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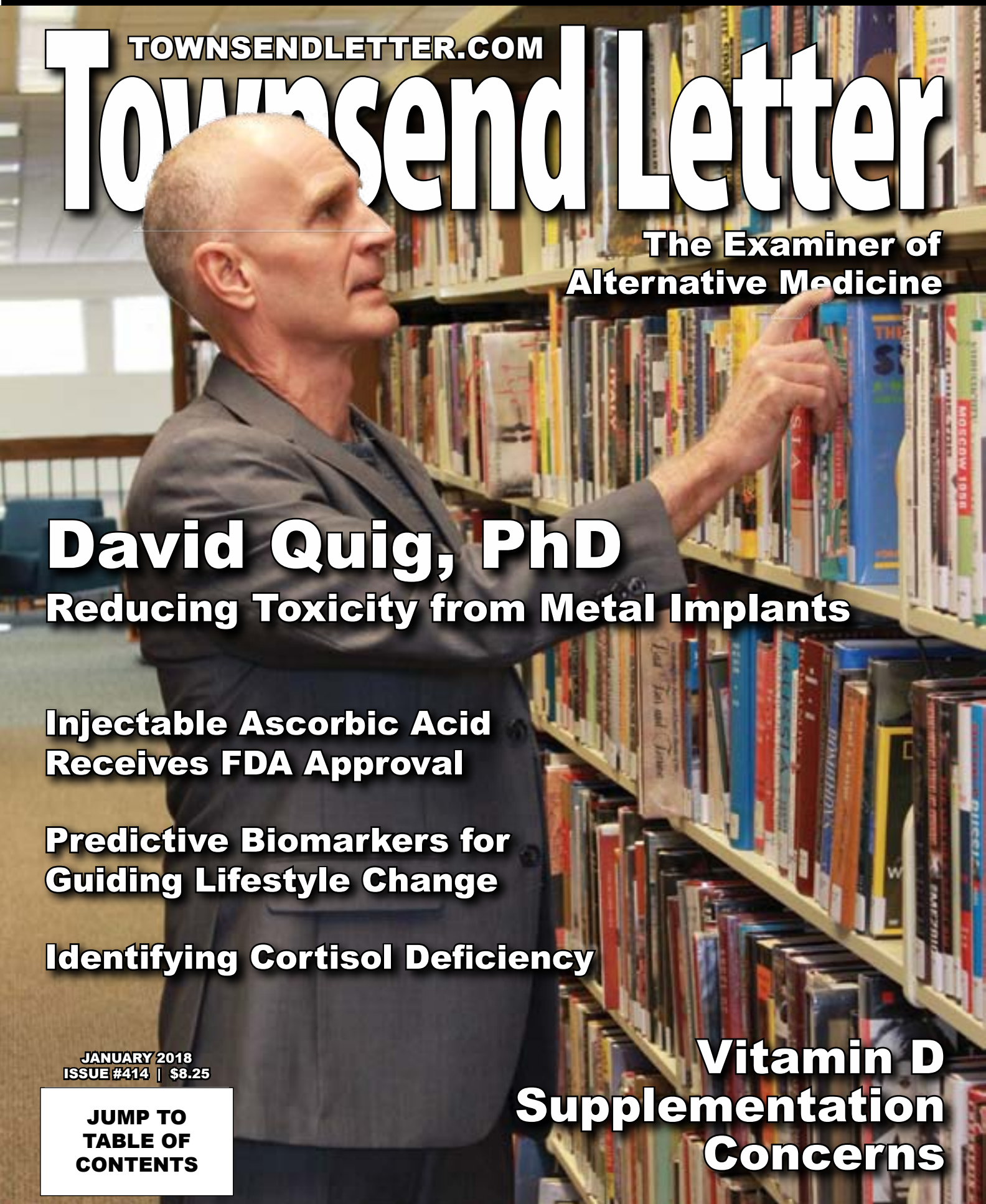

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From the Publisher

The Ongoing War Against Homeopathy

Wikipedia is well accepted as a digital encyclopedia and is an important “go-to” tool for a quick introduction to any topic with detailed references. Because it is a digital research source, it is edited frequently; however, each Wikipedia topic is assigned to an “editor” and without approval from the editor, text changes may not be made.

Homeopathy is a topic that is discussed in great detail – it exceeds the text length of Wikipedia’s write-up of topics such as “World War 2” and “Physics.” The introductory sidebars are headlined by support of *Skeptical Inquirer,* a group that has a rabid dislike of alternative medicine, naturopathy, and homeopathy. As seen below, the Wikipedia intro finds that homeopathy is unscientific, ineffective, quackery, and a sham. Any benefit from homeopathy is thought to be placebo-based or the result of “tincture of time” without any benefit from the remedy.

Despite new research studies being published, critics argue that the studies yielding positive benefits were due to poor methodology and accepted by journals with biased peer-review; the biased writing observed throughout the Wikipedia report was not considered biased. The studies evaluating homeopathy in the Wikipedia report used a pharmaceutical-based model. Accepted studies required the use of double-blinded, placebo-controlled methodology with the use of non-individualized treatment of all subject patients--this violates all the tenets of homeopathy. Where patients were not randomized, where patients received individualized treatments, there were positive benefits compared to placebo, although the Wikipedia writers called this a minimal effect. Individual case reports were dismissed outright. And, of course, homeopathy’s modus of action based on a highly diluted substance exceeding Avogadro’s number was lambasted as absolute pseudoscience; one physicist was quoted as saying that a remedy of 30C potency would require an inconceivable volume to contain a single molecule of the original substance:

> Physicist Robert L. Park, former executive director of the American Physical Society, is quoted as saying:
>
> ‘…since the least amount of a substance in a solution is one molecule, a 30C solution would have to have at least one molecule of the original substance dissolved in a minimum of 1,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000 [or 10^{60}] molecules of water. This would require a container more than 30,000,000,000 times the size of the Earth.’
>
> Barrett S (December 28, 2004). “Homeopathy: the ultimate fake”. Quackwatch. Retrieved July 25, 2007.

None of this would be terribly of concern except for the fact that politicians and administrators just like the public use Wikipedia as a “go-to” resource to get up to speed on a topic. The Wikipedia write-up is biased with only two types of references – those that are condemnatory and those that are slanted as ineffective. Given the policy decisions that have begun to increasingly curtail public resources for homeopathic treatment, Wikipedia’s report, as shown below, becomes a manifesto to eliminate homeopathy.

> **Homeopathy** is a system of alternative medicine created in 1796 by Samuel Hahnemann, based on his doctrine of like cures like (*similia similibus curentur*), a claim that a substance that causes the symptoms of a disease in healthy people would cure similar symptoms in sick people.[1] Homeopathy is a pseudoscience – a belief that is incorrectly presented as scientific. Homeopathic preparations are not effective for treating any condition;[2][3][4][5] large-scale studies have found homeopathy to be no more effective than a placebo, indicating that any positive effects that follow treatment are only due to the placebo effect, normal recovery from illness, or regression toward the mean.[6][7][8]
>
> “Hahnemann believed the underlying causes of disease were phenomena that he termed miasms, and that homeopathic preparations addressed these. The preparations are manufactured using a process of homeopathic dilution, in which a chosen substance is repeatedly diluted in alcohol or distilled water, each time

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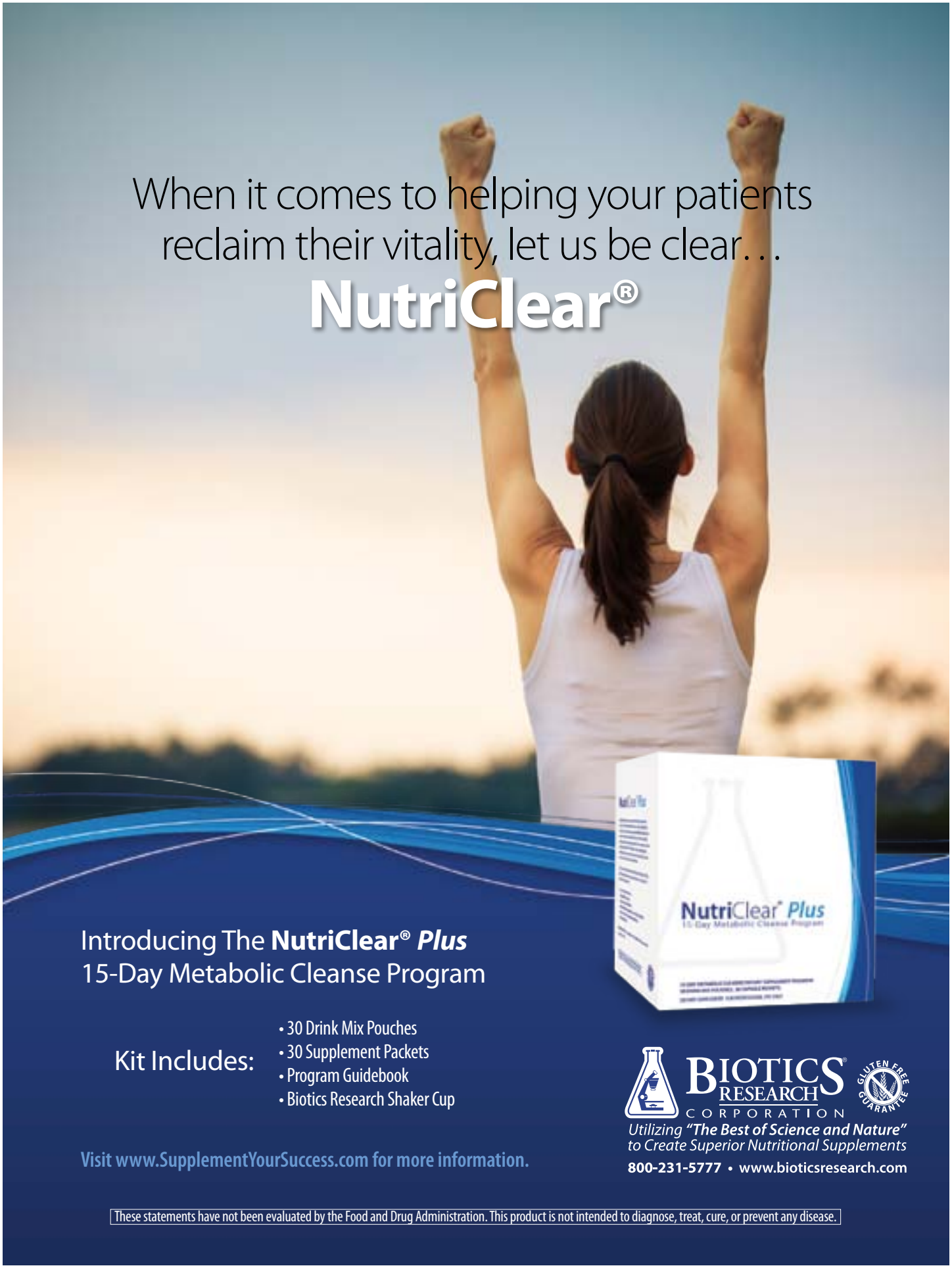
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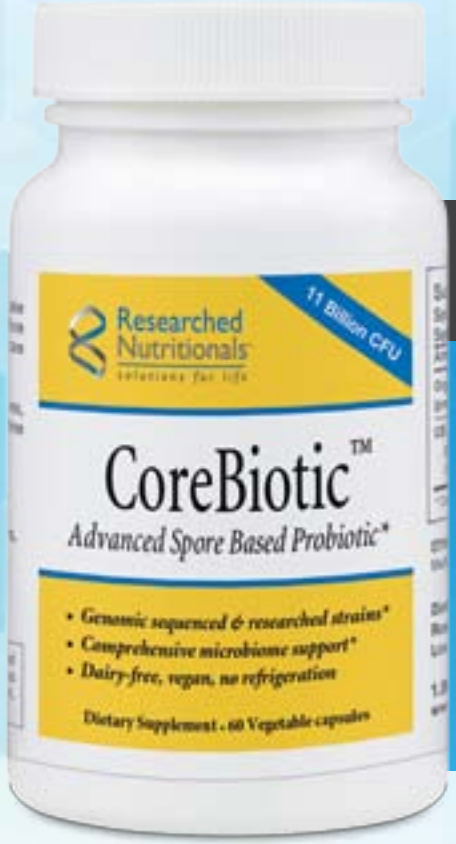

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➤ *continued from inside cover bi-fold*

with the containing vessel being bashed against an elastic material, (commonly a leather-bound book).[9] Dilution typically continues well past the point where no molecules of the original substance remain.[10] Homeopaths select homeopathics[11] by consulting reference books known as repertories, and by considering the totality of the patient's symptoms, personal traits, physical and psychological state, and life history.[12]

Homeopathy is not a plausible system of treatment, as its dogmas about how drugs, illness, the human body, liquids and solutions operate are contradicted by a wide range of discoveries across biology, psychology, physics and chemistry made in the two centuries since its invention.[7][13][14][15][16][17] Although some clinical trials produce positive results,[18][19] multiple systematic reviews have indicated that this is because of chance, flawed research methods, and reporting bias. Continued homeopathic practice, despite the evidence that it does not work, has been criticized as unethical because it discourages the use of effective treatments,[20] with the World Health Organization warning against using homeopathy to try to treat severe diseases such as HIV and malaria.[21] The continued practice of homeopathy, despite a lack of evidence of efficacy,[6][7][22] has led to it being characterized within the scientific and medical communities as nonsense,[23] quackery,[4][24] and a sham.[25]

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From the Publisher

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24. Boyer, Paul S. *The Oxford Companion to United States History.* ISBN 9780195082098. Retrieved January 15, 2013. "After 1847, when regular doctors organized the American Medical Association (AMA), that body led the war on "quackery," especially targeting dissenting medical groups such as homeopaths, who prescribed infinitesimally small doses of medicine. Ironically, even as the AMA attacked all homeopathy as quackery, educated homeopathic physicians were expelling untrained quacks from their ranks."
25. "Supported by science?: What Canadian naturopaths advertise to the public." Retrieved January 15, 2013. "Within the non-CAM scientific community, homeopathy has long been viewed as a sham"

Russell Jaffe, MD, PhD, and Jayashree Mani, MS, CCN, on Predictive Biomarkers

Most laboratory testing is focused on establishing or confirming a medical diagnosis. Of course, it is very important to rule out a disease; and when a lab test does that, both the practitioner and the patient are assured. Contrarily, an abnormal result in laboratory screening may direct the practitioner to a diagnosis that was not even considered or assumed not to be likely. In the former scenario, a series of normal liver function tests generally dismisses liver disease; in the latter case, elevated thyroid hormone tests strongly suggest hyperthyroidism. Of course, there are many situations when an abnormal laboratory screen, while suggestive of a diagnosis, does not predictably confirm one. And, most practitioners routinely face the situation of normal lab test screening despite major acute symptom impairment. Abnormal antibody screening may suggest a disease but generally

continued on page 12 ➤

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1. *L. crispatus* LbV 88
2. *L. jensenii* LbV 116
3. *L. gasseri* LbV 150N
4. *L. rhamnosus* LbV 96

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Clinical Study #1 (1999)

In a study of 319 women visiting three medical clinics, most women's normal vaginal bacterial residents included *L. crispatus* (32%), followed by *L. jensenii* (23%), *L.* 1086V (15%), *L. gasseri* (5%), *L. fermentum* (0.3%), *L. oris* (0.3%), *L. reuteri* (0.3%), *L. ruminis* (0.3%), and *L. vaginalis* (0.3%).*

Antonio MAD, *et al. Journal of Infectious Diseases* 1999;180:1950–6.

Clinical Study #2 (2007)

In another study involving 126 healthy pregnant women, *L. crispatus* and *L. gasseri* were the most dominant species found, followed by *L. jensenii* and *L. rhamnosus*.*

Kiss H, *et al. BJOG: An International Journal of Obstetrics & Gynaecology* 2007;114: 1402-1407.

Clinical Study #3 (2014)

In a double-blind, randomized placebo-controlled trial, 1-week of oral supplementation with the four Astarte strains significantly enriched *Lactobacilli* in the vaginal tract and reduced Nugent score in the neo-vagina of post-operative transsexual women, an environment typically resistant to colonization by *Lactobacilli.*

Kaufmann U, *et al. Eur J Obstet Gynecol Reprod Biol.* 2014 Jan;172:102-5.

Clinical Study #4 (2016)

In immunosuppressed pregnant women with herpes infection, oral supplementation with the four Astarte strains significantly reduced undesirable microbes in the intestines and vagina, and simultaneously increased vaginal *Lactobacilli* 3-fold compared to placebo.* This was accompanied by reduced incidence of placental insufficiency, pre-eclampsia and fetal distress in the probiotic supplemented women.

Anoshina TM, *et al. Perinatologiya I Pediatriya* 2016;4(68):22-25.

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➤ *continued from page 10*

does not confirm it; chronic fatigue and fibromyalgia rarely demonstrate abnormal lab testing. Laboratory screening remains an important component of the diagnosis, and this is the primary function for running tests. What if another goal of laboratory testing was not to make a diagnosis but to assess an individual's long-term survival and quality of life?

As challenging as that may seem, Russell Jaffe, MD, PhD, and Jayashree Mani, MS, CCN, review laboratory tests that serve as predictive biomarkers (PB) to assess one's quality of life and likelihood of surviving for an ensuing ten years. A predictive biomarker not only must have a high degree of sensitivity and specificity but must have the capability of improving with positive changes in lifestyle and, contrariwise, worsening with negative changes in lifestyle. Antibody studies, for example, do not always have a high degree of sensitivity and specificity nor do they change with one's lifestyle. Hence, most antibody studies would not be appropriate PB tests. While the WBC count and RBC count do have a high degree of sensitivity and specificity, these tests are frequently seen to be normal in healthy and sick individuals; hence they would not be appropriate PB tests. On the other hand, glycosylated hemoglobin (a1c), highly-specific C-Reactive Protein (hs-CRP), and homocysteine all have a high degree of sensitivity and specificity and respond positively and negatively to lifestyle changes. More importantly, optimal scores for glycosylated hemoglobin, hs-CRP, and homocysteine correlate well with greater likelihood of ten-year survival, while sub-optimal scores have lesser likelihood of ten-year survival. Furthermore, these tests serve as appropriate monitors of overall treatment success or failure.

Besides these tests, Jaffe and Mani detail five additional tests that also function as predictive biomarkers. With these eight tests the practitioner is able to provide the

continued on page 14 ➤

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➤ *continued from page 12*

patient reasonable reassurance that the treatment strategy is not only sufficient for the immediate future but predicts a long-term positive outcome. When these tests are sub-optimal, the practitioner and patient are obligated to consider significant modification to treatment and lifestyle. The tests are reasonably inexpensive and can be repeated at frequent intervals providing a much more appropriate life assessment than the annual physical exam and basic lab screens.

Shalima Gordon, ND, on Assessing Testosterone and Prostate Cancer Risk

When we want information about prostate cancer risk, we usually measure a PSA level; if we are worried about low testosterone levels, we usually measure total testosterone and free testosterone. Shalima Gordon, ND, in this issue makes the case that these measurements are insufficient for understanding testosterone activity and assessing prostate cancer risk. Indeed, Dr. Gordon would argue that in order to understand testosterone activity and cancer risk we should do a thorough study of testosterone metabolites.

In 2003, the Prostate Cancer Prevention Trial (PCPT), a double-blind trial of finasteride studying 18,882 healthy males, determined that the drug reduced the risk of acquiring prostate cancer by 25%. However, the individuals using the finasteride had a 67% higher risk of developing aggressive high-risk prostate cancer.

How could this be? One of the testosterone metabolites, 3β-Adiol, known to inhibit prostate cancer cell proliferation, is generally reduced in the finasteride treatment group. Finasteride, a 5α-reductase inhibitor, blocks the conversion of testosterone to dihydrotestosterone (DHT). However, while that activity is beneficial it also blocks the production of 3β-Adiol. Hence, an assessment of the 3β-Adiol levels would provide important insight in assessing a patient's prostate cancer risk.

From the Publisher

David Quig, PhD, on Hip Implant Metallosis

One of the major boons in medicine during the past five decades has been hip replacement surgery. Rather than spending old age as a cripple, hip arthroplasty has restored normal functioning to countless individuals not only permitting standing and walking but performance activities such as dancing. However, total hip replacement requires implanting a prosthesis that is composed of metal. Although the metal composition was initially viewed as inert and without adverse effects on individuals, orthopedic research has demonstrated that metal on metal alloys frequently decompose, and the metals do enter the circulation before being absorbed within organ tissues. The prostheses are made from materials composed of cobalt, chromium, molybdenum, titanium, and vanadium. When the alloys decompose, elevated levels of these metals are measurable in blood and urine. In fact, very high levels of cobalt and chromium are not unusual when hip prostheses begin to decompose. For the orthopedic surgeon, routine measurements of cobalt and chromium appear to be reasonable in monitoring the status of patients who have undergone hip arthroplasty.

In this issue David Quig, PhD, examines the iatrogenic metal burdens patients face with metal-on-metal hip prosthesis surgery. Quig also reviews the important role that both oral and intravenous chelation play in removing cobalt, chromium, and other metals from the body. Not surprisingly chelation is very effective in reducing serum levels of the elevated metals. However, Quig is forthright in recommending those patients who do have evidence of metal corrosion in their metal prosthesis consider its removal rather than simply depend on chelation to reduce the burden of metallosis.

Ron McGuff Announces the Vitamin C Struggle is Over!

The past two decades saw the transition from manufactured to compounded injectables including minerals, chelation, vitamins, and more. But for the past three years, the FDA has issued a series of draconian regulations that have hindered the compounding of injectables and interfered with doctor office practices. Ron McGuff details the demise of manufactured injectables, the rise and fall of the compounding of injectables, and the recent approval by the FDA for the new manufacturing of ascorbic acid for the first time in 20 years.

Jonathan Collin, MD

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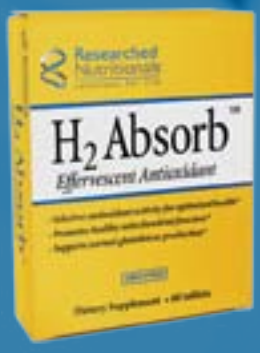

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ON THE COVER: Reducing Toxicity from Metal Implants (pg. 31); Injectable Ascorbic Acid Receives FDA Approval (pg. 21); Predictive Biomarkers for Guiding Lifestyle Change (pg. 74); Identifying Cortisol Deficiency (pg. 52); Vitamin D Supplementation Concerns (pgs. 74 and 98)

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ASCOR® safely and effectively. See full prescribing information for ASCOR.

ASCOR (ascorbic acid injection), for intravenous use

Initial U.S. Approval: 1947

INDICATIONS AND USAGE

ASCOR is vitamin C indicated for the short term (up to 1 week) treatment of scurvy in adult and pediatric patients age 5 months and older for whom oral administration is not possible, insufficient or contraindicated.

Limitations of Use

ASCOR is not indicated for treatment of vitamin C deficiency that is not associated with signs and symptoms of scurvy.

DOSAGE AND ADMINISTRATION

- Supplied in a Pharmacy Bulk Package (PBP). Dispense single doses to multiple patients in a pharmacy admixture program; use within 4 hours of puncture (2.1)
- Must be diluted prior to use (2.1)
- Administer as a slow intravenous infusion (2.1)
- See Full Prescribing Information for important administration instructions (2.1)
- Maximum recommended duration is one week (2.2)

Population (2.2)	**Recommended doses**
Pediatric patients age 5 months to less than 12 months	50 mg once daily
Pediatric patients age 1 year to less than 11 years	100 mg once daily
Adults and pediatric patients age 11 years and older	200 mg once daily
Specific Populations (2.3, 8.1, 8.2)	
Pregnant women, lactating women, patients with glucose-6-phosphate dehydrogenase deficiency	Should not exceed the U.S. Recommended Dietary Allowance (RDA)

DOSAGE FORMS AND STRENGTHS

Injection: 25,000 mg/50 mL (500 mg/mL) – Pharmacy Bulk Package

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Oxalate nephropathy and Nephrolithiasis: Ascorbic acid has been associated with development of acute or chronic oxalate nephropathy following prolonged use of high doses of ascorbic acid infusion. Patients with renal disease including renal impairment, history of oxalate kidney stones, geriatric patients, and pediatric patients less than 2 years old may be at increased risk (5.1).
- Hemolysis: Patients with glucose-6-phosphate dehydrogenase deficiency are at risk of severe hemolysis; a reduced dose is recommended (5.2).
- Laboratory Test Interference: Ascorbic acid may interfere with laboratory tests based on oxidation-reduction reactions, including blood and urine glucose testing (5.3).

ADVERSE REACTIONS

Most common adverse reactions are pain and swelling at the site of infusion (6)

To report SUSPECTED ADVERSE REACTIONS, contact McGuff Pharmaceuticals, Inc., toll free at 1-800-603-4795 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Antibiotics: Ascorbic acid may decrease the activities of erythromycin, kanamycin, streptomycin, doxycycline, and lincomycin. Bleomycin is inactivated in vitro by ascorbic acid (7.1).
- Amphetamine and Other Drugs Affected by Urine Acidification: Ascorbic acid may cause acidification of the urine and result in decreased amphetamine serum levels and affect excretion and plasma concentrations of other drugs sensitive to urine pH (7.2).
- Warfarin: Continue standard monitoring (7.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2017

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*FULL PRESCRIBING INFORMATION: CONTENTS**

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ASCOR® is indicated for the short term (up to 1 week) treatment of scurvy in adult and pediatric patients, age 5 months and older, for whom oral administration is not possible, insufficient or contraindicated.

Limitations of Use

ASCOR is not indicated for the treatment of vitamin C deficiency that is not associated with signs and symptoms of scurvy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Preparation and Administration Instructions

- ASCOR vials contain 25,000 mg of ascorbic acid and the largest recommended single dose is 200 mg. Do not give the entire contents of the vial to a single patient.
- Do not administer ASCOR as an undiluted intravenous injection.
- Minimize exposure to light because ASCOR is light sensitive.
- ASCOR is supplied as a **Pharmacy Bulk Package** (PBP) which is intended for dispensing of single doses to multiple patients in a pharmacy admixture program and is restricted to the preparation of admixtures for infusion:

a. Use only in a suitable ISO Class 5 work area such as a laminar flow hood (or an equivalent clean air compounding area).

b. Penetrate each PBP vial closure **only one time** with a suitable sterile transfer device or dispensing set that allows measured dispensing of the contents. Given that pressure may develop within the vial during storage, exercise caution when withdrawing contents from the vial.

c. Once the closure system has been penetrated, **complete all dispensing from the PBP vial within 4 hours**. Each dose **must be used immediately**. Discard unused portion.

d. Prior to administration, ASCOR must be diluted in a suitable infusion solution and the final solution for infusion must be isotonic (undiluted the osmolarity of ASCOR is approximately 5,900 mOsmol/L). Prior to preparing the admixture for infusion, calculate the osmolarity of the intended admixture for infusion. Add one daily dose of ASCOR directly to an appropriate volume of a suitable infusion solution (e.g., 5% Dextrose Injection, Sterile Water for Injection) and add appropriate solutes, as necessary, to make the final solution isotonic. **Sterile Water for Injection is highly hypotonic; adjust solute content, as necessary, to make the final infusion solution isotonic prior to injection**. Do not mix ASCOR with solutions containing elemental compounds that can be reduced (e.g., copper). The concentration of ascorbic acid in the final, admixture solution for infusion is to be in the range of 1 to 25 mg of ascorbic acid per mL. For example, for the largest recommended dose:

Add 200 mg of ascorbic acid (equivalent to 0.4 mL of ASCOR) to 7.5 mL of Sterile Water for Injection to produce an infusion solution having an approximate osmolarity of 290 mOsmol/L. In this specific example, addition of solute is NOT necessary because the solution is isotonic.

e. Prepare the recommended dose based on the patient population *[see Dosage and Administration (2.2),(2.3)]*.

f. Visually inspect for particulate matter and discoloration prior to administration (the diluted ASCOR solution should appear colorless to pale yellow).

g. Immediately administer the admixture for infusion as a slow intravenous infusion *[see Recommended Dosage 2.2]*

2.2 Recommended Dosage:

Table 1 provides recommended doses of ASCOR based on patient population and infusion rates of diluted ASCOR solution.

Table 1: Recommended Dose of ASCOR and Infusion Rate of Diluted ASCOR Solution

Patient Population	ASCOR Once Daily Dose (mg)	Infusion Rate of Diluted ASCOR Solution (mg/minute)
Pediatric Patients age 5 months to less than 12 months	50	1.3
Pediatric Patients age 1 year to less than 11 years	100	3.3
Adults and Pediatric Patients 11 years and older	200	33

The recommended maximum duration of daily treatment with ASCOR is seven days. If no improvement in scorbutic symptoms is observed after one week of treatment, retreat until resolution of scorbutic symptoms is observed.

Repeat dosing is not recommended in pediatric patients less than 11 years of age.

2.3 Dose Reductions in Specific Populations

Women who are pregnant or lactating and patients with glucose-6-dehydrogenase deficiency should not exceed the U.S. Recommended Dietary Allowance (RDA) or daily Adequate Intake (AI) level for ascorbic acid for their age group and condition *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.2)]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: 25,000 mg /50 mL (500 mg/mL) supplied as a Pharmacy Bulk Package (clear, colorless to pale yellow solution)

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Oxalate Nephropathy and Nephrolithiasis

Acute and chronic oxalate nephropathy have been reported with prolonged administration of high doses of ascorbic acid. Acidification of the urine by ascorbic acid may cause precipitation of cysteine, urate or oxalate stones. Patients with renal disease including renal impairment, history of oxalate kidney stones, and geriatric patients may be at increased risk for oxalate nephropathy while receiving treatment with ascorbic acid. Pediatric patients less than 2 years of age may be at increased risk for oxalate nephropathy during treatment with ascorbic acid because their kidneys are immature [see Use in Specific Populations (8.4, 8.5, 8.6)]. Monitor renal function in patients at increased risk receiving ASCOR. Discontinue ASCOR in

patients who develop oxalate nephropathy and treat any suspected oxalate nephropathy.

ASCOR is not indicated for prolonged administration (the maximum recommended duration is one week) *[see Dosage and Administration (2.1)]*.

5.2 Hemolysis in Patients with Glucose-6-Phosphate Dehydrogenase Deficiency

Hemolysis has been reported with administration of ascorbic acid in patients with glucose-6-phosphate dehydrogenase deficiency. Patients with glucose-6-phosphate dehydrogenase may be at increased risk for severe hemolysis during treatment with ascorbic acid. Monitor hemoglobin and blood count and use a reduced dose of ASCOR in patients with glucose-6-phosphate dehydrogenase deficiency [see Dosage and Administration (2.3)]. Discontinue treatment with ASCOR if hemolysis is suspected and treat as needed.

5.3 Laboratory Test Interference

Ascorbic acid may interfere with laboratory tests based on oxidation-reduction reactions, including blood and urine glucose testing, nitrite and bilirubin levels, and leucocyte count testing. If possible, laboratory tests based on oxidation-reduction reactions should be delayed until 24 hours after infusion of ASCOR *[see Drug Interactions (7.4)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Oxalate nephropathy and Nephrolithiasis *[see Warnings and Precautions (5.1)]*.
- Hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency *[see Warnings and Precautions (5.2)]*

The following adverse reactions associated with the use of ascorbic acid were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure:

Administration site reactions: pain and swelling.

ASCOR should not be rapidly administered. Rapid intravenous administration (>250 mg/minute) of ASCOR may cause temporary faintness or nausea, lethargy, flushing, dizziness, and headache (the recommended infusion rates of diluted ASCOR solution are 1.3 mg/minute (Pediatric Patients age 5 months to less than 12 months), 3.3 mg/minute (Pediatric Patients age 1 year to less than 11 years) and 33 mg/minute (Adults and Pediatric Patients 11 years and older) *[see Dosage and Administration (2.2)]*).

Acute and chronic oxalate nephropathy have occurred with prolonged administration of high doses of ascorbic acid [see Warnings and Precautions (5.1)]. In patients with glucose-6-phosphate dehydrogenase deficiency severe hemolysis has occurred *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

7.1 Antibiotics

Ascorbic acid may decrease activities of erythromycin, kanamycin, streptomycin, doxycycline, and lincomycin. Bleomycin is inactivated in vitro by ascorbic acid. If the antibiotic efficacy is suspected to be decreased by concomitant administration of ASCOR, discontinue ASCOR administration.

7.2 Amphetamine & Other Drugs Affected by Urine Acidification

Ascorbic acid may acidify the urine and lower serum concentrations of amphetamine by increasing renal excretion (as reflected by changes in amphetamine urine recovery rates). In case of decreased amphetamine efficacy discontinue ASCOR administration. Standard monitoring of therapy is warranted.

In addition, acidification of urine by ascorbic acid will alter the excretion of certain drugs affected by the pH of the urine (e.g., fluphenazine) when administered concurrently. It has been reported that concurrent administration of ascorbic acid and fluphenazine has resulted in decreased fluphenazine plasma concentrations. Standard monitoring of therapy is warranted.

7.3 Warfarin

Limited case reports have suggested interference of ascorbic acid with the anticoagulation effects of warfarin, however, patients on warfarin therapy treated with ascorbic acid doses up to 1000 mg/day (5 times the largest recommended single dose) for 2 weeks (twice the maximum recommended duration), no effect was observed. Standard monitoring for anti-coagulation therapy should continue during ascorbic acid treatment, as per standard of care.

7.4 Laboratory Test Interference

Because ascorbic acid is a strong reducing agent, it can interfere with numerous laboratory tests based on oxidation-reduction reactions (e.g., glucose, nitrite and bilirubin levels, leukocyte count, etc.). Chemical detecting methods based on colorimetric reactions are generally those tests affected. Ascorbic acid may lead to inaccurate results (false negatives) obtained for checking blood or urinary glucose levels, nitrite, bilirubin, and leukocytes if tested during or within 24 hours after infusion *[see Warnings and Precautions (5.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on use of ASCOR in pregnant women to inform a drug-associated risk of adverse developmental outcomes; however, use of ascorbic acid (vitamin C) has been used during pregnancy for several decades and no adverse developmental outcomes are reported in the published literature *[see Data]*. There are dose adjustments for ascorbic acid (vitamin C) use during pregnancy *[see Clinical Considerations]*.

Animal reproduction studies have not been conducted with ASCOR.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Dose Adjustments During Pregnancy and Post-Partum Period

Follow the U.S. Recommended Dietary Allowances (RDA) for pregnant women when considering use of ASCOR for treatment of scurvy *[see Dosage and Administration (2.3)]*.

Data

Human Data

There are no available data on use of ASCOR or another ascorbic acid injection in pregnant women. However, a published meta–analysis of randomized studies evaluating a large number of pregnant women who took oral ascorbic acid (vitamin C) (through diet and supplementation) at doses ranging from 500 to1000 mg/day (2.5 to 5 times the recommended daily intravenous dose, respectively) [see Dosage and Administration (2.3)] between the 9th and 16th weeks of pregnancy showed no increased risk of adverse pregnancy outcomes such as miscarriage, preterm premature rupture of membranes, preterm delivery or pregnancy induced hypertension when compared to placebo. These data cannot definitely establish or exclude the absence of a risk with ascorbic acid (vitamin C) during pregnancy.

8.2 Lactation

Risk Summary

There are no data on the presence of ascorbic acid (vitamin C) in human milk following intravenous dosing in lactating women. Ascorbic acid (vitamin C) is present in human milk after maternal oral intake. Maternal oral intake of ascorbic acid (vitamin C) exceeding the U.S. Recommended Dietary Allowances (RDA) for lactation does not influence the ascorbic acid (vitamin C) content in breast milk or the estimated daily amount received by breastfed infants. There are no data on the effect of ascorbic acid (vitamin C) on milk production or the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ASCOR and any potential adverse effects on the breastfed child from ASCOR or from the underlying maternal condition. Follow the U.S. Recommended Dietary Allowances (RDA) for lactating women when considering use of ASCOR for treatment of scurvy *[see Dosage and Administration (2.3)]*.

8.4 Pediatric Use

ASCOR is indicated for the short term (up to 1 week) treatment of scurvy in pediatric patients age 5 months and older for whom oral administration is not possible, insufficient or contraindicated. The safety profile of ascorbic acid in pediatric patients is similar to adults; however, pediatric patients less than 2 years of age may be at higher risk of oxalate nephropathy following ascorbic acid administration due to age-related decreased glomerular filtration *[see Warnings and Precautions (5.1)]*.

ASCOR is not indicated for use in pediatric patients less than 5 months of age.

8.5 Geriatric Use

Glomerular filtration rate is known to decrease with age and as such may increase risk for oxalate nephropathy following ascorbic acid administration in elderly population *[see Warnings and Precautions (5.1)]*.

8.6 Renal Impairment

ASCOR should be used with caution in scorbutic patients with a history of or risk of developing renal oxalate stones or evidence of renal impairment or other issues (e.g., patients on dialysis, patients with diabetic nephropathy, and renal transplant recipients). These patients may be at increased risk of developing acute or chronic oxalate nephropathy following high dose ascorbic acid administration *[see Warning and Precaution (5.1]*.

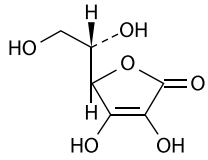
10 OVERDOSAGE

Overdose with ascorbic acid may cause nausea, vomiting, diarrhea, facial flushing, rash, headache, fatigue or disturbed sleep. If overdose of ASCOR occurs, immediately discontinue administration and treat symptoms and signs of overdose, avoiding additional intake of ascorbic acid.

11 DESCRIPTION

ASCOR (ascorbic acid injection) for intravenous use is a colorless to pale yellow, preservative-free, hypertonic, sterile, non-pyrogenic solution of ascorbic acid. ASCOR must be diluted with an appropriate infusion solution (e.g., 5% Dextrose Injection, USP, Sterile Water for Injection, USP) *[see Dosage and Administration (2.1)]*.

The chemical name of Ascorbic Acid is L-ascorbic acid. The molecular formula is $C_6H_8O_6$. It has the following structural formula:



Each ASCOR, 50 mL, Pharmacy Bulk Package vial contains 25,000 mg ascorbic acid, equivalent to 28,125 mg sodium ascorbate.

Each mL of ASCOR contains 500 mg of ascorbic acid (equivalent to 562.5 mg of sodium ascorbate which amounts to 65 mg sodium/mL of ASCOR), 0.25 mg of edetate disodium, and water for injection. Sodium hydroxide and sodium bicarbonate are added for pH adjustment (pH range 5.6 to 6.6). It contains no bacteriostatic or antimicrobial agent.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of action of ascorbic acid for the treatment of symptoms and signs of scurvy (a disorder caused by severe deficiency in vitamin C) is unknown; however, administration of ascorbic acid in patients with scurvy is thought to restore the body pool of ascorbic acid.

12.3 Pharmacokinetics

In a single pharmacokinetic study, healthy male and female adults (n=8) were given a single intravenous dose of 1000 mg ascorbic acid (5 times the largest recommended single dose) infused over a 30 minute period. The mean peak exposure to ascorbic acid was 436.2 µM and occurred at the end of the 30 minute infusion.

Distribution

Ascorbic acid is distributed widely in the body, with large concentrations found in the liver, leukocytes, platelets, glandular tissues, and lens of the eye. Based on data from oral exposure, ascorbic acid is known to be distributed into breast milk and crosses the placental barrier.

Elimination

When the body is saturated with ascorbic acid, the plasma concentration will be about the same as that of the renal threshold; if further amounts are then administered, most of it is excreted in the urine. When body tissues are not saturated and plasma concentration is low, administration of ascorbic acid results in little or no renal excretion. The mean±SD (N=3) half-life observed in the single dose PK study as described above, was 7.4±1.4 h.

Metabolism

A major route of metabolism of ascorbic acid involves its conversion to urinary oxalate, presumably through intermediate formation of its oxidized product, dehydroascorbic acid.

Excretion

There is a renal threshold for ascorbic acid (Vitamin C); the vitamin is excreted by the kidney in large amounts only when the plasma concentration exceeds this threshold, which is approximately 1.4 mg/100 mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and fertility studies have not been performed with ASCOR.

16 HOW SUPPLIED/STORAGE AND HANDLING

ASCOR for intravenous use is a colorless to pale yellow solution supplied as:

- NDC 67157-101-50 One 25,000 mg/50 mL (500 mg/mL) Pharmacy Bulk Package vial
- NDC 67157-101-51 Tray pack of twenty five 25,000 mg/50 mL (500 mg/mL) Pharmacy Bulk Package vials

Store in a refrigerator at 2° to 8°C (36° to 46°F).

Protect from light. This product contains no preservative. See Dosage and Administration (2.1), for detailed instructions on preparation, dilution, and administration of ASCOR.

17 PATIENT COUNSELING INFORMATION

- Inform patients that treatment with ASCOR may increase their risk of oxalate nephropathy *[see Warnings and Precautions (5.1)]*.
- Inform patients that treatment with ASCOR may impact laboratory results, including blood and urine glucose tests, up to 24 hours after infusion *[see Warnings and Precautions (5.3)]*.
- Inform patients with glucose-6-phosphate dehydrogenase deficiency that treatment with ASCOR may increase their risk of hemolysis *[see Warnings and Precautions (5.2)]*.

Manufactured By:

McGuff Pharmaceuticals, Inc., Santa Ana, CA 92704

M381-0073

The Trials and Tribulations of Assuring Ascorbic Acid Injection Availability – The Struggle Is Over!

by Ronald M. McGuff
President, McGuff Pharmaceuticals, Inc.

For those of us on the supply side who have lived it, keeping ascorbic acid injection (AAI) available to physicians has been a roller-coaster of events ever since 1998. As an unapproved drug in the US, AAI's availability to physicians has at many times been sporadic and always susceptible to regulatory changes. Even now, the ability of compounding pharmacies and outsourcing facilities to provide AAI in the future is in question.

