

Entry Level Clinical Nutrition Part XI

Micronutrient imbalances:
Zinc, Selenium, and Iodine

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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. Gershowitz

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 ideas less transparent.

The students learned not only to deliver babies and suture wounds, but also to order unnecessary tests as protection against lawsuits, to become specialists in seeing Medicaid patients, to watch patients with prescriptions on Wal-Mart's \$4 list. And they saw firsthand what Mr. O'Guinn 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. O'Guinn said.

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

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 248.

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 arrangements, 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 time to lose.

http://www.nytimes.com/2009/09/09/health/policy/09medschool.html?_r=1&ft=9&sum=6&... 9/9/2009

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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."**

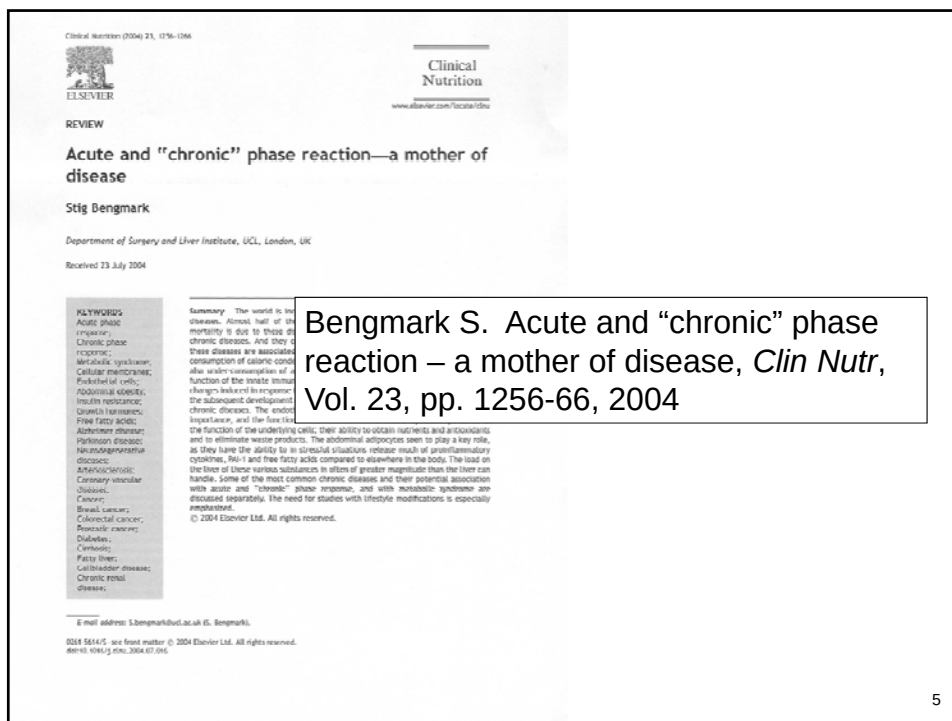
**"All stresses may be
presumed to be associated
with characteristic
modifications in the
metabolism of lipids,
carbohydrates, amino acids,
and micronutrients."**

KARGER **Nestlé**
NUTRITION

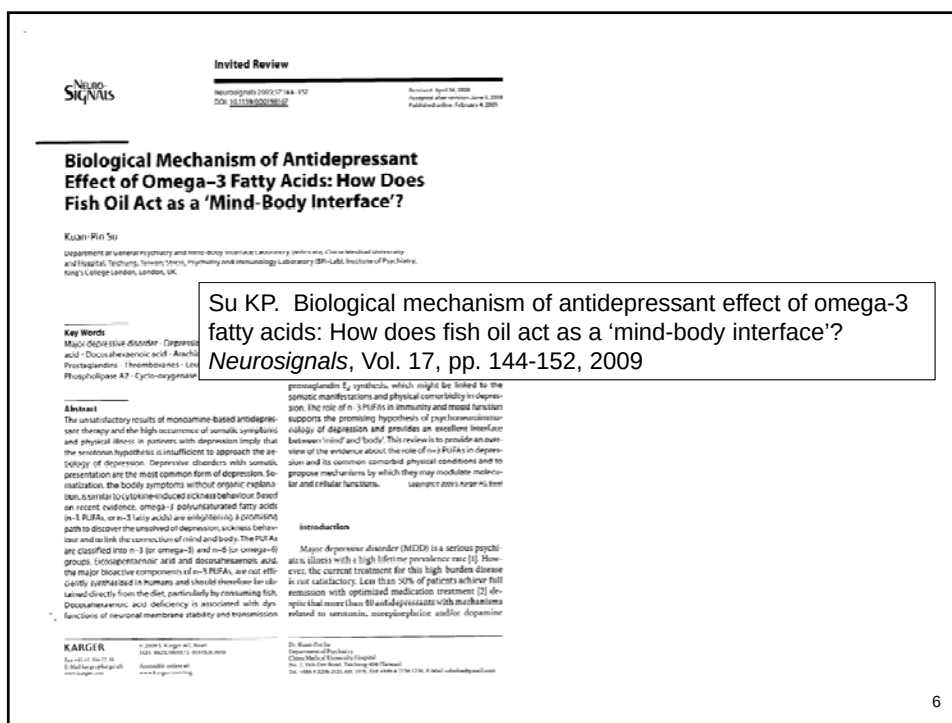
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Table 1. Overlapping of symptoms of acute sickness behaviour associated with IFN- α therapy and the somatic symptoms in MDD

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 ^c
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:

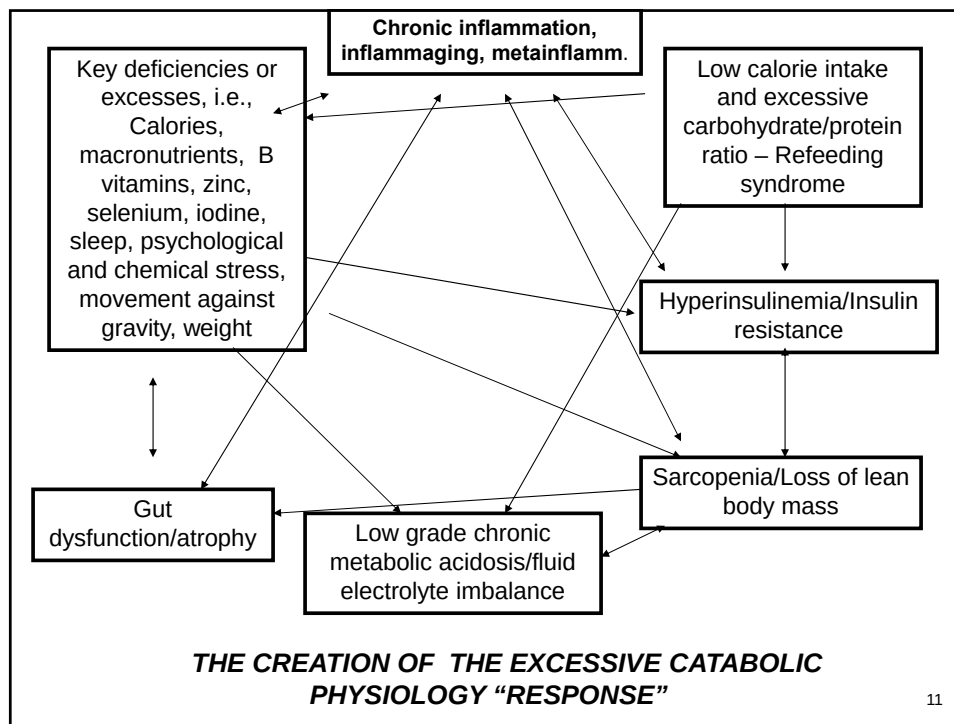
- Chief complaints in chronically ill patients are not diseases but responses that have gone on too long (Allostatic load).
- The metabolic imbalances that combine to form this response have been well defined by critical care nutritionists.

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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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Foundational hypothesis

- Issues relating to micronutrient status in chronically ill patients are more than just issues of dietary adequacy and bioavailability.
- How nutrients are metabolized after absorption may be just as important to resolving chief complaints in chronically ill patients, if not more so.

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Foundational hypotheses

- What is the major driver of aberrant micronutrient metabolism in chronically ill patients?

INFLAMMATION!!

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Journal of Clinical Nutrition (2006) 25, 1-13

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http://www.clinicalnutrition.com/journal/contents

REVIEW

The key role of micronutrients[☆]

Alan Shenkin*

Division of Clinical Chemistry, Forth

Received 7 November 2005; accepted

Shenkin A. The key role of micronutrients, *Clin Nutr*, Vol. 25, pp. 1-13, 2006

Abstract

Micronutrients play a central role in metabolism and in the maintenance of tissue function, but effects in preventing or treating disease which is not due to micronutrient deficiency cannot be expected from increasing the intake.

