

Entry Level Clinical Nutrition Part XX

GI Function from a metabolic point of view

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Traditional nutritional/functional medicine viewpoint on the gut

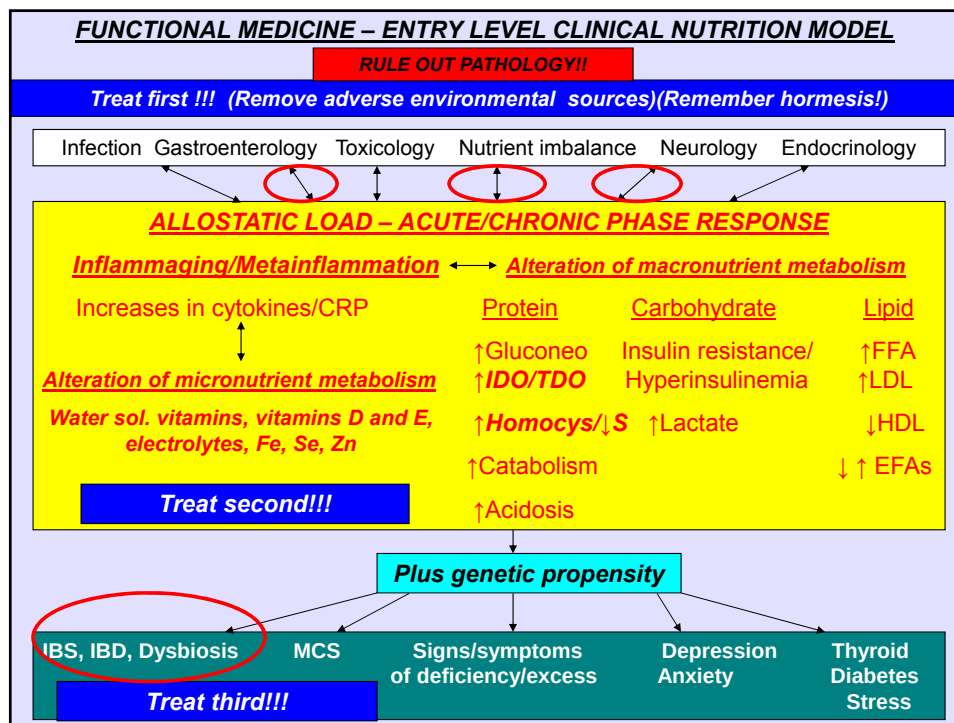
- Somewhat isolated physiologic entity that, when functioning suboptimally, can have a systemic impact.
- Most dysfunction (which includes dysbiosis) is directly caused by environmental stressors and genetic propensity.
- Treatment generally consists of removal of environmental stressors and introducing supplements that directly address function, tissue repair, and/or microflora imbalances.

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Entry Level Clinical Nutrition viewpoint of the gut

In addition to the preceding, the impact of systemic health on the gut needs to be addressed.

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**Quality of life issues are the
major concerns more than
ever now.**

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Summer of Work Exposes Medical Students to System's Ills - NYTimes.com

Page 1 of 3

The New York Times

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September 9, 2009

Summer of Work Exposes Medical Students to System's Ills

By NEENA DESAI

SEATTLE — This summer, medical students from the University of Washington took a long look under the hood of the health care system they are about to inherit, and many returned to campus last week with their eyes wide open and their idealism tempered.

Jacob R. Olsgaard, a third-year medical student, eschewed the traditional summer rotations in favor of a more hands-on experience, treating patients in a rural clinic.

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

The students learned not only to deliver babies and suture wounds, but also to order unnecessary tests as protection against lawsuits, to hector specialists into seeing Medicaid patients, to match patients with prescriptions on Wal-Mart's \$4 list. And they saw firsthand what Mr. Olsgaard called "a tidal wave of chronic disease" — 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. Olsgaard said.

Not surprisingly, the students found the system devalued the work of primary care physicians.

"You had to be reimbursed for your work, but the reimbursement was so low that it was almost impossible to make a living," Mr. Olsgaard said.

For 71 years, the University of Washington School of Medicine has dispatched its rising second-year students across the Northwest to provide primary care in rural or underserved areas. The monthlong program is elective, but a record number of students took part this year — 117 from a class of 216.

The school has a cooperative agreement to train medical students from Alaska, Idaho, Montana and Wyoming, none of which has a medical college of its own. The summer program is one of several vehicles, along with loan forgiveness enticements, designed to lure students back to their home states to practice in areas with a shortage of primary care doctors.

This year, the students set out as negotiations were intensifying in Washington over wholesale changes to the health care system they will soon be joining. Whether there will be improvements to the system remains to be seen, but few students returned thinking there was little to fix.

http://www.nytimes.com/2009/09/09/health/policy/09medschool.html?_r=1&th=&mc=th&... 9/9/2009

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**Nestlé Nutrition Workshop Series
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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."

