

Entry Level Clinical Nutrition Part XV

Inflammation: Inflammaging

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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

September 9, 2009

Summer of Work Exposes Medical Students to System's Ills

BY JACOB R. OLSGAARD

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 second-year medical student, said he was struck by the "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 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.

"You had to be able to do everything, from suturing to ordering tests, and you were often the only one who could do it," Mr. Olsgaard said.

For 21 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 givers.

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=&cmc=th&... 9/9/2009

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**Nutrition and
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**Luc Cynober
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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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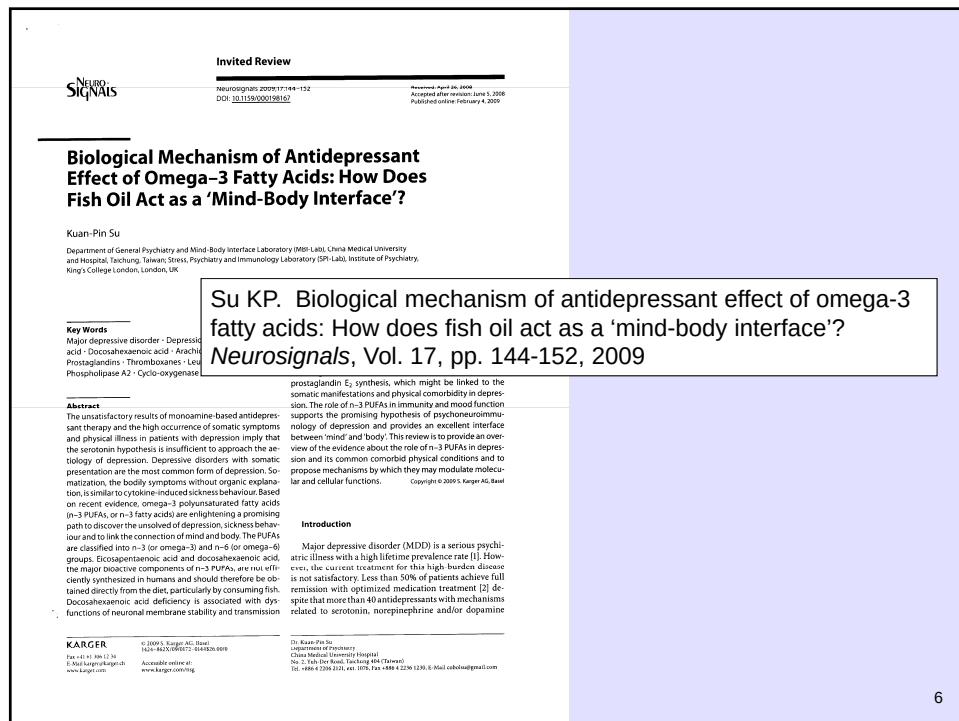
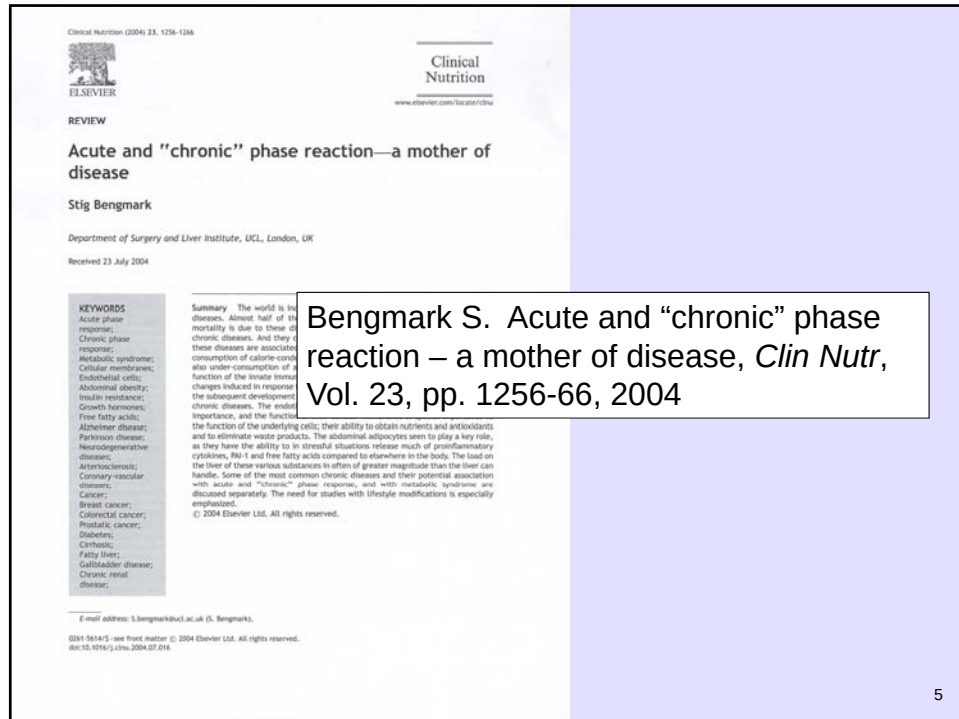


Table 1. Overlapping of symptoms of acute sickness behaviour associated with IFN- α therapy and the somatic symptoms in MDD

Symptoms	Prevalence in IFN- α therapy ^a , %	Prevalence in MDD ^b , %
Fatigue/asthenia	39–90	73
Headache	27–67	33 ^e
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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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:

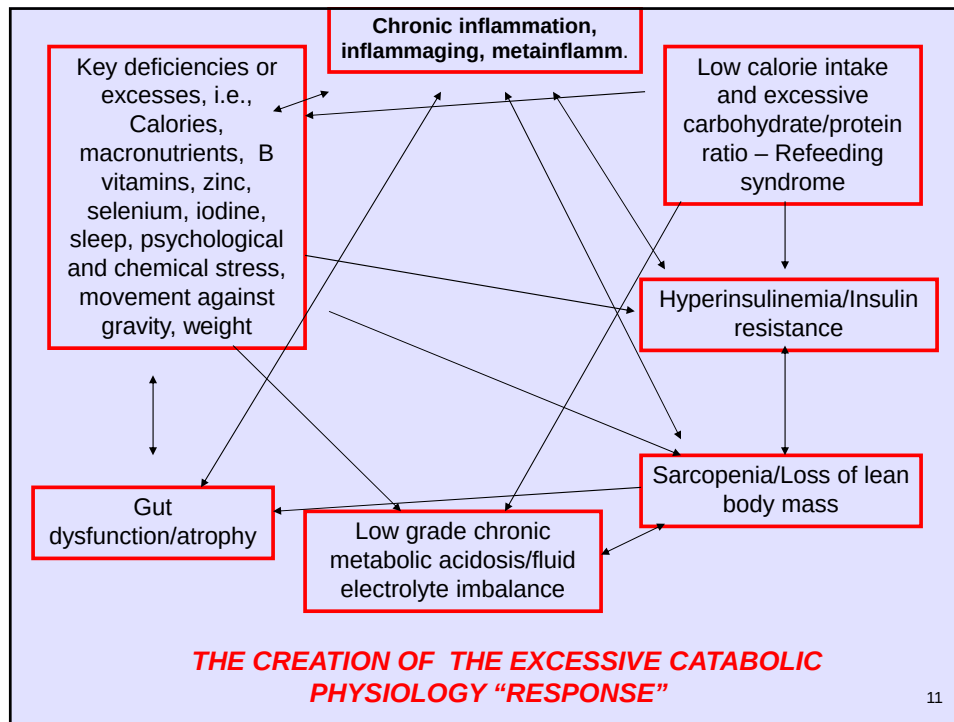
- Chief complaints in chronically ill patients are not diseases but responses that have gone on too long (Allostatic load).
- The metabolic imbalances that combine to form this response have been well defined by critical care nutritionists.

