ACAM
AMERICAN COLLEGE FOR ADVANCEMENT IN MEDICINE

Chelation Therapy Training

November 4-5, 2009 - Las Vegas
www.acamvegas.com

this activity is supported, in part, by an educational grant from:

DOCTOR'S DATA INC.

Chelation Therapy Workshop

About the Workshop

Heart disease is the #1 health problem for both women and men in the United States. Almost 700,000 people die of heart disease in the U.S. each year. That is about 29% of all U.S. deaths. The risk of coronary heart disease can be reduced by taking steps to prevent and control those adverse factors that put people at greater risk for heart disease and heart attack. Risk factors that need more attention include diet, nutrition and elimination of toxic metals from the body.

EDTA Chelation therapy involves repeated administration of a synthetic amino acid to reduce atherosclerotic plaque and other toxic mineral deposits throughout the body. It's use for heart disease is studied at NCCAM ; additionally toxic minerals, like lead, that cause heart disease are published in the medical literature as is the effect of diet and nutrition on cardiac health.

Your patients have a significant risk of developing heart disease during their lifetime. With this knowledge, many are becoming interested and self-educated in non-conventional treatment options that will prevent, augment or replace their current pharmacologic regimens. These patients want to work with a physician that is able to identify their risk for heart disease, recommend preventative nutritional suggestions and feel comfortable implementing a treatment strategy that is effective and safe.

To meet this growing need, this course will provide you with essential information including:

- Practical strategies for incorporating Chelation Therapy for heart disease into your practice and on how to diagnose and treat patients with heavy metal burden
- Tools to evaluate risk factors for developing heart disease
- How to use diet and nutrition to optimize cardiac health

Course Learning Objectives

At the end of the course, participants should be able to:

1. Review current risk factors and methods for testing cardiovascular disease.
2. Discuss how to apply the various tests for lead and heavy metal exposure.
3. Understand how to use EDTA chelation therapy safely for heart disease and lead chelation.
4. Apply the appropriate chelating agent to properly treat heavy metal accumulation.
5. Gain competence in applying diet and nutrition in the clinical setting to improve cardiac health.
6. Explain case studies and clinical strategies to indentify and treat heart disease.
7. Apply IV technique for chelation therapy.

Disclaimer

The information provided at this activity is for continuing education purposes only and is not meant to substitute for the independent medical judgment of a healthcare provider relative to diagnostic and treatment options of a specific patient's medical condition.

Instructions on How to Receive a Certificate of Attendance

Please fill out the enclosed "Certificate Request Form" found in the workshop syllabus or online. At the completion of the workshop, drop off your completed form at the registration desk.

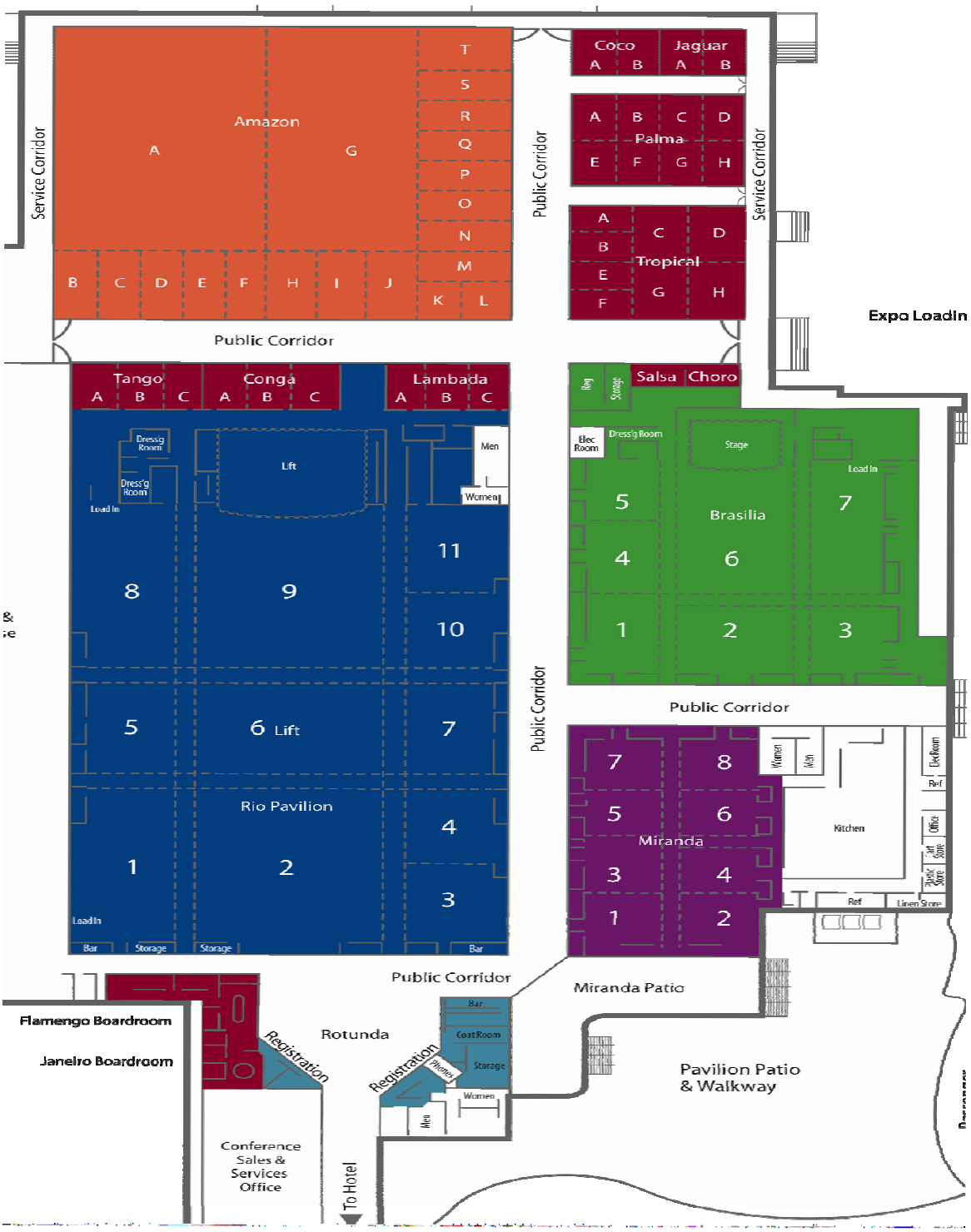
American College for Advancement in Medicine

November 4-5, 2009 Las Vegas, Nevada

Chelation Therapy Workshop

Workshop Information

Activity	Location	Time
Chelation Workshop	Rio Pavilion 3-4	8:00 am - 5:30 pm
AM Break	Miranda 3-6	10:00 - 10:30 am
Lunch	Miranda 3-6	12:00 - 1:00 pm
PM Break	Miranda 3-6	3:00 - 3:30 pm



American College for Advancement in Medicine

November 4-5, 2009 Las Vegas, Nevada

Chelation Therapy Workshop

Workshop Schedule

Wednesday

8:00-9:00 am	*History of chelation therapy*	
		Richard Linchitz, MD
9:00-10:00 am	*Relationship of heavy metals to cardiovascular disease*	
		Lyn Patrick, ND
10:30-11:30 am	*DMPS and DMSA protocols*	
		Richard Nahas, MD
11:30-12:00 pm	*Expert Panel/Q & A*	
		Richard Linchitz, MD, Lyn Patrick, ND, Richard Nahas, MD
1:00-2:00 pm	*The use of NaEDTA for cardiovascular disease*	
		Jeffrey Morrison, MD
2:00-3:30 pm	*Testing for heavy metals*	
		David Quig, PhD
4:00-5:30 pm	*Expert Panel/Q & A*	
		Jeffrey Morrison, MD, David Quig, PhD

Thursday

8:00-9:00 am	*The role of dentistry in causing and preventing heart disease*	
		Reid Winick, DDS
9:00-10:00 am	*Overview of heavy metal toxicity*	
		James Biddle, MD
10:30-11:30 am	*Legal update*	
		Rick Jaffe, ESQ
11:30-12:00 pm	*Expert Panel/Q & A*	
		Reid Winick, DDS, James Biddle, MD, Rick Jaffe, ESQ
1:00-2:00 pm	*Glutathione in metals detoxification*	
		Tim Guilford, MD
2:00-2:30 pm	*TACT Update*	
		Representative
3:00-5:30 pm	*The nuts and bolts of EDTA chelation therapy*	
		W.A. Shrader, Jr., MD

Autoimmune Disease: 21st Century Approaches
November 4-8, 2009
Las Vegas, Nevada

Attendance Certificate Request
Chelation Workshop

Help us reduce our environmental impact. Complete this form online.

Instructions:

To receive an attendance certificate for this activity, this form must be completed in full and returned along with the activity evaluation to the Registration Desk at the conclusion of the activity (before you leave).

Attendees submitting a certificate request form must be registered and paid attendees. ACAM will not honor certificate request form without paid registration to the educational activity.

Please PRINT CLEARLY:

First Name: M.I.: Last Name:

Credentials:

Address for Certificate Mailing: ☐ Mail my certificate to the address on-file.

Street:

City: State: Zip:

Telephone Number: ( ) Fax #: ( )

Signature: Date:

Please return this form to the registration desk or mail to ACAM within 30 post conference. Request form is null and void 30 days post conference.
Your attendance certificate will be mailed 6-8 weeks after the conference. If you have any questions regarding your certificate, please contact the ACAM office at 949.309.3526.

American College for Advancement in Medicine 8001 Irvine Center Drive, Suite 825, Irvine, CA 92618

Form code: 10452009

Autoimmune Disease: 21st Century Approaches

November 4-8, 2009
Las Vegas, Nevada

Help us reduce our environmental impact. Complete this form online.

Directions: Please **clearly** circle or otherwise indicate your responses. Thank You!

A. Tell us about yourself

☐ MD/DO ☐ PhD ☐ ND ☐ Nurse/PA ☐ Student ☐ Other: _____

Specialty: _____ Years in practice: _____

B. Please rate each of the following faculty on their presentation skills, knowledge of content and degree to which presentation was balanced, objective and scientifically rigorous.

Scale: 1 = Poor, 2 = Below Average, 3 = Average, 4 = Above Average, 5 = Outstanding

	Presentation Skills	***Knowledge of Content***	***Degree of Balance, Objectivity & Scientific Rigor***
Wednesday, November 4			
History of chelation therapy **Richard Linchitz, MD**	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Relationship of heavy metals to cardiovascular disease **Lyn Patrick, ND**	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
DMPS and DMSA protocols **Richard Nahas, MD**	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
The use of NaEDTA for cardiovascular disease **Jeffrey Morrison, MD**	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Testing for heavy metals **David Quig, PhD**	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Thursday, November 5			
The role of dentistry in causing and preventing heart disease **Reid Winick, DDS**	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Overview of heavy metal toxicity **James Biddle, MD**	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Legal update **Rick Jaffe, ESQ**	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Glutathione in metals detoxification **F.T. Guilford, MD**	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
The nuts and bolts of EDTA chelation therapy **W.A. Shrader, Jr., MD**	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5

Over ----->

Please complete and return this evaluation form to the registration table before you leave the conference. Thank you!

American College for Advancement in Medicine 8001 Irvine Center Dr., Suite 825, Irvine, CA 92618

ACAM
AMERICAN COLLEGE FOR ADVANCEMENT IN MEDICINE

Autoimmune Disease: 21st Century Approaches
November 4-8, 2009
Las Vegas, Nevada

C. Please indicate how well this activity met its stated learning objectives.

Scale: 1= not at all, 2= slightly, 3= moderately, 4= mostly, 5= completely

1. Review current risk factors and methods for testing cardiovascular disease.	1	2	3	4	5
2. Discuss how to apply the various tests for lead and heavy metal exposure.	1	2	3	4	5
3. Understand how to use EDTA chelation therapy safely for heart disease and lead chelation.	1	2	3	4	5
4. Apply the appropriate chelating agent to properly treat heavy metal accumulation.	1	2	3	4	5
5. Gain competence in applying diet and nutrition in the clinical setting to improve cardiac health.	1	2	3	4	5
6. Explain case studies and clinical strategies to indentify and treat heart disease.	1	2	3	4	5
7. Apply IV technique for chelation therapy.	1	2	3	4	5

D. Please provide a rating for the course materials and the course overall.

Scale: 1 = Poor, 2 = Below Average, 3 = Average, 4 = Above Average, 5 = Outstanding

	Quality, organization and contribution to your learning	***Degree of Balance, Objectivity & Scientific Rigor***
The course syllabus	1 2 3 4 5	1 2 3 4 5
Overall rating for the entire course	1 2 3 4 5	1 2 3 4 5

E. Did you have the opportunity to discuss practice-relevant issues with the speakers?

Scale: 1 = Not at all, 2 = Slightly, 3 = Moderately, 4 = Mostly, 5 = Completely

1	2	3	4	5

F. What will you do differently in the care of your patients?

_____

_____

G. Do any clinical questions remain? _____ **No** _____ **Yes**

If so, please describe:

_____

_____

H. Please mention any barriers that you feel might prevent you from making additional changes in your practice that were promoted by this activity. (e.g., costs, logistics, paperwork, approval from others, lack of access insurance coverage, etc.)

_____

_____

Please complete and return this evaluation form to the registration table before you leave the conference. Thank you!

American College for Advancement in Medicine 8001 Irvine Center Dr., Suite 825, Irvine, CA 92618

Autoimmune Disease: 21st Century Approaches

November 4-8, 2009

Las Vegas, Nevada

I. What clinical challenge(s) have you encountered recently in your practice for which you feel you need additional information or skill(s) to optimally diagnose and/or treat/manage? (please be as specific as possible)

_____

_____

J. Comments, feedback or suggestions for improvement:

_____

_____

Optional:

Please provide us with your name and e-mail address so we may follow up with you regarding changes you have made in your practice as a result of this educational activity. *(all self report information will de-identified. please print clearly)*

Name:_____ **e-mail:**_____

CW10452009

Please complete and return this evaluation form to the registration table before you leave the conference. Thank you!

American College for Advancement in Medicine 8001 Irvine Center Dr., Suite 825, Irvine, CA 92618

Richard M. Linchitz, MD

History of chelation therapy

Bio

Dr. Linchitz graduated from Cornell University Medical College in the Alph Omega Alpha Honor Medical Society in 1973. After internship and residency at U.C. San Francisco Moffit Hospital he spent over 25 yrs as a Pain Management specialist, serving on the Board of Directors of the American Board of Pain Medicine. In 1998, he was diagnosed with Non Small Cell Lung Cancer and after lobectomy and back surgery for three herniated discs and spinal stenosis, and was forced to retire from medicine. It was during this time that he developed a passion for integrative medicine and proceeded to read everything he could get his hands on. Understandably, cancer became his primary personal and academic interest. When he finally was able to resume the practice of medicine in 2003, he began to develop a cancer program which was eventually to include Insulin Potentiation Therapy as well as the supplements and lifestyle changes which had become an essential part of his own life. He received his IPT degree from Donato Peres Garcia and has been granted certification as an instructor in this method of treatment. He is the founder and Medical Director of Linchitz Medical Wellness in Glen Cove, New York.

Lecture Overview

There will be a brief overview of the science of heavy metal toxicity and the various common toxic metals. There will also be a brief overview of the common chelating agents in use. The history of chelation therapy will then be presented including political issues as well as the history of ACAM's involvement.

Contact Information

Linchitz Medical Wellness
70 Glen Street, Suite 240
Glen Cove, NY 11542

rlinchitz@msn.com

INTRODUCTION TO THE HISTORY AND THEORY OF CHELATION THERAPY

The Science of Heavy Metal Toxicity

- Much of the toxicity associated with heavy metals is due to their effects on mitochondria (uncoupling or short-circuiting their function), but also by creating haptens (small molecules which sensitize the immune system), enzyme inhibition, depletion of ascorbate and glutathione, and inhibition of B1 and B6.
- Examples: Lead, Mercury, Arsenic, Cadmium, Nickel, Aluminum, each of which have additional specific toxic effects. All of their toxic effects are potentiated by magnesium deficiency and calcium excess.

Heavy Metal Toxicity, cont'd

- Lead toxicity:
  1) Inhibits phosphodiesterase.
  2) Inhibits cytochrome c.
  3) Inhibits SOD.
  4) Inhibits Thiol enzymes.
  5) Interferes with DNA/RNA translation/transcription.
  6) Immunotoxic.

Heavy Metal Toxicity, cont'd

- Mercury toxicity:
  1) poisons nerve growth.
  2) Inhibits cytochrome c.
  3) Inhibits SOD.
  4) Inhibits thiol enzymes.
  5) Inhibits DNA/RNA translation/transcription.
  6) Immunotoxic.

Heavy Metal Toxicity, cont'd

- Arsenic toxicity:
  1. Endocrine disruptor.
  2. Inhibits cytochrome c.
  3. Immune potentiator.
  4. Inhibits thiol enzymes.
  5. Inhibits DNA/RNA translation/transcription.
  6. Immunotoxic (forms haptens).

Heavy Metal Toxicity, cont'd

- Cadmium toxicity:
  1. Inhibits phosphodiesterase.
  2. Inhibits cytochrome c.
  3. Inhibits SOD.
  4. Inhibits thiol enzymes.
  5. Inhibit DNA/RNA translation/transcription.
  6. Immunotoxic (forms haptens).

Heavy Metal Toxicity, cont'd

- Nickel toxicity:
  1. Inhibits phophodiesterase.
  2. Inhibits cytochrome c.
  3. Inhibits SOD and other antioxidants.
  4. Inhibits thiol enzymes.
  5. Inhibits DNA/RNA translation/transcription.
  6. Immunotoxic (forms haptens).

Heavy Metal Toxicity, cont'd

- Aluminum toxicity:
  1. Inhibits histone function in DNA.
  2. Interferes with RNA receptors.
  3. Interferes with hormone receptors.
  4. Inhibits recycling of cell debris ("neurofibrillary tangles").
  5. Inhibits DNA/RNA translation/transcription.
  6. Immunotoxic (forms haptens).

Heavy Metal Toxicity, cont'd

Clinical conditions associated with metal toxicity:

1. ASCVD
2. Cancer
3. Alzheimer's disease.
4. Diabetic neuropathy and renal disease.
5. Fibromyalgia and myofascial pain.
6. Chronic fatigue.
7. Autoimmune diseases.

Chelating Agents, overview

- EDTA-disodium calcium salt of EDTA which is a polyamine carboxylic acid.
- Forms complexes with metal ions (up to six bonds). The bonding affinity is determined by the "stability constant". Strong affinity for Cr, Fe, Hg, Cu, Pb, etc.
- These complexes are excreted by the kidneys.

Chelating Agents, overview cont'd

- BAL (British Anti-Lewisite)-First of the sulfhydryl chelating compounds.
- Developed by the British during WWII as an antidote to Arsenical war gases.
- Forms stable chelates with Hg, As, Bi, Cd, Cr, Co, Pb, Au, Ni, etc.
- Only neutral chelator and soluble in water and lipids easily passing intra-cellularly.
- Excreted in the bile so it can be used in renal impairment.

Chelating Agents, overview cont'd

- DMSA-Succimer or Chemet
- Reacts with the same group of toxic metals as BAL.
- No clinically significant effects on essential minerals.
- Orally effective (23% absorbed) and can be used IM, not IV.

Chelating Agents, overview cont'd

- DMPS—3-dimercaptopropane-1-sulfonate
- Analogue of BAL and similar affinities to BAL and DMSA but especially for copper and zinc (even higher than its affinity for Hg).
- Can be given orally or IV (60% oral absorption). It is an extracellular chelator like DMSA.
- May have a higher affinity for inorganic but lower for organic Hg than DMSA.

Chelating Agents, overview cont'd

- Deferoxamine or DFO
- Iron chelator which also can complex with aluminum and other trivalent metal ions.
- Given SQ, IM or IV.
- Iron removal enhanced by vitamin C.

Chelating Agents, overview cont'd

- D-Penicillamine
- Used primarily as a copper chelator in Wilson's disease. It is used orally.
- Also chelates Fe, Hg, Pb, As.
- Has been associated with unexpected and serious renal and hematologic toxicity.

History of Chelation Therapy

- 1913-Alfred Werner received the Nobel Prize in chemistry for describing "complexion chemistry" (metal-ligand complexes).

  1920-Morgan and Drew first defined "chelation": incorporation of a metal ion into a heterocyclic ring.

History of Chelation, cont'd

- 1933-Frederick Berswerth combined formaldehyde and cyanide to form EDTA ("Versene").
- 1945-first patent granted for Versene.
- 1945-BAL first used as treatment for lead toxicity. This was the first "chelation therapy".
- 1947-Rubin and Berswerth explored use of EDTA for chelation (lavender-top tube).

History of Chelation, cont'd

- 1950-When EDTA introduced IV, plasma calcium was chelated, leading to hypocalcemia and urinary excretion of Ca EDTA. (Proceedings of the Society for Experimental Biology and Medicine).
- 1952-Rubin showed that CaEDTA exchanged with lead forming PbEDTA. (Medical Annals District of Columbia).

History of Chelation, cont'd

- 1952-Bessman successfully treated a child with lead poisoning with EDTA. "Experts" claimed "it's not possible". (Medical Annals District of Columbia).
- !950's-Norman E. Clark, the "Father of Chelation Therapy in America" first studied EDTA therapy for ASCVD. (American Journal Of Medical Sciences).

History of Chelation, cont'd

- 1955-Dudley first discovered kidney tubule damage from EDTA treatment (New England Journal of Medicine).
- 1956-Clarke and Mosher-20 angina patients treated with EDTA chelation. Angina and EKG abnormalities improved. (Amer. J Med. Sci. 232: 654-666).
- 1956-Forman reported nephrotoxicity in humans with high-dose EDTA (JAMA).

History of Chelation, cont'd

- 1959-Marvin Seven hosted first symposium on "Metal Binding in Medicine" at Hahnemann Medical College in Philadelphia.
- 1960-Seven hosted the 2nd symposium but died in a car accident in 1961.
- 1960-Clarke and Mosher-283 ASCVD treated over 4 years with EDTA. Showed 87% improvement (Amer. J. Cardiol. 6: 233).

History of Chelation, cont'd

- 1960-Meltzer, Ural and Kitchell: Treated 10 men with ASCVD with EDTA-improvement in 90% with no toxicity (Metal Binding in Medicine).
- 1961-Boyle and Clarke-found EDTA helps scleroderma, rheumatoid arthritis and circulatory disease (Fed. Proceed. 20 (10): 243-252).

History of Chelation, cont'd

- 1961-Meltzer, Kitchell and Palmon-comprehensive evaluation of EDTA toxicology in 81 patients with ASCVD over 2 years. Showed "no danger" (Amer. J. Med. Sci.).
- 1964-Albert Soffer edited monograph: "Chelation Therapy" describing benefits of EDTA in ASCVD.

History of Chelation, cont'd

- 1976-Tamburino: osteoporosis reversed with NaMgEDTA through inc. PTH which increases osteoblastic activity (IRCS Medical Science Library Compendium).
- 1977-Peng: EDTA improves mitochondrial energy production in the ischemic myocardium (J of Molecular and Chemical Cardiol.).

History of Chelation, cont'd

- 1980-Blumer and Reich: EDTA reduced cancer incidence by 90% in 59 patients over 10 years (Environmental International).
- 1980's -1990's: McDonaugh, Rudolph and Cheraskin found improvements in:
  - Cornell Medical Index of "clinical change".
  - fatigue.
  - arterial stenosis.
  - bone density.
  - heart rate and systolic BP.
  - pulmonary function.
  - HbA1c.
  - total cholesterol, HDL.
  - BUN and creatinine.

History of Chelation, cont'd

- 1988-Olszewer and Carter: 2870 patients treated with EDTA-77% of those with CAD and 91% of those with ASCVD markedly improved. (Med. Hypoth. 27:41-49).
- 1990-Olszewer, Sabbag, and Carter: 10 patients with claudication studied double blind, 5 walked significantly better with 1.5 gms EDTA chelation. Code then broken and eventually all patients improved (J Nat. Med. Assoc.).

History of Chelation, cont'd

- 1989-Elmer Cranton edited special protocol edition of the Journal of Advancement in Medicine detailing safe and effective method of administration of EDTA.
- 1993-Chappell and Stahl: meta-analysis of 19 studies with 22,765 patients with ASCVD showed 87% improved (r=0.88) (Journal of Advancement in Medicine).

History of Chelation, cont'd

- 1993-Hancke and Flytlie: Danish study (Journal of Advancement in Medicine) of patients awaiting CABG for CAD or amputation for PAD. 58 out of 65 (89%) cancelled CABG and 24 of 27 (89%) cancelled amputation.
- 1994-Van Rij, et al: double blind, placebo-controlled New Zealand study on 15 PAD patients (Circulation), showed no benefit.

History of Chelation, cont'd

- 1995-Escobar, et al: marked improvement in 76 of 80 patients treated with EDTA for PAD (Surgery and Surgeons).
- 1997-"Zinecard" approved by the FDA (accelerated approval) listed in the 1997 PDR as a "cardioprotective agent". It's described as a cyclic derivative of EDTA and "a potent intracellular chelating agent" and that is "interferes with iron-mediated generation of free radical formation thought to be responsible for cardiomyopathy".

History of Chelation, cont'd

- 1996-Martin Rubin, PhD: Professor Emeritus at Georgetown University School of Medicine, wrote a chapter "Magnesium EDTA Chelation" in textbook Cardiovascular Drug Therapy, Messertli, 2nd Edition, WB Saunders.
- 1998-Stephen Olmstead, MD, cardiologist and Professor of Medicine at University of Washington, School of Medicine, Seattle, wrote a monograph on chelation. He states that: "The preponderance of clinical reports in the medical literature supports claim of medical efficacy for symptomatic angina pectoris, intermittent claudication and critical leg ischemia."

History of Chelation, cont'd

- 1999-J. of the Amer. Col. Of Cardiol. Vol 33, #6, 1999 reported that patients with idiopathic dilated cardiomyopathy have increased concentration of heavy metals in the myocardium compared with skeletal muscle:
  - Mercury 22,000x
  - Antimony 12,000x
  - Gold 11x
  - Chromium 13x
  - Cobalt 4x

  They postulated that "increased trace elements in IDCM may adversely affect mitochondrial activity and myocardial metabolism and worsen cellular function."

History of Chelation, cont'd

- 2003-Environmental Lead Exposure and Progression of Chronic Renal Disease in Patients Without Diabetes. (NEJM 348:345-347) "Blood Pb and Body Pb burden (BLB) was far less than the upper limit of normal range for the general population in the US and Europe".
  - Conclusions:
    - Improved renal function and slowed renal impairment-persisted >two years.
    - Delayed need for dialysis.

History of Chelation, cont'd

- 2003 study conclusions cont'd:
  - Cost for 30 patients in chelation group $3,750/pt vs. $61,000/pt over 3 yrs of dialysis. (analogous to Hancke data).
  - "Chelation therapy likely to be cost-effective".
  - "EDTA at small dose and long intervals...safe for treating chronic renal impairment."
  - "Consider EDTA chelation to treat patients with progressive renal impairment and high-normal BLB."

Political History of Chelation

- To put the political history into perspective, it first must be recognized that chelation therapy, if recognized to be effective, would represent a major threat to the multi-billion dollar bypass and drug industries.
- In the NEJM, 9/22/1977, Braunwald states that: "an industry is being built around this operation (bypass)….This rapidly growing industry is building a momentum and constituency of its own…it will be progressively more difficult and costly to curtail it materially…The financial implications of CABG are profound…the enormous funds already being devoted to this procedure divert support available for other, perhaps more necessary aspects of medical care."

Political History of Chelation, cont'd

- 1961-Albert Soffer, formerly a proponent of chelation, arbitrarily reverses his opinion after appointment as editor of the Journal of Thoracic Diseases.
- 1962-EDTA package insert indication for CVD is removed.
- 1963-Kichell, Palmon, Aytan, and Meltzer, published "a reappraisal" in the American Journal of Cardiology (11:501-506,1963) and arbitrarily reversed their opinion claiming that EDTA "is not a useful clinical tool." (despite an overall improvement of 40% even in their reappraisal).

Political History of Chelation, cont'd

- 1989-Cranton and Frackelton published an appraisal of the Kitchell and Meltzer "reappraisal" questioning why maintenance treatments were not done to preserve initial clear benefits. Their analysis of the study data showed that patients were extremely high risk and were previously refractory to all therapy. Despite this, there was subjective and exercise tolerance improvement in 64% and EKG improvement in 46% after only 20 EDTA infusions.