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Clinical Nutrition (2004) 23, 1256-1266



REVIEW

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

Stig Bengmark

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

Received 23 July 2004

KEYWORDS

Acute phase response;
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Metabolic syndrome;
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;
Cirrhosis;
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, TNF- α 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 acute and "chronic" phase response, and with 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

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

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Key Words

Major depressive disorder · Depressed
acid · Docosahexaenoic acid · Arachidonic
Prostaglandins · Thromboxanes · Lipo
Phospholipase A2 · Cyclo-oxygenase

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. Eicosapentaenoic acid and docosahexaenoic 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.

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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

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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.

Key metabolic imbalances seen with the acute phase response

- Metabolic acidosis
- Loss of lean body mass (sarcopenia)
- Insulin resistance
- Inflamm-aging (Increased innate immunity and decreased adaptive immunity)
- Suboptimal caloric intake and carbohydrate:protein ratio (Refeeding syndrome)
- Gastrointestinal dysfunction/gut atrophy
- Deficiencies of key micronutrients such as zinc, selenium, and vitamin D

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Underlying hypotheses of Entry Level Clinical Nutrition:

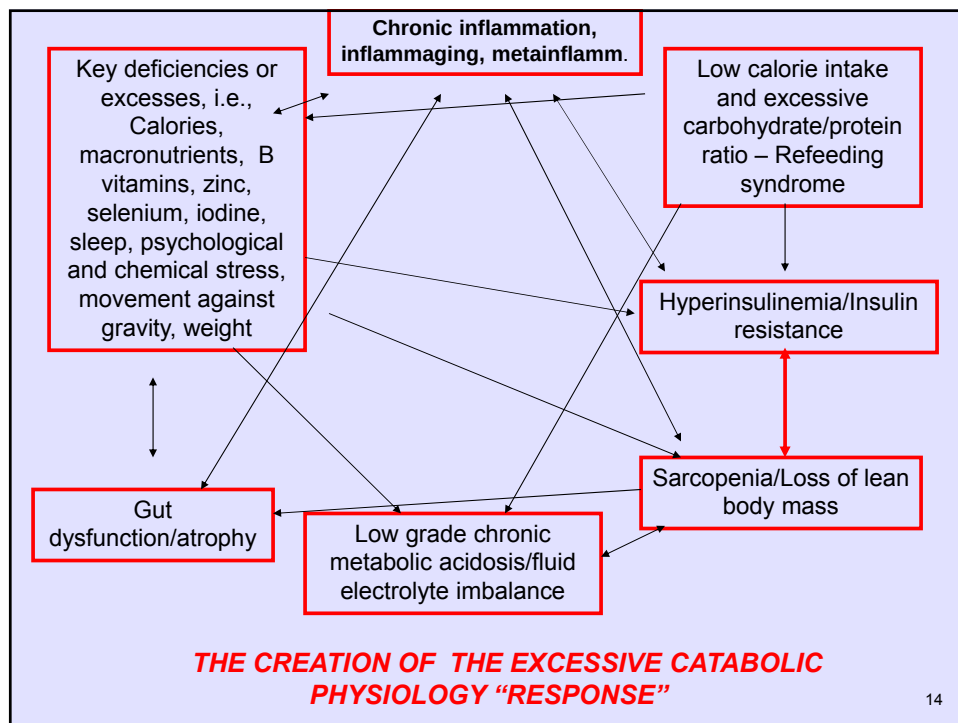
- Chief complaints in chronically ill patients are not diseases but responses that have gone on too long (Allostatic load).
- The metabolic imbalances that combine to form this response have been well defined by critical care nutritionists.

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Entry Level Clinical Nutrition:

A new model of functional medicine that incorporates allostatic load and the “chronic” acute phase response

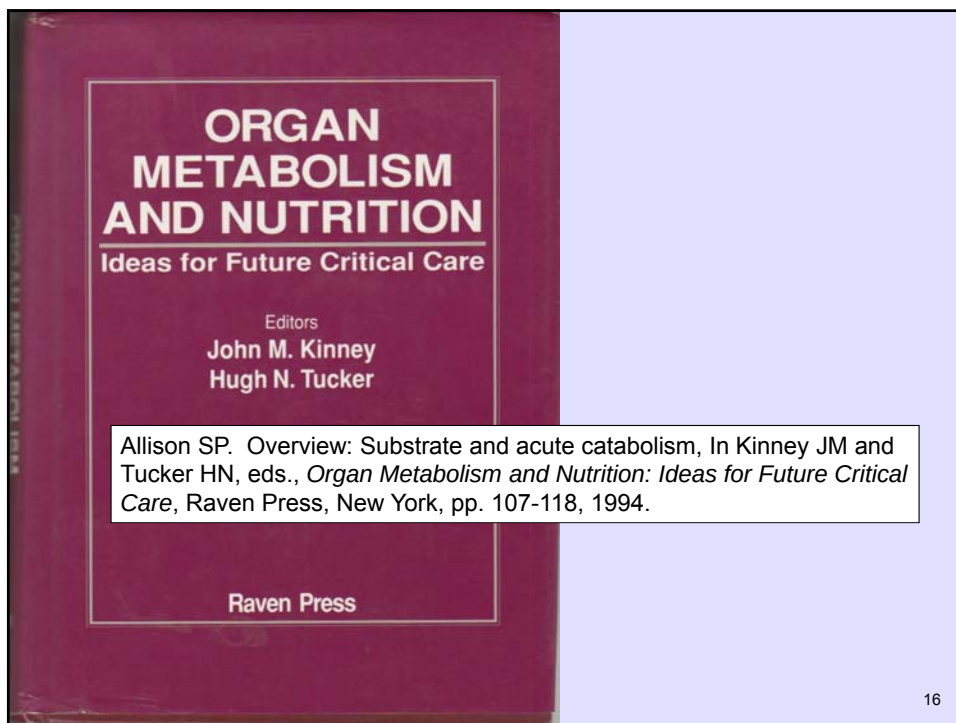
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Systemic health and the gut