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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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Inflammation Research

Commentary

Exploring the complex relations between inflammation and aging (inflamm-aging): anti-inflamm-aging remodelling of inflamm-aging, from robustness to frailty

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Sergio G. Exploring the complex relations between inflammation and aging (inflamm-aging): anti-inflamm-aging remodelling of inflamm-aging, from robustness to frailty, *Inflamm Res*, Vol. 57, pp. 558-563, 2008.

Abstract
The inflammatory response is the main defense against pathogens and constitutes: a) the main specific response and counterbalance to “inflammaging” (“anti-inflammaging”), b) an explanation for the well known paradox of immune-senescence, i.e. the coexistence of inflammation and immunodeficiency, as well as c) a complex mechanism of remodeling elicited by inflammaging, explaining the long and winding pathophysiological road that goes from robustness to frailty.
Indeed, the phenomenon of anti-inflammaging, mainly exerted by cortisol, with the passage of time becomes the cause of a marked decline of immunological functions, and its coexistence with the increased levels of pro-inflammatory cytokines of inflammaging, ultimately have negative impacts on metabolism, bone density, strength, exercise tolerance, the vascular system, cognitive function, and mood. Thus inflammaging and anti-inflammaging together determine many of the progressive pathophysiological changes that characterize the “aged-phenotype”, and the struggle to maintain robustness finally results in frailty.
The same consequences also result the age-dependent decline of dehydroepiandrosterone (DHEA).
Key words: Inflammaging – Hypothalamic-pituitary-adrenocortical (HPA) axis – Cortisol and aging – Oxidative stress and aging – Dehydroepiandrosterone (DHEA).
Correspondence to: G. Sergio

Increased circulating levels of pro-inflammatory cytokines (primarily IL-1, IL-6, TNF- α , and also IL-12, IFN- α , IFN- γ) (3) (6). It is the final result of the counterbalance between pro- and anti-inflammatory cytokines (IL-4, IL-6, IL-13, IL-10) that ultimately sees an up-regulation of the pro-inflammatory response (7).
A key role is played by polymorphisms in the promoter regions of genes encoding these proteins (7), i.e. the polymorphisms shape the rate of translation. Indeed, such polymorphisms likely contribute to the rate of human aging and to the rate that pre-symptomatic pathologic changes accumulate for most age-associated disorders. Specifically, genetic variants that tend to increase production of anti-inflammatory cytokines and those that decrease the production of pro-inflammatory cytokines have been associated with successful aging and are more common among persons attaining oldest ages (7).
One striking feature of cytokines is their ability to exert many different actions, i.e. “pleiotropy”. Conversely, many different cytokines exert the same biological actions (i.e. “redundancy”) (8) (9). These properties are presumably mediated by the widespread and overlapping distributions of cytokine receptors on numerous cell types including neuronal cells, and by the ability of signal transduction mechanisms activated by cytokines to alter expression of a wide variety of target genes (10) (11).
Reactive Oxygen Species (ROS) are released during inflammation. They cause both oxidative damage and elicit the

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- “The term ‘Inflamm-aging’ was coined by Franceschi and his group to denote the up-regulation of the inflammatory response at older ages, the resultant low-grade chronic systemic pro-inflammatory state, and that this state underlies most age-associated diseases.”
- “It is mediated by increased circulating levels of proinflammatory cytokines (primarily IL-1, IL-6, TNF-alpha, and also IL-12, IFN-alpha, IFN-beta).”

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- “It is the final result of the counterbalance between pro- and anti-inflammatory cytokines (IL-4, IL-6, IL-13, IL-10) that ultimately sees an up-regulation of the pro-inflammatory response.”
- “Reactive Oxygen Species (ROS) are released during inflammation.”

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“They cause both oxidative damage and elicit the release of additional ‘inflammaging-cytokines’, perpetuating a vicious cycle resulting in a chronic pro-inflammatory state where pathophysiological changes, tissue injury and healing mechanisms proceed simultaneously and damage slowly accumulates asymptotically over decades.”

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- “One important and essentially inevitable response to inflammaging is neuro-endocrine activation: numerous cytokines have receptors on neuronal cells able to influence the secretory activity of the HPA axis.”
- “The net final result is a cytokine-induced increase in glucocorticoid secretion, which, in turn, inhibits cytokines’ secretion by decreasing cytokines’ mRNA expression and stability.”