Today, the FDA has a *very* restrictive policy towards compounding pharmacies and the compounded medications they create. One especially restrictive policy is known as the "Memorandum of Understanding" (MOU) between the States and FDA. When the MOU is implemented by FDA, compounding pharmacies will be restricted from selling more than thirty percent of their total sales outside their state of residence. This may be further reduced to only five percent if a state declines to sign the FDA's MOU. If you are a physician that resides in a state that does not have a compounding pharmacy that compounds sterile drugs, your ability to obtain sterile compounded drugs may be significantly impacted. The MOU applies to all compounded drugs both sterile and non-sterile. To further complicate supply, compounding pharmacies are required by FDA guidelines to only compound based on their history of receiving prescriptions. When the MOU is implemented, compounding pharmacies may not be able to immediately support out-of-state physicians.

Additionally, when the MOU is implemented, a physician who resides in a state that does not have a compounding pharmacy producing AAI then the MOU will make it difficult or impossible for this physician to obtain it. This physician will be completely at the mercy of out-of-state compounding pharmacies that are limited by FDA guidelines to provide AAI.

The MOU is but one of the roller-coaster events that continue to re-shape access to compounded drugs.

A Brief History of Ascorbic Acid Injection's Tenuous Supply

Prior to October 1998, AAI supply was dependable and available to physicians. In 1998, everything changed. Steris Laboratories, Inc., the only company actively manufacturing AAI, had failed multiple FDA inspections and signed a Consent Decree of Condemnation and Permanent Injunction.[1] The FDA seized large stocks of drugs, including AAI. This decree eliminated manufactured AAI from the market without any warning to wholesalers or physicians.

This began nineteen years of roller-coaster events that led to many AAI drug shortages. Reasons for these shortages include regulatory instabilities along with industry non-compliance issues. Table 1 identifies the most significant roller-coaster supply events of AAI.

The Role of McGuff Pharmaceuticals

In June 2006, McGuff management realized that AAI supply was in dire jeopardy due to the recently published *Guidance for FDA Staff and Industry Marketed Unapproved Drugs – Marketed New Drugs Without Approved NDAs or ANDAs*. In 2006 AAI was *not* an approved drug. The writing was on the wall; FDA declared their policy on how unapproved drugs (read AAI) would be removed from the market.

McGuff management recognized the FDA may, at any moment, stop the manufacture of AAI. Additionally, management understood the long-term regulatory risk of compounding AAI. In July 2006 Ronald M. McGuff as President of the McGuff family of companies directed all companies to immediately initiate a strategic operational and financial strategy to secure AAI from the regulatory upheaval within the compounding pharmacy market. McGuff Pharmaceuticals, Inc. was directed to apply for and receive Orphan Drug Designation and New Drug Approval (NDA) for AAI to assure its unrestricted availability to physicians and patients.

Each roller-coaster event following McGuff's 2006 decision reassured McGuff's management that its chosen course was necessary and appropriate to assure long-term, unrestricted availability of AAI.

Orphan drug and NDA approvals are difficult to achieve. This was an eleven-year process. McGuff invested heavily into the process; money, human resources, research, test method development, human clinical trials, and significant technical help from outside consultants were employed. Some of the approval milestones of this eleven-year effort are listed in Table 2.

McGuff Pharmaceutical's FDA approval of Ascor® (ascorbic acid injection)[11] provides the regulatory pathway for AAI availability of the manufactured drug no matter what happens to the regulatory restrictions on compounding pharmacies and outsourcing facilities. Currently, only one of the seventy-one registered Outsourcing Facilities manufactures AAI and only in 1 mL and 5 mL Glass. [12]

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Further, with the FDA approval of Ascor® (ascorbic acid injection), physicians will no longer need to write patient specific prescriptions or have restrictions on office use. Ascor® may be ordered in the same manner as any other approved drug.

FDA approval means much more than a consistent supply of AAI. There are other advantages as well. McGuff is currently supporting nine Investigational New Drug (IND) human clinical trials using AAI. The documentation required to receive FDA IND approval will be significantly reduced by the use of Ascor® (ascorbic acid injection) in the IND clinical trial documentation. This may potentially allow more IND clinical trials to be submitted for FDA review.

All of us at McGuff are proud of our eleven-year effort to secure the supply of ascorbic acid injection now and well into the future. We are also very proud of the knowledge, enthusiasm, and persistence our employees displayed while performing this monumental task.

References

1. Consent Decree of Condemnation and Permanent Injunction previously entered against Steris Laboratories, Inc. http://www.secinfo.com/ds4Px.715d.c.htm
2. Guidance on Marketed Unapproved Drugs; Compliance Policy Guide. https://www.federalregister.gov/documents/2006/06/09/E6-9032/guidance-on-marketed-unapproved-drugs-compliance-policy-guide-availability

Table 1. Major Events That Created and Alleviated Ascorbic Acid Injection Shortages in the US

Date	Event	Affect on Availability of Ascorbic Acid Injection (AAI)	Result
10/1998	Steris Laboratories, the only manufacturer of AAI, signed a Consent Decree of Condemnation and Permanent Injunction that prevented future manufacturing of AAI.	Immediate and critical AAI shortage without warning. Manufacture of all AAI ceased. Manufacturer recalled all AAI produced.	Significant AAI Shortages. There were few compounding pharmacies producing sterile drugs in 1998.
10/1999	Multiple compounding pharmacies begin producing AAI.	Gradual improvement in AAI availability.	AAI is generally available and office use is common.
4/2002	McGuff Pharmaceuticals, Inc. begins AAI manufacturing and distribution.	AAI is sold as a grandfathered commercial drug product. Multiple manufacturers enter market.	AAI is available in quantities needed. AAI is available from manufacturers and a few compounding pharmacies.
6/2006	FDA publishes *Guidance for FDA Staff and Industry Marketed Unapproved Drugs – Marketed New Drugs Without Approved NDAs or ANDAs*.[2]	Possible immediate effect of removing AAI as a manufactured drug. No warning required.	FDA warns industry that drugs marketed without approval may be removed from market. AAI does not have NDA or ANDA approval.
12/2010	FDA declares AAI is not a grandfathered drug and is not an approved drug. Manufactured AAI is recalled by all manufacturers except Mylan. FDA uses its enforcement discretion to allow Mylan to continue to import and sell AAI in US. All US manufacturers remove themselves from US market.	Immediate and critical shortage without warning. US AAI manufacturing shut down.	Loss of all manufactured AAI in US except Mylan's limited production. Compounding pharmacies gradually re-enter market. Mylan, realizing they have FDA enforced monopoly starts raising AAI price.
9/2012	New England Compounding Center meningitis outbreak sickened 753 individuals and resulted in the death of 64 due to fungal infections resulting from contaminated steroid injections.[3]	No immediate effect, AAI availability good.	FDA and State investigations lead to increased regulatory overview of compounding pharmacy.
11/2013	Federal Drug Quality and Security Act adds significant restraints to pharmacy compounding, distribution, and requires individual prescriptions to obtain AAI. FDA starts to inspect 503(a) compounding pharmacies.[4]	Gradual loss of AAI availability. Nineteen FDA draft and final guidances on compounding pharmacy published since July 1, 2014 put extraordinary pressure and uncertainty on compounding pharmacies.[5]	As compounding pharmacies leave sterile drug market AAI becomes more difficult to obtain. Complex procedures required for prescription ordering and production.
2/2015	FDA Draft Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the State…and the US Food and Drug Administration[6]	No immediate effect but significantly detrimental to inter-state dispensing / distribution when enforced.	Combines the words dispense and distribute to mean distribute. Will limit interstate shipment of AAI (and all other compounded drugs) to five or 30 percent of all drugs compounded per month.
12/2016	FDA Final Guidance, Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act	Additional restrictions on compounding pharmacies, e.g. compounding in anticipation of prescription.	Further complicates a compounding pharmacy's ability to produce appropriate quantities of AAI.
10/2017	McGuff Pharmaceuticals receives approval of NDA 209112 for Ascor® (Ascorbic Acid Injection).[7,8]	AAI as an approved drug will be manufactured now and into the future.	Eliminates AAI dependency on compounding pharmacy and outsourcing facility law and regulations. Eliminates need for prescriptions that are required for compounding. Eliminates office use restrictions.

3. Multistate Outbreak of Fungal Meningitis and Other Infections – Case Count. https://www.cdc.gov/hai/outbreaks/meningitis-map-large.html
4. FDA draft and final guidances on compounding pharmacy were published since July 1, 2014. https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm452240.htm
5. Drug Quality and Security Act. https://www.gpo.gov/fdsys/pkg/PLAW-113publ54/pdf/PLAW-113publ54.pdf
6. Draft Memorandum of Understanding. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Pharmacy Compounding/UCM434233.pdf
7. FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=209112
8. Prescribing information and package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209112s000lbl.pdf
9. Orphan Drug Designations and Approvals. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=243707
10. A Pharmacokinetics Study of Intravenous Ascorbic Acid. https://www.clinicaltrials.gov/ct2/show/NCT02534753?term=mcguff&rank=1
11. For complete prescribing information for Ascor® (Ascorbic Acid Injection): http://www.mcguffpharmaceuticals.com/PDF/Ascor%20Package%20Insert.pdf
12. Outsourcing facilities manufacture's registration of drug products produced. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM577376.xlsx

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Ascorbic Acid Injection

Ronald M. McGuff has been actively involved in the supply of quality drugs and devices to complementary care physicians for 38 years. As owner and President/CEO of the McGuff Family of Companies, Mr. McGuff chairs the management team that crafts policy that includes corporate purpose, governance, business principles, and ethical requirements. The McGuff Family of Companies consists of one foreign and four US corporations. All corporations are family held and veteran owned. McGuff Company, Inc. and subsidiaries provide the following diverse capabilities: aseptic drug manufacturing, medical products distribution 3PL logistics, pharmacy compounded drugs and Canadian drug distribution.

Table 2. Significant Events of McGuff's Effort to Assure Ascorbic Acid Injection Availability

Date	Event	Intent	Result
6/2006	FDA publishes *Guidance for FDA Staff and Industry Marketed Unapproved Drugs – Marketed New Drugs Without Approved NDAs or ANDAs.*	Possible immediate effect of removing AAI as a manufactured drug.	"The writing is on the wall." FDA warns industry that drugs marketed without approval may be removed from market. AAI does not have NDA or ANDA approval.
7/2006	Ronald M. McGuff declares the strategic goal of the McGuff family of companies is to obtain FDA approval of AAI, which will assure future unrestricted availability in the US.	As a strategic goal McGuff will direct a major share of all future profit to the pursuit of AAI NDA approval.	Inter-organizational expertise is brought together to prioritize the Orphan Drug and NDA projects. Process to obtain NDA approval created and implemented. FDA notified of intent.
8/2007	The FDA Office of Orphan Drug Products Development grants MPI's orphan-drug request of Ascorbic Acid Injection.[9]	An orphan drug is a pharmaceutical agent that has been developed specifically to treat a rare medical condition, the condition itself being referred to as an orphan disease.	Completion of the first major step for McGuff Pharmaceuticals to submit NDA to FDA.
8/2015	McGuff starts a human clinical trial "A Pharmacokinetics Study of Intravenous Ascorbic Acid."[10]	This is a Phase 1, single-dose study to evaluate the pharmacokinetics of intravenous ascorbic acid.	One Secondary Outcome Measure: Incidence of treatment-emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) grouped by body system.
9/2016	FDA Center for Drug Evaluation and Research (CDER) acknowledges the receipt of MPI's new drug application (NDA) for ascorbic acid injection assigning NDA Reference Number 209112.	The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the US	10/2016 FDA review team formally decides the NDA application is complete. This is an important milestone towards gaining AAI approval.
3/2017	McGuff Pharmaceuticals undergoes a 7-day pre-approval inspection (PAI) by FDA. A (PAI) is performed to contribute to FDA's assurance that a manufacturing establishment named in a drug application is capable of manufacturing a drug, and that submitted data are accurate and complete. The PAI is one of the last reviews of the drug approval process, which may affect the availability to the consumer.	Audited for: • Compliance with Current Good Manufacturing Practices. • For conformance with application commitments. • Authentic and accurate data. • Laboratory testing of product, including evaluations of the adequacy of analytical methodology.	Result of FDA PAI inspection: FDA recommendation for approval of McGuff Pharmaceuticals manufacturing facility.
6/2017	McGuff designs and validates a new stability-indicating assay using advanced analytical methodologies to further quantify ascorbic acid. This assay includes the ability to identify dehydroascorbic acid.	Validated laboratory methods approved by FDA as part of the NDA requirements.	Utilization of new highly sensitive stability-indicating assay methods assures greater product quality.
10/2017	McGuff Pharmaceuticals receives approval of NDA 209112 for Ascor® (Ascorbic Acid Injection).	Ascorbic acid injection becomes an FDA approved drug in the US.	The approved Ascor® (Ascorbic Acid Injection) drug will be sold by the manufacturer, wholesalers and pharmacies as any other approved drug.

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Predictive Biomarkers: Clinical Opportunity to Save Lives and Prosper

by Russell Jaffe, MD, PhD, CCN, and Jayashree Mani, MS, CCN

Too many people sacrifice their health to gain wealth. Then they sacrifice their wealth to regain their health, too often living in the past and the future rather than in the moment that when they pass they barely have lived.

Predictive biomarkers can speed the transition from the current sick care system, which is unsustainable, to a more promising healthcare. A heavy lift, agreed, yet an attainable objective.

Predictive Biomarkers – Selection and Significance

Predictive biomarkers (PB) are defined here as the specific subset of tests that, when referenced to best outcome goal values rather than usual or normal statistical ranges, predict ten-year survival. Standards are rigorous for inclusion as a PB. To qualify, each test must predict all-cause mortality. This means the test has been performed and observed in every region, socioeconomic group, and with sufficient tracking of tests results over time to confirm ten-year predictive value. Each PB covers an aspect of epigenetics, lifestyle choices, and habits of daily living.

For the first time, interpretation of these functional PB tests can include a lifestyle action plan based on *quantitative* risk reduction. Functional goals listed here cover all of epigenetics. Epigenetics includes the 92% of lifetime health determined by habits of daily living. This aspect of personalized medicine is proving effective in cost and outcome in studies to date. When compared to current best standards of care, a million lives lost prematurely and at high medical expense can be prevented at lower costs. The net result is to enrich society and reduce resource drain. This loss of life is predicted by modifiable epigenetic habits of daily living that can add life to years and years to life at high value to clients and communities and low human and financial costs.

This proactive approach is evidence based and has been shown to lower costs while enhancing individual outcomes, reducing risks, and adding 'years to life and life to years.' This also helps to fulfill the triple aim of better health, better care, and lower costs.

This systems biology application of PB is the first conceptual advancement in lab medicine since sensitivity, specificity, and predictive index were introduced a generation ago. Integrative, comprehensive, personalized medicine *now* has evidence-based, objective, predictive biomarkers to determine and quantify both risk and response to therapy.

Usual (Statistical; 'Normal') Test Results vs. Predictive (Best Outcome; Anticipatory) Goal Value Results

Conventional clinical lab tests provide information about "usual" or "normal" statistical ranges for a particular item analyzed. They are useful for population studies yet not individually predictive.

PB tests provide information that delivers 'feel the difference results' within a few months of implementing individual habit changes based on the PB tests results.

The goal values recommended here for each predictive biomarker are designed to achieve the least risk or highest gain for each physiologic function measured. When predictive biomarker tests are at their goal value, all cause morbidity and mortality are at their best outcome value; quality of life and lifespan are optimized; net costs of care are reduced. PB goal values are not age adjusted because the interpretations of the tests results reported here are based on "least risk, best outcome" healthier goal values. Healthy people at all ages have the same lab ranges. As people accumulate age, there are more unhealthy people in each progressive decade. What we call aging is not only dependent on our genetic destiny but also on habits of daily living. While chronology is fixed, functional age is a choice. This is a reason why using predictive biomarkers based on goal values is an advancement compared to the previous statistical normality approach. The predictive goal values for the PB explained here are also based on evidence from many studies covering all ethnic groups over long periods of time in regard to all cause morbidity and mortality, that is, life expectancy. The probability of living ten plus years for these predictive biomarkers is also based on large scale, long-term community-based outcome studies.

Table 1 gives an overview of the predictive biomarkers here suggested with their clinical significance.

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Predictive Biomarkers-The Smart Choice for Long-Term Health

Predictive biomarkers referenced to goal values and interpreted with a focus on epigenetic opportunities and lifestyle habit changes can stimulate virtuous behavior cycles, and be more cost effective and outcome effective when systematically applied. While each of the predictive biomarkers *is* anticipatory, when four or more are interpreted together, their predictive power increases, covering the 92% of lifetime health determined by choice and habit when all eight are included.

Although each PB test is a separate marker of a specific aspect of physiology, human systems are interdependent. When one biomarker is no longer at best outcome goal value, the entire organism is distressed, less resilient, and more at risk. Taken together this set of PB can identify both where healthy resilience exists and where risks should be reduced.

While too many people live in denial about their health until some catastrophe occurs, professionals and consumers today are using predictive biomarkers to help assure and guide their lifestyle. These proactive consumers of health caring are likely to live well and prosper. It is possible to have a high quality of life throughout one's lifespan by living in harmony with individual nature and the season of that life. The 21st century poses a more challenging set of health risks than centuries before. The approach we outline herein acknowledges the challenges and addresses them in ways that are scientifically proactive, individual, and that utilize resources. This is a cradle-to-cradle approach employed in a system serving people in ways that are more efficient and personal.

When a biomarker shows higher risk, sooner rather than later is the time to take action and bring that marker back to or toward the best outcome value based on habits of daily living - what people eat, drink, think and do.

Physicians and consumers can choose to acknowledge the challenges of contemporary living and incorporate advances in informatics, human behavior, and enhanced caring. Incentives do change behavior. Emotional, psychological, and financial incentives affect choices people make. It is time for healthcare to embrace the opportunities of systems biology, evidence-based predictive testing, and individual care whose outcomes can be verified within months while predicting favorable results decades ahead.

References available on request

This approach builds upon the concept of "optimum" or "high-level health" reference ranges pioneered by Emanuel Cheraskin and colleagues, (Cheraskin E, Ringsdorf WM. *Predictive Medicine*. 1977) and makes the elegant biochemical individuality concept useful in individual practice. (Williams RJ, et al. *The Wonderful World Within You.* John Wiley, 1998, 3rd edition)

Resources

For information on obtaining functional predictive biomarker testing: ELISA/ACT Biotechnologies: 1.800.553.5472, www.ELISAACT.com

Healthcare practitioners can watch a recorded virtual workshop on Predictive Biomarkers. https://www.elisaact.com/workshop/

Clinical protocols for these eight predictive biomarkers can be obtained by contacting:

- PERQUE Integrative Health: 800-525-7372; clientservices2@PERQUE.com
- ELISA/ACT Biotechnologies: 800-553-5472; clientservices@ELISAACT.com
- Health Studies Collegium: 800-328-7372; info@4HSC.org
- Dr. Russell Jaffe, www.DrRussellJaffe.com

Dr. Russell Jaffe received his AB, MD (with Senior Thesis Honors), and PhD (in biochemistry and physiology) from Boston University, all in May 1972. Dr. Jaffe served his medical internship at University Hospital and was awarded a United States Public Health Service Officer Commission, assigned to the Clinical Center of the National Institutes of Health in June 1973. He is board certified in clinical and subspecialty certified in chemical pathology. Dr. Jaffe remained on the permanent senior staff of the NIH Clinical Pathology Department where he continued method innovation and was active in collaborative research with the Laboratory of Experimental Atherosclerosis (of the Heart, Lung, and Blood Institute). Concurrently, Dr. Jaffe's interests in the mechanisms of health and the evoking of human healing responses led him to apprentice in such healing arts as acupuncture, mindfulness, massage, music, art and color therapy, and a variety of eclectic therapeutic approaches.

Dr. Jaffe developed the first method of measuring cell-mediated immunity using a modified ELISA system in a lymphocyte mitogenesis/blastogenesis brief cell culture known as lymphocyte response assays (LRA).

Dr. Jaffe is a Fellow of the Health Studies Collegium and Director of ELISA/ACT Biotechnologies, LLC and PERQUE, LLC. Dr. Jaffe may be reached at 800-525-7372 x 5101 and by email at rjaffe@4HSC.org, rjaffe@ELISAACT.com or rjaffe@PERQUE.com.

Jayashree Mani is a certified clinical nutritionist (CCN). She is experienced in the effective implementation of the comprehensive program described in this article involving these predictive biomarkers, LRA by ELISA/ACT tests, Health Appraisal Questionnaires (HAQ), Alkaline Way diet, and PERQUE nutraceuticals.

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Table1. Predictive Biomarkers and Clinical Significance

Predictive Biomarker Test (PB)	Best Outcome Goal Value	Measures
Hgb A1c, HbA1c, (Hemoglobin A1c)	< 5%	Blood sugar, diabetic risk and insulin resistance
hsCRP (high sensitivity C-Reactive Protein)	< 0.5 mg/L	Repair and inflammation status
hsHomocysteine (high sensitivity homocysteine)	< 6 µmol/L	Methylation, detoxification, cardiovascular risk
LRA by ELISA/ACT	No Delayed Allergies	Immune tolerance to foods and other chemicals
First AM Urine pH	6.5–7.5	Mineral need assessment and cellular acid/alkaline balance
Vitamin D (25-OH cholecalciferol)	50–80 ng/mL	Cellular equilibrium and communication.
Omega-3 Index	8-12%	Omega-3 level of oxidative stress.
DNA Oxidative Stress 0(8-OHdG)	<5 ng/mg creatinine	Oxidative Stress and Nuclear Antioxidant Status

Lyme Disease: Differentiating Between Detection and Diagnosis

by Blanche Grube, DMD, and Leslie Douglas, PhD

At the various conferences they attend throughout the year, members of the DNA Connexions team sometimes hear that the Lyme panel we offer is too sensitive. Recently, we even were told by a doctor that our test was detecting Lyme – at the incubational phase – in patients who were both non-symptomatic and regionally excluded (i.e., living in non-Lyme parts of the country). We take these concerns seriously, as they directly impact the health and subsequent treatment plans of those who seek our testing services.

Accordingly, in this article we would like to discuss several issues. To begin, we need to have a look at the general principles of scientific testing. After having done that, we will turn our gaze to the particular question of the DNA Connexions Lyme panel. After doing the latter, we will address the above-referenced questions of hypersensitivity and false-positivity, as well as our plans for the immediate future.

Scientific and Clinical Laboratory Testing in General

Sensitivity and specificity are common terms for assessing in quantitative terms the accuracy of a given testing method. In other words, they measure whether and how well that method is able to distinguish between disease and its absence. They are, thus, the two elements that measure the validity (i.e., accuracy) of a given test. Let's look closely at them in order to see how they are related and, more importantly, how they are distinct.

Sensitivity "is the probability that a test will indicate 'disease' among those with a disease."[1] A given person is tested for Lyme disease. Being in fact infected with Lyme, his or her test results accurately indicate this diseased, or infected, state. Thus, sensitivity indicates "positive in disease."

Specificity, meanwhile, refers to that same test's ability to exclude those who are not diseased. In other words, specificity "is the fraction of those without disease who will have a negative test result."[1] What does this mean in practice? Taking the example given above, another person, who is not diseased, is tested for Lyme. The test results accurately exclude a Lyme diagnosis from that person.

These characteristics of sensitivity and specificity are inversely proportional to one another. The higher the sensitivity, the lower the specificity; the higher the specificity, the lower the sensitivity.[2]

Let's attempt to sum up all of this succinctly. A tested subject is either diseased or non-diseased. A test result, meanwhile, is either positive or negative. And, both positives and negatives can be either true or false. A "true positive" is an accurate diagnosis of some disease. A "false positive" is an inaccurate diagnosis (i.e., a misdiagnosis) of a disease. A "true negative," for its part, is an accurate conclusion of being non-diseased, while a "false negative" is an inaccurate conclusion of being non-diseased (i.e., where the tested individual is in fact infected.)

Finally, a highly sensitive test runs the risk of yielding some false positives, while a highly specific one is liable to yield a number of false negatives. While these distinctions may require some reflection, one thing is abundantly clear: both false positives and false negatives should be minimal in a good test. In other words, a good test is highly accurate. It diagnoses disease where it is present and excludes it where it is absent.

The DNA Connexions Lyme Panel

Now, let's consider the DNA Connexions Lyme panel in particular. What makes it a uniquely efficient and highly valuable tool for detecting Lyme?

With regard to specificity, our panel is designed to be on the species-specific level. In this case, specificity particularly refers to the capacity of a testing method to discriminate or differentiate between molecular or cellular compounds that have similar characteristics. In other words, we do not just want to identify the genus of *Borrelia*. Rather, we want to determine which species of *Borrelia* we can accurately detect. The primers

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we use are continually checked against GenBank to ensure they are only amplifying the target species. This kind of testing modality in turn allows for the most direct methods of detection and subsequent treatment.

To apply statistical numeration to our test – when individuals ask what is the specificity of our test – the answer is as follows: In order to establish true specificity, there needs to be a gold standard testing method against which all other testing methods can be compared. Such a standard, however, does not yet exist for Lyme. If it did, then we would have individuals tested with both that gold standard and our own test, and we would compare the results to statistically evaluate our test's strengths and eventual weaknesses. At present, this is not possible.[3] We are, however, working toward establishing estimates of both sensitivity and specificity, but this requires a considerable amount of time and effort. Up to this point, both have been necessarily directed toward fulfilling test orders, due to our young company's rapid expansion. We will update our website and associated literature as this information becomes available.

Nonetheless, we do have the medical questionnaire that patients often return with their intake paperwork. It is worth noting that our test results are very frequently in agreement with those of prior testing methods, as well as with these self-reported histories. We also have a number of practitioners who commonly report that our results are in agreement with their own diagnoses and previous testing results. On that note, it is important to reiterate that Lyme is a multi-regional and multi-symptomatic disease. In fact, it can be relatively asymptomatic, even masked by a plethora of seemingly unrelated symptoms. And, today it can be contracted anywhere.

Sensitivity, meanwhile, refers to the capacity of a given testing method to detect the compounds for which it has been designed. For example, we have been able to effectively kill *Borrelia* in our dilution studies with heat. We can, moreover, detect as few as ten organisms in a sample. So, yes, our test is fairly sensitive!

Admittedly, sensitivity is something of a two-edged sword. Yet, it is generally better to have too much of it rather than too little. After all, we live in an increasingly toxic world, and there is a lot of toxicity to be detected!

Finally, we must clearly distinguish between detection and diagnosis. Our test is graded as either positive or negative for *Borrelia burgdorferi* and other tick-borne disease co-infectors. If the DNA is present, then we can detect it. We are, however, limited to what is present in the sample provided for testing. This detection is not a diagnosis of Lyme disease. Some people are infected by *B. Burgdorferi* and/or certain co-infectors without ever knowing that they are so infected. Sometimes, a body's strong immunological response is sufficient to clear the infection. ArminLabs in Germany, for instance, can measure the strength of such a response. We'll speak more about this lab towards the end of this article.

On the other hand, some people are infected, and they are physically wiped out. We can detect *B. burgdorferi* in their submitted sample, and after that, we leave the business of making a formal diagnosis to appropriate medical professionals. We molecularly detect; they medically diagnose. This is a critical distinction to keep in mind.

Closing Thoughts

Should anyone really be upset at being accurately diagnosed with an infectious disease different than the one for which he or she has been tested? For example, Lyme disease and mercury toxicity share twenty-one identical symptoms. Only highly accurate lab testing can distinguish between the two.

A Promising Step Forward

Frankly, we are confused by someone arguing that our test is either too sensitive or even too specific. After all, when it comes to disease, ignorance is definitely not bliss, especially when there are so many promising detection and treatment methods available today.

That having been said, this month we are now offering the Elispot test of Armin Labs, in conjunction with our existing Lyme assay. The Elispot can detect a single *B. burgdorferi* T-cell, and its sensitivity and specificity are estimated at 84% and 94%, respectively. The end result of this union will be a new, two-tiered testing modality, incorporating both direct and indirect methods. Thus, pathogenic presence and immunological response can be assayed together, making for even greater overall accuracy. Moreover, we intend this to be a constructive step toward establishing that much needed gold standard for Lyme detection and diagnosis.

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3. https://bootcampmilitaryfitnessinstitute.com/outdoor-fitness-literature/understanding-sensitivity-specificity/ "The gold standard is the best single test (or a combination of tests) that is considered the current preferred method of diagnosing a particular disease (X). All other methods of diagnosing X, including any new test, need to be compared against this 'gold standard'. The gold standard is different for different diseases. The gold standard for X may be considered outdated or inadequate, but any new test designed to replace the gold standard has to be, initially, validated against the gold standard. If the new test is indeed better, there are ways to prove that; following which the new test may become the gold standard."

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Blanche D Grube, graduated from Queens College, CUNY and received her doctorate from UMDNJ, now Rutgers School of Dental Medicine. She holds a second doctorate from Capital University of Integrative Medicine, Washington DC, and is a board-certified biological dentist and a past president of IABDM. Besides holding several fellowships, she is the owner and CEO of DNA Connexions, BIocomp Laboratories, Huggins Applied Healing and Centers for Healing.

Dr. Leslie J. Douglas completed her undergraduate studies in biology at the University of Hawaii at Hilo (UHH) before attending the University of Hawaii at Manoa (UHM), Department of Genetics and Molecular Biology. Currently, she is the Principal Investigator and Laboratory Manager of DNA Connexions, a Colorado-based company focusing on bacterial, viral, fungal, and parasitic molecular-based detection assays. Her main focus is the research and development of a PCR-based Lyme test inclusive of Borrelia burgdorferi and a number of prevalent tick-borne disease co-infections, as well as the ongoing development of various molecular-based assays. Dr. Douglas's research and patient demographics is yielding invaluable data to better understand the relationships between Lyme and other chronic conditions.

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DNA Connexions is a sophisticated laboratory specializing in the detection of microbial DNA. Polymerase chain reaction technology (PCR), with its high specificity and sensitivity, is the cornerstone of our testing methodology.

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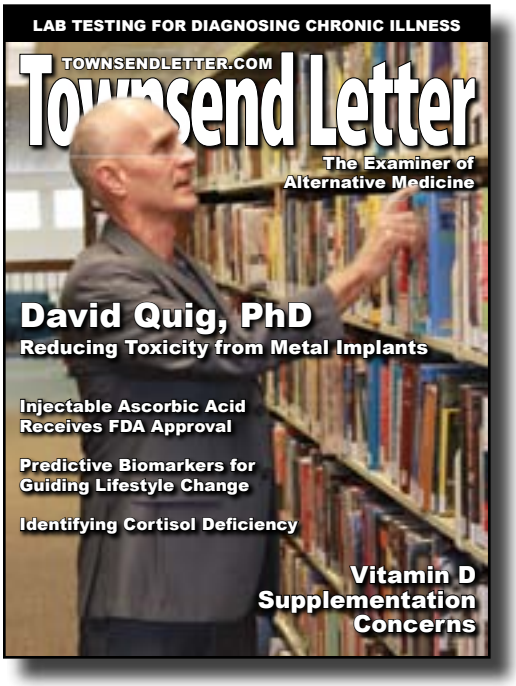


On the cover

Iatrogenic Metal Burdens

by David Quig, PhD

An abundance of recent research has drawn attention to the potential, toxic effects of elements associated with metal alloy implants and prosthesis devices. This medically-induced issue warrants serious consideration since it is well established that a variety of toxic elements can have additive or even synergistic toxic effects, and we are all subjected to at least low-level chronic exposure to xenobiotic elements from the environment. Further, too many patients have also been subjected to gadolinium-enhanced MRIs prior to implantation of metal-on-metal prostheses. This review will highlight the potential local and systemic clinical consequences of the persistent release of specific medically introduced metals, and address the current recommendations for assessing the levels of the metals in patients. Rationale for possible clinical interventions to mitigate toxic effects of the persistently released metals will also be discussed.

Dental Metal Alloy Implants

Dental implants composed primarily of titanium (Ti) have been used for decades to replace missing teeth or to support crowns and bridges. In the vast majority of cases, the implants help maintain the integrity of the underlying bone. Some patients develop immediate or delayed hypersensitivity to the Ti alloy implants. Of potential concern is corrosion, especially when dissimilar metals (mercury, nickel) are in the mouth and galvanic currents are created.[1] There is a paucity of research regarding local and systemic effects of Ti dental implants in part because of difficulties in accurately measuring Ti levels (polyatomic interferents).[2,3] Potential adverse effects of corrosion-released Ti alloys will be further discussed with respect to metal-on-metal total hip arthroplasty, but it is clear that Ti ion release by electro-corrosion is far less a concern in comparison to metal on metal wear. Titanium levels can be assessed accurately in serum, blood or plasma, by a few commercial laboratories.[4] Normal serum Ti levels in the absence of implants are < 1 ng/ml.[5] More recently, ceramic and zirconium dental implants have been used to avoid Ti alloy corrosion issues.

Orthopedic Metal Alloy Implants

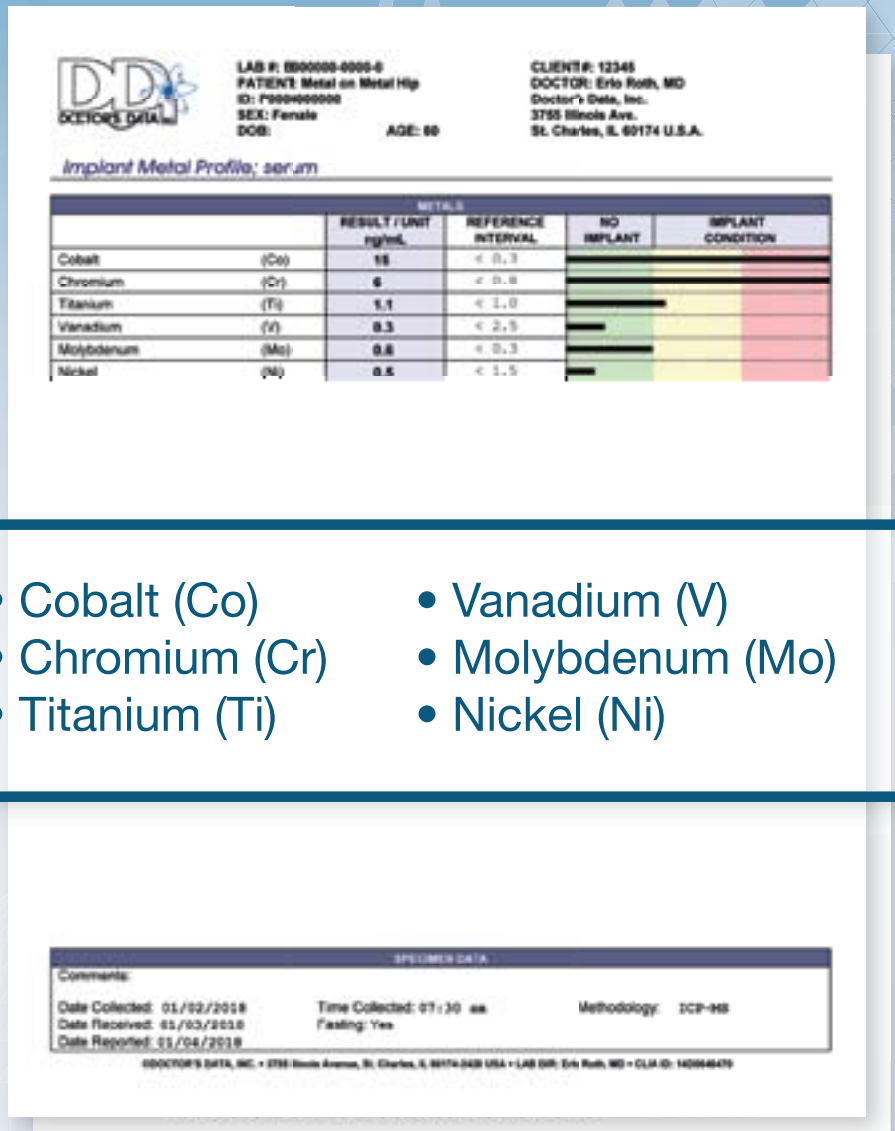
It is well established that levels of metals in serum are increased indefinitely following all types of metal-on-metal total hip arthroplasty procedures[6,7] and there are indeed local and remote adverse tissue responses.[8] The long-term physiological responses to elevated levels of the specific metals are largely unknown.[7,9] Moreover, there is no acceptable threshold above which serum concentrations of metals such as cobalt, chromium, and titanium are known to be toxic[9]; individual variability to toxic effects confounds the issue. Additional concern is heightened by the fact that the procedure is being performed on younger and more active patients, which raises questions of potential reproductive effects.[6] In that regard, it has been reported that metal concentrations in blood from neonates whose mothers had metal implants were higher than those of controls.[10]

Total hip arthroplasty (THA) is one of the most successful treatments for patients with severe rheumatism and osteoarthritis, and most THA devices remain functionally intact for upwards of 20-plus years. THA can be a necessary blessing or a major calamity. Development of durable and

continued on page 33 ➤

Introducing a New Test from Doctor's Data

Comprehensive Metal Implant Profile; Serum



LAB #: [redacted]
PATIENT: Metal on Metal Hip
ID: [redacted]
SEX: Female
DOB: [redacted] AGE: 60

CLIENT#: 12345
DOCTOR: Erlo Roth, MD
Doctor's Data, Inc.
3755 Illinois Ave.
St. Charles, IL 60174 U.S.A.

Implant Metal Profile; serum

METALS

		RESULT / UNIT ng/mL	REFERENCE INTERVAL	NO IMPLANT	IMPLANT CONDITION
Cobalt	(Co)	15	< 0.3		
Chromium	(Cr)	6	< 0.6		
Titanium	(Ti)	1.1	< 1.0		
Vanadium	(V)	0.3	< 2.5		
Molybdenum	(Mo)	0.6	< 0.3		
Nickel	(Ni)	0.5	< 1.5		

SPECIMEN DATA

Comments:

Date Collected: 01/02/2018
Date Received: 01/03/2018
Date Reported: 01/04/2018

Time Collected: 07:30 am
Fasting: Yes

Methodology: ICP-MS

[redacted]

Elements Tested:

- Cobalt (Co)
- Chromium (Cr)
- Titanium (Ti)
- Vanadium (V)
- Molybdenum (Mo)
- Nickel (Ni)

This comprehensive profile contains all of the current metals of interest for patients who have dental or orthopedic prostheses implants. Local and systemic adverse effects of the elevated levels of the metal debris may be severe.

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safe prosthetic materials has proven to be a major challenge, and for decades millions of people have received metal-on-metal paired (M/M) THA prostheses. Until very recently the vast majority of prostheses consisted of pairings of alloys of cobalt (Co), chromium (Cr), and molybdenum (Mo) for the acetabular cup and femoral head (Co:Cr:Mo about 60:30;7).[6] The femoral head is attached to a femoral stem/shaft that is composed of Ti alloy; vanadium is a minor component of Ti alloys. The M/M prosthesis bearing surfaces invariably wear and release Co and Cr^3. Rates of wear are highly dependent on device design, surgical technique, level of physical activity and other factors that affect the health of involved bone and surrounding soft tissue. There is controversy about the continuous corrosion of the metals, including the more resistant Ti alloys, but it is apparent that physical wear is by far the biggest factor in M/M THA-induced metallosis.

The primary concern from the orthopedic perspective is excessive wear and failure of the prostheses due to periprosthetic tissue reactions to the metals. The CAM/integrative practitioner is also very concerned about remote tissue deposition and potential systemic toxic effects of the incompatible metal debris. All patients with M/M THA will have elevated levels of Co and Cr in serum as well as in periprosthetic soft tissue and bone, and in remote tissues in the body up to 20 years post-operatively.[11,12] Local metallosis can cause pseudotumors (inflammatory soft tissue mass), decreased viability of osteoblastic bone marrow cells, osteoclastic bone resorption (release of lead), necrosis, and infiltration of macrophages, eosinophilic granulocytes, and lymphocytes.[13] The net effect can be an aseptic loosening/misalignment of the components that, in turn, further increases wear and release of metal debris. Because it is not possible to assess wear radiographically, the levels of metals in serum (Table 1) are used as *part* of the evaluation of the functional condition of prosthetic implants and decisions regarding revision surgery.[14] However, there is limited published data on appropriate reference ranges for the metals, which raises questions regarding the clinical utility of the data. It has been emphasized that elevated serum Co and Cr levels in the absence of corroborating symptoms do not independently predict prosthesis failure.[15]

In addition to local toxic effects, CAM doctors are also very much concerned about *systemic* effects of the released metal debris. Transition metals such as Co, Cr, Ti, Mo, nickel, manganese, and iron induce production of highly reactive oxygen species (ROS) by Fenton or Fenton-like reactions in fluids in the body. Excessive ROS compromise redox buffering and can diminish levels of quintessential glutathione. The extremely reactive hydroxyl radical is of particular concern because it causes oxidative damage to proteins, lipids, and nuclear and mitochondrial DNA and RNA.[16] Clinical studies have linked M/M THA to white blood cell DNA and chromosomal damage.[17] However, underpowered epidemiological studies to date have not found increased risk or incidence of cancer.[11] Nonetheless, excessive exposure to such metals can result in excessive oxidative stress, inflammation, low levels of quintessential glutathione, and compromised redox capacity. Further, excessive Co has been shown to compromise hepatic cytochrome P450 activity in laboratory rats (Phase I detoxification).[18]

It should be noted that it appears that little if any hexavalent Cr (Cr^6) is released from the CoCr alloy prostheses.[14] Highly genotoxic Cr^6 from occupational/environmental exposure is preferentially taken up, reduced, and retained by red blood cells (RBC). Juxtaposed, implant-derived and dietary trivalent Cr is excluded from RBC. RBC Cr is not elevated in association with M/M THA.[11,14,19] It is emphasized that Cr in RBCs is attributable specifically to exposure to Cr^6 and provides no indication of the nutritional status of physiological Cr.[19]

The most abundantly released metal from the CoCrMo alloys is Co. Cobalt and Cr particles/ions accumulating in lymph nodes can cause necrosis and fibrosis, and associated inflammation is primarily an immunological response.[20] Research regarding systemic toxic effects is rather sparse.[21] However there are case reports regarding neurotoxicity and cardiomyopathy associated with the disseminated metal debris, particularly Co.[22,23] Possible toxic effects include somatic mutations (animal models), aberrant immune function, impaired renal function, compromised endogenous detoxification (Phases I and II), excessive inflammation, and breakdown of arterial endothelial cell tight junctions.[7] Safe levels of serum Co ions have not been established, and Co poisoning is defined by serum Co levels ≥ 5 ng/ml.[7] Is one not to be concerned about potential systemic toxic effects when serum Co levels are 4-10 ng/ml just because a prosthetic implant is thereby implied to be in "good condition"?