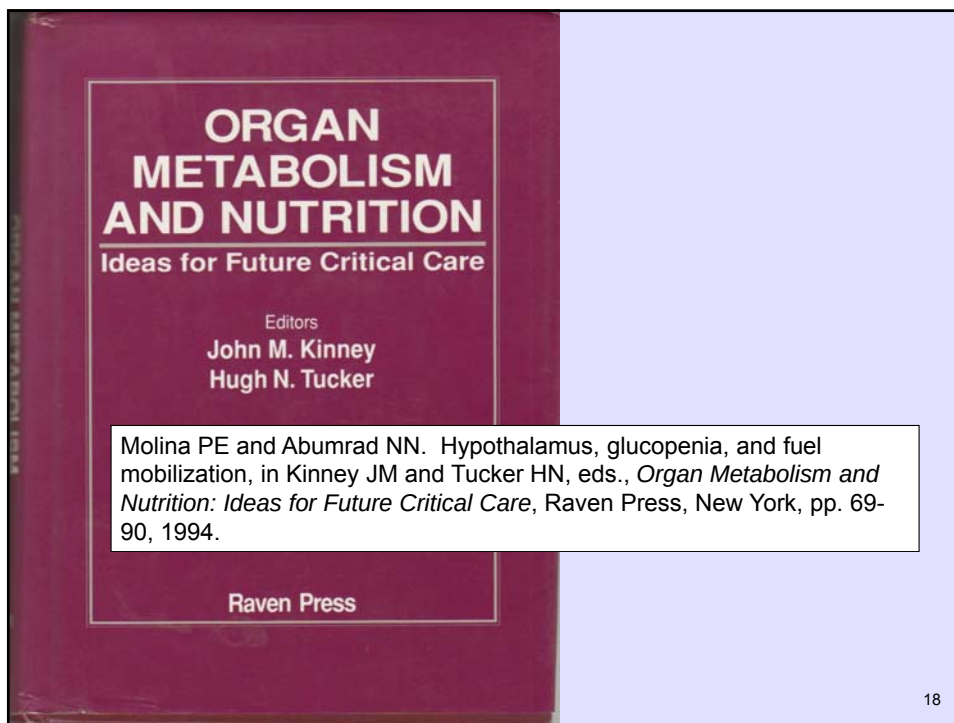
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- “An exciting new observation is the finding that, in response to hypoglycemia, amino acids for gluconeogenesis are released from the gut not from muscle.”
- “It seemed most likely that amino acids are derived from the digestion and absorption of cells shed from the tip of the mucosal villus, although the possibility of a labile pool of amino acids within the mucosa was suggested by Dr. Soeters.”
- “It is clear that, whatever the details of the mechanism, the amino acids are derived from the mucosal rather than the smooth-muscle layer of the gut wall.”

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- “The primary site of this proteolytic response is not skeletal muscle but primarily the gastrointestinal tract, resulting in an increased net release of both essential and nonessential amino acids across the extrahepatic splanchnic tissues.”
- “During this process, the majority of amino acids released by the gut are taken up by the liver, but a significant component, specifically that of branched-chain amino acids, is released into the systemic circulation and taken up by other organs, mainly skeletal muscle.”

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World J. Surg. 24, 705-711, 2000
DOI: 10.1007/s002699910113



Metabolic Response to Severe Surgical Illness: Overview

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Abstract. Severe surgical illness results in metabolic responses that mobilize substrate (amino acids and fatty acids) from body stores to support vital organs, enhance resistance to infection, and ensure wound healing. Central to this response is the release of amino acids from skeletal muscle and protein-wound intensity, at central nervous system, metabolic, and inflammatory responses.

These responses are mediated by the hypothalamus and anterior pituitary to dampen during the later stages of severe surgical illness, and the possibility of hormonal replacement therapy needs to be explored.