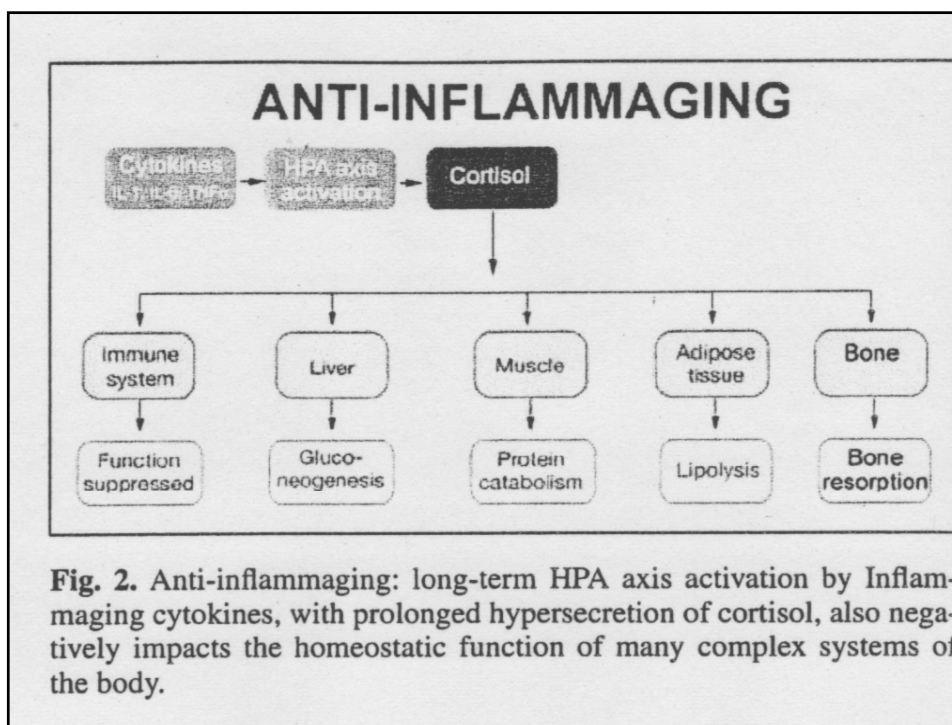
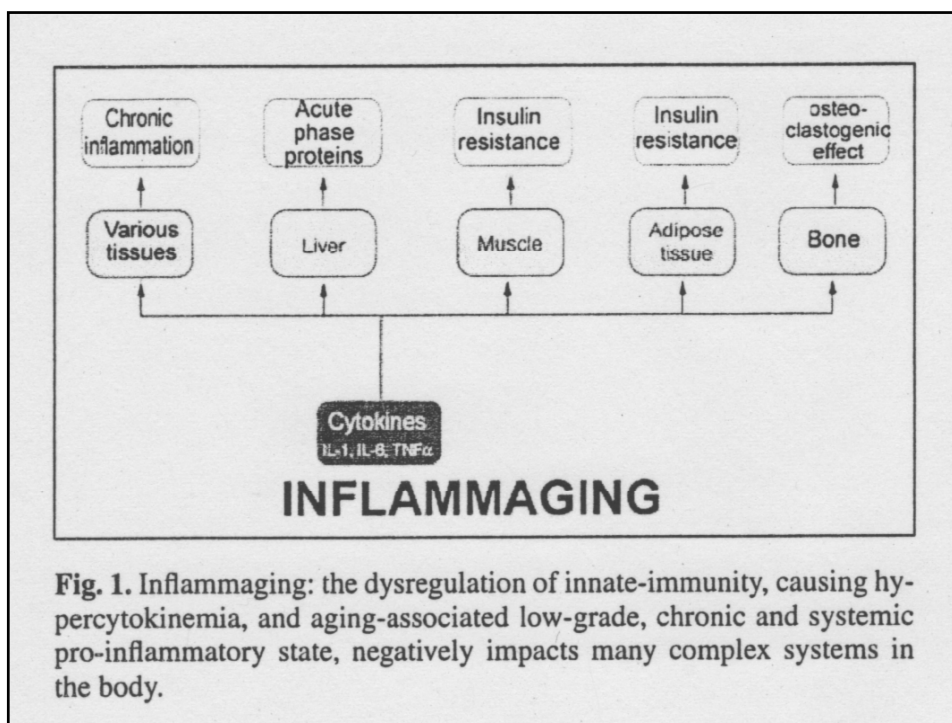
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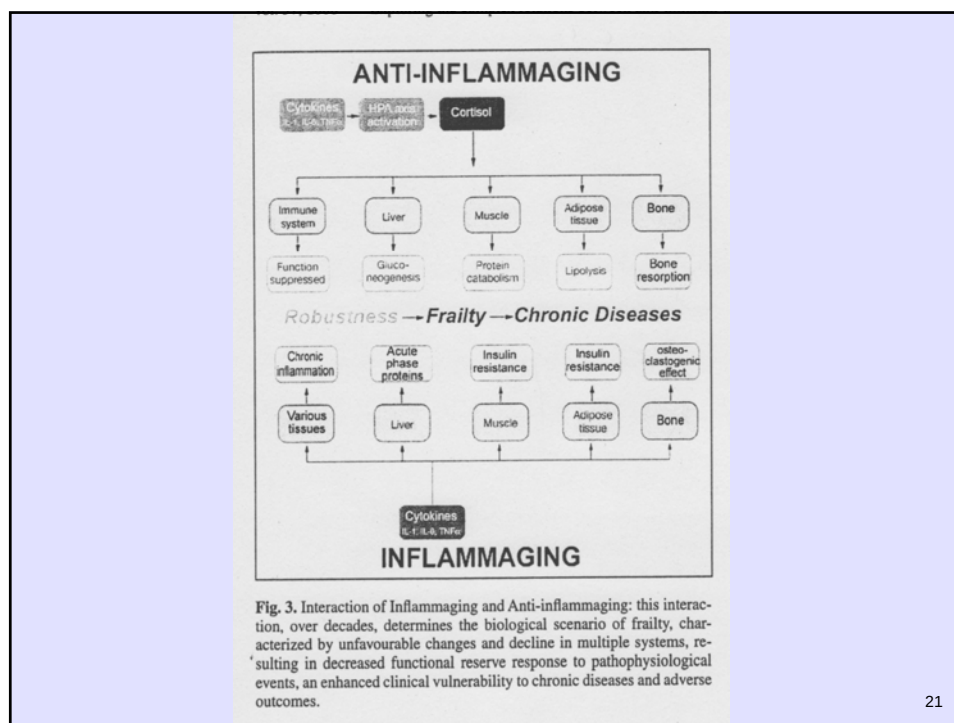
- “Thus an activation of the HPA axis with cortisol secretion by the adrenals in response to inflammaging cytokines is likely providing a sort of adaptive defense response, acting as a potent immunoregulator and anti-inflammaging agent that can prevent the immune system from overacting, causing injury and damaging tissues.”
- “Aging is associated with a complex remodelling of the immune system often in the direction of apparently decreased immune competence, and is therefore associated with the paradox co-existence of chronic inflammation (evidence of a hyperactive immune system) and immunodeficiency.”

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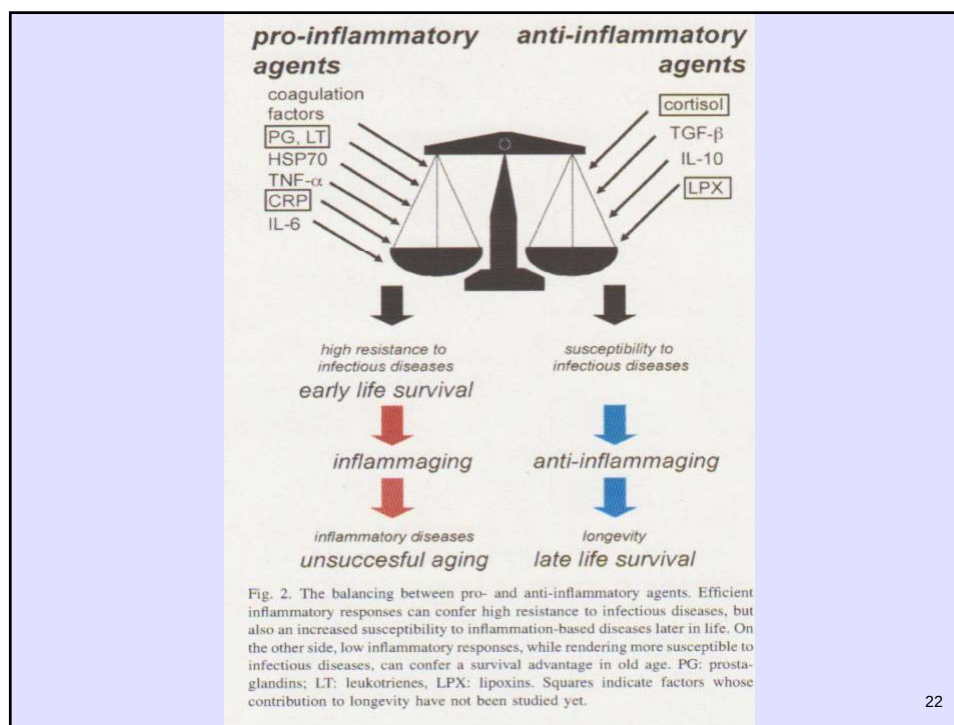
“The Inflammaging/anti-inflammaging model herein proposed gives a more satisfactory and comprehensive interpretation of the apparent paradox of aging-associated inflammation and immunodeficiency: chronic HPA activation and increased cortisol levels elicited by inflammaging can modulate the activity of immune cells to produce immunosuppression (also by apoptotic mechanisms) and contribute to the lymphopenia that characterizes elderly persons.”

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- “Both innate immunity and clonotypical adaptive immunity appear to be *hyper-stimulated* in old people, owing to decades of evolutionary unpredicted antigenic exposure, mostly due to sub-chronic bacterial and viral infections;”
- “The end result of such stimulation is *inflammaging*, i.e. an *activation* of innate immunity, involving the most ancestral type of responses, mostly based on macrophage, as well as of clonotypical immunity.”