Political History of Chelation, cont'd

- 1969-Abbott's patent on EDTA expires ending any financial incentive to pursue research on EDTA
- 1976-in EDTA package insert, under "Contraindications", Abbott inserts a line: "EDTA is not indicated for the treatment of generalized arteriosclerosis associated with advancing age.."

Political History of Chelation, cont'd

- 1965-Interestingly, Kitchell, Meltzer and Rutman in the Am. J. Physiol. 208:841-846, 1965, cited beneficial effects of EDTA chelation in CVD and diabetes.
- However, the damage was already done in their earlier article.

History of Chelation, cont'd

- Major blows to chelation include:
  - Death of Dr. Martin Seven.
  - Kitchell and Meltzer's "reappraisal".
  - Expiration of Abbott's patent in 1969.

Political History of Chelation, cont'd

- 1978-Ray Evers won a precedent-setting case in Federal court allowing the "off-label" use of EDTA (and all other drugs). "Congress did not intend the FDA to interfere with medical practice as between the physician and the patient."
- 1980-Robert J. Rogers pursued his case to the Florida Supreme Court which established his right to practice chelation for cardiovascular disease. "It appears that the action of the Board of Medical Examiners…was an arbitrary and unreasonable exercise of the state's police power."

Political History of Chelation, Cont'd

- 1991-J. Sloth-Nielson, Bernadette Guldager, et, al., published in the Amer. J. Surg., the first paper ever to show no benefit from chelation. This was a purported double-blind placebo controlled trial. 50-60% of treated patients improved but due to an unusually high placebo response, they concluded that the data did not support a benefit for EDTA chelation.

Political History of Chelation, cont'd

- 1992-ACAM experts attempted to review the raw data. They found that no Mg was used in the EDTA infusion (even though Sloth-Nielson, et al claimed to use the ACAM protocol). Patients were interviewed and said they had no pain at the needle site (unusual since no Mg or lidocaine used) and also said they grabbed their own bottle and "hooked themselves up" to their hep-lok which they had in from the previous day, without close supervision. Raw data was destroyed by researchers.

Political History of Chelation, cont'd

- 1998-Hancke won his case in the Danish courts for legal hearings against the surgeons who were persecuting him for his 1993 study showing surgery cancellations in the EDTA group.

ACAM's Role in the History of Chelation Therapy

- 1973-The American Academy of Medical Preventics formed in California to help promote the use of EDTA chelation therapy by physicians. Harold Harper, MD-first president.
- 1983-The American Board of Chelation Therapy (subsequently changed to the American Board of Clinical Metal Toxicology) formed. Charles Farr, MD, PhD first chairman.
- 1986-The American Institute of Medical Preventics and the International Chelation Research Foundation granted IND by FDA to study the use of "Disodium EDTA with Magnesium" in the treatment of claudicatory peripheral vascular disease.
- 1986-The American Academy of Medical Preventics name is changed to the American College for Advancement in Medicine (ACAM).
- 1988-the first issue of the Journal of Advancement in Medicine was published. Elmer Cranton, MD was first editor.

ACAM's Role, cont'd

- 1989-The Journal of Advancement in Medicine publishes "A Textbook on EDTA Chelation Therapy, edited by Elmer Cranton, MD (J Adv Med 2(1,2), 1989). It included an article containing the ACAM protocol for safe and effective administration of EDTA.
- 1989-ACAM receives provisional status to offer category one CME credits. Full approval granted by ACCME in 1990.
- Numerous papers published by ACAM members over the years showing safety and effectiveness of EDTA chelation therapy.

ACAM's Role, cont'd

- Also numerous papers published by conventional physicians criticizing chelation therapy. Often these papers seem to have a political overtone.
- 2002- The NIH (National Center for Complementary and Alternative Medicine and the National Heart, Blood and Lung Institute) announced funding ($35 million) for a 5 year, multicenter "Trial to Assess Chelation Therapy" (TACT). The recruitment of subjects is ongoing (as of this writing they are about 100 subjects shy of their recruitment goal).

Lyn Patrick, ND

Heavy metals and cardiovascular disease

Bio

Lyn Patrick ND graduated from Bastyr University in 1984 with a degree in naturopathic medicine and has been in private practice as a licensed naturopathic physician in Tucson, Az. and Durango, Co. specializing in HIV infection, environmental medicine and hepatitis C for the last 20 years. She is currently on the faculty of the postgraduate Certification Course in Environmental Medicine at the Southwest College of Naturopathic Medicine, and is a former faculty member of the Southwest College. A Contributing Editor of Alternative Medicine Review, a Medline-indexed peer reviewed journal, she has published multiple literature reviews and is an author for the Alternative Medicine Review Monograph series. She is also a physician-member of the Hepatitis C Ambassadors Team, a national interdisciplinary team of providers and hepatologists seeking answers to chronic hepatitis C treatment through research in complementary/alternative medicine. She is also an active member of the American Association of Naturopathic Physicians and speaks internationally on the subjects of chronic hepatitis C infection, eating disorders, and environmental medicine. She has been a prior speaker at ACAM.

Lecture Overview

In order to understand the relationship of heavy metal exposure to the etiology and incidence of cardiovascular disease this lecture will address the prevalence of heavy metal exposure in the U.S. and pathophysiology of heavy metals (lead, arsenic, mercury, and cadmium) as it relates to the chemical characteristics of heavy metals affects their absorption, tissue distribution, excretion, and ultimate toxicity. The toxicokinetics, celular pathology, biotransformation, storage and excretion of lead, arsenic, mercury and cadmium will be reviewed as is relevant to the pathophysiology of cardiovascular The lecture will also review current studies that address the epidemiology of heavy metal exposure and cardiovascular events. and discuss Utilizing a Symptoms Survey to identify patients in need of evaluation for heavy metal toxicity.

Contact Information

Durango Natural Medicine
117 CR 250, Suite A
Durango, CO 81301

dr.lynpatrick.nd@gmail.com

American College for Advancement in Medicine
Chelation Therapy Workshop
November 4-5, 2009
Las Vegas, Nevada

Heavy Metals and Cardiovascular Disease

ACAM Fall 2009

Lyn Patrick ND

2003 CERCLA Priority List of Hazardous Substances

These hazardous substances are ranked based on frequency of occurrence at NPL sites, toxicity, and potential for human exposure. Toxicological profiles are developed from a priority list of 275 substances.

http://www.atsdr.cdc.gov/clist.html

2003 CERCLA Priority List of Hazardous Substances

1. arsenic- 1,149/1,684 NPL sites
2. lead-1,272/1,684 NPL sites
3. mercury- 714/1,467 NPL sites
7. cadmium- 776/1,467 sites
17. chromium (hexavalent)- 1,036/1,591 NPL sites

Recognition of Heavy Metal Exposure

"Much about metals toxicity, such as the genetic factors that may render some individuals especially vulnerable to metals toxicity, remains a subject of intense investigation."

"It is possible that low-level metals exposure contributes much more towards the causation of chronic disease and impaired functioning than previously thought."

Recognition of Heavy Metal Exposure

"Chronic exposure to metals at a high enough level to cause chronic toxicity effects (such as hypertension in individuals exposed to lead and renal toxicity in cadmium exposure) can also occur in individuals who have no symptoms."

Howard Hu MD MPH

Harvard School of Environmental and Occupational Health

NOEL
No Observable Effect Level ?

Lead is unique as a toxicant in that there is agreement among:

- Centers for Disease Control (CDC)
- Agency for Toxic Substances and Disease Registry
- Environmental Protection Agency:

"There is no toxic threshold for lead. This means there is no measurable level of lead in the body below which no harm occurs."

Lead and Vascular Disease

- Lead exposure is associated with an increased incidence of:
- Coronary heart disease
- Stroke
- Peripheral arterial disease
- Left ventricular hypertrophy
- Arrythmias
- Hypertension

Environ Health Perspect 2007;15:472-482.

Lead and Hypertension in Pre- and Postmenopausal Women

- "At blood levels 4.0-31.1 µg/dL there is a positive association between both systolic and diastolic blood pressure and risks of both systolic and diastolic hypertension among women aged 40-59."

- JAMA 2003;289:1523-32.

Risk for Cardiovascular Disease Mortality Based on Blood Lead Levels

- Data from NHANES 1988-1994:
- 13,946 adults followed for up to 12 years- all had blood lead levels under 10 mcg/dL
- Mean blood lead for all participants was 2.58 mcg/dL
- Prevalence of reduced GFR, hx CVD, mean total cholesterol, HTN all increased with increasing blood lead levels.
- Postmenopausal women had higher mean blood lead levels than those who were not postmenopausal.

- Circulation 2006;114:1388-1394.

Risk for Cardiovascular Disease Mortality Based on Blood Lead Levels

- Blood lead levels were associated with increased all-cause mortality.(highest vs. lowest tertile HR 1.25)
- Hazard Ratio for highest to lowest tertile:

CVD mortality: 1.55

MI mortality: 1.89

Stroke mortality: 2.51

Risk for Cardiovascular Disease Mortality Based on Blood Lead Levels

- Increase in all-cause and cardiovascular deaths was evident at blood lead levels over 2.0 mcg/dL.
- 38% of US adults from 1999-2000 NHANES had lead levels above 2.0 mcg/dL
- Association of CVD mortality and blood lead persisted after adjusting for estimated GFR and hypertension, and C reactive protein- indicating that there may be other mechanisms involved.
- There was no evidence of increased cancer mortality at these ranges of exposure.

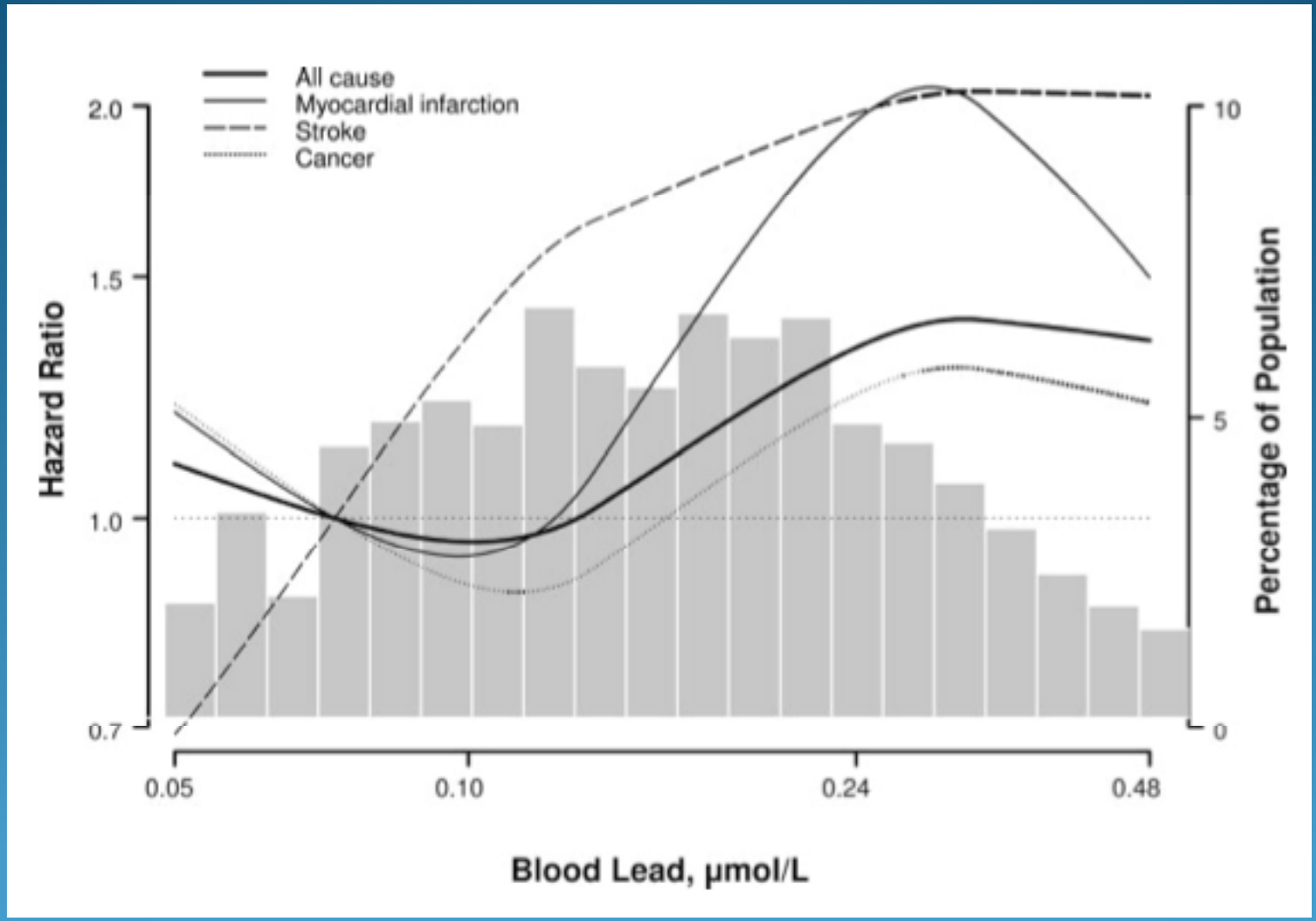
TABLE 2. Hazard Ratios (95% CIs) of All-Cause, Cardiovascular Disease, Myocardial Infarction, Stroke, and Cancer Mortality Associated With Tertile of Lead

	Tertile 1 (<0.09 μmol/L or <1.93 μg/dL)	Tertile 2 (0.09–0.17 μmol/L or 1.94–3.62 μg/dL)	Tertile 3 (≥0.18 μmol/L or ≥3.63 μg/dL)	P_{trend}
All-cause mortality, n	252	470	939	
Age, race-ethnicity, and sex adjusted	1.00	0.97 (0.76–1.23)	1.37 (1.15–1.64)	<0.001
Multivariable 1 adjusted*	1.00	0.93 (0.73–1.19)	1.30 (1.08–1.56)	<0.001
Multivariable 2 adjusted†	1.00	0.91 (0.72–1.15)	1.25 (1.04–1.51)	0.002
Cardiovascular disease mortality, n	104	219	443	
Age, race-ethnicity, and sex adjusted	1.00	1.01 (0.68–1.51)	1.51 (1.07–2.14)	0.004
Multivariable 1 adjusted*	1.00	1.06 (0.70–1.60)	1.64 (1.14–2.35)	0.001
Multivariable 2 adjusted†	1.00	1.03 (0.69–1.55)	1.55 (1.08–2.24)	0.003
Myocardial infarction mortality, n	50	83	234	
Age, race-ethnicity, sex adjusted	1.00	0.99 (0.55–1.79)	1.70 (0.99–2.90)	0.011
Multivariable 1 adjusted*	1.00	1.05 (0.56–1.97)	2.01 (1.12–3.61)	0.003
Multivariable 2 adjusted†	1.00	1.02 (0.55–1.89)	1.89 (1.04–3.43)	0.007
Stroke mortality, n	22	56	63	
Age, race-ethnicity, sex adjusted	1.00	1.89 (0.80–4.48)	2.04 (1.13–3.67)	0.017
Multivariable 1 adjusted*	1.00	2.23 (0.89–5.60)	2.61 (1.24–5.49)	0.013
Multivariable 2 adjusted†	1.00	2.19 (0.87–5.53)	2.51 (1.20–5.26)	0.017
Cancer mortality, n	67	106	238	
Age, race-ethnicity, sex adjusted	1.00	0.78 (0.50–1.22)	1.28 (0.96–1.71)	0.010
Multivariable 1 adjusted*	1.00	0.72 (0.46–1.13)	1.08 (0.81–1.45)	0.130
Multivariable 2 adjusted†	1.00	0.72 (0.46–1.12)	1.10 (0.82–1.47)	0.101

*Adjustment included age, race-ethnicity, sex, diabetes mellitus, body mass index, current or former smoking, alcohol consumption, physical activity, low income, CRP, total cholesterol, high school education, urban residence, and postmenopausal status.

†Adjustment includes variables in model 1, hypertension, and level of kidney function.

Sample sizes (n) refer to the number of events.


All cause
Myocardial infarction
Stroke
Cancer
Hazard Ratio
2.0
1.5
1.0
0.7
Percentage of Population
10
5
0
0.05
0.10
0.24
0.48
Blood Lead, µmol/L

Research | Mini-Monograph

Lead Exposure and Cardiovascular Disease—A Systematic Review

Ana Navas-Acien,[1] Eliseo Guallar,[2,3] Ellen K. Silbergeld,[1] and Stephen J. Rothenberg[4,5]

[1]Department of Environmental Health Sciences, and [2]Departments of Epidemiology and Medicine, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [3]Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, Maryland, USA; [4]Centro de Investigación y de Estudios Avanzados – Instituto Politécnico Nacional (CINVESTAV-IPN), Mérida, Yucatán, México; [5]Instituto Nacional de Salud Pública, Cuernavaca, Morelos, México

CONCLUSIONS: We conclude that the evidence is sufficient to infer a causal relationship of lead exposure with hypertension. We conclude that the evidence is suggestive but not sufficient to infer a causal relationship of lead exposure with clinical cardiovascular outcomes. There is also suggestive but insufficient evidence to infer a causal relationship of lead exposure with heart rate variability.

PUBLIC HEALTH IMPLICATIONS: These findings have immediate public health implications. Current occupational safety standards for blood lead must be lowered and a criterion for screening elevated lead exposure needs to be established in adults. Risk assessment and economic analyses of lead exposure impact must include the cardiovascular effects of lead. Finally, regulatory and public health interventions must be developed and implemented to further prevent and reduce lead exposure.

KEY WORDS: atherosclerosis, blood pressure, cardiovascular disease, heart rate variability, hypertension, lead, systematic review. *Environ Health Perspect* 115:472–482 (2007). doi:10.1289/ehp.9785 available via *http://dx.doi.org/* [Online 22 December 2006]

Conclusions of Meta-Analysis

1. Sufficient evidence to infer a causal relationship between lead exposure and hypertension.
2. Cross-sectional studies suggest an association between increased lead exposure and decreased heart rate variability possibly via interference with autonomic regulation at levels lower than 5 mcg/dL.
3. "....the cardiovascular endpoints described above plus the substantial evidence that chronic lead exposure affects cognitive function and renal function at levels

   < 5 mcg/dL indicate that the CDC criterion for elevated blood levels in children 10 mcg/dL is too high for adults."

Environ Health Perspect 2007;15:472-482.

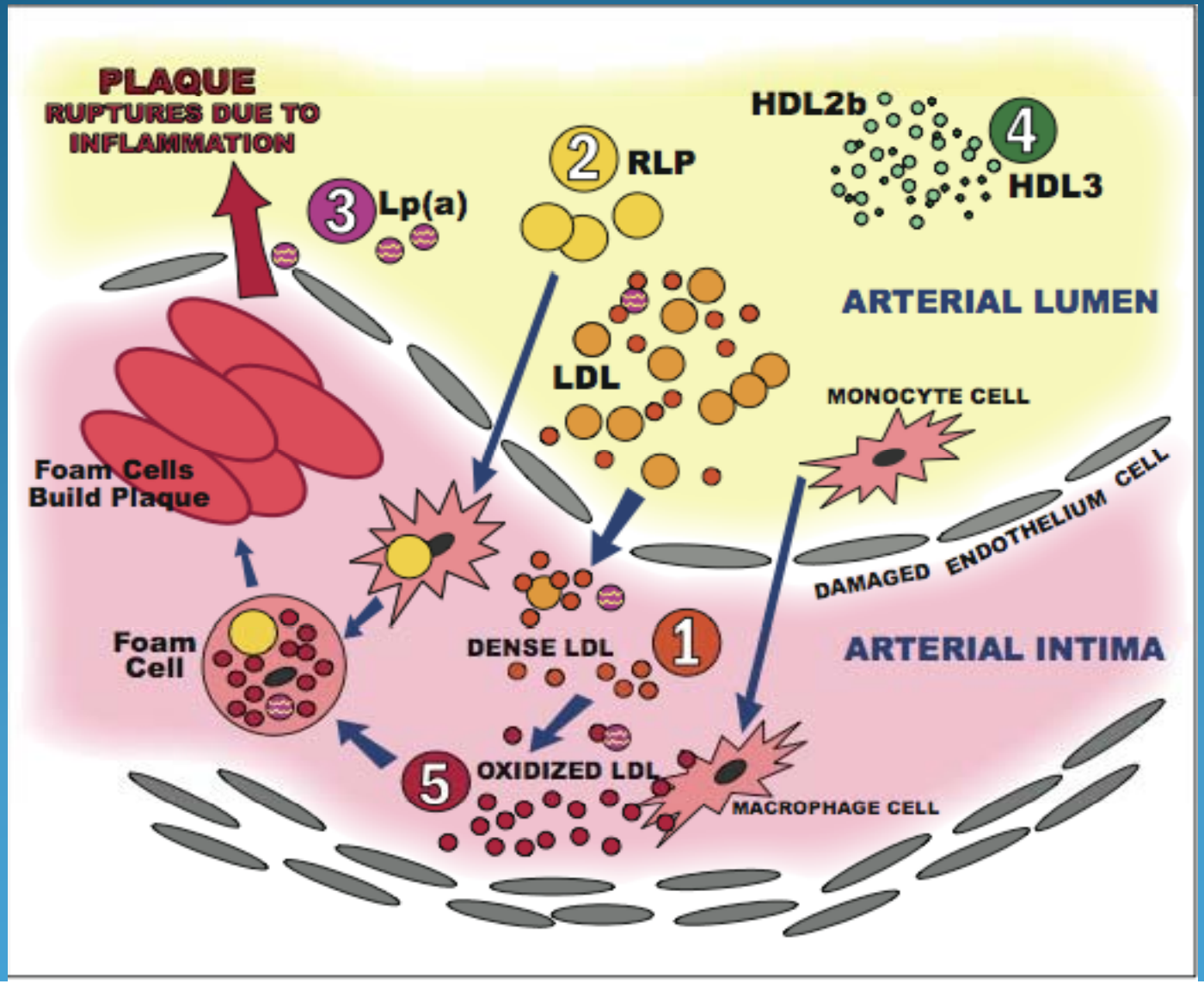
Mechanisms of Lead Toxicity

- Stimulation of renin-angiotensin system
- Down-regulation of nitric oxide and soluble guanylate cyclase
- Decreased glomerular filtration
- Increased oxidative stress
- Autonomic dysregulation affecting heart rate variability
- Endothelial inflammation-smooth muscle cell proliferation
- Endothelial dysfunction

- Environ Health Perspect 2007; 115;472-482.

Atherosclerotic Plaque Formation

slide courtesy of SpectraCell Laboratory



Environmental Lead Exposure and Progression of Chronic Renal Diseases in Patients without Diabetes

- 202 patients with chronic renal insufficiency (indicated by a serum creatinine level between 1.5-3.9 mg/dL) who had a normal total-body lead burden and no history of exposure to lead were observed for 24 months.
- The primary end point (need for hemodialysis or an increase of 1.5x baseline serum creatinine) occurred in 24 patients during the observation period; serum creatinine levels and body lead burden at base line were the most important risk factors.
- NEJM 2003;348:277-286.

Mechanisms of Lead Toxicity

- The two important enzymes that lead inactivates:
- delta- aminolevulinic acid dehydrogenase (ALAD)
- glutathione reductase (GR) – has been demonstrated to be depressed in both animal and human lead-exposure studies.