Injury and infection/inflammation are the bases for most severe surgical illness. Metabolic changes following these events result in the increased mobilization and utilization of substrate: fatty acids, amino acids, and glucose. These substances or their precursors arise primarily from tissue in the carcass (skeletal muscle and adipose tissue), and this abundance of substrate is provided to ensure the function of essential visceral organs, supply building blocks for tissue repair, and support an upregulated and expanding immunologic system. This sequence of events that redistributes substrate from the carcass to visceral organs is initiated and mediated by alterations in the hormonal environment and, directly or indirectly, by signals elaborated by the inflammatory process (cytokines and other mediators). Complete or partial starvation, immobilization, regional ischemia, acidosis, some therapeutic interventions, and other systemic factors support and amplify these catabolic changes. Exceedingly powerful local factors mediate proliferation of immunologic cells and signal for repair at the site of injury or infection, both highly anabolic processes.

The metabolic response, which has evolved to enhance survival, provides a mechanism to resolve our own biologic problems created by tissue injury or inflammation. We feed ourselves, mobilizing energy from stored body fat and deriving amino acids from our lean body mass. The latter nitrogen-containing substrates are used as building blocks for new protein (both tissue and acute-phase proteins) and provide precursors for gluconeogenesis and

antioxidant defenses. Fat is a stored fuel source readily utilizable for such purposes, but the amino acids arise primarily from skeletal muscle stores, limiting efficient locomotor function, which is

stores fat stores and protein-containing lean tissue. Enter the miracle of modern medicine and contemporary intensive care. Through our therapeutic interventions, we can now resolve many of the problems our body is programmed to solve. We can alter pain perception, modify inflammation, stimulate skeletal muscle anabolism, provide an abundance of substrate (by forced enteral feedings or intravenous infusion of nutrients), create states of hyperoxia, correct acid-base disturbances, and alter mentation, to just name a few therapeutic maneuvers performed in an intensive care unit (ICU). As a result, modern therapy is often at odds with our indelible metabolic program created through evolutionary forces to enhance survival. The tensions caused by our modern medical practice and our innate metabolic program are frequently associated with a variety of iatrogenic complications observed in ICU patients. For example, the injury response results in insulin resistance and mild hyperglycemia. Is it any wonder that patients frequently develop clinically significant hyperglycemia and fatty liver infiltration with the infusion of large amounts of hypertonic glucose-containing nutritional solutions?

How do we resolve these conflicts between modern intensive care and our innate metabolic responses? A conservative approach would be to allow the body to respond to the stresses of severe surgical illness (e.g., following severe burns, fecal peritonitis, multiple trauma) without major metabolic intervention and assume that the evolutionary program would provide for a successful recovery. Although this approach is acceptable in the previously healthy patient undergoing an elective operative procedure without complications, it nevertheless is retrogressive in patients with severe critical illness. Such a treatment course would result in severe wasting and prolonged convalescence, and it is frequently associated with late deaths due to infection. In individuals with severe surgical illness, the mortality rate has significantly decreased because of our new medical knowledge and the in-

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Wilmore DW. Metabolic response to severe surgical illness: Overview. *World J Surg.* 2000;24:705-711

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- “Taken together with the human studies these investigations confirm that protein turnover responds to injury and infection in a manner that redistributes body protein to satisfy the body’s needs.”
- “The synthesis rate is decreased in ‘nonessential’ tissues (e.g., limb skeletal muscle or gut) and is maintained or enhanced in tissues where work is increased (respiratory and cardiac muscle, lung, liver, spleen).”
- “Data generally support the hypothesis that serious surgical illness stimulates enhanced protein turnover.”

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Effects of Stress on Immune Cell Distribution Dynamics and Hormonal Mechanisms¹

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Immune cell trafficking is crucial to the performance of the surveillance as well as effector functions of the immune system. Because immune cells travel between tissues through the bloodstream, the numbers and proportions of leukocytes in the circulation provide an important representation of the state of leukocyte distribution in the body. The studies described here examine significant and selective changes in numbers and percentages of peripheral blood leukocyte subpopulations in the rat. These changes were rapidly induced under conditions of mild acute stress. Stress-induced increases in plasma corticosterone were accompanied by a significant decrease in numbers and percentages of lymphocytes, and by an increase in numbers and percentages of neutrophils. Flow cytometric analysis revealed that B cell, NK cell, and monocyte numbers showed a greater stress-induced decrease than did T cells. All stress-induced changes were observed during the light (inactive) as well as the dark (active) period of the animal's diurnal cycle. Importantly, the stress-induced changes in leukocyte numbers and percentages were rapidly reversed upon the cessation of stress. Furthermore, the effects of stress were largely dependent on adrenal hormones, because the magnitude of the stress-induced changes was significantly reduced in adrenalectomized animals. Moreover, administration of corticosterone to adrenalectomized animals resulted in a close replication of stress-induced changes observed in adrenalectomized animals. These results suggest that endocrine factors released during stress modulate leukocyte trafficking and result in the redistribution of leukocytes between the blood and other immune compartments. Such a redistribution may significantly affect the ability of the immune system to respond to potential or ongoing immune challenge. *The Journal of Immunology*, 1995, 154: 5511–5527.