Keywords: Micronutrients; Antioxidants; Zinc; Selenium; Vitamin E; Effect of inadequate supply of micronutrients

Introduction

of tissue function, but effects in preventing or treating disease which is not due to micronutrient deficiency cannot be expected from increasing the intake. There is a highly integrated system to control the flux of micronutrients in illness, and this demonstrates just how important the body maintains the micronutrients to be. An adequate intake therefore is necessary to sustain metabolism and tissue function, but provision of excess supplementation to individuals who do not need them may be harmful. Clinical benefit is most likely in those individuals who are severely depleted and at risk

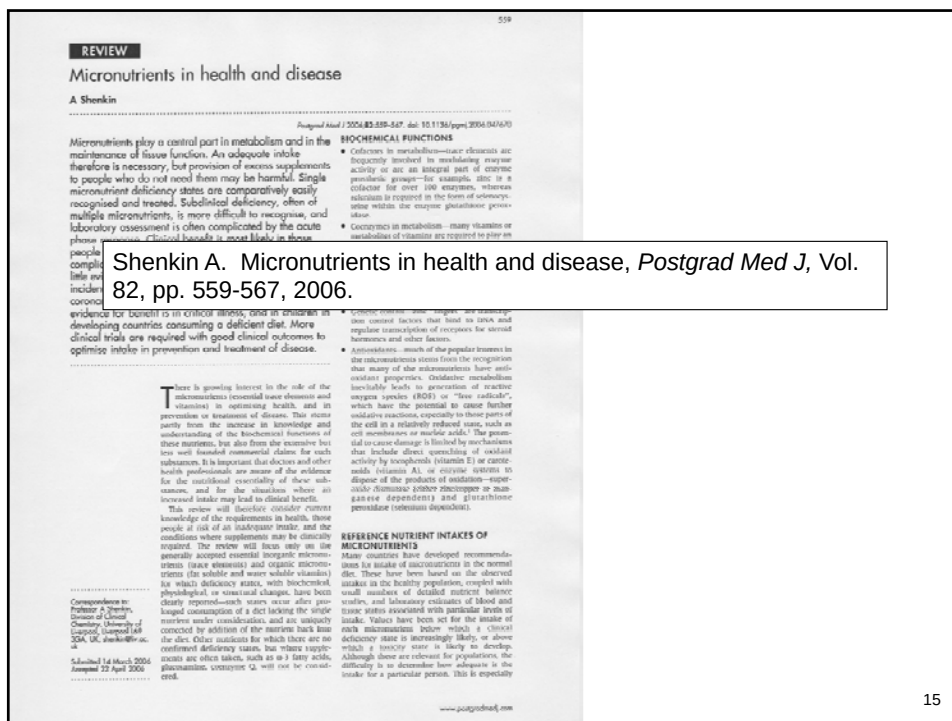
Conclusion

There is a highly integrated system to control the flux of micronutrients in illness...

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Shenkin A. Micronutrients in health and disease, *Postgrad Med J*, Vol. 82, pp. 559-567, 2006.

- “The catabolism associated with acute infection, surgery, or trauma leads to increased energy expenditure and net protein breakdown.”
- “Requirements for water soluble vitamins, as coenzymes for these metabolic pathways, will be increased, as will the requirements for various trace elements.”

- “Anabolism increases the requirement for all nutrients; hence increased micronutrients should be supplied when patients are gaining weight.”
- “Trace element deficiencies are more likely when patients become anabolic, after a prolonged period of catabolism.”

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Review Article *Ann Clin Biochem* 2000; 37: 289-297

Effect of the inflammatory response on trace element and vitamin status

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Trace elements and vitamins are required in milligram amounts per day to sustain normal health. If insufficient or excessive amounts are present, illness can result. Improvements in atomic absorption spectroscopy for trace metals in the 1970s and high performance chromatography methods for vitamins in the 1990s now allow us to detect physiological and pathological variations in blood concentrations of these substances in the absence of clinical evidence of deficiency or toxicity.

Several epidemiological studies highlighted the association of a circulating concentration of micronutrients and trace elements with an increased cardiovascular disease and cancer risk. It is proposed to reduce this risk by depleting concentrations of these by increased intake. However, in some large-scale supplementation studies in tobacco, it is emphasized that the relationship between serum concentration and risk is more complex than this and would suggest.

Inflammation is also increasingly recognized as playing an important role in the pathogenesis of cardiovascular disease¹ and of cancer.^{2,3} In cardiovascular disease, there is a strong relationship between circulating C-reactive protein (CRP) concentrations and future myocardial events and infarction stroke.⁴ Similarly, in cancer it has been known for some time that disease progression and lower survival in patients with elevated serum is associated with higher CRP concentrations.⁵⁻⁸ Indeed,

when promising markers of the progression of cardiovascular and gastrointestinal cancer (e.g. plasminogen activator inhibitor 1) can be related to the presence of an inflammatory response (i.e. CRP) and its magnitude.⁹

The acute phase inflammatory response is a coordinated sequence of reactions involving biochemical and physiological changes whose aim is to limit damage and aid repair.¹⁰ In the short term these changes are primarily coordinated towards stimulating defence against

Galloway P et al. Effect of the inflammatory response on trace element and vitamin status, *Ann Clin Biochem*, Vol. 37, pp. 289-297, 2000.

protein, transferrin, albumin and ceruloplasmin, and those of selenium and commonly measured vitamins, in various clinical settings. We discuss the significance of such changes in the monitoring of nutritional status in acutely and chronically ill patients.

TRACE METALS

Iron

It is well established that iron is a negative acute-phase reactant, serum iron concentrations decrease in a wide variety of stressful situations such as surgery, major trauma, infections or neurological events.¹¹ The fall in serum iron concentration is pronounced, commonly around 20-25%. Even greater decreases (> 50%) have been noted when two stressful events occur simultaneously.¹² The reduction in iron concentration is also marked (around 40%) after major trauma such as ingested bullet impact, when CRP concentration increases to approximately

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E-mail: naveed.sattar@nhs.uk

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TABLE 1. Relationship of the inflammatory response and circulating micronutrient concentrations

Analytes	Reference range	Minor inflammation (CRP < 15 mg/L)	Major inflammation (CRP ~ 100-200 mg/L)	Comments
Iron	8-30 µmol/L	Decreased by 40%	Decreased by 60-90%	Liver uptake
Zinc	12-18 µmol/L	Decreased by 10%	Decreased by 40-60%	Liver uptake
Selenium	0.8-2.0 µmol/L	Decreased by 10%	Decreased by 40-60%	? Redistribution
Copper	11.5-23.5 µmol/L	Increased by 10-15%	Increased by 30%	? Liver extraction
Vitamin A	1.0-2.8 µmol/L	Decreased by 30-40%	Decreased by 30%	Probable redistribution
Vitamin E	15-40 µmol/L	Negligible	Decreased by 20-30%	More data needed
Vitamin C	10-115 µmol/L	No data	Minimal to > 75% dec.	More data needed
Vitamin B ₁	280-540 ng TDP/gHb	No data	No change	More data needed
Vitamin B ₂	< 70% activation*	No data	No change	More data needed
Vitamin B ₆	18-135 nmol/L (PP)	No data	Decreased by 40-50%	More data needed
Vitamin B ₁₂	188-1059 pg/mL	No data	No change	More data needed
Folate	3.5-16.0 ng/mL	No data	No change	More data needed
Lycopene	100-300 µg/L	Decreased by ~50%	Decreased by > 90%	More data needed
β-carotene	92-312 µg/L	Decreased by ~50%	Decreased by > 90%	More data needed
α-carotene	14-60 µg/L	Decreased by ~50%	Decreased by > 90%	More data needed
Lutein	82-202 µg/L	Minimal change	Decreased by ~70%	More data needed

An approximate guide to the extent of change seen in analytes with different degrees of inflammation. The figures quoted are collated from disparate sources and the effects of diverse factors in different pathophysiologies may be important. TDP = thiamine diphosphate; * = of red cell glutathione reductase; PP = pyridoxal phosphate.

Ann Clin Biochem 2000; 37

Zinc

Zinc

“A wide range of factors loosely grouped as stresses decrease plasma zinc concentration of an animal to about the same extent as severe dietary deficiency of zinc and greatly complicate the diagnosis of inadequate zinc supply.”

Chesters JK. Zinc, in O'Dell BL & Sunde RA eds., Handbook of Nutritionally Essential Mineral Elements, Marcel Dekker, New York, 1997, pp. 185-230.

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Zinc

“They include infection, bacterial endotoxins, surgery, burns, and pregnancy.”

Chesters JK. Zinc, in O'Dell BL & Sunde RA eds., Handbook of Nutritionally Essential Mineral Elements, Marcel Dekker, New York, 1997, pp. 185-230.

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Zinc

“Zinc deficiency is humans is widespread and athletes may be particularly prone to lower plasma zinc levels.”

DiPasquale M. Amino Acids and proteins for the Athlete: The Anabolic Edge, CRC Press, Boca Raton, 1997, pp. 174-176.

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Effects of endotoxin on zinc metabolism in human volunteers

LISA M. GAETKE, CRAIG J. MCCLAIN, RAMESH T. TALWALKAR, AND STEVEN I. SIEDELOFSKY
Departments of Nutritional Sciences and Internal Medicine, University of Kentucky, and the Lexington Veterans Administration Medical Center, Lexington, Kentucky 40506

GAETKE, LISA M., CRAIG J. MCCLAIN, RAMESH T. TALWALKAR, AND STEVEN I. SIEDELOFSKY. Effects of endotoxin on zinc metabolism in human volunteers. *Am. J. Physiol.* 272: E952-E956, 1997. After stress or trauma, the serum zinc concentration decreases. This study evaluated possible mechanisms for hypozincemia with the use of a human endotoxemia model. Two doses of endotoxin (lipopolysaccharide [LPS]) were administered on consecutive mornings to 12 healthy volunteers, and each subject was also studied after saline injection. Blood was analyzed for zinc, cytokines (tumor necrosis factor- α and interleukin-6), albumin, albumin-zinc binding, and C-reactive protein (CRP). Serial 24-h urine collections were obtained for zinc. Both LPS doses locally increased plasma cytokine concentrations and decreased the serum zinc concentration. Serum albumin, the major zinc binding protein, did not decrease, but a progressive increase in CRP was found. LPS did not alter zinc loading effects to serum albumin. Urine zinc losses were not increased. We conclude that hypozincemia in this model cannot be explained by decreased serum albumin, changes in serum albumin zinc binding, or increased urinary zinc excretion. Because hypozincemia was transient and followed cytokine peaks, we indicate that LPS-stimulated hypozincemia is mediated, at least partly, by a cytokine-directed internal redistribution of zinc.