Figure 1. Inhibition of ALAD Results in Elevated ALA

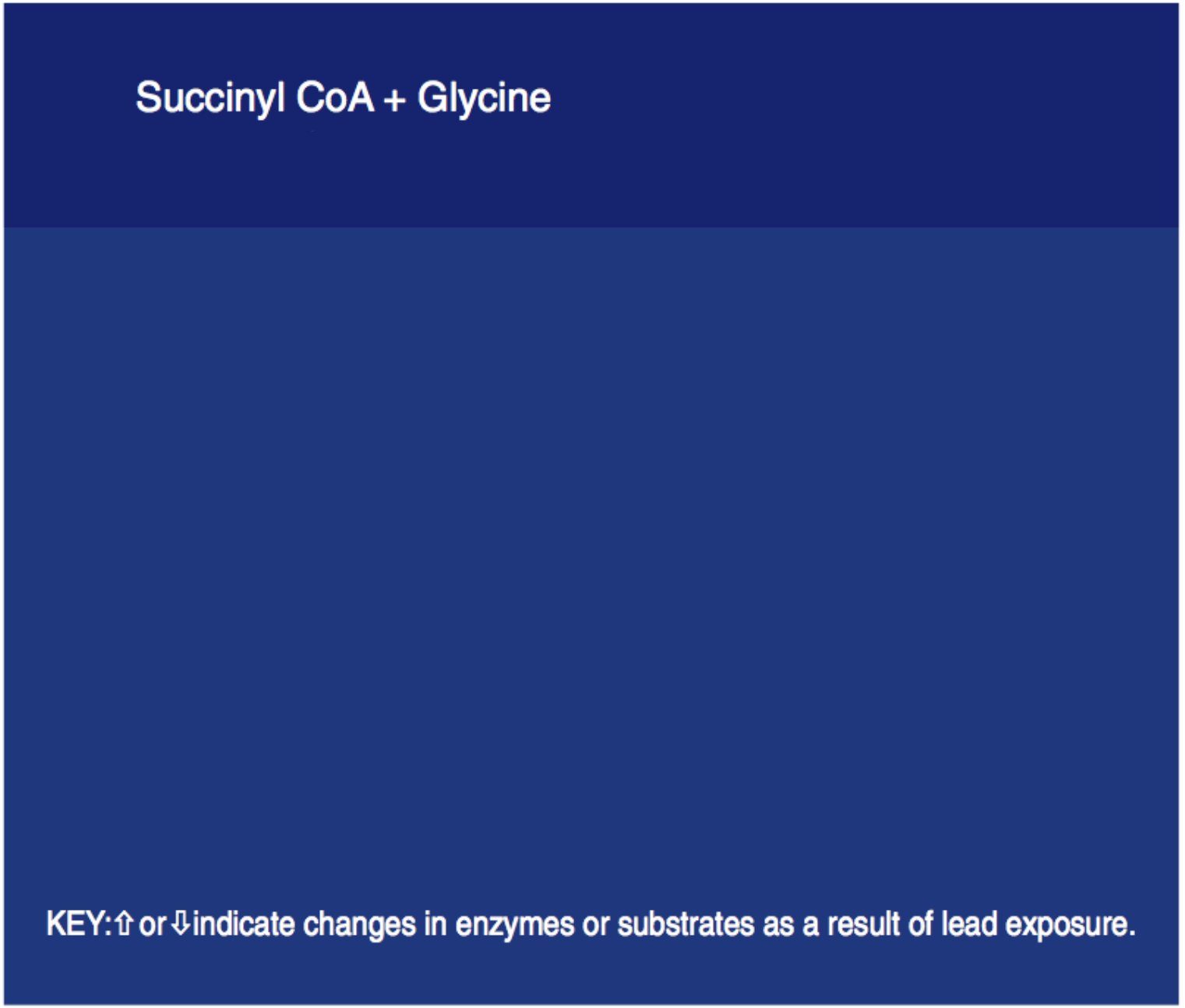


Figure 1. Inhibition of ALAD Results in Elevated ALA

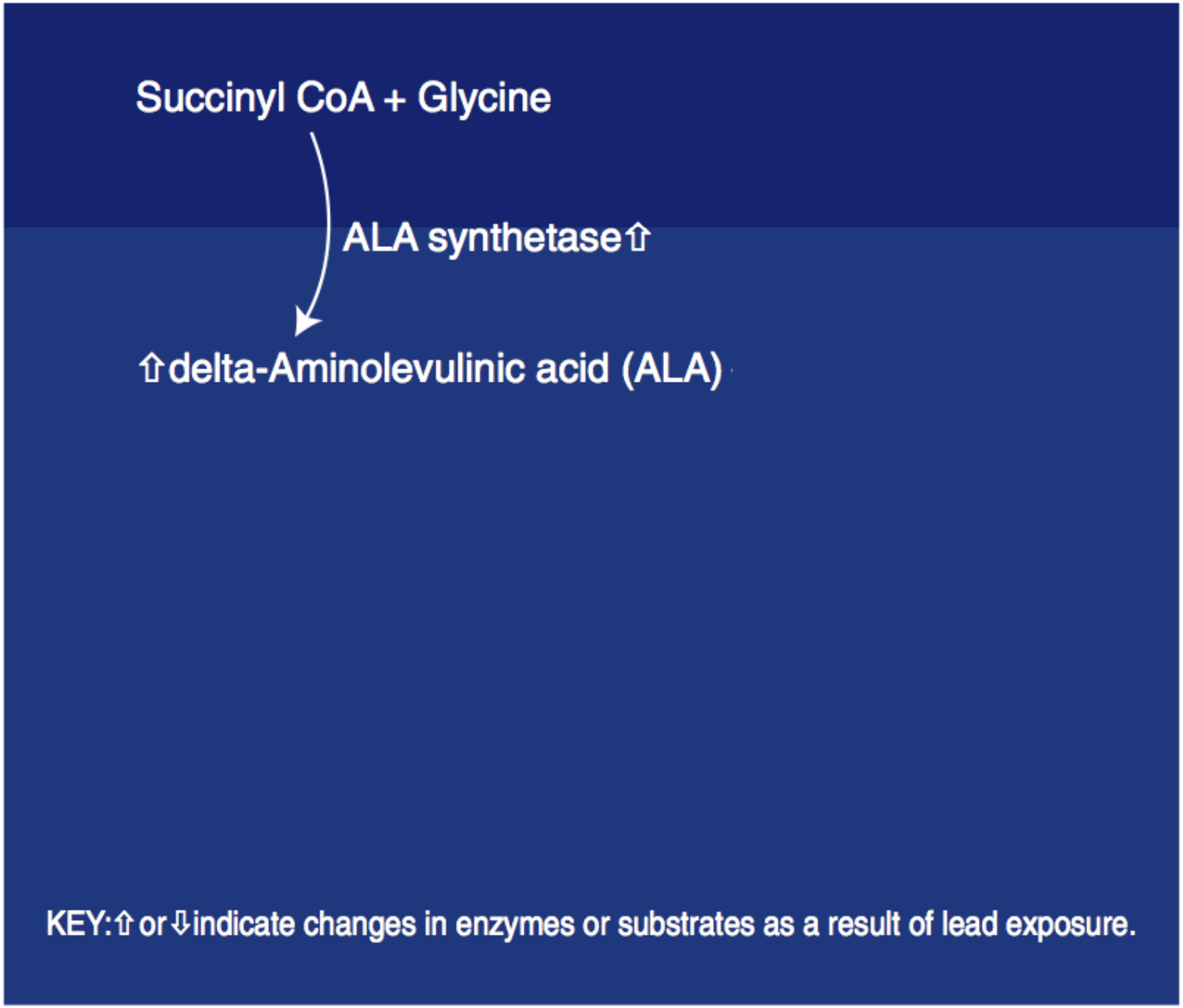


Figure 1. Inhibition of ALAD Results in Elevated ALA

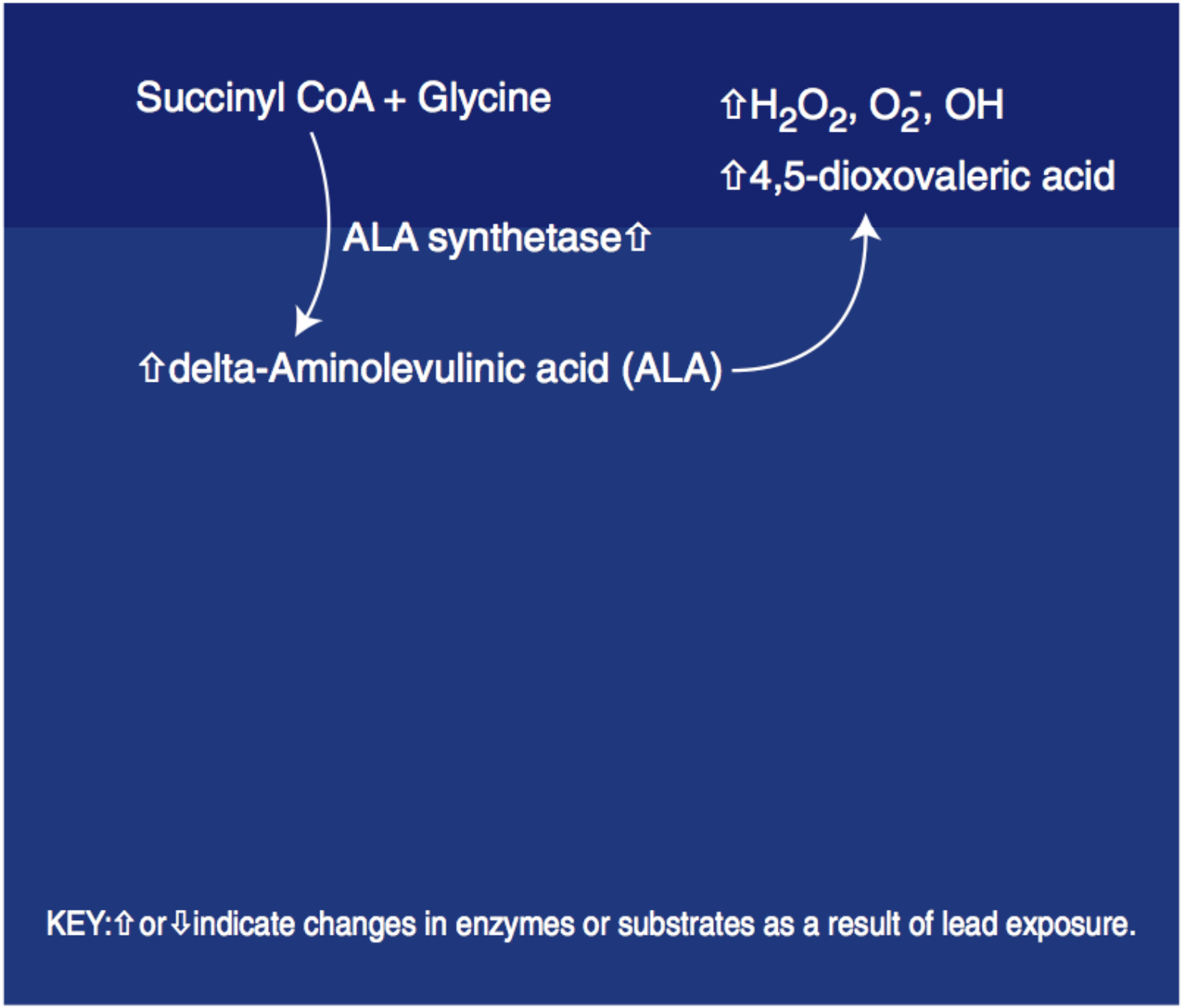


Figure 1. Inhibition of ALAD Results in Elevated ALA

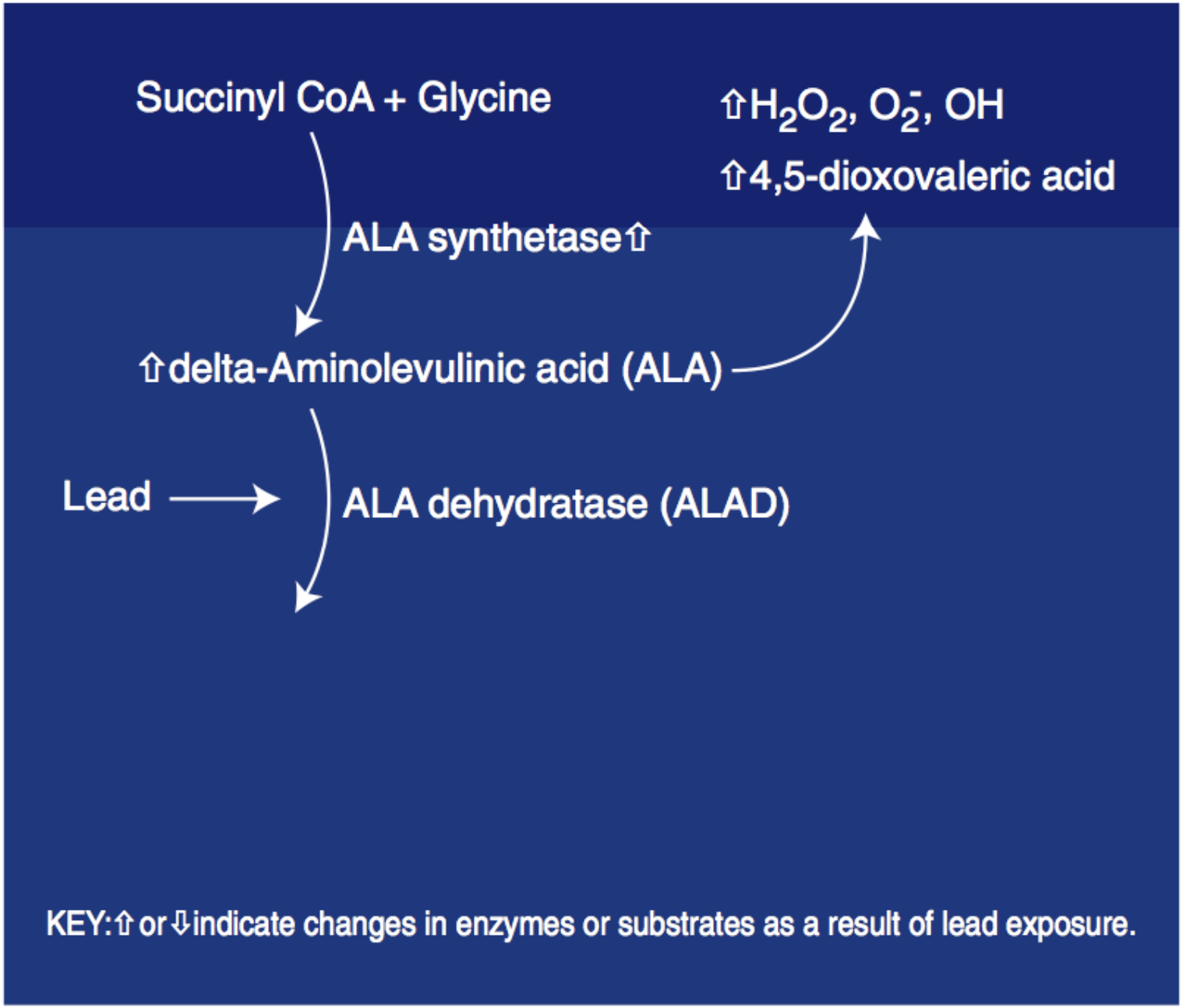


Figure 1. Inhibition of ALAD Results in Elevated ALA

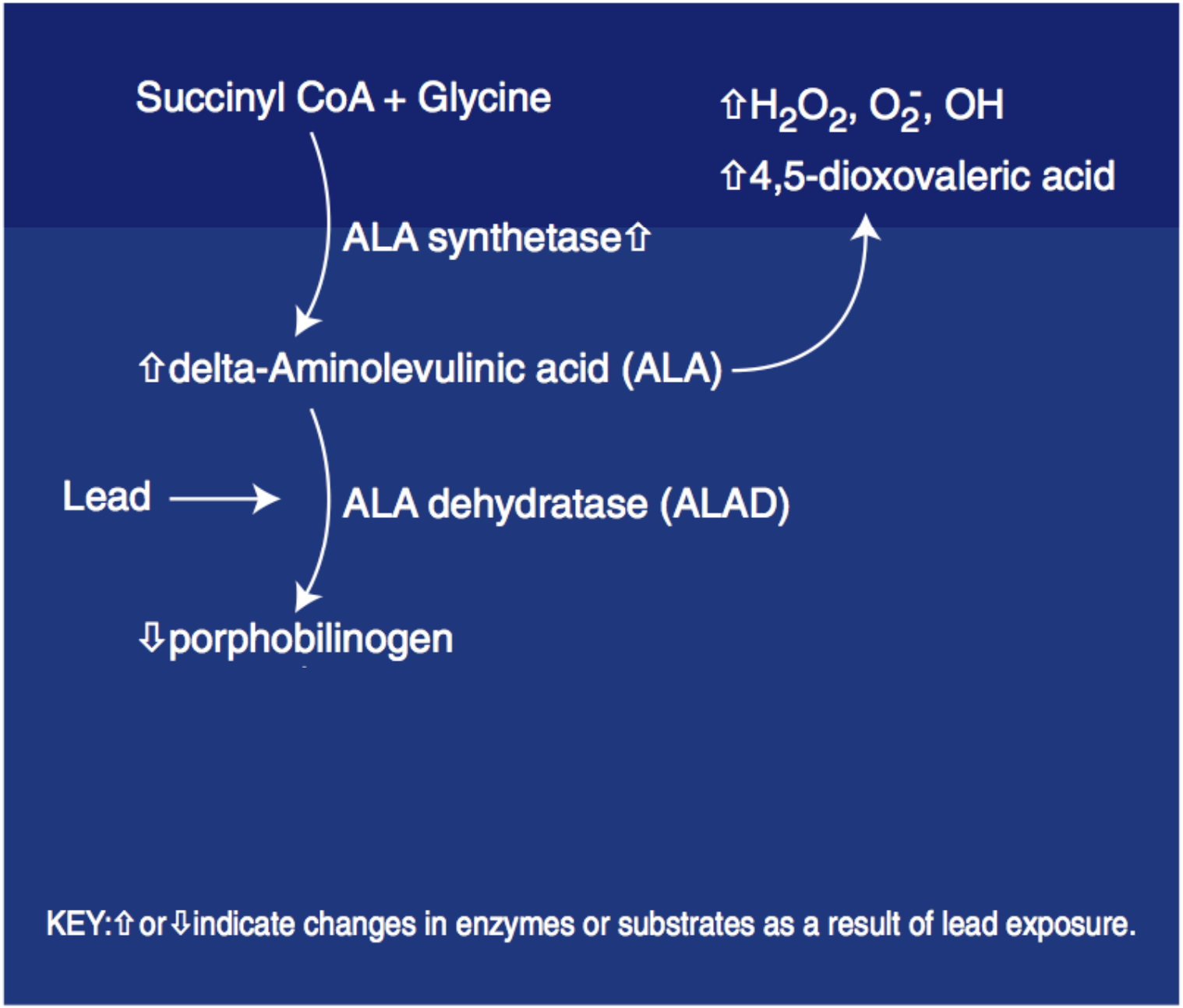


Figure 1. Inhibition of ALAD Results in Elevated ALA

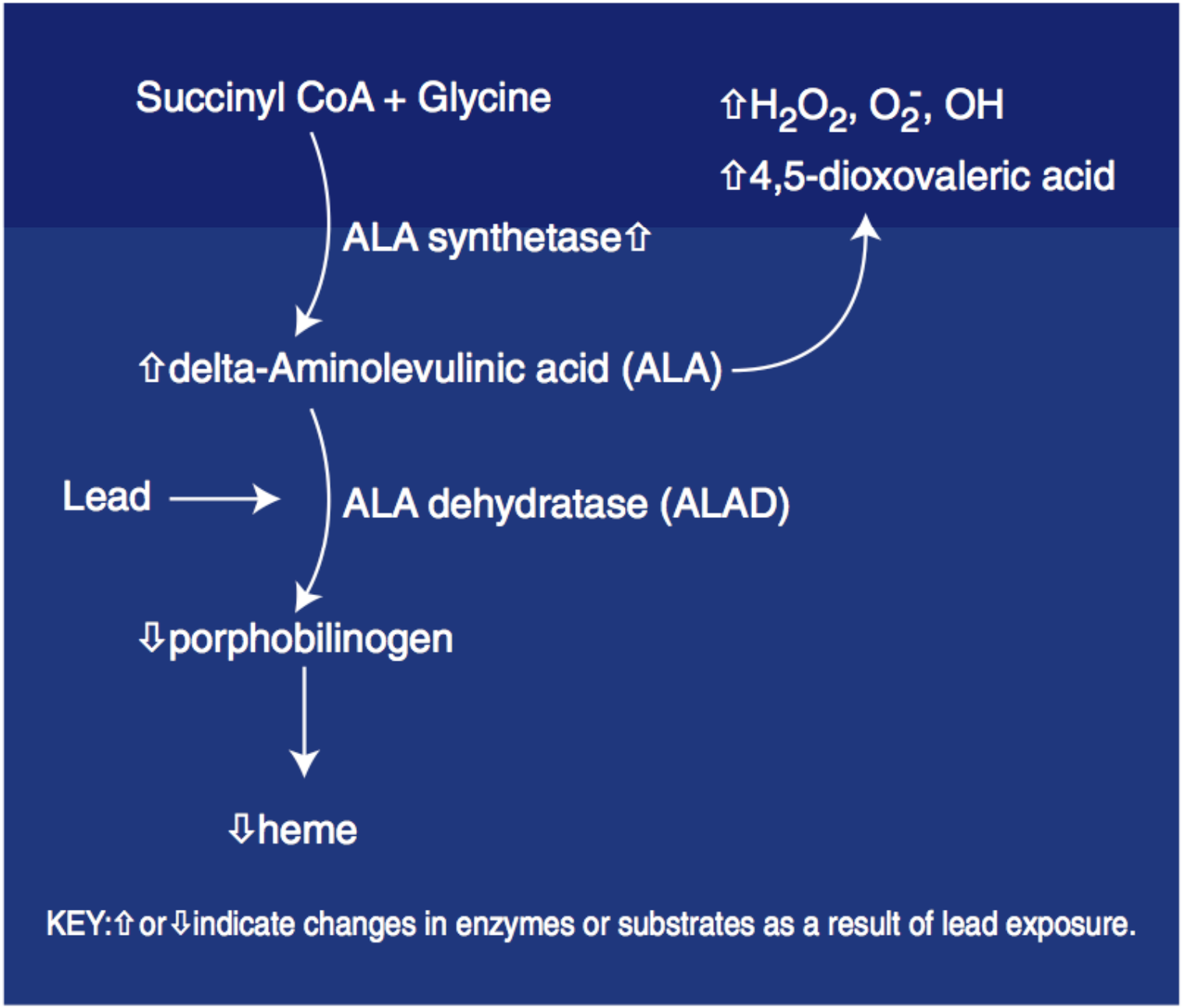
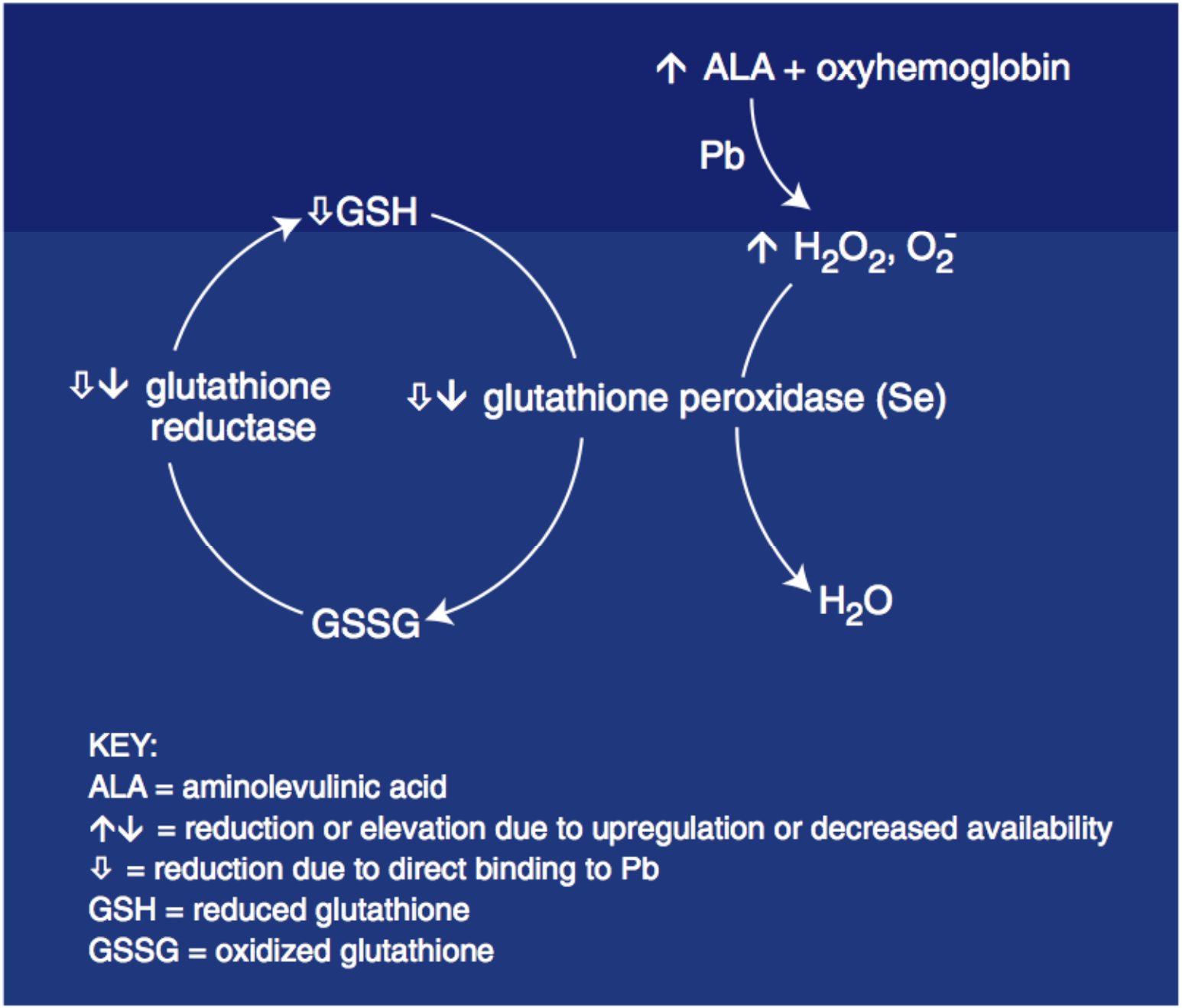


Figure 2. Effect of Lead on Glutathione Metabolism



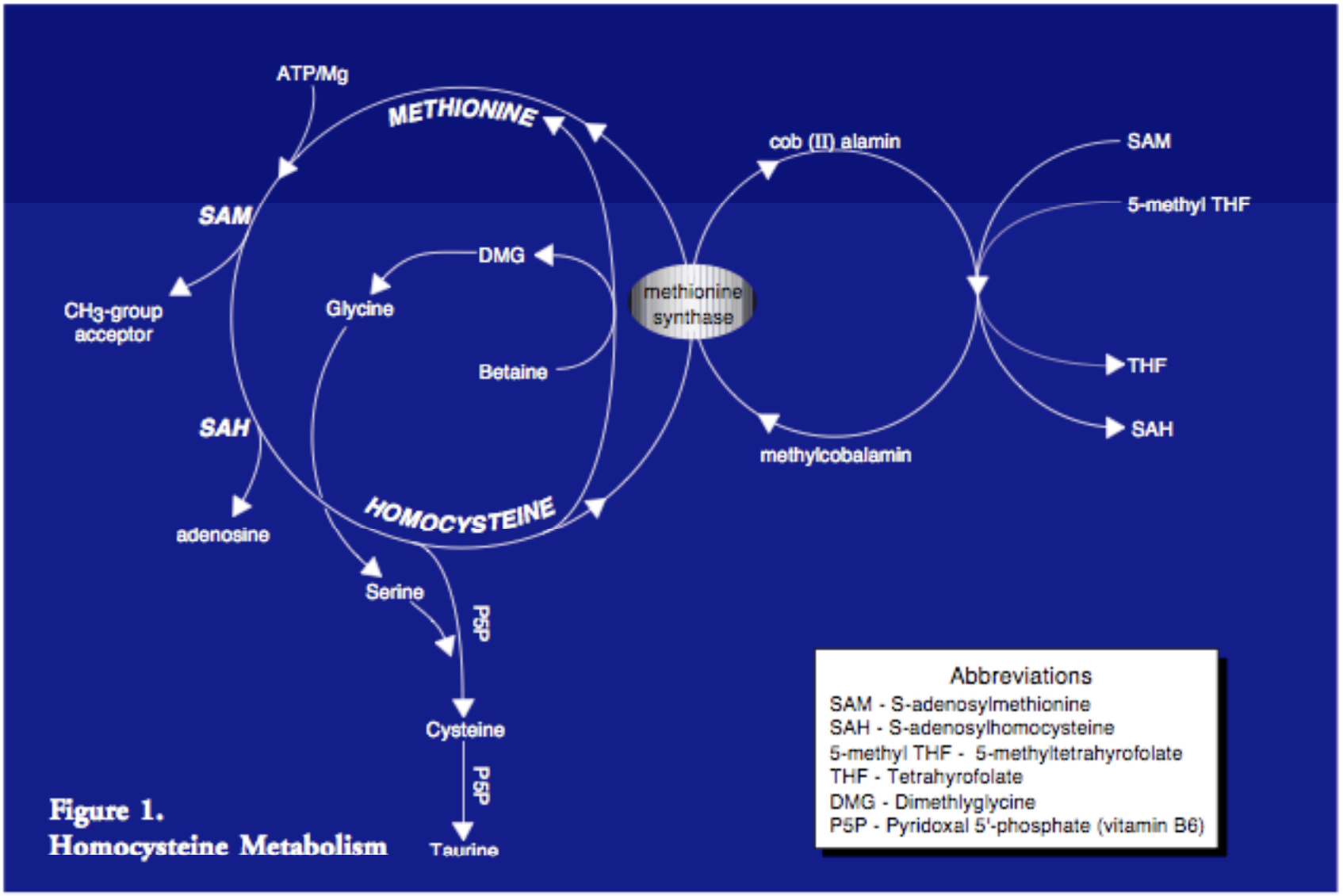


Figure 1.
Homocysteine Metabolism

Lead and Homocysteine

- Lead and homocysteine are both positively associated with cardiovascular disease and cognitive dysfunction.
- In the Baltimore Memory Study, data from a longitudinal study of 1,140 randomly selected residents in Baltimore, Maryland (50–70 years of age) showed a significant correlation between blood (but not tibial) lead and serum homocysteine levels.
- Environ Health Perspect 113:31–35 (2005).

Lead and Homocysteine

After adjustment for age, sex, race/ethnicity, educational level, tobacco and alcohol consumption, and body mass index using multiple linear regression:

Homocysteine levels ↑ 0.35 µmol/L per 1.0 µg/dL ↑ blood lead ($p < 0.01$).

How Significant is Homocysteine as a Predictive Factor?

- A meta-analysis of 20 prospective studies found that for an increase in serum homocysteine of 5 μmol/L, the OR for ischemic heart disease was increased (OR=1.32; 95% CI, 1.19–1.45), as was the OR for stroke (OR = 1.59; 95% CI)

- Br Med J 325:1202–1206.

Table 2. Demographic characteristics of study subjects by homocysteine quartiles, Baltimore Memory Study, 2001–2002.

Characteristic	Homocysteine quartile				*p*-Value[a]
	Quartile 1 (*n* = 245)	Quartile 2 (*n* = 269)	Quartile 3 (*n* = 259)	Quartile 4 (*n* = 264)	
Homocysteine [mean (range) μmol/L]	6.6 (4.4–7.5)	8.3 (7.6–9.0)	10.0 (9.1–11.2)	15.0 (11.3–48.6)	
Blood lead level [mean ± SD (μg/dL)]	2.8 ± 1.6	3.2 ± 2.4	3.7 ± 2.1	4.4 ± 2.8	< 0.001
Age [mean ± SD (years)]	57.9 ± 5.5	59.1 ± 5.8	60.0 ± 6.0	60.3 ± 6.2	< 0.001
Sex (% female)	87.8	69.1	59.5	48.9	< 0.001
Race/ethnicity (%)					0.001
Non-Hispanic black/African American	39.2	36.1	42.9	47.4	
Non-Hispanic white or white/Native American	51.8	62.4	53.6	47.3	
African American/mixed race/ethnicity	5.7	0.4	2.7	2.3	
Asian, Hawaiian, Native American or other	3.3	1.1	0.8	3.0	
BMI [mean ± SD (kg/m^2)]	29.2 ± 6.6	29.6 ± 7.0	30.2 ± 6.8	30.2 ± 7.0	0.27
Current cigarette use (%)					0.001
None	84.5	85.1	79.1	70.8	
< Half pack per day	6.1	4.5	4.2	7.6	
Half pack to less than 1 pack per day	5.3	5.6	9.7	9.9	
≥ 1 pack per day	4.1	4.8	7.0	11.7	
Alcoholic beverage use (%)					0.007
None	44.5	39.0	40.9	38.3	
< 4 per month	15.9	15.6	14.7	14.0	
4–8 per month	18.0	13.0	12.0	8.7	
> 8 per month	21.6	32.4	32.4	39.0	

Hyperhomocysteinemia

- Lead-induced enzyme inhibition leads to increased production of homocysteine
- Homocysteine causes increased intra-vascular binding of lead
- Homocysteine stimulates production of chemokines that lead to plaque formation

Peripheral Artery Disease

- Approximately 25% of all patients with symptomatic PAD will die within 2 years.
- Established PAD patients are at a 4x greater risk of fatal MI or other CHD death and at a 2x-3x greater risk of stroke.
- Patients with symptomatic PAD face up to a 15x greater risk of death from CVD, including MI and stroke.
- Symptomatic peripheral arterial disease (PAD) affects up to 5 million patients in the United States more than breast cancer, AIDS, and prostate cancer combined.