Signs and symptoms of arthroprosthetic cobaltism include visual and auditory impairment, tinnitus, vertigo, cardiomyopathy, cognitive dysfunction/dementia, mood disorders, hypothyroidism, peripheral neuropathy, and skin rashes.[15,22] Adverse reactions to Co ion release can be clinically silent yet severe, so early detection is very important. The American Academy of Orthopaedic Surgeons generally recommended follow up testing/evaluation of M/M THA patients annually (asymptomatic), and every four-six months with mild symptoms.

Serum Ti levels will be elevated in patients with M/M THA even when only the femoral shaft is composed of Ti alloy.[9] Titanium has been long regarded as an inert biocompatible metal due to its corrosion resistance. However, recent studies have shown that Ti and vanadium (minor component of Ti alloys) from non-bearing implant components can be released with potentially consequential effects both locally and systemically. Specifically, Ti may have adverse effects in blood, fibrotic tissues, and osteogenic cells after transport through the circulatory or

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lymphatic systems.[4] That Ti corrosion occurs in bone in the absence of wear was demonstrated in a well-designed long-term study (18 months) in which a Ti wire was implanted into the femurs of rats.[4] The corrosion-released Ti increased blood Ti levels, and Ti concentrated primarily in the spleen and lungs. Titanium was also sequestered to a lesser extent in the heart, kidneys, and liver. It has been stated that elevated serum Ti levels associated with prostheses are not necessarily associated with toxicity.[5] However, there is a dearth of clinical data regarding potential adverse health effects. The lack of clinical studies is disconcerting since it has been reported that serum Ti levels can be 18 times greater 10 years post-surgery than at baseline; the M/M hip prostheses in the subjects consisted of Ti alloy acetabular sockets (bearing) and Ti femoral stems.[9]

Vanadium (V), an element that interferes with a vast array of biochemical reactions, is another metal that is released from THA prostheses. Vanadium is a minor constituent of titanium-aluminum-vanadium alloys used in hip prostheses, both in the femoral stem and less frequently in bearing surfaces (acetabular sockets). Serum V levels are expected to be higher than normal (< 1ng/ml) with Ti-alloy prostheses in good condition (1-2 ng/ml), and even higher with significant prosthesis wear (>5 ng/ml).[15] A case report indicated V toxicity associated with a broken Ti alloy femoral stem and a serum V level of 5.8 ng/ml.[24] The patient exhibited sensory-motor axonal neuropathy and bilateral sensorineural hearing loss, and did not have Ti alloy bearing surfaces.

Clinical Intervention

The most fundamental rule of toxicology is to eliminate the exposure(s). Dreadful revision surgery with non-M/M prosthetic materials goes a long way in that regard. However, patients that do not have revisions have perpetual exposure to the offending metals. It is generally recommended that chelation therapy should be reserved for patients who cannot undergo revision. A strong case could be made for consideration of chelation after revision. In one reported case the symptoms of severe arthroprosthetic cobaltism, except deafness, were gradually resolved with DMPS-enhanced decorporation of Co after revision.[23] Chelation with EDTA has also been suggested as a treatment option post-revision.[25] In animal models of cobaltism, EDTA has been shown to be the most effective chelator.[26,27]

The big question is what can be done on an ongoing basis for asymptomatic patients who still bear functional M/M THA prosthetics? Aminothiols such as N-acetyl-cysteine (N-AC) and glutathione (GSH) have been long known to increase Co excretion and decrease tissue Co levels following acute Co intoxication in animal models.[26,27] More recently, various aminothiols administered in different forms orally or intravenously were compared with respect to enhancing ^{60}Co excretion in a rat model.[28] After five daily doses, intravenous and oral liposomal GSH were most effective at enhancing ^{60}Co excretion; 64% and 47%, respectively. Oral cysteine was slightly less effective in lowering tissue ^{60}Co than IV cysteine. Poorly bioavailable powdered oral GSH was without effect. In patients, the beneficial effects of N-AC to enhance Co excretion have been reported as well.[22,27] Of particular interest was the efficacy of very high-dose oral N-AC (300 mg/kg) for ten days to markedly lower blood Co *and* Cr (up to 87%), and enhance urinary Co excretion.[27] In one case the effects of the N-AC to lower blood Co persisted for about six months. That data from the patients who did not undergo revision surgery are very encouraging, but it would seem to make more sense to use an aminothiol at a reasonable dose habitually.

Chelation

Chelation therapy should be given serious consideration for managing the perpetual release of Co and Cr and associated pro-oxidative effects after M/M THA. Selection of a chelating agent, timing of administration, and clinical efficiency are subjects of debate.[29,30] Currently there are no established indications for chelation therapy for asymptomatic M/M THA patients. There are case reports regarding chelation with Ca-Na_2-EDTA or DMPS for asymptomatic M/M THA patients, but that application has not been appropriately evaluated. EDTA has good affinities for Co, Cr^{III} V, and Ti, *in vitro*,[31] and it has been used to treat severe acute experimental cobaltism (animal models).[32] Intravenous EDTA also enhanced free Cr^3 excretion in human subjects, and significantly decreased oxidative stress and damage to DNA.[33] Without revision that uses more compatible prosthetic materials, the source of exposure is still present, and metal levels would no doubt rebound over time after chelation.

Clinical research regarding chelation after M/M THA is long overdue. Intravenous EDTA appears to be the agent of choice, but issues regarding the frequency and number of rounds of periodic chelation are open for discussion. There is no evidence

Table 1. Serum Metal Concentrations (ng/ml) and Implied Condition of Prosthetic Implants. Data compiled from Mayo Medical Laboratories[15]

	Implied Condition of Implant (ng/ml)		
Metal	**No Implant**	**Good Condition**	**Significant Wear**
Cobalt	0-0.9	4-10	>10
Chromium	<0.3	0.3-0.6	>1.0
Molybdenum	0.3-2.0	NA	>10
Titanium	<1.0	1-3.0	>10
Vanadium	<1.0	1-2.0	>5

that chelation will adversely affect the integrity of the prostheses or increase the rate of release of the metals from the devices. It is proposed that a protocol incorporating dietary/supplemental antioxidants, and metal conjugating agents (e.g. liposomal GSH, N-AC), and intermittent chelation may greatly ameliorate the potential, local and systemic toxic effects associated with the life-long release of metals in patients with M/M THA prosthetic devices. What say you?

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David Quig, PhD, received his BS and MS degrees in human nutrition from Virginia Tech and a PhD in nutritional biochemistry from the University of Illinois. After a five-year stint as a research associate studying lipid biochemistry and cardiovascular disease at Cornell University, he worked as a senior cardiovascular pharmacologist for seven years with a major pharmaceutical company. For the past 22 years, David has served as the Vice President of Scientific Support for Doctor's Data, Inc. He has focused on toxic metals, methylation and amino acid metabolism, the clinical application of the biochemistry of endogenous detoxification, and the influence of the gastrointestinal metabolome on health and sustained adverse conditions. David regularly speaks at national and international medical conferences and has facilitated and co-authored an array of studies, spanning exposure and retention of environmental toxicants, nutritional status, and gastrointestinal dysbiosis.

Pathways to Healing

by Elaine Zablocki

Checkered Progress in Integrative Medicine

When you ask John Weeks about current progress in integrative medicine he describes a checkered pattern. You might call it one step backward, two steps forward.

For example, the end of 2016 and the beginning of 2017 were marked by a number of closures. The Penny George Institute for Health and Healing closed its research department. The Samueli Institute, which produced a great deal of the evidence that led to the military and VA significantly engaging integrative strategies, announced it was shutting down. They had been two significant contributors to the research base, and their loss was felt. In New York, the Continuum Center for Health and Healing shut down. To Weeks, these changes signaled the end of an era. At the same time, new initiatives were developing, and new doors were opening.

Weeks has been a presence in integrative health and medicine since 1983 as chronicler, speaker, organizer, consultant, and executive. He publishes the *Integrator Blog*, the leading North American source on the field's policy, education, business, and organizational activity. For the last 18 months, he's been serving as editor-in-chief of the *Journal of Alternative and Complementary Medicine*, and he writes frequently for the *Huffington Post*.

Recently Weeks took the time to describe some important developments in integrative medicine for *Townsend Letter* readers. "These closures led many of us to reflect on the way isolated integrative medicine centers have never been fully integrated into medical delivery organizations," he says. "They were a way to put forward complementary therapies as potential models without fully engaging the medical director and medical and administrative staff throughout the organization. Nowadays, we see integrative medical doctors and other practitioners taking on significant roles within these organizations, and they're finding ways to use integrated therapies in fields such as pain treatment and oncology that most of us couldn't have imagined 20 years ago."

Meanwhile, it turned out the Samuelis had big ideas simmering. They announced a $200 million investment in new research and clinical initiatives at the University of California, Irvine. They plan $50 million as an initial investment, plus another $150 million as an endowment for long-term support. This initiative is particularly significant because it will create a broad, integrative health-focused program within a medical school. Weeks says, "It includes a clinical initiative on how to embed integrative thinking and practices more deeply in care delivery. This is a gutsy, ambitious program that could create a model for the nation, and it is designed as an enduring campaign. Since it is endowment-based, it could last forever."

Surprisingly, this initiative was greeted with derision by a significant portion of the mainstream media, which described it as fraudulent medicine. "When they call the Samueli investment fraudulent and quackery, that is science denial," Weeks says. He points to recent guidelines from highly respected medical institutions, which now recommend non-pharmacologic, integrative strategies as the initial treatments for pain.

The American College of Physicians updated its low back pain guideline to recommend that "physicians and patients initially select non-drug therapy with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, tai chi, yoga, motor control exercise (MCE), progressive relaxation, electromyography biofeedback, low level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation."

The Joint Commission 2015 revision of its pain standard recommends strategies that include acupuncture, massage, chiropractic, and relaxation therapies.

Mayo Clinical Proceedings published an "Evidence-Based Evaluation of Complementary Health Approaches for Pain Management," offering scientific evidence for multiple integrative modalities and practices.

A Broader View of Health and Healthcare

Weeks praises the Samuelis because they take a broad view when they think about health, healthcare, and delivery systems. "Creating and supporting health depends on many factors in addition to clinical medicine," he notes. One estimate suggests that healthcare is only responsible for 10% of someone's health. Family genetics account for 30%, behavioral patterns account for 40% while social conditions are responsible for 15% and environmental exposures about 5%.

"When our goal is to actually increase the health of the people we're serving, we need to take a view that includes lifestyle issues as well as broader things such as access to education,

healthy food, and economic opportunity," Weeks says. "When we invigorate clinical practice to include a strong focus on nutrition, mind-body practices, behavior change, awareness of toxins and environmental issues, then clinical practice will influence a wider range of the determinants of health. We begin to influence behavioral and environmental and even genetic components – which means a stronger impact from clinical care. This is a strong argument for integrative, naturopathic, and functional medicine practice that we don't usually don't see presented in these terms."

The opioid crisis has sparked a real debate, a national readiness to reconsider what Weeks calls "the therapeutic order." The basic idea here – Weeks says he learned it from the naturopathic doctors though it's also just common sense – is that you start by using non-pharmacological, natural, integrative therapies, practices, and practitioners. Then you use approaches that are challenging to the body, invasive, potentially harmful, only when necessary and appropriate.

John Weeks

So, what does "changing the therapeutic order" look like? Weeks cites Dean Ornish's program for heart health as a model. "Ornish is saying we can reverse atherosclerosis with diet, group work, exercise and meditation. He's got a full integrated package there. That's what a real lifestyle push looks like. It's not simply saying 'take this pill and you might also consider going for a walk occasionally.'"

Another example might be the work of Dale Bredesen, who's published work suggesting that the MEND protocol (Metabolic Enhancement for Neuro-Degeneration) can have a significant effect reversing memory loss due to Alzheimer's disease. The protocol is complex and includes recommendations for an anti-inflammatory diet, eight hours of sleep per night, exercise, vitamins, antioxidants, natural remedies such as curcumin, and much more. The initial study only covered 10 subjects. Still, any hint that a combination of natural remedies could prevent or reverse Alzheimer's disease sounds worth pursuing!

Weeks hopes that as the nation learns about putting non-pharmacologic, integrative practices first in care for chronic pain, we will also begin to think about the therapeutic order as a basic principle in other conditions.

Weeks' takeaway, when he looks at the Ornish program and the MEND protocol, is that we need to take behavior change seriously and make it a priority in everyday healthcare. "At some moments there's a pervasive resignation in mainstream medicine, as if people don't really have the energy to change so let's just give them what they want. However, in my experience, integrative practitioners believe that people really do want to change, and they deserve practitioners who will guide them towards change."

Is it Time for Payment Reform?

Of course, one major challenge for noninvasive health promotion strategies is the current payment structure, which incentivizes surgical procedures, medications, and brief office visits. The current opioid crisis means that many organizations are taking a second look at the hidden costs of pharmaceutical-based healthcare. The Center for Disease Control and Prevention called for public comment while it was developing guidelines on opioid prescriptions for chronic pain. In response, many mainstream healthcare organizations pointed out that it is essential for payers to cover non-pharmacological approaches.

This September, the National Association of Attorneys General (NAAG) wrote to America's Health Insurance Plans, urging health plans to change payment policies to support non-opioid pain management therapies. "Doctors should be encouraged to explore and prescribe effective non-opioid alternatives, ranging from non-opioid medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) to physical therapy, acupuncture, massage, and chiropractic care," reads the letter signed by 37 state and territorial attorneys general. They hope to start a dialogue with the insurance industry to discuss revised incentive structures. "The status quo, in which there may be financial incentives to prescribe opioids for pain which they are ill-suited to treat, is unacceptable," the letter says.

"This is a welcome initiative on the payment side," Weeks says. "To have 37 of the nation's attorneys general telling the insurance industry that they – the attorneys general – plan to work with insurance commissioners state-by-state to force broader coverage of integrative strategies is an announcement that the sheriff is in town."

Then Weeks, who has helped organize policy activity on integrative health in multiple arenas, adds a practical activist note: "Of course, it will be very helpful if integrative health advocates get their organizations to knock on the doors of their attorneys general and announce that they are happy to be part of their posse in making these changes."

Resources

The Integrator Blog
http://theintegratorblog.com/

The Journal of Alternative and Complementary Medicine
http://www.liebertpub.com/overview/journal-of-alternative-and-complementary-medicine-the/26/

Integrative Approaches to Alzheimer's Disease
https://www.integrativepractitioner.com/whats-new/all-news/can-the-mend-protocol-elevate-integrative-approaches-to-alzheimers-disease/

Reversal of cognitive decline: A novel therapeutic program, by Dale E. Bredesen
http://www.aging-us.com/article/100690/text

John Weeks – Recent Articles in the Huffington Post

- Shameful Media Response to the Samueli's Visionary $200-Million Integrative Health Investment at UC Irvine. https://www.huffingtonpost.com/entry/shameful-media-response-to-the-samuelis-visionary_us_59c7d9a0e4b0b7022a646b73
- Wayne Jonas, MD, and the Closure of the Influential Samueli Institute: Next Steps. https://www.huffingtonpost.com/entry/wayne-jonas-md-and-the-closure-of-the-influential_us_58d013ede4b0537abd957351
- Penny George Institute & Allina: Big Changes in Nation's Leading Integrative Health Model. https://www.huffingtonpost.com/entry/penny-george-institute--a_b_14351264.html
- AMA, Other Leading Medical Organizations Urge Insurance for Non-Pharma/Integrative Pain Care. https://www.huffingtonpost.com/entry/ama-other-leading-medical_b_13696232.html

Elaine Zablocki is the former editor of CHRF News Files.

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Shorts

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Homeopathic Research

George Washington University School of Medicine recently hosted a Research in Homeopathy Webinar (available on YouTube, 9/28/2017) on "The State of Research in Homeopathic Medicine and Understanding the Biological Basis for Homeopathic Remedy Response." Citing recent studies, researcher Iris Bell, MD, PhD, spoke about the current hypothesis that explains homeopathy's biological effects. In the past decade, researchers have found that homeopathic dilutions, beyond Avogadro's number, of gold (*Aurum metallicum*), copper (*Cuprum metallicum*), and the plant *Gelsemium* contain nanoparticles of the original materials. Today's technological advances are allowing researchers to observe particles less than 10 nanometers in size, and these nanoparticles can produce biological effects, giving rise to the new field of nanopathology. It appears that electromagnetic signals from these homeopathic nanoparticles cause water to form nanostructures unique to the original source. The present hypothesis, says Dr. Bell, is that "resonance between the electromagnetic wave properties of a well-chosen remedy and the physiological disease process in the patient... activates endogenous self-regulatory or modulatory adaptive mechanisms" that are part of the body's healing response.

In the other half of the webinar, Peter Fisher, MD, director of research at Royal London Hospital for Integrated Medicine, University College London Hospitals, and Queens' Physician, presented information about clinical trials and homeopathy's use. He said that there were 2289 homeopathic studies involving animals, plants, human tissue, bacteria and viruses, and fungi in medical literature (as of August 2017), 55% of which involved ultramolecular dilutions. Ninety percent of these showed at least one positive result. Dr. Fisher also reported the existence of 1137 clinical trials involving homeopathy, as of August 2017; 41% showed positive results, 54% were inconclusive, and 5% had negative results. In comparison, systematic reviews of conventional treatments had 44% positive, 49% inconclusive, 7% negative results. Interestingly, the higher the quality of a randomized controlled homeopathic trial, the stronger the positive effect.

Dr. Fisher also discussed European studies that evaluate the use of homeopathy in healthcare. A German comparative effectiveness study in primary care, involving 493 patients, found no significant difference in cost between homeopathic and conventional care. In addition, both patients and physicians were more satisfied with the homeopathic treatment at 6 and 12 months (adjusted for gender, education, age, and symptom duration). Homeopathy use also showed "significant cost savings" in a French health system study. The Swiss Health Technology Assessment of homeopathy, used to support homeopathy's reimbursement in the country's national health insurance program, was also supportive of homeopathy's use in the healthcare system. The Swiss assessment reported that homeopathy was equal to standard care for upper respiratory illnesses and respiratory allergies, according to 24 of 29 studies that compared homeopathy treatment to placebo or standard care. Despite these positive findings, Dr. Fisher reports that homeopathy is under attack in the United Kingdom.

Although Dr. Fisher focused on the reports and studies supporting homeopathy's use, not all government reports are positive. The Australian National Health and Medical Research Council (NHMRC) published an information paper in March 2015, which concludes: "'...there are no health conditions for which there is reliable evidence that homeopathy is effective.'" News media and skeptics have taken that statement to mean that homeopathy doesn't work. As is too often the case, the devil is in the details.

Homeopathy Research Institute (HRI) points out that the March 2015 report was actually the second homeopathy review; the first report, dated July 2012, was never released to the public. The Australian Homeopathic Association learned about the first report from information gained from its Freedom of Information (FOI) requests. NHMRC rejected

the first report because of "poor quality." Oddly, the scientist responsible for this report had authored NHMRC's guidelines on how to conduct evidence reviews. Moreover, a least one member of NHMRC's expert committee that was overseeing that first report stated that it was "high quality," according to FOI material. The second report committee was initially chaired by Peter Brooks, a member of an anti-homeopathy lobby group, a conflict of interest that Brooks initially failed to admit. When the conflict of interest came to light, Brooks relinquished his position as chair but remained on the committee.

This second committee used unusually restrictive criteria for study inclusion in the review: "...for a trial to be deemed 'reliable' it had to have at least 150 participants and a quality score of 5/5 on the Jadad scale (or equivalent on other scales). Trials that failed to meet either of these criteria were dismissed as being of 'insufficient quality and/or size to warrant further consideration of their findings.'" Consequently, NHMRC whittled the bulk of homeopathic studies down to five "reliable" trials – all of which they assessed as showing no support for homeopathic use. Two independent expert opinions, one of which came from the Australasian Cochrane Centre, questioned the NHMRC's conclusion of 'no reliable evidence,' according to FOI documents.

Complementary Medicines Australia, Australian Homoeopathic Association, and Australian Traditional Medicine Society submitted a complaint against NHMRC to Australia's Commonwealth Ombudsman in August 2016, based on the FOI material and HRI's scientific analysis of the March 2015 report. The complaint alleges procedural and research flaws, conflicts of interest, and misleading the public.

Homeopathy Research Institute. The Australian Report. www.hri-research.org.

Homeopathic Plant Extracts Alter Genetic Expression

Highly diluted extracts from *Hydrastis canadensis* (goldenseal) and *Marsdenia condurango* (an Ecudorian vine), both of which are used in cancer treatment, altered gene expression and caused epigenetic modifications in HeLa cervical cancer cells, according to a 2015 Indian study. The researchers looked at methylation-specific epigenetic processes and gene expression profiles in HeLa cells treated with a homeopathic preparation (30C) of a plant extract (HC-30 or Condu-30), a placebo consisting of the ethanol carrier solution that underwent the same homeopathic dilution-succussion process, or a no-treatment control. The extracts and placebo were made at Boiron Laboratories (Lyon, France). The observer was blinded until data analysis.

After 48 hours incubation, the cells underwent microarray gene expression analysis. Interestingly, the placebo showed some effect compared to the no-treatment control, but not as much as the plant extracts. Cell sets exposed to HC-30 and Condu-30 had a total of 1182 genes that were oppositely expressed compared to the control, but only 36 genes had ≥ 1.5-fold differential expression. The researchers used RT-PCR and qRT-PCR of cancer-related SMAD4 gene to validate the microarray data. (They did not have the money or resources to study more genes.) "There was down-regulation [of SMAD4 gene] observed in Pl-30, HC-30, and Condu-30-treated series compared to the untreated control," the authors write. "Fold change values [in SMAD4 gene] were as follows: for placebo it was 1.76, for HC-30C the fold change was 3.867, and for Condu-30C it was 4.72." In addition, apoptosis increased in treated cultures.

This study supports earlier findings that homeopathic dilutions affect gene expression, say the authors.

Saha SK, et al. Ultra-highly diluted plant extracts of *Hydrastis canadensis* and *Marsdenia condurango* induce epigenetic modifications and alter gene expression profiles in HeLa cells in vitro. *J Integrative Med.* 2015;13(6):400-411.

Micro- and Nanocontamination in Vaccines

About 15 years ago, doctors at a university hospital in Mainz, Germany, asked Antonietta M. Gatti, PhD, and pharmacist Stefano Montanari to analyze an anti-allergy vaccine that was causing painful swellings that would not resolve around injection sites. The two researchers, recognized European experts in the field of nanopathology, had developed a new method for detecting and identifying inorganic, particulate contaminants. Gatti and Montanari found solid particles, which should not have been present, in the vaccine and in the swollen tissue.

"We had never questioned the purity of vaccines before," Gatti told James Lyons-Weiler in an interview. "In fact, for us the problem did not even exist. All injectable solutions had to be perfectly pure and that was an act of faith on which it sounded impossible to have doubts. For that reason, we repeated our analyses several times to be certain. In the end, we accepted the evidence." That experience prompted them to take a look at 44 vaccines distributed in Italy and France, one of which was a veterinary vaccine for cats. The result was a controversial 2017 study published in *International Journal of Vaccines and Vaccination.* ➤

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Gatti and Montanari use a Field Emission Gun Environmental Electron Scanning Microscope equipped with the X-ray microprobe of an Energy Dispersive Spectroscope to identify inorganic particulates: "The method identified clearly inorganic bodies with a higher atomic density (looking whiter) than the biological substrate." Their investigations confirmed the presence of inorganic components, such as saline and aluminum salts, whose presence was acknowledged by the manufacturer; but the researchers also found micro-, sub-micro- and nanosized, inorganic, foreign bodies (ranging from 100 nm to about ten microns) that were not listed in the package inserts in all of the human vaccines. The vaccine for cats was the only one without inorganic contaminants. The authors found a variety of inorganic particles in the biological substrate, including lead, stainless steel, tungsten, gold, silver, silicon, titanium, and numerous compounds. The contamination differed among the vaccines, but batches of the same vaccine had similar contamination profiles.

"The quantity of foreign bodies detected and, in some cases, their unusual chemical compositions baffled us," the authors wrote in their study. They say that a nano-bio-interaction occurs when these nanoparticles come in contact with the proteic fluids in vaccines. This interaction forms compounds that are bio-persistent and not bio-degradable or bio-compatible: "The link between these two entities generates an unfolding of the proteins that can induce an autoimmune effect once those proteins are injected into humans" – such as the persistent inflammation and swelling observed in patients receiving the German anti-allergy vaccine. These compounds can also be carried to other parts of the body via blood circulation.

Gatti and Montanari see their results as an opportunity for manufacturers to increase quality control and, thereby, make vaccines safer: "Our hypothesis is that this contamination is unintentional, since it is probably due to polluted components or procedures of industrial processes (e.g. filtrations) used by the Producers." They believe that the problem of inorganic particulates in human vaccines is solvable if manufacturers are willing to have their plants inspected for sources of contamination and use methods to improve quality. Dr. Gatti told Robert F. Kennedy, Jr., "...there are no regulations requiring manufacturers to do this kind of quality control, even though the manufacturers know that there is something wrong."

Kennedy says that this study has been denounced as "pseudoscience" and that Gatti and Montanari have been the targets of threats. The publisher of *International Journal of Vaccines and Vaccination* briefly removed the study from the internet in July, in response to pro-industry bloggers and trolls. The study is available online at this time (November). Kennedy states, "Gatti and Montanari believe so strongly in the integrity of their findings that they have made known that they will sue if the journal takes down the paper."

Gatti AM, Montanari S. New Quality-Control Investigations on Vaccines: Micro- and Nanocontamination. *Inter J Vaccines and Vaccination.* January 2017; 4(1).

Kennedy RF, Jr. Fast-Tracking Mandatory Vaccination While Government and Media Muzzle Scientists. August 29, 2017.

Lyons-Weiler J. Micro- and Nanocontamination in Vaccines: the Gatti Interview. February 3, 2017.

Saliva Testing and Environmental Research

Saliva testing would be highly useful for repeat testing during longitudinal studies that look for associations between environmental exposures and chronic diseases, according to Vincent Bessonneau and colleagues. Bessonneau et al conducted a study to show that saliva, a filtrate of the blood, contains ample information about the body's metabolic processes. Saliva sampling, unlike blood testing, is easily performed by study volunteers, supplied with collection kits. This ease would allow multiple samples to be taken throughout long-term studies, increasing the likelihood of finding associations between exposures and disease.

For their study, Bessonneau et al classified 1,233 known molecules, metals, and ions found in saliva with a source: a) host endogenous (879), b) microbial endogenous (52), c) food (225), d) drugs (15), e) pollutants (25), and f) metals (37). Bessonneau et al expect that other salivary metabolites (present in lower concentrations) will be discovered as new technology and analytical techniques evolve. In addition to classifying by source, the researchers connected the molecules to human metabolic pathways and PubMed Medical Subject Heading (MeSH) terms. Even though saliva contains fewer metabolites than blood, the researchers were able to map 196 salivary metabolites into 49 metabolic pathways, which are connected to human metabolic diseases, central nervous system diseases, and neoplasms. They were able to gain information about amino acid metabolism, TCA cycle, gluconeogenesis, glutathione metabolism, pantothenate and CoA biosynthesis, and butanoate metabolism.

While this information is not definitive, it would allow researchers to find associations between environmental exposures and chronic illnesses that could then be investigated further in specific studies.

Bessonneau V, et al. The Saliva Exposome for Monitoring of Individuals' health Trajectories. *Environmental Health Perspectives.* 20 July 2017.

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Literature Review & Commentary

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L-Carnitine Improves Lipoprotein(a) Levels

Fifty-eight patients with mixed hyperlipidemia (low-density lipoprotein [LDL] cholesterol above 160 mg/dl and triglycerides above 150 mg/dl) and an elevated lipoprotein(a) (Lp[a]) level (greater than 20 mg/dl) were randomly assigned to receive 20 mg per day of simvastatin (control group) or simvastatin plus 1 g of L-carnitine twice a day for 12 weeks. The mean reduction in the Lp(a) level was significantly greater in the L-carnitine group than in the control group (-19.4% vs. -6.7%; $p < 0.02$). The mean reduction in the levels of total cholesterol, LDL cholesterol, and triglycerides was similar between groups.

Comment: Lp(a) consists of an LDL molecule bound by a disulfide linkage to a glycoprotein, apolipoprotein(a). Many, though not all, studies have found that an elevated serum Lp(a) concentration is an independent risk factor for cardiovascular disease. Although this association does not prove causation, there is evidence that Lp(a) is atherogenic. In addition, because it is structurally similar to plasminogen, Lp(a) might inhibit fibrinolysis, an effect that could promote the development of cardiovascular disease. The results of the present study indicate that administration of L-carnitine, as an adjunct to statin medication, can improve Lp(a) levels in people with mixed hyperlipidemia. This finding adds to the other cardioprotective effects that have been demonstrated for L-carnitine (such as increasing survival following a myocardial infarction and improving congestive heart failure).

Florentin M, et al. L-Carnitine/simvastatin reduces lipoprotein (a) levels compared with simvastatin monotherapy: a randomized double-blind placebo-controlled study. *Lipids*. 2017;52:1-9.

Probiotic Chewing Gum Prevents Dental Caries

One hundred thirty-eight children (aged 2-3 years) living in a low socioeconomic multicultural area in Sweden were randomly assigned to receive, in double-blind fashion, probiotic chewing gum or placebo gum once a day for one year. The probiotic chewing gum (EvoraKids) contained at least 10^8 colony-forming units of ProBiora3, which is a blend of three probiotic organisms (*Streptococcus uberis* KJ2, *S. oralis* KJ3, and *S. rattus* JH145). Parents were instructed to brush their children's teeth twice a day with fluoride toothpaste. Around two-thirds of the parents in each group reported acceptable compliance. The incidence of new caries was significantly lower by 75% in the probiotic group than in the placebo group ($p < 0.05$).

Comment: In this study, a proprietary probiotic preparation, when used as an adjunct to fluoride toothpaste, decreased the incidence of dental caries in young children. The treatment would presumably have been even more effective if the parents had adhered better to the recommendations. Probiotics may work by competing with cariogenic bacteria that colonize the mouth, such as *S. mutans*. The product used in this study (EvoraKids) is no longer commercially available. EvoraPlus mints are available, and they contain the same probiotic organisms as those used in the present study. However, EvoraPlus mints are officially recommended only for children aged 11 years or older.

Hedayati-Hajikand T, et al. Effect of probiotic chewing tablets on early childhood caries - a randomized controlled trial. *BMC Oral Health*. 2015;15:112.

Intravenous Iron for Children Who Do Not Respond to Oral Iron

A retrospective study was conducted on 72 children (median age, 13.7 years; range, 9 months to 18 years) with iron-deficiency anemia that had failed to respond to oral iron supplementation, who were subsequently treated with one or more intravenous infusions of iron (ferric carboxymaltose). The total number of iron infusions in the group was 116. In the majority of cases, iron-deficiency anemia was due to heavy menstrual bleeding or gastrointestinal disorders. Median pre-infusion and post-infusion

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hemoglobin levels were 9.1 g/dl and 12.3 g/dl, respectively, at 4-12 weeks after the initial infusion. Sixty-five patients (84%) experienced no adverse effects. Minor transient complications such as pruritus or urticaria occurred during or immediately after seven infusions. One patient developed dyspnea without wheezing at two minutes into the infusion. This resolved within minutes of stopping the infusion and administering diphenhydramine, hydrocortisone, and normal saline.

Comment: Iron deficiency-anemia is a common problem both in adults and children. While most people respond adequately to oral iron supplementation, some fail to absorb oral iron sufficiently and others are unable to take oral iron because of gastrointestinal side effects. The results of the present study indicate that intravenous administration of iron (as ferric carboxymaltose) is a viable alternative in infants, children, and adolescents with iron-deficiency anemia who fail to respond to oral iron therapy. Practitioners should familiarize themselves with the contraindications and precautions before administering intravenous iron.

Powers JM, et al. Intravenous ferric carboxymaltose in children with iron deficiency anemia who respond poorly to oral iron. *J Pediatr*. 2017;180:212-216.

Folic Acid Prevents Progression of Chronic Kidney Disease

In a sub-study of the China Stroke Primary Prevention Trial, 15,104 adults (mean age, 60 years) with hypertension were randomly assigned to receive, in double-blind fashion, a single daily tablet containing 10 mg of enalapril and 0.8 mg of folic acid or 10 mg of enalapril alone (control group). There was no folic acid fortification of foods in these regions at the time. The primary endpoint was the progression of chronic kidney disease, defined as a decrease in estimated glomerular filtration rate (eGFR) of 30% or more and to a level of less than 60 ml/minute/1.73 m^2 if the baseline eGFR was 60 ml/minute/1.73 m^2 or more; or a decrease in eGFR of 50% or more if the baseline eGFR was less than 60 ml/minute/1.73 m^2; or end-stage renal disease. During a median follow-up period of 4.4 years, the incidence of the primary endpoint was significantly lower by 21% in the folic acid group than in the control group. In addition, the mean rate of decline of eGFR was significantly lower by 10% in the folic acid group than in the control group ($p = 0.02$). Among participants with chronic kidney disease at baseline (defined as eGFR between 30 and 60 ml/minute/1.73 m^2), folic acid reduced the rate of decline of renal function by 44% ($p < 0.001$). Among those without chronic kidney disease at baseline, there was no difference between groups in the progression of chronic kidney disease.

Comment: These results indicated that folic acid supplementation, when given as an adjunct to enalapril, slowed the progression of mild-to-moderate chronic kidney disease in Chinese patients with hypertension. Further research is needed to determine whether folic acid would have a similar effect in regions of the world where grains are fortified with folic acid (such as the United States).

Xu X, et al. Efficacy of folic acid therapy on the progression of chronic kidney disease: the renal substudy of the China Stroke Primary Prevention Trial. *JAMA Intern Med*. 2016;176:1443-1450.

Does Fish Oil During Pregnancy Prevent Asthma in Children?

Some 736 pregnant Danish women were randomly assigned to receive, in double-blind fashion, 2.4 g per day of omega-3 fatty acids (55% eicosapentaenoic acid [EPA] and 37% docosahexaenoic acid [DHA]) or placebo (olive oil), beginning at 25 weeks of gestation and continuing until one week after delivery. The incidence of persistent wheeze or asthma in the offspring at three-to-five years of age was 30.7% lower in the omega-3 group than in the placebo group (16.9% vs. 23.7%; $p < 0.04$). The effect was strongest in the children of women whose blood levels of EPA and DHA were in the lowest third of the study population at baseline (54% reduction in incidence; $p = 0.01$).

In another study, 533 pregnant Danish women were randomly assigned to receive 4 g per day of fish oil (providing 1,280 mg per day of EPA and 920 mg per day of DHA), olive oil, or no oil from week 30 of gestation until delivery. The offspring were followed for 24 years in a mandatory national prescription register. In intent-to-treat analyses, the probability of having had asthma medication prescribed was significantly lower by 46% ($p = 0.02$) in the fish oil group than in the olive oil group. Outcomes in the group not receiving oil were similar to outcomes in the fish oil group.

Comment: These studies raise the possibility that supplementation with fish oil during pregnancy may prevent the development of asthma in the offspring. However, it is also possible that fish oil had no effect, while maternal olive oil supplementation promoted the development of asthma in the offspring. The latter possibility is supported by the results of the second study, in which taking no oil supplement resulted in a better outcome than taking olive oil.

We know from previous research that consuming adequate amounts of omega-3 fatty acids during pregnancy is important for the development of the child's brain and visual system, and may also reduce the risk of preterm delivery. Therefore, there is good reason to supplement with fish oil in selected cases, regardless of whether it prevents the development of asthma. I have reviewed the above studies in part to remind the reader that some "placebos" are biologically active and that, when evaluating research, one should consider what placebo was used. If olive oil does have an adverse effect, the mechanism might be related to competing with omega-3 fatty acids in women whose baseline omega-3 fatty acid status is marginal or low.

Bisgaard H, et al. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. *N Engl J Med*. 2016;375:2530-2539.

Hansen S, et al. Fish oil supplementation during pregnancy and allergic respiratory disease in the adult offspring. *J Allergy Clin Immunol*. 2017;139:104-111.e4.

Iron Deficiency Associated with Poor Outcomes in Patients with Heart Failure

Serum ferritin levels and transferrin saturation were measured in 626 patients (mean age, 73.4 years) hospitalized for acute heart failure. Absolute iron deficiency was defined as a serum ferritin level less than 100 µg/L, and functional iron deficiency was defined as a ferritin level of 100-299 µg/L with transferrin saturation below 20%. Absolute iron deficiency was present in 48.2% of the patients (mean serum ferritin level in that group, 56 µg/L) and functional iron deficiency was present in 25.7%. The incidence of readmission within 30 days after hospital discharge in patients with absolute iron deficiency,

functional iron deficiency, and no iron deficiency was (19.9%, 13%, and 13.5%, respectively; p = 0.005 for absolute iron deficiency vs. each of the other categories). Compared with patients without iron deficiency, those with functional iron deficiency did not have an increased risk of readmission.

Comment: Iron is a component of hemoglobin, which delivers oxygen to the tissues. In addition, iron is a cofactor for the enzyme, cytochrome oxidase, which plays a role in mitochondrial ATP production via the electron-transport chain. ATP is essential for the pumping action of the heart; therefore, iron deficiency could exacerbate heart failure whether or not the patient is anemic.

Patients with heart failure are considered to have absolute iron deficiency if their serum ferritin level is below 100 µg/L. This cut-off level is well above that used to diagnose iron deficiency in healthy individuals. The higher value takes into account the fact that heart failure is associated with chronic inflammation, and that serum ferritin levels rise in response to inflammation. Heart failure patients are thought to have functional iron deficiency if their serum ferritin level is between 100 and 300 µg/L (which is frequently seen in patients with chronic inflammatory diseases) and their transferrin saturation is below 20%.

In previous observational studies, the presence of iron deficiency (absolute or functional) was associated with worse outcomes in patients with heart failure. In double-blind trials, intravenous administration of iron to patients with heart failure and iron deficiency (absolute or functional) improved functional capacity, symptoms, and quality of life, and decreased the number of hospitalizations for worsening heart failure. The results of the present study confirm that it is important to treat absolute iron deficiency in patients with heart failure, but suggest that it may not be useful to give iron supplements to heart failure patients with functional iron deficiency.

Nunez J, et al. Iron deficiency and risk of early readmission following a hospitalization for acute heart failure. *Eur J Heart Fail*. 2016;18:798-802.

Possible Adverse Effect of High-Dose Lutein

An Asian woman in her 60s was found to have bilateral "fovial sparkles," further described as intraretinal round yellow deposits in the fovea, further described as crystalline maculopathy. She had no visual complaints, and her visual acuity was 20/20. She reported an eight-year history of taking 20 mg per day of lutein in supplement form and consuming large amounts of high-lutein foods (broccoli, kale, spinach, and avocado) in a smoothie every morning. Seven months after discontinuing the lutein supplement but making no dietary changes, there was partial resolution of the crystals in one eye and no change in the other eye.

Comment: In this case report, long-term consumption of large amounts of lutein was associated with the formation of crystals (presumably containing lutein) in the fovea region of the macula. While these crystals did not cause any obvious adverse effects, it is conceivable the progressive accumulation of such crystals from continued consumption of large doses of lutein could damage the retina. Kale and spinach contain about 20 mg and 7 mg, respectively, per typical serving, so this woman may have been consuming more than 50 mg of lutein per day. In contrast, clinical trials of lutein for the prevention or treatment of macular degeneration have usually used 10-20 mg per day.

Choi RY, et al. Crystalline maculopathy associated with high-dose lutein supplementation. *JAMA Ophthalmol*. 2016;134:1445-1448.

Gaby's Literature Review

Intranasal Vitamin A for Post-Infectious Loss of Smell Function

One hundred seventy patients (aged 18-70 years; mean age, 52 years) with post-infectious (n = 102) or posttraumatic (n = 68) loss of olfactory function (mean duration of illness, 14 months) were evaluated retrospectively. Forty-six patients were treated with smell training for 12 weeks (control group), while 124 patients received smell training plus eight weeks of topical vitamin A drops (10,000 IU instilled into the nose with the head tilted back, once a day). Treatment was assigned "pseudo-randomly" (nature of randomization not described). Smell training consisted of twice-daily exposure to four intense odors (phenylethyl alcohol, eucalyptol, citronellal, and eugenol). Olfactory function was assessed using the Sniffin' Sticks test kit, which measures odor thresholds, discrimination, and identification. Follow-up testing was performed 10 months after the first assessment. The proportion of patients with post-infectious olfactory dysfunction who were improved at follow-up was significantly higher in the vitamin A group than in the control group (37% vs. 23%; p = 0.03). In the group with posttraumatic smell dysfunction, the proportion of patients who improved did not differ significantly between groups.