KEYWORDS: hypozincemia; acute phase response; inflammation; zinc

ZINC IS AN ESSENTIAL trace mineral required for normal growth, protein metabolism, the function of over 200 zinc metalloenzymes, maintain integrity of gene expression, wound healing, and immune function (5, 14). The acute phase host response to stress, trauma, inflammation, and infection includes a pronounced decrease in the serum zinc concentration and an internal redistribution of total body zinc stores, with increased levels of zinc in the liver (5, 9, 10). This profound drop in serum zinc and internal redistribution appears to be part of the acute phase response designed to withhold important minerals such as zinc and iron necessary for bacterial growth in the blood stream and to reprogram hepatic protein synthesis in a fashion beneficial to the host in times of stress or infection (5, 21, 25, 30). Cytokines such as tumor necrosis factor- α (TNF- α) and interleukin 6 (IL-6) appear to mediate many of the alterations seen during the acute phase response (3, 16, 22, 26). However, their role in mediating stress-related hypozincemia in humans is not known, and the mechanism by which hypozincemia occurs in humans requires further study.

Although internal redistribution of zinc during the acute phase response might explain hypozincemia in humans, other mechanisms also have been reported to

play an important role. These include increased urinary zinc excretion, decreased serum albumin concentration, and changes in serum albumin-zinc binding (7-9, 11, 23). Increased urinary zinc excretion has been reported after various types of injuries (7, 13). Because the acute phase response results in decreased serum albumin concentration and albumin is the major zinc binding protein (12), there is potentially less zinc binding protein available. Finally, it has also been reported that serum albumin from stressed patients had less affinity for zinc than does serum albumin from normal subjects (7, 20).

Endotoxin (lipopolysaccharide [LPS]) is an integral component of the outer membrane of gram-negative bacteria that is responsible for many of the deleterious effects of gram-negative bacterial infections (11, 20). Administration of LPS to experimental animals initiates the acute phase response and produces profound decreases in serum zinc levels (5, 11, 17). A human model of sepsis using a safe dose of LPS to give a reproducible inflammatory response has been used to study physiological changes with inflammation (13, 16, 19, 21, 24). In a previous study, we used this low dose of endotoxin given on two consecutive days to study subjects as a model of endotoxemia to determine both the cytokine response and effects of inflammation on hepatic cytochrome P-450-mediated drug metabolism (22).

The overall goal of the current study was to evaluate possible mechanisms for stress-related hypozincemia in mice and humans. The specific objectives were to determine 1) the time course of hypozincemia after LPS administration, 2) whether the LPS-induced cytokine response temporally preceded hypozincemia, 3) whether reductions in serum albumin correlate with hypozincemia, 4) whether changes in serum albumin-zinc binding were during endotoxemia, 5) whether increases in urine zinc excretion help explain the hypozincemia, and 6) whether there are sex differences in LPS-induced hypozincemia.

MATERIALS AND METHODS

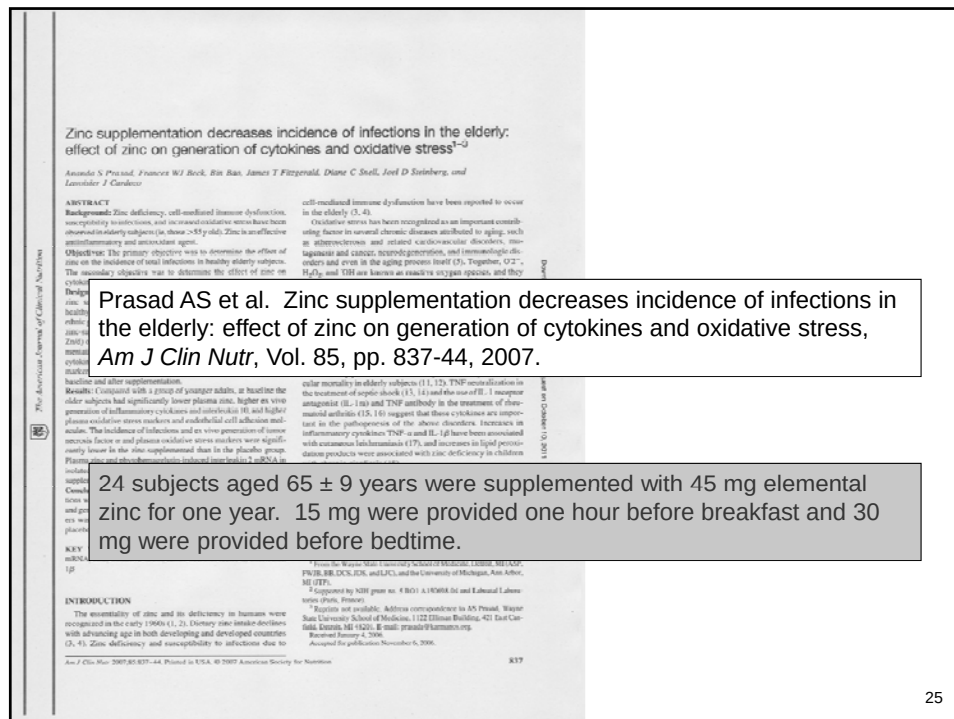
Subjects. Twelve normal volunteers, six men and six women, 19-40 yr of age, participated in the study. Clinical, biochemical, and cytokine data from the men were reported previously (22). All subjects were healthy, as confirmed by medical history, physical exam, blood chemistry, urinalysis, and electrocardiogram. The study was approved by the University of Kentucky Institutional Review Board, and written consent was obtained from each subject. Studies were performed at the University of Kentucky General Clinical Research Center. Each volunteer participated in two study periods separated by 2 weeks. During the first study period, the LPS study, each volunteer received two intravenous 100 mg of LPS

Gaetke LM et al. Effects of endotoxin on zinc metabolism in human volunteers, *Am J Physiol*, Vol. 272, No. 6, Pt 1, pp. E952-6, June 1997

“There is strong support in experimental animals to suggest that cytokine-mediated induction of the intracellular zinc binding protein metallothionein causes the reduction in serum zinc by transiently sequestering the zinc in metallothionein-rich organs, such as the liver.”

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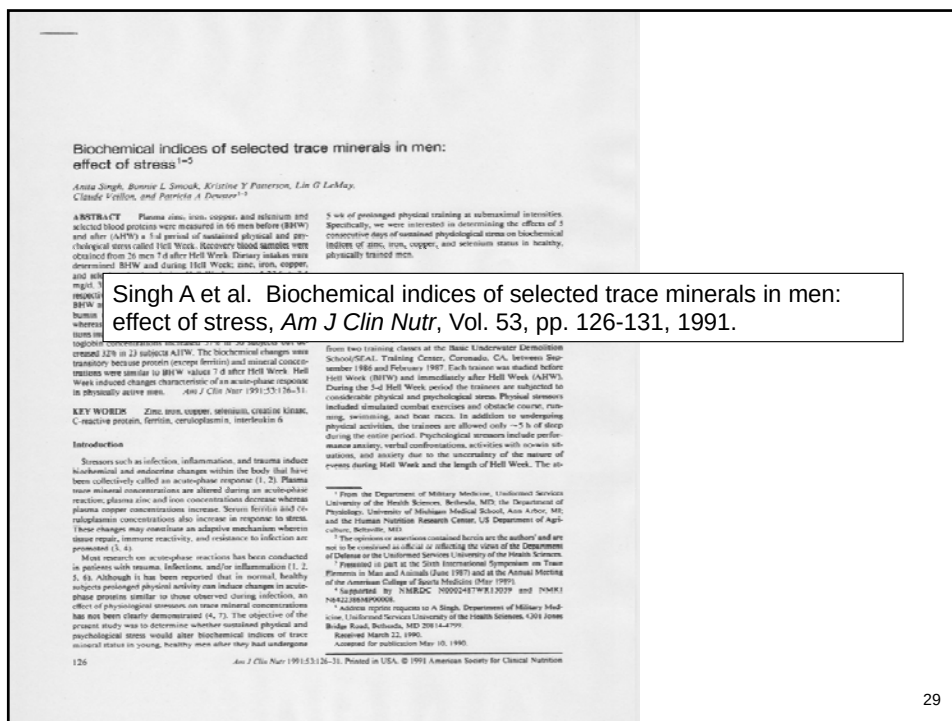
- **“Compared with a group of younger adults, at baseline the older subjects had significantly lower plasma zinc, higher ex vivo generation of inflammatory cytokines and interleukin 10, and higher plasma oxidative stress markers and endothelial cell adhesion molecules. The incidence of infections and ex vivo generation of tumor necrosis factor α and plasma oxidative stress markers were significantly lower in the zinc-supplemented than in the placebo group.”**

- **“After zinc supplementation, the incidence of infections was significantly lower...”**
- **“The administration of 45 mg of elemental zinc/d did not reduce plasma copper concentrations in zinc-supplemented elderly subjects.”**