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- “The latter is characterized by a filling of the immunological space with functionally inefficient megaclones of memory T cells directed towards antigens of common pathogens (CMV, EBV), accompanied by an extreme reduction of naïve, antigen not-experienced T cells. This situation highly reduces the capability of the organism to respond to new antigenic challenges;”

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- “The inflammatory response which develops lifelong should be considered *physiological and beneficial*, but it becomes *detrimental* with increasing age likely because the physiological and anti-inflammatory mechanisms (*anti-inflammaging*) fail on the long run to neutralize all the inflammatory processes that are continuously triggered and impact on the organism;”

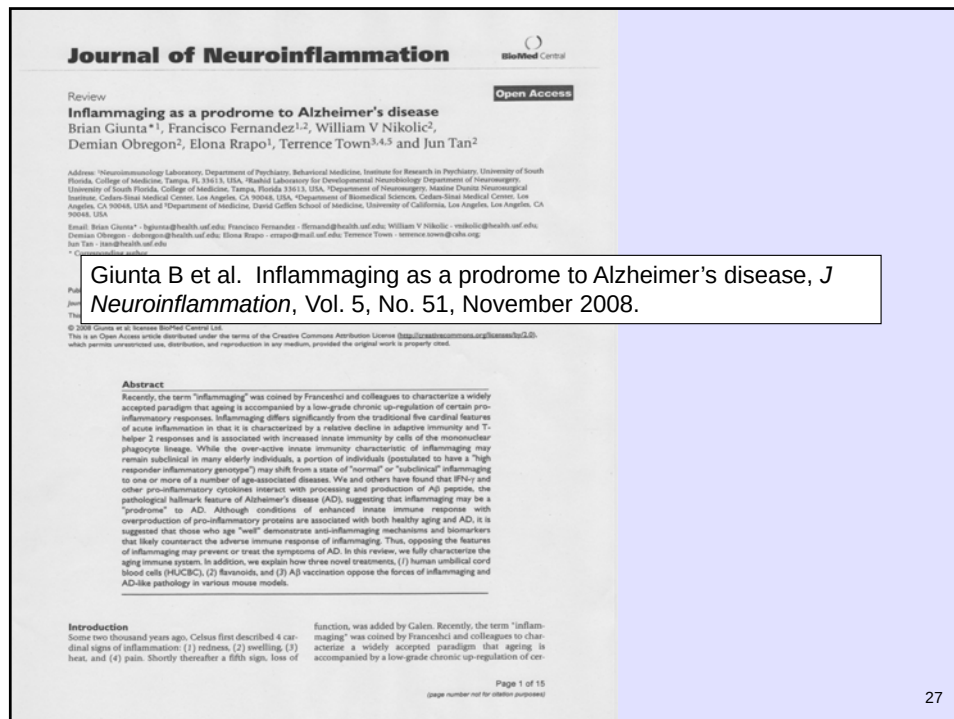
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- “This hypothesis anticipates a major role in the development of frailty and age-related pathologies not only for an excessive inflammatory stimulation, but also for an *insufficient anti-inflammatory response*;”
- “*Anti-inflammation* includes anti-inflammatory cytokines and cytokine inhibitors, but also stress hormones (glucocorticoids) and other molecules (lipoxin, annexin 5)...”

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- “Recently, the term ‘inflammaging’ was coined by Franceschi and colleagues to characterize a widely accepted paradigm that ageing is accompanied by a low-grade chronic up-regulation of certain inflammatory responses. Inflammaging differs significantly from the traditional five cardinal features of acute inflammation in that it is a (a) low-grade, (b) controlled, (c) asymptomatic, (d) chronic, and (e) systemic state of inflammation. This systemic inflammatory response is evidenced by increased serum levels of proinflammatory cytokines (IL-6, IL-15, IL-8) and other inflammatory biomarkers, such as coagulation factors.”

- “Additionally, subclinical infection with common viruses such as cytomegalovirus (CMV) is a hallmark feature of inflammaging.”
- “According to Franceschi’s original description of inflammaging, innate immunity progresses to a chronically active state secondary to exhaustion of the more evolutionary recent adaptive (specific) immune system. This exhaustion is in large part due to age-associated reduction of T-cells for various reasons including thymic involution, as well as fewer bone marrow early progenitor B cells.”

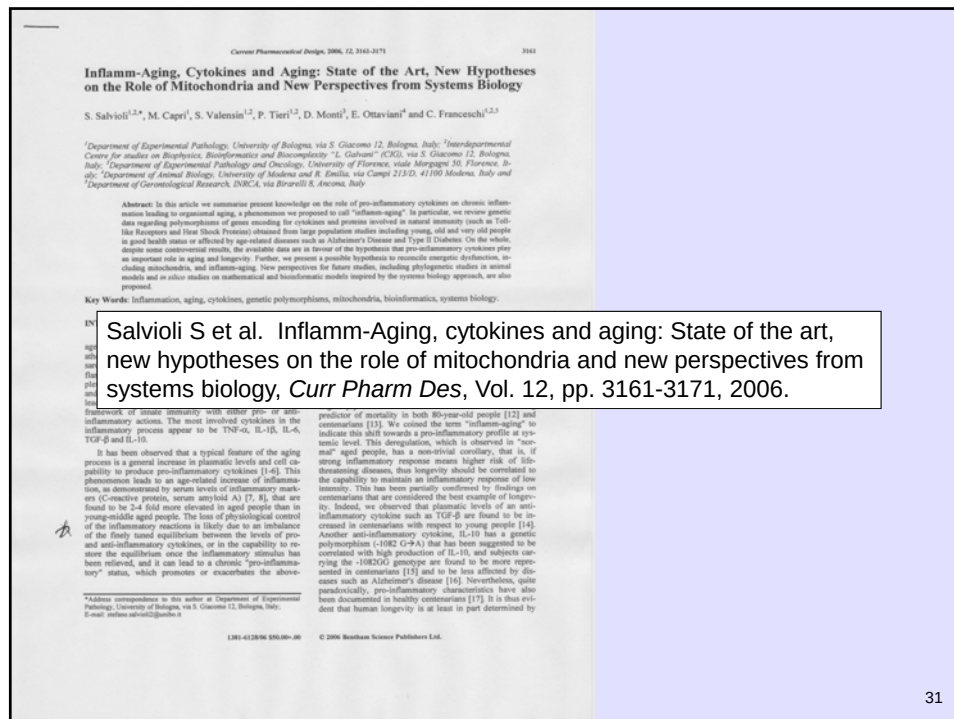
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“The net result of this is (1) to reduce adaptive immunity to previously encountered pathogens, and (2) to weaken the host adaptive immune response to novel pathogens due to a reduction in the diversity of the antigen-recognition repertoire with age.”

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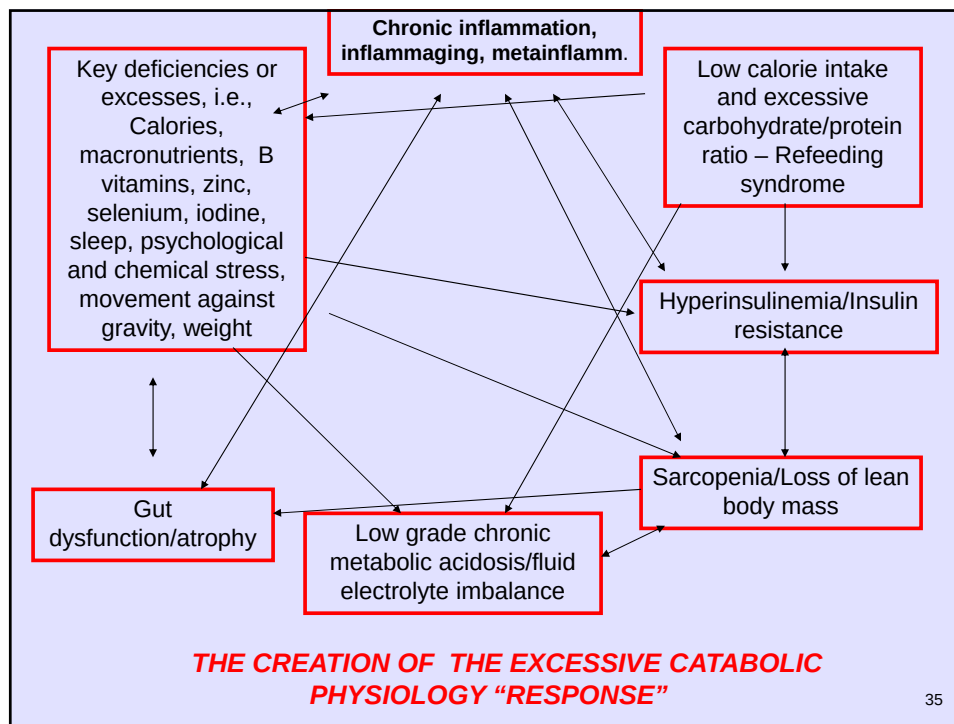
- “...it is likely that an altered inflammatory response can be the result of a life-long exposure to stresses such as antigens, as well as chemical and physical agents that threaten the integrity of the organism.”
- “In this perspective, chronic inflammatory response would be nothing than an attempt of the organism to cope (unsuccessfully) with stressing agents and to restore homeostasis.”

