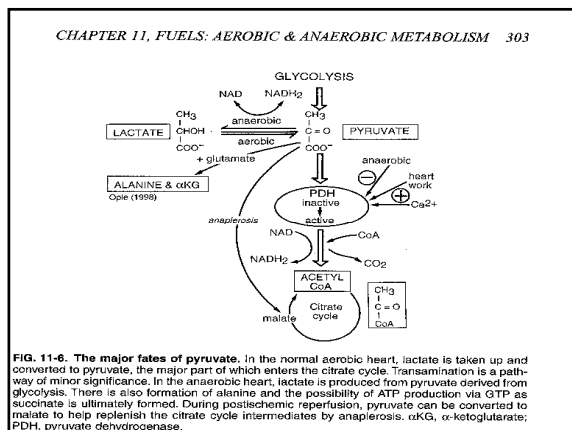


Fuels of the heart

Pyruvate

- "Pyruvate stands at the crossroads of glycolysis and oxidative metabolism in the citrate cycle. It is formed from lactate taken up by the heart and from glycolysis."
- "In the anaerobic heart, pyruvate forms lactate. In the aerobic heart, the major fate of pyruvate is oxidative decarboxylation and entry into the citrate cycle, which requires the activity of pyruvate dehydrogenase."

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