The appropriate distribution of immune cells between different tissues in the body is crucial to the performance of the surveillance as well as the effector functions of the immune system. The continuous circulation of immune cells from the blood into various immune compartments, and back into the blood, is essential for the maintenance of an effective immune defense network (1). The numbers and proportions of leukocytes in the blood provide an important representation of the state

of distribution of leukocytes in the body and of the state of activation of the immune system. We have established a model in which relatively mild acute stress produces rapid and selective changes in numbers and percentages of blood leukocyte subpopulations (2). The magnitude and specificity of these changes make this a very useful model for studying the kinetics, hormone dependency, and consequences of an effect regulated by the immune system in response to acute stress.

Numerous studies have investigated the effects of environmental and psychological stress on alterations in immune parameters, and in susceptibility to disease (3, 4). However, the majority of these studies have focused on stress-induced changes in immune cell function as opposed to changes in immune cell distribution as a possible mechanism for the effects of stress on the immune system. We have previously hypothesized that an important effect of acute stress may be the regulation of immune cell distribution between different body compartments and that such a redistribution may have significant consequences for the immune response (2). Support for this hypothesis also

Dhabhar FS et al. Effects of stress on immune cell distribution, *J Immunol*, Vol. 154, pp. 5511-5527, 1995.

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- “We hypothesize that an important function of endocrine mediators released under conditions of acute stress may be to ensure that appropriate leukocytes are present in the right place and at the right time to respond to an immune challenge that might be initiated by the stress-inducing agent (e.g., attack by a predator, invasion by a pathogen, etc.).”

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- “The modulation of immune cell distribution by acute stress may be an adaptive response designed to enhance immune vigilance and increase the capacity of the immune system to respond to challenge in immune compartments (such as the skin and epithelia of the lung, gastrointestinal and urogenital tracts), which serve as major defense barriers for the body.”
- “Thus, endocrine mediators released during stress may serve to enhance immune preparedness for potential (or ongoing) immune challenge.”

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Stress-induced redistribution of immune cells—From barracks to boulevards to battlefields: A tale of three hormones – Curt Ritcher Award Winner

Firdaus S. Dhabhar^{a,b,c,d,*}, William B. Malarkey^{e,f},
Eric Neri^a, Bruce S. McEwen^g,
Presented at the 2011 ISPNE meeting

Dhabhar FS et al. Stress-induced redistribution of immune cells - From barracks to boulevards to battlefields: A tale of three hormones – Curt Ritcher Award Winner, *Psychoneuroendocrinology*, published online ahead of print June 2012.

KEYWORDS

KEYWORDS
Psychoneuroimmunology;
Stress;
Immune cell trafficking;
Catecholamine and
glucocorticoid stress
hormones;
Surgical recovery;
Vaccine or cancer
adjuvant;
Interactive immunology

Summary

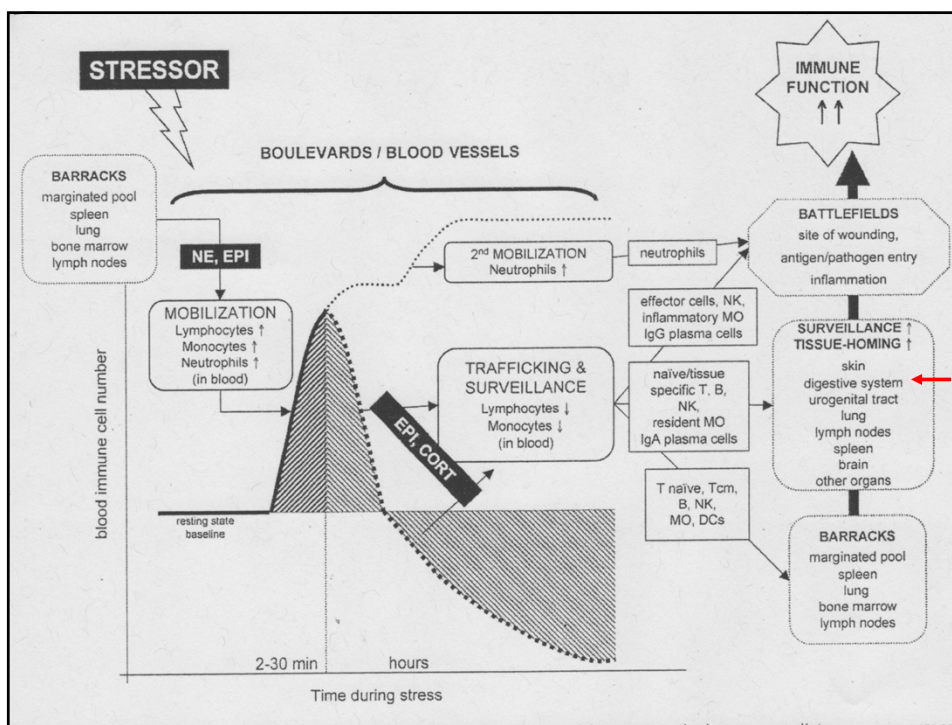
Background: The surveillance and effector functions of the immune system are critically dependent on the appropriate distribution of immune cells in the body. An acute or short-term stress response induces a rapid and significant redistribution of immune cells among different body compartments. The aim of this study was to determine whether the stress response is mediated that directs leukocyte subpopulations to specific target organs during stress, and significantly enhances the speed, efficacy and regulation of an immune response. Immune responses are expressed in compartments that are depleted of leukocytes during/following stress. The experiments described here were designed to elucidate the: (1) Time-course, trajectory, and intensity of leukocyte redistribution; (2) Individual and combined actions of the principal stress hormones, norepinephrine (NE), epinephrine (EP), and corticosterone (CORT), in mediating mobilization or trafficking of specific leukocyte subpopulations; (3) Effects of stress/stress hormones on adhesion molecules, L-selectin and ICAM-1 expression.