Comment: Vitamin A plays a role in the regeneration of olfactory receptor neurons. In case reports and an uncontrolled trial from a half-century ago, intramuscular administration of large doses of vitamin A restored lost smell sensation, both in patients with and without associated nasal pathology. In contrast, oral administration of vitamin A was not effective in these patients. Topical application of vitamin A, as used in the present study, might be more effective than oral administration, since it delivers a relatively high concentration of the vitamin directly to the nasal mucosa.

Hummel T, et al. Intranasal vitamin A is beneficial in post-infectious olfactory loss. *Eur Arch Otorhinolaryngol*. 2017;274:2819-2825.

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Vitamin C Prevents Side Effects from the MMR Vaccine

by Helen Saul Case

Orthomolecular Medicine News Service
http://orthomolecular.org/resources/omns/index.shtml

This is not an article about whether vaccinations are "good" or "bad." This is an article about how high-dose vitamin C can protect children from vaccination side effects. Until we have real choice as to whether or not we vaccinate our children, we must seek ways to make immunizations safer. High-dose vitamin C makes immunizations safer, as Thomas E. Levy, MD, JD, explains.

Giving the MMR Shot to a Child with Known Vaccination Sensitivity

Our daughter recently received the MMR (measles, mumps, and rubella) vaccination. In fact, she received two. New York State recently changed the law requiring an additional MMR shot in order for children to attend kindergarten. We had to make sure that she received both injections this summer before school started. We were concerned about giving her two MMR shots (and so close together) because after a previous vaccination she had a serious reaction.

Years ago, before we learned to give huge doses of vitamin C ***before, during, and after*** immunizations, our daughter (then age 15 months) had a severe reaction to the DPT (diphtheria, pertussis, and tetanus) vaccination: she lost her coordination, was screaming, falling over, and spiked a high fever. High-dose, saturation-level vitamin C cured her reaction to the DPT vaccine and taught us an important lesson: give more vitamin C. Much, much more. Now, in order to protect our children from any vaccination side effects, we give very high doses of vitamin C before, during (yes, even at the doctor's office), and after immunizations.

No, the MMR shot is not the same as a DPT shot. Just because our child reacted to one vaccine, doesn't necessarily mean she will react to another. However, according to the Centers for Disease Control and Prevention (CDC), "Any vaccine can cause side effects" and "like any medicine, is capable of causing serious problems." When you consider *just how much vitamin C* our daughter held after the MMR vaccinations, we have to ask ourselves one question: *where* was it all going?

How Much C? A Lot. A Whole Lot.

Our five-year-old, 37-pound (about 17 kg) daughter received saturation-level doses of 8,000 to 11,000 milligrams (mg) of vitamin C every day the week before her first MMR vaccination. The day of her shot, she happily and comfortably held 24,000 mg. For the next couple of days after the shot, her dose was reduced to 20,000 mg/day. Then, for the next four days, her vitamin C dose went down to 15,000 mg/day. The next four: 14,000 mg, 13,000 mg, 12,000 mg and 11,000 mg per day respectively.

For the next several weeks leading all the way up to her second MMR shot, she was getting between 8,000 and 11,000 mg of vitamin C each day.

On the day of her second MMR shot, just a little over a month from the first one, she once again received and comfortably held 24,000 mg of vitamin C. The day after: 19,000 mg. Once again, using bowel tolerance as an indicator, we gradually decreased this dose over the two weeks following this second immunization to an average of 9,000 mg/day. Eventually, we went back to her regular dose of 5,000 mg/day or 1,000 mg/day per year of age, following the recommendation of Frederick Robert Klenner, MD.

According to the CDC Vaccine Information Statement we received from our daughter's pediatrician, the MMR vaccine can cause "mild problems" including fever, rash, and glandular swelling; "moderate problems" including fever-induced seizure and painful joints; and "severe problems" such as serious allergic reactions, deafness, coma, and permanent brain damage.

Our daughter did not experience a single one of these side effects from the MMR shots. She had no vaccination reaction whatsoever. She had no fever, no swelling, no nothing. She was (and is) happy and healthy. How would things have gone if she had not been given high-dose vitamin C? We don't know. And we aren't about to take chances with potential side effects like coma or permanent brain damage.

Using Bowel Tolerance as an Indicator of "Enough" Vitamin C

Everyone wants to know, "How much vitamin C?" There is no set amount. This is why bowel tolerance is the ideal indicator. When warranted by such events as illness, potential illness, or immunizations, we give our children enough vitamin C to get just to the point of saturation, or loose stool. This is often indicated by a rumbling tummy or some gas. If stools become loose, we decrease the amount of vitamin C we give. If our children are happy and tooting away, that is just about right. After each MMR shot, our daughter's body accepted up to 24,000 mg/day of vitamin C. On any other regular day, she would reach bowel tolerance at much lower doses.

To reiterate, we give vitamin C to bowel tolerance when our kids show signs of sickness (runny nose, coughing, sneezing) and before, during, and after immunizations. We get them to bowel tolerance of vitamin C *before* there is a full-blown illness, and to *prevent* side effects from vaccinations.

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Vitamin D Deficiency Increases Risk of Chronic Headache

Vitamin D deficiency may increase the risk of chronic headache, according to a new study from the University of Eastern Finland. The findings were published in *Scientific Reports*.

The Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) analyzed the serum vitamin D levels and occurrence of headache in approximately 2,600 men aged between 42 and 60 years in 1984–1989. In 68% of these men, the serum vitamin D level was below 50 nmol/l, which is generally considered the threshold for vitamin D deficiency. Chronic headache occurring at least on a weekly basis was reported by 250 men, and men reporting chronic headache had lower serum vitamin D levels than others.

When the study population was divided into four groups based on their serum vitamin D levels, the group with the lowest levels had over a twofold risk of chronic headache in comparison to the group with the highest levels. Chronic headache was also more frequently reported by men who were examined outside the summer months of June through September. Thanks to UVB radiation from the sun, the average serum vitamin D levels are higher during the summer months.

The study adds to the accumulating body of evidence linking a low intake of vitamin D to an increased risk of chronic diseases. Low vitamin D levels have been associated with the risk of headache also by some earlier, mainly considerably smaller studies.

In Finland and in other countries far from the equator, UVB radiation from the sun is a sufficient source of vitamin D during the summer months, but outside the summer season, people need to make sure that they get sufficient vitamin D from food or from vitamin D supplements.

No scientific evidence relating to the benefits and possible adverse effects of long-term use in higher doses yet exists. The Finnish Vitamin D Trial, FIND, currently ongoing at the University of Eastern Finland will shed light on the question, as the five-year trial analyses the effects of high daily doses of vitamin D on the risk factors and development of diseases. The trial participants are taking a vitamin D supplement of 40 or 80 micrograms per day. The trial also investigates the effects of vitamin D supplementation on various pain conditions.

For further information, please contact Jyrki Virtanen, PhD, adjunct professor in nutritional epidemiology, University of Eastern Finland Institute of Public Health and Clinical Nutrition, tel. +358 40 355 2957, jyrki.virtanen@uef.fi.

Virtanen JK, et al. Low serum 25-hydroxyvitamin D is associated with higher risk of frequent headache in middle-aged and older men. *Sci Rep*. 2017; 7: 39697. Published online on January 3, 2017. http://rdcu.be/ogtQ

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The titration (bowel tolerance) method or large intravenous doses are absolutely necessary to obtain excellent results. The method produces spectacular effects in all patients capable of tolerating these doses. A placebo could not possibly work so reliably, even in infants and children, and have such a profound effect on critically ill patients.

Robert F. Cathcart III, MD

This is how we apply Dr. Robert F. Cathcart's bowel tolerance method. For our five-year-old daughter, we give vitamin C throughout the day in divided doses, beginning the day with a larger "loading dose" (about 3,000 mg) and then give frequent, smaller doses (about 2,000 mg every two hours) right up to about an hour before bedtime. When she was younger, we gave less, and she "held" less. Bowel tolerance is an excellent indicator of "enough" vitamin C no matter how old your child is.

When in Doubt, Give Vitamin C

Our daughter may be a special case. Maybe your child won't need nearly this much vitamin C. However, knowing the incredible safety and effectiveness of high-dose vitamin C, we are very comfortable giving our daughter what I would like to call "take no chances" sized doses at immunization time.

No, we don't take chances. We take vitamins. And we take a lot of them.

To learn more:

Case HS. Don't vaccinate without vitamin C. http://orthomolecular.org/resources/omns/v11n09.shtml
Case HS. Vaccinations, vitamin C, and "choice." http://www.orthomolecular.org/resources/omns/v12n07.shtml
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Downing D. Why this doctor questions flu vaccination. http://orthomolecular.org/resources/omns/v05n06.shtml
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Munsterhjelm-Ahumada K. Health authorities now admit severe side effects of vaccination: swine flu, pandemrix and narcolepsy http://orthomolecular.org/resources/omns/v08n10.shtml
Saul AW. Notes on orthomolecular (megavitamin) use of vitamin C. http://www.doctoryourself.com/ortho_c.html
Saul AW. Shots or not? The plague, the flu, and you. http://orthomolecular.org/resources/omns/v05n05.shtml
Yanagisawa A. Orthomolecular treatment for adverse effects of human papilloma virus (HPV) vaccine. http://orthomolecular.org/resources/omns/v11n05.shtml

OMNS Assistant Editor Helen Saul Case is the author of *The Vitamin Cure for Women's Health Problems* and coauthor of *Vegetable Juicing for Everyone*. Her latest book is *Vitamins & Pregnancy: The Real Story.*

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An Assessment of Testosterone and its Essential Metabolites for Prostate Cancer Risk

by Shalima Gordon, ND

5a-Androstane-3β,17β-diol, 3β-Adiol, is a testosterone metabolite that has been shown to provide protection against prostate cancer. In vitro and in vivo studies have shown that 3β-Adiol inhibits the proliferation, migration, invasiveness, and metastasis of prostate cancer cell lines via estrogen receptor β (ERβ) activation in the prostate gland.[1-6] Further, 3β-Adiol has no androgenic activity. It does not bind to the androgen receptor, nor is it converted to androgenic compounds. Theoretically, these properties make 3β-Adiol an attractive biomarker for prostate cancer risk and a potential novel agent in the treatment of this disease. Meridian Valley Lab offers the only androgen steroid hormone profile that provides an assessment of 3β-Adiol.

The Prostate Cancer Prevention Trial

The clinical relevance and utility of 3β-Adiol came out of the surprising findings of the Prostate Cancer Prevention Trial (PCPT). The PCPT was a Phase III, randomized, double-blind, placebo-controlled clinical trial of finasteride, a 5a-reductase inhibitor, for the prevention of prostate cancer. A total of 18,882 essentially healthy men, aged 55 and older, were randomized to receive finasteride (5 mg daily) or placebo for seven years. The study began in October 1993 and ended June 2003. The results showed that finasteride reduced the risk of developing prostate cancer by 25 percent. However, the incidence of high-grade prostate cancer (Gleason score 7-10) was 67 percent higher in the finasteride-treated group compared to placebo.

An explanation of this finding comes from the research of Imamov et al,[7] who suggest that the increased incidence of high-grade prostate cancer in the finasteride-treated group was a deleterious consequence of blocking testosterone to dihydrotestosterone conversion. Specifically, the down-stream production of 3β-Adiol from dihydrotestosterone is also blocked. 3β-Adiol is the natural ligand for ERβ, which is highly expressed in adult prostatic epithelium. Activation of ERβ suppresses proliferation and promotes differentiation of the prostatic epithelium. Without its ligand, ERβ activation is diminished and the proliferative action of androgen receptor activation within the prostate goes un-opposed. Akin to the Chinese Yin and Yang relationship, Imamov et al suggest a dynamic balance between ERβ activation vs androgen receptor activation within the prostate, controlling cell growth. This balance is disrupted through inhibition of testosterone-dihydrotestosterone conversion.

The Testosterone Metabolites Profile

As a research and investigational tool, Meridian Valley Laboratory has been offering the measurement of 3β-Adiol through serum for the last six years as part of a full Testosterone Metabolites Profile. This test further evaluates the balance of 3β-Adiol with "proliferative" testosterone metabolites. Practitioners have found this test particularly helpful for their male patients whom they regard at higher risk for prostate cancer. Male patients on testosterone replacement therapy, those with a past medical or family history of prostate cancer, those currently or with a history of using 5a-reductase inhibitors (i.e., finasteride, dutasteride, and high-dose saw palmetto), or those with low 5a-reductase activity as previously measured on a urine hormone profile are all candidates for further evaluation.

Specifically, this test measures and reports the following analytes: Androstenedione; Total Testosterone; 5α-Dihydrotestosterone (5α-DHT); ratio of Total Testosterone/5α-DHT; 3β-Adiol; 5α-Androstane-3α,17β-diol (3α-Adiol); and the ratio 3β-Adiol/(5α-DHT+3α-Adiol). A brief explanation of each follows.

Androstenedione

Androstenedione is considered a weak androgen in men and is secreted primarily by the testes. In the prostate

gland androstenedione is synthesized from the adrenal precursor steroids dehydroepiandrosterone sulfate (DHEA-S) and DHEA. Androstenedione is the primary precursor to testosterone, which is readily reconverted to androstenedione via the enzyme 17β-hydroxysteroid dehydrogenase (17β-HSD). It is also an intermediate in the biotransformation of DHEA to estrone via the aromatase enzyme. Aromatase can also synthesize estradiol using testosterone as the precursor. For this test, elevated levels of androstenedione typically suggest increased aromatization and should be followed-up with a screen for levels of carcinogenic estrogen metabolites. Aberrant high expression of aromatase enzyme activity and estrogen synthesis have been identified in prostate cancer and are implicated in prostate cancer genesis. Conversely, low levels of androstenedione in serum may suggest low upstream substrate or DHEA, the precursor for androstenedione.

Testosterone

Testosterone is the principle circulating androgen in men, secreted primarily by the testes. Testosterone and its metabolites are synthesized in the prostate as well. Adrenal-derived DHEA-S and DHEA is converted by 3β-hydroxysteroid dehydrogenase (3β-HSD) into androstenedione and testosterone – the latter being the downstream metabolite of androstenediol produced from DHEA via 17β-HSD Type V, which is in close proximity to 3β-HSD in the prostate epithelium. Interestingly, following medical or surgical castration, the intraprostatic concentration of DHT is about 40% of that measured in the prostates of intact 65-yr-old men.[8] This signifies a significant level of local androgen production and a reservoir capable of stimulating growth.

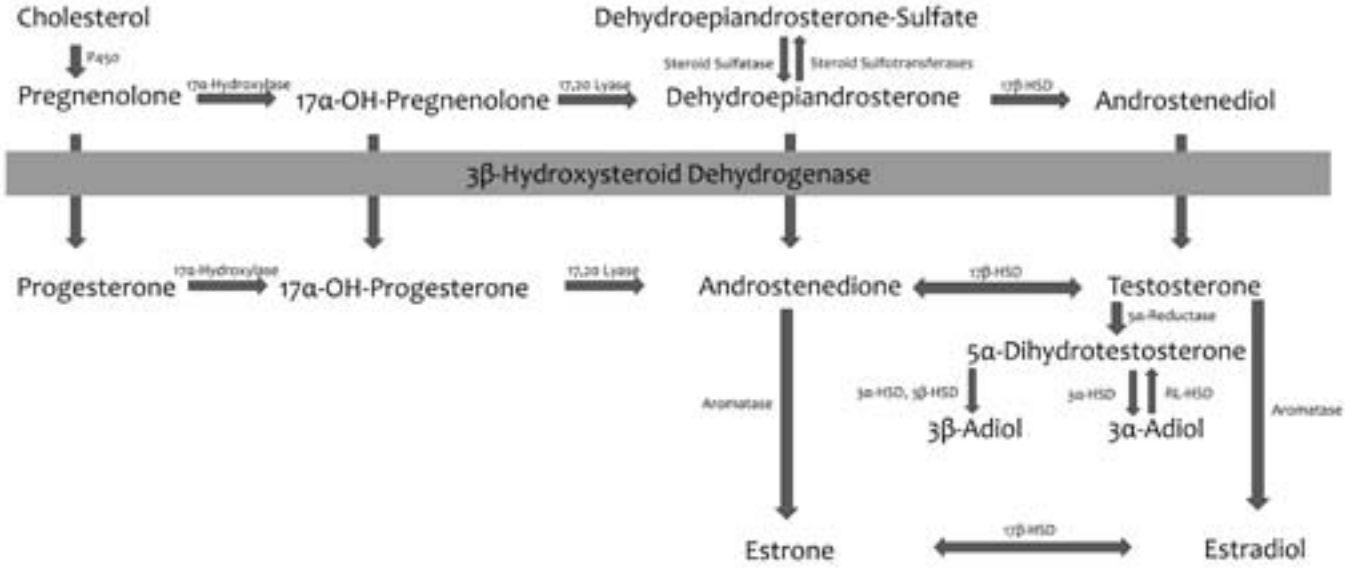
Most testosterone circulates in the blood bound to sex hormone binding globulin (SHBG) and to a lesser extent, albumin. Under physiologic conditions, only 1-2% of total circulating testosterone is free or biologically available. The Testosterone Metabolites Profile measures total testosterone in serum. Typically, elevated levels of total testosterone on this test are commonly seen in patients on testosterone replacement therapy simply because of the demographics commonly tested: the andropausal male. In cases like this, the indication is to decrease exogenous testosterone dosage. Although its long-term effects on the prostate are unknown, the mainstream view is that testosterone is contraindicated in men with prostate cancer or those at risk.

Currently, there is no clear evidence that an elevated testosterone level promotes the development of prostate cancer.[9] However, it seems reasonable that elevated levels may fuel excess aromatization to estradiol in addition to increasing 5a-DHT, both of which are proliferative to the prostate. 5a-DHT for example, derived from testosterone within prostate cells, mediates prostatic growth and is the initiating factor to androgen-dependent prostate disease. Low endogenous serum testosterone levels, on the other hand, may be associated with androgen deficiency-type symptoms, such as decreased energy and libido, erectile dysfunction, and a host of symptoms central to the pathology of metabolic syndrome – insulin resistance, dyslipidemia, hypertension and obesity. For these reasons, further evaluation of a high or low out-of-range serum total testosterone should be assessed against a serum measurement of free testosterone and SHBG. Measurements of luteinizing hormone and follicle-stimulating hormone to assess any suspected abnormalities of testosterone homeostasis in depth may also be clinically warranted.

Testosterone/DHT Ratio

Testosterone is primarily measured on this test as a participant in the testosterone/DHT ratio. Measurement of this ratio assesses for 5a-reductase enzyme activity. A high ratio can bring to the doctor's attention the deleterious inhibiting actions of a patient's ➤

Figure 1: Schematic representation of steroid hormone biosynthesis



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prescribed 5a-reductase inhibitor (i.e., finasteride, dutasteride). As noted above from the PCPT, 5a-reductase inhibition is associated with a reduced risk of developing low-grade prostate cancer but increased risk of developing high-grade, more aggressive forms of prostate cancer. A low T/DHT ratio on the other hand may suggest enhanced 5a-reduction, which has been implicated in the pathogenesis of pancreatic cancer, benign prostate growth (BPH) and lower urinary tract symptoms, obesity, insulin resistance and type 2 diabetes.

DHT and Its Metabolites

Testosterone is converted to the more potent androgen, 5a-DHT, by the 5a-reductase enzyme within the prostate. 5a-DHT is the principle androgenic stimulus with trophic action on the prostate via the androgen receptor. Unlike testosterone, 5a-DHT is not aromatized to estrogens; rather it is converted to two principle metabolites, 3a-Adiol and 3β-Adiol. Both of these 5a-DHT metabolites possess little activity at the androgen receptor; however, 3β-Adiol binds to and activates ERβ within the prostate epithelium. ERβ activation with its ligand mediates against excess cell proliferation and stimulates apoptosis and re-differentiation. Notably, ERβ expression is significantly decreased in malignant prostate tissue.

The conversion of 5a-DHT to 3a-Adiol is reversible. 3a-Adiol is synthesized from 5a-DHT through the action of 3a-HSD and back to 5a-DHT via the "3a-HSD-like" enzyme, RL-HSD, which is highly expressed in the prostate. As a "reservoir" for 5a-DHT, 3a-Adiol may indirectly potentiate the proliferative or trophic actions of 5a-DHT. 3β-Adiol is synthesized from 5a-DHT via 3a- and 3β-HSD. Unlike the conversion of 3a-Adiol from 5a-DHT, the synthesis of 3β-Adiol from 5a-DHT is not reversible.[10]

The combined total of 3a-Adiol and 5a-DHT serve as a basis for comparison to 3β-Adiol in assessing 3β-Adiol sufficiency. The optimum ratio of 3β-Adiol/(5a-DHT+3a-Adiol) is yet to be determined but is expected to be greater than 1.0, which would theoretically suggest a greater proportion of the anti-proliferative 5a-DHT metabolite. In other words, higher ratios are favorable.

3β-HSD

Noteworthy to this discussion is the pivotal role played by the enzyme 3β-HSD. The 3β-HSD isoenzymes catalyze an essential first step in the formation of all steroid hormones: sex steroids, mineralocorticoids, and glucocorticoids. In addition to its role in the biosynthesis of 3β-Adiol from 5a-DHT, this nicotinamide adenine dinucleotide (NAD^+)-dependent enzyme catalyzes the conversion of pregnenolone, 17α-hydroxypregnenolone, DHEA, and androstenediol into their respective ketosteroids: progesterone, 17a-hydroxyprogesterone, androstenedione, and testosterone (Figure 1). The 3β-HSD isoenzymes control crucial steroid-forming reactions and are found not only in "classical" steroidogenic tissues, namely the adrenal cortex, ovary, and testis, but also in a variety of peripheral target tissues, such as the breast, skin, brain, and prostate. The isoenzyme Type I 3β-HSD is predominantly expressed in peripheral tissues. Type II 3β-HSD is predominantly expressed in the adrenal gland, ovary, and testis.[8]

Interestingly, 3β-HSD genes are associated with prostate cancer risk. There is a significant association between genetic variants of either Type I and Type II 3β-HSD enzyme and prostate cancer susceptibility. More importantly, a joint effect of a genetic variant of both Type I and II combined has been shown to provide a stronger association for prostate cancer risk than a single variant genotype of either Type I or II.[11] According to Dr. Bruce Ames,* as many as one-third of mutations in a gene result in the corresponding enzyme having a poorer binding affinity (an increased K_m) for its coenzyme. This in turn lowers the rate of its reaction. Dr. Ames further suggests that many of the carriers of over fifty human genetic diseases caused by defective enzymes can be remedied by administering high doses of B-vitamin cofactors of the corresponding coenzyme. This may increase levels of the coenzyme and partially restore enzymatic activity.[12] For those with a genetic predisposition for prostate cancer, NAD supplementation and other factors to support this enzyme may prove beneficial.

It is important to note that steroid hormone biosynthesis begins in the mitochondria where the conversion of cholesterol to pregnenolone (the precursor for all steroid hormones) takes place.[13] From Dr. Ames' research, age-associated mitochondrial decay (i.e., oxidative damage) can also decrease the functional capacity of key enzymes, lowering their rate of reaction. And, high doses of the corresponding cofactors, which will raise the coenzyme level, may at least partially restore enzymatic activity. Thus, supporting mitochondrial function becomes a crucial component in supporting steroidogenesis.

Factors Affecting 3β-HSD Activity

A number of natural agents have been shown to influence 3β-HSD and/or 17β-HSD enzyme activity in various tissues. These include NAD, lithium, T3, zinc, vitamin A, olive oil and coconut oil. These agents could have a beneficial effect in supporting the synthesis of 3β-Adiol in the prostate gland.

The 3β-HSD enzyme belongs to the NADPH/NAD^+-dependent oxidoreductases which as its name implies catalyzes the oxidation-reduction of its steroidal substrate at the corresponding 3β-position. As mentioned, both 5a-DHT metabolites, 3a-Adiol and 3β-Adiol, are products of hydroxysteroid dehydrogenases.

Both enzymes have the same cofactor requirement: Vitamin B3, the

*The renowned Dr. Ames is a Senior Scientist at Children's Hospital Oakland Research Institute (CHORI), director of their Nutrition & Metabolism Center, and a professor emeritus of biochemistry and molecular biology, University of California, Berkeley. His research has focused on illuminating the mechanisms by which poor nutrition accelerates the degenerative diseases of aging. With over 550 scientific publications, he is among the few hundred most-cited scientists, in all fields.

component of niacinamide adenine dinucleotide (NAD). While there are no studies linking improved levels of 3β-Adiol with NAD intake, NAD supplementation may hold promise in light of the fact that 3β-HSD enzyme genetic variants are associated with prostate cancer susceptibility. As suggested by Dr. Ames, increasing cofactors may improve enzyme activity.

In a study on 3β-HSD enzyme activity of the adrenal gland in rats, lithium treatment was reported to stimulate the synthesis of 3β-HSD Type II, the isozyme predominantly expressed in the adrenals, ovary, and testis.[14] A simultaneous increase in corticosterone levels, a steroid product of 3β-HSD enzyme activity, was also noted following lithium treatment *in vivo*. In both measures, corticosterone levels and 3β-HSD enzyme activity, lithium action was largely dependent on the duration of treatment with long-term treatment (25 days) showing a greater response than short-term treatment (10 days).

From a clinical perspective, although adverse effects such as adrenocortical hyperactivity, hypothyroidism, and diabetes mellitus have been noted with long-term pharmacologic doses, lithium at 20 mg or less carries no ill side effects. This represents a physiologic dose that may fulfil the needs of individuals with a lithium deficiency and/or those that have a genetically-driven higher requirement for lithium.[15]

Triiodothyronine (T3) has also been shown to stimulate 3β-HSD Type II. In a study on 3β-HSD enzyme activity of the porcine corpus luteum, *in vitro* treatment of cultured luteal cells with T3 showed a marked increase in progesterone concentrations, measured via radioimmunoassay, against trilostane, a competitive inhibitor 3β-HSD.[16] In the corpus luteum, 3β-HSD catalyzes the conversion from pregnenolone to progesterone.

Zinc plays a key role in the activity of 3β-HSD and hence testicular steroidogenesis. In a study of male rats, a great reduction in the activity of 3β-HSD and testosterone levels was demonstrated histochemically in the testes of zinc-deficient rats compared to both control and zinc-supplemented ones. The authors of this study conclude that a hypogonadal state or Leydig cell failure can be induced with zinc deficiency altering testicular steroidogenesis.[17] It can be presumed from these results that a decrease in 3β-HSD activity and testosterone levels would also result in decreased downstream production of 3β-Adiol in the testes.

The vitamin A derivatives, retinoic acids and retinol, have been reported to regulate steroid biosynthesis in steroidogenic tissues such as human glial cells, adrenal gland, ovary and testis. In adult rat Leydig cell cultures, both retinol and retinoic acid-enriched media showed a direct stimulatory effect on testosterone biosynthesis via 3β-HSD compared to control media, as measured by radioimmunoassay.[18] All-*trans*-retinoic acid (ATRA), an active metabolite of vitamin A, has been shown to induce the expression of the 3β-HSD gene and its activity in cultured human glial cells.[19] The synthetic form of this retinoid is available by prescription only as it is toxic in high doses. Both studies described above establish an integral role for vitamin A in enhancing 3β-HSD activity and steroidogenesis.

Dietary fats show a direct impact not only on the lipid composition of the Leydig cells of the testes but, in turn, influence local steroidogenesis. Specifically, male rats supplemented with coconut oil or olive oil for sixty days showed a marked increase in testosterone levels compared to their counterparts supplemented with soybean or grape seed oil. In agreement with this finding, the activity of 3β-HSD and 17β-HSD was higher in the olive and coconut oil-supplemented groups compared to those supplemented with soybean or grape seed oil, where no significant effect was seen.[20,21]

The studies described above suggest that certain natural agents may support the production of 3β-Adiol via stimulation of 3β-HSD and/or 17β-HSD. However, there are a few points to consider. 3α-Adiol is also a product of this enzyme family, via 3α-HSD. 3a-Adiol is readily transformed back to 5a-DHT and functions as a secondary pool for 5a-DHT. Both enzymes, 3β-HSD and 3a-HSD have the same cofactor requirements. With regards to Type I vs Type II 3β-HSD, Type I is predominantly expressed in peripheral tissues such as the prostate and adipose tissue. Type II is predominantly expressed in the adrenal gland, ovary and testis. Although, Type II shares 93.5% identity with Type I, it's quite possible that Type I vs Type II may be under differential regulatory influences. They may also differ in their binding affinities for their coenzymes and cofactors. For example, in the presence of its coenzyme, NADH, Type I is reported to show a higher activity in the conversion of 5a-DHT to 3β-Adiol than Type II.[22] Further, there are no publications definitively linking the use of these natural agents in the production of 3β-Adiol and a resulting clinical effect. In other words, no "before-and-after" clinical studies. Still, the research on these agents in influencing 3β-HSD activity is interesting and offers therapeutic promise.

Test Logistics

For the purpose of the Testosterone Metabolites Profile, it is advised that the patient have his blood drawn early morning when endogenous testosterone levels are at their highest. For the male patient on testosterone replacement therapy, it is recommended to collect the blood sample mid-point from the time of his last dose to the time of his next dose. This is to avoid a bolus effect on the measured value. To make this easy for the patient, the patient should decide when he plans to have his blood drawn in the morning and then apply his testosterone twelve hours prior, the previous evening. In other words, if he is planning on having his blood drawn at 7 am, he would apply his testosterone at 7 pm. As this test requires a fasting

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morning blood sample, preparing for an early draw will allow him to eat breakfast sooner rather than later.

In Conclusion

The prostate is one of the major targets for DHT. DHT acts as the principle androgenic stimulus within this gland. Binding to the androgen receptors promotes proliferation and dedifferentiation of the prostatic epithelium. DHT can be metabolized to 3α-Adiol and 3β-Adiol, the latter of which binds to and activates ERβ. Activation of ERβ can suppress proliferation and promote differentiation of the prostatic epithelium, counteracting the physiological action of androgen receptor activation. 3β-Adiol is a potent inducer of ERβ expression but is then rapidly and irreversibly converted to downstream inactive metabolites for excretion. 3α-Adiol, on the other hand, may be converted back to DHT, thus serving as a reservoir for this potent androgen. With this in mind, supporting the production of 3β-Adiol as a strategy to inhibit prostate cancer cell growth seems intuitive for the forward-thinking clinician, and the select nutrients described are innovative measures in this respect. Though not yet proven by prospective or controlled studies, the use of 3β-Adiol as a laboratory marker and treatment strategy are revolutionary approaches to promote prostate health.

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Cortisol Deficiency: Frequent, Life-Impairing, and How to Give Patients Their Lives Back by Correcting It Part 1

by Thierry Hertoghe, MD

Cortisol is essential for human life. To stay alive, humans need cortisol. Life is not possible without it. In the absence of cortisol, the sugar level drops below 30 mg/dl, and the systolic blood pressure drops below 50 mmHg, which will cause a patient to fall into a deep coma and die about 24 hours later.[1-3]

Cortisol is also essential to enjoy a good quality of life.[4-7] When the cortisol level drops below a threshold in the blood, life is experienced as increasingly more difficult and stressful. If the level of cortisol drops further, life literally becomes miserable and plagued with anxiety, fatigue, and suffering.

Frequency of Cortisol Deficiency in an Ambulatory Setting

How many individuals in a population are cortisol-deficient? Data about the frequency of cortisol deficiency is scarce, if nonexistent. One study reported that 7% of hospitalized patients received glucocorticoid therapy during their stay,[8] but this percentage probably does not reflect the incidence of permanent states of cortisol deficiency in the global population.

An epidemiological study covering the whole population of Iceland over 18 years of age concluded that only 0.02% (22.1 per 100,000) of the population were suffering from primary adrenal deficiency.[9] Spanish researchers found an even lower prevalence of 0.01% (10 cases per 100,000) in Spain suffering from Addison's disease.[10] These low numbers are based on the extremely low number of patients receiving the diagnosis of Addison's disease and treatment for it in Iceland and Spain. Most cases are likely diagnosed with the traditional ACTH test, which is done with an inaccurate 250-fold too high dose (read further for more information). The numbers probably indicate that local physicians are not accustomed in diagnosing and treating primary adrenal insufficiency, leaving many cases of Addison's disease undiagnosed.

To get more accurate information through broader investigations including both clinical and laboratory findings, together with my colleagues of the clinic, we investigated the prevalence of cortisol deficiency in 56 consecutive and untreated (not receiving any glucocorticoid treatment) patients visiting our clinic for hormone therapy for the first time (36 females, mean age: 50.6 years (20-78); 20 males, mean age: 42.3 years (20-61)). Depending on the severity of clinical and laboratory diagnostic criteria, **4%, 13%, 50%, or 84%** of these patients can be considered cortisol-deficient and could potentially benefit from cortisol treatment.[11]

Diagnosis was based on an association of both clinical findings and laboratory test results, and not on a single laboratory test or sets of signs and symptoms alone without a suggestive laboratory test.

The following five symptoms of cortisol deficiency were checked through a questionnaire filled in by the patient: low resistance to stress, fatigue in stressful situations, low blood pressure, sugar cravings, and allergic reactions (skin, ENT, and/or asthma). The five physical signs of cortisol deficiency that were assessed were hollow face, pigmented spots on the face, conjunctivitis, dark circles under the eyes, and wet palms (due to peak secretions of adrenaline and noradrenaline in stress situations compensating for the low cortisol levels). Thus, a list was made of five symptoms and five signs suggestive of cortisol deficiency. The simple presence of one of the complaints or signs, whatever its intensity, was considered as contributing to (but not establishing) the diagnosis of cortisol deficiency.

The laboratory tests checking for diagnosis of cortisol deficiency included serum-free cortisol, 24-hour urinary-free cortisol, and 24-hour urinary 17-hydroxysteroids (i.e., the cortisol metabolites). We considered any test value below a critical level in laboratory tests as suggestive of (but not decisive for) the diagnosis of cortisol deficiency. The critical level was a level halfway between the average and the lower reference limit of the laboratory. The reason we used a critical level that is above the lower reference limit and not the lower limit itself is that the lower reference limit is a statistical - and not a health limit – and that many lower levels within the reference range are significantly associated with disease. These relationships are explained further

in the paragraph on "Cortisol Reference Ranges." For serum-free cortisol, the cutoff level was 12 (reference range: 7-27 ng/mL). For 24-hour urinary-free cortisol, the threshold was 30 (reference range: 10-90 µg/24 h). For the 17-hydroxycorticoids in 24-hour urines, the limit was fixed at 4.54 (reference range: 3.17-8.63 mg/24 h) in females and 7.5 (reference range: 6.10-11.70 g/24 h) in males.

Four categories of diagnostic criteria of increasing severity were applied to establish the prevalence. All of these criteria categories have medical legitimacy for diagnosis of cortisol deficiency.

The first type of diagnostic criteria is the presence of at least three of the ten possible signs or symptoms, with at least one of the three laboratory test results suggestive of cortisol deficiency. As shown in Figure 1, 84% of our patients fit into this category.

The second type necessitated the presence of at least five of the ten possible signs or symptoms, with at least two of the three laboratory test results suggestive of cortisol deficiency. As shown in Figure 1, half of the patients belonged to this category.

Criteria of the third category were severe. Only 13% of the patients presented the required minimum of six of the ten possible signs or symptoms and all three laboratory tests suggestive of cortisol deficiency, and could be classified in this group of undoubtedly cortisol-deficient patients. Only 4% (2 of 56) of patients belonged to the fourth group of severe diagnostic criteria with seven or more symptoms and signs and all three laboratory tests being conclusive.

The results of this small study show a high frequency of cortisol deficiency, which increases when criteria are less severe. They should not be considered representative of the general population but merely illustrative of the incidence of adrenal deficiency in a selected group within the general population, i.e., those individuals who are sent or go spontaneously to a clinic focusing on hormone therapy. The frequency of cortisol deficiency within this group is almost certainly greater than in the general population because many of our patients had levels in the lower third of the reference range in the laboratory tests.[11]

Incidence of Cortisol Deficiency with Aging

Some studies have shown lower serum cortisol levels with aging,[12-13] others no change,[14] while several investigations showed higher levels, especially in the evening,[15-16] which is at a time when the cortisol levels should considerably drop to allow the body to calm down and relax and prepare for sleep. However, as the metabolic clearance of cortisol decreases with age, thus allowing cortisol to remain for a longer time in the blood and less in the target cells,[17-19] the higher evening cortisol level may not reflect a higher cortisol activity in the target cells.

On the contrary, cortisol metabolic activity may substantially decrease with age following a study that showed that the 24-hour urinary excretion of the 17-hydroxycorticoids - the main metabolites of cortisol (and, thus, a reflection of cortisol metabolic activity in target cells) - are nearly 80% lower: 2 mg/day in older adults compared to 9.3 mg in young adults![20]

The Great Cortisol Discovery

In the mid-1930s, Kendall and Reichstein isolated several hormones of the adrenal glands, including compound E or cortisol, which was the most effective in prolonging the life of adrenalectomized animals. In 1946, Louis Sarettt succeeded in synthetizing cortisol for the first time. In 1948, sufficient quantities of compound E became available for the rheumatologist Philip Hench to test it successfully for the first time in a patient with rheumatoid arthritis.[21-23] The improvement in this patient and others was so impressive that it triggered enthusiasm all over the medical world so that, in 1950, Kendall, Reichstein, and Hench soon after received the Nobel Prize in medicine for their work on cortisol.

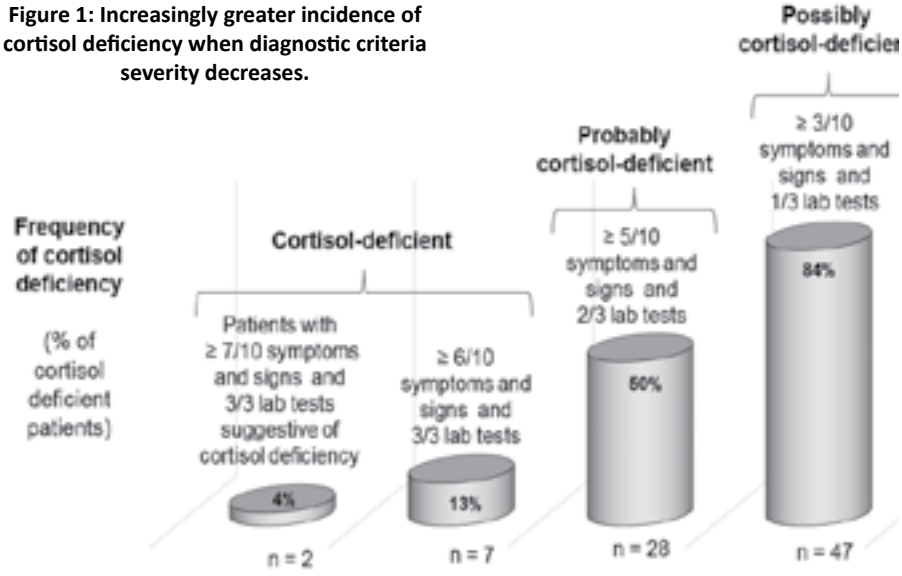
However, three errors were and still are made with cortisol treatment, which have triggered controversies on cortisol's use ever since and have probably made cortisol the most misunderstood and unjustly rejected treatment in medicine.

Three Therapy Errors That Spoil Outcome

What are these common errors? Firstly, excessive doses of cortisol were administered to quickly treat rheumatoid and other inflammatory disorders. Prolonged use of high cortisol doses reduces skin thickness, muscle volume, and bone density and provokes swelling, weight gain, bruising, pathological effects on the cardiovascular system, and at times a euphoric, excessively agitated character.[8,24-27] in contrast, low doses of cortisol (i.e. 20-30 mg/day of hydrocortisone) or of one of its derivatives (5 mg of prednisolone for example) are relatively safe.[28-31] In septic shock, a low dose appears to show efficacy in decreasing mortality, whereas a high dose does not.[32-33]

Secondly, cortisol or its glucocorticoid derivatives were administered alone without the protection of other hormone supplements, such as DHEA (dehydroepiandrosterone – the other ➤

Figure 1: Increasingly greater incidence of cortisol deficiency when diagnostic criteria severity decreases.



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primary adrenal hormone), that prevents any excessive tissue catabolism from cortisol. In healthy individuals, each time the adrenal glands secrete the catabolic hormone cortisol, they also secrete protective anabolic hormones such as DHEA, androstenedione, and other androgens.[19,34-39]

Thirdly, no attention was given - and is often still not given - to increasing the intake of protein-rich foods to protect against cortisol side effects. Experimental research in animals has shown that catabolic effects of glucocorticoids, even at overdoses, can be neutralized by proportionately increasing in the diet the intake of proteins[40-43] or amino acids, such as creatine.[44-45]

Four Principal Actions of Cortisol

The four main actions of cortisol consist of producing energy and resistance to stress, reducing inflammation, reducing oxidative stress, and breaking down fat. Let's examine them in greater detail.

The first major effect of cortisol is to boost energy levels and stress resistance. Cortisol increases energy in stressful situations where higher energy levels and endurance are necessary to cope with the difficulties.[46-50] In my experience, the increase in energy is felt after about 3 to 15 minutes when endogenous cortisol is increased by a stress and a little longer, 15 to 30 minutes, after taking a cortisol (hydrocortisone) supplement.