Lead, Cadmium, Homocysteine, and Peripheral Arterial Disease

- In the general population(4,447 subjects over 40)
- Homocysteine elevation = almost 2x higher risk for PAD
- This association can be completely explained by: blood lead, urinary cadmium, smoking, and impaired renal function.

- Am J Epidemiol 2006;163:700-708.

Homocysteine and Peripheral Arterial Disease

- In observational studies, elevated homocysteine levels are associated with peripheral arterial disease often more strongly than with other cardiovascular disease endpoints.
- Randomized trials have shown no effect of homocysteine-lowering interventions on cardiovascular outcomes.

Lead, Cadmium and PAD

- “ In this context, our findings indicate that the homocysteine elevations observed among PAD cases were more likely to be a consequence of their association with lead and cadmium exposure, impaired renal function, and smoking rather than a cause of PAD. “

Cadmium

- Urinary Cd .5-2.0 µg/g creatinine (found in 50% of Swedish cohort) indicated early renal damage
- Urinary Cd of 2.5 µg/g creatinine:
  4-fold higher risk of tubular damage

CDC NHANES Data

Alt Med Rev 2009;14(1):3-13.

Metal	Sample	Mean	50th%	75th%	90th%	95th%
Cadmium	Blood µg/L	0.412	0.300	0.400	0.900	1.30
Cadmium	Urine µg/L	0.210	0.229	0.458	0.839	1.20
Cadmium	Urine µg/g cr	0.199	0.212	0.404	0.690	0.917
Lead	Blood µg/dL	1.45	1.40	2.20	3.40	4.40
Lead	Urine µg/L	0.677	0.600	1.20	2.00	2.60
Lead	Urine µg/g cr	0.639	0.634	1.03	1.52	2.03
Mercury	Blood µg/L	0.318	0.300	0.700	1.20	1.90
Mercury	Urine µg/L	0.606	0.580	1.37	2.91	3.99
Mercury	Urine µg/g cr	0.620	0.650	1.27	2.30	3.00

cr = creatinine

Association of Urinary Cadmium and MI

- 4912 participants 45–79 years of age in the (1988–1994) NHANES III.
- Framingham risk score, pack-years of smoking, race-ethnicity, and family history of heart attack, and diabetes as covariates.

- Environ Res 2008;106:284-286.

Association of Urinary Cadmium and MI

- Urinary cadmium 0.88 mcg/g creatinine (both genders) = OR 1.86 for MI
- Women- 1.80 x more likely to have MI
- Men- 1.26 x more likely to have MI

Cadmium and Hypertension

- CONCLUSIONS: “Cadmium levels in blood, but not in urine, were associated with a modest elevation in blood pressure levels.
- Our findings add to the concern of renal and cardiovascular cadmium toxicity at chronic low levels of exposure in the general population.”

- Environ Health Perspect 116:51–56 (2008).

Arsenic

- In the United States, approximately 13 million individuals live in areas with a concentration of inorganic arsenic in the public water supply that exceeds 10 μg/L, which is the US Environmental Protection Agency's standard for arsenic concentration in public water systems.

- EPA Fed Regist . 2001; 66(14) : 6976-7066.

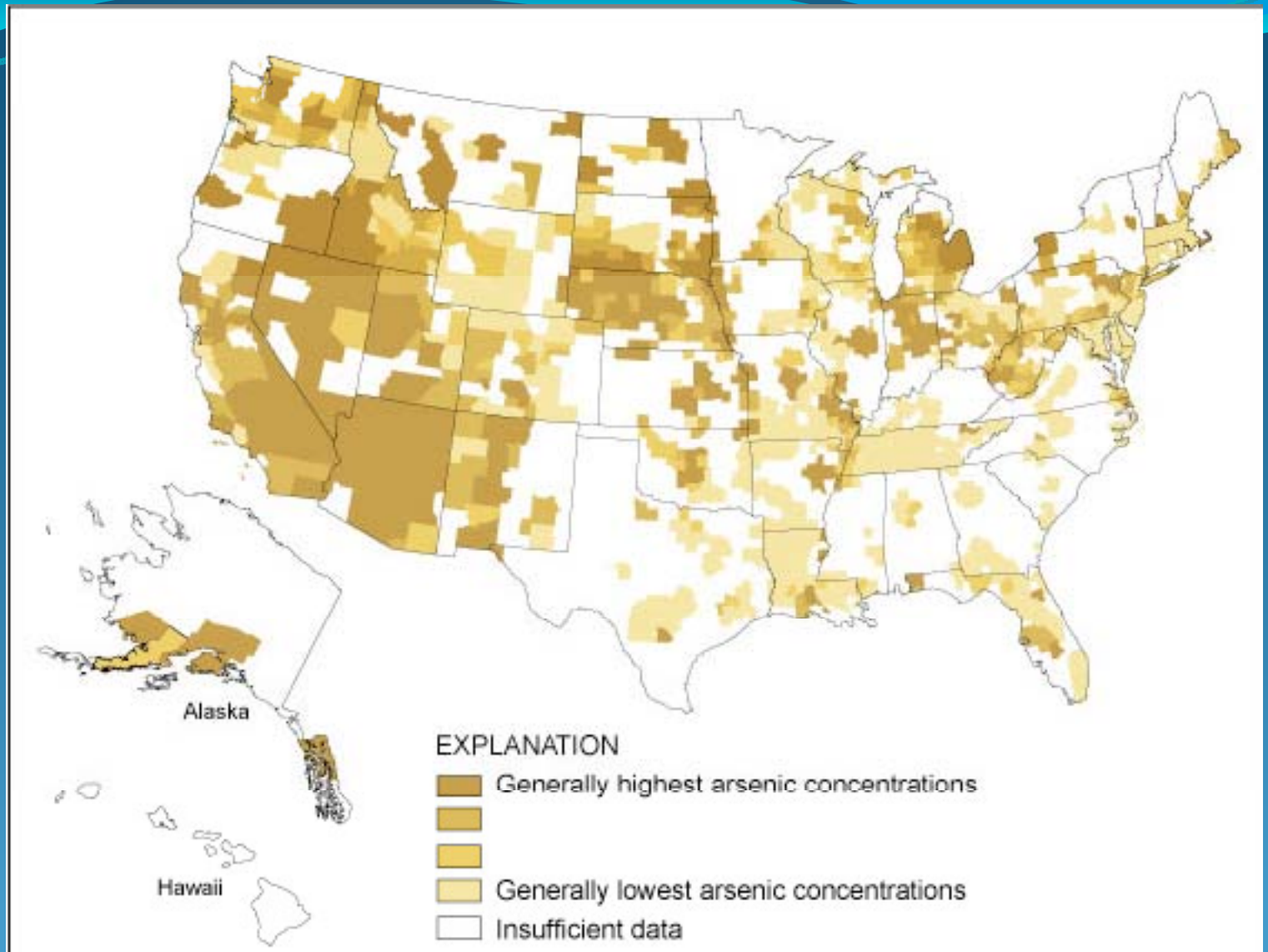


Figure 3. *Counties with arsenic concentrations exceeding possible new MCLs in 10 percent or more of ground-water samples.*

Context High chronic exposure to inorganic arsenic in drinking water has been related to diabetes development, but the effect of exposure to low to moderate levels of inorganic arsenic on diabetes risk is unknown. In contrast, arsenobetaine, an organic arsenic compound derived from seafood intake, is considered nontoxic.

Objective To investigate the association of arsenic exposure, as measured in urine, with the prevalence of type 2 diabetes in a representative sample of US adults.

Design, Setting, and Participants Cross-sectional study in 788 adults aged 20 years or older who participated in the 2003-2004 National Health and Nutrition Examination Survey (NHANES) and had urine arsenic determinations.

Main Outcome Measure Prevalence of type 2 diabetes across intake of arsenic.

Results The median urine levels of total arsenic, dimethylarsinate, and arsenobetaine were 7.1, 3.0, and 0.9 μg/L, respectively. The prevalence of type 2 diabetes was 7.7%. After adjustment for diabetes risk factors and markers of seafood intake, participants with type 2 diabetes had a 26% higher level of total arsenic (95% confidence interval [CI], 2.0%-56.0%) and a nonsignificant 10% higher level of dimethylarsinate (95% CI, –8.0% to 33.0%) than participants without type 2 diabetes, and levels of arsenobetaine were similar to those of participants without type 2 diabetes. After similar adjustment, the odds ratios for type 2 diabetes comparing participants at the 80th vs the 20th percentiles were 3.58 for the level of total arsenic (95% CI, 1.18-10.83), 1.57 for dimethylarsinate (95% CI, 0.89-2.76), and 0.69 for arsenobetaine (95% CI, 0.33-1.48).

Conclusions After adjustment for biomarkers of seafood intake, total urine arsenic was associated with increased prevalence of type 2 diabetes. This finding supports the hypothesis that low levels of exposure to inorganic arsenic in drinking water, a widespread exposure worldwide, may play a role in diabetes prevalence. Prospective studies in populations exposed to a range of inorganic arsenic levels are needed to establish whether this association is causal.

JAMA. 2008;300(7):814-822 www.jama.com

Arsenic Intake

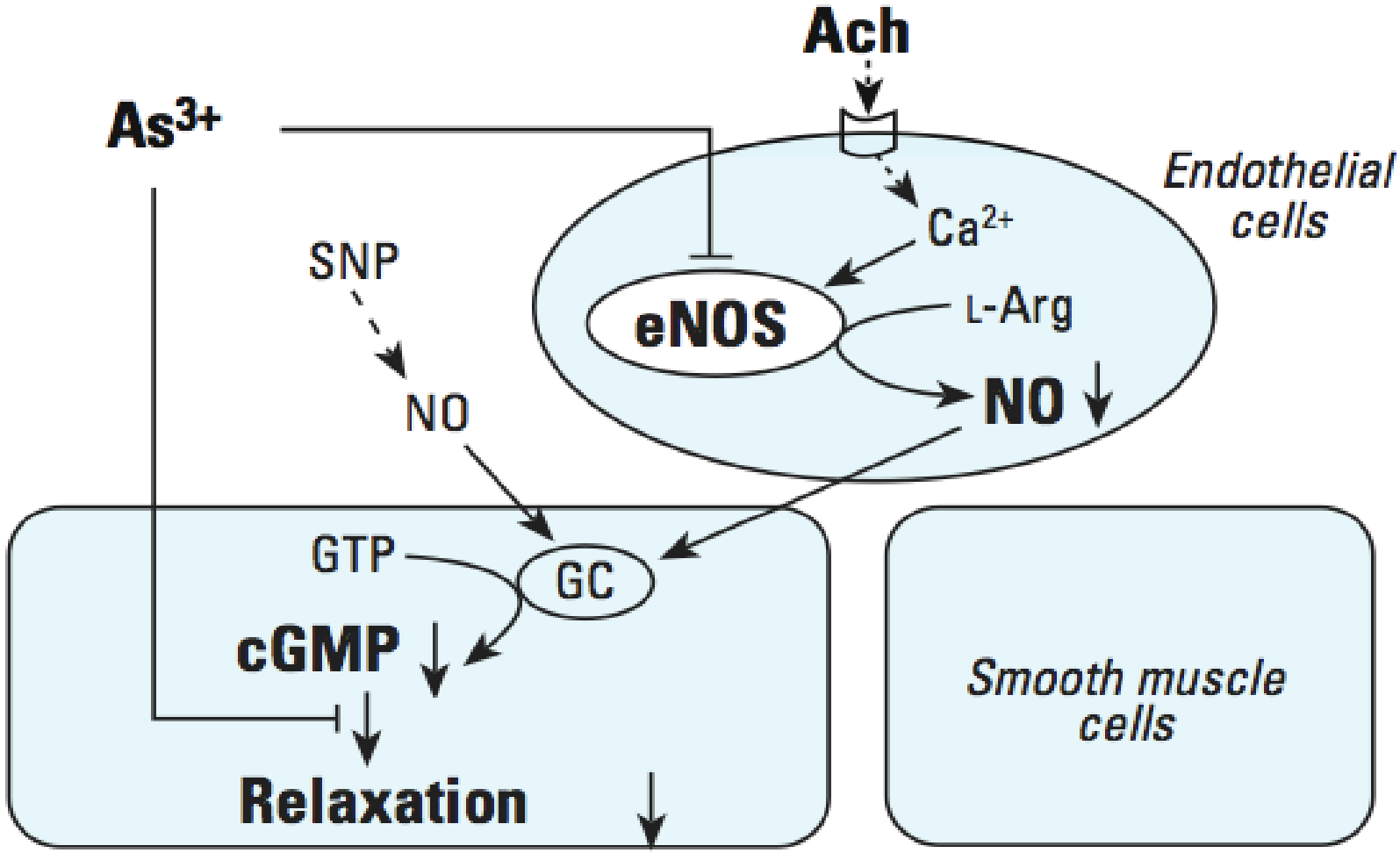
- EPA MRL (minimum risk level) for arsenic exposure via ingestion = .1-.8 µg/kg/day

  (7.0 – 56.0 µg for an adult)
- Average daily dietary intake of arsenic by adults in the United States is 11 to 14 µg/day
- Meat, fish, and poultry account for 80% of dietary arsenic intake.

Arsenic

- Cardiovascular effects associated with high levels of arsenic in drinking water:
- Atherosclerosis
- Hypertension
- Cerebrovascular diseases
- Ischemic heart disease
- Peripheral vascular disorders

- Circulation 2002;105:1804.
- Hypertension 1999;33:74
- Environ Health Perspec 2000;108:847
- Stroke 1997;28:1717-1723.


Ach
As3+
Endothelial cells
Ca2+
SNP
eNOS
L-Arg
NO
NO
GTP
GC
cGMP
Smooth muscle cells
Relaxation

Adult Women's Blood Mercury Concentrations

Table 1. Percent of examinees and population estimates (in millions) of women with BHg concentrations ≥ 3.5 µg/L and ≥5.8 µg/L by U.S. Census Region and coastal status

	Geographic Distribution						
		U.S. Census Regions				Coastal Status[1]	
Blood Hg, µg/L	Nation	Northeast	South	Midwest	West	Coastal	Non-Coastal
% ≥ 3.5 µg/L (SE)	10.4 (1.0)	19.3 (4.1)	10.8 (1.0)	2.8 (0.9)	10.3 (1.3)	16.3 (1.8)	6.0 (1.0)
# of women ≥ 3.5 µg/L (millions)	6.92	2.15	2.85	0.41	1.51		
% ≥ 5.8 µg/L (SE)	4.7 (0.7)	9.0 (2.3)	4.6 (1.0)	1.2 (0.6)	4.9 (0.9)	8.1 (1.2)	2.1 (0.4)
# of women ≥ 5.8 µg/L (millions)	3.1	1.0	1.21	0.17	0.72		

[1]NHANES was not designed to provide population estimates for Coastal and Non-Coastal areas, therefore unbiased estimates of the number of women having blood mercury concentrations ≥ 3.5 µg/L and ≥ to 5.8 µg/L cannot be developed.

Mercury and CVD

- Men in the highest tertile (2.0 µg/g) of hair mercury:

  2.0-fold (p = 0.005) risk of anterior myocardial infarction

  2.9-fold (p = 0.014) adjusted risk of cardiovascular death

  compared with those in the lowest tertile

  Atherosclerosis 2000;148:265-273

Marked elevation of myocardial trace elements in idiopathic dilated cardiomyopathy compared with secondary cardiac dysfunction

Andrea Frustaci, Nicola Magnavita, Cristina Chimenti, Marina Caldarulo, Enrico Sabbioni, Romano Pietra, Carlo Cellini, Gian Federico Possati, and Attilio Maseri

J. Am. Coll. Cardiol. 1999;33;1578-1583

Idiopathic Dilated Cardiomyopathy

Element	Normal Range	Group A	Group B		Group C	Group D
			Valvular	Ischemic		
Ag	3.3–260	116	17	13	4	7
As	4.4–14	625	9.3	10.3	2.5	4
Au	0.045	26	7	11	2.3	3.2
Ba	7.6–2,020	7,360	6,200	5,300	1,500	1,250
Co	10–210	86.5	100	89	20	15
Cr	11–480	2,300	630	720	177	100
Fe	36,000–180,000	106,700	130,200	148,700	39,000	34,000
Hg	5–480	178,400	30	23	8	6
La	1	43.3	5	3.5	1.2	0.9
Rb	1,200–8,100	18,700	3,200	3,565	3,880	3,200
Sb	2–35	19,260	6	6.5	1.5	1.1
Se	49–5,000	383	270	230	250	220
Zn	17,800–113,000	128,000	16,000	21,000	9,000	7,500

Idiopathic Dilated Cardiomyopathy

- Mercury, Tin, Silver:
- Induce free radicals in affected tissues
- Superoxide anions and radicals can inhibit the sodium pump and other ion transport mechanisms in plasma membrane.
- This may lead to mitochondrial damage in myocardiocytes seen in IDCM.

- Toxicol Appl Pharmacol 1995;130:41-47.
- J Mol Cell Cardiol 1990;22:911-920.

Websites for Toxic Metal Info

Agency for Toxic Substances and Disease Registry (ATSDR):
www.atsdr.cdc.gov/toxprofiles

Environmental Health Perspectives Journal:
http://ehp.niehs.nih.gov

Collaborative for Health and the Environment- Toxicant and Disease Database:
http://database.healthandenvironment.org/

Dr. Jim Roberts Cardiologist website on methylation genomics:
http://www.heartfixer.com/AMRI-Nutrigenomics.htm

CDC National Report on Human Exposure to Environmental Chemicals:
http://www.cdc.gov/exposurereport/

Richard Nahas, MD

DMPS and DMSA protocols

Bio

Dr. Nahas practices integrative medicine in Ottawa and is Lecturer in the Department of Family Medicine at the University of Ottawa, where he teaches an evidence-based CAM curriculum to undergraduate medical students. He also practices ER medicine and is involved in short-term medical missions in the developing world.

Lecture Overview

The speaker will summarize the results of a systematic review and critical appraisal of the clinical evidence supporting the diagnosis and treatment of chronic mercury toxicity, and the correlation between elevated mercury and various diseases.

Contact Information

2211 Riverside Drive, Suite 200
Ottawa, ON K1H 7X5
Canada

richard@seekerscentre.com

American College for Advancement in Medicine
Chelation Therapy Workshop
November 4-5, 2009
Las Vegas, Nevada

Mercury Toxicity

Overview – Diagnosis - Treatment

Richard Nahas MD CCFP

Founder and Medical Director - Seekers Centre for Integrative Medicine

Undergraduate curriculum CAM content expert - Department of Family Medicine

University of Ottawa, Canada

richard@seekerscentre.com

1. History and Overview

Cinnabar

Early uses

Ancient cinnabar mines
- Konya 1500 BC
- Etruscan Italy
- Spain 200 BC - today

Ancient civilizations used it
- found at Mohenjo-Daro
- Mayans and in Peru 500 BC

Early uses
- stamp ink used for seals
- Decorating furniture
- Bodypainting and tattooing
- Protective paint on warships

Ritual and myth

- Taoist China
  - Smeared on feet – walk on water
  - Held in hands – ward of ghosts
- Indian tantrism
  - Formed into phallus to ward off sins
  - Sanskrit for alchemy – knowledge of mercury
- Banned by Diocletian
- Alchemy

Syphilis

- Doses of up to 4 pounds of liquid Hg ingested
- Sweating in tubs
- IM injections
- Did it do any good?
- Quacksilber and quackery Hg for everything

Other uses

- BP, temp
- barometer

for Their Protection

MERCUROCHROME

IT is dangerous to neglect wounds, however small; even scratches and small cuts may cause serious infections if they are not properly treated.

Merchrochrome (H. W. & D. brand of merbromin, dibromoxymercurifluorescein-sodium) is one of the best antiseptics for first aid use. It is accepted by the Council on Pharmacy and Chemistry of the American Medical Association for this purpose.

The 2% aqueous solution in applicator bottles does not sting and can be applied safely to small wounds. Children do not hesitate to report their injuries promptly when Mercurochrome is the household antiseptic, because they know that they will not be hurt. Other advantages are that solutions keep indefinitely and the color shows just where it has been applied.

Doctors have used Mercurochrome in their practice for more than 24 years.

Keep a bottle of Mercurochrome handy for the first aid care of all minor wounds. Do not fail to call a physician in more serious cases.

This seal denotes acceptance of Mercurochrome for New and Non-official Remedies by the Council on Pharmacy and Chemistry of the American Medical Association.

ACCEPTED AMERICAN MEDICAL ASSN

HYNSON, WESTCOTT & DUNNING, INC.

Baltimore 1, Maryland

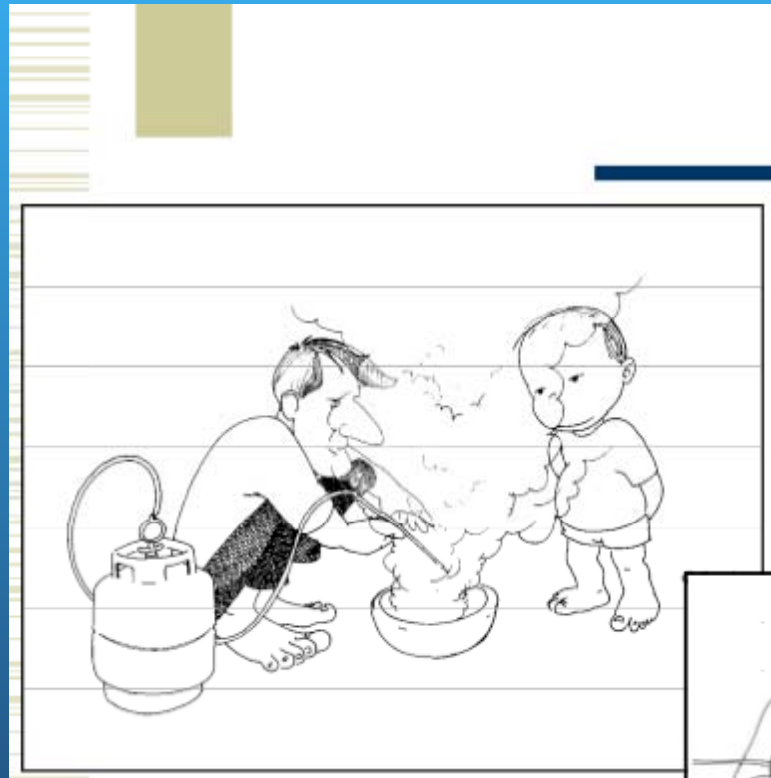
3. Mercury and Disease

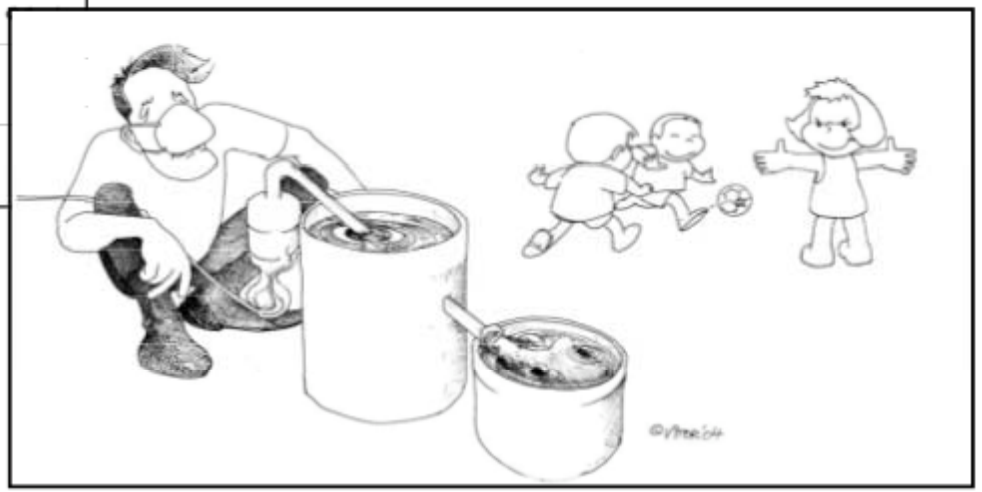
Erethism

Minamata Bay, Japan

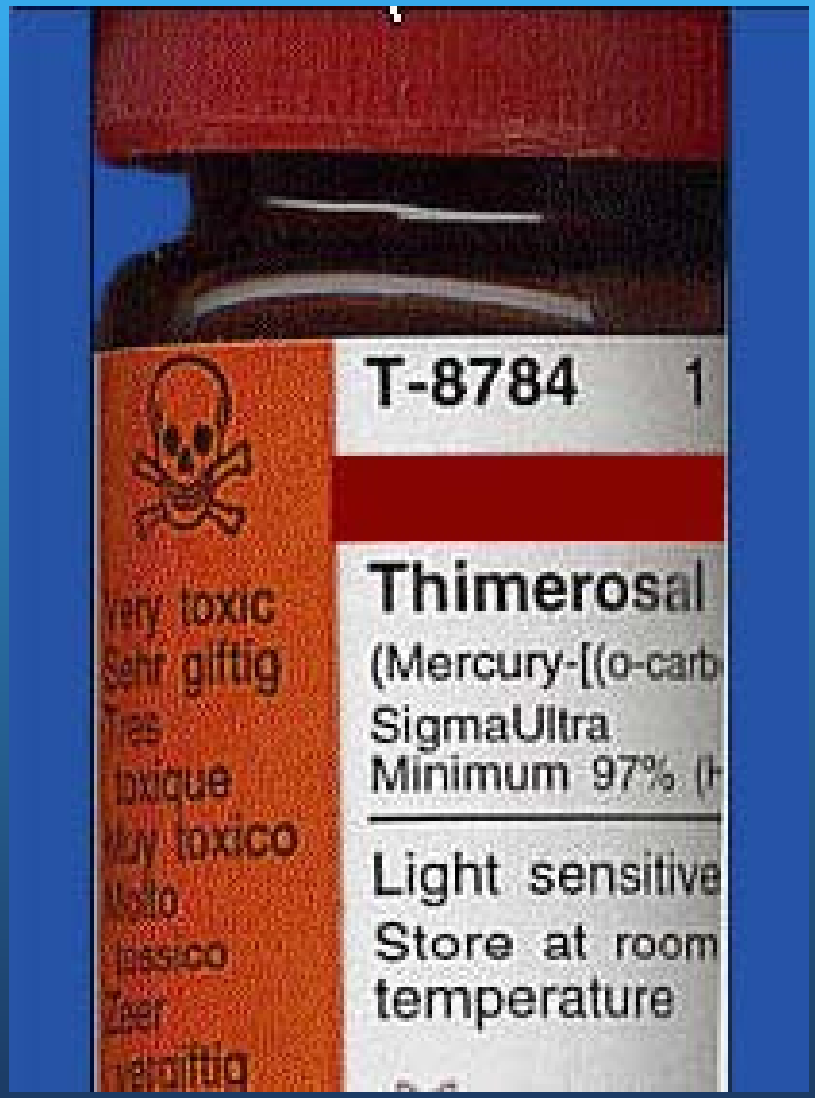
Iraqi Grain crisis

Artesanal gold mining





Thimerosal


T-8784 1
Thimerosal
(Mercury-[(o-carb
SigmaUltra
Minimum 97%
Light sensitive
Store at room
temperature