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ORIGINAL ARTICLE

Inflammation rather than nutritional depletion determines glutamine concentrations and intestinal permeability

Karel W.E. Hulsewé^{a,*}, Rene W.W.J. van der Hulst^b,
Bernadette A.C. van Acker^c, Maarten F. von Meyenfeldt^d,
Peter B. Soeters^a

Hulsewe KWE et al. Inflammation rather than nutritional depletion determines glutamine concentrations and intestinal permeability, *Clin Nutr*, Vol. 23, pp. 1209–1216, 2004.

Glutamine; Depletion; Amino acid metabolism; Inflammation; Gut; Post-operative; Anthropometric parameters were calculated from 26 patients who

mucosal glutamine concentrations and with increased intestinal permeability. Since nutritional depletion often is associated with (chronic) inflammatory stress, this study was designed to establish the influence of depletion and inflammation on glutamine concentrations and gut barrier function.

Conclusions: Systemic inflammation significantly affects glutamine concentrations and gut permeability, in contrast to the presence of depletion of body cell mass per se. On the other hand, villus morphology is not influenced by changes in systemic inflammatory activity whereas nutritional status possibly does affect villus height.

“To our surprise and in contrast to previous studies no effects of glutamine supplementation were found on plasma and mucosal concentrations, gut permeability and villus height.”

“Unchanged glutamine concentrations after supplementation in humans has been described before.”

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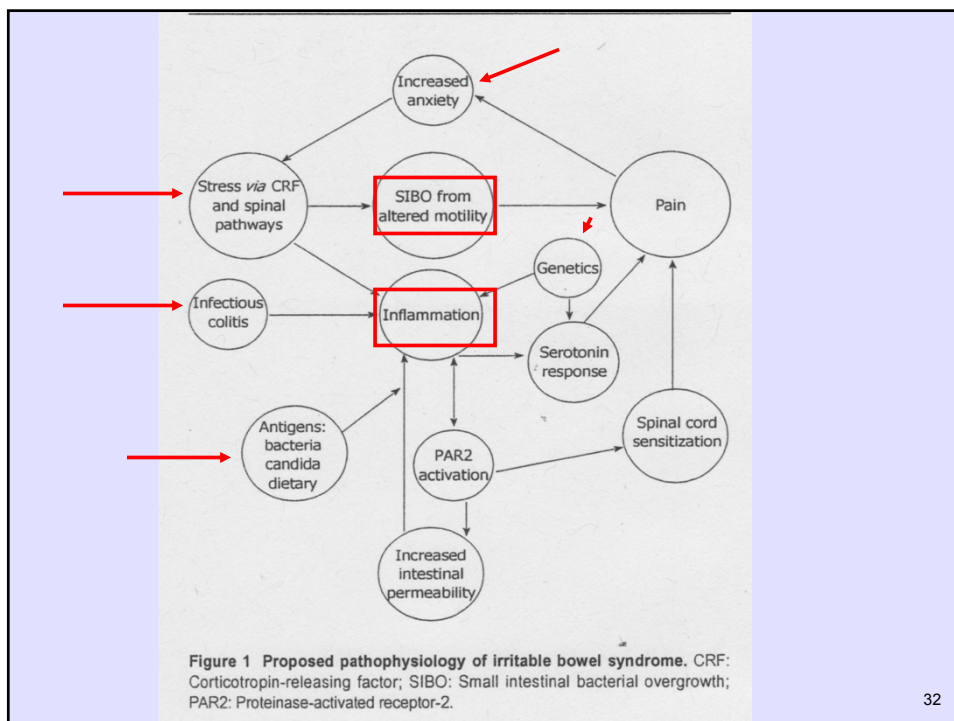
- “In this limited population plasma and mucosal glutamine concentrations as well as gut permeability were consistently correlated with the presence and severity of inflammatory stress in contrast to standard parameters of nutritional depletion.”
- “Systemic inflammation profoundly affects (inter)organ glutamine metabolism, resulting in enhanced release by muscle and lung and increased consumption by other organs.”