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Selenium

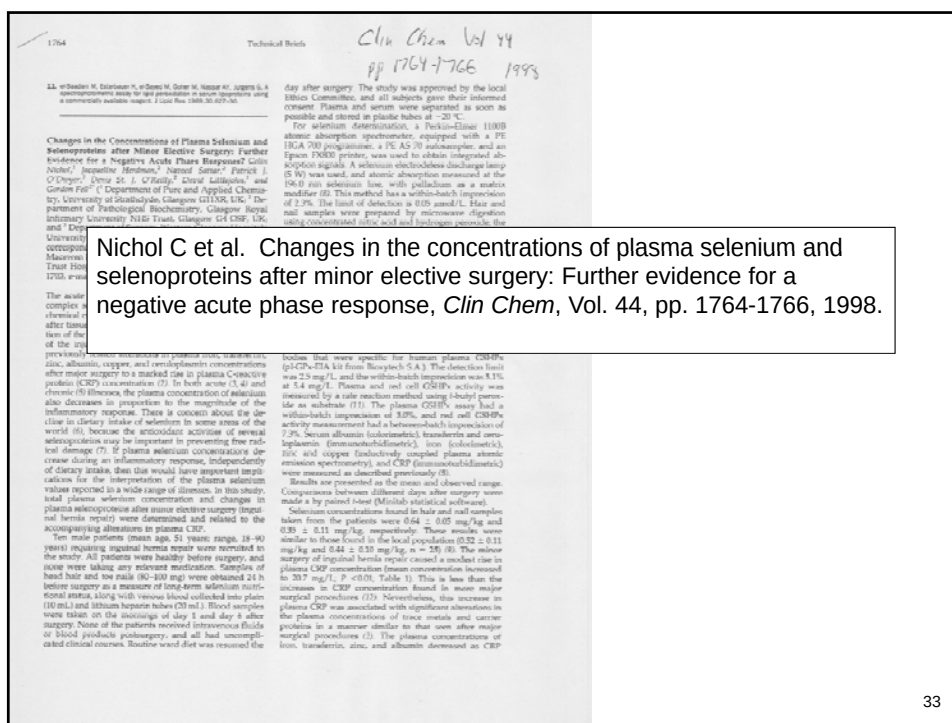
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- **“Stressors such as infection, inflammation, and trauma induce biochemical and endocrine changes within the body that have been collectively call an acute-phase response. Plasma trace mineral concentrations are altered during an acute-phase reaction: plasma zinc and iron concentrations decrease whereas plasma copper concentrations increase. Serum ferritin and ceruloplasmin concentrations also increase in response to stress. These changes may constitute an adaptive mechanism wherein tissue repair, immune reactivity, and resistance to infection are promoted.”**

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- “In both acute and chronic illnesses, the plasma concentration of selenium also decreases in proportion to the magnitude of the inflammatory response.”
- “If plasma selenium concentrations decrease during an inflammatory response, independently of dietary intake, then this would have important implications for the interpretation of the plasma selenium values reported in a wide range of illnesses.”

- **“The minor surgery of inguinal hernia repair caused a modest rise in plasma CRP concentration (mean concentration increased to 20.7 mg/L; $P < 0.01$). This is less than the increases in CRP concentration found in more major surgical procedures. Nevertheless, this increase in plasma CRP was associated with significant alterations in the plasma concentrations of trace minerals and carrier proteins in manner similar to that seen after major surgical procedures. The plasma concentrations of iron, transferrin, zinc, and albumin decreased as CRP increased; all significantly fell (by 64%, 8%, 10%, and 7% respectively) one day after surgery ($P < 0.05$). By day 6, concentrations of all these analytes had returned towards the starting values.”**

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- **“Given the above expected changes in established acute phase reactants, it was interesting to note that plasma selenium concentrations followed a similar pattern, decreasing by 10% ($P < 0.01$) at day 1, followed by a subsequent increase ($P < 0.05$) toward the starting concentration by day 6.”**

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- **“Whatever the mechanism, the observation that plasma selenium decreases as part of the inflammatory response is important. Low plasma selenium concentrations have been described in a variety of acute clinical conditions such as myocardial infarction, severe burns, acute pancreatitis, and in intensive care patients. Because these conditions are accompanied by variable degrees of inflammatory response, the low plasma selenium concentration may be caused, in part, by an appropriate acute phase response.”**

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- **“Low plasma selenium concentrations have also been described in chronic conditions. In a group of terminally ill cancer patients, we found a strong negative correlation between CRP and plasma selenium concentration, patients with CRP values >30 mg/L have the lowest plasma selenium results.”**

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“We conclude that when interpreting plasma selenium concentrations, a marker of the inflammatory response, such as CRP, should be included to distinguish true nutritional depletion from the inherent effects of disease.”

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Clinica Chimica Acta 316 (2002) 137–146



Alterations of serum selenium concentrations in the acute phase of pathological conditions

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Motoshika Yamane^b, Mutsuo Kuba^c, Yukiya Nakanishi^d

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^cNational Okinawa Hospital, Okinawa, Japan
^dThird Life Hospital, Okinawa, Japan

Maehira F et al. Alterations of serum selenium concentrations in the acute phase of pathological conditions, *Clinica Chimica Acta*, Vol. 316, pp. 137-146, 2002.

Abstract
 (1) 0.1 ± 0.01 $\mu\text{g/g}$ of serum protein, (2) 0.001 vs. males in their $206 \pm 1.59 \pm 0.203$, whereas a peak was observed in females in their $206 \pm 1.87 \pm 0.21$ (10%, $P=0.025$) vs. those in their $206 \pm 1.57 \pm 0.22$. The serum Se concentrations in the high CRP value group ($n=40$, 1.97 ± 0.29 $\mu\text{g/g}$, 64.5%), the rheumatoid arthritis (RA) low positive group ($n=24$, 1.37 ± 0.26 , 82.0%), the lung cancer group ($n=16$, 1.28 ± 0.39 , 82.6%), and the adult T-cell leukemia (ATL) group ($n=22$, 1.28 ± 0.35 , 73.1%) were significantly lower ($P<0.001$) than those in the healthy subjects (1.57 ± 0.29 $\mu\text{g/g}$). This finding was confirmed by inducing acute phase response (APR) in rats by injection of lipopolysaccharide (LPS), which produced a significant decrease of Se in plasma and liver (89.5% and 81.8% vs. untreated rats, $P<0.05$). In contrast, the Se content in muscle, kidney, lung, spleen, heart, and thymus showed increases of $<10\%$. Se excreted from liver after LPS-challenge appeared to be transferred to muscle, and Se concentrations increased by 46% after APR in the control concentration in parallel with the reduction of APR. **Conclusions:** The reduction of Se in the liver and plasma during APR may be associated with the increased CRP synthesis in the liver. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Serum selenium; C-reactive protein; Acute phase response; Selenium metabolism; Liver selenium; Muscle selenium

1. Introduction

Selenium deficiency is related to several pathological conditions such as cardiomyopathy [1], while Se toxicity and carcinogenic effects [2,3] have been shown at the supranutritional concentrations. An anti-carcinogenic role of Se is supported by epidemiological and cohort studies [4–6], while an association between serum Se and the risk of coronary heart diseases has been shown by several population studies [7,8]. Selenium also has immunopotentiating effects: a

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E-mail address: machira@med.u-ryukyus.ac.jp (F. Machira).

0009-8912/\$ - see front matter © 2002 Elsevier Science B.V. All rights reserved.
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- **“We suggest that low serum Se concentrations in these patients may be a biological response that functions to increase CRP production in the acute phase reaction. This interpretation was supported by animal experiments in which mobilization of selenium from liver and serum to muscle during the induction of the acute inflammatory reaction were observed. It is tempting to speculate that this mobilization of Se to muscle may serve as a storage mechanism until the inflammatory response subsides.”**

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- **“The present findings of low serum Se concentrations in acute and chronic clinical conditions with high serum CRP concentrations and in rats in which APR has been induced raise two questions. Where does the Se depleted from plasma and liver go within the short period of time during APR?”**

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- “This study suggested that the Se lost from the circulation and liver was redistributed to muscle in order to balance the Se-loss due to catabolic losses of muscle during APR, possibly followed by its partial excretion in urine.”

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Biochemical indices of selected trace minerals in men: effect of stress¹⁻⁵

Anita Singh, Ranjit L. Singh, Kristine Y. Furstner, Lin G. LeMay, Claude Veillon, and Patricia A. Deuster^{1,2}

ABSTRACT Plasma zinc, iron, copper, and selenium and selected blood proteins were measured in 16 men before (BW) and after (AW) a 1-wk period of sustained physical and psychological stress, called Hell Week. Recovery blood samples were obtained from 26 men 7 d after Hell Week. Dietary intakes were determined. BW and during Hell Week, zinc, iron, copper, and selenium concentrations were similar to those reported in healthy men.

5 wk of prolonged physical training at submaximal intensities. Specifically, we were interested in determining the effects of 5 consecutive days of sustained physiological stress on biochemical indices of zinc, iron, copper, and selenium status in healthy, physically trained men.

KEY WORDS Zinc, iron, copper, selenium, oxidative stress, C-reactive protein, ferritin, ceruloplasmin, interleukin 6

Introduction

Stressors such as infection, inflammation, and trauma induce biochemical and endocrine changes within the body that have been collectively called an acute-phase response (1, 2). Plasma trace mineral concentrations are altered during an acute-phase reaction; plasma zinc and iron concentrations decrease whereas plasma copper concentrations increase. Serum ferritin and ceruloplasmin concentrations also increase in response to stress. These changes may constitute an adaptive mechanism wherein stress repair, immune reactivity, and resistance to infection are promoted (3, 4).