Diagnostic considerations

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- Physical examination – Eczema, psoriasis, etc.
- History
- C-reactive protein
- Low normal WBC
- %polys and lymphs almost equal
- Elevated monocytes
- Sedimentation rate
- Food sensitivities
- Serum 25 (OH)D

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- Sleep
- Movement against gravity
- First morning urine pH
- Lean body mass
- 3-day dietary history (Caloric intake, deficiencies of key macro- and micronutrients)
- Fasting glucose, hemoglobin A1C
- Gut dysfunction
- Toxicology
- Salivary cortisol

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Treatment considerations

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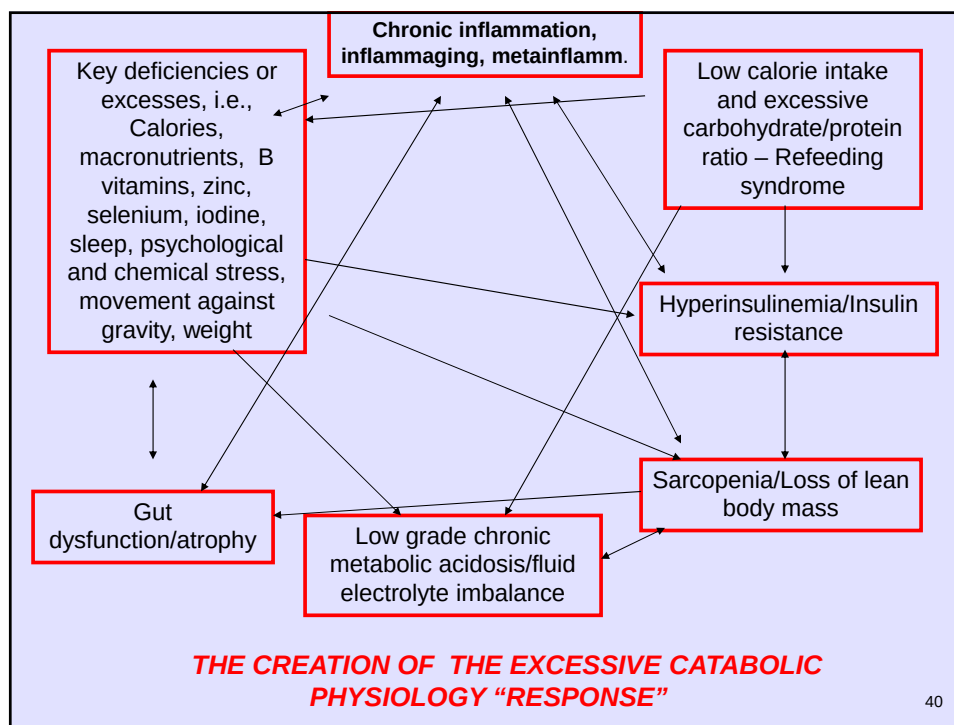
Foundational approaches

- Food sensitivities
- Sleep
- Movement against gravity
- Optimization of GI function
- Vitamin D
- EPA/DHA
- Herbal antiinflammatory substances, i.e., curcumin, boswellia, etc.
- Proteolytic enzymes

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What are the underlying metabolic issues?

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- Sleep
- Movement against gravity
- First morning urine pH
- Lean body mass
- 3-day dietary history (Caloric intake, deficiencies of key macro- and micronutrients)
- Fasting glucose, hemoglobin A1C
- Gut dysfunction
- Toxicology
- Salivary cortisol

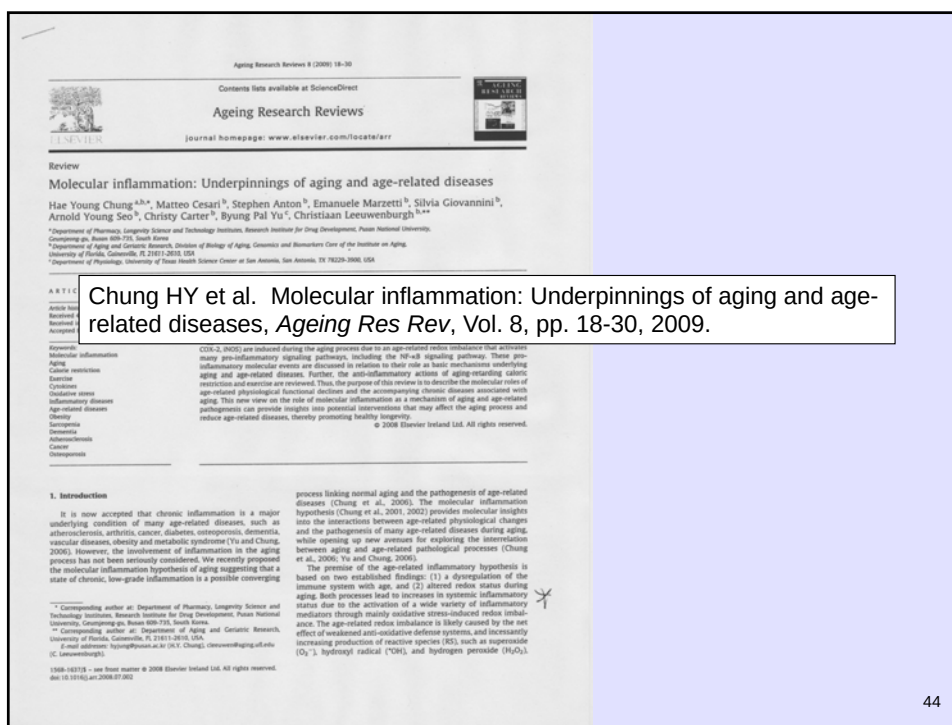
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**Chronic inflammation is more
than just an issue of immune
dysregulation**

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It also involves suboptimal
oxidant/antioxidant balance

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- “The premise of the age-related inflammatory hypothesis is based on two established findings: (1) a dysregulation of the immune system with age, and (2) altered redox status during aging.”
- “Both processes lead to increases in systemic inflammatory status due to the activation of a wide variety of inflammatory mediators through mainly oxidative stress-induced redox imbalance.”

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- “The age-related redox imbalance is likely caused by the net effect of weakened anti-oxidative defense systems, and incessantly increasing production of reactive species (RS), such as superoxide (O_2^-), hydroxyl radical ($\cdot OH$), and hydrogen peroxide (H_2O_2), reactive nitric oxide (NO), peroxynitrite ($ONOO^-$) and reactive lipid aldehydes.”

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“Overproduced and unregulated RS during aging are a major causative factor in the activation of immune systems, as exemplified in over-reactive macrophages in the inflammatory process.”

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ORIGINAL COMMUNICATION

Effects of antioxidants on immune system ageing

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One of the most widely accepted theories proposed to explain ageing is the free radical theory, according to which oxygen-derived free radicals cause age-related impairment through oxidative damage to biomolecules, with mitochondria being the main target of free radical attack. Since oxygen radicals are needed for many metabolic and physiological processes, an equilibrium between radical production and their antioxidant-linked inactivation is required to preserve health. Thus, senescence is the result of an imbalance between these two processes. In this review, we discuss the role of oxidative stress and ageing, their functions in our own, have at by oxidative stress predictor, the per achieve a healthy European Journal.

De la Fuente M. Effects of antioxidants on immune system ageing, *Eur J Clin Nutr*, Vol. 56, Suppl 3, pp. 55-58, 2002.