- “Another attractive hypothesis is that in times of severe injury or inflammatory stress, decreases in membrane potential result in release of glutamine.”
- “Endotoxaemia and inflammatory mediators have been shown to decrease the resting membrane potential.”
- “This is the result of marked increases in intracellular sodium and chloride concentrations and a decrease in intracellular potassium.”

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- “Since transport of glutamine into the cell depends on this membrane potential, this process can lead to a net efflux of glutamine out of the cell into the plasma compartment.”
- “This phenomenon can explain the sudden and unalterable decrease of intracellular glutamine seen during conditions of severe inflammatory stress.”

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Therapeutics: Protein and amino acids

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Original article

Absence of post-prandial gut anabolism after intake of a low quality protein meal

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SUMMARY

Background: Gut health relies on a diet with a high digestibility and quality. Limited data are available on

FOODS THE "GUT" OF THE PROTEIN.

Conclusions: In the post-prandial phase after intake of a low quality protein meal, net anabolism in the healthy intestine is absent. It is likely that the intestine responds with a net breakdown of endogenous (skeletal) proteins to secure amino acid availability for the body. Addition of the first limiting essential amino acid to this meal improved protein anabolism in the intestine. Protein quality of a meal is related to the anabolic response of the intestine during the meal.

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1. Introduction

A healthy gut is important for overall body health. The gut controls digestion and absorption of dietary proteins and amino acids (AA), and therefore regulates the availability of substrates to the liver, muscle and other organs. Although the intestine in the prandial phase receives AA both from the small intestinal luminal side and via the systemic circulation, it has been observed that the intestine preferentially utilizes AA from the diet for its own metabolism. Luminal contact with nutrients is very important in the regulation of intestinal protein metabolism. Feeding is known to rapidly stimulate protein synthesis in the intestine^{1,2} as reflected by the large intestinal extraction during enteral feeding. Approximately 50% of dietary amino acid intake is used by the portal drained viscera, but this percentage varies between different amino acids and diets.^{3–6}

Stimulation of overall protein anabolism by protein meals is reflected by the rapid stimulation of intestinal protein synthesis.^{7–10} This means that the protein synthesizing capacity of the intestine depends on the same factors as whole body anabolism like the quality of the dietary protein source and the presence of carbohydrates in the protein meal.¹¹ We postulated that a high-quality dietary protein source stimulates amino acid utilization in the intestine for protein synthesis.¹² After temporary retention of dietary protein as newly synthesized protein in the intestine, a tapered release of AA after the meal will ensure a more prolonged supply of AA to other tissues of the body. In this way, the intestine can act as a "buffer" or what is called, the table protein pool.¹³

A low quality protein meal is defined as a meal containing a normal amount of macronutrients and a protein source with low digestibility or a deficient/low amount of essential (indispensable) amino acids (EAA). In disease states, a meal with a low amount of functional and/or conditional EAA is also considered as low quality.^{1,12,13} It is hypothesized that intake of low quality food plays

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- “Although the intestine in the prandial phase receives amino acids both from the small intestinal luminal side and via the systemic circulation, it has been observed that the intestine preferentially utilizes amino acids from the diet for its own metabolism.”
- “Feeding is known to rapidly stimulate protein synthesis in the intestine as reflected by the large intestinal extraction during enteral feeding.”

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- “Approximately 50% of dietary amino acid intake is used by the portal-drained viscera, but this percentage varies between different amino acids and diets.”
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- “We postulated that a high-quality dietary protein source stimulates amino acids utilization in the intestine for protein synthesis.”
- “A low quality protein meal is defined as a meal containing a normal amount of macronutrients and a protein source with low digestibility or a deficient/low amount of essential (indispensable) amino acids (EAA).”

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“In disease states, a meal with a low amount of functional and/or conditional EAA is also considered as low quality.”

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What happens with a low quality protein meal?

- “In the present study, we examined the effects of a low quality protein meal (gelatin protein in a protein carbohydrate meal) on intestinal metabolism, and whether improving the biological value of this meal (by adding tryptophan) would affect intestinal, hepatic metabolism and systemic availability of nutrients.”

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- “We observed that after intake of a low protein quality meal (Gel), the healthy intestine released into the portal vein an equivalent amount of amino acids that was given with the meal together with a substantial amount of the deficient tryptophan.”
- “We also observed a tendency that more EAAs were released to the portal system than consumed.”

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“It is likely that the intestine responds to such a meal by net breakdown of endogenous (labile) gut protein.”

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- “...adding the deficient amino acid tryptophan to the meal resulted in normalized intestinal net balance but not the systemic EAA and urea levels, suggesting improved intestinal metabolism without improved whole body response.”

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Conclusions

- “After a low quality protein meal, the healthy gut is not able to generate an anabolic response.”
- “Our data suggest that in this situation, the intestine breaks down its own *labile* protein pool to fulfill the increased systemic amino acid demand.”