Most research on acute-phase reactions has been conducted in patients with trauma, infection, and/or inflammation (1, 2, 5, 6). Although it has been reported that in normal, healthy subjects prolonged physical activity can induce changes in acute-phase proteins similar to those observed during infection, an effect of physiological stressors on trace mineral concentrations has not been clearly demonstrated (6, 7). The objective of the present study was to determine whether sustained physical and psychological stress would alter biochemical indices of trace mineral status in young, healthy men after they had undergone

from two training camps at the Basic Underwater Demolition School (BUDS), Training Center, Coronado, CA, between September 1989 and February 1990. Each training was divided into Hell Week (HW) and immediately after Hell Week (IAHW). During the 1st Hell Week period the trainees are subjected to considerable physical and psychological stress. Physical stresses included simulated combat exercises and obstacle course, running, swimming, and boat races. In addition to undergoing physical activities, the trainees are allowed only ~2 h of sleep during the entire period. Psychological stresses include performance anxiety, verbal reprimands, activities with no-win situations, and anxiety due to the uncertainty of the nature of events during Hell Week and the length of Hell Week. The ad-

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² The opinions or assertions contained herein are the authors' and are not to be construed as official or reflecting the views of the Department of Defense or the Uniformed Services University of the Health Sciences.

³ Presented in part at the 10th International Symposium on Trace Elements in Man and Animals (June 1989) and at the Annual Meeting of the American College of Sports Medicine (May 1990).

⁴ Supported by NIDDK N0001457W110399 and NMRJ N0001457W110399.

⁵ Address reprint requests to A. Singh, Department of Military Medicine, Uniformed Services University of the Health Sciences, 4301 Scotts Bridge Road, Bethesda, MD 20814-4779.

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- **“During the 5-d Hell Week period the trainees are subjected to considerable physical and psychological stress. Physical stressors included simulated combat exercises and obstacle course, running, swimming, and boat races. In addition to undergoing physical activities, the trainees are allowed only ~5 h of sleep during the entire period. Psychological stressors include performance anxiety, verbal confrontations, activities with no-win situations, and anxiety due to the uncertainty of the nature of events during Hell Week and the length of Hell Week.”**

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- **“In the present study, young, healthy, physically active men exhibited changes in selected blood trace minerals and proteins that were characteristic of an acute-phase reaction in response to sustained physical activity, psychological stress, and sleep deprivation.”**
- **“Our findings indicate that plasma selenium concentrations decrease significantly in response to stress and that this decrease is transient.”**

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Diagnostic considerations

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Semba RD et al. Serum antioxidants and inflammation predict red cell distribution width in older women: The Women's Health and Aging Study I, *Clin Nutr*, Vol. 29, pp. 600-604, 2010.

Results: Selenium was significantly associated with RDW at baseline and predicted RDW over five years. Before up to separate multivariate mixed-effects models that adjusted for other covariates. As expected, the addition of β -t to the models attenuated the association of serum selenium with RDW, as the antioxidant levels are known to upregulate it. In total, carotenoids were associated with serum selenium and were not fully up. Protein metabolism and a metabolic score not significantly associated with RDW. C-reactive protein (CRP) is an independent predictor of RDW and may potentially mediate effects on RDW through β -t.

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1. Introduction

Red blood cell distribution width (RDW) is a measure of the variability in size of circulating erythrocytes and a parameter that is routinely reported as part of a complete blood count. Higher RDW values indicate greater heterogeneity in the size of circulating erythrocytes. Recently, elevated RDW was shown to predict mortality with great consistency across several different study populations. The biological mechanisms that underlie the association of RDW with survival are unknown. RDW is elevated under conditions of erythropoietic stress, such as during iron, vitamin B₁₂, and folate deficiencies. Oxidative stress and inflammation have been suggested to influence RDW, but the relationships of biomarkers of oxidative stress and inflammation with RDW have not been well characterized.

Oxidative stress refers to the condition in which the balance between oxidants and antioxidant defenses is upset and excess reactive oxygen species cause oxidative damage to nucleic acids, proteins, and lipids. Oxidative stress is related to red cell survival¹ and could be a possible mechanism for RDW. Superoxide dismutase (SOD) and glutathione peroxidase (GPx) are important antioxidant enzymes involved in erythropoiesis. Mice with transplanted hematopoietic stem cells from SOD knockout mice had decreased red cell survival, and antioxidant treatment of the mice increased red cell survival.² In humans with selenium deficiency, selenium supplementation decreased GPx activity in erythrocytes.^{3,4} The antioxidant defense system in humans includes carotenoids, α -tocopherol (vitamin E), and selenium. The six major dietary carotenoids found in the blood are α -carotene, β -carotene, α -cryptoxanthin, lutein, zeaxanthin, and lycopene. α -tocopherol is a chain-breaking antioxidant that protects polyunsaturated fatty acids within membrane phospholipids and plasma proteins by scavenging peroxyl radicals. Selenium is an essential trace element and normal constituent of the diet. The biochemical functions of selenium are related to its role in selenoproteins, and

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- **“The present study shows that serum selenium is independently associated with RDW and predicts RDW over a two-year period in older, disabled community-dwelling women.”**
- **“The results suggest that oxidative stress may be a potential underlying biological mechanism for increased RDW.”**

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Treatment considerations

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- **“A number of different selenium preparations are available, including sodium selenite, sodium selenite, selenomethionine, selenocysteine, and high-selenium yeast. None of these preparations has clearly been shown to be preferable to the others.”**

- Alan Gaby, MD (Gaby A. *Nutritional Medicine*, Fritz Perlberg Publishing, Concord, NH, 2011).

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Iodine

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Entry Level Clinical Nutrition – Part 11
Dr. Jeff Moss

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A PERSPECTIVE ON HIGH DOSE IODINE SUPPLEMENTATION – PART I – DO WE NEED TO CONSIDER MORE ABOUT SCIENTISTS THAN JUST THEIR SCIENCE

"Blind faith is no faith"

Taro Gold
Open Your Mind, Open Your Life: A Book of Eastern Wisdom

INTRODUCTION

As I am in the process of writing this newsletter, a phenomenon is occurring in the clinical nutrition community that, for me, is unprecedented in my 22 years in the industry. Based entirely on the research and recommendations of three medical doctors, Guy Abraham, MD, Jorge Flechas, MD, and David Greenstein, MD, many clinicians are now routinely recommending to their patients supplemental doses of iodine that are 6333% of the current, generally accepted RDA. Furthermore, these recommendations are occurring in spite of a large body of published research that suggests daily doses of iodine in this amount are highly likely to lead to adverse effects. Are these clinicians taking advantage of the huge wisdom of visionaries whose approach to iodine nutrition represents a portal to great advancements in patient health or demonstrating yet another turn of blind faith that has led to so much disillusionment, disappointment, and suffering throughout human history? As an introduction to the somewhat lengthy philosophical and scientific discussion that follows, I would like to begin by simply answering the question by asking at this time, "I don't know." Why do I state this up front? For reasons that I will present shortly, I am finding the publications by Dr. Abraham, the sole author of the majority of the articles on this approach to iodine supplementation, both incredibly intriguing and frightfully disturbing. Furthermore, I am not quite sure whether my very mixed reaction is due more to defects in these publications, personal inadequacies on my part, or a combination of the two. Therefore, with all this

confusion and a variety of mixed feelings, my first impulse is to ignore the issue completely and let someone else sort it all out. However, being someone who prides himself for never backing down from a challenge, no matter how daunting, I would like to continue this discussion by, in part I of this series, educating you through my process of evaluating and forming impressions of scientific publications, specifically as it relates to those by Dr. Abraham. Subsequently, in future parts of this series, I will, as is customary in these newsletters, examine and comment more specifically on the research and clinical reports provided not only by Dr. Abraham but also by Drs. Flechas and Greenstein. Then, I will evaluate how these publications compare to the majority of peer-reviewed publications on iodine nutrition that have appeared in the literature over the last few years in sum, it is my hope that my efforts will assist you in making a decision on iodine supplementation that is appropriate for your patients.

To begin this process, I would like to make ten confessions. First, I would like to tell you one of the most important reasons why I write these newsletters. Of course, your immediate thought might be that I want to create increased financial success for my business, Moss Nutrition. While I cannot deny that I have a desire to gain the financial resources necessary to feed my family, pay the mortgage, and perform the many other tasks involved in today's life in the US, this alone does not give enough pleasure to continue an effort such as this. In fact, what truly motivates me every other month to spend time reading research and then to put down on paper my thoughts on this research is the sense that I am in some way contributing to your ability to better address the needs of your patients. Therefore, in most of my newsletters, at this point in the introduction I have a fairly strong feeling that, at least for some of you, I am going to accomplish this latter aim. Unfortunately, in this case, due to the aforementioned compromise that I will delineate shortly, I am still not quite sure whether you will find my discourse informative, relevant, or just plain misleading.

The second confession I would like to make concerns the reason why I feel confident enough to feel that every other month you should find what I am writing seriously. For every newsletter the answer is virtually always the same: the strength of

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A PERSPECTIVE ON HIGH DOSE IODINE SUPPLEMENTATION – PART II – GUY ABRAHAM, MD AND HIS WORLD VIEW ON IODINE

INTRODUCTION

In part I of this series I departed significantly from the usual format of these newsletters by suggesting that issues of character and credibility need to be examined right along with the science when we are making decisions about whether we should let our nutritional recommendations stem from those that are generally accepted as true by the nutritional community. Specifically, as you may recall, I was highly critical of what appeared to be Dr. Guy Abraham's personal vendetta against any researcher or clinician who disagreed with his stand on supplemental iodine. Furthermore, I felt strongly that the possibility exists that such obvious distortion for those who disagree on the iodine issue could lead Dr. Abraham, who I would guess is as honest and fair as the rest of us, to view the body of research and clinical information on iodine with less than total objectivity.