How does cortisol provide energy and stress resistance? Cortisol boosts energy by four mechanisms, which are triggered in stressful conditions. Firstly, cortisol increases the glucose supply to the tissues. When the needs for glucose are low, such as in rest periods, cortisol increases the storage of glucose in the form of a bigger molecule, glycogen. In rodents whose adrenal glands have been removed (adrenalectomy) and, thus, are deprived of glucocorticoids, glycogen levels drastically decrease. When corticosterone, the cortisol of rodents, is given to these rats, it increases more than tenfold the glycogen content in the liver and muscles. In stressful conditions, cortisol breaks down the glycogen into glucose through glycogenolysis and converts amino acids into glucose through gluconeogenesis, increasing the blood sugar levels. This hyperglycemia[51] brings an abundance of glucose available for the target cells, thus improving a patient's reactions and helping him or her cope with stress.

Secondly, cortisol elevates the dopamine activity in the brain by increasing the number of dopamine receptors.[52] As dopamine is a potent energy neurotransmitter, more dopamine activity results in higher energy levels.

Thirdly, cortisol increases the supply of blood, oxygen, and nutrients to the brain, muscles, and inner organs by raising the blood pressure[53] through an increase in salt and water retention in the kidneys and vasoconstriction and through the stimulation of contractions of the thick smooth muscle layers that wrap up the arteries. Fourthly, cortisol "burns" fat.[54-55] This lipolysis liberates energy.

A second important action of glucocorticoids is to reduce inflammation. Cortisol considerably reduces the migration of leukocytes into inflammatory zones.[56-57] The accumulation of these white blood cells at the sites of inflammation causes swelling, compression, and pain. Cortisol also blocks collagen overproduction,[57] which makes inflamed tissues thick and hard. Collagen is the main protein that fills up the spaces between cells in the tissues. By reducing collagen formation during inflammation, cortisol prevents fibrosis and, thus, formation of excessively thick scars or keloids and scleroderma, which is the disease that affects the skin and organs with fibrosis.

At high doses, cortisol's anti-inflammatory effect may atrophy the major immune gland, the thymus. However, thymus atrophy and immune depression only appear when cortisol treatment is imbalanced (i.e., too much cortisol without sufficient addition and protection by anabolic hormones and protein-rich foods). High doses of glucocorticoids without DHEA protection also produce skin, muscle, and bone atrophy, which are other well-known side effects of cortisol overdoses.

It is always the same story: too much of a good thing is too much. To use cortisol safely, it is important to administer physiological doses. In cases of higher needs, to the doses of cortisol can be temporarily increased if supplementary doses of anabolic hormones, such as DHEA, are also added.

By reducing inflammation, cortisol may also block the appearance of allergies. The increasingly higher frequency of allergies in people is partially due to pollution and intestinal problems – the known triggers of allergies – but is almost always a sign of adrenal deficiency. The adrenals glands do not secrete sufficient amounts of cortisol, which is the anti-allergy hormone. The loss of cortisol's anti-inflammatory action also explains why cortisol-deficient patients typically suffer from intolerance to all kinds of medications.

Cortisol also provides beneficial effects through its insufficiently known antioxidant activity. Cortisol neutralizes free radicals preventing free radical tissue damage,[58-60] a property especially useful in stressful conditions, which are associated with an increase in free radical production. Free radicals originate from oxygen molecules through the loss of an electron and become, for this reason, tissue-damaging compounds. The more free radicals are formed, the greater "oxidative stress" is inflicted on the body, thus damaging tissues, and the more tissues prematurely age.

Last, but not least, and contrary to belief, cortisol does not increase fat but breaks down fat.[54-55] Weight gain that tends to appear with high-dosed cortisol supplements is not due to a direct stimulation of fat production by cortisol but through a stimulation of the appetite and an increased intake of weight-increasing foods, such as sugar and grains (bread, porridge, muesli, pasta, etc.).

Types of Cortisol Deficiency

There are three types of cortisol deficiency depending on the tissue that causes the deficiency. In primary cortisol deficiency, also called Addison's disease (following the name of Dr. Addison, who was the first to describe the disease), the *adrenal glands* themselves are weak and unable to secrete a sufficient amount of cortisol. President Kennedy suffered from Addison's disease and took a treatment for it.[61] In secondary cortisol deficiency, the production by the *pituitary gland* of ACTH, the hormone that stimulates the adrenals to produce cortisol, is deficient. In tertiary cortisol deficiency, the production by the *hypothalamus* of CRH

(corticotropin releasing hormone) that stimulates the secretion of ACTH is failing.

Diagnosis of Cortisol Deficiency

The diagnosis of cortisol deficiency is based on clinical and laboratory assessments confirmed by a successful therapeutic trial. To diagnose cortisol deficiency, laboratory tests (blood and urinary), an evaluation of all complaints, and physical signs of cortisol deficiency are needed. When sufficient findings suggest a cortisol deficiency, a glucocorticoid treatment trial should be engaged to confirm the deficiency. If the patient feels better, looks much better, and laboratory tests show no excess with the glucocorticoid therapy, then the diagnosis of cortisol deficiency is confirmed, and cortisol treatment should be continued. If the glucocorticoid treatment does not give any result, doses may be too low and a trial at higher doses should be undertaken. If the treatment provides overdose symptoms, even at low doses, then the treatment is contraindicated.

Psychological Complaints of Cortisol Deficiency

Individuals with cortisol deficiency are tired[62-66] as soon as they have to exert effort or fall into stressful situations. People with adrenal deficiency lack the punch to react efficiently to stressful events. If they react, they quickly feel tired, even exhausted, and cannot face any new strains. If demands are high at their work, they end up being burned out, which is almost literally an "adrenal burnout" or a severe depletion of the adrenals stocks of cortisol-making patients no longer able to face normal daily life difficulties. Cortisol deficiency is the main deficiency behind the feelings of burnout.

The fatigue in cortisol deficiency has in my experience several characteristics. It consists of a lack of energy, flu-like feelings, a lower capacity to react well to stress, and a foggy feeling in the head. The lack of energy of cortisol deficiency[62-65] predominantly results from hypoglycemia - the lack of sugar. In stressful conditions, it exponentially worsens. The flu-like character of fatigue,[67-68] where every part of the body feels uncomfortable, is due to the generalized inflammation of cortisol deficiency. The lack of punch to react to stress, typical of patients with cortisol deficiency, is due to low glycogen stores and low dopamine receptor numbers. The glucose stocks and dopamine activity are insufficient to increase the energy levels and cope with new stressful situations. In severe cortisol deficiency, the lack of energy to react to events can become an inability to react, literally paralyzing the patient in stressful conditions where more energy is required. Coping with new stressors then becomes difficult or even impossible.

The fogginess and empty headedness of cortisol-deficient patients is due to a low blood pressure[69] that substantially reduces the blood supply to the highest parts of the body when standing, particularly the brain.

In the early stages of cortisol deficiency, patients may react very emotionally to events in an outburst of anger or anxiety, compensating for the lack of cortisol by peaks of adrenaline and noradrenaline. In later stages of increasingly greater adrenal deficiency, the adrenal medulla that secretes the catecholamines also wears out, leaving the patient without reaction to a new stressor. This severe situation is typical of burnout.

Cortisol Deficiency

Cortisol-deficient patients are excessively sensitive to stress.[70-73] They feel the world is stressful and difficult to live in because it is full of worries and aggressiveness. Cortisol-deficient patients tend to find that others, especially people close to them, family members, and colleagues at work, put excessive pressure on them.

Because of this feeling of excessive pressure, cortisol-deficient patients tend to be nervous and irritated. Irritability is the most typical psychological symptom of cortisol deficiency[74-76] due to increased secretions of adrenaline and noradrenaline. These neurotransmitters make individuals nervous and are secreted in higher amounts to compensate for the low cortisol. Outpourings of adrenaline and noradrenaline not only cause nervous behavior but also anger and anxiety outbursts.

In cortisol deficiency, the brain and nerves easily inflame. Brain inflammation makes patients feel that life is "inflamed," more stressful, and even dramatic. ➤

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This dramatization of problems and life events, which seems minor and easy to treat for healthy individuals, may appear to be extremely important and difficult to cortisol-deficient patients and make them use harsh, sharp words that reveal their inflamed perception of the world, such as "terrible," "horrible," "miserable," "a catastrophe," a disaster," and "you are killing me."

The Paranoid Behavior of Cortisol-Deficient Patients

Patients with cortisol deficiency suffer more than the average population would in similar stressful conditions. Because their suffering feels unbearable, they seek causes to their pain, hoping that they may find solutions by finding causes outside themselves. As it is easier to find a cause outside than inside of oneself, they tend to suspect others of being the cause of their suffering, often their closest relatives, such as the partner, family members, friends, or colleagues at work. In cortisol-deficient patients, a suspicion quickly becomes a conviction and transforms into accusations. They accuse others of being the cause of their suffering and tend to persecute them, surprising them by their overreactions.

The recurrent accusatory behavior explains the paranoid tendencies of cortisol-deficient patients and is the basis of the paranoid character typical to cortisol deficiency.[76-79] One of cortisol's roles is to reduce the production and levels of adrenaline and noradrenaline – neurotransmitters that make us overreact in a crazy, violent way and giving us the sudden desire to harm a person or oneself, sometimes even to murder or suicide!

The accusations form the base of the quarrelsomeness, which is another typical symptom of cortisol-deficiency. Patients tend to quickly interpret others' offhand words as negative criticisms. In reaction, they utter sudden and violent accusations. In turn, these nervous reactions trigger heavy protest from the accused person in self-defense, and quarrels start over again. This quarrelsomeness induced by minor stresses makes life difficult for family members or colleagues at work.

Cortisol Deficiency and Stress

Cortisol deficiency complaints increase in intensity during stressful conditions. In calm, relaxing situations, patients with cortisol deficiency do not suffer much, if any, from their disorder. In stressful conditions, however, cortisol deficiency complaints come up and increase almost exponentially in intensity because these patients cannot make the supplementary amounts of cortisol necessary to cope with stress. Their adrenals barely make enough cortisol for the needs of an easy sedentary life where rest is central, and work or performance is secondary.

Healthy adrenal glands produce supplementary amounts of cortisol whenever supplementary work has to be done or whenever a dangerous situation occurs (i.e., to respond to the difficult situation, fight back, or run away from it). The energy comes from a higher sugar level, blood pressure, and number of dopamine receptors.

Inevitably, due to their negative life experiences, patients with cortisol deficiency tend to express negative thinking and have a low mood.[80] Table 1 shows the most typical psychological complaints of cortisol deficiency.

Table 1. Psychological Complaints of Cortisol Deficiency

(Particularly frequent and intense in stressful conditions)

- Flu-like fatigue
- Outbursts of nervousness, anger, fear
- Lack of punch
- Use of intensely negative words: horrible, terrible, dramatic, disaster, the end of the world, etc.
- Poor resistance to stress
- Intense dislike of stress
- Irritability, aggressiveness, even meanness
- Try to avoid stressful situations, jobs, partner
- Quarrelsomeness
- Accusations, meanness toward others

Physical Complaints of Cortisol Deficiency

In adrenal deficiency, the body feels tense, particularly the muscles, due to high catecholamine levels, producing tachycardia and (heart) palpitations in stressful conditions. Wet armpits, wet hand palms, and wet foot soles occur in stressful conditions due to excessive sweating, also resulting from high adrenaline and noradrenaline secretions. The body tries to compensate for the lack of cortisol by increasing the secretion of catecholamines.

Other complaints are due to inflammation. Cortisol-deficient patients easily complain that the body hurts all over,[81] including abdominal (digestive),[82-83] muscle,[84-85] and joint pain,[85-89] and even the hair and skin may feel unpleasant to the simple touch due to compression of the nerves by inflammation. Table 2 shows the physical complaints of cortisol deficiency. The same type of pain sensation is also seen during the flu. Patients with cortisol deficiency have a weak immune system that makes them prone to infections. They can get one infection after the other.

The flu puts people in a state of cortisol deficiency.[67-68] The influenza virus blocks the secretion of ACTH, which is the pituitary gland hormone that stimulates the adrenal glands to make cortisol. The lack of ACTH causes the cortisol production to drop, and the flu-like symptoms of cortisol deficiency to appear.[90]

A generalized lack of energy caused by low sugar levels is a predominant sign of the flu and of cortisol deficiency. A desire to lie down, caused by low blood pressure, pain aches in the whole body, and sore throat and red eyes initiated by inflammation are other dominant signs of the flu due to cortisol deficiency.

If cortisol supplements are taken in small bits (5 to 10 mg of hydrocortisone, for example) every half hour at the very beginning of the flu (in the minutes or first hour that the infection/inflammation begins), the flu disappears within one to two hours,[91] as explained later when discussing cortisol therapy.

Table 2. Physical Complaints of Cortisol Deficiency

(Particularly frequent and intense in stressful conditions)

- Fatigue-like fatigue with the desire to lie down
- Deformed joints
- Tensed muscles
- Allergies: skin, nose-ear-throat with reddish coloration of inflamed zones, asthma, food allergies
- Tachycardia
- Intolerance to medications
- Palpitations, especially in stressful conditions
- Frequent infections: Sore throat, red eyes, ear pain, flu, etc.

- Excessive sweating in armpits, on hand palms, and on foot soles
- Reduced appetite
- Localized pains in structures that are put under pressure, such as the eyes, abdomen, joints, tendons, and muscles
- Weight loss in people caused by a low appetite

Physical signs of cortisol deficiency also predominate at physical examinations. Four types of signs are found differing from each other by their cause: hyperpigmentation, malnutrition, adrenaline excess, low blood pressure, or inflammation (See Table 3).

Pigmentation signs are specific to primary adrenal deficiency or Addison's disease, where the adrenal glands are weak but not the pituitary gland, which overproduces the hormone ACTH to stimulate cortisol production.[82-83,92-93] As ACTH is a pigmenting hormone, pigmentation increases with greater intensity in some areas: dark circles under the eyes, hyperpigmented skin folds, and spots on the face and body. In cortisol deficiency, the pigmentation is **irregular** and reflects desperate attempts by the body to increase cortisol production by the adrenals. When it is not successful, it pours down increasingly greater amounts of ACTH, pigmenting the skin, which darkens even without sun exposure.

Cortisol-deficient patients also tend to have a hollow face and often thin body[94-96] because they eat less or absorb the food less because their intestines are less effective at absorbing food.

The reduced food intake usually results from poor appetite, particularly for protein-rich foods, such as meat, because the nitrogen contained in the proteins tends to accumulate in the blood, a process called "azotemia." The deficient food absorption in the intestines is the consequence of the inflammation of the intestinal mucosa, impairing its absorptive actions. Patients with cortisol deficiency also weigh less because they lack body water due to the loss of cortisol's water-retaining effects.

As most patients overproduce adrenaline and noradrenaline to compensate for the cortisol deficit, signs of adrenaline excess, such as wet armpits, palms, and soles and trembling fingers, tachycardia,[95] and acute systolic hypertension (the "white coat" arterial hypertension) may be found during the physical examination.

As cortisol is also a hormone that raises the blood pressure, the blood pressure is often low at rest in people with a lack of cortisol.[69,97-98] Finally, signs of inflammation are often found due to the loss of cortisol's anti-inflammatory effects: conjunctivitis, otitis, rhinitis, eczema,[99-100] psoriasis, arthritis (with joint deformations, especially in the fingers),[101-105] gastritis, enteritis, colitis, and so on.

Cortisol deficiency favors the development of the following pathological conditions: allergies, including asthma and eczema, and generalized inflammatory diseases, such as rheumatoid arthritis,[101-105] lupus erythematosus disseminatosus,[106] systemic sclerosis, etc. Also, Hodgkin's disease and lymphomas may be facilitated by cortisol deficiency, as these diseases tend to regress with cortisol treatment.[107-109]

Cortisol Deficiency

Laboratory Tests to Screen for Cortisol Deficiency

Three types of cortisol tests may help diagnose cortisol deficiency: blood, saliva, and 24-hour urine. They are all complementary to each other.

Firstly, blood or, better, **serum tests** of total cortisol,[110] free cortisol, and transcortin (the protein that transports cortisol to the target cells in blood)[111] can be assessed. Total cortisol consists of all cortisol found in the blood, regardless of whether it is bound or not to a transporting protein. Free cortisol is the small fraction of total cortisol that is not bound to any protein and easily diffuses into cells. The usefulness of testing for transcortin is that high levels of this transporter attach to cortisol excessively, so it remains in blood much longer, not sufficiently getting into the target cells.

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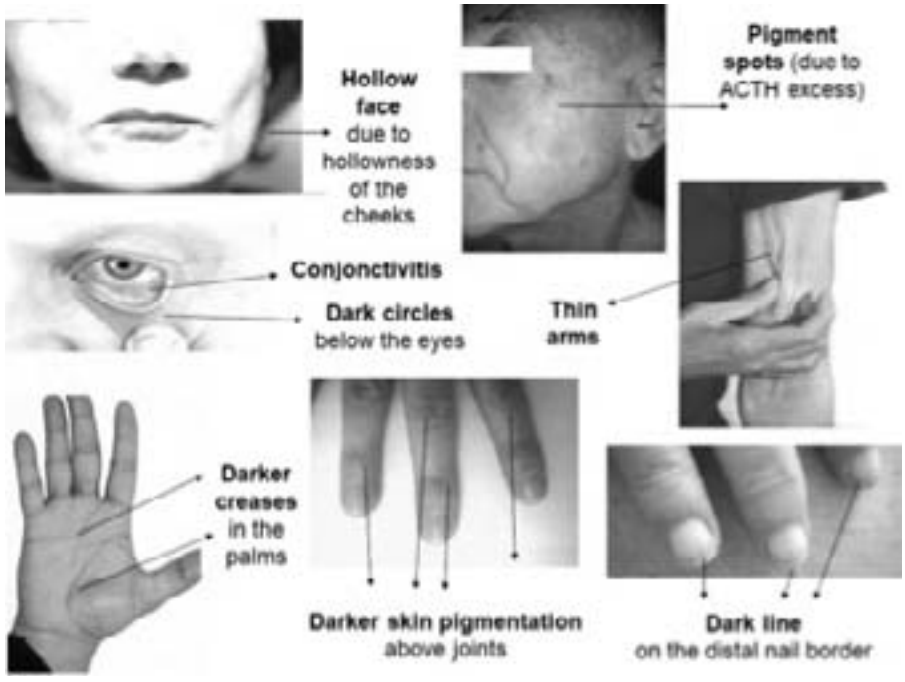
Table 3. Physical Signs of Cortisol Deficiency
(Particularly frequent and intense after months of stressful conditions)



- Hollow face
- Thin body or weight loss
- Red eyes (inflamed conjunctives)
- Wet armpits, hand palms, and foot soles in stressful conditions
- Dark circles under the eyes
- Pigmentation spots on face, back of the hands
- Tachycardia
- Skin rashes
- Low blood pressure
- Signs of nose–ear–throat infections or allergic reactions
- Deformed joints, especially of the hands and feet

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In the previous study where the prevalence of cortisol deficiency in our clinic was studied, we also checked the relationship between clinical findings and serum levels of free cortisol in 55 consecutive patients (36 females, mean age: 50.6 years; 19 males, mean age: 42.0 years). The study showed that serum levels of free cortisol reflect the number of signs and symptoms of cortisol deficiency relatively well through an inverse association. Progressively lower serum-free cortisol levels are observed with increasingly greater numbers of clinical signs and symptoms (on a scale from 0 to 10) as pictured in Figure 2.[112]

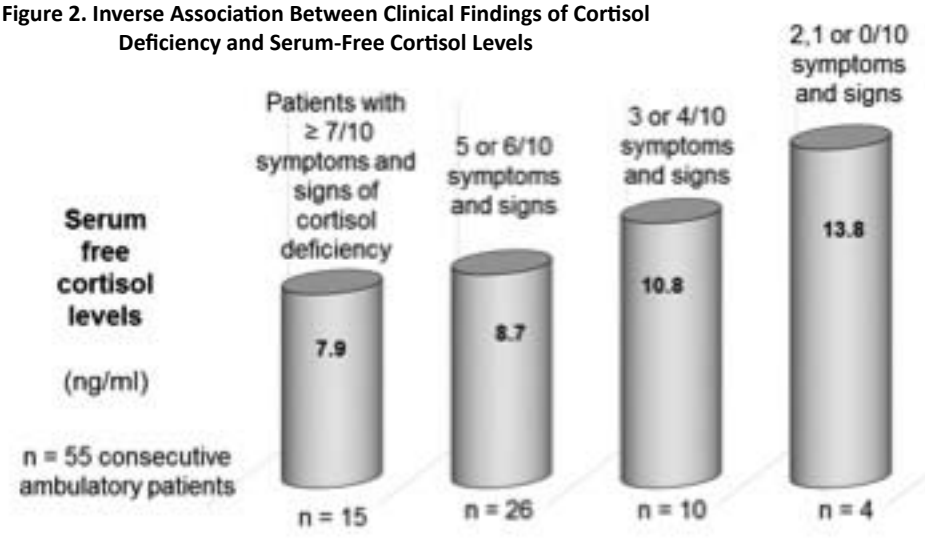
The ACTH-stimulation test is another blood test that evaluates the adrenal reserve, whether the adrenal glands have sufficient cortisol stored to supply supplementary cortisol in case of increased need. Injecting ACTH, the pituitary hormone that stimulates the secretion of cortisol, into a vein directly stimulates the adrenal glands. Check it every 30 minutes by withdrawing a blood sample and measuring the increase of cortisol obtained. Any doubling or more of the level of cortisol from the initial level indicates an adequate adrenal reserve and the likelihood that there is no cortisol deficiency. Unfortunately, in most clinics, the test is done by injecting 250 µg of ACTH, a huge overdose. Almost any adrenal glands, even weaker ones, will react to this overdose. Two studies have shown that using a more natural or physiological dose of 1 µg of ACTH allows for a much better differentiation between patients with adrenal deficiency from subjects without it. Whenever the cortisol level does not double with ACTH (whatever the initial serum cortisol level is), it indicates an intermediate degree of deficiency in the adrenal reserve.[113] Studies have shown that critically ill patients in emergency rooms whose adrenal glands do not secrete enough cortisol after an ACTH injection die in the following days and weeks, while most other patients with good ACTH test survive.[114-115] Thus, an abnormally low ACTH test helps detect critical persons who need a cortisol supplement for survival.

The saliva cortisol test checks the cortisol circadian rhythm with four samples taken at distant times.[116-117] A higher morning peak of cortisol must appear in this test. Burnout patients usually have an insufficient morning cortisol peak. In the most severe cases, the cortisol morning rise may even be absent, and the cortisol circadian rhythm flat and inexistent.

The **24-hour urine test** evaluates the excretion of cortisol and its metabolites in the urine during a full day and night cycle. The urinary cortisol level in this test reflects cortisol production during a 24-hour period.[118-124] The measurement of cortisol's major metabolites, the 17-hydroxycorticoids, informs on cortisol's metabolic activity – how much cortisol is really used for action – during the same period.[125-128] It is important to collect baseline urinary excretions of adrenal hormones, which are representative of the patient's adrenal activity, not stress-induced ones. Patients should therefore collect their urine in relaxed, sedentary conditions during the 24 hours that precede the test and during the 24 hours of the urine collection) to avoid increases in cortisol metabolites due to physical activity or high-stress conditions.

In all these tests, the measurements of protective anabolic hormones, such as DHEA, the sex hormones, and IGF-1, should be included, as most treatments with cortisol include one or more of these hormones in the treatment to ensure an adequate catabolic/anabolic hormone balance.

Figure 2. Inverse Association Between Clinical Findings of Cortisol Deficiency and Serum-Free Cortisol Levels



Serum free cortisol levels reflect the number of signs and symptoms of cortisol deficiency through an inverse association. The serum free cortisol level declines progressively at increasingly greater numbers of clinical signs and symptoms.

Cortisol Reference Ranges

Cortisol reference ranges are statistical ranges, not health ranges. If the reference range for cortisol in laboratory tests would be a range of serum levels corresponding to health, cortisol deficiency would only be diagnosed in 2.5% of the population, those whose cortisol level is below the lower reference limit.

However, the laboratory reference limits for cortisol are purely statistical parameters. Just as for other hormones, 2.5% of the population statistically have a cortisol level above the upper limit, 2.5% have a value below the lower limit, and the cortisol level of the remaining 95% is within the reference range,[129] regardless of whether these subjects have a deficiency. The laboratory "normal" limits are, thus, not limits separating "healthy" levels, which would be all the levels within the reference interval, from the levels that are below or above the reference interval and that would correspond to levels of cortisol deficiency or excess. Reference limits only indicate where a patient's hormone level is compared to that of other patients who attend that laboratory.

Even if an entire population is deficient in a hormone, such as postmenopausal women who are all deficient in estradiol, 95% of this population would still have

a hormone level within the reference range.

Both low and high serum cortisol levels within the reference range are associated with increased risks of pathology and mortality. Hormone levels are not necessarily adequate when they are within the "normal" range between the upper and lower reference limits of the laboratory tests. On the contrary, for most hormones – including cortisol – scientific research has shown that many serum levels within the reference range are significantly associated with disease and even mortality.[130-150]

Researchers have shown that serum cortisol levels within the reference range but near the lower reference limit are usually inadequate because they are associated with an increased likelihood of disease, suggesting that these lower levels within the reference range should also be treated. In my experience, borderline low limits are also associated with complaints and physical signs of cortisol deficiency. Studies have also shown that cortisol levels near the upper limits may be associated with an increased risk of disease, suggesting that the optimal cortisol level in sedentary conditions should be an average level, neither too high nor too low. However, in stressful situations, cortisol levels may need to increase to provide additional energy to respond to the stress; this is the reason that levels near the upper limit were associated with better outcome than lower levels in some studies.

Table 4 shows an overview of several of the studies showing the association of serum total cortisol levels within the reference range with increased risk of psychological and physical disease, and premature death.

Cortisol Binding Globulin (Transcortin)

High serum levels of cortisol binding globulin (CBG or transcortin) often cause intracellular cortisol deficiency. For a correct evaluation, physicians should also check the serum level of cortisol binding globulin, the main plasma protein that binds cortisol and transports it to the target tissues. The ideal transcortin level in the plasma is situated at the average or slightly below the average of the reference range. High concentrations (positioned in the upper half of the reference range) to very high levels (above the upper limit) of CBG are usually excessive because they bind excessive amounts of cortisol, literally "imprisoning" cortisol in the blood.[151] This cortisol sequestration in the blood prevents most of it from penetrating into target cells and exerting their beneficial effects, thus producing – at least a mild degree of – intracellular cortisol deficiency.

A good example of excessive CBG levels with intracellular and, thus, physical and mental cortisol deficiency can be found in women who take birth control pills.[152-153] The estrogen compound of these pills makes the women's livers overproduce transcortin through the accumulation of the pill's estrogen compound in the liver after absorption.

Part 2 will address the treatments for cortisol deficiency.

References available online

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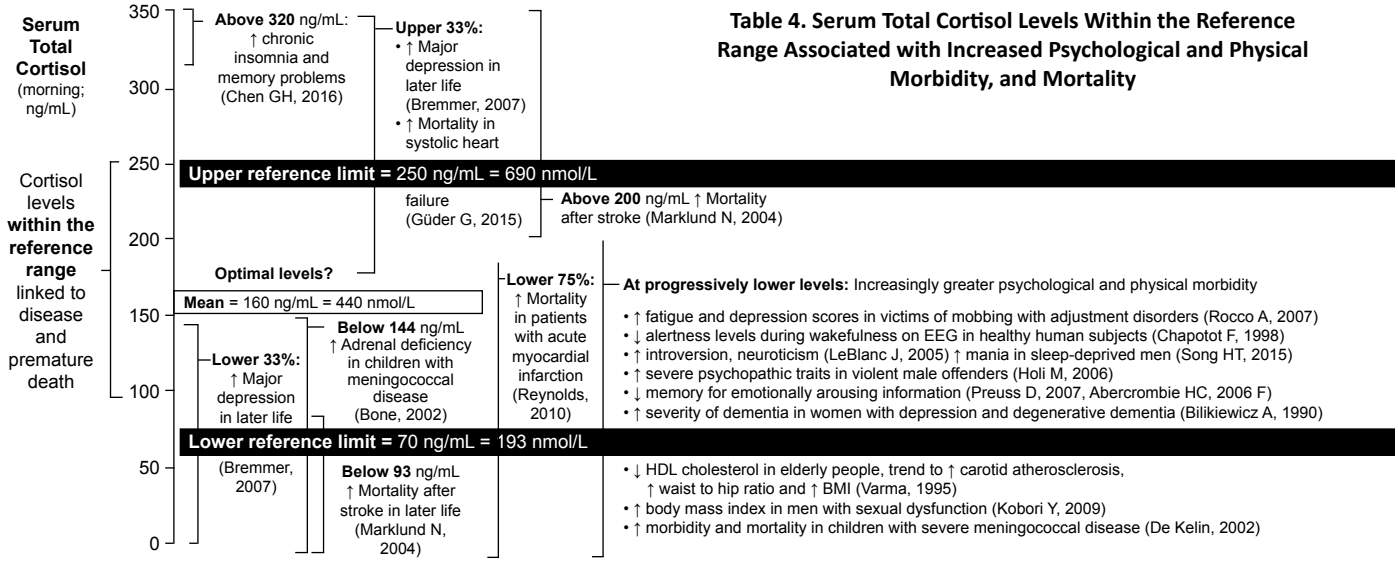
Table 4. Serum Total Cortisol Levels Within the Reference Range Associated with Increased Psychological and Physical Morbidity, and Mortality



Born in Antwerp, Belgium, Dr. Hertoghe practices his medicine in his clinic in Brussels. With his sister, Dr. Thérèse Hertoghe, they proudly represent the fourth successive generation of physicians working with hormonal treatments – and this since 1892 (after Eugène Hertoghe, former vice president of the Royal Academy of Medicine in Belgium, and Luc and Jacques Hertoghe, endocrinologists). Dr. Thierry Hertoghe devotes his life to the promotion of a better, patient-oriented, and evidence-based medicine.

Author of numerous books, Dr. Thierry Hertoghe also travels a lot to take part in numerous conferences and congresses throughout the world. He co-organizes many of these specialized gatherings and holds important positions in several international and national medical organizations (which usually tend to fight against aging). He is the president of the International Hormone Society (over 2500 physicians), and of the World Society of Anti-Aging Medicine (over 7000 physicians), as well as the supervisor of two important postacademic trainings for doctors.

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Naturopathic Interpretation of Common Blood Tests

by Dr. Douglas Lobay, BSc, ND

Naturopathic interpretation of blood tests provides nutritional and biochemical insight into each person's unique biological chemistry. This interpretation does not necessarily focus on pathology per se, but provides attention to variances of the norms and what this means. I have found that the common blood tests provide an incredible amount of nutritional and biochemical information about each individual patient. From an allopathic perspective you are considered healthy if nothing shows out of range on a blood test. By attending many different seminars and conferences, networking with other doctors, both naturopathic and allopathic, I have developed a systematic approach to evaluating basic medical blood tests from a naturopathic perspective.

I remember listening to the esteemed nutritionally oriented physician Dr. Alan Gaby talking about lab testing. He said something to the effect that he likes to do basic common blood tests on a patient. It provides him with a wealth of nutritional information about the patient upon which he would, in part, form his clinical assessment and treatment plan. I also remember a valuable lesson many years ago when I performed a 24-hour urine adrenal hormone assessment on a patient. I received a complicated diagram of the biochemical pathway of urine steroids that were evaluated. The patient asked about an obscure adrenal steroid that was low. I looked at the same diagram, scratched my head a bit, and said it probably means your adrenals are taxed and you need adrenal support. The complicated test did not change my assessment or treatment plan. Keep it simple, observe slowly and read between the lines. See if you gain nutritional and biochemical insight in common blood tests. There is more there than meets the eye at first glance.

HGB or HEMOGLOBIN. Hemoglobin is the oxygen-carrying molecule in red blood cells. It consists of iron and a protein called heme. In every red blood cell there are approximately 270 million hemoglobin molecules, each capable of carrying four oxygen molecules. Reference values are 120-160 grams hemoglobin per liter for women and 140 to 180 grams hemoglobin per liter for men. Low levels of hemoglobin indicate low oxygen carrying capacity of blood. Symptoms of low hemoglobin include fatigue and lethargy. Iron, B12, folic acid, and protein deficiencies, poor absorption, and blood loss are frequent causes of low hemoglobin. High levels of hemoglobin can be caused by iron overload disease, and high-altitude conditioning.

RBC or RED BLOOD CELL COUNT is the number of red blood cells per volume of blood. Reference values are 3.8 to 5.2 trillion cells per liter of blood for women and 4.5 to 6.0 trillion cells per liter of blood for men. Low values of RBCs can be caused by anemia, acute or chronic blood loss, and chronic disease. Symptoms of low red blood cell count include fatigue, weakness, and lethargy. High values of RBCs can be caused by iron overload disease, hemochromatosis, and high-altitude conditioning.

HCT or HEMATOCRIT is the percentage of red blood cells in total blood volume. After blood is spun down in a centrifuge, the height of the column of red blood cells is measured and compared to the column of original whole blood. Reference values frequently quoted are 37 to 47% for females and 40 to 54% for males. Low values of HCT can be caused by anemia, acute and chronic blood loss, and chronic disease. High values of HCT can be caused by iron overload disease, hemochromatosis and high-altitude conditioning.

MCV or MEAN CORPUSCULAR VOLUME measures the average size or volume of a red blood cell. Reference values for MCV are 80 to 100 femtoliters or cubic micrometers. A MCV value of 95 or higher indicates a larger than average red blood cell. An increased MCV can indicate vitamin B12, folic acid, and vitamin B6 deficiencies. A MCV value of 85 or lower indicates a smaller than average red blood cell. A decreased MCV can occur with iron deficiency, anemia, chronic disease, lead poisoning and elevated red blood cell counts.

MCH of MEAN CORPUSCULAR HEMOGLOBIN indicates the weight of hemoglobin in the average red blood cell. Reference values are 27 to 31 picograms. The MCH depends on the amount of hemoglobin in red blood cells and the size of red blood cells. The same factors that affect hemoglobin and red blood cell count affect the mean corpuscular hemoglobin.

MCHC or MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION estimates the average concentration of hemoglobin in the average red blood cell. MCHC depends on the relationship of the amount of hemoglobin to the volume of the red blood cell. Thus, MCHC does not depend on cell size alone. MCHC can be decreased in iron deficiency, anemia, and chronic disease. MCHC can be increased in heavy smokers, autoimmune disease, and people with high blood fats.

RDW or RED CELL DIAMETER AND WIDTH measures the amount of variation in the red cell diameter or width. Reference values are less than 15.6%. There should be less than 15.6% variation in the diameter or width of all red blood cells. Variation in RDW can be caused by vitamin B12, folic acid, and iron deficiencies, illness, and certain types of cancer.

PLT or PLATELETS measure the number of platelets per volume of blood. Reference values are 150 to 450 billion platelets per liter of blood. Platelets are involved in bleeding and blood coagulation. Low platelet values are associated with an increased tendency to bruise and bleed. Causes of low platelet values are disease, anemia, infection, enlarged spleen or lymph nodes, bone marrow abnormalities or various toxins. Elevated platelet values can be caused by certain malignancies, acute blood loss, autoimmune disease, and acute infection.

WBC or WHITE BLOOD CELL COUNT measures the number of white blood cells in the blood. White blood cells are the main part of the immune system that protects the body from invading micro-organisms and foreign toxins. The normal reference value for total white blood cell count is 4.0 to 11.0 billion cells per liter of blood. A low or decreased value less than 4.5 may suggest low immune system status. A high or elevated value may suggest acute infection, cancer, or inflammation. Some nutritionally oriented doctors suggest that a WBC count of 8.0 or greater is consistent with generalized inflammation or sub-acute infection in the body.

NEUT or NEUTROPHILS are the foot soldiers of the immune system. They are the first line of defense that most micro-organisms and toxins encounter in the blood stream. They are also the most abundant type of white blood cell. The normal reference value for neutrophils is 1.8 to 7.5 billion cells per liter of blood. They normally account for 50 to 70% of all white blood cells. Bacterial infection and acute inflammation are the most common causes of elevated neutrophil count. Low neutrophil count can indicate low immune system status and may follow after an acute infection. An elevated neutrophil count may indicate acute infection (especially bacteria), inflammation, or in rare cases, certain types of cancer.

LYMPH or LYMPHOCYTES are the second most abundant type of white blood cell in the immune system. Lymphocytes have several different and important functions in overall immune stature. Certain lymphocytes called T-lymphocytes, or thymus-developed lymphocytes, are associated with the lymphatic system. Other lymphocytes called B-lymphocytes produce many different proteins or antibodies to infectious micro-organisms and toxic chemicals. The normal reference value for lymphocytes is 1.0 to 4.5 billion cells per liter of blood. They normally account for 20 to 40% of all white blood cells. Low lymphocyte count can indicate low immune stature. Elevated lymphocyte count usually occurs with viral infection or in rare cases in certain types of cancer. Some nutritionally oriented doctors consider a lymphocyte value of 1.5 or less as indicative of low functioning immune system.

MONO or MONOCYTES are the third most abundant type of white blood cell in the immune system. Monocytes usually show up later in cases of infection or inflammation. They perform "mop up" duty and help clean up after the acute battle is finished. The normal reference value for monocytes is 0.0 to 1.1 billion cells per liter of blood. They normally account for O to 7% of all white blood cells. Low monocyte value can indicate low immune system status. Elevated monocyte value can indicate chronic infection including parasites, autoimmune disease, or certain types of cancers.

EOS or EOSINOPHILS are white blood cells that are associated with parasitic infection and allergies. The normal reference value for eosinophils is 0.0 to 0.7 billion cells per liter of blood. They normally account for 0 to 5% of all white blood cells. An elevated eosinophil count can indicate parasitic infection or the presence of allergic reactions.

BAS or BASOPHILS play a background role in the immune system. The normal reference value for basophils is 0.0 to 0.3 billion cells per liter of blood. They normally account for 0 to 1% of all white blood cells. Elevated basophil count can indicate acute disease, including certain types of cancer.

SODIUM is the most abundant extracellular electrolyte in blood. Only small amounts occur inside cells. Sodium regulates electrolyte balance, pH, body and blood fluid volume and nerve conduction. The body requires 1000 to 3500 milligrams of sodium per day. The normal reference value for sodium is 133 to 146 millimoles per liter. Low sodium levels can indicate low dietary intake of salt, sodium loss through the kidneys or as a side effect of certain prescription medicines or inherited genetic disorders. High sodium levels can indicate excessive dietary intake of salt, high blood pressure, edema or swelling, and heart disease.

POTASSIUM is the major intracellular electrolyte in the body. The body requires 1875 to 5625 milligrams of potassium per day. Potassium plays a major role in regulating fluid and blood pH, acid-base balance, water retention, muscle activity, and nerve conduction. A deficiency of potassium can cause muscle weakness, muscle cramps, fatigue, and heartbeat disturbance. Excess potassium can cause heartbeat disturbance, paralysis, and death. The normal reference value for potassium is 3.5 to 5.0 millimoles per liter.

CHLORIDE is the major negative electrolyte in the blood and tissue. It functions in combination with sodium. Chloride serves as a buffer in pH regulation and an enzyme activator. It is also a component of hydrochloric acid

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in the stomach. Most chloride is present in fluid outside cells and less than 15% is found within cells. The normal reference value for chloride is 96 to 107 millimoles per liter. Low chloride values can occur with low salt intake, dehydration, or profuse sweating. High-chloride levels are associated with excessive salt intake, high blood pressure, or edema.

TOTAL C02 measures total carbon dioxide value in your blood. Carbon dioxide values depend on the amount produced in the body, acid-base balance, and the breathing capacity in the lungs. C02 is produced during the normal metabolism of carbohydrates in the body. It is buffered in the blood to help eliminate acids. C02 is eliminated through normal respiration through the lungs. The normal reference value for total C02 is 23 to 32 millimoles per liter. A low C02 value can indicate alkaline body pH or hyper-ventilation through the lungs. A high C02 value can indicate an acid body pH or hypo-ventilation through the lungs.

CREATININE is a waste material that is produced by metabolic activity in muscles. It is produced at a fairly constant rate and is filtered by the kidneys. It measures how well the kidneys are filtering. The normal reference value for creatinine is 40 to 115 micromoles per liter. A low creatinine value can indicate low muscle turnover or very good kidney filtration. A high creatinine value can indicate high muscle turnover or poor kidney filtration and function. Generally, the higher the creatinine value, the weaker the kidneys.

GLUCOSE refers to blood sugar levels. Blood sugar levels are affected by dietary intake, insulin production in the pancreas, liver metabolism of glucose, and certain hormones. Blood sugar dysregulation can be caused by excessive sugar and consumption of carbohydrates, poor pancreas and liver function, and hormone dysfunction. The normal reference value for fasting blood glucose is 3.3 to 6.0 millimoles per liter. Low blood glucose levels are associated with hypoglycemia. High blood glucose levels are associated with pre-diabetes or end diabetes. Three classic signs of diabetes include increased frequency of urination, increased thirst with increased fluid intake, and increased food intake with increased food consumption. Nutritionally oriented doctors consider blood sugar to be tightly regulated and consider 4.2 to 6.0 millimoles per liter as well regulated, normal blood glucose values.

CALCIUM refers to blood levels of calcium. 99% of body stores of calcium is in bones and teeth. Calcium is necessary for electrolyte transport across membranes. Calcium is also required for muscle contraction, blood clotting, and heart contraction. The normal reference value for calcium is 2.10 to 2.60 millimoles per liter. Low levels of calcium can be caused by low dietary intake, hypoparathyroidism, and poor absorption. Long-term dietary deficiency is one of the main causes of bone thinning and osteoporosis. Deficiency is also associated with muscle excitability and cramps. High levels of calcium can be caused by excess digestive disturbances, kidney disease, and certain bone diseases and cancer.