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- “Supplementation of the deficient essential amino acid does improve intestinal metabolism, but the next limiting amino acid will determine the quality of the ingested protein for the remainder of the body.”
- ***“It is likely that chronic intake of low quality proteins can lead to exhaustion of the labile intestinal protein pool, possibly resulting in reduced function of the gut and susceptibility to intestinal and other disease states.”***

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- “These data...support the hypothesis that the total amino acid profile of a protein meal determines the biological value of the meal for the intestine and is independent of the sources of the proteins.”
- “Therefore, it is important particularly in vegetarian diets that a meal contains different protein sources to prevent that a complete meal becomes of very low quality because of one deficient EAA.”

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- “The lower liver amino-acid uptake and lower urea efflux suggest less nitrogen wastage.”
- “The gut appears to be an important site for nitrogen retention induced by the addition of carbohydrates to a protein meal.”
- “Changes in insulin levels may play an important role in the phenomenon.”

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LEADING ARTICLE

The protein sparing function of the gut and the quality of food protein

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Several studies have revealed that the body accumulates Nitrogen after a meal and loses Nitrogen in between meals. This can be proven beyond any doubt, just by carefully measuring Nitrogen balance, if we take into account, that the changes in free amino acid pool content cannot explain the Nitrogen balance changes. In

the influence of factors that were known to either decrease or increase plasma ammonia levels and the ammonia generating potential of the gut. As might be expected, a simulated bleeding (ingesting erythrocytes in the gut) in pigs gave rise to an increase in net ammonia production by the intestine, increased systemic plasma

the all de spe th m after the meal there is a net accumulation of protein, whereas in the post-absorptive state a net loss of protein takes place (1, 2).

It has been assumed that this 'labile protein pool' predominantly resides in muscle, probably because of the intuitive viewpoint, that muscle is a large organ and therefore is the most likely organ, in which this protein is temporarily stored and from which it is subsequently released. The logic of this feeling is weak, because the fractional synthesis rate of muscle, i.e. the percentage of the total muscle protein pool that is newly synthesized per day, is very low. As a consequence it can be calculated, that the protein accumulated during and after a meal, can only be present in muscle to a limited degree (3). Much more likely, is the suggestion that protein accumulation takes place in the splanchnic area, as protein turnover in this area can change very rapidly and substantially, because the fractional synthesis rate is much higher than in muscle, and because changes in protein synthetic rate can occur within hours. Proof for this suggestion has not yet been furnished directly, but indirect evidence is available, that will be reviewed in this article. Another question that will be addressed is what the potential role of this labile protein pool is.

Postprandial Nitrogen accumulation in experimental animals and humans

Our interest in protein turnover in the splanchnic area dates back to the seventies and eighties when we studied

to less than half normal levels. Also, the apparent digestibility of blood protein was much better than that of normal protein, of which much less appeared in the portal vein within 4 h after ingestion. Scrutiny of the amino acid sequence of Hemoglobin showed that it did not contain any isoleucine, and that Albumin and Globulin contained very little.

As a consequence of this observation we developed the hypothesis that a protein with an unbalanced amino acid composition like Hemoglobin would, when degraded, yield an unbalanced amino acid mixture, which would be unfit to serve as substrate for protein synthesis inside the gut wall, and would therefore, quickly appear in the portal vein as free amino acids.

High free amino acid levels in the portal blood reaching the liver are known to stimulate ureagenesis, which may explain the high plasma urea levels after gastrointestinal bleeding. If the hypothesis is true, 'balancing' the amino acid mixture, in case of Hemoglobin by supplementing isoleucine, would promote protein synthesis in the gut wall, leading to a slower appearance of amino acids in the portal vein, and consequently to decreased ureagenesis. In a multi-catheterized pig model that we developed more than ten years ago we confirmed this hypothesis, by demonstrating, that isoleucine supplementation to erythrocytes, ingested in the gut, did indeed decrease the net appearance of amino acids and the total alpha-amino acid level in the portal vein, and decreased liver urea production. These findings led to further specification of the hypothesis, namely, that the more

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- "...consensus exists that indeed after the meal there is a net accumulation of protein, whereas in the post-absorptive state a net loss of protein takes place."
- "It has been assumed that this 'labile protein pool' predominantly resides in muscle, probably because of intuitive viewpoint, that muscle is a large organ and therefore is the most likely organ, in which this protein is temporarily stored and from which it is subsequently released."

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- "The logic of this feeling is weak, because the fractional synthesis rate of muscle, i.e. the percentage of the total muscle protein pool that is newly synthesized per day, is very low."
- "As a consequence it can be calculated, that the protein accumulated during and after a meal, can only be present in muscle to a limited degree."
- Much more likely, is the suggestion that protein accumulation takes place in the splanchnic area, as protein turnover in this area can change very rapidly and substantially, because the fractional synthesis rate is much higher than in muscle, and because changes in protein synthetic rate can occur within hours."

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Thank you!!

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