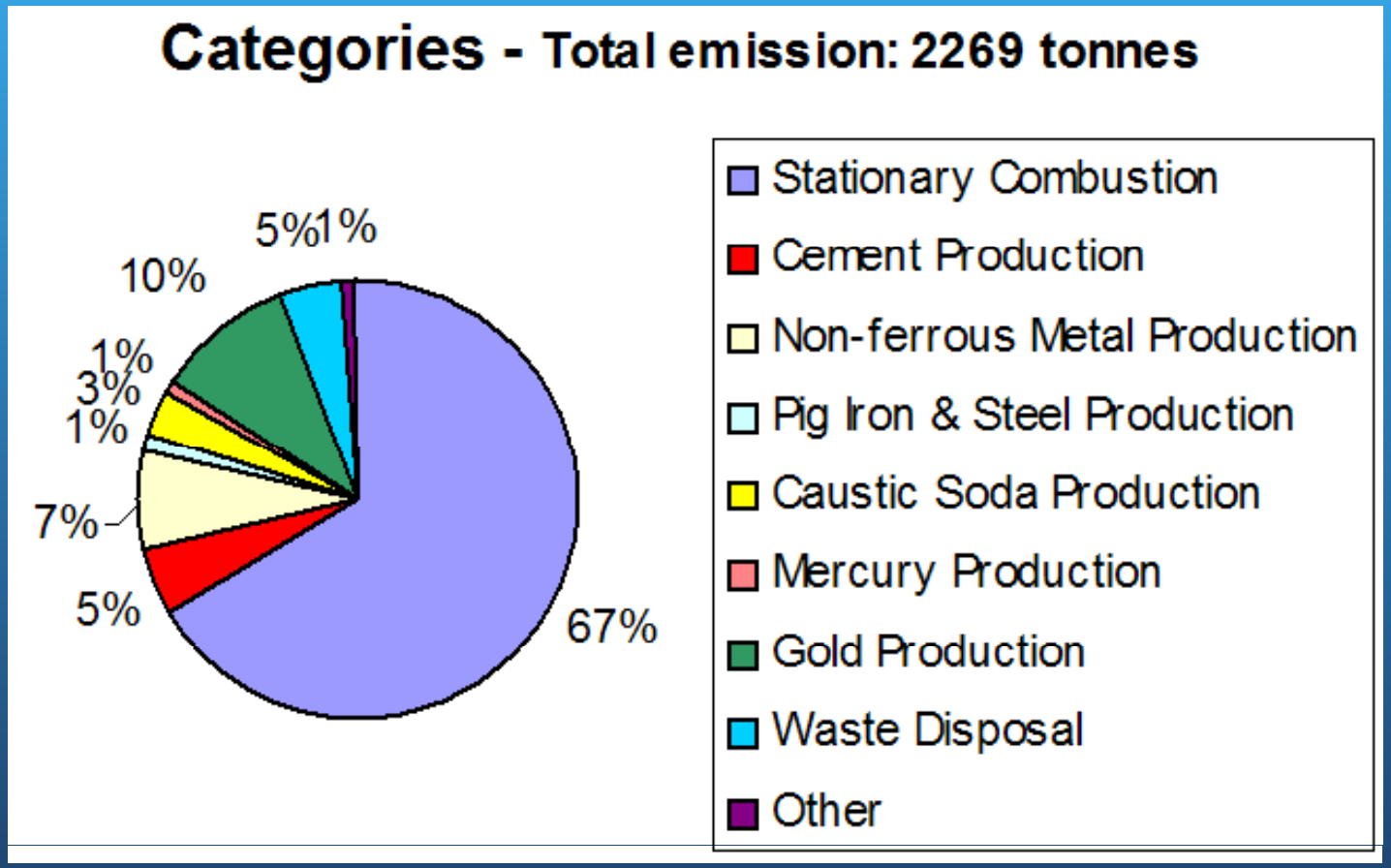
2. Current sources of Mercury

- Proximate sources of human exposure
  - MeHg fish
  - Hg Amalgam fillings
- Other sources
  - High-fructose corn syrup
  - Occupational – dentists, alkali workers
  - skin whitening creams in the third world
  - Some vaccines

MeHg - Sources

- fish
  - Enters the atmosphere
  - Falls as rainwater
  - Methylated by sulphate-reducing bacteria
  - Bio-accumulation in fish rising up the food chain
- Livestock that are fed fish
  - Poultry, dairy cows, etc
- Other sources
  - seed fungicides

MeHg - Sources



MeHg in Fish

NHANES data (ug/g)

Shark	1.33
Swordfish	0.95
Walleye	0.52
Tuna	0.43
Bass	0.38
Pike	0.31
Lobster	0.23
Trout	0.15

Cod	0.121
Crab	0.11
Sardines	0.10
Haddock	0.089
Shrimp	0.047
Scallops	0.042
Salmon	0.035
Oyster	0.023

Environ Res 2008;107:20

MeHg - Absorption

- 95% absorbed into the bloodstream
- 95% of this enters tissue within 30-40h
  - Forms –SH complexes with GSH, proteins, enzymes
  - Enters cells bound to cysteine via neutral AA carrier
  - Demethylated to HgSe in the brain
- Most excretion occurs in feces
  - Liver excretes Hg-GSH complex in bile
  - Does not occur in rats until post-suckling period
  - Demethylation and reabsorption by gut flora
  - 5% in blood was eliminated in 44d in 6 healthy pts
    - *Toxicol Appl Pharmacol 1994;128:251*

MeHg Safety Limits

- 2003 – EPA 0.1ug/kg/d – 7ug per day for a 70kg adult
  - Estimated from a physiologic model
    - based on developmental delay in Faroes study
    - maternal hair and blood levels yielding 10% risk
    - blood 50ug/L and hair 14.5ug/g
  - 10x 'safety factor' - invented by the FDA
    - blood 5ug/L and hair 1.45ug/g
  - Additional 10x safety factor
    - 3x for variance in half-time
    - 3x to cover 'range of prenatal sensitivity'
    - 3 x 3 = 9 rounded off to 10
  - *Risk Anal 2003;23:107*

Hg^0 - Sources

- amalgam fillings

Hg^0 - Amalgam fillings

- No debate that amalgam exposes the body to Hg
  - Correlated with
    - urine Hg in 3 large studies
    - breast milk Hg in 2 studies
    - kidney and brain in multiple small studies
    - fetal kidney and brain in 3 animal studies
- Some debate about how much is actually released
  - Estimates based on one study of 6 healthy volunteers

Hg^0 - Factors affecting release

- Depends on number of amalgam surfaces
- in one study of 35 pts – 8ug/d if 1-4 fillings
- Hot liquids 3x
- Chewing 4-6x – for up to 2h per meal
- High-copper fillings 20-40x
- Multiple metals 10x – battery in your mouth

Hg^0 - absorption

- Inhaled Hg^0 vapor
  - crosses alveolar membrane into plasma
  - Highly mobile – into RBCs, crosses BBB
- Oxidized to highly reactive Hg^{2+}
  - Intracellular – via catalase H_2O_2 pathway
  - Hg^{2+} deposits in tissue wherever this occurs
  - Inhibited by ethanol
    - dentists who don't drink have higher urine Hg
    - Danish factory workers absorbed more Hg after lunch
- Retrograde axonal transport to CN V

High Fructose Corn Syrup

- Produced using caustic soda
  - 50 chloralkali plants worldwide – 400,000lb of Hg per plant
  - Seven tons of missing Hg per plant per year
- Measured in HFCS
  - 20 samples collected from 3 manufacturers
  - 2 of 3 manufacturers were Hg contaminated – 0.07-0.57ug/g
- Potential exposure
  - Average consumption 50g/d (USDA) is 3-30ug/d
  - Dental amalgam estimates in children 1-2ug/d
- Is this a concern? GI methylation

Documented toxicity

- Binds to microtubules and denatures them
- Apoptosis of monocytes, phagocytes
- Binds irreversibly to 2x GSH – oxidative stress
- Inhibits GSH reductase and GSH synthetase
- Binds to and inactivates Se
- CNS demyelination
- Na-, K- and Mg- ATPase inhibition destroys astrocytes
- Inhibit uptake of 5HT, DA, NE

MeHg and Cardiovascular disease

Heavy Metals and MI Study group

684 men post-MI vs 724 controls

Toenail Hg adjusted for DHA level, CV risk factors

OR 2.16 in highest vs lowest quintile – p 0.006

N Engl J Med 2002;347:1747

Kuopio IHD Study group

1871 Finnish men followed for 13.9y

Hair Hg adjusted for DHA, CV risk factors, Se, vitamin C, E

Top 1/3 (>2.03 µg/g) RR 1.60 acute coronary event

RR 1.38 all-cause mortality

Arterioscler Thromb Vasc Biol 2005;25:228

Does mercury cause disease?

- Autism
- Multiple sclerosis
- ALS
- Parkinson’s
- Other autoimmune diseases
- Infertility

Alzheimer's disease

- More Hg in AD brains than controls – 1 of 2 studies
  - And levels correlate with exposure in 8 studies
- Lower hair and nail Hg in AD patients – 2 of 2 studies
- Hg triggers formation of NF tangles in vitro
  - Interferes with microtubules
  - Oxidative stress
- ApoE4 allele
  - Cys-Arg – fewer –SH groups on the lipoprotein
  - increases risk of AD by 14.9x in homozygotes
  - Increases risk of CMT symptoms

MeHg - Maternal fish consumption

- Maternal hair levels of MeHg all much higher than typical
- 74 NZ kids
  - maternal hair > 6µg/g vs 163 controls <3µg/g
  - poorer IQ, language and gross motor skills at 12-30m
- 1022 Faroe kids
  - CORD BLOOD, hair 4.3µg/g – subgroup of 112 had 12.5ppm
  - Abnormal hearing, neurologic exam and HRV in boys up to 14yo
  - BP 14mmHg higher at 7yo but not 14yo
- 789 Seychelles kids
  - 60 neuropsych tests up to 9yo – all negative
  - Massive canned tuna industry in the Seychelles

Key point

Direct toxicity to the brain is probably not the most important factor unless very high levels are reached

Hg binds to –SH groups in enzymes and structural proteins

This is the key to understanding toxicity IN AN INDIVIDUAL

Polymorphisms make some enzymes more vulnerable than others

Individual variability

ApoE4 polymorphisms

CPOX4 polymorphisms

Se levels

Tropical fruit consumption

Alleles of catalase

Gut flora

Ethanol consumption

Glutathione-S-transferase polymorphisms

NB - 0.2% of kids who used calomel developed acrodynia

4. Diagnosis

Diagnosis - overview

- Hair and blood to estimate MeHg
  - Blood only reflects recent exposure
  - Hair only reflects what the body is able to eliminate
- Urine to estimate Hg
  - But poor estimate of total body burden
- Chelation challenge test
  - DMPS or DMSA
  - The MOST reliable diagnostic test
  - But it is not perfect

Blood Hg

- Most often used to estimate MeHg exposure
- Many epidemiologic studies have measured this
- Safety limits of MeHg are based on serum levels
- Not useful in clinical practice except to justify treatment to insurance companies

Urine Hg

- Most often used to estimate inorganic Hg exposure
- May be useful to collect pre-challenge sample
  - Medico-legal concerns
  - Recent fish consumption
  - Other unknown ongoing exposure
- Otherwise very little use in clinical practice

Hair testing

- Often used by practitioners for toxic & essential metals
- Easy and safe but not standardized or validated
- Believed to reflect long-term exposure
- Over 80% is MeHg only 20% is Hg

Does not measure Hg in the body

Simply measures Hg the body has been able to put into hair

Hair Hg - problems

- Many cases of contamination
  - Especially occupational exposure
- Hair has poor correlation with body burden

  Case series in our practice – low hair – VERY high Hg
- Autistic children have abnormally LOW levels of hair Hg

  <50% MeHg in hair vs typical >90%

Hair Hg in autism

- 94 autistic children vs 45 controls
  - 0.47 parts per million **vs 3.63**
    - Mild 0.79
    - Moderate 0.46
    - Severe 0.21
  - *Int J Toxicol 2003;22:277*

Reduced Levels of Mercury in First Baby Haircuts of Autistic Children

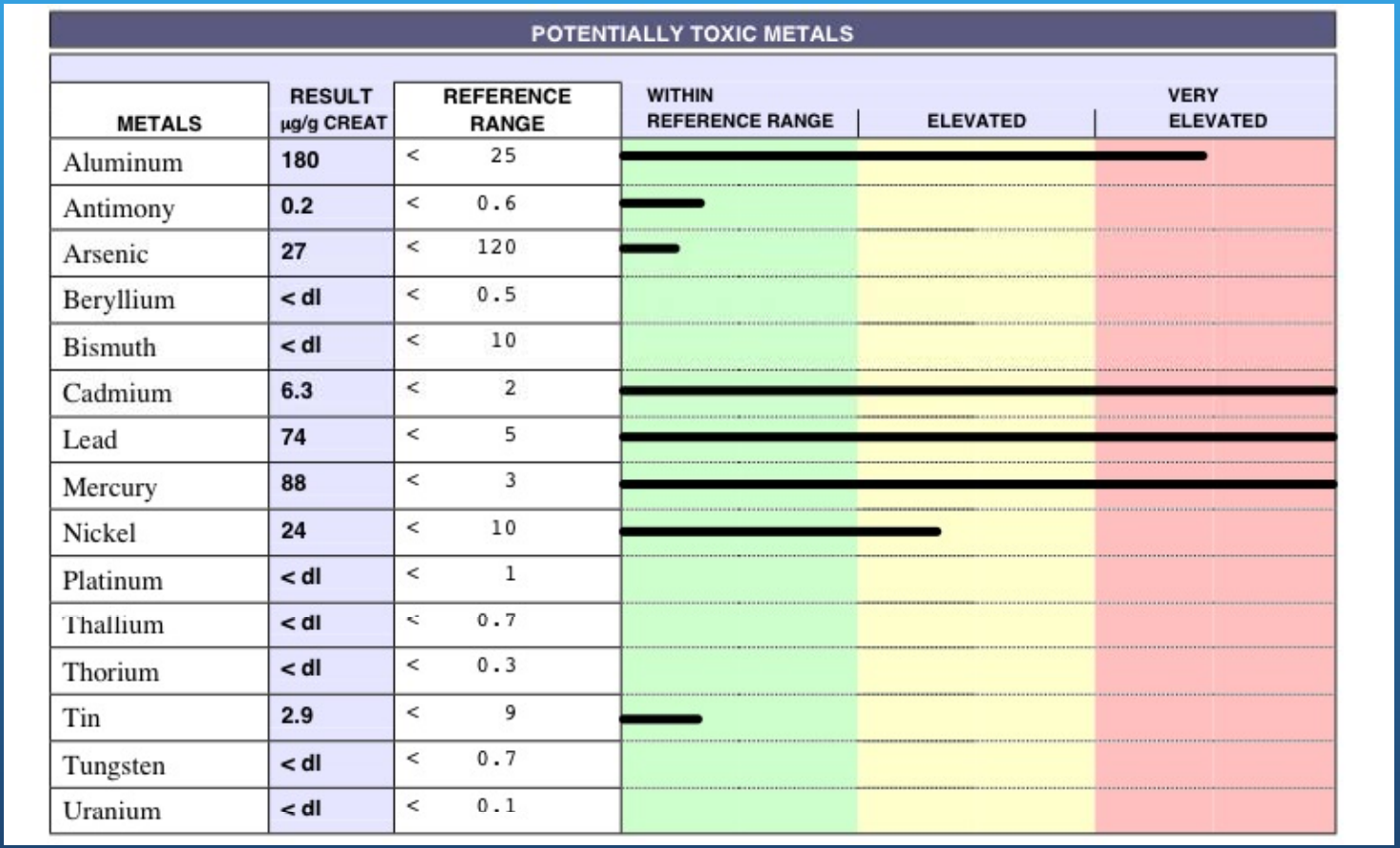
Amy S. Holmes,[1] Mark F. Blaxill,[2] and Boyd E. Haley[3]

[1]Baton Rouge, Louisiana, USA
[2]SafeMinds, Cambridge, Massachusetts, USA
[3]Chemistry Department, University of Kentucky, Lexington, Kentucky, USA

Other tools

- Electrodermal testing
  - Vega etc
  - Variable results with different operators and settings
  - May reflect hypersensitivity

Diagnosis – DMPS/DMSA Challenge



POTENTIALLY TOXIC METALS

METALS	RESULT µg/g CREAT	REFERENCE RANGE	WITHIN REFERENCE RANGE / ELEVATED / VERY ELEVATED
Aluminum	180	< 25	
Antimony	0.2	< 0.6	
Arsenic	27	< 120	
Beryllium	< dl	< 0.5	
Bismuth	< dl	< 10	
Cadmium	6.3	< 2	
Lead	74	< 5	
Mercury	88	< 3	
Nickel	24	< 10	
Platinum	< dl	< 1	
Thallium	< dl	< 0.7	
Thorium	< dl	< 0.3	
Tin	2.9	< 9	
Tungsten	< dl	< 0.7	
Uranium	< dl	< 0.1	

DMPS Challenge vs hair and urine

- Hansen 2004

  Laboratoire National de Sante in Luxembourg

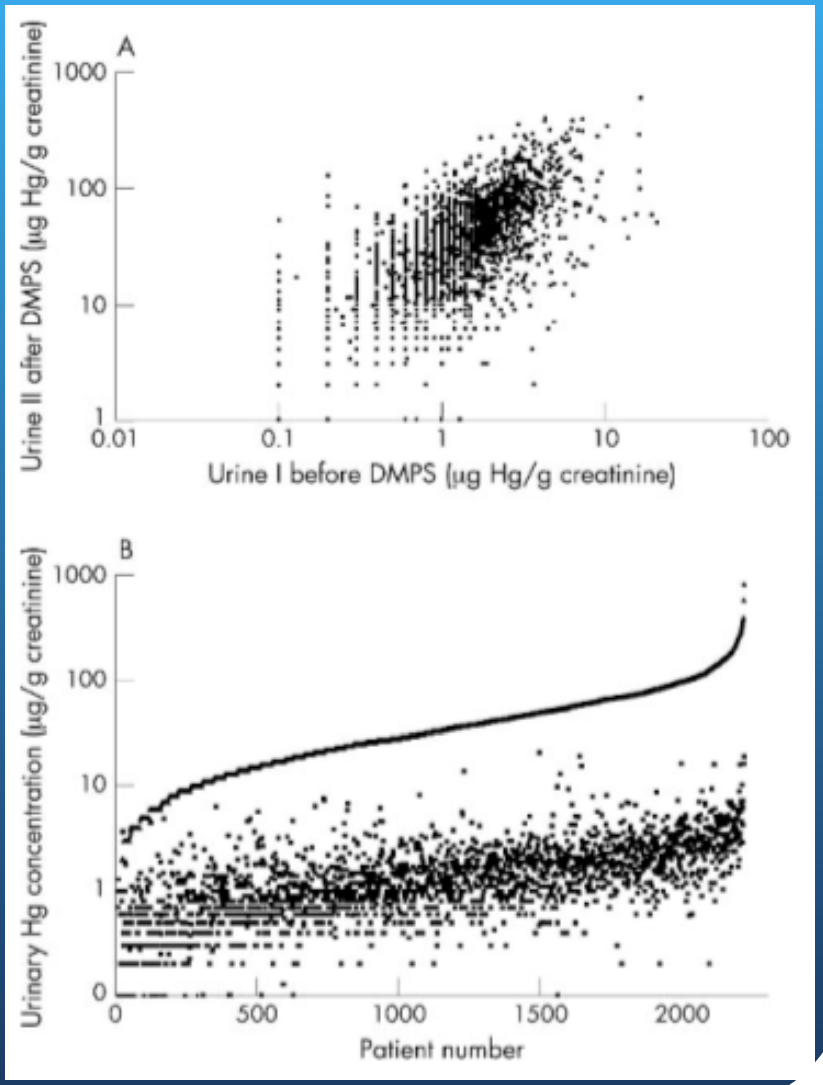
  2223 pts – hair, urine and DMPS challenge test

Table 1 Statistical data on basal urine Hg content, DMPS test, chew test, and hair test based evaluation of the Hg burden of 2223 patients (1709 patients for hair test)

	Basal urine µg Hg/g creatinine	DMPS test µg Hg/g creatinine	Chew test µg Hg/g chewing gum	Hair test ng Hg/g hair
95th centile	4.4	134	134	3214
75th centile	2.1	61	63	869
50th centile	1.3	32	27	454
25th centile	0.7	17	9	291
Mean value	1.7	47	43	904
Standard deviation	1.7	51	48	1455
Minimum value	0	0	0	20
Maximum value	21	837	393	32557

Diagnosis

- Hair vs DMPS
  - no correlation
- Urine vs DMPS
  - Poor correlation
  - Most toxic patients missed



DMSA

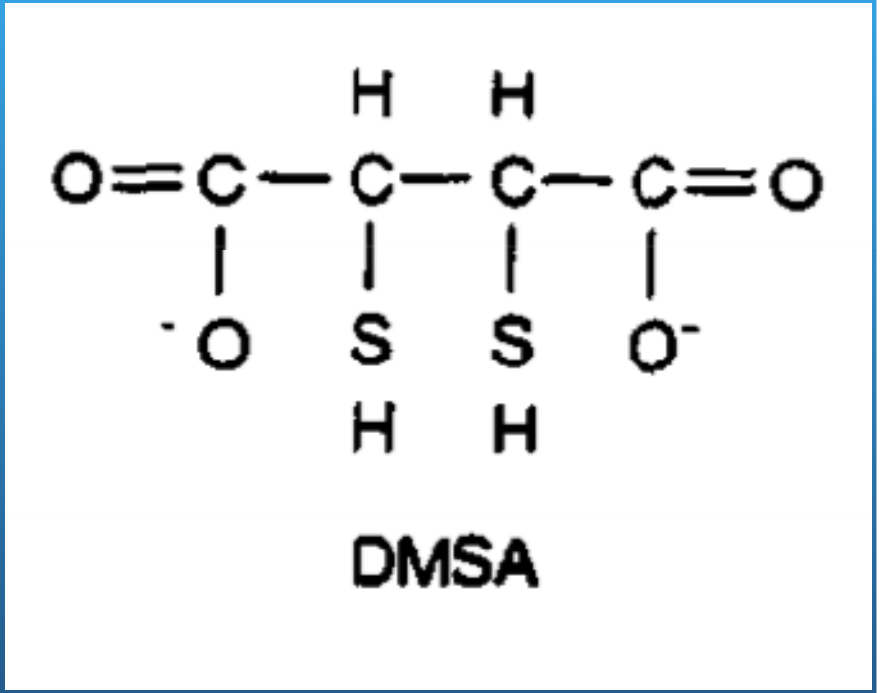
2,3-dimercaptosuccinic acid

10-30mk PO

20% absorbed – $t_{1/2}$ 3.5h

6h urine collection

SE rash, nausea



DMSA

14 healthy patients

DMSA 30mg/kg

3h urine collection

Pre-DMSA	2.2 nM
Post-DMSA	13.7 nM
AVG RATIO	7.1

Ann Clin Biochem 2004;41:233

65 patients with CMT

DMSA 30mg/kg

urine collection (time?)

Pre-DMSA	5.0 µg/L
Post-DMSA	13.1 µg/L
AVG RATIO	2.65

J Nutr Environ Med 1998;8:219

DMPS

2,3-dimercapto-1-propanesulfonic acid

1958 developed in USSR

1978 marketed as Dimaval in Germany

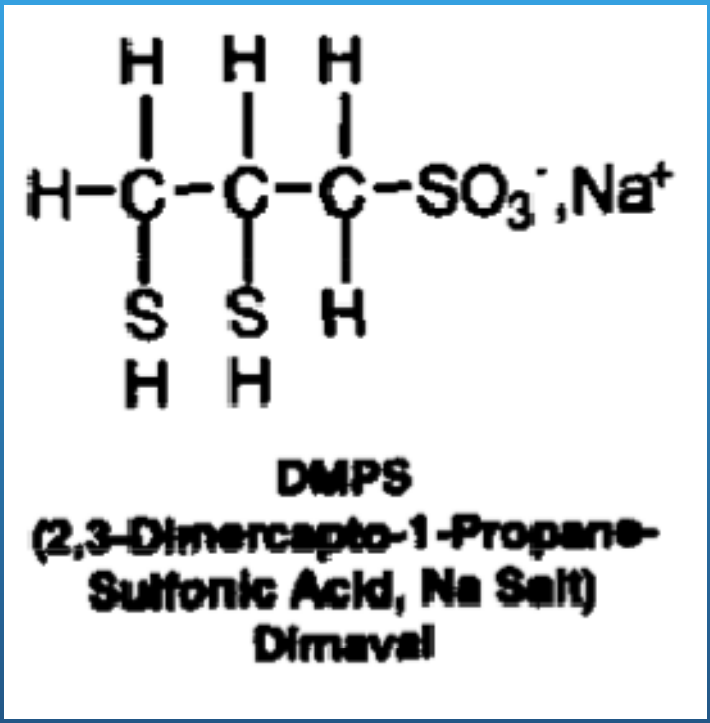
PO 10mg/kg

- 40% absorbed in healthy adults

IV 3mg/kg max 250mg

- shorter half-life only 1.5h
- 1-6h urine collection

SE HA, fatigue, nausea, rash

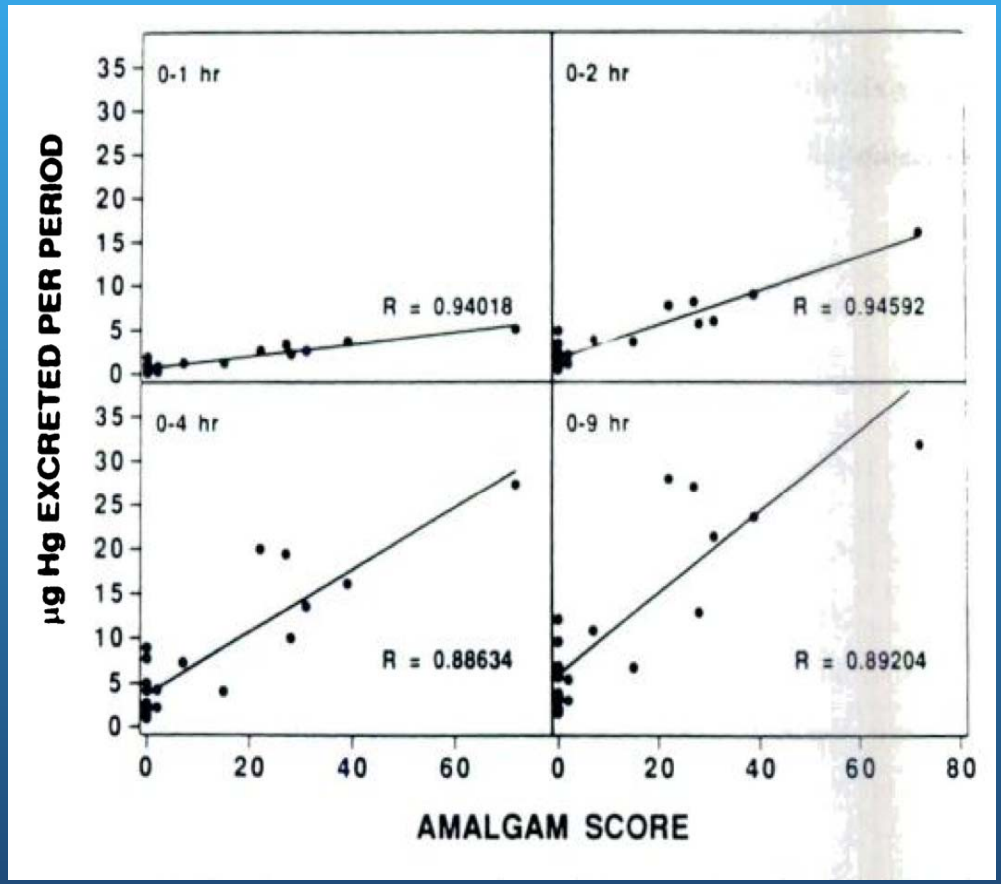


DIAGNOSIS - DMPS

19 healthy pts

300mg DMPS PO

	Amalgam	Control
9h Pre	0.70 µg	0.27 µg
9h Post	17.2 ug	5.1 µg
RATIO	24.6	18.9



DMSA vs DMPS

DMSA		Oral, relatively safe
		absorbs much more Pb
	but	less effective if GSH is depleted
		Mrp2 in the kidney requires GSH
DMPS		removes more mercury
		higher binding coefficient
		pre-post ratio DMPS 18-27
		DMSA 1.5-7 lower in CMT

Diagnosis – DMPS/DMSA Challenge

CAVEATS

- Assumed to reflect total body burden
  - Based on mouse studies but never compared with direct measurements in humans
  - Do not cross the BBB to reflect brain levels
  - Some pts excrete abnormally low amounts NYD
- Long-term safety unproven
  - In vitro studies documenting neurotoxicity but this is not relevant to humans
  - No real evidence for or against

Treatment

DMPS

- 3mg/kg IV max 250mg in NS or slow push over 15-30min
- Add vitamin C, B vitamins, procaine as desired
- Repeat every 1-2 weeks as needed
- Serial challenge testing as needed

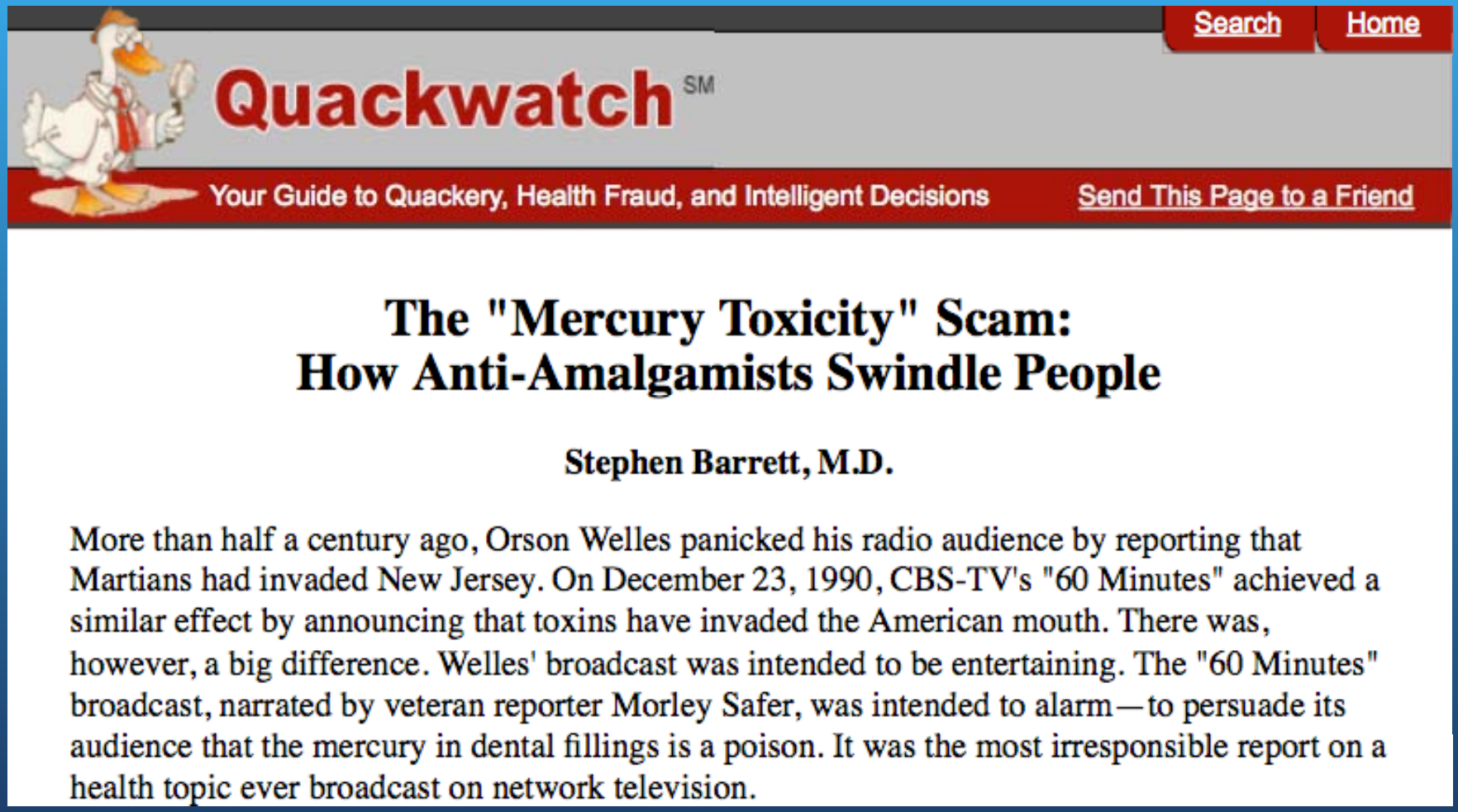
DMSA

- 30mg/kg PO divided tid
- various regimens – pulsed dosing or lower daily doses

Treatment

- Research evidence that REMOVING Hg improves CLINICAL outcomes is still lacking
  - Autism
  - Alzheimer's dementia
  - Parkinson's disease
  - ALS
  - Infertility
  - Cardiovascular disease

Treatment



Search Home

Quackwatch SM

Your Guide to Quackery, Health Fraud, and Intelligent Decisions

Send This Page to a Friend

The "Mercury Toxicity" Scam: How Anti-Amalgamists Swindle People

Stephen Barrett, M.D.