Of course, with the above stated, an old saying needs to be kept in mind.

"Judge not lest ye be judged."

In the last issue I also suggested that, in passing judgment on such a subjective issue, there exists the possibility that I may be oversteering. In turn, could my ability to accurately read and interpret Dr. Abraham's various scientific disclosures be impaired? So that you can best answer this question, in this issue I am going to do my best to set aside any thoughts on character and intent and focus purely on the scientific and research aspects of Dr. Abraham's many articles on iodine that have been published within the last 4-5 years. While, as I mentioned in part I, many researchers have published, in my opinion, credible studies that refute Dr. Abraham's position, I will reserve all but fleeting discussions of these studies for part III.

THE WORLD OF IODINE ACCORDING TO GUY ABRAHAM, MD

For ease of discussion I will be grouping Dr. Abraham's various commentaries on iodine into seven major subsections. These subsections are:

- Is iodine deficiency a major health concern?
- Is iodine involved in major physiologic pathways outside of those related to thyroid function?
- Do dietary population studies exist that support the idea that iodine intake above RDA levels of 150 mcg per day is healthy?
- Does Dr. Abraham's condemnation of these researchers who continue to support maximum daily iodine intake of 150 mcg per day have a scientific, biochemical basis?
- Do laboratory tests exist that can be used to clinically ascertain need for supplemental iodine?
- If it is true that daily intake of iodine should be higher than 150 mcg per day for most healthy and aging populations, what exactly is the right amount and what is the best form?
- What clinical outcomes were observed by Abraham when using milligram dosing iodine?

While many of Dr. Abraham's discussions focus on the basics of human iodine metabolism, I will not address them here. This is not only due to space considerations but due to the fact these discussions are relatively non-controversial and contain information that can be readily found in most basic nutritional biochemistry texts.

Is iodine deficiency a major health concern?

As you will see when I discuss papers written on the subject from 1949-1968/1978, this question is actually quite non-controversial. For many now feel that even after years of adding iodine to table salt, iodine deficiency is a significant issue not only in this country but worldwide. What specifically does Abraham have to say about prevalence of iodine deficiency? The following comes from the article "Optimum levels of iodine for greatest mental and physical health" (1).

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A PERSPECTIVE ON HIGH DOSE IODINE SUPPLEMENTATION – PART III – DOES ABRAHAM’S APPROACH WORK AND WHAT DOES THE REST OF THE WORLD THINK? CLINICAL OUTCOMES OBSERVED BY ABRAHAM WHEN USING MILLIGRAM DOSING IODINE – PUBLISHED RESEARCH While it is certainly important, in my opinion, to understand Abraham’s world view of the biochemistry and physiology of iodine, as clinicians I would assume we are going to be equally interested in issues of efficacy. How did actual patients respond clinically to Abraham’s approach to iodine supplementation? I found four studies reporting patient response in three of Abraham’s papers. “Optimum levels of iodine for greatest mental and physical health” (1). “The concept of orthoiodosupplementation and its clinical implications” (2), and “The historical background of the iodine project” (3). As you will see, the studies can be divided into three major categories. One study did not employ iodine load testing either prior to the onset of supplementation or during supplementation to monitor progress. Another pair of studies employed iodine load testing both prior to and during supplementation. Finally, a fourth study did not employ load testing prior to supplementation but did so during the course of supplementation to monitor progress. Milligram dosing without use of the iodine loading test In “Optimum levels of iodine for greatest mental and physical health” (1), Abraham performed a study that examined the use of milligram supplementation of iodine without use of the iodine loading test. To begin the discussion of this study, I would first like to precisely define its purpose by quoting the authors’ goals:	“Our goal was to assess the effect of a standardized fixed amount of iodine within the range of daily amount of iodine previously used in fibrocystic disease of the breast (FDB), on blood chemistry, hematology, thyroid volume and function tests in clinically euthyroid women with normal thyroid volume by ultrasonometry, and subsequently trying the same women with FDB if there was no evidence of toxicity and adverse effects on the thyroid gland. The equivalent of 0.1 ml of a 5% Lugol solution, that is 12.5 mg I used chosen, a value close to the average intake of 13.8 mg consumed in Japan, a country with very low incidence of FDB; slightly higher than the 9 mg amount used in Marlene’s original study of adolescents, with a very low 0.5% incidence of iodism following this level of iodine supplementation; also within the range of the 10 to 20 mg amount used in the Russian study of FDB, without any side effects reported; and five times less than the largest amount of 62 mg used in Ohtani’s studies with a 3% iodism reported.” While I realize that the above quote is somewhat lengthy and involved, I feel it is important to diligently consider. Why? Many clinicians are now basing their clinical use of supplemental iodine solely on Abraham’s research. Because of this, I also feel it is important that my discussion of Abraham’s research identifies as best as possible the strengths and limitations of this research. Furthermore, I feel it is imperative that clinicians do not extrapolate more from these studies than what was originally intended by Abraham. Who were the participants in the study? Initially, they were 12 females who were basically healthy. What does “healthy” mean in the context of this study? The authors of this paper state: “They were ambulatory, without any serious medical problems, clinically euthyroid and on no medication known to affect thyroid functions.” Of the twelve, two were dropped from the study. One was dropped due to the presence of an enlarged thyroid that was detected upon physical examination. The other was dropped from the study due to lack of compliance.

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A PERSPECTIVE ON HIGH DOSE IODINE SUPPLEMENTATION – PART IV – IODINE AND BREAST HEALTH As I mentioned at the end of part III of this series, I do feel that one of greatest services provided by Guy Abraham’s writings on iodine was emphasizing to the professional nutrition community that iodine is much more than just “the thyroid nutrient.” In fact, a large body of research which has been almost totally ignored by most of us until Abraham brought it to our attention makes a very strong argument that iodine is as much a “breast nutrient” as it is a “thyroid nutrient.” In closing the last installment of this series, I presented the intriguing title of a paper by Abovitz et al (1), “Is iodine a paleowomen of the integrity of the mammary gland?” While this title is certainly very dramatic given the distinct lack of attention the iodine/breast relationship has received over the years, is it deserved? Based on the body of literature I am about to present, I hope we can agree that the answer to this question is certainly in the affirmative. However, according to Abraham, the relationship is only part of the story. As you may recall, Abraham recommends a supplement that is composed of both molecular iodine (I₂) and iodide (I⁻) in the form of potassium iodide. Why? As I mentioned in part II, one major reason is that he feels that different organs have different uptake of different forms of iodine. In particular, according to Abraham, the breast seems to favor molecular iodine. As I hope you will also see from the literature I am about to present, this claim by Abraham certainly has merit. However, before diving into the specific facet of iodine’s relationship with the breast, I would like to present some introductory information that explains why the relationship exists at all. SOME BACKGROUND INFORMATION ON THE IODINE/BREAST CONNECTION Why do we need iodine at all? Venturi et al (2) proposes an interesting evolutionary perspective to this question:	“Over three billion years ago, algae, which contain the highest amount of iodine, were the first living cells to produce oxygen, which was toxic at that time, in the terrestrial atmosphere. So, algae cells required a protective antioxidant action in which iodides might have had a specific role. In fact, iodides are greatly present and available in seawater, where algae phytoplankton serve as a principal accumulator of iodides.” Venturi et al (2) continue: “When primitive marine vertebrates started to emerge from the iodine-rich sea and transgressed to iodine-deficient fresh water and finally land, their diet became iodine deficient and algae harbored vegetable iodide competitors such as nitrates, nitrites, thiocyanates, and some glycosides.” With this evolutionary perspective in mind, what role does iodine play in cellular metabolism? The authors state: “We may chronologically differentiate on the basis of the phylogenetic and embryogenesis three ways of action of iodine: 1) an ancient and direct action, on endodermal fore-gut and stomach and on ectodermal epidermis, where inorganic iodine probably act as antioxidants. 2) a recent and direct action, on fetal pre-hormonal thyroid and on salivary and mammary glands, thymus, ovary and on nervous, arterial and skeletal systems, where inorganic iodides are active. 3) a recent and indirect action on the thyroid and its iodinated hormones, on all vertebrate cells, which makes use of specific organic iodine-compounds: thyroxine (T4) and triiodothyronine (T3), which act in very small quantities and utilize T2-receptors. Indeed, thyroid hormones contain less than 1 mg of iodine and less than 1/100 – 1/60 of total iodine amount.” Thus, as I hope you can see, Abraham’s claim that iodine has varied functions throughout the body beyond those relating to thyroid hormones is certainly supported by other peer-reviewed papers. Furthermore, other researchers certainly seem to

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A PERSPECTIVE ON HIGH DOSE IODINE SUPPLEMENTATION – PART V – THE JAPANESE EXPERIENCE WITH DIETARY IODINE INTRODUCTION

So far, as you may have noticed, this examination of published iodine research as it relates to Gary Abraham's world view of dietary and supplemental iodine has offered very little conflict or disagreement. Why? As I have suggested in the last two newsletters, a large body of credible research strongly supports two of Abraham's primary issues of contention. First, there appears to be little disagreement that iodine deficiency is a major health concern worldwide. Second, a large body of research makes it clear that iodine plays a major role in human physiology: outside of thyroid function, particularly in relation to breast health. However, as you will see, the discussion in this newsletter on the epidemiologic issue for Abraham's claims will take on a much more contentious overtone.