PHOSPHORUS refers to blood levels of phosphorus. About 80% of phosphorus is in bones and teeth. Phosphorus is a component of every cell and of highly important substances such as nucleic acids found in DNA and ATP, the high energy molecule, and is a vital component of cell walls. The normal reference value for phosphorus is 0.80 to 1.45 millimoles per liter. Low levels of phosphorus are associated with low protein and essential fatty acid intake. High levels can be caused by excess intake or kidney disease.

UREA is a normal breakdown product of protein that is produced in the body. It is filtered by the kidneys and reflects kidney function. The normal reference value for urea is 2.5 to 8.0 millimoles per liter. A low urea value can indicate low protein turnover. A high urea value can indicate poor kidney function. Other causes of high urea value include excess protein breakdown, shock, dehydration, bladder or prostate obstruction.

URATE also known as uric acid is a protein breakdown product normally produced in the body. The normal reference value for urate is 150 to 400 micromoles per liter for females and 200 to 450 micromoles per liter for males. Low levels or urate are associated with low protein intake and turnover. High urate levels are associated with blood over-acidity and gout. Increased production of urate in the body or an inability to excrete urate through the kidneys may be responsible for elevated levels in the blood. Nutritionally oriented doctors also consider high urate levels associated with oxidation of DNA in the cell nucleus and an indicator of systemic candida yeast in the body.

TOTAL PROTEIN refers to total protein content in the blood. Total protein is made up of the amount of albumin and globulin. The normal reference value for total protein is 64 to 84 grams per liter. Low protein levels can be caused by low dietary intake, poor absorption, or systemic loss of protein through the kidneys, digestive system or skin. High levels of protein are rarely caused by excessive intake. High levels are more often caused by inflammatory conditions in the body, dehydration, or certain types of cancer.

ALBUMIN is the most common protein subtype in the blood. Albumin is responsible for maintaining fluid pressure in the blood and as a transport vehicle for drugs, hormones, and a few other substances. The normal reference value for albumin is 35 to 50 grams per liter. Low levels can be associated with low dietary intake, poor absorption, or loss of albumin. High levels of albumin can be associated with certain inflammatory conditions, dehydration, or certain types of cancer.

GLOBULIN is considered to be the remaining non-albumin fraction of total protein. Globulin is made up of several subtypes including alpha, beta,

and gamma globulin. Globulin plays an integral part of the immune system. Immunoglobulins refer to antibodies utilized by the immune system to attack and recognize micro-organisms and foreign chemicals. The normal reference value for globulin is 24 to 37 grams per liter. Low levels of globulin can be caused by low dietary protein intake, protein loss, and chronic illness. High levels of globulin rarely occur with high dietary protein intake. High levels can be caused by inflammatory conditions, certain cancers, and chronic disease.

A/G RATIO or the ALBUMIN TO GLOBULIN RATIO refers to the ratio of the protein subtypes albumin to globulin. Albumin and globulin are normally distributed in a specific ratio, where there is more albumin than globulin. The normal reference value for albumin to globulin ratio is greater than 0.9. Irregularities in the A/G ratio reflect abnormalities in the amount or distribution of albumin or globulin.

BILIRUBIN, TOTAL is a breakdown product of the hemoglobin in old red blood cells. Bilirubin is produced in the lymphatic system and liver. The normal reference value for total bilirubin is less than 20 micromoles per liter. Some nutritionally oriented doctors suggest that bilirubin levels reflect liver drainage as does creatinine in the kidneys. Low levels of bilirubin reflect low red blood cell turnover and good liver drainage. High levels of bilirubin in the blood cause jaundice, which is manifest as a distinct yellowing of the skin because of high circulating bilirubin levels. Three major causes of high bilirubin are hemolysis of red blood cells, liver disease or damage, or biliary outflow obstruction. Abnormal liver drainage and outflow are considered the most common causes of high bilirubin. Gilbert's syndrome, a genetic condition that affects about 5% of the population, is marked by a deficiency in the liver that causes elevated bilirubin levels.

BILIRUBIN, CONJUGATED refers to the part of the total bilirubin that is further broken down or conjugated in the liver. The normal reference value for conjugated bilirubin is less than 7 micromoles per liter. Abnormal liver function can cause elevated levels of conjugated bilirubin.

LD or LACTATE DEHYROGENASE is an enzyme found in heart, skeletal muscle, red blood cells, and to lesser extent in lung, lymphoid tissue, liver, and kidney. Lactate dehydrogenase breaks down lactate produced in the body from breakdown of sugars. The normal reference value for LD is 100 to 225 units per liter. Low levels of LD indicate low enzyme in those tissues that contain the enzyme. High levels of LD can be caused by acute or chronic inflammation of those tissues especially red blood cells, muscles, and liver. Some nutritionally oriented doctors suggest that one of the most common causes of LD elevation are caused by essential fatty acid deficiency.

ALT or ALANINE TRANSAMINASE is an enzyme found predominantly in liver and to a lesser extent heart and skeletal muscle. The normal reference value for ALT is less than 50 units per liter. Low levels of ALT indicate low enzyme activity and low levels of liver inflammation. High levels of ALT indicate liver inflammation. Many nutritionally oriented doctors consider ALT values of 25 or higher to indicate some degree of liver inflammation.

AST or ASPARTATE TRANSAMINASE is an enzyme found in several organs and tissues including liver, heart, skeletal muscle, and red blood cells. The normal reference value for AST is less than 40 units per liter. Low levels of AST indicate low enzyme activity and low levels of inflammation. High levels of AST indicate inflammation and damage in those tissues and organs. Many nutritionally oriented doctors consider AST value of 20 or higher indicating some degree of inflammation or damage in those tissues or organs.

GGT or GAMMA GLUTAMYL TRANSPEPTIDASE is an enzyme found predominantly in liver and gall bladder and to lesser extent in intestines, heart, brain, pancreas, and spleen. The normal reference value for GGT is less than 55 units per liter. Low levels of GGT indicate low enzyme activity and low levels of inflammation. High levels of GGT indicate high levels of inflammation. Many nutritionally oriented doctors consider GGT value of 27 or higher indicating some degree of inflammation or damage in those tissues and organs.

Keep it simple, observe slowly and read between the lines. See if you gain nutritional and biochemical insight in common blood tests. There is more there than meets the eye at first glance.

ALKALINE PHOSPHATASE is an enzyme found in many tissues, with highest concentration in liver, gall bladder and bone. The normal reference value for alkaline phosphatase is between 30 to 130 units per liter. Low levels of alkaline phosphatase indicate low enzyme activity in the liver and low bone activity. High levels of alkaline phosphatase indicate inflammation of those tissues or high degree of bone activity. Many nutritionally oriented doctors consider alkaline phosphatase values of 80 or more to indicate some degree of inflammation in those affected tissues.

CHOLESTEROL refers to total blood levels of cholesterol and is usually measured in a fasting state. Cholesterol plays an important role in the body including in hormones and cell membranes. The body produces 60 to 80% of total cholesterol, while dietary sources account for 20 to 40%. The normal reference value for total cholesterol is less than 5.20 millimoles per liter. Low levels of total cholesterol can be caused by low dietary fat intake and can be associated with fatigue,

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essential fatty acid deficiency, and hormone irregularities. High levels of total cholesterol can be caused by excessive intake of fat or abnormal cholesterol production in the liver. High values of total cholesterol have been associated with increased risk of atherosclerosis, heart disease, and stroke.

TRIGLYCERIDE refers to total blood levels of fats that aren't cholesterol. Triglycerides are made up of glycerol and fatty acids. Triglycerides reflect dietary intake of fat and sugar, or abnormal liver production of fat. Excessive intake of sugars and refined carbohydrates can increase triglyceride values. The normal reference value for triglycerides is less than 2.30 millimoles per liter. Low levels of triglycerides can be caused by low dietary intake of fats and sugars. High levels of triglycerides can be caused by excessive intake of fats, sugars, and refined carbohydrates. High values of triglycerides are just as bad as high cholesterol levels and are associated with increased risk of atherosclerosis, heart disease, stroke, and diabetes.

HDL CHOLESTEROL or HIGH-DENSITY LIPOPROTEIN refers to "good" cholesterol. This type of cholesterol returns circulating cholesterol and fats back to the liver for processing. HDL cholesterol consists of a lot of un-oxidized forms of total cholesterol. The normal reference value for HDL cholesterol is greater than 0.90 millimoles per liter. Low levels of HDL cholesterol have been associated with increased risk of atherosclerosis, heart disease and stroke. High levels of HDL cholesterol have been shown to dramatically lower the risk of cardiovascular disease.

LDL CHOLESTEROL or LOW-DENSITY LIPOPROTEIN refers to "bad" cholesterol. This type of cholesterol takes circulating cholesterol and fats from the liver into systemic circulation where it can be deposited in arteries in atherosclerotic plaques. LDL cholesterol consists of a lot of oxidized cholesterol. The normal reference value for LDL cholesterol is less than 3.40 millimoles per liter. Low levels of LDL cholesterol have been shown to lower the risk of atherosclerosis, heart disease, and stroke. High levels of LDL cholesterol have been associated with a dramatically increased risk of cardiovascular disease. Nutritionally oriented doctors like to see LDL cholesterol levels less than 3.0 in high-risk patents.

TOTAL CHOL/HDL RATIO measures the ratio of total cholesterol to "good" HDL cholesterol. Some individuals can have levels of total cholesterol greater than 5.20 and have high HDL levels in excess of 0.90. Other individuals can have high total cholesterol levels and low HDL cholesterol levels. If total cholesterol levels are elevated above 5.20 it is much better to have high HDL levels. Generally, the higher the HDL levels the better. The normal reference value for cholesterol to HDL cholesterol ration is less than 4.5 millimoles per liter.

IRON reflects the iron in the blood bound to serum proteins. The normal reference of iron is 8 to 25 micromoles per liter. Iron levels are decreased with poor absorption, iron deficient anemia, or blood loss. Iron levels are increased in iron overload disease, hemolysis of red blood cells, excessive iron, or liver disease.

TIBC or TOTAL IRON BINDING CAPACITY measures the ability of a protein called transferrin to bind iron. The normal reference value for TIBC is between 40 to 80 micromoles per liter. TIBC values are low in cases of iron overload, protein deficiency, and certain chronic diseases. TIBC values are high in cases of iron deficiency, liver disease, pregnancy, alcoholism, and with certain drugs.

SATURATION INDEX measures the degree of transferrin saturation. The normal reference value for saturation index is 0.16 to 0.60. Under normal circumstances transferrin is about one-third saturated. Low levels of saturation index can be caused by iron deficiency and certain chronic diseases. High levels of saturation index can be caused by iron excess and protein deficiency.

FREE T4 or FREE THYROXINE measures the free, unbound levels of T4 or thyroxine circulating in the blood. The thyroid gland, which produces thyroxine, controls the rate of metabolic activity in the body. The normal reference value for free T4 is 9.0 to 23.0 picomoles per liter. Low levels of T4 indicate low levels of thyroid functioning. Symptoms of low thyroid function include fatigue, lethargy, weakness, sluggish activity of all organs, and cold temperature throughout the body. High levels of T4 indicate high levels of thyroid functioning. Many nutritionally oriented doctors consider a low normal level of free T4 to indicate a sluggish thyroid.

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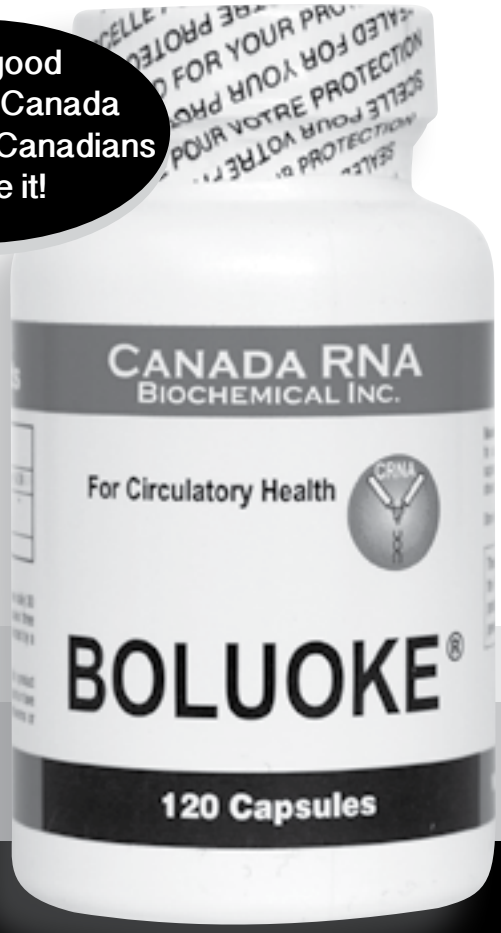

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Multiple Chemical Sensitivity: The Paradigm Breaker for Doctors

by Don Want

Multiple chemical sensitivity (MCS), or toxicant-induced loss of tolerance, was first recognised in 1954 by Dr Theron Randolph. The sufferer experiences sensitised reactions to various manufactured chemicals.[1]

The resulting symptoms of MCS vary from one individual to another, although they are usually consistent/repeatable in each individual in response to the same triggers. The symptoms overlap with those of closely related health conditions such as chronic fatigue, fibromyalgia, and Gulf War syndrome. There can be from one to multiple organs/body systems affected. An unfortunate feature of this condition is that the sensitisation and reactions can progressively get worse with repeated exposures. The symptoms can conversely abate if exposures to such incitants are avoided.

MCS sufferers react to very low concentration levels of the inciting chemicals, such as experiencing headaches and fatigue symptoms due to deodoriser or perfume presence at levels not able to be smelt. Depending upon how sensitive the individual is, triggering concentrations may be orders of magnitude lower than normally accepted exposure levels derived from classical toxicology approaches. It is this aspect that creates general disbelief about the existence of this condition. The multiple symptoms also result in disbelief by conventional medical profession practitioners: their training frequently leads them to regard individuals complaining of multiple organ problems and accompanying neurological symptoms as having a psychological problem. No characteristically unique signs, laboratory test abnormalities, tissue pathology, or course of illness have been clearly established for diagnosis purposes. Thus, the general trend by the conventional medical system is to give the sufferers a diagnosis of somatoform disorder or other psychological diagnoses. The mainstream medical system operates without recognition of the central sensitivity condition. As there is no training in environmental factors initiating health conditions, most doctors do not recognise their significance.

The incidence of people with chemical sensitivities in the population is significant, with figures ranging between 2% and 22% of the population.[2-14]

Central Sensitisation

Central sensitivity (CS) refers to a heightened sensitivity condition through the central nervous system. This frequently precipitates chronic pain. It has an initial wind-up period in respect to pain intensity over time. Peripheral, repeated nociceptive input establishes improved neuronal pathways for such pain transmission producing functional changes in the brain.[15-17] Even after the initial source of pain may have healed, the same pain pathways may remain active with pain still being felt by the sufferer.[18] A source of chronic inflammation, e.g., arthritis, can act as a source of nociception. Neuroendocrine-immune pathology can also develop CS.[19]

Many doctors fail to recognise a CS condition in patients: it needs a different approach than would otherwise be taken from a non-detailed diagnosis approach.[20] It is a challenging idea that localised pain is not necessarily an indicator of a local physiological problem

As explained later for MCS, N-methyl-D-aspartate (NMDA) receptors seem to play an essential role in human chronic pain and are vital for nervous system functioning: they are widely present in both the peripheral and the central nervous system tissues. NMDA agonists are involved in CS and MCS.

So, there is an increasingly recognised CS condition which loosely fits sensitisation phenomena typical of MCS. Recognition of MCS and overlapping conditions as being a CS is gradually occurring.[20]

The Growing Awareness of Environmental Effects on Health

The incidence of many diseases has significantly increased over the past five decades: autism, Alzheimer's, chronic obstructive pulmonary disease, diabetes, sleep apnea, celiac disease, ADHD, asthma, depression, bipolar disease in youth, osteoarthritis, lupus, inflammatory bowel disease, chronic fatigue syndrome, fibromyalgia, multiple sclerosis, and hypothyroidism.

The cause of, or a pathogen for, each of these diseases has not been established. As the general human genome has not significantly altered in this time, it has been suggested that environmental exposures are highly suspect.[21-23]

Centuries ago, Hippocrates stated that one's diet, lifestyle and environment have profound consequences for health and wellbeing.[24] In 2011, it was estimated by the World Health Organisation that 4.9 million deaths and 86 million Disability Adjusted Life Years could be attributed to environmental chemicals.[23,25] Furthermore, approximately one-quarter of the global disease burden and more than one-third of the burden among children under the age of five were due to modifiable environmental factors.[23,26]

Recent studies on epigenetics and new terms such as "exposome" (total exposures over a lifetime) are increasingly being associated with chronic disease.[27,28] These represent a paradigm shift for chronic diseases aetiology as it is gradually recognised that infectious diseases are primarily only encountered in developing countries.[29]

As will be seen below, peroxynitrite (ONOO-) is postulated by Martin Pall to be a key player in the MCS exposure mechanism. In 2007, prominent scientists from the US National Institute of Health identified this chemical as a key factor in more than 60 chronic diseases through its chemical disruption, cytotoxic effects, and tissue damage.[30] These diseases include neurodegenerative disorders, heart disease, vascular disease, accelerated aging, hypertension, inflammatory disease, cancer, stroke, arthritis, IBS, kidney disease, liver disease, Alzheimer's, multiple sclerosis, and diabetes.

The MCS condition is commonly initiated by an environmental exposure, and the subsequent sensitivities result in reactions from most chemical exposures. So, is this condition highlighting environmental effects on human health? Shouldn't there then be more interest in the MCS condition because it signals heightened sensitivity? If MCS sufferers are on the leading edge of a trend curve for the general population, it is an important and immediate problem which needs addressing.[31]

Possible Mechanisms For MCS

To propose biological mechanisms to explain MCS is, in itself, a display of 'normalisation' in a medical system with a 'positivist' view. To some experienced doctors, it is apparent that susceptible individuals are suffering neurotoxic injuries, so to focus on underlying hypersensitivity mechanisms is missing the point in addressing the real problem.[31] There are clearly people affected, so let's take care of them rather than ignore or dismiss them due to no established mechanism being found. Nevertheless, it can be worthwhile to examine a popular hypothesised mechanism in light of recent studies.

A quite plausible MCS mechanism has been put together over the last 15 years. This started with genetically modified mice with enhanced NMDA receptors being used in Alzheimer's disease research.[32] NMDA is a receptor for glutamate which is a primary excitatory neurotransmitter. As NMDA is known to be a key factor in the formation of memory, hence intelligence, the mice were unusually smart. But what the researchers also noticed was that the mice felt pain more acutely than normal. The researchers went on to determine whether this was because the mice remembered the pain, but concluded that they were sensitised to pain.

It is believed by many psychologists that the most basic form of learning is in experiencing pain. Increasing sensitivity with each exposure is normal in such learning processes.[32] This is reinforced with neurons in the spinal cord becoming hypersensitive to sustained pain signals,[33] thus lowering the pain threshold. Furthermore, as long-term memory is established by the brain creating permanent new branches and connections between neurons, the same can happen with pain-sensing neurons after severe or prolonged pain. So enhanced pain neural pathways can also be created as typical of the central sensitivity condition. The memory-pain duality and the enhanced neural connections have been suggested as a model for MCS.[34,35] It was also found, separately, that NMDA receptor antagonists, such as dextromethorphan and ketamine, administered shortly after exposure can block an MCS reaction,[36] adding additional support for such a model.

Dr. Martin Pall, in 2000,[37] argued that an initial chemical exposure (citing 7 chemical groups in particular) creates hypersensitivity in brain neurons[38] which then react by increasing inflammatory cytokines, in turn increasing the levels of nitric oxide (NO), which then reacts with superoxide to form peroxynitrite, which in turn increases the cytokines, etc. The NO stimulates the release of glutamate and aspartate, stimulating NMDA receptors, which then further elevate NO levels causing a dramatic sensitisation of neural pathways. The increased peroxinitrite can also damage cell mitochondria (initiating inflammations[39]) and damage DNA leading to downstream genotoxic effects cultivating an ideal biological environment for disease.[21] Peroxynitrite can also break down the blood brain barrier allowing greater chemical access to the brain. NO and peroxynitrite can interact with the regulatory system governing synthesis of porphyrin biosynthetic enzymes: reduced enzymes can then lead to disruption of porphyrin metabolism (accounting for many of the simultaneous MCS symptoms).[40] NO also inhibits cytochrome P450 activity (a detoxification pathway).[40] A complex mechanism results for the MCS condition due to the clear possibility of synergism between these reactions.

A more recent study on suppressed redox defences incorporating the above discussed substances,[41] and another documenting polymorphism of CCK-B in MCS patients,[42] further develop the proposed MCS mechanism. Other studies reinforce that many neurological conditions, such as depression, are related to NMDA receptors and NO.[43,44] Recently research has emerged relating elevated nitrosine, a peroxynitrate marker, as a possible indicator for MCS.[45]

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Over the same period, studies have identified six genes whose products have roles in the metabolism of organic solvents and related compounds, and in some cases the metabolism of pesticides, and that influence susceptibility.[46-49] Four of these genes particularly help determine susceptibility.[50] Pall asserted that there is only one way that all these genes could be involved, namely where a chemical from an exposure would act as a toxicant. Enzymes that influence the metabolism of such toxicants then determine how sensitive the individual is in their chemical sensitivity. For example, one of these enzymes, also a gene, MTHFR, has long been recognised as important for clearing environmental chemicals via the methylation process. Testing for MTHFR deficiency has been used for testing the risk in reacting to adjuvant chemicals in vaccines[51-53] although the simple test is rarely used by doctors prior to vaccine injections.

Implications for Conventional Medical Practitioners

In general, MCS has been dismissed by conventional doctors as a psychological problem.[2,5,37,54] If MCS were accepted as having a physiological basis, this would constitute a radical change in direction for the conventional medical system. At the most basic level, a physiological mechanism recognises the modern environment as causing health problems, whereas in the past medical authorities have actively criticised any practitioner considering such a mechanism. Environmental causation of MCS challenges the one-size-fits-all mentality of a medical system, influenced by the pharmaceutical industry, according to which diagnosis, drug administration, and vaccination are done on the basis that everyone is similar. Drug research and treatment of patients are based on an 'average' human, never making any allowance for a sensitive subset of the population.

Rather than doctors establishing a diagnosis based on a short list of symptoms in a brief visit, environmental causation of MCS suggests they should carefully listen to the patient's history and observations on cause and effect. The outcome would be far different than a typical visit ending in the doctor handing out a prescription for drugs based on symptoms.

In endeavouring to address an MCS potential condition in patients, the condition recognised as 'adaptation' needs to be adequately dealt with. Adaptation, or acclimatisation, has been recognised in workers who become accustomed to exposures in their workplace.[55] Such workers can undergo withdrawal symptoms over the weekend and perhaps start peaking in symptom intensity on the Monday morning, which gradually disappears as exposures begin again. Workers in the dynamite industry of the past, for example, would adapt to nitro-glycerine exposure and have to place some under their hatbands to avoid withdrawal, or breathe in their clothes over the weekend. The adaptation phenomenon appears to be the body's first response to chemical exposures until it seems to reach a limit, varying in individuals, from which it can no longer tolerate the exposures and descends into an MCS condition. To determine whether a patient is exhibiting a degree of adaptation, minor symptoms such as irritability, moodiness, drowsiness, fatigue, migraines, runny nose, etc would need to be noted as to whether they relate to an underlying condition. The doctor who makes a quick diagnosis from such symptoms, such as cold/flu, would be missing something more systemic and serious.

The best way to unmask adaptation is through the use of an Environmental Isolation Unit.[56] The unit protects the patient from all environmental exposures, including most foods, for about five days. Then different food groups and exposures are measurably re-introduced. Since all adaptations are unmasked, such a unit can define a patient's sensitivities. Health authorities effectively closed down most such units 20 to 30 years ago after making the situation intolerable for the doctors (mostly clinical ecologists) to keep operating such clinics.[56,57]

The approaches used by clinical ecologists are quite foreign to conventional doctors. It is generally known that many doctors will not even diagnose conditions for which they do not have any training or background, and sometimes simply because they cannot bring themselves to recognise a condition questioned by health departments or in media reports. Many chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS) and Lyme disease sufferers can recount situations going from one doctor to another until they find one who actually will recognise and diagnose their condition. This is even more so for MCS.[58,59]

Industry has long been opposed to the recognition of MCS. [5,60] A recognition of this illness on a pathological basis would acknowledge that many industrial products can affect human health in low doses. Industry-backed studies and scientists dismissing the growing mountain of research on MCS would be expected to be welcomed and even supported by many conventional practitioners so that they do not have to change their beliefs or practices.

Recognizing the Kuhnian Crisis

Kuhn put forward that a paradigm crisis can occur when many observations/occurrences conflict with the current paradigm. In some cases, a 'scientific revolution' can gradually lead to the end of the current paradigm.

To most doctors there is no Kuhnian crisis in relation to MCS and related conditions. There is no need to question their training or knowledge. MCS can be attributed to odour aversion or other subjective psychiatric conditions.

The extent to which a doctor may apply a conventional line of reasoning to an emergent condition will determine whether they become a skeptic or a sympathiser.

The skeptic's positivist requirements will demand clear pathology for mainstream conformance as well as their own standard of proof. As in all scientific controversies, it is common for experts to claim their approach is more scientific: more logical, more objective and closer to pure fact. This "affords an impregnable position from which to

snipe at the enemy."[61] These doctors will not focus on their profession's lack of knowledge on low-level chemical exposures but rather focus on clear-cut areas of advancement, e.g., neural imaging advancements, successful drugs, etc.

The skeptical doctors also reference 'weight of evidence' and 'scientific consensus' to circularly reinforce their paradigm. So, an emergent health condition is pushed aside until this scientific precipice is considered to be reached. As already commented, there are many acknowledged health conditions, documented for decades in medical journals, which do not have clear pathology. Added to this, the pharmaceutical and chemical industries actively try to confuse the science on MCS recognition, just as the tobacco industry attempted to confound recognition of the health effects from smoking.

Many studies on doctor and patient communication have been performed[62] and prominent in these are the importance of listening to the needs and preferences of the patient and avoiding unjustified psychological explanation. However, with the absence of training for doctors in the effects of low-level chemical exposures, and the MCS condition not yet fully recognised, the affected patients commonly experience dissatisfaction interfacing with doctors.[58,63] In all too many cases, a parent has seen cause and effect situations with common everyday chemical exposure, eg, with deodorisers, pesticide use, etc, and the doctor seemingly dismisses the importance of such reports. Some doctors may even accuse the parents of making fictitious claims (Munchausen Syndrome by Proxy).[64,65] The use of convenient psychological diagnoses such as this appears to have been used in an apparent retaliatory approach by some doctors when mothers of young patients have questioned diagnoses or made a complaint.[65] Of course there are many variations and degrees of such behaviour by skeptical doctors that tend to be more vocal/questioning. Nowhere in the Hippocratic oath is the requirement that service and respect must be only to those with structured pathology.

The sympathetic doctor is more ready to rely on experiential knowledge. This may come from their experience with a number of patients through observation, consistencies and logical reasoning: fundamental scientific approaches. The patient's story and experience with their health condition is respected. The doctor doesn't try to fit a subjective psychosomatic condition to the patient, instead remaining open to different possible understandings of the problem. If they are questioned about the MCS mechanism they are likely to reply along the lines of "medicine doesn't know" illustrating their own acceptance of questioning of the current paradigm. In respect

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to doubts on the MCS condition, it would be one of doubting the medical system's understanding of health effects from low level exposures and the level of proof required for an emerging condition rather than one of doubting the patient.[54]

Both sides think the other is not being scientific or logical. Scientific reasoning by both sides comes to different conclusions. The skeptics remain undeterred. The sympathisers become disillusioned with their profession's attitudes and lack of understanding.

Closing Remarks

The sceptical response to MCS is typical of how many emergent conditions are treated by the medical system. Even the central concepts of individual sensitisation and the environmental triggering are not in the vocabulary of most doctors. If a portion of the population reacts to environmental triggers, thereby highlighting environmental effects on health, why isn't this attracting significant interest from the medical system which has no explanation for the cause and rise of so many illnesses and diseases?

Accepting the environmental triggering of health effects from manufactured products would create many problems for industry. In these days of synthetic consumer products, from paints to deodorants, recognition would be commercially disastrous. Furthermore, if this condition can highlight environmental causation of health effects then a Pandora's box may be opened on the many other unexplained health problems suspected of having similar links. There is, perhaps, more money to be made in simply treating the symptoms than recognising the causes. Hence, it is politically advantageous for the medical profession to debunk this condition, creating the impression of MCS being a 'contentious' issue in medical science.

Don Want is doing a PhD in the School of Humanities and Social Inquiry at the University of Wollongong, Australia. While his professional background is as a specialist engineer, he has been in supportive roles for people with MCS for the last 35 years.

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My Experience with Organic Germanium and Cancer

by Professor Serge Jurasunas

Author of *Health and Disease Begin in the Colon*

During my 50 years of practice, I have used many natural compounds that I investigated especially for treating cancer and other degenerative diseases. I recall organic germanium sesquioxide from the Japanese researcher K. Asai as one of the most interesting, effective, and fascinating experiences in my professional life.

Dr. Alfred Vogel and I were both in close contact, and one day Dr. Vogel phoned me to say he was coming back from Japan and heard about a new substance to treat cancer called germanium developed by Dr. Asai. He suggested that I invite him to speak at my 1974 International Congress that I set up in the city of Aix en Provence, France. I then invited K. Asai, and he graciously accepted.

At that time, germanium was almost unknown in Japan and totally unknown in the Western world; but my intuition told me that what we had here was a miraculous compound that will soon be adopted in most countries. I was not mistaken since the publication of Dr. Asai's book, *Germanium-Miraculous Cure,* started to attract considerable interest. In fact, the following year I was invited to Los Angeles for a cancer convention. I introduced germanium in my lecture; but at the time, it was still too early for the audience to understand its impact.

I was an early adopter in the use of organic germanium or Geoxy 132 in my clinic. It was first synthesized and manufactured by K. Asai and his team in 1967, at the Asai Germanium Institute. I discovered organic germanium had amazing curative powers. Basically, germanium is an organic, semi-metal semi-conductor with electrical properties found in the coal mines; but Asai also discovered its curative properties. By 1980, little by little many more positive reports came from the Asai Germanium Institute and other laboratories. The power of germanium is based on the fact that it increases oxygen in the body by expelling accumulated hydrogen as well as heavy metals. Geoxy 132 has been shown to increase gamma interferon (anti-viral activity) in the blood, activate macrophages and NK cells, T-cells, B-cells and demonstrate anti-tumor activity. However Geoxy 132, because of its electrical property, may disrupt the membrane of cancer cells and make them much less resistant and easier to destroy via chemotherapy or immune cell activation.

Dr. Serge Jurasunas with K. Asai and Dr. Bernard Jensen

My Personal Experience with Germanium

Now, it is important to mention that after my initial meeting with K. Asai I began to use his Geoxy 132 from the

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Organic Germanium and Cancer

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Asai Germanium Institute over the next 16 years on several hundred cancer cases but also with other diseases, obtaining unique and memorable results. I kept close contact with him; and the following year, he came again to Europe to lecture and also to my home. Then over the years, I built up patient cases; and by 1987, I decided that I had enough experience to write a book on germanium based upon my clinical experience, including a large number of illustrated patient cases. During the ensuing the years, I used Geoxy 132 with adults, aged patients, and with many children. One was a 17-month-old baby girl with liver cirrhosis (after a blood transfusion) using 100 mg. of Geoxy 132 per day with a spectacular result. There was no toxicity even after taking organic germanium for 18 months. There were already misleading reports about toxicity, found only in inorganic germanium. In both children and adults, I used 400 mg and up to 600 mg per day, as in the case of an advanced cancer, obtaining complete recovery.

My book on germanium and cancer shows an example of a case where, in 1988, an 11-year-old boy with a desperate brain tumor condition and a prognosis of six months or little more to live came into my clinic with his father. This boy recuperated totally after taking my treatment of 250 mg of Geoxy 132 per day, up until 1990. Today, the boy is a medical doctor using alternative methods as well. In my new book *Health and Disease Begin in the Colon Featuring Prof. Serge Jurasunas Natural Medicine,* you can read about young patients treated in 1983 to 1988, in the chapter on clinical cases on pages 314-315 and from 318-319, with some very impressive outcomes. After 30 years have gone by, these patients were still healthy reaching adulthood.

My First Cancer Patient Treated with Organic Germanium

The patient was diagnosed with a tumor of the hypophysis and lost 90% of his vision from the left eye. On the way to surgery, he decided to first try something natural first. I started with 300 mg of germanium per day; and after two months, he recovered 100% of the vision. After three months, the tumor was gone. This really showed me how germanium is powerful even on a solid tumor. The patient had no surgery and no chemotherapy. I have a similar case with a large tumor that was eliminated without surgery. Today things can be different; I would recommend surgery for most primary tumors.

Germanium and Toxicity

As far back as 1971, toxicology tests made by the Asai Germanium Institute found that organic germanium sesquioxide was incredibly safe, even with a high dose. These results had been replicated by other laboratories in Japan and US, confirming no organic germanium toxicity. Even with long-term usage, there was no accumulation in the organs. It had been found that after a period of 20-30 hours that no traces of germanium could be found in the body, having been eliminated by the kidneys. In testing done on rats by the Japan Experimental Medical Institute after 90 minutes, you find only a very small quantity of germanium in kidney, such as 15.00 ppm, nothing in sufficient quantity that could damage the kidneys.

However, there have been reported cases of acute renal failure with patients taking inorganic germanium and not the original organic Geoxy 132 from K. Asai. Inorganic germanium dioxide is toxic and accumulates in the body. It was associated with nephrotoxicity and acute renal failure after being given to aged sick and weak patients, who probably already had bad kidneys. The patients had been taking 600 mg of inorganic germanium daily for 18 months. The first report by Okada et al, in 1987, damaged the reputation of the germanium Geoxy 132 with two cases of renal compromise. Again, this was inorganic germanium dioxide and not organic Geoxy 132.

Two years later, Okada revised his early position on organic germanium sesquioxide by demonstrating the safety of chronic high doses just as I had done with my patients over so many years. Unfortunately, the damage had already been done; the original misleading Okada error from 1987 had

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For more information and to learn about cancer treatment, colon detox, and molecular markers, please visit www.sergejurasunas.com. Follow my blog to learn more about germanium and read more patient cases: https://naturopathiconcology.blogspot.com

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been continually cited for over 20 years with articles and TV programs warning people that germanium was not only toxic but dangerous, leading to kidney damage and fatality.

By 1990, the reaction in France and England, after publication of my book, reached hysterical proportion, but one interesting question stood out: Why, from 1967 to 1987, had organic germanium demonstrated a consistent safety record and been in use with no sign of kidney compromise whatsoever? How come after nearly 20 years using Geoxy 132 in different dosages with a high dose up to 600 mg, and even in the long term, there were no complaints and no one died?

The real problem was bad germanium, contaminated inorganic germanium coming from various Asian sources to exploit the need of a growing market. Of course, we can also refer to pharmaceutical drugs; how many thousands die every year from toxic effects? Did you ever see such discussion on TV? A few months ago, three infants died in France after receiving a vaccine against gastroenteritis and intestinal gases. Only a small article was released in the middle section of a national newspaper, mentioning the vaccine would not be removed but only needed to have a warning to medical doctors and parents about the risk. There would no longer be any further reimbursement from social security, but the vaccine would still be available. Anti-psychiatric prescriptions to aged patients are responsible for the death of 15,000 cases per year in the USA.

Finally, I have accumulated considerable experience treating diseases such as cancer, scleroderma, Raynaud's disease, and rheumatoid arthritis with Geoxy 132 from 1973 to about 1992, after importation of germanium was prohibited in Europe. Portugal was the last country where it could be freely imported until Austria put strong pressure on the Portuguese health authority to prohibit germanium. This was no surprise, especially after the sad story about the prohibition of the anticancer agent Ukrain. See my article in *Townsend Letter*, February-March 2013 ("A Medico-Political Plot in Austria against the Natural Anticancer Agent Ukrain").

Of course, today there are several sources of germanium on the market, but one has to be careful about quality, purity and source. It is true that Geoxy 132 is a miraculous compound and not a drug, but a real gift from Nature or God. I really have lived through some great moments in my life with cancer patients and other cases of diseases that I presented in my book on germanium. I am not exaggerating about the power of this substance and will publish more stories about organic germanium and include cases with photos in my new blog (https://naturopathiconcology.blogspot.com).

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Vitamin D for Dogs

by CJ Puotinen

Reprinted from *Whole Dog Journal*, July 2016

We all need vitamin D – and so do our dogs. Without it, we suffer from bone diseases and a host of other problems.

But vitamin D is controversial and not well understood. When it comes to deciding how much is required, which sources are best, and how to supplement safely, experts disagree. Learning about vitamin D can help you make informed choices for your best friend as well as yourself.

Vitamin D research began long before it was identified and named. Between 1880 and 1930, the bone disease rickets affected children in industrialized areas where infections, crowding, and a lack of sunlight were common. Rickets causes soft, fragile bones. Cod liver oil, which contains vitamin D, was shown to prevent and cure the disease, and studies conducted on dogs and other animals proved that a nutritional deficiency of vitamin D caused rickets.

A steroid vitamin which is also classified as a hormone, vitamin D aids in the absorption of calcium and phosphate, increases bone cell activity, influences the formation and growth of long bones, and speeds the healing of fractures. But vitamin D does far more than build a strong skeleton. Adequate D levels may help prevent heart disease, joint inflammation, skin and coat problems, cancer, vision problems, depression, mental illness, infections, inflammatory bowel disease, dental problems, hyperparathyroidism, and kidney disease.

It is called the sunshine vitamin because sunlight on human skin produces vitamin D, which our bodies convert to a substance known as 25(OH)D, 25-hydroxycholecalciferol, 25-hydroxy, or vitamin D3. Sunlight is not considered a significant source of vitamin D for dogs. We can help prevent canine vitamin D deficiencies with specific foods and supplements.

Measuring D Levels

Vitamin D levels in pets and people can be measured with a blood test. Depending on the testing laboratory, results are measured in nanograms of 25-hydroxyvitamin D (calcifediol) per milliliter of blood, abbreviated ng/mL, or as nanomoles per liter, abbreviated nmol/L. To convert ng/mL to nmol/L, multiply by 2.5; to convert nmol/L to ng/mL, divide by 2.5.

Michigan State University's College of Veterinary Medicine began offering canine vitamin D tests to veterinarians in the late 1980s. "That's when we established a reference range based on the D levels of healthy dogs," says Professor Kent Refsal, DVM. "The test became a diagnostic tool that helped veterinarians identify dogs with rickets, gastrointestinal disease, or other symptoms of vitamin D malabsorption or insufficiency as well as dogs with excessive vitamin D levels."

Professor Refsal and his colleagues consult with veterinarians about their patients' test results. The MSU laboratory's vitamin D radioimmunoassay reference range for dogs is 60 to 215 nmol/L, or 24 to 86 ng/mL. "We consider this range to be a general indication of adequate to normal vitamin D levels for healthy dogs of all ages," he says.

Veterinary Diagnostic Institute (VDI), which uses chemiluminescence immunoassay, reports its canine vitamin D blood test results as deficient (less than 25 ng/mL), insufficient (25 to 100 ng/mL), or sufficient (100 to 120 ng/mL). These measurements convert to less than 62.5 nmol/L (deficient), 62.5 to 249 nmol/L (insufficient), and 250 nmol/L (sufficient). However, because chemiluminescence immunoassay(CIA) and radioimmunoassay (RIA) have been shown to produce different results, a direct comparison of their reference ranges can be misleading and is not recommended.

In the May 2016 *Critical Reviews in Food Science and Nutrition,* veterinarians N. Weidner and A. Verbrugghe at the University of Guelph in Ontario, Canada, reviewed the current knowledge of vitamin D in dogs. After discussing the use of vitamin D tests for health screening, research on D levels and canine illnesses, and target D levels for optimum health, they concluded, "Further work is necessary before any consensus statements on blood 25(OH)D concentrations that define sufficiency in dogs can be made."

In May 2016, researchers at Edinburgh University's Royal School of Veterinary Studies in Scotland announced a series of research projects on pet dogs and vitamin D. Dr. Richard Mellanby, the university's head of small animal medicine, explained, "Our research aims to understand whether dogs' vitamin D levels fluctuate throughout the year, which is important for making sure we're feeding our pets the right diet. We're also interested in how vitamin D affects recovery after surgery and whether having less vitamin D is a cause or consequence of inflammation. Untangling this complex relationship will help us to devise new approaches to improve the welfare of animals after surgery." Dr. Mallanby's review article "Beyond the skeleton: The role of vitamin D in companion animal health" appeared in the April 2016 *Journal of Small Animal Practice*.

Pennsylvania veterinarian Linda Stern, DVM, began screening feline and canine

patients with the VDI test last fall. "Of the 24 dogs we have tested so far," she says, "only 29 percent had adequate vitamin D levels."

Dr. Stern checks her patients' D levels, supplements as necessary and retests after 10 to 12 weeks. "Dogs with arthritis tend to have significantly low vitamin D levels," she says, "and when their levels improve, so does their range of motion. My general observation is that dogs feel better, have more energy, and look happier and healthier when their D levels are adequate. Some show dramatic improvement right away, which happened with one of our patients with liver disease. Monitoring patients with follow-up tests ensures that they maintain safe, optimum D levels."

Too Much Is Toxic

Because vitamin D is fat-soluble, it accumulates in body fat. Overdoses can be toxic and even fatal.

Most canine fatalities related to vitamin D stem from the accidental ingestion of prescription drugs that contain vitamin D, such as topical medications for human skin conditions like psoriasis, and from the ingestion of rodenticides, which are poisons designed to control rats, mice, and other rodents.