More than half a century ago, Orson Welles panicked his radio audience by reporting that Martians had invaded New Jersey. On December 23, 1990, CBS-TV's "60 Minutes" achieved a similar effect by announcing that toxins have invaded the American mouth. There was, however, a big difference. Welles' broadcast was intended to be entertaining. The "60 Minutes" broadcast, narrated by veteran reporter Morley Safer, was intended to alarm—to persuade its audience that the mercury in dental fillings is a poison. It was the most irresponsible report on a health topic ever broadcast on network television.

Chronic Mercury Toxicity

- Does Removing Mercury treat Disease?

- A.K.A. oral galvanism

  micromercurialism

  metal syndrome

Symptoms and signs

- IAOMT 124-point score chronic mercury toxicity (CMT)

Fatigue	Weakness	Numbness
Sleep	Depression	Anxiety
Pain	Memory	Concentration
Tremor	Spasm	Tinnitus
Taste	Cold hands	Dizziness

- Clinical diagnosis is important
  - no clearly defined criteria
  - Overlap with Lyme, MCS, FM, CFS, chronic infection

Etiology

- Mercury toxicity
- Symptoms do not correlate with # of fillings
- Symptoms do not correlate with Hg levels
    - several studies using the wrong test
    - 2 studies using challenge test

Treatment - Amalgam removal

SUMMARY OF EVIDENCE IDENTIFIED

- 2 retrospective case series
  - 75 pts improvement in 80%
  - 463 pts improvement in 70%
- 1 case-control study of 288 pts – DMPS predicts outcome
- 1 randomized controlled trial of 90 pts – no benefit

Stenman 1997

- Case-control study 288 pts
  - CMT vs controls
    - Urine Hg – 30 min after DMPS 300mg IV
  - 3-year follow-up
    - 26 pts cured after amalgam removal
  - OR 7.2 for top quartile urine Hg

Engel 1998

- Case series of 75 patients from a Swiss dental practice
  52 women and 23 men ‘mostly >30yo’
- Self-reported symptoms of CMT
  - 69% much better
  - 13% better
  - 9% somewhat better
  - 8% no change
  - 1% worse
- Retrospective, did not report untreated patients
- Poor reporting of follow-up

Schweiz Monatsschr f Zahnmed 1998;108

Engel 1998

Symptoms reported

- migraine 48%
- headache 43%
- GI symptoms 36%
- neck tension 33%
- paraesthesia 25%
- dizziness 24%
- allergies, visual symptoms, back pain, mental disorder, joint pain

Lindh 2002

- Centre for Clinical Metal Biology in Uppsala, Sweden
- 796 patients ‘out of 2000’ referred by MD or DDS
  - 45-60yo, 2/3 women
  - 463 pts responded to questionnaire
  - most had seen many clinicians – no Dx missed
- Intervention
  - amalgam removal
  - vit B1, B2, B3, B5, B6, C, E, Selenium

Lindh 2002

- Average 19 of 30 symptoms of CMT
- 72% improved, 15% no change, 13% worse
- Most improved symptoms
  - blisters in the mouth
  - chronic fatigue
  - depression
  - pain in all muscles
- Correlated with serum Hg – initial AND decline

Lindh 2002

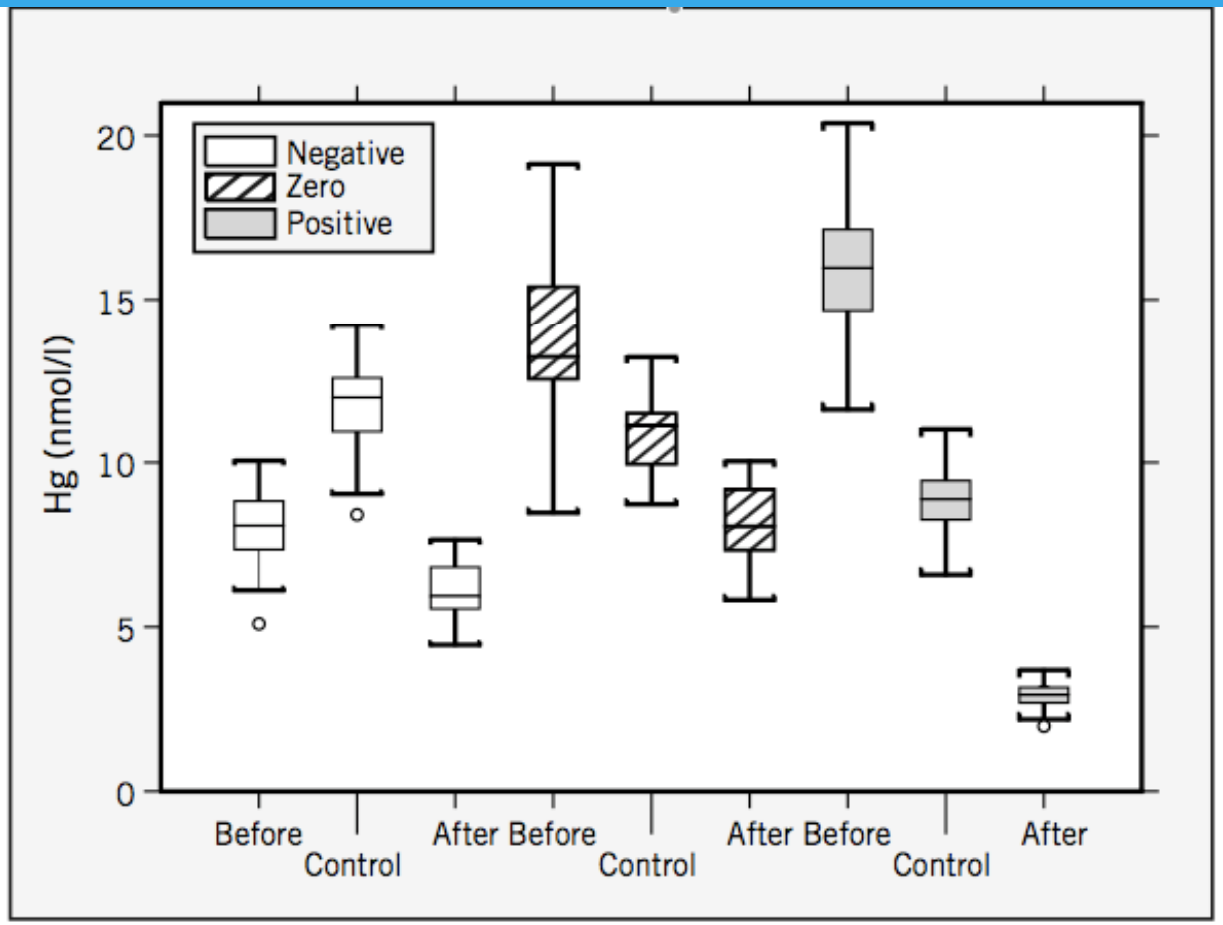


Figure 6. Mercury concentrations in blood plasma before and after RID in the negative, zero and positive groups. For each group, the values of matched control groups (healthy individuals) are inserted.

Lygre 2005

- Dental Biomaterials Adverse Reaction Unit in Norway
- 142 CMT pts and 880 controls sent a questionnaire
    - 85 vs 441 responses
    - 12 were advised to remove amalgam
        - 11 documented allergy
        - 1 oral lichenoid reaction

Lygre 2005

- Intraoral sx — burning, pain, taste, stiff, dry, saliva
- Orofacial sx — burning, pain, stiff, skin, TMJ
- General sx — pain, GI, CV, skin, vision, ENT

  tired, dizzy, HA, cognition, mood

Melchart 2008

- Centre for Complementary Medicine Research in Munich, Germany
- 90 CMT pts self-referred
- Intervention
  - Amalgam removal
  - Amalgam removal + B6, C, Se, Zn, Ca, garlic
  - Group counselling x 14 sessions

	Group A Removal of Dental Amalgam		Group B Removal Plus Biological Detoxification		Group C Health Promotion Program without Removal		
	n	Mean (SD[1])	n	Mean (SD[1])	n	Mean (SD[1])	p[2]
Participant questionnaires							
Total symptom score (0-150)	27	- 21.8 (17.6)	25	- 24.0 (16.5)	23	- 16.3 (12.2)	0.230
No. of complaints (0-50)	27	- 9.7 (8.4)	25	- 10.5 (9.2)	23	- 7.6 (7.7)	0.487
No. of strong complaints (0-50)	27	- 4.5 (3.2)	25	- 4.7 (3.0)	23	- 3.6 (2.5)	0.437
SF-36 physical health[3,4]	26	3.9 (8.5)	24	2.4 (11.5)	21	1.0 (6.9)	0.546
SF-36 mental health[3,4]	26	3.5 (8.3)	24	4.4 (10.6)	21	5.0 (9.1)	0.858
SCL-90-R Global Severity Index[4]	26	- 5.5 (7.4)	26	- 4.9 (8.9)	22	- 6.9 (5.4)	0.633
KKG internal locus of control[5]	26	- 0.2 (9.3)	26	2.3 (7.8)	22	4.1 (7.2)	0.197
KKG external locus of control[5]	26	1.1 (11.8)	26	0.2 (10.4)	22	0.7 (8.9)	0.947
KKG fatalistic externality[5]	26	0.8 (12.1)	26	- 0.4 (9.2)	22	- 1.8 (11.0)	0.711
Mercury concentrations							
Total in blood plasma (ng/mL)	26	- 0.43 (0.39)	26	- 0.46 (0.63)	23	- 0.16 (0.27)	0.049
Inorganic in blood plasma (ng/mL)	26	- 0.44 (0.38)	26	- 0.45 (0.57)	21	- 0.12 (0.17)	0.013
Total in erythrocytes (ng/mL)	26	0.06 (1.77)	26	- 0.42 (1.69)	23	- 0.73 (1.57)	0.259
Inorganic in erythrocytes (ng/mL)	26	- 0.41 (0.38)	26	- 0.43 (0.49)	22	- 0.12 (0.19)	0.012
In urine (ng/mL)	26	- 1.15 (1.42)	26	- 1.86 (2.71)	23	- 0.48 (1.43)	0.054
In urine excretion (ng/8 hrs)	25	-489.4 (470.0)	26	-718.5 (1004.3)	23	-162.3 (373.6)	0.022

Hypersensitivity

- Patch testing

  Finnish Contact Dermatitis Group

  Frequency of documented metal allergy in 4000 patients

Ni	14.6%
Hg	10.3%
Au	7.7%

  Am J Contact Dermatitis 2001;12:83

  Comment – allergies are ALL on the rise

Hypersensitivity

- Oral lichen planus treated by amalgam removal

  Arch Dermatol 2004;140:1434

Table 4. Clinical Results of Partial or Complete Replacement of Dental Amalgam Restorations in Patients With OLP With Positive Patch Test Reactions to 1 or More Mercury Compounds

Result	Group A (n=13)*	Group B (n=8)*	Group C (n=2)*
Healed (++)	11	5	. . .
Improved (+)	2	3	1
Unchanged (±)	. . .	. . .	1
Worse (–)	. . .	. . .	. . .

Abbreviation: OLP, oral lichen planus; ++, healed; –, worse; +, improved; ±, unchanged.
Ellipses indicate not present.

Hypersensitivity - GU Symptoms

- 39 CMT pts
- Inhaled air containing Hg 25-200ug/m^3 vs control x 5min
  - Translates into 0.6-10ug Hg
  - Approx 200 of each done over 2y period
- Positive reaction in 20.8% vs 14.6% - p=0.18
- 9 pts with urogenital symptoms
  - Much more reactive to Hg than control p<0.02

Eur J Oral Sci 1999;107:208

Symptoms ≠ Hg levels

Author	Patients	Test	Results
Melchart 1998	4787 pts	amalgam score	No correlation
Bratel 1997	50 CMT 50 controls	Blood, urine, plasma	No difference *Craniofacial 74% vs 24%*
Gottwald 2001	40 CMT 40 controls	Blood, urine, saliva	No difference *Atopy in 11 vs 5* *Saliva 83 vs 39 p<0.02*
Bailer 2001	40 CMT 43 controls	Blood, urine, saliva	No difference
Zimmer 2002	40 CMT 40 controls	Blood, urine, saliva	No difference
Schuurs 2000	68 'CMT' 52 none	DMPS 300mg PO 24h	No difference *6.1 vs 5.9 µg/g*
Vamnes 2002	19 CMT 21 healthy 20 out 20 controls	DMPS 2mk IV 30m, 2h 24h (µg/g Cr)	No difference Amalgam > none

MELISA test

- 2 additional studies of amalgam removal based on lymphocyte reactivity measured in whole blood
- Autoimmune thyroiditis
  - 27 pts tested + vs 12 pts tested –ve
  - 15 had amalgam out and 12 did not
  - Predicted decreased anti-TG and TPO after amalgam removal
- Mixed AI disease
  - 35 pts with SLE, thyroid, MS and eczema
  - All had amalgam fillings removed
  - Responders were more reactive than non-responders (nonsig)

Treatment – Chelation only

- Chelation without amalgam removal is generally not recommended
- Removing the source of toxicity is a basic principle of toxicology
- But no evidence of adverse outcomes

- 3 Trials – 2 controlled and 1 uncontrolled

Sandborgh-Englund 1994

- Population
  - 20 pts referred by DDS
  - self-reported amalgam symptoms
  - fatigue, pain, depression, weakness, dizziness, HA, irritability
- Intervention
  - DMSA 20mkd or placebo - daily for 14d
  - ‘vitamins and Se’ in 12 – ‘pain killers’ in 8

Sandborgh-Englund 1994

- Outcomes

excretion of Hg	148ug vs 85ug
serum and urine Hg	NS
amalgam symptoms	NS
POMS and KSP	NS

- Hypersensitivity rash in 3 patients on days 12 and 14

Grandjean 1997

- Population
  - 50 CMT pts – self-described CMT and >4 amalgams
  - Patch testing for allergy – 4 positive
- Intervention
  - DMSA 30mg/kg/d or placebo for 5 consecutive days
- Outcomes
  - EPQ (personality) and SCL-90 (CNS co mplaints) – NS
    - Improvement in 16 pts – no difference between groups
  - 24h urine Hg – 4x increase with DMSA

Gonzalez-Ramirez 1998

8 Mexican calomel factory workers with known Hg toxicity

DMPS 400mg PO daily

	8d	5d off	7d	5d off	6d	5d off
24h U ug	1741	106	314	48	173	53

Did not measure symptoms

Much higher than CMT patients – assume Cr 0.5-2.0/d

- Conclusion – DMSA reduces tissue burden

Amalgam removal AND chelation

- Treatment of choice
- Two case series

Kidd 2000

- 60 consecutive pts – retrospective
- amalgam replacement, DMPS and neural therapy
- 42 responded to questionnaire about symptoms

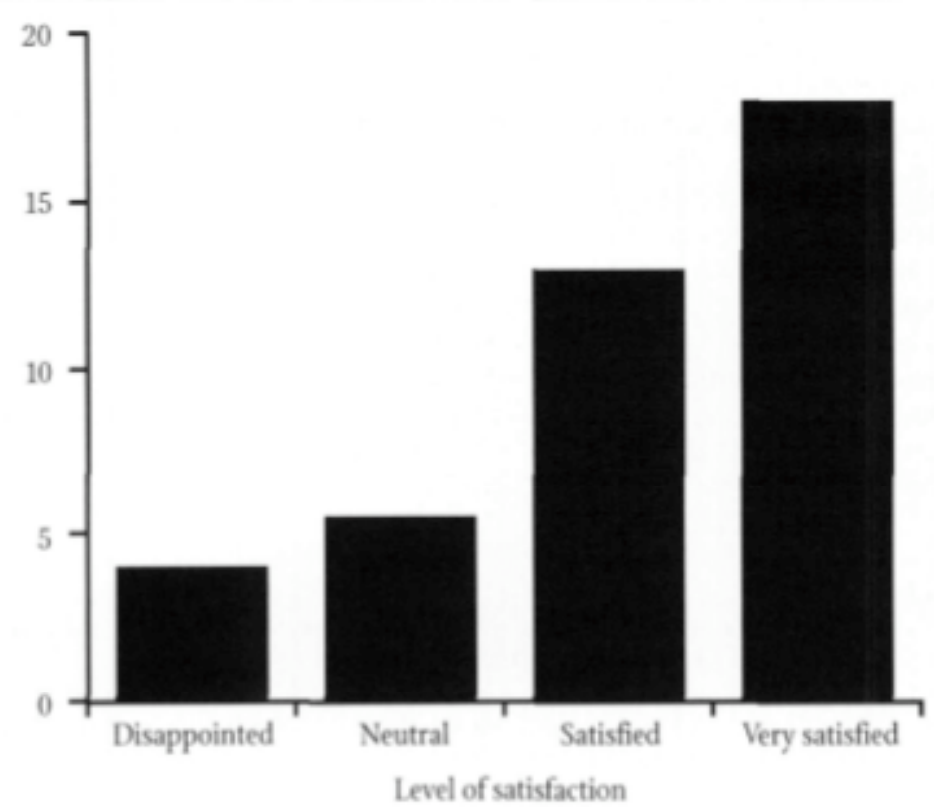


FIGURE 4 Overall satisfaction. Scale used to indicate level of satisfaction: -1 indicates disappointed; 0, neither disappointed nor satisfied; 1, satisfied; 2, very satisfied.

Incidence of symptoms

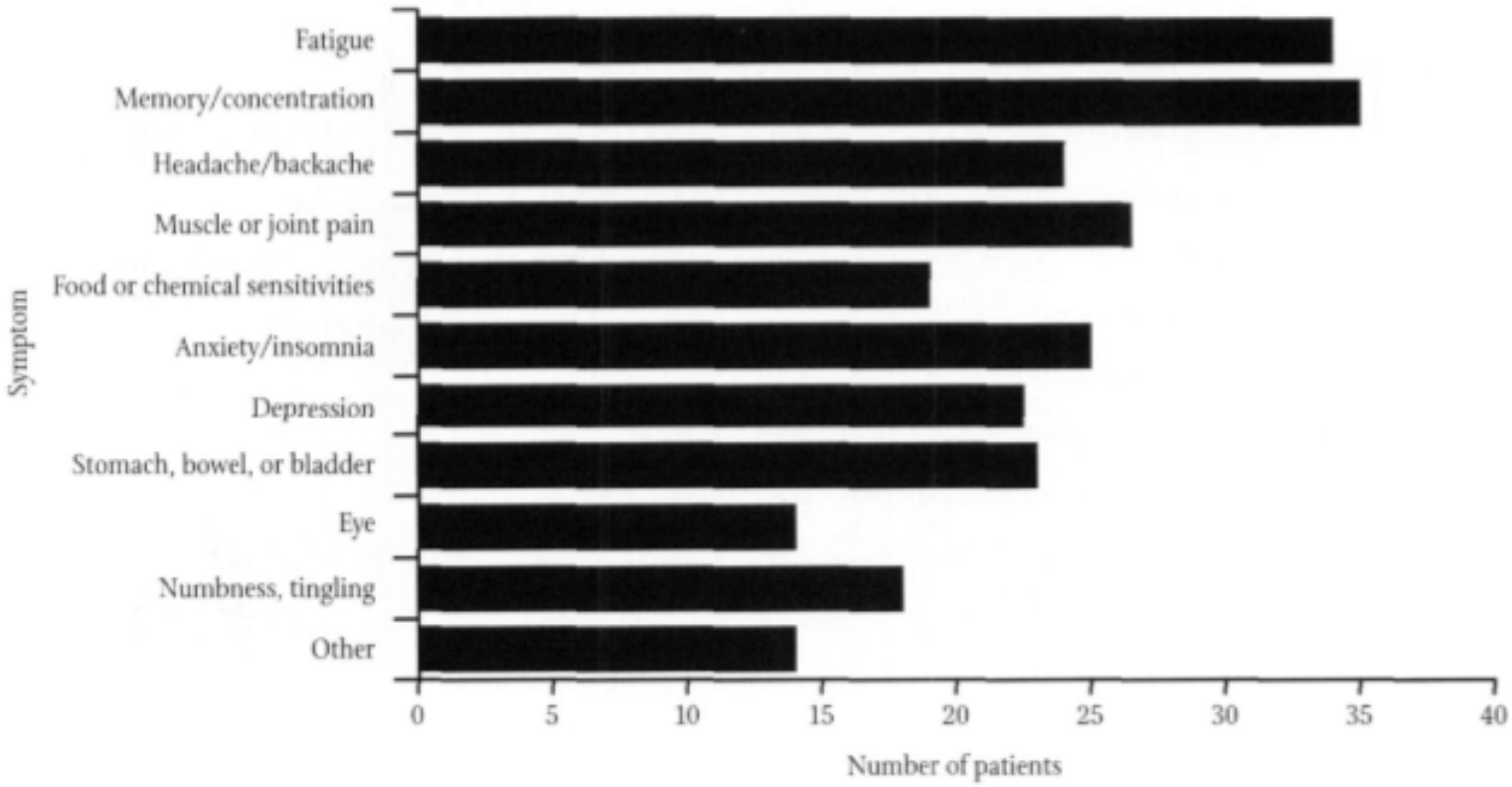


FIGURE 1 Incidence of symptoms

Improvement after treatment

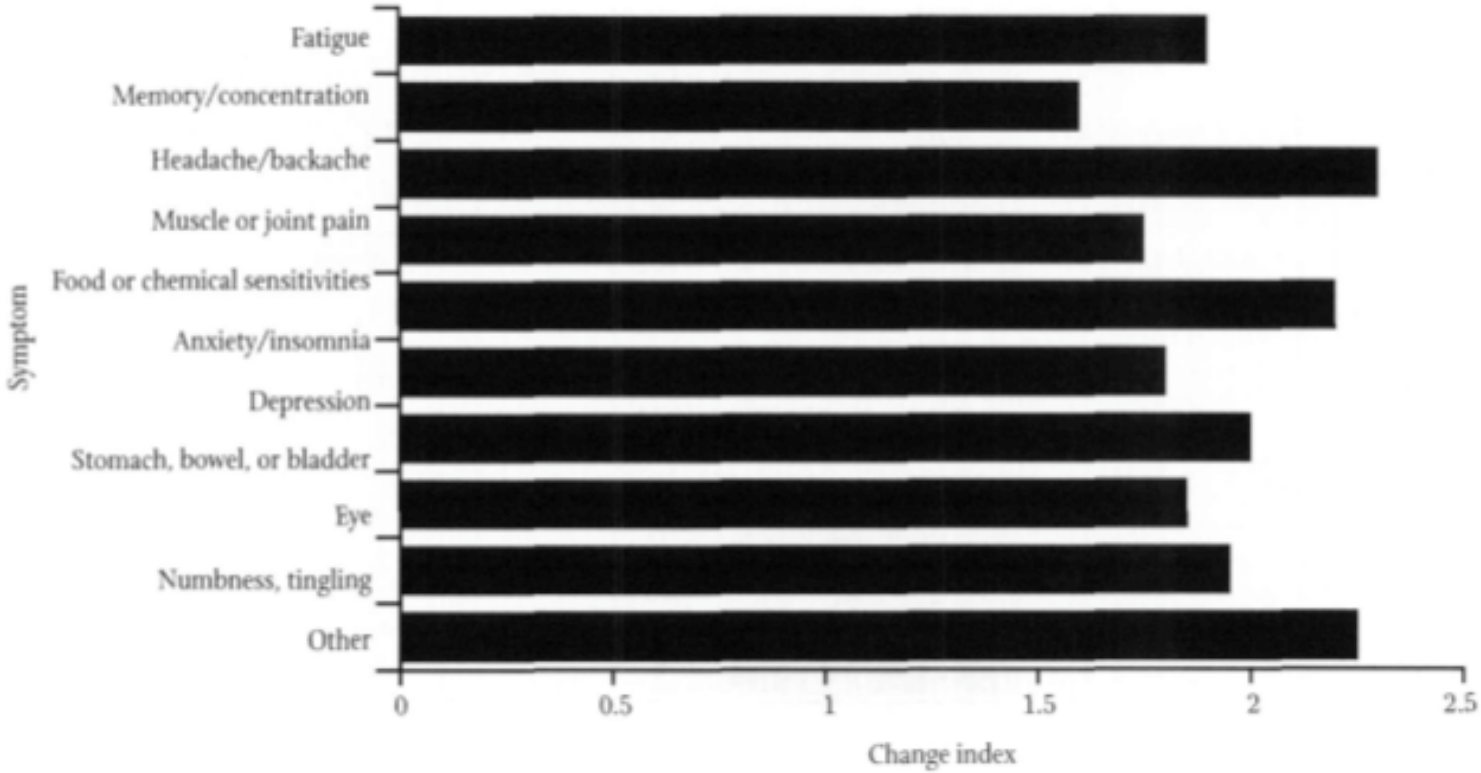


FIGURE 3 Scale used to indicate changes in symptoms: -1 indicates worsening of symptoms; 0, no change; 1, some improvement; 2, moderate improvement; 3, almost free of symptoms; 4, symptom entirely gone.