Specifically, I will be examining one of the four primary scientific and clinical pillars that Abraham tries to support his contention that most Americans need to be ingesting large, milligram doses of supplemental iodine instead of microgram doses. What are these pillars? As you have seen in this series, three of them are more classically oriented. One refers to the many published clinical reports on the beneficial use of milligram dosing of supplemental iodine that appeared in the early 20th century. A second is the assertion that the iodine loading test is a valid way of determining iodine need and dosage. I will explore this pillar in more detail in a future newsletter. The third is that people feel better with five, if any, side effects when ingesting large milligram doses of supplemental iodine. I will also examine this pillar in greater detail in a future newsletter, with particular emphasis on incidence of side effects.

The fourth pillar, though, is the only one that, in my opinion, has more of a scientific basis. What is

this pillar? It is Abraham's review of the published epidemiologic studies on the Japanese experience with large dietary sources of iodine, principally via the ingestion of seaweed. Specifically, as you saw in part II of this series, Abraham presents research to support his claim that the Japanese are among the healthiest people on earth, largely due to seaweed-based dietary consumption of 13.8 mg of iodine per day. In turn, Abraham repeatedly refers to the Japanese data to justify routine intake of 12-15 mg or more of supplemental iodine by the vast majority of adult Americans.

As examples of Abraham's many claims about the Japanese and their experience with dietary iodine, I presented the following quotes in part II of this series:

"Due to the large consumption of seaweeds in the Japanese diet, this population ingests several milligrams of I daily without ill effects and in fact with some very good results evidenced by the very low incidence of fibrocystic disease of breast and of the low mortality rates for cancers of the female reproductive organs."¹

"Pittman, et al., were referring to mainland Japanese who consume a daily average of 13.8 mg (13,800 µg) of iodine from seaweed when they mentioned 'groups ingesting diets unusually rich with iodine.' Based on statistics generated some 20 years ago, mainland Japanese represent one of the healthiest nations on earth."

"According to the Japanese Ministry of Health and Welfare, the average daily intake of seaweed is 4.6 gm. At an average of 0.3% I content (range = 0.08-0.43%), that is an estimated daily I intake of 12.8 mg. Japanese living in the coastal areas consume more than 13.8 mg."

In summary, I feel that Abraham's claims about the Japanese experience with dietary iodine can be distilled down to the following:

- The Japanese are some of the healthiest people on earth.
- This good health is due to ingestion of dietary iodine.
- The Japanese ingest dietary iodine in amounts of 13.8 mg per day or more.

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A PERSPECTIVE ON HIGH DOSE IODINE SUPPLEMENTATION – PART VI – RACIES CONCERNING IODINE ABSORPTION, METABOLISM AND THEIR IMPACT ON THYROID FUNCTION INTRODUCTION

In concluding the last installment of this series, I stated that the installment would be devoted to discussing research on dose, efficacy, and side effects in western societies. Stated more simply, I would be addressing the major controversy concerning milligram dosing of iodine: whether or not it truly causes thyroid related side effects in a significant number of patients. However, it has occurred to me that this discussion may be a bit premature at this point. Why? It is my belief that this discussion will have the most value if it is understood how supplemental iodine, very specifically, makes its way into the body. Ironically, though, in today's world of research and information overload relating to clinical nutrition, iodine occupies a somewhat unique niche. As we all know, discussions of virtually all vitamins and minerals are incomplete unless information concerning digestion, absorption, and tissue uptake are included. Therefore, we can learn to almost any quality text or article in our personal libraries and find astounding descriptions of digestion, absorption, tissue uptake, and metabolism of nutrients such as vitamins C or magnesium. Can the same be said about iodine? After a fairly extensive examination of several high quality textbooks and papers on micronutrients, I was very surprised to find out that the answer to this question is "No". In fact, I found out, much to my frustration, that in contrast to the other micronutrients, hard information as to what happens to iodine between the time it is ingested and before it gets into the thyroid is in fact ignored and almost nonexistent in the literature. With this unfortunate reality in mind, can we ever fully understand how to effectively administer supplemental iodine to patients or why some patients have adverse reactions? To answer this question, I would like to ask another question. Can we fully understand how to effectively and safely administer supplemental vitamin C or calcium or magnesium without at least a basic knowledge of their digestion, absorption, tissue uptake, and metabolism? I would expect that the vast majority of you would emphatically answer "No" to the latter question. It is my

opinion that if you answer to the latter question is "No", so you must your answer be "No" to the former. In fact, there is no question in my mind that one of the reasons why the subject of iodine nutrition is so controversial right now is the fact that we as clinicians know so little about what happens to dietary iodine in the body before it gets into the thyroid. Just one example of this is the interesting relationship between iodine and breast health. As you read in part IV of this series, supplemental molecular iodine (I₂) is much more effective in optimizing breast health than the more common form of supplemental iodine, iodate (I⁻). However, as you will see, common lore suggests that all dietary iodine is converted to the iodide form in the gut before it is absorbed. Obviously, both of these statements cannot be correct. So what exactly is the truth? As you will see, some very good but seldom read and quoted research resolves this seemingly unresolvable quandary very simply. Could many of the other aging iodine controversies concerning dose and safety that we are discussing about daily now be resolved as simply if we just had a better understanding of what happens to dietary iodine before it gets into the thyroid? I do believe so. Therefore, I would now like to explore an issue that, ironically, has been a major focus of attention with almost every micronutrient except the one that is so many ways may be receiving more attention than any other right now: iodine.

Before continuing, though, I would like to offer a sincere thank you and appreciation to Dr. Abraham. While, as you have seen, I have been highly critical of many of his statements on iodine nutrition, I applaud his efforts to enlighten the idea that we need to seriously consider the neglected research on the different forms of dietary iodine and how they are digested, absorbed, and metabolized outside of the thyroid. There is no question that I would not be presenting this vitally important discussion that follows without his writings on the subject. Furthermore, I would not be more of much of the research that follows without his assistance. Therefore, for all that follows, I offer a sincere "Thank you" to Dr. Abraham.

IODINE DIGESTION AND ABSORPTION

As I suggested, this discussion primarily revolves around the different forms of iodine. Therefore, I would like to begin by again briefly reviewing the two different forms of iodine that were initially highlighted in the iodine and breast health newsletters. "Iodate", in this context refers to molecular iodine, often referred to as "I₂". "Iodide"

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A PERSPECTIVE ON HIGH DOSE IODINE SUPPLEMENTATION – PART VII: CAN HIGH DOSE IODINE SUPPLEMENTATION SUPPRESS IODINE UPTAKE INTO THE THYROID?

INTRODUCTION

In the last installment of this series I examined in detail how iodine finds its way into the thyroid. As you may recall, this process is largely regulated by a mechanism called the sodium iodide symporter (NIS). Given its complexity, though, why exactly is it important that we understand the NIS and the whole process of transport into the thyroid? The reason, as I suggested, is the fact that, despite all the very positive iodine and breast health and negative information I have presented on iodine so far, the main controversy underlying the issue of milligram iodine dosing in the impact high dosing has on the thyroid. *Is it harmful to the thyroid?* As I have suggested throughout this series, it is indeed unfortunate that this question seems to have divided the nutrition community into two passionate and somewhat confrontational camps. One camp very often answers the question with a bit righteous, self-assured, all-encompassing “No”. The other camp, in turn, answers “Yes” with equal fervor. Nevertheless, for me, as I have suggested all along, the position that each camp has for positions that are diametrically opposed leaves me with more confusion, not less. Of course, this confusion was partially ameliorated when we learned that Abraham’s claim that high levels of dietary iodine had no adverse effect on the Japanese was incorrect. In fact, a significant volume of literature suggests that a small but significant portion of the Japanese population has suffered thyroid problems due to high levels of dietary iodine. However, in this epidemiologic association enough to confidently and, with absolute assurance, answer the question mentioned above that has created so much passion and controversy? In my opinion, no.

Ultimately, I do believe that if we are ever to take this question out of the realm of fanaticism and passion and into a world of logic and dispassionate evaluation, we must have a much better understanding of what exactly happens when the thyroid first encounters milligram doses of iodine. For me, this understanding can only come when the workings of the NIS are fully appreciated.

Based on part VI of this series, what do we know about the NIS? First, because of large fluctuations in the amount of iodine to which we are exposed in the food supply, the NIS is a necessary “checkpoint” to keep the amount of iodine entering into the thyroid fairly constant. Second, genetic aberrations plus a series of environmental factors such as toxicity and inflammation can adversely affect the ability of the NIS to do its job correctly. Before continuing, I would like to elaborate a bit on this aspect of NIS function. On the surface, knowing that functional medicine issues such as inflammation and toxicity can affect the rate of iodine flow into the thyroid may seem relatively insignificant. However, I do feel that once this relationship is fully appreciated, our attitudes on this controversy of milligram dosing of supplemental iodine must be profoundly altered. In turn, the simple question of whether high dose iodine is “good” or “bad” for the patient becomes completely inappropriate. Instead, we must now ask whether certain unique aspects of the patient’s overall biochemistry and physiology are causing the patient to react negatively or positively to high dose iodine. If this is true, we can no longer simply condemn or praise iodine when bad or good things happen after iodine administration. In particular, if something bad happens, we must now ask, in addition to the question of whether high dose iodine per se is causing problems, whether something else in the patient’s unique biochemical/physiologic profile is contributing to a negative reaction to iodine. Next, if we find that this is true, we must make efforts to correct the underlying biochemical/physiologic imbalances first.