Keywords: ageing; antioxidants; immune system

The free radical theory of ageing

More than 300 theories have been proposed to explain the ageing process (Medvedev, 1990), and although none has yet been generally accepted by gerontologists, one of them, namely the free radical theory, proposed by Harman in 1956, has steadily gained acceptance as a plausible explanation of the primary chemical reactions involved in ageing. Presently, due in part to further contributions by authors such as Harman (1986) and Miquel (1990), the free radical (or oxygen stress) theory is almost generally accepted. According to this molecular theory, oxygen-derived free radicals are responsible (due to their high reactivity) for the age-associated damage at the cellular and tissue levels through the oxidative modification of biological molecules (lipids, proteins and nucleic acids), which leads to functional impairment. Moreover, mitochondria, in which there is a continuous generation of free radicals throughout cell life, and especially mitochondrial DNA, are key targets of free radical attack. Cells which use oxygen and consequently

produce reactive oxygen species (ROS) had to evolve complex antioxidant defence systems to neutralize ROS and protect themselves against free radical damage. Thus, the increasing oxidative stress in ageing seems to be a consequence of the imbalance between free radical production and antioxidant defences with a higher production of the former (Santoro et al., 2000).

Ageing and the immune system

A wealth of data support the view that the above mechanisms are associated with a decline of many physiological functions, including those of the immune system, which leads to a loss of homeostasis. The importance of senescence of the immune system is evidenced by the high incidence of tumours and the greater susceptibility to infections from pathogens shown by the aged. Moreover, aged subjects who maintain their immune functions at an exceptionally high level probably have a long life span and may even become centenarians (Pawelec et al., 1995). Thus, the immune system has been proposed as a marker of biological age and life span since a suboptimal immune function may significantly contribute to morbidity and mortality in the elderly. Moreover, an association between immune function and individual longevity has been suggested (Wainwright et al., 1990).

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- “...the immune cell functions are strongly influenced by the antioxidant/oxidant balance and, therefore, the antioxidant levels in these cells play a pivotal role in maintaining immune cells in a reduced environment and in protecting them from oxidative stress and preserving their adequate function.”
- “...the immune cells are particularly sensitive to changes in their antioxidant status. Moreover, since the immune system cells have a high percentage of polyunsaturated fatty acids in their plasma membrane, it is not surprising that these cells usually contain higher concentrations of antioxidants than do other cells.”

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- “Antioxidants, namely ascorbic acid (vitamin c in humans and guinea pigs, which is an important cytoplasmic antioxidant), vitamin E (which is considered the principal antioxidant defense against lipid peroxidation in the cell membrane of mammals), glutathione (GSH, which is the most abundant nonprotein thiol-containing substance in living organisms and, in its reduced form, is one of the key links in the chain of antioxidant defenses protecting molecules against ROS damage) or other compounds which raise the tissue levels of thiol groups, such as thioproline (which is anti-toxic in the liver and increases life span in mice) or N-acetylcysteine (NAC, which shows a wide range of effects at all cellular levels such as inhibitory action on apoptosis, proinflammatory cytokine production, carcinogenic action of some compounds and metastasis), seem to be excellent controllers of injurious oxidation.”

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- “Moreover, the levels of these antioxidants decrease during oxidative stress.”
- “All of these antioxidants have been shown to improve the immune functions *in vitro* and *in vivo*.”

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“Apparently the antioxidants are able to raise the decreased functions and lower the very stimulated functions in immune cells from aged animals.”

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Table 1 Changes with ageing in different functions of immune cells. Effects of a diet supplemented with antioxidants

Cells	Function	Ageing	Antioxidants in age
1. Phagocytes	Adherence	Increase	Decrease (= adult)
	Migration	Decrease	Increase (= adult)
	Phagocytosis	Decrease	Increase (= adult)
	ROS production	Increase	Decrease (= adult)
	TNF- α production	Increase	Decrease (= adult)
	IL-1 production	Increase	Decrease (= adult)
2. Lymphocytes	Adherence	Increase	Decrease (= adult)
	Migration	Decrease	Increase (= adult)
	Proliferation	Decrease	Increase (= adult)
	IL-2 production	Decrease	Increase (= adult)
3. NK cells	Cytotoxicity	Decrease	Increase (= adult)

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Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Glutathione: A key player in autoimmunity

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Perricone C et al. Glutathione: A key player in autoimmunity, *Autoimmunity Rev*, Vol. 8, pp. 697–701, 2009.

“...most of the studies have pointed out that GSH depletion is a mainstream in the pathogenesis of several inflammatory/immunomediated diseases.”

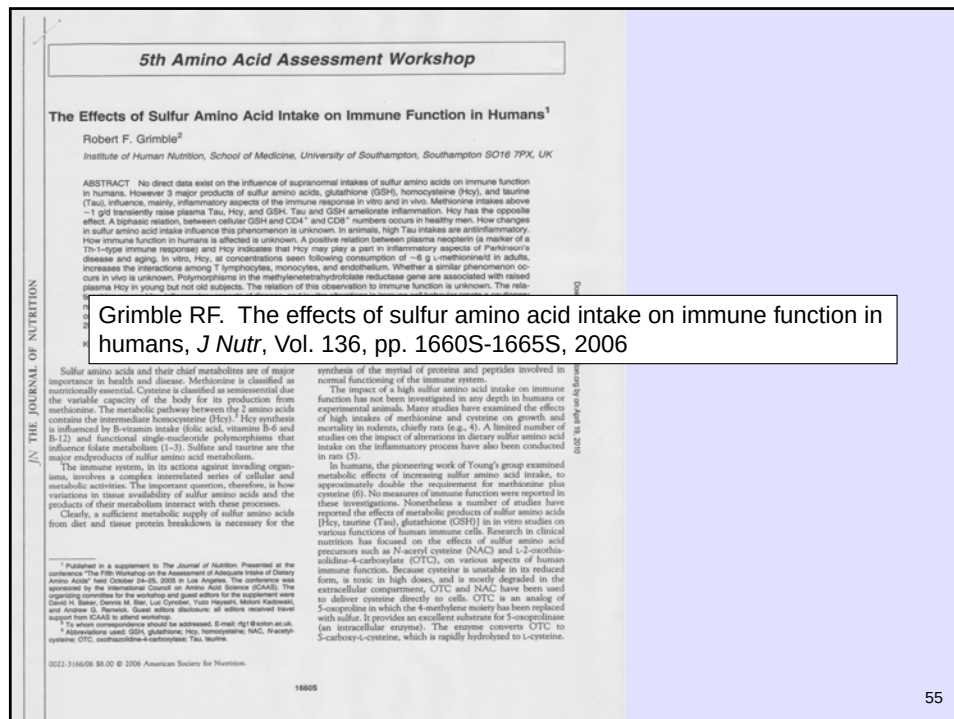
1. Introduction

Increasing attention in the physiopathology of inflammatory/immunomediated diseases has been focused on the role of reactive oxygen species (ROS), oxygen-based molecules

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- “The biochemistry of an infected individual is fundamentally changed in a way that will ensure that the immune system receives nutrients from within the body.”
- “Muscle protein is catabolized to provide amino acids for synthesizing new cells, GSH, and proteins for the immune response.”
- “Furthermore, amino acids are converted to glucose (preferred fuel, together with glutamine, for the immune system.”

- “An increase in urinary nitrogen and sulfur excretion occurs as a result of this catabolic process.”
- “In malaria, tuberculosis, sepsis, cancer, HIV infection, and rheumatoid arthritis, inflammatory cytokines bring about a loss of lean tissue, which is associated with depleted tissue GSH content and an increased output of nitrogenous and sulfur-containing excretion products in the urine.”

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- “The extent of this process is highlighted by the significant increase in urinary nitrogen excretion from 9 g/d in mild infection to 20-30 g/d following major burn or severe traumatic injury.”
- “The loss of nitrogen from the body of an adult during a bacterial infection may be equivalent to 60 g of tissue protein and, in malaria, equivalent to over 500 g of protein.”