Cholecalciferol (synthetic vitamin D3) was registered as a rodenticide in the United States in 1984. Toxic doses lead to too much calcium in the blood, which can affect the central nervous system, muscles, gastrointestinal tract, cardiovascular system, and kidneys.

Although less common, overdoses of vitamin D from foods and supplements can occur. Excessive vitamin D causes hypercalcemia (elevated calcium levels); anorexia (loss of appetite and extreme weight loss); excessive thirst, urination, drooling, and vomiting; muscle weakness; soft tissue mineralization; and lameness. In growing dogs, excessive vitamin D supplementation can disrupt normal skeletal development as a result of increased calcium and phosphate absorption.

In 1999, DVM Nutri-Balance high protein dog food and Golden Sun Feeds Hi-Pro Hunter dog food were recalled because of excessive vitamin D3 due to a feed-mixing error. This caused the illness and death of at least 25 dogs.

Seven years later, Royal Canin Veterinary Diet recalled four products due to a misformulation in the vitamin premix. Six dogs and five cats were reported to have clinical signs consistent with vitamin D3 toxicity.

In 2010, Blue Buffalo recalled packages of its Wilderness Chicken, Basics Salmon, and Large Breed Adult Chicken dry dog foods because of a sequencing error at the dry ingredients supplier, which allowed a more potent vitamin D used in chicken feeds to contaminate the dog formulas and increase their vitamin D to unacceptable levels. Vitamin D3 toxicity from the error affected at least 36 dogs.

In March 2016, four varieties of canned Fromm Family pet food were voluntarily recalled because the company's analysis showed that these diets may contain excessive levels of vitamin D3.

Vitamin D in Commercial Pet Foods

"It is widely assumed that properly formulated commercial pet foods contain adequate D levels for canine health," says Susan Howell, DVM, "but that isn't true." Dr. Howell provides veterinary technical support for Standard Process, Inc., a nutritional supplement manufacturer. "Foods are formulated to meet minimum nutrient requirements set forth by the Association of American Feed Control Officials, or AAFCO," she says. "They are not formulated to meet optimal requirements."

Dr. Howell cites a 2015 Tufts University study funded by VDI Laboratories that examined the effects of diet on the serum vitamin D levels of golden retrievers, German shepherds, and white shepherds. Most of the study's 320 dogs were fed commercial diets from 40 different manufacturers, and some were fed homemade diets or a combination of commercial and homemade diets. As the report concluded:

> Serum 25(OH)D concentrations in dogs vary widely, which likely reflects varying dietary vitamin D content. Notable differences exist among manufacturers and brands and may reflect differences in proprietary formulations. Given the variability of measured serum 25(OH) D concentrations in dogs and the importance vitamin D appears to have on health status, dietary vitamin D content should be optimized.

The study found that dogs on home-prepared diets had some of the most deficient vitamin D levels.

"In addition," says Dr. Howell, "I spoke to a representative from VDI who said they had recently tested three golden retrievers, all having the same body weight and all eating the same diet. Each dog had a different serum vitamin D level. This shows that every animal is unique. They are dealing with their own variances, particularly in their ability to absorb and utilize vitamin D. Vitamin D absorption depends on good digestion. In my opinion, if D levels are deficient or insufficient, it may be as much a matter of addressing digestion as an issue of providing more vitamin D."

Increasing D Levels by Improving Digestion

Dr. Howell recommends feeding dogs a variety of meat-based diets that are free from corn, wheat, soy, rice, white potatoes, tapioca, and peas: "Those foods are alkalizing to the stomach, and dogs need an acidic stomach for food to be digested and nutrients like vitamin D to be absorbed. The other problem with these ingredients is that they cause inflammation, which decreases nutrient absorption. As animals age, their stomachs become more alkaline, which explains why older animals may have a harder time breaking down and absorbing vitamin D from their food."

For dogs fed dry food, she suggests adding bone broth or warm water before feeding. "Adding raw organic apple cider vinegar to food helps acidify the stomach," she adds, "and it provides prebiotics, which feed gut microbes. Add 1/8 teaspoon to each meal for small dogs; 1/4 teaspoon for dogs weighing 21 to 50 pounds; and 1/2 teaspoon for dogs over 50 pounds."

Whole Dog Journal contributor Mary Straus, whose dogaware.com website offers nutrition and feeding tips, recommends supplementing the diet with probiotics (active beneficial bacteria), prebiotics (foods that feed beneficial bacteria), and digestive enzymes to improve digestion and the assimilation of nutrients.

Like other fat-soluble vitamins, vitamin D requires dietary fat for assimilation. In the September 2006 *Journal of the American Veterinary Medical Association*, John E. Bauer, DVM, compared facilitative and functional fats in the canine diet. Saturated fats are facilitative, he wrote, ➤

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because they enhance palatability, provide fuel for energy, can be stored in the body for future use, do not pose a health threat unless fed in excessive amounts, and assist in the digestion and assimilation of fat-soluble vitamins.

Coconut oil and butter contain saturated fats and are often listed as good companions to fat-soluble vitamins. Consider adding 1 teaspoon per 25 pounds of body weight to your dog's dinner to help improve his or her vitamin D levels.

D in Home-Prepared Diets

While home-prepared diets may show the greatest variation in canine vitamin D levels, Dr. Howell notes that not every home-prepared diet has to be supplemented with vitamin D. "I'll refer you back to the Tufts study," she says. "Animals on balanced home-prepared diets may have sufficient D levels. It's a matter of feeding foods that contain vitamin D, fostering healthy digestion, and possibly supplementing Vitamin D in a whole-food form or in a synthetic form if necessary. What I worry about is that people may over-supplement unknowingly and cause a toxicity in their pet."

For this reason, she recommends that pet parents ask their veterinarians for help with homemade diets or turn to Balance IT (balanceit.com), a pet diet-planning website associated with the University of California, Davis. The dogaware.com website is another source of diet-planning information.

"I'm a big believer in animals getting their nutrients from real food," says Dr. Howell. "Instead of supplementing with a synthetic form of vitamin D3, I think it's worth getting some fresh foods into the diet that are good sources of D, such as salmon, liver, and eggs. It's less likely that you will over-supplement if you give a food source of vitamin D rather than cholecalciferol, which is a high-dose synthetic form of vitamin D."

"If an animal with insufficient D levels doesn't have adequate levels after trying food sources of D," she says, "I think it's worth looking at digestion and then at a synthetic D supplement. A conservative amount of synthetic D can bring an animal into the sufficient range. Some popular synthetic vitamin D supplements are from Rx Vitamins and Thorne Research. These products are liquid and easy to dose and administer to your pet. Both are available by prescription and should be monitored by your veterinarian in conjunction with the diet in order to avoid over-supplementation."

D-Insufficiency Risk Factors

Any dog can be D-deficient if his or her diet doesn't supply the vitamin, but older animals, animals with compromised digestive health, spayed and neutered dogs, and dogs on corticosteroids, antacids, or anti-seizure medications are at added risk.

Dogs with illnesses like cancer, chronic inflammatory conditions, heart disease, renal disease, hyperparathyroidism, or inflammatory bowel disease are likely to have low vitamin D levels.

A 2014 study published in the *Journal of Veterinary Internal Medicine* examined the vitamin D status of 31 dogs with congestive heart failure (CHF) and 51 unaffected dogs. The dogs with CHF had significantly lower serum D levels than the unaffected dogs even though their vitamin D intake per kilogram of metabolic weight was the same. The study concluded that low concentrations of 25(OH)D may be a risk factor for CHF in dogs, that low levels were associated with poor outcomes in dogs with CHF, and that strategies to improve vitamin D status in some dogs with CHF may prove beneficial without causing toxicity.

In human heart disease, vitamin D deficiency is associated with disease progression and a poor prognosis. A 2015 cross-sectional study of dogs at different stages of chronic valvular heart disease (CVHD) found a similar correlation. As reported in the *Journal of Veterinary Internal Medicine,* the affected dogs' vitamin D status declined prior to the onset of heart failure.

In the previously mentioned Tufts study, German shepherd dogs were found to have a 26-percent higher median amount of serum vitamin D than golden retrievers. "This means that intestinal absorption of vitamin D differed according to breed," says Dr. Howell. "Spayed and neutered animals were found to have lower D levels than sexually intact dogs, and intact males had significantly higher serum D levels than intact females."

Synthetic Vitamin D

In the wild, canines obtain vitamin D from the fat of prey animals. In the supplement aisle, vitamin D can come from natural sources but it's more often synthetic.

The pharmaceutical drug cholecalciferol (synthetic vitamin D3) is produced by the ultraviolet irradiation of 7-dehydrocholesterol extracted from lanolin in sheep's wool. Unwanted isomers formed during irradiation are removed in a purification process, leaving a concentrated resin that melts at room temperature.

Ergosterol, also called provitamin D2, is found in fungi such as *Saccharomyces* and other yeasts, mushrooms, and *Claviceps purpurea*, which causes the fungal disease ergot, for which ergosterol is named. Ergot affects rye, barley, wheat, and other cereal grasses. Ergosterol is converted by ultraviolet irradiation into ergocalciferol, or synthetic vitamin D2.

In 2006, the *Journal of the American Academy of Dermatology* reviewed vitamin D studies in order to answer the question, "How much vitamin D do you need, and how should you get it?" Although synthetic vitamin D2 is widely used as a prescription drug and is added to some processed foods, the study's authors concluded that vitamin D3 is superior to vitamin D2 because it is less toxic at higher concentrations, is more potent, has a more stable shelf life, and is more effective than vitamin D2 at raising and maintaining vitamin D blood levels.

Food Sources of Vitamin D

If you're interested in supplying natural vitamin D, it makes sense to look for foods that provide it, but finding them may not be easy.

Salmon is widely described as a significant source of vitamin D, but in 2007 the *Journal of Steroid Biochemistry and Molecular Biology* published an evaluation of the vitamin D content in fish. It found that salmon flesh does contain vitamin D, but farmed salmon – which is far more common and less expensive than wild salmon – had only 25 percent of the vitamin D of wild salmon. The report explained:

> It has been assumed that fish, especially oily fish such as salmon, mackerel, and blue fish are excellent sources of vitamin D3. However, our analysis of the vitamin D content in

a variety of fish species that were thought to contain an adequate amount of vitamin D did not have an amount of vitamin D that is listed in food charts. There needs to be a re-evaluation of the vitamin D content in foods that have been traditionally recommended as good sources of naturally occurring vitamin D.

Salmon oil may provide some vitamin D along with the fatty acids for which it is famous. In the Tufts study mentioned above, dogs receiving salmon oil as a supplement had higher serum 25(OH)D (on average a 19.6 ng/mL increase) than those not receiving a supplement, but other forms of fish oil surprisingly had no effect.

Dairy products are not naturally high in vitamin D, but milk and yogurt are often fortified with synthetic vitamin D. Check labels to be sure.

Cod liver oil is the traditional food source of vitamin D. A hundred years ago, fermented cod liver oil, which can have a powerfully fishy smell, was the world's most widely prescribed nutritional supplement. Perhaps your grandparents remember having to swallow a spoonful at a time. Cod liver oil contains vitamins D and A, both of which are essential for human and canine health. But cod liver oil's manufacturing methods have changed, and so has its vitamin content.

Fully cleaned and deodorized (e.g., molecularly distilled) cod liver oil to which nothing has been added contains very low levels of vitamin A and little or no vitamin D. Some manufacturers add synthetic or natural vitamins A and D to their cleaned and deodorized oil.

To compare brands, read labels – especially their vitamin A and D content – and check product literature or websites for information about manufacturing methods and the source of any added vitamins A and D.

Vitamins A and D are measured in International Units, abbreviated IU. The vitamin A content of natural (unprocessed) cod liver oil is usually 2 to 10 times that of its vitamin D.

To make cod liver oil more palatable to humans, some brands are available in lemon, orange, cinnamon, mint, or other flavors. Most dogs enjoy the plain, unflavored oil.

Carlson Labs cod liver oil, which is molecularly distilled and bottled in Norway, provides 850 IU vitamin A and 400 IU vitamin D per teaspoon. According to the label, its vitamins A and D, which are added after distillation, are derived from cod liver oil (500 ml or 16.9 fluid ounces, $55.00).

Garden of Life Olde World cod liver oil, made in Iceland, is molecularly distilled and contains vitamins A (4,500 IU per teaspoon) and D (450 IU per teaspoon). According to the label, these added vitamins are naturally occurring (8 fluid ounces, $17.45).

Green Pasture's Blue Ice fermented cod liver oil. Fermented fish livers were valued in ancient Rome as a health tonic, and the same natural process is used to make Green Pasture's cod liver oil. Because nutrients vary in fermented foods, the manufacturer labels this product a food without listing its vitamin D content, but current values are available on request. Based on the past four years of test data, one teaspoon of fermented cod liver oil contains approximately 8500 IU vitamin A and 3400 IU vitamin D (8 fluid ounces, $44.00).

Nordic Naturals arctic cod liver oil is molecularly distilled, and no vitamins are added after distillation. Each teaspoon provides 1580 IU vitamin A and 6 IU vitamin D. While this cod liver oil contains natural rather than synthetic vitamin D, 6 IU is an extremely small amount (8 fluid ounces, $25.95).

Nordic Naturals pet cod liver oil (16 fluid ounces, $44.95) and Nordic Naturals pet cod liver oil for medium to large breed dogs (8 fluid ounces, $24.95) contain omega-3 fatty acids and vitamin A (550 IU per teaspoon) but do not contain vitamin D. This brand will not correct vitamin D deficiencies.

Nutra Pro virgin cod liver oil from Norway is separated from fresh cod fish livers using cold-pressing and advanced purifying technologies without the use of chemicals. One teaspoon contains 5,000 IU vitamin A and 500 IU vitamin D (8 fluid ounces, $32.99).

Rosita extra virgin cod liver oil, or EVCLO, is manufactured in Norway from wild cod livers using an ancient extraction method that does not utilize heat, chemicals, fermentation, solvents, or mechanical devices. One teaspoon contains 3,000 to 5,000 IU vitamin A and 400 to 500 IU vitamin D (150 ml or 5 fluid ounces, $49.00).

Unlike "virgin" and "extra virgin" olive oils, whose labels reflect legally defined manufacturing and grading methods, the terms "virgin" and "extra virgin" have no specific meaning when applied to cod liver oil. They imply that the product is minimally processed.

The chemistry of naturally occurring cod liver oil is complicated. According to Christopher Masterjohn, PhD, assistant professor of health and nutrition sciences at Brooklyn College in New York, "Research in the 1930s suggested that there were at least four if not six forms of vitamin D in cod liver oil, and recent research has shown that fish metabolize vitamin D into at least three other compounds and probably more." As conventional tests measure only vitamins D2 and D3, unrefined cod liver oil may provide significant health benefits that are not reflected by its D2 and D3 content.

Vitamin A Safety

Vitamin A is essential to human and canine bone growth, reproduction, immune system health, and vision. Like vitamin D, it is fat soluble. Synthetic

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vitamin A (retinyl acetate, retinol acetate, vitamin A acetate, vitamin A palmitate, retinyl palmitate, retinoids, or 13-cis-retinoic acid) should be used with care to avoid accidental overdoses, which can cause bone loss, hair loss, liver damage, and confusion.

Is natural vitamin A dangerous? According to some scientists and health experts, cod liver oil's vitamin A content makes it potentially toxic. In 2008, Dr. John Cannell of the Vitamin D Council (vitamindcouncil.org) warned against using cod liver oil because of its vitamin A.

Other scientists and health experts disagreed, noting that vitamin A by itself (such as in molecularly distilled cod liver oil or cod liver oil containing synthetic vitamins) can be dangerous but that traditional cod liver oil contains a safe and effective ratio of naturally occurring vitamins A and D. In reply to the warnings against cod liver oil, Sally Fallon Morell, founder of the Weston A. Price Foundation (westonaprice.org), reviewed cod liver oil's history and safety:

> We at the Weston A. Price Foundation have continually pointed out that vitamins A and D work together and that without vitamin D, vitamin A can be ineffective or even toxic," she explained. "We do not recommend Nordic Naturals or any brand of cod liver oil that is low in vitamin D. But it is completely inappropriate to conclude that cod liver oil is toxic because of its vitamin A content. Similar reviews could be put together showing the benefits of vitamin A and cod liver oil in numerous studies, including studies from the 1930s. Obviously the solution is to use the type of cod liver oil that does not have most of its vitamin D removed by modern processing techniques.

CJ Puotinen, author of *The Encyclopedia of Natural Pet Care* (McGraw-Hill, 2000) and other books, writes for *The Whole Dog Journal* and other publications. She lives in Montana.

A Fermented Cod Liver Oil Controversy

In 2015, fans of fermented cod liver oil were rocked by the report "Hook, Line, and Stinker" by nutritionist Kaayla Daniel, PhD, in which she claimed that Green Pasture's fermented cod liver oil is not a cod liver oil at all but rather rancid pollock oil.

Health researcher Craig Elding at the British site Health Cloud (healthcloud.co.uk), American health writer Chris Kresser (chriskresser.com/important-update-on-cod-liver-oil), and others examined these accusations in detail. See the Weston A. Price Foundation's review of the controversy, including Morell's November 2015 report titled "Hook, Line, and Thinker." Years of independent tests have never shown Green Pasture's Fermented Cod Liver Oil to have oxidative rancidity, and its source fish, Alaskan pollock (*Gadus chalcogrammus*), is not a member of the pollock fish family but rather a cod (*Gadidae* family) fish.

Cod Liver Oil in Home-Prepared Diets

One of the pioneers of home-prepared dog diets is Wendy Volhard, whose *Holistic Guide for a Healthy Dog* describes years of research she conducted with Kerry Brown, DVM, as they documented the effects of raw, home-prepared diets on hundreds of dogs.

"Since 1984, when I first published my recipes," she says, "it's no exaggeration to say that thousands of dogs have been fed the Volhard way. My diet recommends 1 teaspoon cod liver oil daily for a 50-pound dog. This dose was established in 1973, when I started feeding my own dogs a raw, home-prepared diet, and the amount was based on guidelines from the National Science Foundation."

Volhard's cod liver oil dose depends on the dog's weight (1/2 teaspoon per 25 pounds). She says, "We have found no need to adjust the diet to a dog's age or lifestyle. Puppies grow beautifully, and old dogs thrive." She does not recommend a specific brand but prefers a minimally processed, high-quality cod liver oil containing natural vitamins A and D.

The Importance of Vitamin K

Vitamin K, another fat-soluble vitamin, influences proper blood clotting, healthy bone growth, the conversion of glucose into glycogen for energy storage in the liver, and healthy liver function. Vitamin K is thought to promote longevity and protect against cancers that involve the inner lining of body organs.

Vitamin K exists as vitamin K1 (phylloquinone), which is abundant in many vegetables; vitamin K2 (menaquinone), which the body produces in the digestive tract and which is provided by some animal products; and vitamin K3, the synthetic form known as menadione.

Vitamin K deficiencies can cause internal or external bleeding, most commonly resulting from the ingestion of rodent poisons containing warfarin or similar chemicals, and it is used as a first-aid treatment or antidote for dogs poisoned by blood-thinning rodenticides.

Vitamin K toxicity is unusual in pets, though excessive menadione (synthetic vitamin K3) can cause fatal anemia and jaundice. Menadione, which has been banned by the FDA for use in human supplements, is an ingredient in commercial pet foods, where it is labelled Vitamin K supplement, dimethylprimidinol sulphite or bisulfate, or menadione sodium bisulfite or bisulfate,

Supporters of K3's use argue that natural vitamin K may lose its potency during processing, intestinal disease can prevent gut bacteria from making the vitamin, and not all pet foods contain green leafy vegetables. Opponents argue that synthetic vitamin K can promote allergic reactions, weaken the immune system, cause toxic reactions in liver cells, and induce red blood cell toxicity.

The leading food sources of vitamin K1 are green tea and dark green leafy vegetables such as kale, turnip greens, spinach, broccoli, lettuce, and cabbage.

Sources of natural vitamin K2 include meat, eggs, and dairy from grass-fed or pastured animals; high-vitamin butter oil, which is extracted by centrifusion from the raw milk of grass-fed cows; and natto (a traditional Japanese food) or MK-7 supplements made from fermented organic soybeans.

Because vitamin D is said to work best in combination with vitamins A and K, some veterinarians recommend supplementing dog diets, especially home-prepared diets, with natural sources of all three vitamins combined with an appropriate fat. Look for whole foods or supplements derived from whole foods and, if using a vitamin K supplement, adjust the recommended human adult dose for your dog's weight.

In Review

Vitamin D is an essential nutrient for canine bone, heart, joint, skin, coat, vision, dental, kidney, and immune system health. Low vitamin D risk factors include age, spaying/neutering, digestive problems, illness, and some commonly prescribed medications.

Commercial pet foods vary in their vitamin D content and sources, producing different D levels in dogs. Some home-prepared diets contain insufficient vitamin D. Although many American dogs are D-deficient, their D levels can safely be increased by improving digestion, feeding whole foods that contain D, using vitamin D supplements if needed, and monitoring vitamin D blood levels through testing.

Because vitamin D is fat soluble, it needs dietary fat for digestion and assimilation. Vitamin D combines well with saturated fats such as coconut oil and butter. Its nutritional partners are the fat-soluble vitamins A and K. Maintaining adequate vitamin D, A, and K levels is a simple but effective canine health strategy.

Natural, unprocessed cod liver oil is a food source of vitamins D and A. Supplements containing synthetic vitamin D or vitamin A are more concentrated and require more careful monitoring.

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Resources

Linda Stern, DVM, Healing Creatures Animal Hospital, Camp Hill, PA. (717) 730-3755; healingcreatures.com.

Susan Howell, DVM. Standard Process, Inc., standardprocess.com. Technical support for veterinarians.

Carlson Labs Cod Liver Oil, carlsonlabs.com. Sold in natural food stores and online.

Garden of Life Olde World Cod Liver Oil, gardenoflife.com. Sold in natural food stores and online.

Grassroots Health, grassrootshealth.net. Information and affordable at-home vitamin D blood tests for humans. (Not a canine information site.)

Green Pasture's Blue Ice Fermented Cod Liver Oil and X-Factor Gold High-Vitamin Butter Oil, greenpasture.org. Sold online.

Michigan State University College of Veterinary Medicine Diagnostic Center for Population and Animal Health, animalhealth.msu.edu. Vitamin D blood tests for dogs.

Nutra Pro International Virgin Cod Liver Oil and Grass-Fed High-Vitamin Butter Oil, nutraprointl.com. Sold online.

Rosita Extra Virgin Cod Liver Oil, rositarealfoods.com or evclo.com. Sold online.

Rx Vitamins, rxvitamins.com. Liqui-D3 supplement provides 2,000 IU synthetic vitamin D per drop. Sold to veterinarians.

Thorne Research, thorne.com. Liquid synthetic vitamin D3, or D3 combined with vitamin K-2, 500 IU vitamin D per drop.

Veterinary Diagnostics Institute, vdilab.com. Vitamin D blood tests for dogs.

Weston A. Price Foundation, westonaprice.org. Information about vitamin D and cod liver oil.

Author's Note

This article, which was published in the July 2016 *Whole Dog Journal* (whole-dog-journal.com), won the Dog Writers Association of America's Maxwell Award for the outstanding canine health-related magazine article of 2016. ◆

Surviving Natural Disasters

review by Craig Soderberg

Emergency Food Storage and Survival Handbook: Everything you need to know to keep your family safe in a crisis
by Peggy Layton
Three Rivers Press, New York, New York; 2002; 286 pages; paperback; $16.00 (US)

What if your life were disrupted by a natural disaster, or a food or water supply contamination? Do you have the essentials for you and your family? Do you have a plan in the event that your power, telephone, water, and food supply are cut off for an extended period of time? With this guide, you and your family will learn how to plan, purchase, and store a three-month supply of all the necessities – food, water, fuel, first aid supplies, clothing and more – simply and economically.

Chapter 1 explains how to prepare for short-term emergencies, including alternative systems of communications, sanitation, and utilities. Chapter 2 explains how to store water and how much of it you should store. Chapter 3 discusses the economics of emergency storage and shows how practical planning can enable you to become more self-sufficient. Chapter 4 explains where in your home to locate your stored items and how to prepare an inventory to prevent spoilage. Chapter 5 shows the variety of foods that are suitable for storage as well as some non-food items you will need to store. Chapter 6 explains various ways you might obtain the items to stock - through purchasing, growing your own food, sprouting seeds, and by doing your own dehydrating and canning. Chapter 7 provides a plan of action tailored to your family's needs. Finally, chapter 8 offers many nutritious and delicious recipes that are composed of ingredients that you stored.

I was intrigued by the various *emergency kits* mentioned in chapter one. Peggy mentioned the 26 items that might be helpful in an emergency car kit in case you break down on the road in the middle of nowhere. She also described an emergency shelter kit including a tent and tent-related items. There was a 72-hour kit for baby including various items needed by babies, a first-aid kit, communications kit, sanitation kit, emergency lighting kit, and a kit of cooking supplies.

Chapter 2 relates to water. The first issue is how to purify water. Peggy discussed the boiling method, the stabilized oxygen method, and other methods using bleach, iodine, halazone tablets, and other types of purification tablets. She also discussed water storage containers: heavy plastic, glass, milk jugs and others.

If you store food properly, you can actually save money because you will be buying in bulk for several months or a year at a time and taking advantage of seasonal sales. Peggy also recommends storing at least a three-month stash of cash in a fireproof cashbox because there may come a day when we can no longer get cash from ATM machines. Businesses may not take large bills during a crisis situation (or if they do, they might not give you back your change), so your stash of cash should include approximately one-third coins, one-third small bills (under $20) and one-third should be $20 and $50 bills.

The rest of the book describes what to store, where to store it, and how to obtain it. I recommend this book for anyone who is beginning to think about having the family essentials in the event of an emergency. The only caution I have is to realize that some of the items Peggy recommends storing may contain genetically modified ingredients[1], high fructose corn syrup, and other harmful ingredients. However, each family needs to make their own decisions about what to store.

Other recommended resources:
Skousen, Joel. Ten Packs for Survival. http://www.joelskousen.com/Secure/reports.html#10pak

1. This site lists companies that use genetically modified ingredients: http://www.livestrong.com/article/314824-list-of-foods-containing-gmos/

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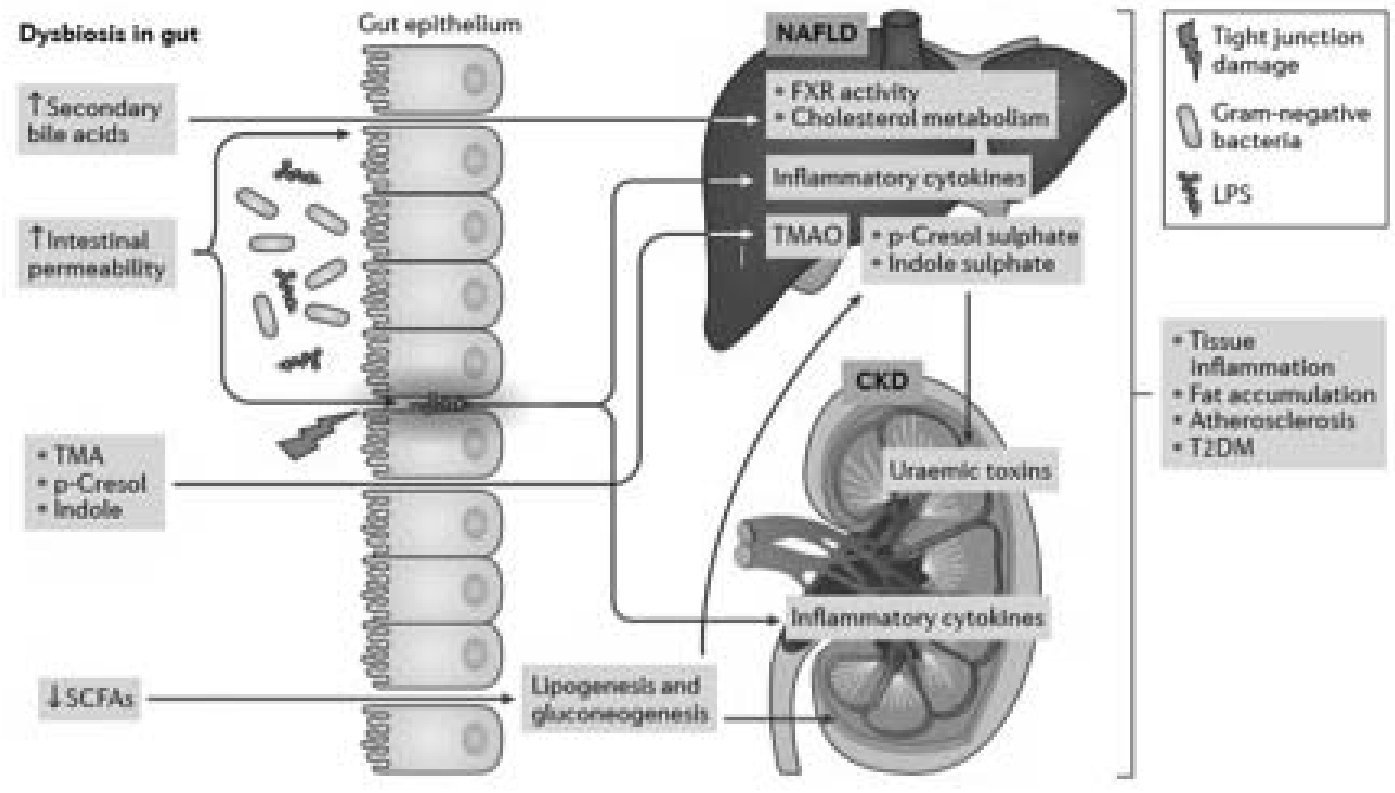
Functional Gastroenterology Bolus

by Steven Sandberg-Lewis, ND, DHANP

Does It Start in the Gut? Relationships Between the GI Tract and Chronic Kidney Disease

Chronic kidney disease (CKD) affects 10% of Americans and 25% of those over age 75. The first three stages of CKD are usually asymptomatic. Insulin resistance, prediabetes, and diabetes are conditions that link the GI tract and CKD. According to the CDC, the combination of prediabetes and diabetes affect 52% of the US population. In my experience, **most patients with CKD stages 1-3 do not know that they have this condition because it is generally asymptomatic and is not revealed to them by their physicians**. Referral to a nephrologist typically is limited to stages 3b, 4, and 5 (glomerular filtration rate below 44 mL/min).

CKD may be caused by poorly controlled hypertension or diabetes and by autoimmune conditions such as lupus erythematosus. A factor often underlying the "essential hypertension" is intestinal dysbiosis (Ahmadmehrabi, 2017). CKD patients have altered flora marked by significantly lower *Bifidobacteria*, *Lactobacillus,* and ➤



From Targher G, Byrne CD. Non-alcoholic fatty liver disease: an emerging driving force in chronic kidney disease. *Nat Rev Nephrol.* 2017 May;13(5):297-310.

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Prevotella genera and increased *Clostridium perfringens* and *Enterobacteriaceae* (Sampaio-Maia, 2016). Altered intestinal flora trigger gastrointestinal and systemic inflammation and hyperpermeability. The hyperpermeability stretches from the stomach to the colon allowing for increased lipopolysaccharide absorption and bacterial translocation (Vaziri, 2012) (Vaziri, 2013).

In addition, these increases in permeability allow higher absorption of protein fermentation (putrification) products such as indole from tryptophan, phenol from tyrosine and phenylalanine, and trimethylamine from choline and carnitine (Rossi, 2014). Once absorbed systemically, hepatocytes convert these into indoxyl sulfate, p-cresol sulfate and triethylamine-N-oxide (Stubbs JR, 2016 & Missailidis C, 2016). These three compounds are renotoxic and cardiotoxic due in part to the promotion of endothelial dysfunction. Endothelial cells typically elaborate antithrombotic, anti-inflammatory and vasodilatory substances. In endothelial dysfunction, there is a shift to prothrombotic, pro-inflammatory and vasoconstrictive patterns (Kumar, 2010).

Cytokines rise and as the intestinal protein metabolites increase, there is insulin resistance, suppression of erythropoiesis, premature cellular senescence, activation of the renin-angiotensin-aldosterone system, and enhanced atherogenesis, and vascular calcification (Rossi, 2014).

In addition, there is a decrease in short chain fatty acids (SCFA), which leads to an increase in hepatic lipogenesis and gluconeogenesis – fueling the insulin resistance and metabolic syndrome (Scorletti, 2016). Cardiovascular disease, fatty liver, and more advanced chronic renal disease become more likely. SCFAs, when present in sufficient quantities, regulate PPAR gamma as well as increasing incretin production in gut enteroendocrine cells. This allows a shift in metabolism to increased lipid synthesis and decreased beta-oxidation. Decreased SCFAs promote fatty liver and hepatic insulin resistance (Higashimura, 2015). Type 2 diabetes may ensue if the necessary hereditary, dietary (high fructose corn syrup, high carbohydrate diet) and environmental factors (persistent organic pollutants) are present.

Rather than "watchful waiting" in the setting of dysbiosis, is it not best to be proactive as early as possible and educate the patient when in the earliest stages of chronic kidney disease? Options for prevention of CKD progression include the following:

- Treat small intestinal bacterial overgrowth when present and balance GI flora as needed (Strid, 2003);
- Modify protein intake - vegans and vegetarians have lower circulating TMAO levels, PCS and IS compared to omnivores (Koeth, 2013) (Patel, 2012);
- Modify carbohydrate intake with gluten or grain-free diets such as the specific carbohydrate, low FODMAPs or SIBO specific food guide. Increase soluble fiber if tolerated using foods such as inulin, flax, chia, psyllium, vegetable fiber (Rossi, 2015);
- Use of probiotic supplements such as *Lactobacillus reuteri* (Rossi, 2015);
- Balance cortisol/DHEA levels;
- Employ properly prescribed botanical medicines: *Cordyceps sinensis*, *Rheum palmatum* (Guan, 2015), *Astragalus membranaceus, Salvia miltiorrhiza (Danshen*), *Angelica sinensis (dong quai)* (Hsieh, 2017) and *Portulaca oleracea* (purslane) (Iranshahy, 2017) These herbs may prove useful in preventing progression of chronic kidney disease;
- Recommend moderate daily exercise such as walking; and
- Improve sleep hygiene to promote 7-8 hours of quality sleep per night.

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Steven Sandberg-Lewis, ND, has been practicing since 1978, teaching gastroenterology at National University of Natural Medicine and in private practice at 8 Hearts Health and Wellness in Portland, Oregon. He lectures, presents webinars and interviews on issues of digestive health. He is the author of the medical textbook *Functional Gastroenterology: Assessing and Addressing the Causes of Functional Digestive Disorders*, Second Edition, 2017. Within gastroenterology, he has special interest and expertise in inflammatory bowel disease (including microscopic colitis), irritable bowel syndrome (including post-infectious IBS), Small Intestine Bacterial Overgrowth (SIBO), hiatal hernia, gastroesophageal and bile reflux (GERD), biliary dyskinesia, and chronic states of nausea and vomiting.

Dr. Sandberg-Lewis lives in Portland with his wife, Kayle. His interests include mandolin, guitar, writing, and lecturing.

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Healing with Homeopathy

by Judyth Reichenberg-Ullman, ND, MSW, and Robert Ullman, ND
www.healthyhomeopathy.com

Homeopathic Chelation of Methotrexate

We have been in homeopathic practice for thirty-five years and have seen quite a bit. But, this was one of the most amazing examples of detoxification, thanks only to homeopathy, that we have witnessed. We have heard of other cases of chelation of metals, such as mercury, exclusively through homeopathy. This case corroborates that homeopathy alone can be sufficient for detoxification/chelation.

Immunologist: *"You will need immunosuppressants for life."*

We first saw Carolyn, a high-power business consultant, thirteen years ago for a severe, debilitating vertigo. She responded beautifully to homeopathic *Conium* (hemlock), which is a common homeopathic remedy for dizziness. At her six-week follow-up appointment, Carolyn told us that the vertigo was completely gone, "not even a twinge" remaining: "I could tell a difference by the morning after I took the remedy and it was totally gone the next day. I'm back to my normal self. It was amazing. But I know homeopathy can work like that." She followed up with us for some months. Then we didn't hear from her again for some time.

Seven years later, now 60 years old, Carolyn contacted us again. Carolyn had great confidence in homeopathy, and she hoped that we could help her again. Two years earlier she began to develop a rash on her forearms, neck, and midriff. She suffered incredible fatigue and a loss of muscle strength. Her diagnosis was dermatomyositis. She received a prescription for prednisone (60 mg) for four days then weekly self-administered injections of methotrexate for seventeen months. Methotrexate is used to treat certain types of skin, head, neck, lung, and breast cancer as well as severe psoriasis and rheumatoid arthritis. It is usually a medicine of last resort, when other medications have been unsuccessful.

Carolyn lost forty pounds. Despite the methotrexate, she continued to suffer from rashes on her legs, neck, arm, chest, and hands. An intense, managerial-type person, Carolyn loved her work despite the stress, and she was taking on tremendous responsibility, both at work and at home:

> Two weeks before I got sick, I was told that the 15 staff members I was managing would lose their jobs unless I could prove their work. I worked eight days straight to compile a cohesive report and ultimately saved the team. But I couldn't take the pressure, the weight of the job. There were far too many expectations. I couldn't bear the thought of letting down other people. It would be like committing a crime against myself. I'm a person of my word and I never could have forgiven myself. I would rather work till I drop.

The recommendation of Carolyn's immunologist was immunosuppressive drugs for the rest of her life. This was not acceptable to her.

At this time, Carolyn's remedy was very clear: *Aurum metallicum* (gold). It is excellent for extremely conscientious, responsible individuals who take on excessive, often impossible, amounts of responsibility in an attempt to reach impossible goals. They may verge on destroying themselves in doing so and, if they fail, they can sink into a deep, even suicidal depression. The classic example of a failed *Aurum* individual is a stockbroker who jumps off a building after a market crash. These are highly principled individuals of great integrity, like Carolyn. She did not at all fail in the process, but she nearly lost her health. The dermatomyositis was merely a physical manifestation of her underlying energetic imbalance.

We prescribed only one dose of *Aurum metallicum* 30C out of concern for an aggravation of Carolyn's dermatomyositis. Three weeks later she reported:

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I have more energy. I feel much better than I have for many years. The rash is starting to be less pronounced, less red. But my skin started to become like paper. Huge pieces of skin were peeling off, first from my hands, then my arms. I knew that I was healing. That it was a natural process. Now all the redness is gone except for my arm. I am on no medications. I have no muscle weakness. I feel better than way before I was diagnosed with the autoimmune condition. I feel like a different person.

We knew that there can be healing reactions, such as the peeling of Carolyn's skin, in the curative process, but this was extreme.

Another three weeks later, Carolyn's legs again developed a bright red rash, but she had no other symptoms. She shared more about how she had felt before quitting her job:

I almost killed myself to save those people's jobs. How much can I risk to save other people? I put everything, including my health, at risk. I knew that I made a difference, but I paid a terrible price for it. I never want to do that again. But all of those employees whom I saved still have their jobs!

She repeated the *Aurum* 30C infrequently over the next year and a half, and we spoke with Carolyn every few months.

Once she noticed that she was experiencing a healing crisis. She experienced a small, itchy rash on her stomach and said: "I'm doing deeper levels of healing. The heart-shaped rash is exactly where I used to give myself the methotrexate injections." We gave Carolyn one dose of *Aurum* 200C, a higher dose than she had previously, to take if needed.

A Remarkable, Spontaneous Chelation Thanks to Homeopathy

When we next heard from Carolyn, two and a half months ago, she had a remarkable tale of healing to share with us:

I'm doing really well. When I did take the single dose of the *Aurum* 200C, you won't believe what happened! You remember that I had suffered from a rash on my stomach near the site of the 5 cc methotrexate injections that I had given myself once a week for two-and-a-half years until mid-2014 for the dermatomyositis? Well, that 200 C dose of the *Aurum* pushed the methotrexate out through my skin and bowels. I almost ruined my clothes. Every little pinprick returned where I had given myself those injections!

Between you and me, I stopped those injections months before I told my doctor. When I took that 200C dose of the *Aurum*, the rash started coming up to the surface. I could tell the metallic smell of the methotrexate coming out. My entire closet smelled metallic. Sometimes I would have to change my nightclothes! It was literally pouring out through my pores. As soon as I smelled it, I knew it was methotrexate…. It would come up in layers. For a while my abdomen would heal, my skin would get less red. I would start to feel physically nauseated. Then a whole other layer of pinpricks from where I stuck myself with the needle would come up. I could see them and count them! It was truly amazing. I don't think I've been through anything like that in my life. My skin would become red and inflamed. I would see all the little pinpricks. I didn't call you because the process was still happening. Now I have the rash on my stomach, arms. My body is not yet finished healing. Nothing happened for six weeks. Then they came up again. The itching is going away. I feel really great. When my body tries to get rid of the methotrexate, it lasts three to four hours. I can even smell the methotrexate in my bowel movements. I know my body is getting rid of it. I can remember when my sister came to visit. She told me that my skin smelled like metal! I even had to throw out some of my clothes. It was like my body couldn't push it out fast enough!

I am so grateful that you raised the potency of the *Aurum* to 200C! I would *never* do chemotherapy again. This has been such a lesson for me. It has totally changed my view of what healing is!

My husband and I have gone through a lot of changes. I realize I can't take care of everything. We are both in a really, really good place. We both want to live a life with less pressure. You obviously prescribed the right remedy. It works like a hot damn!

Carolyn asked if she could take another dose of the *Aurum* 200C to stimulate the healing process, and we agreed.