Wojcik 2006

465 pts with clinical CMT symptoms

Patients chose their own treatment

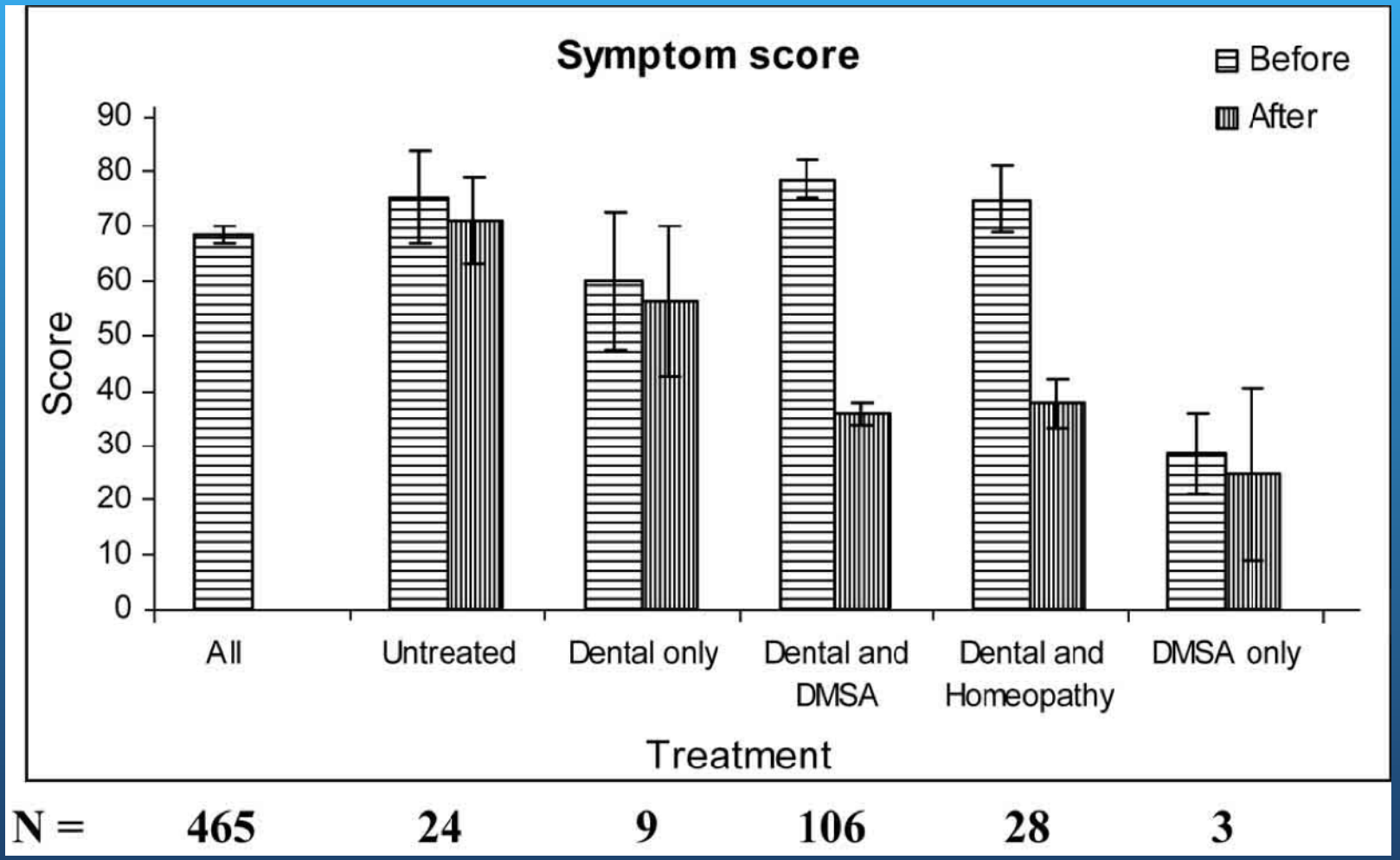
abstain from fish

amalgam removal

+/- DMSA 500mg MWF q2w x 6 and chlorella 3g/d

OR homeopathy

Wojcik 2006


Symptom score
Before
After
Score
90
80
70
60
50
40
30
20
10
0
All
Untreated
Dental only
Dental and DMSA
Dental and Homeopathy
DMSA only
Treatment
N = 465 24 9 106 28 3

Wojcik 2006

- Poor methodology
  - Did not report time intervals
  - Confounding reasons for treatment
  - Many patients lost to follow-up
  - No placebo control group
- Amalgam removal was not sufficient
- DMSA was equal to homeopathy

Loss of essential minerals

- Hol and Vamnes 2003

  80 dental pts – 4 groups +/- amalgam, +/- CMT

  DMPS 2mg/kg IV

24h urine excretion	Zn 1.2mg	ratio 1.7
	Cu 0.25mg	ratio 8.3

- Sallsten et al 1994

  12 former chloralkali workers

  DMPS 3-4.5mg/kg IV

24h urine excretion	Zn 1.13mg	ratio 1.5
	Cu 0.17mg	ratio 12

- Zn not a major concern – watch Cu

Other therapies

Sweating / Sauna detoxification

- Used for centuries for Hg miners in Almaden, Spain
- Lovejoy 1995

  7 pts – 3 miners – 3 unexposed miners – 1 control

  Sweat collected for 90min while in rubber chest waders

  Urine collected for 16h

Sweat	300-650mL	exposed	130-350ug/L
		unexposed	5-8ug/L

- Numerous uncontrolled case series/reports of benefit but little documentation of excretion

Rx - Alpha Lipoic Acid

- Multiple mechanisms
  - Chelates Fe, Cu, Hg and Cd
  - Regenerates GSH
  - Quenches ROS
- DHLA is the active form
- PO up to 1800mg/d or IV up to 600mg/d
- No human data - in vitro and anmial studies only

Rx - Chlorella

- Algae that can take up heavy metals
  - Mostly *in vitro* data
  - Industrial use several publications
- No clinical trials in humans or animals
- May take up essential minerals as well …

Rx - Cilantro

1 case series

- Patient in China with gum cancer
- 3 fillings removed – curing light was used
- Diagnosed by low-voltage ECG after IV thallium ?!?
- Chinese parsley 100mg qid for 3 weeks
- Also given EPA and DHA
- Improvement based on ECG improvements ?!?

Rx - Melatonin

- Potent antioxidant
  - Most potent quencher of lipid peroxyl radicals
  - 5x better than GSH at quenching –OH radical
  - Stimulates SOD mRNA in many tissues
- May protect proteins in the lipid bilayer
  - Lipophilic and hydrophilic
  - Indole group may protect thiol groups
- Animal studies in several metals
  - As in mice – reduced cytotoxicity
  - Pb in mice – improved NK, macrophage and PMN activity
  - Cd in mice – decreased renal, hepatic, GI levels

HMD

- Proprietary blend of chlorella and cilantro
- Georgiou – Da Vinci center in Cyprus
  - 84 patients mixed conditions
  - 6h urine pre- 24h urine post- HMD or placebo
  - Increased excretion of Hg, As, Pb, Sn
  - Poor reporting of data, conflicting numbers in the paper

OSR

- N1, N3-bis(2-mercaptoethyl)isophthalamide
- Boyd Haley
- Antioxidant with high-ORAC score
- Little experience to date
- 100mg PO od

Jeffrey A. Morrison, MD

The use of NaEDTA for cardiovascular disease

Bio

Dr Jeffrey Morrison is a medical doctor who champions a nutritional approach to healthcare as well as preventing and reversing degenerative diseases. Dr. Morrison's specific treatments are aimed at enhancing the body's ability to heal and detoxify itself. These safe, non-toxic and non-invasive therapies are proving to be more powerful than conventional treatments, which utilize often dangerous drugs and surgeries. Dr Morrison completed his undergraduate training at the University of Rochester and received his medical doctorate from Jefferson Medical College in Philadelphia. He is trained and Board Certified in Family Practice and has completed additional training in Environmental Medicine. In 2001, Dr Morrison was on the medical staff at the Atkins Center for Complementary and Alternative Medicine in New York City, where he worked under Dr Robert Atkins, developer of the low carbohydrate lifestyle. He then went on to become the medical director of the Wellness Medical Center of Integrative Medicine in New York City. In 2002, Dr Morrison opened The Morrison Center on Fifth Avenue just steps from Manhattan's Union Square. Since then, Dr Morrison has used his successful integrative medicine and nutritional approach for both Health Optimization and the treatment and prevention of degenerative diseases, like: arthritis, high blood pressure, hormone imbalance, obesity, diabetes, chronic fatigue, anxiety, depression, heavy metal poisoning, and many other ailments. Dr Morrison is a member of the American Academy of Environmental Medicine (AAEM) as well as a lecturer and Board Member for the American College for the Advancement in Medicine (ACAM). Dr Morrison has made television appearances, written journal articles, chapters for textbooks, and has lectured throughout the country in the field of integrative and complementary medicine. Dr. Morrison has been featured as a health specialist on the Discovery Channel, Next Top Model, and several documentaries related to Anti-Aging. He has also contributed to articles in such publications as Cosmopolitan Magazine as well recommended through the bestselling Author Suzanne Somers in her most recent book "Ageless" focusing on Bio-identical Hormone Replacement Therapy.

Lecture Overview

The word chelation is derived from the Greek word chele meaning claw, such as the claw of a crab. In practice, the mechanism by which chelation works is by creating a firm grasp or bond between a chemical (i.e., EDTA) to a metal or mineral ion. A more complete definition is "the molecular incorporation of a mineral ion or cation into a heterocyclic ring structure by an organic molecule, the chelating agent." EDTA (EthyleneDiameneTetraAcetic acid) is currently approved for use as a chelating agent in the United States by the FDA for lead poisoning, hypercalcemia, and for the control of ventricular Arrhythmias associated with Digitalis Toxicity. During this lecture we will discuss the basic biochemistry by which chelation therapy works as well as the rational for approved and off label use of this agent.

Contact Information

The Morrison Center
103 Fifth Avenue
New York, NY 10003

drmorrison@themorrisoncenter.com

American College for Advancement in Medicine
Chelation Therapy Workshop
November 4-5, 2009
Las Vegas, Nevada

CaEDTA / NaEDTA – Basic Biochemistry, Indications for On and Off label use

Jeffrey A. Morrison, M.D., C.N.S.
103 Fifth Avenue, 6th Floor
New York, NY 10003

The following table summarizes chelating agents, the heavy metals they are used to treat, their route of administration, and their brand name.

Chelating Agent	Toxin	Route	Drug
Dimercaprol (BAL)	Arsenic Lead Mercury (inorganic)	i.m.	Dimercaptol Injection B.P. BAL in Oil
Dimercaptosiccinic acid (DMSA, Succimer)	Arsenic Lead Mercury	p.o.	Chemet
Dimercaptopropane-sulfonate (DMPS)	Arsenic Mercury	p.o. i.v.	Bulk form (for compounding by pharmacists)
D-pencillamine	Arsenic Mercury Lead	p.o.	Metalcaptase Pencillamine Cuprimine Depen
Ethylenediamintetra-acetic acid (EDTA) (Edetate disodium)	**Iron Lead Cadmium Aluminum**	**IV**	**Chealamide Versenate**

EDTA – Basic Biochemistry, Indications for On and Off label use

During this lecture you will learn:

1. The terminology and basic biochemistry of CaEDTA and NaEDTA chelation therapy
2. The on and off label uses of chelation therapy.
3. How to use EDTA chelation therapy in clinical practice
4. The potential benefits and adverse reactions of chelation therapy.
5. Case studies

What is EDTA Chelation Therapy?

- EDTA chelation therapy is an Intravenous treatment used for:
  - FDA approved uses:
    - Removing heavy metals (lead) - CaEDTA
    - Treating hypercalcemia - NaEDTA
    - Controling ventricular arrhythmias secondary to digitalis toxicity - NaEDTA
  - Non-FDA approved uses:
    - As an anti-oxidant by controlling lipid peroxidation
    - Reducing platelet stickiness in the management of atherosclerosis

The Definition of Chelation

- The work ***chelate*** is derived from the Greek word ***chele***, which refers to the claw of a crab, implying the firm binding action of a chemical to a metal ion.
- **Morgan** and **Drew** defined the term chelation in 1920 as - the incorporation of a **metal ion** into a **Heterocyclic Ring Structure**

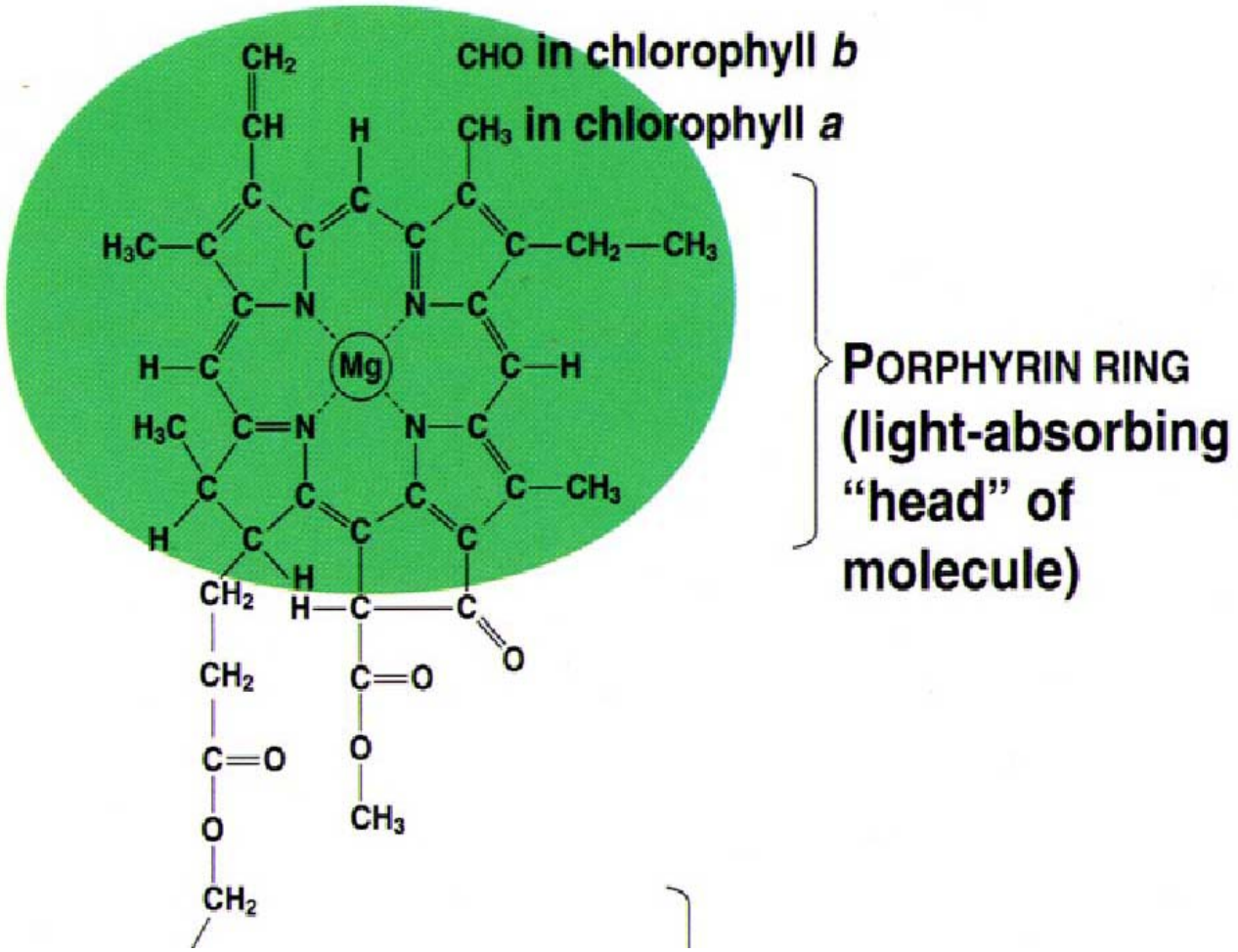
Basic Biochemistry

Heterocyclic Ring Structure

Chlorophyll

is a chelate of

Magnesium



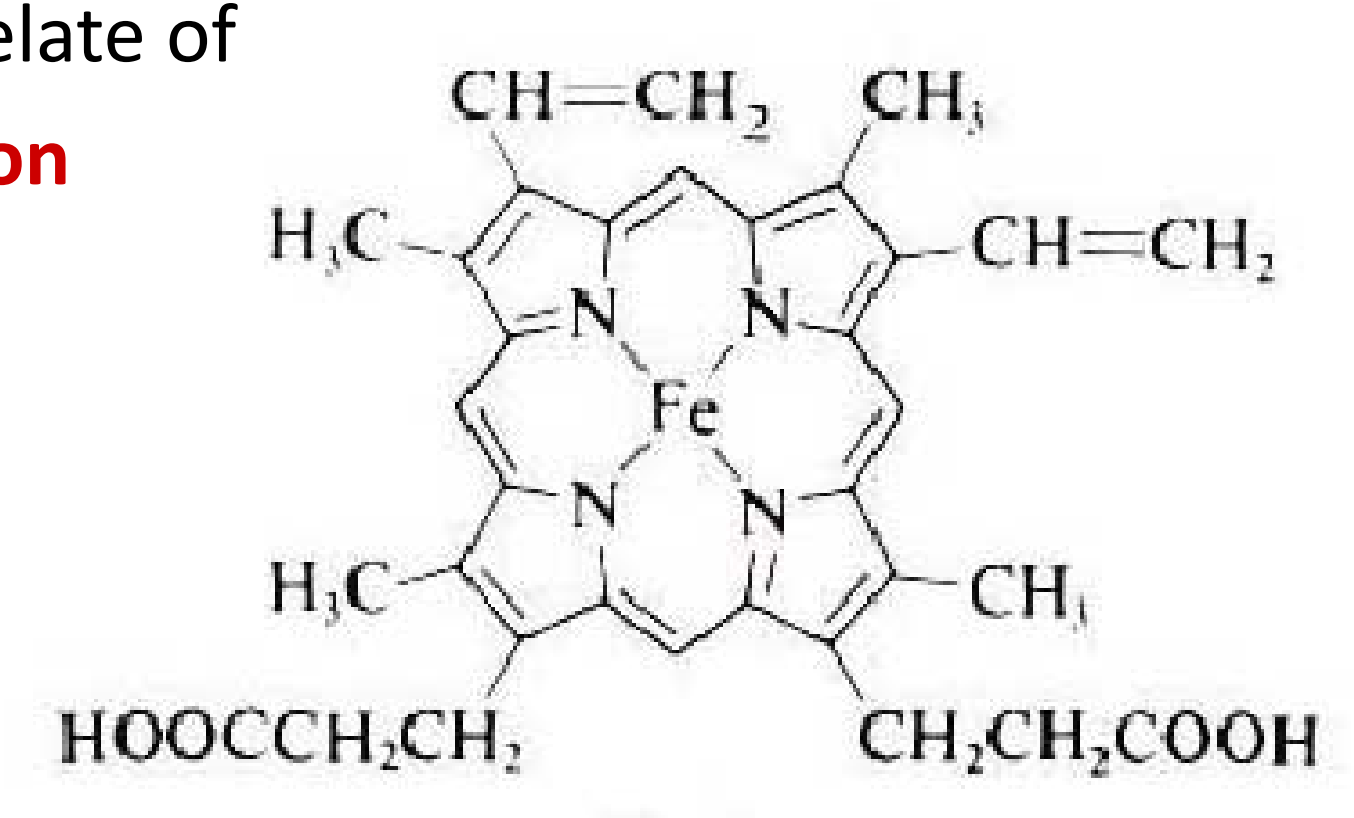
Basic Biochemistry

Heterocyclic Ring Structure

Hemoglobin

is a chelate of

Iron



Chelation Terminology

- Ion
  - A charged Particle
- Cation
  - Positively charged ion (Ca^{++})
  - Metals are positively-charged ions (cations)
- Anion
  - Negatively charged ion (Cl^{-})
  - Metal cations react to surround themselves with Anions

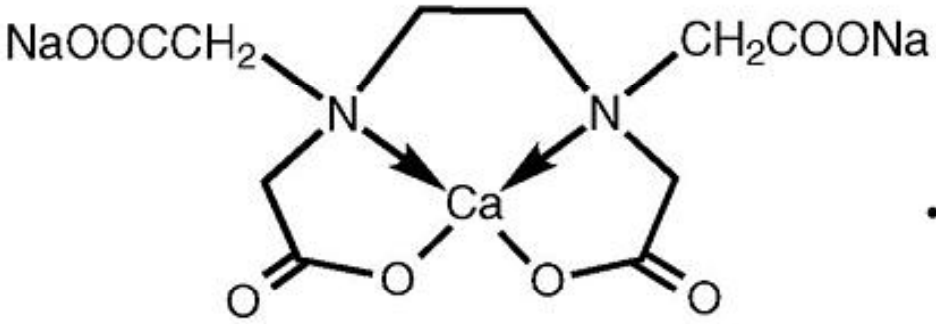
EDTA

(EthyleneDiamineTetraacetic Acid)

Octahedral structure:

- The EDTA molecule binds to a mineral or metal cation by donating up to 6 electron groups.
- By binding at these positions, a cation is surrounded by the EDTA molecule to form an **8 sided (octahedral) structure.**

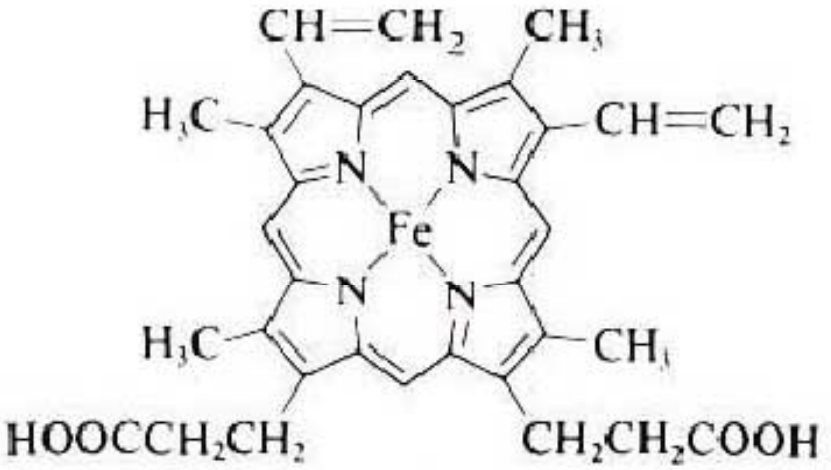
Calcium DiSodium EDTA



$C_{10}H_{12}CaN_2Na_2O_8 \bullet x\ H_2O$

Molecular weight 374.27 (anhydrous)

Hemoglobin



In Vitro Factors that determine the structure of EDTA complex

- **pH** - In low pH (more acidic), EDTA chelates become less stable and will release its ion more easily.
- **Binding Constant** - The higher the *binding constant*, the stronger a cation is bound to EDTA.
- **Concentration** - The higher the *concentration* of a cation, the more likely it is to bind to EDTA.

In Vitro Binding Constants

Metal Cation	Log K	Metal Cation	Log K
Cr^{++} (Chromium)	????	Cd^{++} (Cadmium)	16.5
Fe^{+++} (Iron)	25.1	Co^{++} (Cobalt)	16.3
Hg^{++} (Mercury)	21.8	Al^{+++} (Aluminum)	16.1
Cu^{++} (Copper)	18.8	Fe^{++} (Iron)	14.3
Pb^{++} (Lead)	18.5	Mn^{++} (Manganese)	13.7
Ni^{++} (Nickle)	18.0	Ca^{++} (Calcium)	10.7
Zn^{++} (Zinc)	16.5	Mg^{++} (Magnesium)	8.7

In Vivo binding constants
Special considerations

- **pH** - is not as much a factor in clinical practice due the tight regulation of physiologic buffers.
  - High pH (basic pH) in vitro is associated with greater binding stability
  - It is still important to encourage an alkaline diet as part of the chelation protocol to optimize outcomes

In Vivo binding constants
Special considerations

- **Concentration of Metals**
  - Through mass action – a high concentration of lower binding constant metals can displace metals of greater stability when they are present in low concentrations.
  - For example, **Calcium** is low in the stability constant table, however, a great deal of it is chelated by NaEDTA, because of its relative high concentration in the plasma.
    - This is why a patient may become hypocalcemic and it is unsafe to infuse NaEDTA quickly.

In Vivo binding constants
Special considerations

- **Concentration of Metals**
  - Although the binding constant for **zinc** is in the moderate range, great quantities of **Zinc** are removed with EDTA because of the relatively high concentration of **Zinc** in the body.

Important

  - This is why **Zinc** must be replenished when a patient undergoes a course of EDTA chelation therapy.

In Vivo binding constants
Special considerations

- **Binding constants** help direct treatment plan
  - **Fe+++** (ferric iron) has a high binding constant and is **easily removed with EDTA**.
    - This is good for patients with iron overload (hemochromatosis)
    - This may be bad for patients with iron deficiency anemia

In Vivo binding constants
Special considerations

- The binding of **Mercury (Hg)** to EDTA **In Vivo** is not consistent with it's binding constant
  - Although **mercury** has a relatively high binding constant **In Vitro**, EDTA does not extract much **mercury** out of the tissues **In Vivo**.
  - This is because **mercury** is extremely tightly bound to organic Sulfhydral groups in tissues.

Additional Points

- The addition of Magnesium to a bottle of DiSodium EDTA prior to administration produces **Magnesium DiSodium EDTA**. However, because Mg^{++} has a low binding constant, the complex is not very stable and Mg^{++} is easily replaced by any of the metals with higher binding constants like **lead** or **cadmium**

Selecting Patients

May Decrease MI and Stroke

- **Blood lead level** was significantly associated with both MI and stroke mortality in a nationally representative sample of 13,946 adult participants of the Third National Health and Nutrition Examination Survey recruited in 1988 to 1994 and followed up for up to 12 years for all-cause and cause-specific mortality. The association was evident at levels >0.10 µmol/L (>2 µg/dL)
    - Low-Level Enviromental Exposure to Lead Unmasked as Silent Killer, Circulation, Sept 26, 2006;114(13):1347-49.
    - Blood Lead Below 0.48 µmol/L (10 µg/dL) and Mortality Among US Adults, Circulation, Sept 26, 2006;114:1388-94.

Selecting Patients

May Help Reverse Hypertenstion

- The improvement of Hypertension with EDTA chelation therapy may be due to the binding of heavy metals like Pb^{++} (lead) and Cd^{++} (Cadmium), both of which have been found to increase blood pressure.
  - JAMA 2003; 289: 1523-1532. – Lead stored in women's bones and released when they reach menopause multiplies their risk of potentially fatal high blood pressure (study of over 2000 women aged 40-59)
  - JAMA 1996, 275: 1171-1176. – Lead accumulation may be an independent risk factor for developing hypertension in men.
- Magnesium in NaMgEDTA may lower BP by decreasing vasospasm

Selecting Patients

EDTA may improve Bone Mineral Density

- DisodiumEDTA binds with circulating unbound serum Calcium to form a Ca-EDTA complex. As a result of lowering serum Calcium levels, the body's homeostatic mechanisms are stimulated to release Parathyroid hormone (PTH). With repeated treatments, the pulsatile stimulation of PTH stimulates Osteoblastic bone activity, thereby recalcifying demineralized bone.
    - J Ad Med 1988: 1(2); 79-85. - …edta therapy might enhance bone growth in patients with osteoporosis and has no negative effect on patients with normal bone density readings.

Selecting Patients

EDTA may improve kidney function

- Low-level environmental **Pb^{++} (lead)** exposure may accelerate progressive renal insufficiency in non-diabetic adults who have chronic renal disease. Repeated chelation therapy may improve renal function and slow the progression of renal insufficiency by lowering **Pb^{++}** levels.
    - NEJM 2003; 348: 277-286.

Selecting Patients

EDTA may improve degenerative processes

- EDTA is responsible for the reduction of intracellular heavy metals that impair enzyme reactions and block metabolic pathways.
- Heavy metal accumulation has been associated with:
  - Alzheimers disease
  - Parkinsons disease
    - Int J Occup Med Environ Health 2001; 14(3): 209-218. – Lead, mercury, manganese and copper have been implicated in ALS and Parkinsons disease. There is elevated risk for Alzheimers disease in areas where aluminum is in the drinking water
  - Cardiac Arrhythmias
    - Am J Card 1998; 82(5): 594-599. – Cumulative exposure to lead, even at low levels, may depress cardiac conduction.