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A PERSPECTIVE ON HIGH DOSE IODINE SUPPLEMENTATION – PART VII: SOME “BIG PICTURE” THOUGHTS ON ALL THAT I HAVE WRITTEN IN THIS SERIES SO FAR

“What is there that is not poison? All things are poison and nothing (is) without poison. Solely the dose determines that a thing is not a poison.” – Paracelsus (1493-1541)

As I mentioned at the end of the last installment, it was my intention in this issue to focus on Abraham’s position on the Wolff-Chaikoff effect. However, recent discussion with many of you on the subject of iodine supplementation has led me to conclude that, after spending over a year examining iodine research through my own eyes as well as the eyes of Abraham and the world’s foremost iodine researchers, it is time to step back for a bit and ponder some “big picture” thoughts in terms of what it all means from a clinical, patient management perspective. In taking this time to detach myself from the minutia inherent to the research world, my focus on the “big picture” really led me to what seems to be, based on your comments, the major clinical concern. *Can milligram dosing of supplemental iodine cause side effects and adverse reactions?* Because of your ongoing and very necessary concern about this question, I am going to devote this installment of the series to this issue. In contrast, to typical discussions in this series, though, I will not be presenting a parade of studies that prove milligram dosing of iodine will cause adverse effects with some individuals. Why? I have already done this in previous installments, yet the controversy and passions still persist.

Because of this I am going to approach the controversy from a different perspective. First, I am going to discuss why the possibility that milligram dosing of iodine might cause adverse effects in some individuals has aroused such intense passions on both sides. Second, I am also going to outline my perspective by exploring the idea that, as suggested by Paracelsus, everything on earth under the right circumstances will cause adverse reactions. Finally, I am going to present some thoughts and ideas as to why we in the clinical nutrition community have such a difficult time dealing with this reality.

SOME “BIG PICTURE” THOUGHTS ON ABRAHAM’S ATTITUDES ON IODINE RELATED SIDE EFFECTS

As I mentioned, after examining iodine research from the point of view of Abraham and when for over a year now as well as from your point of view via your feedback, it appears that the same clinical controversy that is first and foremost in the minds of most of us is the risk of significant adverse, thyroid-related effects of milligram dosing of supplemental iodine for significant segments of the population. Of course, as suggested by Paracelsus above, anything at a certain dose will cause adverse effects in someone. However, as I have tried to point out so far in this series, Abraham seems to suggest that iodine is exempt from this scenario, being safe for everyone at virtually any dose up to 60-100 mg per day, an amount that is several thousand percent higher than RDA levels. Other than his personal assurance and limited clinical research, what proof does he offer that his position is correct? Based on my examination of his writings that you have been reading over the past year, it appears to me that research-based proof offered by Abraham can be distilled down to two key assertions. First, the Japanese have been ingesting approximately 12 mg per day of iodine *on average* (which means many Japanese have been ingesting amounts that are considerably higher) for generations with no ill-effects whatsoever. As I hope I conveyed to you in the argument of this series in which I explored both Abraham’s references and the research produced by others in relation to this issue, it appears that Abraham’s beliefs about the Japanese experience with dietary iodine is in error.

The second assertion is that the Wolff-Chaikoff effect was only a non-existent but reversible “plot by medical inadequacies” to keep daily intake of iodine for the average American at levels no higher than 150 mcg. In the last issue I explored both the impact of iodine on thyroid function in general and specifically its relationship to the Wolff-Chaikoff effect, looking through the eyes of researchers publishing in peer-reviewed journals. In the next issue I will begin to explore the Wolff-Chaikoff effect through Abraham’s eyes as detailed in his

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A PERSPECTIVE ON HIGH DOSE IODINE SUPPLEMENTATION – PART IX – BREAKING IODINE NEWS PLUS A DISCUSSION OF ABRAHAM'S PERSPECTIVE ON THE WOLFF-CHAIKOFF EFFECT

BREAKING NEWS ON THE IODINE CONTROVERSY

Update on the daily iodine intake in Japan

Since writing part VIII of this series, two documents have been brought to my attention that I feel have tremendous significance in relation to two of the major controversies being discussed in this series. The first document is a recently published letter to the editor entitled "The average of dietary iodine intake due to the ingestion of seaweed is 1.2 mg/day in Japan" by Nagasaki (1). As the title suggests, it supports my conclusion published in part V of this series, based on a review of the literature available to me at that time, that Abraham's claim concerning the Japanese average daily intake of dietary iodine, primarily from seaweed ingestion, is incorrect. As you may recall, Abraham has claimed that the average intake of iodine in Japan is approximately 13.8 mg per day, mostly from seaweed. In contrast, my review of the literature suggested that the average Japanese intake ranges from 1–5 mg per day. However, Nagasaki (1) in his recently published paper suggests that the average intake may even be less than this.

In addressing this issue, Nagasaki (1) first points out the important but often ignored fact that iodine content can often vary greatly depending on the species of seaweed:

"Iodine content of seaweeds differ greatly according to species. *Laminaria* (Konbu) contains 0.3% of iodine by dry weight; *Enteromorpha* (Wakame) 0.02–0.03%, and *Porphyra* (Nori) <0.01%."

With these differences in mind, iodine intake was calculated using the following criteria:

"Konbu was selected to calculate the average dietary iodine intake. The Family

Income and Expenditure Survey by the Statistics Bureau, Ministry of Internal Affairs and Communications included 8749 target households in 2006 and the survey included items pertaining to specific consumption, such as Konbu. The other method was to calculate iodine intake from the total consumption of Konbu in Japan using data obtained from the Japan Konbu Association."

Using the first methodology based on household evaluation, the following results were noted:

"The average annual consumption of Konbu per household (two or more persons per household, average of 3.16 persons per household) in Japan is 450 g by dry weight, that is, 1.17 mg of iodine per day per person. Consumption of Konbu per household has decreased gradually by 10% in the last 10 years; from 641 g in 1996 to 450 g in 2006."

Using the second methodology based on total consumption of Konbu in Japan, the following results were noted:

"Total consumption of Konbu in Japan is 20,000 tons per year by dry weight. Since the population of Japan is 130 million, the iodine intake by the ingestion of Konbu is 1.36 mg/d per person."

Given the similarity of the results from these two different methodologies, Nagasaki (1) concluded:

"The results of methods numerically derived from independent two sources are remarkably similar and it may be concluded that the average of daily iodine intake through Konbu is about 1.2 mg in Japan."

Of course, it can rightly be stated that these findings do not necessarily indicate total average daily intake from all sources. In response to this concern, the author notes:

"Of course, iodine intake from Konbu is not the total iodine intake, but the answer to the question 'What is the iodine intake in Japan?' may be that excessive iodine intake in Japan is due to the ingestion of

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⇒ Literature Review & Commentary ⇒

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A PERSPECTIVE ON HIGH DOSE IODINE SUPPLEMENTATION – PART X – MORE THOUGHTS ON ABRAHAM'S PERSPECTIVE ON THE WOLFF-CHAIKOFF EFFECT AND THE OVERALL RISKS OF SUPPLEMENTAL IODINE ON THYROID FUNCTION

As I resume my exploration of controversies relating to the biochemistry, physiology, and clinical applications of high dose iodine, I would like to thank you for your many kind comments on the dossier I have taken over the last three issues of the Moss Nutrition Report where I explored the subject of fear as it relates to the practice of clinical nutrition. While, at first glance, I admit it might have seemed a bit abrupt and out of place, I hope you can relate to my desire to fully address and understand a key question that has been bothering in my mind right from the time I first began this iodine series:

Why are so many proponents of clinical use of milligram dosing of iodine so hard and determined to convince everyone that, unlike every other substance on earth, iodine is totally and completely risk free for everyone at doses that are several thousand times the RDA?

For me, and hopefully for you, the research that I presented in the just completed "Fear and Loathing in Clinical Nutrition" series provides at least a satisfactory answer as to why so many are so driven on this issue. In short, now that this question is no longer burning around in my mind and creating a distraction, I am ready to focus again more fully on iodine physiology, biochemistry and clinical application. As a review, I would like to present some conclusions that can be made about milligram dosing of supplemental iodine based on the literature and commentary presented thus far:

1. Abraham and his colleagues appear to be in agreement with a large body of research that suggests iodine has important physiologic applications outside of the thyroid. In turn, doses higher than the RDA (150 mcg per

day) appear to be warranted in a large percentage of both healthy and chronically ill populations.

2. Abraham and his colleagues appear to be in agreement with a large body of research that suggests different forms of supplemental iodine may be appropriate depending on patient need. More specifically, iodine appear to be more appropriate for thyroid related issues and molecular iodine appears to be more appropriate for extrathyroidal issues such as breast health.
3. It is my opinion that use of the term "medical iodophore" to describe researchers and authors who disagree with the positions taken by Abraham and colleagues is highly unprofessional and has no place in scientific publications.
4. The claims by Abraham and colleagues that double-digit levels of daily iodine intake are completely without risk to anyone is primarily based on two hypotheses. The first relates to the Japanese experience with dietary iodine intake from kelp. My examination of the literature suggests that the claim made by Abraham and colleagues that the population at large should be ingesting 12–13 mg of iodine per day based on epidemiologic observations that the Japanese have long been ingesting the same amount daily without any side effects via the kelp contents of their diet is not in agreement with published data. As you may recall, concerning quantity, the reference used by Abraham to justify this claim was incorrectly quoted. Furthermore, the recently published paper by Nagasaki (1) makes it clear that the average daily intake of the Japanese is 1.2 mg per day. Finally, Nagasaki (1) is in agreement with several other researchers I have quoted who note that daily double-digit doses of dietary iodine have been linked with many cases of thyroid related side effects among Japanese

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Thank you!!

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