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- “However, during the response to infection and injury the urinary excretion of sulfur increases lesser extent than that of nitrogen, suggesting that sulfur amino acids are preferentially retained.”
- “It has been proposed that the increased retention results from raised requirements for sulfur amino acids during the inflammatory response.”

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- “Infection with human immunodeficiency virus (HIV) causes substantial urinary excretion of sulfate during the asymptomatic phase of the disease.”
- “The losses reported were equivalent to 10 g of cysteine per day, in contrast to losses of ~3 g/d for healthy individuals on a ‘Westernized’ diet.”
- “Because cysteine is the precursor for sulfates, taurine and GSH, this finding or increased loss of ‘sulfur’ from the body in the form of sulfate, may be linked with the decline in tissue GSH pools in HIV infection.”

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- “In patients undergoing elective abdominal operations, the GSH content of blood and skeletal muscle fell by over 10% and 42% respectively, with 24h of the operation.”
- “Furthermore, reduced tissue GSH concentrations have been noted in hepatitis C, ulcerative colitis, cancer, and cirrhosis.”

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- “Antioxidants not only suppress inflammatory components of the response to infection and trauma but enhance components related to cell-mediated immunity.”
- “Thus, it can be hypothesized that antioxidants exert an immunoenhancing effect by activating transcription factors that are strongly associated with cell proliferation and an antiinflammatory effect by preventing activation of NF- κ B by oxidants produced during the inflammatory response.”
- “An increased intake of methionine may facilitate this situation.”

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- “Three potential ways of enhancing cellular GSH content are administration of the 3 amino acids (cysteine, glutamic acid, and glycine) that comprise the tripeptide, either singly or in various combinations; administration of cofactors for the metabolic pathways leading to GSH production (i.e., vitamin B-6, riboflavin, and folic acid); and administration of NAC...”

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“Although not affecting mortality rates, administration of NAC shortened hospital length of stay by >60%.”

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- “Taurine and sulfate can be regarded as biochemical endproducts of cysteine metabolism.”
- “However, it is apparent that taurine also plays a role in immune function.”
- “It is the most abundant free nitrogenous compound in cells.”
- “It is a membrane stabilizer and regulates calcium flux, thereby controlling cell stability.”
- “It has been shown to possess antioxidant properties and to regulate the release of proinflammatory cytokines in hamsters, rats, and humans.”

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Intracellular Thiol Concentration Modulating Inflammatory Response: Influence on the Regulation of Cell Functions Through Cysteine Prodrug Approach

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Abstract: Oxidative stress is defined as the consequence of overproduction of the immune system's reaction, which causes increased production of the reactive oxidative species (ROS) greater than the antioxidant protection. Tissue injury and oxidation of the circulating molecules may be the consequences.

Moreover, the sulphur-containing amino acids (SAA) fate is perturbed during stress. The altered biochemical roles during inflammation weaken the anti-oxidant mechanism, and the extra-supply of SAA under inflammatory conditions can help to restore homeostasis.

In brief, the main biochemical steps during inflammation are:

- The production of Cytokines, Acute Phase Protein, and Glutathione (GSH) pool are strongly modified during inflammation.
- The GSH participates in many important physiological processes controlling the homeostasis of the cells.



Santangelo F. Intracellular thiol concentration modulating inflammatory response: Influence on the regulation of cell functions through cysteine prodrug approach, *Curr Med Chem*, Vol. 10, pp. 2599-2610, 2003.

INTRODUCTION

To defend against infection, the organism physiologically releases radicals and oxidants from its cells. However, when reactive oxygen species (ROS) are produced at a higher rate than antioxidant protection, such a protective and physiological function turns into a damaging mechanism. In this respect, oxidative stress is defined as the consequence of an overpowering of the immune system's reaction, which causes tissue injury affected by ROS. Over 45,000 entries under Glutathione (GSH; L-γ-glutamyl-L-cysteinylglycine) were found in the Medline database, underlining the enormous interest of such a molecule. Two enzymes, i.e. γ-glutamylcystine synthetase (γ-GCS, EC 6.3.2.2) and glutathione synthetase (EC 6.3.2.3), catalyze GSH biosynthesis (Fig. 1). γ-Glutamyl transpeptidase is able to transfer glutamic acid on other moieties as amino acids; γ-glutamyl cyclotransferase cleaves the glutamic acid to 5-oxoproline that is finally open to glutamic acid by the 5-oxoproline action. The reaction catalyzed by γ-GCS was

shown to be rate limiting. On the other hand, it has been reported that the transcription of γ-GCS is controlled by a variety of factors that are not fully elucidated [1], but this review is focused only on the approach to increase the supply of the product-limiting step, i.e. cysteine. Thus, even though the key enzymes of GSH synthesis have a physiological importance [2], the approach to increase the availability of cysteine has fully demonstrated the capacity of the organism to raise the intracellular concentration of GSH.

The cellular GSH is mainly present in a reduced form and GSH participates as reductive species to protect from radical injury. The glutathione disulfide (GSSG) produced is reduced intracellularly to GSH by GSSG reductase, or excreted from the cell. GSH is the major intracellular free thiol [3] reaching a high concentration of up to 10 mM in the liver, whereas the extracellular concentration is as low as 2-10 μM in the plasma. The liver is the main source of circulating GSH, and it is estimated that approximately 45 mmol (14 g) of GSH are released into the human circulatory system during a 24 hour period [4]. Together with ascorbic acid, GSH constitutes the body's major antioxidant defence system [5].

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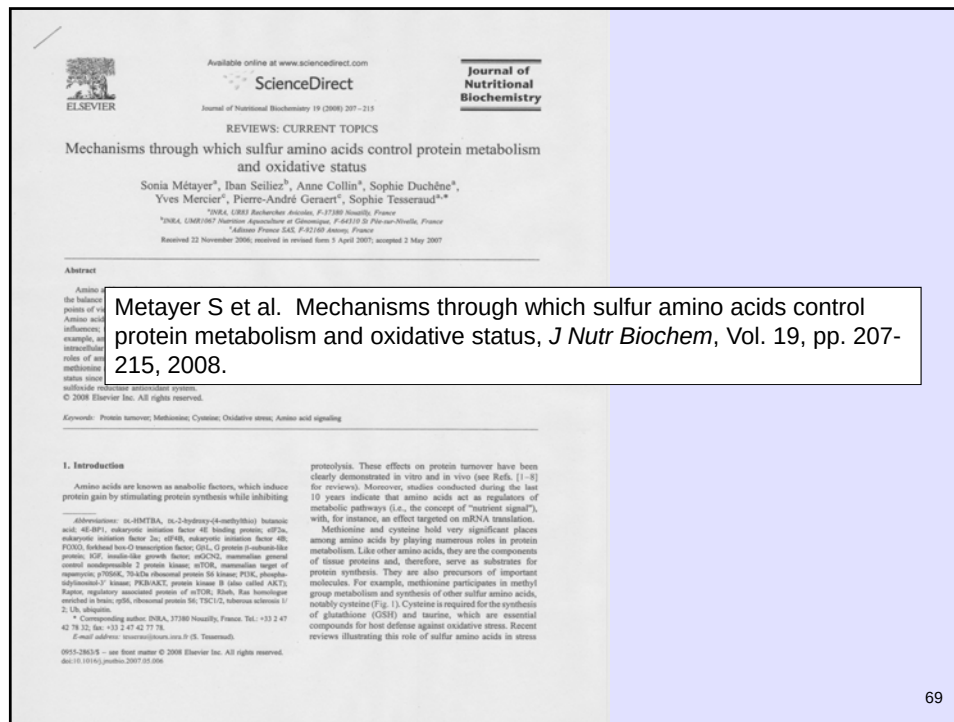
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- “In fact, the cellular sulphur amino acid pool is required for both acute phase protein and GSH synthesis.”
- “The incorporation of Cys into both of these end products, during the inflammatory response, is therefore influenced by its availability.”
- “An insufficient intake of SAA will consequently exert a pro-inflammatory influence due to the role of GSH in controlling the cytokines’ production in response to inflammatory stimuli.”
- “It is known that there is a stimulating influence on oxidant molecules and THF-alpha on the NF- κ B activity, which is decreased by GSH and other sulphur-containing compounds.”