A month later Carolyn emailed us that she had been experiencing some vertigo, similar to what brought her in to see us initially eight years ago: "It came on very suddenly. It's not constant. Since taking the *Aurum*, I feel like my body has been healing, in reverse order, every skin condition and illness that I have had in my lifetime. It has been a really interesting and beneficial experience to move through these different levels of healing." Later that same day, she wrote back, "the vertigo was quite severe at first, but today it has been somewhat better." She waited on taking any more remedy. Two days later: "The vertigo has improved greatly. It's nearly gone."

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Judyth Reichenberg-Ullman and Robert Ullman are licensed naturopathic physicians, board certified in homeopathy. We have written eight books on homeopathy as well as *Mystics, Masters, Saints and Sages – Stories of Enlightenment*. We also have an app: Natural Travel Doctor. Apple version: https://tinyurl.com/l7song8 and Android: https://tinyurl.com/m7cnexh

We practice at The Northwest Center for Homeopathic Medicine in Edmonds, Washington, and by Skype. The Edmonds office address has just changed, as you will see on our website. We live on Whidbey Island, Washington, and in Pucón, Chile. Visit our website www.healthyhomeopathy.com. Please friend us on Facebook at Healthy Homeopathy. Call us at (425) 774-5599 or email us at drreichenberg@gmail.com or drbobullman@gmail.com.

Curmudgeon's Corner

by Jacob Schor, ND, FABNO
drjacobschor1@msn.com

Nightly Fasting Improves Cancer Prognosis

When it comes to diet and cancer, we've added a new idea into our practice. Patients are encouraged to extend the gap between eating dinner and breakfast. This idea comes from a pair of studies by Catherine Marinac and colleagues at the University of California in San Diego.

Ample evidence has been published that suggest a solid association between caloric restriction and increased longevity and decreased cancer mortality. While this sounds good in theory, getting patients to adopt a caloric restricted lifestyle is in most cases challenging. The technique investigated by Marinac is relatively easy to adopt; it only requires a few tweaks in meal times.

The most recent of these papers was published March 31, 2016, in *JAMA Oncology* while the first was published in August 2015. Both papers look at the effect duration of nightly fasting, (those are fancy words for how long you go without eating between dinner and breakfast) on breast cancer risk.

The 2015 study analyzed data from 2,212 women gathered through the US National Health and Nutrition Examination Survey (NHANES).[1] Longer fasting was associated with lower average blood sugar as calculated via A1c levels. Elevated blood sugar is a risk factor for breast cancer recurrence. While this first paper was interesting, the 2016 paper is fascinating.

In the newer study, data from 2413 women who were part of the Women's Healthy Eating and Living Study (WHEL) were analyzed seeking correlation between poor breast cancer outcome and fasting duration.[2] Marinac et al report that fasting for less than 13 hours per night was associated with an increase in breast cancer recurrence compared to fasting more than 13 hours per night. Data from women with shorter fasting periods trended toward increased breast cancer mortality but did not reach statistical significance. Longer nightly fasting was again associated with lower hemoglobin A1c results.

The WHEL women fasted for a mean duration of 12.5 hours per night. Fasting less than 13 hours per night was associated with a 36% increase in the risk of breast cancer recurrence compared with fasting 13 or more hours per night. Nightly fasting for less than 13 hours was associated with a 21% non-significant trend toward higher risk of breast cancer mortality, and a non-significant 22% increase in all-cause mortality. Women, who fasted an average of 12.5 hours, had a 36% higher risk of breast cancer recurrence than those who fasted 13 hours per night.[2] Each two-hour increase in the nightly fasting duration was associated with significantly lower hemoglobin A1c levels and a longer duration of nighttime sleep

The authors write, "Prolonging the length of the nightly fasting interval may be a simple, non-pharmacologic strategy for reducing the risk of breast cancer recurrence. Improvements in sugar regulation and sleep may be mechanisms linking nightly fasting with breast cancer prognosis."

This is a simple lifestyle change that may improve health. Still, some patients will make it feel like we are negotiating a business deal with them. Anytime we ask them to change their life, they find excuses to resist. Thus, over time, the easier the change is for patients to do, the more attractive it becomes to the practitioner.

These Marinac studies suggest an easier approach will obtain similar benefit as fasting or periods of caloric restriction. Simply prolonging the period of time in which women abstain from food at night, the fasting period between dinner and breakfast, is adequate to achieve significant benefit.

Patients generally resist and for the most part want to avoid anything that requires effort or sacrifice. On the effort scale, increasing duration of nightly fasts by half an hour is flat out easy, especially if one starts out by talking about extreme caloric restriction or fasting and then offer this Marinac scheme as another option.

All we need to do is ask a few simple questions and help patients do the math. "What time to do you finish supper?" "What time do you eat breakfast?" "Can you eat a little earlier in the evening or later in the morning?" This is easy.

I qualify what I wrote above, suggesting that most people are resistant to extended fasting or caloric restriction. There are some exceptions, some people are willing and eager to do and try anything. They have what I think of as a genetic tendency toward sacrifice. In their minds any sacrifice, any voluntarily encountered discomfort or hardship, earns them a reward from the universe, and in this equation, better health. I think this is the same tendency that once led people to line up at sacrificial altars; the same impulse now inspires them to limit their diet and seek out food restrictions and accept that

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idea that various unappealing foods are in fact beneficial if consumed. But I digress.

These two Marinac papers appear to be the first human studies that have sought a direct association between nightly fasting and breast cancer outcome. In animals, caloric restriction is an effective way to reduce cancer risk.[3] Intermittent caloric restriction prevents breast cancer development as well or even better than chronic caloric restriction in animals.[4] There is only one study that has examined whether meal timing has an effect on tumor progression in mice. Mice whose feeding times were restricted had smaller tumors than mice fed as much as they wanted.[5] Feeding mice during the light phase of their day was associated with less tumor growth. How do we translate that? Mice are nocturnal. Would this be equivalent to feeding people late at night or waking people during sleep to eat? Probably not; mice experiments only go so far in duplicating human biology.

In both groups of women in the Marinac studies, members of either the NHANES or WHEL study cohorts, longer nightly fasting was associated with a lower hemoglobin A1c levels. Giovanucci et al, also having analyzed data from NHANES, reported a similar finding in 2010.[6] Longer fasting is associated with lower blood sugar, a measure that may limit growth of breast cancer cells. Erickson et al reported in 2011, in a separate analysis of data from the WHEL cohort, that women with a A1c > 7.0%, were more than twice as likely to die during the study than women with an A1c less than 6.5%.[7]

In an August 2015 analysis of NHANES data, Marinac et al reported that among 2019 women, longer night time fasting was associated with significantly lower c-reactive protein levels, but only in women who ate less than 30% of their daily calories after 5 PM.[1] So we might modify our diet instructions and suggest eating bigger lunches and smaller suppers. This is starting to sound like things we learned back in naturopathic school.

In the 2016 paper, longer nightly fasting was not associated with basal metabolic index (BMI). Longer fasting was however associated with longer sleep duration. Late night eating disrupts circadian rhythms. Eva Schernhammer's multiple studies looking at night-shift workers have produced convincing evidence that circadian misalignment is linked with increased cancer risk, including increased risk of breast cancer.[8]

While these new findings are the result of retrospective analysis of data gathered two decades ago, the results are intriguing. As always, there will be those who suggest waiting for more definitive data gathered from a large prospective randomized trial before bringing this practice into clinical use. This writer is not among that group as, at this point, there is no evidence that longer night-time fasting is associated with any increase in risk. At the worst, this idea may prove to be ineffective. Given that this study suggests a nearly 40% shift in cancer recurrence rates, longer night time fasts may have clinically significant value.

Obviously, we cannot yet know whether the association revealed by this data is causal or not. It could be that women who produce higher amounts of insulin choose to forgo long night time fasts for the simple reason that they become hypoglycemic easily if they wait too long to eat. In simpler words, they wake up hungry and don't hold off breakfast. Eating patterns may simply select for differing levels of insulin production. Length of night-time fasts may simply be a biomarker of insulin production and not serve as an intervention. Still, what's it going to hurt to try?

In fact, what would it hurt to try this night-time fasting routine in people at risk for other types of cancer recurrence? No good reasons not to try it come to mind.

Up until now, we have had a number of unappealing choices on the menu for patients seeking the benefits of caloric restriction. There are the three-to-four-day 500 calorie diets Valter Longo has experimented with. There are the alternate-day-caloric restricted diets that switch from regular food intake to significantly restricted calorie intake every other day. Then there is the once-a-week fasting or low-calorie day approach. While patients may brave one of these diets, the practice is often of short duration; basically, few people love the experience and quickly find an excuse to discontinue. These night-time 'fasts' are different; patients see them as simply having a late breakfast. There is something leisurely, almost pleasant in starting the day a bit later. Rather than hardship, it feels somewhat laidback if not luxurious, a kind of every-day-is-a-holiday feeling. Patients are able to do this day after day and week after week. We do not yet know if they are as effective as other approaches, but we certainly know they are doable.

So, at our clinic, in addition to simple prescriptions for daily exercise, a healthy Mediterranean patterned diet, and adequate sleep, we now tell our breast and other cancer patients to "eat an early dinner and a late breakfast."

It sounds almost too simple. Often the best of naturopathic medicine is like that. Simple. It feels natural.

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Jacob Schor is a 1991 graduate of National College of Naturopathic Medicine (NCNM) and has practiced in Denver, Colorado ever since. He is a past president of the Colorado Association of Naturopathic Physicians (a group whose name has been changed to naturopathic doctors under pressure from you know who), a past board member of the American Association of Naturopathic Doctors (AANP), a past president of the Oncology Association of Naturopathic Physicians (ONCANP), and a frequent contributor to this and other publications for the naturopathic profession. He is associate editor of the *Natural Medicine Journal* (NaturalMedicineJournal.com), the official journal of the AANP.

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Ask Dr. J

by Jim Cross, ND, LAc
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Eeny, Meeny, Miny, or Moe: The Pitfalls of Thyroid Lab Testing

Let's start with one of the most important endocrine glands in the body, the thyroid. It rightfully attracts a large amount of attention in clinics and on lab testing. Why? Because it has system-wide effects. Thus, if there is an issue with the production, peripheral conversion, or nuclear attachment of their thyroid hormones, patients will have multiple complaints, including many non-specific, body-wide ones such as extreme fatigue, brain fog, and depression as thyroid hormone is the thermostat for human's metabolism.

Thyroid issues are extremely common, and their symptoms and signs are also similar to a variety of other hormonal disorders as well. We, as modern health care providers, are lucky enough to be able to employ brilliant lab tests. We must, however, understand how to interpret these lab tests, so they can actually be useful for us and our patients. Our modern standards of diagnosis do not allow us to reveal non-thyroidal illness or NTI.[1] After 30 years of looking at lab tests and the complaints of many patients, I'm convinced that they suffer from NTI, which is a syndrome that is not directly related to the production of T3/T4 by the thyroid gland. Applying new information and knowledge, especially how T4 is processed to either T3 or Reverse T3/RT3, will give us the ability to better understand our patient's lab results and allow us to give our patients treatments that will actually deal with the source of their problems.

When stimulated by thyroid stimulating hormone/TSH from the anterior pituitary gland in response to decreased circulating thyroid hormone leading to decreased negative feedback and TSH release, the thyroid gland releases about 90% T4 (pre-hormone), about 9% T3 (the active, stimulating form of thyroid hormone), about 1% RT3 (an inhibitory version of thyroid hormone), and a smidgen of T2.[2,3]

First off, why would the thyroid gland release a pre-hormone instead of just making the active T3 form? According to Alan McDaniel, MD, for the same reason Campbell's puts soup in cans instead of steaming hot bowls: it is safer to transport, and it has a long shelf life.

Next, a potentially large issue arises because converting T4 to T3 is not automatic.[4] There are multiple negative scenarios involved that can make this simple transformation from an inactive into an active form of thyroid hormone dysfunctional.

To start with let's look at some of my favorite science: biochemical physiology. Eighty percent of our daily T3 arises from removing the iodine from the 5-locus on the outer ring of T4 by enzyme 5'-de-iodinase or 5' DI in peripheral tissues. T4 can also become RT3 by removing the iodine from the 5-locus on the inner ring via enzyme 5 (***not prime***) de-iodinase or 5 DI.[5]

Reverse T3 acts as an inhibitor by blocking two forms of 5' DI, Type-2 5' DI or D2 and Type-1 5' DI or D1, from binding to their nuclear receptors.[6-9] D1 converts T4 to T3 throughout the body but is not a significant determinant of pituitary T4 to T3 conversion. D2 is responsible for pituitary conversion of T4 to T3.

RT3 then is inhibiting the increase in metabolism or the calorigenic effect of thyroid hormone.[10] What is directing the body to make less T3 and more RT3: the chronic stress response from multiple areas:[11]

- Physical stress (e.g., injury, MI, cancer, or CHF),
- Physiological stress (e.g., starvation or hypothermia),
- Psychological stress (e.g., long-term unhappiness in a marriage or students attempting to obtain good enough grades to enter medical school).

In our society, the psychological cause of increased RT3 appears to be one of the primary causes of NTI.[12,13] This altered metabolism of T4 is an adaptive response to make the metabolism conservative and efficient in times of stress. In human's past, this would be a transient affair if attacked by a saber tooth tiger or maybe if the fall harvest was insufficient and there wasn't enough food to make it until the next harvest. In our modern society, this formation of RT3 can persist for years. Now this beautiful adaptive response for saber tooth tigers and meager fall harvests becomes maladaptive. The result is NTI. ➤

Ask Dr. J

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We know what to recommend to our patients to decrease their stress level, but let's review what I think are some of the best choices:

- Sleep (7 ½ – 8 ½ hours per night),
- Gentle exercise (30-60 minutes per day such as yoga or walking),
- Meditation or praying,
- Improve the body's ability to respond to stress through adrenal nutrition,
- Diet (dysglycemia can lead to chronic cortisol release),
- Identifying food allergies/intolerances,
- Limbic breathing, developed by Majid Ali, MD (I described this in a prior article. Please e-mail me for the details. It is simply practiced and has extremely powerful anti-stress results.)

Let's look at a clinical success story pertaining to what I have written above. This patient is a 34-year-old female with an eight-year-old son and four-year-old daughter. She states that she never recovered completely from the birth of her daughter. Her fatigue has become almost unbearable. She wakes up exhausted and somehow makes it through the day to come home, make dinner, try to talk to her husband and kids, and fall asleep. She has multiple other hypothyroid symptoms and signs, but for her the worst were the 80 pounds she had gained since her daughter's birth and a small, palpable goiter. She rates the stress of her work life and home life a 12 out of 10. Her TSH was 2.5, total T4 was 6.2, and free T4 was 0.99. All were within normal limits although TSH is high normal and T4 and free T4 are at the low end of the optimal ranges. Her doctor had not tested for T3 or RT3. Her cholesterol and LDL were mildly elevated, but no other lab values were amiss. She also had multiple GI symptoms such as chronic constipation, severe bloating after meals, and chronic epigastric pain. She had been offered anti-anxiety drugs and had refused and came to see me as, of course, a last resort.

How can you also explain to patients that their doctors aren't necessarily testing for the relevant lab results, in her case free and total T3 and Reverse T3. Alan McDaniel has an apropos 11th commandment quote: Thou shalt not look at a normal lab result and tell your patient: "There is nothing wrong with you." **Remember: It is accurate to state: "This test doesn't show what is wrong with you."**

We had a long conversation about the thyroid gland and how chronic stress can lead to NTI which isn't diagnosable by regular lab testing. I gave her several options to decrease her stress. She chose 30 minutes of walking at lunchtime and to limbic breathe whenever she found herself breathing shallowly.

I also used NAET to test for food allergies and found her allergic to only wheat and citrus. She reported that she sometimes drank orange juice but craved bread, donuts, cookies, etc. and ate them several times per day. She was committed and said she would start to follow a non-gluten diet.

She returned in two weeks with an extremely mild improvement but basically said she had not been able to implement either the dietary or stress changes. She just did not have the energy to add any other routine to her life. I asked her what she really wanted to have happen. Without hesitation, she said to lose the 80 pounds. I was silent; and after what seemed like an eternity, she looked at me and said, "I'll do it." I love it when my patients finally figure out that they have the power to succeed.

She returned a month later and appeared to have had a nice transformation. She had lost eight pounds, had twice as much energy, and she reported that she didn't feel a tightness in her anterior neck area. I palpated, and her goiter appeared to be gone. (I'll admit I'm not the best thyroid palpator, but the goiter was either greatly reduced or gone.) She reported she had successfully stopped eating all gluten and had developed the ability to detect when she was breathing shallowly and to limbic breathe. She was able to limbic breathe at work or at home when she found herself breathing shallowly.

I find it extremely exhilarating when a patient really does the leg work from my recommendations. Success or failure really does boil down to convincing them to actually implement your suggestions. If you can accomplish this feat, it's a win/win scenario. Their health will improve, and their confidence in their ability to succeed will shoot through the roof.

This brings be to my last point. Majid Ali, MD, has written numerous books that are intellectually stimulating. One book is *The Ghoraa and Limbic Exercise*. In it he talks about limbic exercise and limbic breathing. Basically, he is talking about not letting our conscious cerebral cortex (what he calls the cortical monkey) interfere with our autonomic nervous system (what he calls the limbic dog.) so that our bodies are able to harmoniously function as a unit. I'm going to take Dr. Ali one step further. Basically, this is what I attempt to tell my physiology students and my patients: "Your body is smarter than you. Don't get in its way, meaning don't allow the cortical monkey to stress yourself to disease. In other words, live limbicly!"

Addendum: I quoted Alan McDaniel twice today. He has written for the *Townsend Letter* in the past. I am extremely fortunate to have access to rough chapters for his book on functional endocrinology. Now, in my estimation, Alan is the Michael Jordan of functional endocrinologists. The applicable clinical knowledge in these chapters is absolutely stunning, and several of my friends will concur who have read his thyroid and adrenal chapters. This information needs to be made available for two reasons: it will dramatically increase our knowledge of clinically relevant endocrinology, and it will allow us to, then, much better serve our patients! I feel Alan could use some help editing and proofreading his chapters. If you feel so inclined, please e-mail me or Dr. Collin for Alan's e-mail and help shepherd an extremely valuable resource into publication.

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Jim Cross graduated with a degree in Biology from the University of California at Davis in 1975, and with a secondary teaching credential in life science from California State University, Sacramento, in 1976. After beginning to study naturopathic medicine at Pacific College of Naturopathic Medicine in tiny Monte Rio, California, he finished his naturopathic studies at National College of Natural Medicine in Portland, Oregon, in 1984. He later earned his LAc at San Francisco College of Acupuncture in 1989. He has practiced acupuncture and naturopathy in the Northern Sierra town of Quincy since 1990. He has also taught anatomy and physiology at Feather River College in Quincy since moving there.

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Monthly Miracles

by Michael Gerber, MD, HMD
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Just a Fluke – Parasites Are Always with Us

I first read about *Fasciolopis buski*, the giant human liver fluke, in Hulda Clark, PhD, ND's book humbly titled *The Cure for All Cancers* in 1993. After being thrashed by the quackbusters that a human liver fluke endemic to Southeast Asia could be causal in cancer cases, scientists from the Queensland Institute of Medical Research collaborating with George Washington University have found that another human liver fluke (*Opisthorchis viverrini*) contributes to the development of liver cancer by secreting granulin, a growth hormone that is known to cause uncontrolled cell growth.[1] The International Agency for Research on Cancer classifies the human liver fluke as a Group I Carcinogen, meaning that *O. viverrini* is a proven cause of cancer of the bile ducts, cholangiocarcinoma.

Apologists for Clark note that flukes inhabit pigs and that many Americans have visited Southeast Asia. Clark further postulates that we must have exposure to propyl alcohol in our system to facilitate the fluke's propagation and its multiple disease-causing diatheses. Propyl alcohol is in many cosmetics, rubbing alcohol, fruit juice, bottled water, decaffeinated coffee, and white sugar among many other products.

A Case of Jaundice

A 36-year-old male presented with a two-month history of jaundice, bilirubin of 11.6 (N = 0-1.2), direct bilirubin of 9 and indirect of 2.3. Liver enzymes were moderately elevated as was the ammonia level. He was lethargic, diffusely itching, and had multiple joint pains. His medical workup was negative for hepatitis A, B, and C and autoimmune markers. Radiology showed no liver, gallbladder, or pancreatic pathology. He is an avid hunter, shoots and eats wild pigs, has been in many "nasty" swamps, owns 31 dogs and many chickens, goats and horses, and recalls having a tick bite this year.

After my standard EAV (ElectroAcupuncture by Voll) workup which Voll initiated in Germany in the late 1940s, I found *Fasciolopus buski* was weakening him as well as *Borrelia burgdorferi* (Lyme disease). After testing multiple anti-parasitical drugs and herbs, I prescribed 1800 mg Biltricide (praziquantel) three times per day for one day; it is the most frequently recommended drug for flukes. Praziquantel is available from compounding pharmacies in 300 mg caps for about $150.00. Retail pharmacies charge around $925.00 for one day's dosing. The patient also tested well for azithromycin 250 mg daily for one month to treat the *Borrelia* along with NutriMedix's Samento (Cat's claw), Cumanda, anti-bacterial herbs, and Burbur, a drainage remedy to soothe any Herksheimer reactions, die off, from the Lyme therapy.

The patient returned in three weeks feeling well. His dark urine cleared in several days after commencing therapy, the itching had subsided, and scabs on his skin were shedding. At this visit, his bilirubin was 1.1 and his LFT's were still mildly elevated. He again tested positive for flukes but the *Borrelia* was negative. He noted many white objects in his stool which he described as teardrop shaped. I prescribed a second course of Biltricide. He felt well enough to go bow hunting elk that weekend.

Omar Amin, PhD's lab (www.parasitetesting.com) is a very reliable lab for stool testing. *Fasciolopis buski* and *Fasciola hepatica* appear similar in stool samples. Mild infestations are sometimes asymptomatic. Heavier infections can appear as allergic reactions, anemia, ascites, diarrhea, fever, bowel obstruction, abdominal pain, and swelling of the skin. It was named by George Busk in London in 1843, who found it in the duodenum of a sailor. Adult flukes can be as large as 20 to 75 mm by 8 to 20 mm.

Testing for parasites, including amoeba, round worms (*Ascaris lumbricoides*), Cestodes (tapeworms, including fish tapeworms), *Toxoplasma gondii* (cat feces parasites), *Babesia* (one co-infection of Lyme), pork tapeworm (*Taenia solium*), pinworms with rectal itching (*Enterobius vermicularis*) and scores of others are worth seeking and treating in our patients. Our colleague, Shirley Scott, MD, teacher of parasitology from Sante Fe, New Mexico, suggests treating parasites on day one, day 30, day 90, and day 180 because of the eggs and larvae they shed with possible reoccurrences. Having an awareness of the prevalence of parasites and their impact on our patient's health is important, especially those with GI complaints such as abdominal pain or diarrhea.

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Calendar

Please submit an announcement of your event 90 days in advance.
Event publication must be limited to 25 words or less.
Multiple event listings require paid advertising.
Contact calendar@townsendletter.com for details.

JANUARY 12-14: MATRIX REFLEX TESTING (MRT) BASIC COURSE with Dr. Louisa Williams in Austin, Texas. CONTACT: info@radicalmedicine.com

JANUARY 25-FEBRUARY 9: INTENSIVE CLINICAL TRAINING IN INDIA in Calcutta, India. 200+ live cases demonstrated to show action of homeopathy in gross pathologies. CONTACT: http://www.homeopathy-course.com/index.php/training-courses/india-homoeopathy-training/2-week-clinical-training-in-calcutta

JANUARY 27: MODERN DAY ADDICTIONS – Emerging Integrative Care in Scottsdale, Arizona. Neurobiology, pharmacology, food and technology addiction, opioids, pain alternatives, alcohol, anxiety, integrative treatments. CONTACT: http://www.drmarchese.com/

FEBRUARY 1-3: INSTITUTE FOR FUNCTIONAL MEDICINE – CARDIOMETABOLIC APM in Atlanta, Georgia. CONTACT: 800-228-0622; https://www.ifm.org/

FEBRUARY 3-7: 2nd INTERNATIONAL CANCER CONGRESS in Toulouse, France. CONTACT: http://www.toulouse-onco-week.org/

FEBRUARY 4-6: INSTITUTE FOR FUNCTIONAL MEDICINE – IMMUNE APM in Atlanta, Georgia. CONTACT: 800-228-0622; https://www.ifm.org/

FEBRUARY 8-11: 15th ANNUAL NATURAL SUPPLEMENTS CONFERENCE in San Diego, California. CONTACT: https://www.scripps.org/event_schedules/1057-naturalsupplements

FEBRUARY 8-13: A4M & MMI present BIO-IDENTICAL HORMONE REPLACEMENT SYMPOSIUM in Charleston, South Carolina. CONTACT: https://www.a4m.com

FEBRUARY 9-11: LABRIX ADVANCED WORKSHOP in Las Vegas, Nevada. Adrenal/HPA axis hormone and neurotransmitter testing and treatment protocols. CONTACT: https://www.labrix.com/law

FEBRUARY 10-11: GREAT PLAINS LABORATORY PRACTITIONER WORKSHOPS – Organic Acids Testing and Environmental Toxin Testing in Austin, Texas. Includes organic acids testing, toxic chemical testing, and mycotoxin testing. Also, **FEBRUARY 24-25** in Los Angeles, California. CMEs available. CONTACT: http://www.GPLUniversity.com

FEBRUARY 10-11: 2018 FOOD AS MEDICINE SYMPOSIUM @ National University of Natural Medicine in Portland, Oregon. CONTACT: http://career-alumni.nunm.edu/continuing-education/

FEBRUARY 16-18: 7th ANNUAL OncANP NATUROPATHIC ONCOLOGY CONFERENCE in Tempe, Arizona. CONTACT: https://oncanp.org/

FEBRUARY 22-25: BRIMHALL HOMECOMING: The 6 Steps to Wellness in Phoenix, Arizona. CONTACT: Jason Matuszewski, 866-338-4883; http://www.brimhall.com

FEBRUARY 23-25: HOMEOPATHY FOR MUSCULOSKELETAL HEALING with Asa Hershoff, DC, ND, presented by Florida Homeopathic Society, in Orlando, Florida. ACHENA CEUs. CONTACT: https://www.floridahomeopathicsociety.org/

MARCH 2-3: CLINICAL MITOCHONDRIAL AND ENVIRONMENTAL MEDICINE in Heidelberg, Germany. Specialist lectures in English. Also, first of 4 weekends for German curriculum. CONTACT: info@mito-medizin.de; http://www.mito-medizin.de/

MARCH 19-23: INSTITUTE FOR FUNCTIONAL MEDICINE – APPLYING FUNCTIONAL MEDICINE IN CLINICAL PRACTICE in San Diego, California. Also, **OCTOBER 1-5** in Washington, DC; **OCTOBER 4-8** in London, United Kingdom. CONTACT: 800-228-0622; https://www.ifm.org/

MARCH 21-22: THE 2nd PROBIOTICS CONGRESS: EUROPE in Rotterdam, The Netherlands. CONTACT: http://www.global-engage.com/event/probiotics-europe/

MARCH 21-22: THE 5th MICROBIOME R&D AND BUSINESS COLLABORATION FORUM: EUROPE in Rotterdam, The Netherlands. CONTACT: http://www.global-engage.com/event/microbiota/

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Calendar

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MARCH 30-APRIL 1: INJECTION THERAPIES with Dr. Marc Harris – Permanent Pain Relief and So Much More in Orlando, Florida. CONTACT: Jason Matuszewski, 866-338-4883; http://www.brimhall.com

APRIL 5-7: THE FORUM FOR INTEGRATIVE MEDICINE – Treating the Untreatable: Unraveling Complex Chronic Illness in Chicago, Illinois. CONTACT: https://forumforintegrativemedicine.org/

APRIL 6-8: ENVIRONMENTAL HEALTH SYMPOSIUM 2018 in Scottsdale, Arizona. Effective methods and interventions for reducing toxic load and body burden. CONTACT: 855-347-4477; http://www.EHS2018.com

APRIL 6-8: 13th ANNUAL JOINT AMERICAN HOMEOPATHIC CONFERENCE - **Homeopathy: An Affordable Healthcare Solution** in Phoenix, Arizona. CONTACT: http://www.homeopathycenter.org/

APRIL 12-14: A4M ANNUAL SPRING CONFERENCE in Hollywood, Florida. CONTACT: https://www.a4m.com/

APRIL 13-15: GREAT PLAINS LABORATORY MASTER PRACTITIONER WORKSHOP in Chicago, Illinois. In-depth information about the Organic Acids Test, GPL-TOX (Toxic Non-Metal Chemical Profile), Glyphosate Test, GPL MycoTOX Profile, and more. CONTACT: http://www.GPLUniversity.com

APRIL 14-15: CALIFORNIA NATUROPATHIC DOCTORS ASSOCIATION with PsychANP present INTEGRATIVE PSYCHIATRY AND NEURO-IMMUNOLOGY in Torrance, California. CONTACT: http://www.calnd.org/

APRIL 18-22: INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE SPRING CONFERENCE – "What Works" in Cincinnati, Ohio. CONTACT: http://icimed.com/

APRIL 20-21: INTEGRATIVE MEDICINE FOR THE TREATMENT OF TICK-BORNE DISEASES in Baltimore, Maryland. CONTACT: delmarvalyme@yahoo.com; http://integrativelyme.com

APRIL 27-28: 62nd NORTHWEST NATUROPATHIC PHYSICIANS CONVENTION – Golden Nuggets from the Golden Nugget in Las Vegas, Nevada. CONTACT: https://nwnpc.com/

APRIL 27-29: 47th ANNUAL INTERNATIONAL ORTHOMOLECULAR MEDICINE TODAY CONFERENCE in Tokyo, Japan. CONTACT: https://www.isom.ca/omt/

MAY 18-20: 5th ANNUAL TRADITIONAL ROOTS HERBAL CONFERENCE @ National University of Natural Medicine in Portland, Oregon. CONTACT: http://traditionalroots.org/tradrootscon2018/

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The editors of the *Townsend Letter* recommend that all patients (and physicians) review further reports provided in the article's references and investigate the practitioner's techniques before undertaking an alternative diagnosis, examination, or treatment. Please discuss such treatments and examinations with a reputable health practitioner in your community. If you do use an alternative treatment discussed in the *Townsend Letter*, we would appreciate your report of the outcome, any side effects, and costs.

Women's Health Update

by Corina Dunlap, ND, MS, Guest Author
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Botanicals for Women with Infertility and PCOS – Current Evidence

Polycystic ovary syndrome (PCOS) is a common endocrine syndrome that affects women of reproductive age. It is characterized by ovulatory dysfunction, biochemical and/or physical signs of androgen excess (e.g., acne, hirsutism, male-pattern hair loss), and in some women, polycystic ovaries. Concomitant morbidities can include infertility, increased risk for type 2 diabetes, mood disorders, and cardiovascular disease risk factors such as obesity, dyslipidemia, and metabolic syndrome.

For women trying to get pregnant, the complex metabolic and reproductive hormone dysfunction makes it challenging to conceive. Ovulation is infrequent and follicular development abnormal, often resulting in a higher percentage of atretic, or degenerating follicles.[1] Women are generally dissatisfied with pharmaceutical standard of care treatment options. In one study, 648 of 657, or 99% of women stated that they would like an alternative to standard birth control pills and ovulation-induction fertility medication.[2] Evidence suggests that treatment with certain botanicals may have a positive impact on PCOS comorbidities including infertility.

A recently published study in *Phytotherapy Research* (July 2017) examined the effectiveness and safety of an herbal plus lifestyle intervention against lifestyle alone in overweight women aged 18-44 with PCOS.[3] The primary outcome measured was menstrual length. Secondary outcomes measured included serum concentration of reproductive hormones; glucose and insulin sensitivity; anthropometric characteristics; health-related quality of life (HRQoL) for depression, anxiety, and stress; pregnancy and birth outcomes; blood pressure; as well as any adverse events.

One hundred and twenty-two women met the inclusion criteria and were randomized to either intervention (n=60) or control group (n=62). The herbal intervention consisted of two tablets. Tablet 1 contained equal parts of extract equivalent to 750 mg of each of the following dry herbs per tablet: *Cinnamomum verum (stem bark)*, *Glycyrrhiza glabra (root)*, *Hypericum perforatum (flowering herb)*, and *Paeonia lactiflora (root)*. *G. glabra* and *P. lactiflora* were chosen to target androgen reduction, *C. verum* to improve menstrual regularity, and *H. perforatum* to reduce depression, which is more common in women with PCOS.[4] Tablet 2 contained *Tribulus terrestris (aerial parts)* standardized to furostanol saponins 110 mg. *T. terrestris* was chosen as a possible potentiator of follicle stimulating hormone (FSH). Tablet 1 was administered as three tablets daily for three months, and Tablet 2 as three tablets daily for 10 consecutive days during the follicular phase (starting on Day 5 of cycle) for three months. Women were instructed to stop taking the herbal intervention if pregnancy occurred due to concerns over safety. Lifestyle recommendations included dietary instruction aimed at increased nutrient density, blood sugar optimization, and weight loss, and a structured aerobic plus progressive resistance exercise plan.

At three months, statistically significant results included the following:

- Primary Outcome
  - Menstrual length was 43 days shorter than lifestyle alone ($p < 0.001$).
- Secondary Outcomes
  - Lower BMI ($p < 0.01$).
  - Decreased insulin ($p = 0.02$).
  - Decreased luteinizing hormone ($p = 0.04$).
  - Lowering of blood pressure ($p = 0.01$).
  - Improved quality of life ($p < 0.01$).
  - Improved depression, anxiety, and stress ($p < 0.01$).
  - Increased clinical pregnancy rate ($p <0.01$).

The live birth rate was no different in the intervention group after accounting for sample size ($p = 0.06$).

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Women's Health Update

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While lack of a placebo group limits this study, it presents a novel and promising herbal combination treatment approach to the preconception window for overweight women with PCOS who are interested in conceiving.

Vitex agnus-castus (vitex) and *Cimicifuga racemosa* (black cohosh) have also been studied for their impact on fertility in women with PCOS. There is more evidence to support vitex's use in lowering prolactin and improving menstrual regularity than in its treatment of those with infertility.[5] In one study, vitex was administered through a proprietary combination blend consisting of 32.4 mg per day for three months.[6] In a subgroup analysis of those with amenorrhea or luteal insufficiency, the intervention group had more than doubled pregnancy rates over that of the placebo group. However, the study lacked an effect size large enough to show any power. The proprietary blend also contained homeopathic preparations of *Caulophyllum thalictroides*, *Lilium majus*, *Cyclamen*, *Ignatia,* and *Iris,* which may have confounded results.

Cimicifuga racemosa has promising evidence for its treatment of women with PCOS and infertility, in combination with clomiphene citrate therapy. In one study, 194 women <35 years old were randomized to take either clomiphene citrate 150 mg from days 3-7 alone, or in conjunction with *C. racemosa* 120 mg from Day 1 until pregnancy testing.[7] Statistically significant results included the following:

- Higher pregnancies per cycle ($p = 0.01$);
- Higher clinical pregnancies per cycle ($p = 0.01$).

There was no difference between groups in number of biochemical pregnancies, miscarriages, or multiple pregnancies per cycle.

It cannot be assumed that botanical treatments that may be effective for general PCOS may also be effective for patients with PCOS who are trying to get pregnant.

For example, a recent study examining toxicological effects of *Trigonella foenum graecum*, shows it has anti-fertility, anti-implantation, and abortifacient activity related to saponin compounds contained within the herb.[8] It is also important to advise your patients to stop taking any botanical treatments mentioned in this article once pregnancy occurs, as there is a lack of safety data.

We have a long way to go in examining the effects of botanical medicine on the treatment of PCOS and infertility. However, the treatments discussed above have interesting potential, and are worth exploring in patients opting for a more natural approach.

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receiving 800 and 1,200 IU per day than in those receiving 400 IU per day ($p < 0.05$).[7]

Safety Concerns with High-Dose Vitamin D

Aside from its potential to cause kidney stones, there is concern from animal research that high dose-vitamin D could promote the development of atherosclerosis. Swine fed vitamin D_3 at a level of 27,500 IU per kg of diet (equivalent to about 11,500 IU per day for humans[8]) developed pathological changes in the thoracic aorta that were indistinguishable from those found in the thoracic aorta of humans undergoing coronary bypass surgery.[9] Even a modest increase in vitamin D_3 intake[10] (from 331 IU per kg of diet to 2,200 IU per kg of diet) exacerbated coronary atherosclerosis in swine consuming a diet high in saturated fat.[11] A vitamin D dosage of 2,200 IU per kg of diet is equivalent to only 917 IU per day for humans.

Conclusion

The evidence reviewed above raises concerns about the safety and efficacy of high-dose vitamin D. In addition, as I have pointed out elsewhere, serum 25(OH) D appears to be an unreliable indicator of vitamin D status in people who do not have severe vitamin D deficiency or frank toxicity.[12] Moreover, there is no evidence from randomized controlled trials that supplementing with enough vitamin D to increase serum 25(OH)D to a purported "optimal" level improves health outcomes. For the average, reasonably healthy person who might benefit from vitamin D supplementation, it has been my practice to recommend 800-1,200 IU per day and not to measure 25(OH)D levels. I am not convinced that routinely measuring 25(OH) D levels and basing treatment decisions on those laboratory results provides any advantage with respect to safety, effectiveness, or cost-effectiveness.

Alan R. Gaby, MD

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Concerns About High-Dose Vitamin D

For the past decade or so, some researchers and practitioners have been recommending routine use of relatively large doses of vitamin D (such as 4,000-10,000 IU per day for prolonged periods of time). They claim that supplementing with enough vitamin D to achieve a purported "optimal" serum 25-hydroxyvitamin D (25[OH]D) level (such as 36-40 ng/ml or higher) can produce a wide range of health benefits. (The average vitamin D dosage needed to achieve a 25(OH)D concentration above 40 ng/ml is about 6,000 IU per day for normal-weight individuals and 7,000 IU per day for overweight individuals.[1]) Contrary to these claims, I have argued on numerous occasions that using large doses of vitamin D for the sole purpose of achieving an "optimal" serum 25(OH)D level has not been demonstrated to be safe or effective.

The idea that we should aim for 25(OH) D levels of 36-40 ng/ml or higher is based almost entirely on observational studies, which found that these levels were associated with better health outcomes. However, associations do not prove causation. A growing body of evidence from randomized controlled trials indicates one of the following: 1) high doses of vitamin D are not more effective, and may actually be less effective in some instances, than moderate doses of the vitamin, or 2) high doses of vitamin D are not more effective than placebo.

Cardiovascular Disease

Four hundred patients (median age, 55 years) with heart failure (New York Heart Association class II or III) and a serum 25(OH)D level below 30 ng/ml (median, 13 ng/ml) were randomly assigned to receive, in double-blind fashion, 4,000 IU per day of vitamin D or placebo for three years. The mortality rate (the primary endpoint) was non-significantly higher by 9.5% in the vitamin D group than in the placebo group (19.6% vs. 17.9%; p = 0.73). The proportion of patients who needed a mechanical circulatory support implant (a secondary endpoint) was significantly higher in the vitamin D group than in the placebo group (15.4% vs. 9.0%; p = 0.03).[2]

In the Vitamin D Assessment Study, 5,110 New Zealand adults (mean age, 65.9 years) were randomly assigned to receive, in double-blind fashion, vitamin D_3 or placebo for a median duration of 3.3 years. The dosage of vitamin D was 200,000 IU initially, followed by 100,000 IU once a month; a regimen that is equivalent to about 3,300 IU per day. The mean serum 25(OH)D level at baseline was 25.3 ng/ml; this increased after three years of treatment to 54.1 ng/ml in the vitamin D group and to 26.4 ng/ml in the placebo group. The incidence of the composite outcome of death or hospitalization due to cardiovascular disease was 11.8% in the vitamin D group and 11.5% in the placebo group (difference not significant). Similar results were seen when the analysis was restricted to participants with a 25(OH) D level below 20 ng/ml at baseline and to participants with cardiovascular disease at baseline.[3]

Bone Health

In a double-blind study, 297 postmenopausal women (aged 50-80 years) received 800 IU per day or 6,500 IU per day of vitamin D_3 for one year. The mean baseline 25(OH)D level was 28.4 ng/ml. Mean bone mineral density of the total hip, femoral neck, lumbar spine, and total body increased in both groups; these increases were non-significantly greater with 800 IU per day than with 6,500 IU per day at each of the four measured sites.[4] In another study, the incidence of fractures was examined among participants in the Vitamin D Assessment Study (described above, under Cardiovascular Disease). Subjects received the equivalent of 3,300 IU per day of vitamin D or placebo for a median treatment period of 3.4 years. The proportion of participants who had a non-vertebral fracture during the study was non-significantly higher by 19% in the vitamin D group than in the placebo group (6% vs. 5%; p = 0.15).[5]

Multiple Sclerosis

Twenty-three patients with relapsing-remitting multiple sclerosis received high-dose (about 13,000 IU per day) or low-dose (about 1,000 IU per day) vitamin D_2 for six months. The dose in the high-dose group was adjusted to maintain a serum 25(OH)D level of 52-70 ng/ml. The median Expanded Disability Status Scale was significantly worse in the high-dose group than in the low-dose group (3 vs. 2 on a 10-point scale; p = 0.04). The relapse rate was significantly higher in the high-dose group than in the low-dose group (36% vs. 0%; p = 0.04).[6]

Infant Neurological Development

Fifty-five healthy, term breastfed infants from Montreal, Canada, were randomly assigned to receive, in double-blind fashion, 400, 800, or 1,200 IU per day of vitamin D_3, starting at age one month and continuing until 12 months of age. Motor performance was assessed using the Alberta Infant Motor Scale (AIMS). Total AIMS score and the sitting sub-score were significantly worse at six months in infants

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