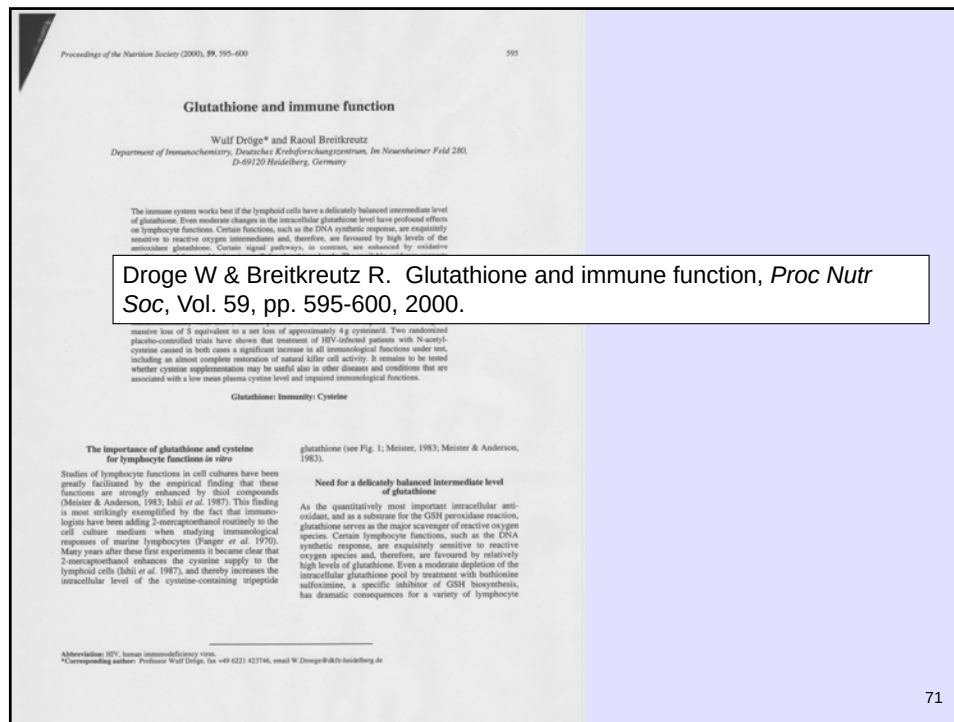
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“These biochemical changes may explain why Cys, a simple, non-essential amino acid, present in large excess in the diet, may be considered to be a conditionally-essential agent.”

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- “Methionine metabolism was also affected in normal volunteers subjected to a mild inflammatory challenge (i.e., vaccination), in agreement with results obtained in acute diseases.”
- “Preferential methionine metabolism toward cysteine synthesis has thus been observed, confirming increased requirement for sulfur amino acids in these situations.”



- “The causative role of this cysteine deficiency in the development of the immunological functions in HIV infection has been demonstrated in two randomized placebo-controlled studies on the therapeutic effects of N-acetyl-cysteine in two groups of asymptomatic HIV-infected patients with and without anti-retroviral therapy respectively.”
- “Both studies consistently showed that treatment of these patients with the additional source of cysteine caused a significant enhancement of several immunological functions under test, including restoration of natural killer cell activity to almost normal levels.”

“Together with the demonstrations of the massive loss of S, the immune restoration achieved with N-acetylcysteine should be sufficient reason to establish cysteine supplementation as a standard therapy complementary to anti-retroviral therapy in HIV infection.”

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Clinical Research

Supplementation of Essential Amino Acids May Reduce the Occurrence of Infections in Rehabilitation Patients With Brain Injury

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Abstract

Background: To investigate whether supplementation with oral essential amino acids (EAAs) may reduce the occurrence of nosocomial infection among patients with brain injury (BI: stroke, trauma, anoxic coma). **Methods:** Patients (n = 122; 77 men, 45 women; mean age 63 ± 13 years) with open head or closed head BI were randomly assigned to receive either EAAs or placebo.

Results: The primary outcome was the occurrence of infection during the index event. Patients of the EAAs group (23 episodes) had a significantly lower rate of infection compared with the placebo group (33 episodes) (P = 0.03). The secondary outcome was the occurrence of infection during the follow-up period (171 ± 6.44, P < 0.01), with BI. Prevalence of infection was significantly lower in the EAAs group (P = 0.01).

Keywords

amino acids, essential, infection, brain injury

Infection often complicates the rehabilitation period of patients with brain injury (BI), whether the cause is ischemic/hemorrhagic stroke (ST), subarachnoid hemorrhage (SH), or anoxic encephalopathy (AE). Infection often affects functional outcome.

Processes contributing to this immuno-brain disturbance include post-acute injury systemic inflammatory response syndrome (SIRS)^{1,2} and counterinflammatory response syndrome (CIRS)^{3,4} which both alter immune status. Additional

“Patients were randomly assigned to 2 months of oral EAAs (n=63; 8 g/d) or placebo (n=62).

the infection rate is 40% in patients with acute BI.⁵

In our tertiary care rehabilitation institute for patients with BI, the rate of development or exacerbation of infection within the first month after admission is about 40% (unpublished data). This high infection rate reflects the severity of the patients' clinical and functional compromise⁶ following their primary disease but also suggests a relative inadequacy of the measures adopted to prevent infection.^{7,8}

Rehabilitation patients with BI are particularly prone to the development or exacerbation of infection because of their immunodeficiency state.⁹⁻¹² Central nervous system injury induces a disturbance of homeostatic mechanisms between the immune system and the brain, responsible for immunodeficiency and infectious complications.¹³ The

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Table 1. Nutrition Composition of an Individual Packet of Supplementation, Containing 4 g of an Amino Acid Mixture, Used in This Study^a

kcal	20.6
KJ	86.1
Total amino acids, including the following:	4 g
L-leucine	1250 mg
L-lysine	650 mg
L-isoleucine	625 mg
L-valine	625 mg
L-threonine	350 mg
L-cysteine	150 mg
L-histidine	150 mg
L-phenylalanine	100 mg
L-methionine	50 mg
L-tyrosine	30 mg
L-tryptophan	20 mg

^aTreated patients were given 2 packets daily (8 g essential amino acids).

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- “Over the first month of rehabilitation, there were 60 infections in the whole population of 125 patients (48%); however the rate was 23.2% lower in the EAA group (23 episodes/63 patients; 36.5%) than in the placebo group (37 episodes/62 patients; 59.7%) ($P < .01$).”
- “The types of infection were similarly distributed between the 2 groups.”

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“Serum levels of prealbumin <20 mg/dL and C-reactive protein (CRP) >0.3 mg/dL were the best predictors of future infection.”

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- “The decrease of infection rate in the treated group was probably due to the actions of EAAs on immune cells.”
- “Indeed, EAAs can potentiate a patient’s immune response through at least 2 mechanisms: inducing protein synthesis in immune cells and directly influencing some metabolic pathways involved in immune function.”

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- “Protein synthesis is crucial to increase bacterial killing, lymphocyte proliferation, macrophage phagocytosis, and antibody and cytokine production.”
- “Some amino acids contained in the formula can directly and specifically affect some metabolic pathways involved in immunity.”
- “For instance, cysteine is a substrate essential for glutathione metabolism and the redox potential of immune cells; methionine (and cysteine) is essential for the synthesis of nucleic bases and, therefore, cell proliferation and differentiation.”

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Thank you!!

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