Selecting Patients

EDTA may improve circulation

- EDTA stimulates improved capillary bed perfusion and a decrease in basement membrane thickening. This subsequently causes a decrease in peripheral resistance with a secondary increase in peripheral flow, particularly in the Diabetic patient.
    - J Cardiovasc Nurs 1996; 10(3): 78-96. – Edta chelation is a valuable therapuetic option for vascular disease, either alone or in conjucntion with standard treatment protocols.

Selecting Patients

Other possible benefits

- May protect against cirrhosis
  - Zhongguo Zhong Xi Yi Jie He Za Zhi 2000; 20(12): 890-892. De-copper therapy with EDTA and / or DMPS could improve liver cirrhosis and liver function.
- May improve Glucose metabolism in diabetics
  - Diabetologia 1967; 3(5): 449-452. EDTA and insulin. A study of the effect of salts of EDTA upon insulin action in vivo and in vitro.
- May improve collagen disease processes (i.e. Rheumatoid Arthritis)
  - Clin Endocrinol (Oxf) 1990; 32(3): 323-328. A high intracellular calcium content is associated with inflammatory disease.
- May remove Calcium from plaque formation in blood vessels
  - Clarke N, et al. Am J Med Sci 1955;229:142. The "in vivo" dissolution of metastatic calcium: An approach to atherosclerosis.

List of diseases that may benefit with chelation therapy (off label use):

Coronary artery disease
Atherosclerosis
Cerebral vascular disease
Peripheral vascular disease
Cardiac Arrhythmias
Collagen vascular disease
(Lupus, Arthritis, etc)
Alzheimers disease
Parkinsons disease
Type I and Type II DM
Heavy Metal Toxicity
Osteoarthritis
Venous stasis disorders
Peripheral neuropathy
Fibromyalgia
Kidney disease
Osteoporosis

Commercial preparations of EDTA

IMPORTANT

- *DiSodium EDTA* (NaEDTA) – approved by the FDA for use in:
  - Hypercalcemia
  - Ventricular Arrhythmias associated with Digitalis Toxicity
- *Calcium DiSodium EDTA* (CaEDTA) – approved by the FDA for use in:
  - Removal of lead and other heavy metals
    - It is excreted primarily by the kidney with about 50% excreted in one hour and over 95% excreted within 24 hours.
    - Almost none of the compound is metabolized
    - Only about 5% is absorbed from oral administration

Commercial preparations of EDTA

WARNING

NaEDTA must only be given by the intravenous (IV) route. If it is administered intramuscularly (IM), the patient will experience severe pain associated with tissue sloughing at the injection site.

NaEDTA must only be given by slow IV infusion at 1gm / hour (16mg/min) or less.

Precautions for using EDTA:

- **Drug Interactions:** None Known
- **Pregnancy:** Category B (however, EDTA should **NOT** be used during pregnancy!)
- **Nursing Mothers:** It is unknown whether CaEDTA is excreted in mother's milk. Caution should be exercised if it is used.
- **Pediatric Use:** Since lead poisoning occurs in children and adults, but is more severe in children, CaEDTA is used in all ages.

Precautions for using EDTA:

- **Contraindications:** Severe allergy to EDTA, pregnancy, anuria or acute lead encephalopathy.
- **Relative Contraindications:** Renal dialysis
- **Possible Side Effects:**
  - Nephrotoxicity – very rare if infused at proper rate, dose and frequency
    - Minimize this risk by re-checking kidney function tests every 5 to 10 treatments and adjust EDTA dose based on creatinine clearance

Precautions for using EDTA:

- **Possible Side Effects:**
  - Hypocalcemia – Occurs if infused too rapidly or in excessive doses
    - Watch for muscle cramps, numbness and tingling
    - May be reversed with IV Calcium gluconate
  - Allergy – True allergy to EDTA is rare
    - Allergic symptoms more likely from an admixture ingredient or preservative
    - Typically allergy to lidocaine or B-vitamin
    - Try to get preservative free ingredients

Precautions for using EDTA:

- **Possible Side Effects:**
  - Thrombophlebitis – From local irritation at the infusion site
  - **Prevention** of thrombophlebitis:
    - Use Heparin 1000iu to 5000iu in infusion mixture
    - Buffer to physiologic pH with Bicarbonate
    - Use a larger vein
    - Reduce the rate of infusion
  - **Treatment** – topical moist heat, NSAIDS, arnica, bromelain

Precautions for using EDTA:

- **Possible Side Effects:**
  - Congestive Heart Failure – In patients with cardiovascular disease, the increased fluid load of the chelation may aggravate CHF.
    - Weigh cardiac patients each visit
    - Continue diuretic use and increase dose if needed
    - Decrease sodium content of infusion (IV Vit C contains 11% sodium by weight)
    - Slow the infusion rate
    - Decrease the calculated therapeutic dose of EDTA in proportionally less fluid

Precautions for using EDTA:

- **Possible Side Effects:**
  - Hypoglycemia – Blood glucose may fall during an EDTA IV
    - Ensure adequate protein intake before and during IV
    - Patients should bring a fruit snack
    - A 50% dextrose solution for IV use should be readily available.
  - Fatigue – patients may complain of feeling "washed out" for 24-48hrs after a single treatment
    - Use IV nutritional infusions without EDTA in between chelation treatments
    - Increase interval between treatments

Before initiating chelation therapy always:

- Perform an H&P on your patient.
- Check
  - **Liver function tests**
  - **BUN / Cr, UA and Creatinine clearance**
  - CBC with Dif, electrolytes, EKG
  - Whole blood lead and provoked urine lead levels
  - condition specific work-up.
- Inform patient of risks and benefits of NaEDTA:
  - Pain / bleeding at infusion site
  - Hypoglycemia
  - Renal toxicity
  - Zinc deficiency

IV Na EDTA Chelation Protocol – 50mg/kg/day at 1gm/hour

250cc – 500cc	Sterile Water
2.0cc	Vitamin B6 (100mg/cc)
1.0cc	B complex 100
20cc	Sodium Bicarbonate 1mEq/ml
5cc	Procaine
1.0cc	Vitamin B5 (250mg/cc)
10.0cc	Vitamin C (500mg/cc)
5.0cc	Magnesium Sulphate
1.0cc	Potassium Chloride 2Meq/cc)
10 - 20cc	DiSodium EDTA (150mg/cc) adjust per Cackcroft Gault Formula
2.5cc	Heparin (5000U/cc)

IV Ca EDTA Chelation Protocol

100cc	Normal Saline
1.0cc	Vitamin B6 (100mg/cc)
0.25cc	Vitamin B1 (100mg/cc)
0.25cc	B complex 100
1.0cc	Vitamin B12 (1000mcg/cc)
2.0cc	Vitamin B5 (250mg/cc)
3.0cc	Vitamin C (500mg/cc)
2.0cc	Magnesium Chloride (200mg/cc)
1.0cc	Potassium Chloride (2Meq/cc)
5 – 10cc	Calcium DiSodium EDTA (300mg/cc) adjust per Cackcroft Gault Formula
0.1cc	Heparin (5000U/cc)

Minimize Pain

Use Magnesium

- Reduce the discomfort of the infusion by releasing the heat in the bottle instead of the patient.
  - The combination of NaEDTA with Magnesium in the infusion bottle prior to administration releases eight (8) kcal of heat in an Exothermic reaction.

Minimize Pain

Alkinalize the solution

- Pain at the infusion site can be due to **acidity** of the solution. The EDTA solution becomes acidic due to the release of Hydrogen ions when Mg^{++} is added to the EDTA. (As the Mg^{++} is chelated by EDTA in the bottle, H^{+} (hydrogen ions) are released).
  - The carrier solution can be made more alkaline by adding **Sodium Bicarbonate**

Minimize Pain

Create an **Isotonic** solution

- Care must be taken to choose the ingredients for the carrier solution to balance the osmolarity. Pain will occur if the solution is Hypertonic (too concentrated) or Hypotonic (too dilute) in relation to the normal osmolarity of blood.
  - An isotonic solution has a similar concentration to blood.

Calculating dose of EDTA

- **Acquire computer program to calculate dose**

or

- 50 mg EDTA per Kg (LBW X 1.33) X (CrCl/100)

Glomerular Filtration Rate Computation

$$CrCl = \frac{(140 - Age) \times (LBW \times 1.33)}{(72 \times Cr)}$$

  - CrCl = computed Creatinine Clearance, approximating renal glomerular filtration rate in ml/min
  - Age =patient's age
  - LBW = computed lean body weight in Kg.
  - Cr = serum creatinine in mg/dL
    - For CrCl in women, multiply the above result by 0.85

Calculating dose of EDTA cont'd…

LEAN BODY WEIGHT (LBW) IN KG AS USED IN ABOVE COMPUTATIONS

- Lean body weight for males is computed at 50 kg plus 2.3 kg for each inch of height over 5 feet.
- Lean body weight for females is computed at 45.5 kg plus 2.3 kg for every inch of height over 5 feet.
- Actual weight is used whenever actual weight is less than computed lean body weight.

Calculating dose of EDTA cont'd…

- The dose is usually limited to a maximum of 3.0 grams (widely accepted as the fully effective dose).
    - Correct for CrCl/100 only if computed creatinine clearance is less than 100 ml/min.
- Maximum rate of infusion is limited in NaEDTA to 1gm per hour.

Case Study CaEDTA: Mr D.

- 81 year old male in good state of health presents with concerns about fatigue and memory changes. (He has trouble remembering names.)
- Pmhx – CAD, MI, hypercholesterolemia
- Pshx – CABG x3 - Dec. 1984
- Meds – ASA, Atenolol, Plavix
- Occupation – Supervisor at Bear Sterns
- Requests chelation therapy

Mr D cont'd…

- Ht: 5' 3"
- Wt: 162lbs
- Cr: 1.2
- Blood lead: 4 mcg/dl (ref range <10)
- EDTA dose calculated to be >3.0gm
- Provoked tests done with 1.5gm CaEDTA
- Treatment done with 2.0gm CaEDTA

Mr D. cont'd…

URINE TOXIC METALS

LAB#: U070823-0635-1
PATIENT:
SEX: Male
AGE: 81

CLIENT#: 25128
DOCTOR: Jeff A. Morrison, MD

103 5th Ave 6th Floor
New York, NY 10003

POTENTIALLY TOXIC METALS

METALS	RESULT µg/g CREAT	REFERENCE RANGE	WITHIN REFERENCE RANGE / ELEVATED / VERY ELEVATED
Aluminum	82	< 25	
Antimony	< dl	< 0.6	
Arsenic	61	< 120	
Beryllium	< dl	< 0.5	
ismuth	< dl	< 10	
Cadmium	2.6	< 2	
Lead	44	< 5	
Mercury	< dl	< 3	
Nickel	7.4	< 10	
Platinum	< dl	< 1	
Thallium	0.1	< 0.7	
Thorium	< dl	< 0.3	
Tin	1.3	< 9	
Tungsten	< dl	< 0.7	
anium	< dl	< 0.1	

CREATININE

	RESULT mg/dL	REFERENCE RANGE	2SD LOW 1SD LOW MEAN 1SD HIGH 2SD HIGH
Creatinine	24	45- 225	

SPECIMEN DATA

Comments:
Date Collected: 8/21/2007
Date Received: 8/23/2007
Date Completed: 8/29/2007

Method: ICP-MS
<dl: less than detection limit
Provoking Agent: CA EDTA

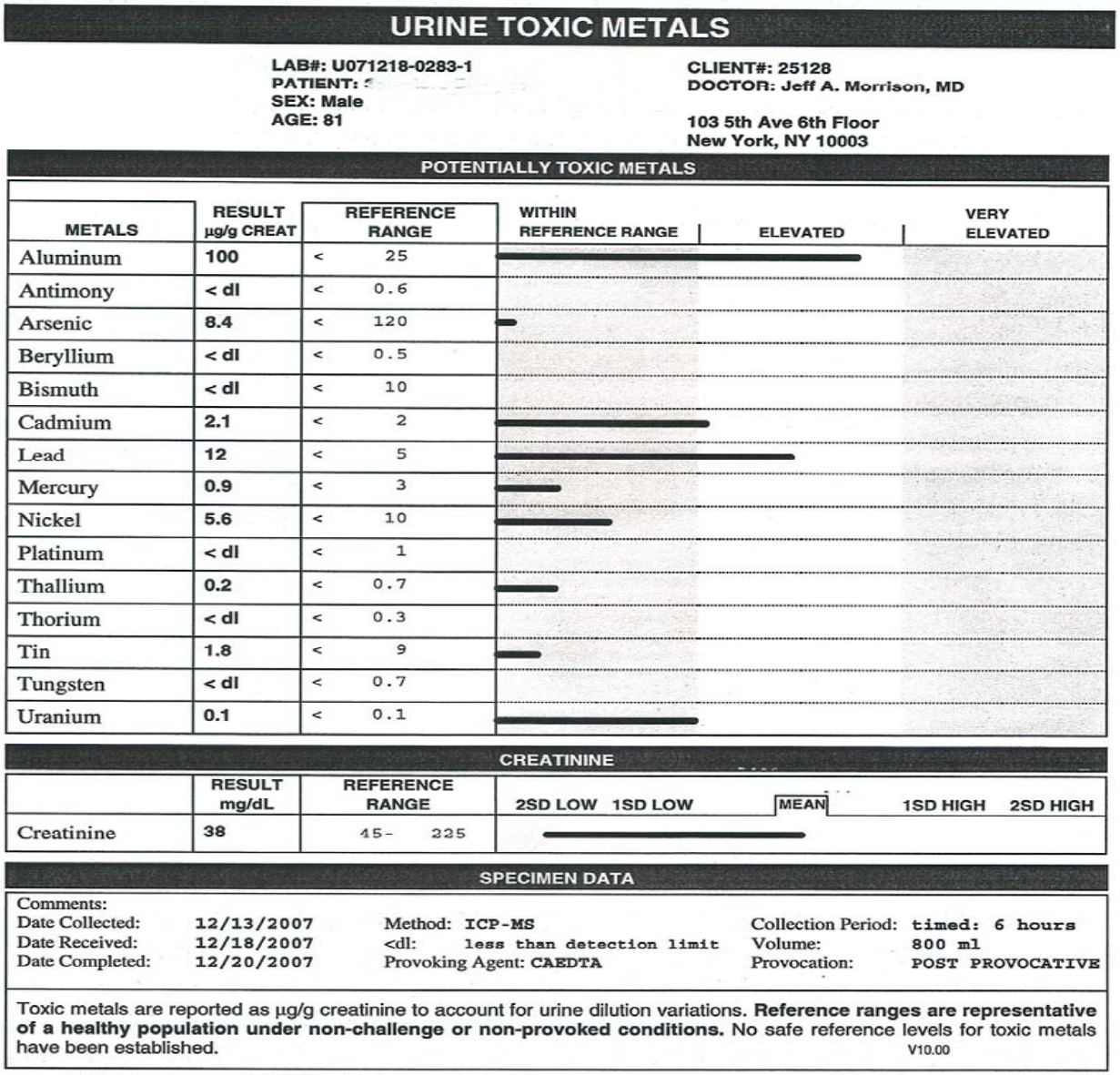
Collection Period: timed: 6 hours
Volume: 1850 ml
Provocation: POST PROVOCATIVE

Toxic metals are reported as µg/g creatinine to account for urine dilution variations. **Reference ranges are representative of a healthy population under non-challenge or non-provoked conditions.** No safe reference levels for toxic metals have been established.

V10.00

After 10 CaEDTA tx

- Improved
  - Memory
  - Energy



URINE TOXIC METALS

LAB#: U071218-0283-1
PATIENT: [redacted]
SEX: Male
AGE: 81

CLIENT#: 25128
DOCTOR: Jeff A. Morrison, MD

103 5th Ave 6th Floor
New York, NY 10003

POTENTIALLY TOXIC METALS

METALS	RESULT µg/g CREAT	REFERENCE RANGE	WITHIN REFERENCE RANGE / ELEVATED / VERY ELEVATED
Aluminum	100	< 25	
Antimony	< dl	< 0.6	
Arsenic	8.4	< 120	
Beryllium	< dl	< 0.5	
Bismuth	< dl	< 10	
Cadmium	2.1	< 2	
Lead	12	< 5	
Mercury	0.9	< 3	
Nickel	5.6	< 10	
Platinum	< dl	< 1	
Thallium	0.2	< 0.7	
Thorium	< dl	< 0.3	
Tin	1.8	< 9	
Tungsten	< dl	< 0.7	
Uranium	0.1	< 0.1	

CREATININE

	RESULT mg/dL	REFERENCE RANGE	2SD LOW 1SD LOW MEAN 1SD HIGH 2SD HIGH
Creatinine	38	45- 225	

SPECIMEN DATA

Comments:
Date Collected: 12/13/2007
Date Received: 12/18/2007
Date Completed: 12/20/2007

Method: ICP-MS
<dl: less than detection limit
Provoking Agent: CAEDTA

Collection Period: timed: 6 hours
Volume: 800 ml
Provocation: POST PROVOCATIVE

Toxic metals are reported as µg/g creatinine to account for urine dilution variations. **Reference ranges are representative of a healthy population under non-challenge or non-provoked conditions.** No safe reference levels for toxic metals have been established.

V10.00

Case Study NaEDTA: Mrs B

- 78 y.o. Female patient present for second opinion on Carotid Endarterectomy, s/p R retinal artery branch occlusion and Carotid Doppler showing B/L Internal carotid artery 50-59% stenosis.
- Patient complained of fatigue, change in vision right eye
- EKG, Holter monitor and Echo showed no source for embolisation.
- Refused TEE
- Refused Carotid Endarterectomy

- Evaluation from Cardiologist #1 4/28/2005
  - Recommendations:
    - TEE
    - Urgent consultation with vascular surgeon for carotid endarterctomy
    - Medical treatment:
      - ACE inhibitor, statin medication, ASA
    - Patient refused all treatment

RICHARD L. MUELLER, MD, FACC, FACP
CARDIOVASCULAR DIAGNOSTICS, PC
MEDICAL ASSOCIATES OF NEW YORK
401 EAST 66th STREET
NEW YORK, NY 10022-4103

Tel: 212.593.9800

Fax: 212.593.5757
Fax: 212.319.1577

Richard L. Mueller, MD, FACC, FACP — Cardiovascular Diseases
Inna Bukharovich, MD, CBNC — Cardiovascular Diseases
Jason T. Slyer, RN, MS, FNP, BC — Cardiac Nurse Practitioner
Brian S. Hoch, MD — Internal Medicine / Nephrology
Yelena Karasina, MD — Internal Medicine
Markos I. Koutsos, MD — Gastroenterology

4/26/05

Susan Klein, MD
120 E. 79 St.
New York, NY 10021

Re: Ms. [redacted]

Dear Dr. Klein: Susan

Thank you for referring Ms. Burns for cardiologic evaluation. As you know, she is a 78 year old woman who recently suffered sudden right visual loss, due to a retinal artery branch occlusion supplying the right upper retinal field; this was, as you know, evaluated expertly by Dr. Levitsky. She was started on aspirin by you, and I suggested increasing it to 325 mg/d pending completion of evaluation.

She denies any cardiac symptoms, including chest pain, dyspnea, palpitations, syncope, edema, other neurologic symptoms, or claudication.

As her past medical history is well known to you, I will not recite it here. Her father had an MI at age 73.

Physical examination reveals blood pressure of 132/70 and pulse of 88 and regular. The remainder of the cardiopulmonary examination reveals only a pectus excavatum; the remainder is normal.

ECG reveals sinus rhythm at 60-70 bpm, with frequent APC's, and minimal (1/4 mm) usploping ST depressions in V5 and V6.

Recent cardiac testing has been forwarded to you; carotid Doppler revealed 50-60% bilateral internal carotid stenosis; echocardiography was a technically difficult study, but did not reveal an obvious source of embolism and had no major abnormalities; Holter monitor did not reveal atrial fibrillation or flutter. Limited additional echo today, performed due to technically difficult echo imaging due to closely spaced ribs and pectus deformity, revealed significant aortic arch and abdominal aortic atherosclerotic plaque, with possible small emboli in transit apparently visualized.

After lengthy discussions today and on 4/24/06 regarding the evaluation of stroke and all diagnostic and therapeutic implications, she has declined to undergo recommended transesophageal echocardiography. She is also reluctant to add a statin and ACEI as I have strongly advised.

The exact cause of Ms. Burns' retinal stroke (permanent / persistent visual defect at this point) is not fully certain, but it could clearly be explained by embolization from her moderate stenosis of the right internal carotid artery. Likewise, it could be explained by the apparent significant aortic arch plaque (with apparent embolic signals detected in transit during imaging). Other theoretic causes cannot be fully ruled out, due to the patient's refusal of TEE.

4

Recommended therapy for symptomatic carotid stenosis of > 50% narrowing would be carotid endarterectomy, aspirin, statin, and ACE inhibitor. Urgent consultation with a vascular surgeon of your choice was advised, but she declines both surgery and even a vascular surgery consultation at present, based on our discussions. Recommended therapy for embolism from aortic plaque is not fully defined, but both coumadin and statins have been advocated; no definite prospective studies or guidelines consensus are available.

As for the report of a positive IgM anticardiolipid antibody, I doubt it would affect therapy, given the probable source of embolism from the carotid artery and/or aortic arch.

The full differential diagnosis of stroke and embolism, as well as all diagnostic and therapeutic implications of findings to date, were discussed in great detail with Ms. Burns. She declines TEE, agrees to continue aspirin at 325 mg/d with food, and is non committal about my recommendation to add a statin (regardless of LDL level) and altace. She also declines to see a vascular surgeon as I advised her to do. She understands the serious risk of stroke, embolism, disability, blindness, and death. She is non committal about whether she wants me to just perform cardiovascular testing only for her, or whether she wishes for me to join in her care. It appears for now that she wishes that I perform the tests only, and that she will follow up with you and with Dr. Levitsky. Follow up carotid Doppler in 1 year, and echocardiography in about 2 years, was advised. Given her frequent APC's, TSH should be checked, if not already done. BP should be well controlled; she states her BP is always normal, and lower than it was here today.

Given diffuse atherosclerotic disease and minimal non specific repolarization changes on ECG, an exercise myoview stress test was recommended, which she declined. Ms. Burns requested that I would only see her as needed, and for future cardiovascular testing.

Thank you again for referring Ms. Burns; as always, you have my warmest personal regards.

Best wishes,

Richard L. Mueller, MD, FACC, FACP, FASE
RM/jm
cc: Dr. Levitsky

4/27/06

ICANL
Nuclear Cardiology
Accredited Nuclear Cardiology Laboratory

04/24/2006 08:12 2125935757 MEDICAL ASSOCIATES

Marjorie Burns
PID: 562407
04/18/2006

CEREBROVASCULAR DUPLEX SCAN

HP 2000

Name: DOB: 8/24/27 Sex: Female Date: 4/18/06 Tape: 21

Referral Source: Dr. Mueller

C.C.:

Risk Factors

Smoking: Angina/MI: No Hypercholesterolemia: COPD: No

Hypertension: No Family History: No Diabetes: No

Indications

Weakness: Syncope: Yes Dysphasia: No Memory Loss: No Dizziness: Yes

Previous CVA: Paresthesias: Paresis: Previous Bruit: No High Risk Patient: No

Previous TIA: Numbness: Head Trauma: No Pre-op Evaluation: No Amaurosis:

Subarachnoid Hemorrhage/Vasospasm: No Previous Carotid Stenosis: No Right: % Left: %

Previous Right Carotid Endarterectomy: No Date: Previous Left Carotid Endarterectomy: No Date:

CAT Scan: No data

Other: No data

Results

RIGHT

Brachial BP: / Bruit: No

Systole	Diastole	% Stenosis
127	29	50-59%
160	36	50-59%
154	27	
111	11	

1.0	ICA/CCA Ratio
0.8	Resistance Index
Prograde	Vertebral Flow
heterogeneous	Plaque Composition
smooth	Plaque Surface

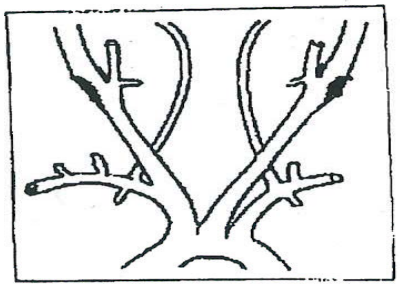
LEFT

Brachial BP: / Bruit: No

Velocity in cm/sec	Systole	Diastole	% Stenosis
Proximal ICA	145	38	50-59%
Distal ICA	126	33	50-59%
Proximal CCA			
Distal CCA	127	27	
Bulb			
Ext. Carotid Artery	93	8	
Subclavian			
Vertebral Artery			

1.1	
0.7	
Prograde	
heterogeneous	
smooth	

Carotid Artery Map:



Conclusions

RIGHT: Plaque formation is present at proximal internal carotid artery, causing 50-59% stenosis on this side. Normal common and external carotid arteries.

LEFT: Plaque formation is present at proximal internal carotid artery, causing 50-59% stenosis on this side. Normal common and external carotid arteries.

Interpreting Physician: Demetrios Georgiou MD

Technologist:

Medical Associates Of New York
401 East 55th St. ; NY, NY 10022-4103.tel# 212-593-9800

4/24/06

4

Document max

Evaluation by me on 6/2006

- 78 yo Female patient c/o fatigue and recent change in R visual field s/p R Retinal artery branch occlusion.
- PE – WNL except noticeable pale skin color and malaise
- Lab work WNL
- NaEDTA 3.0 gm qwk x 40 treatments
- After chelation, refer to new cardiologist for second opinion and retesting when complete course of treatment

ANTHONY J. PEPE, M.D., F.A.C.C.
CARDIOVASCULAR DISEASES

425 W. 59TH STREET, SUITE 8B
NEW YORK, NY 10019
TELEPHONE (212) 376-3180
FAX (212) 376-3190

30 March 2007

Jeffrey Morrison, M.D.
103 5TH Ave.—6th Fl.
N.Y. N.Y. 10003

RE: MS. [redacted]

Dear Jeff,

Thank you for referring Ms. Burns for cardiac evaluation. She has suffered a right retinal embolic event in 2005, although a definite cardiac source was not identified. There was no evidence of serious arrhythmia, atrial fibrillation, or intra-cardiac embolic sources. She has had several trans-thoracic echocardiograms, but has steadfastly refused trans-esophageal echo exams. There was no evidence of an atrial septal defect nor patent foramen ovale on one of her trans-thoracic studies. Of note is the presence of 50-60 % bilateral carotid disease, and some aortic arch and abdominal aortic atherosclerotic disease. The proximal aortic plaques may have shown evidence of embolization during one of her echo tests. She is currently undergoing chelation therapy under your guidance, and is taking an organic "platelet inhibitor" instead of aspirin; she has refused COUMADIN therapy. Her physical examination in my office showed no evidence of active vascular disease, and her BP was 130/70, with a regular pulse. Office ECG showed only APC'S.

After extensive discussion with the patient, she has agreed to undergo a trans-esophageal echocardiogram, which will be done at the Cardiology Division at Roosevelt Hosp. (her main concern was gagging during the procedure). Although the results of the TEE will not alter treatment, it may localize a probable source of the emboli. As far as treatment is concerned, she continues to refuse COUMADIN, but will re-consider ASA treatment, and high dose STATIN therapy. I discussed the importance of PLAQUE STABILIZATION with the patient, as well as possible plaque reversal with STATIN treatment. In addition, it is important to repeat her CAROTID DOPPLER examination, (the last being 4/06), especially after completing a course of chelation therapy.

I will send you the results of the TEE as they become available; thank you again for your kind referral. Best regards for a happy Spring !

Very truly yours,

Tony

Anthony J. Pepe, M.D.,F.A.C.C.

Evaluation from Cardiologist #2

- Recommendation for:
  - TEE
  - Medical treatment:
    - ACE inhibitor, statin medication, ASA
  - Repeat B/L carotid artery doppler

Columbus Cardiology Associates
425W 59th Street
Suite 8B
New York, NY 10019
Tel. (212) 376-3180

Date: 4/10/2007

Patient:
DOB: 8/24/1927

Referring Physician: Dr. Anthony Pepe, MD

Duplex Ultrasound Evaluation of the Carotid Arteries

Evaluation of both carotid arteries was performed using a HP 5000 HDI ultrasound machine. All vessels were evaluated using color Doppler as well as gray scale imaging.
Transverse and sagittal views were obtained and Doppler flow measurements performed in the proximal, mid and distal common carotid artery and proximal mid and distal internal carotid artery.
Direction of flow was determined for the vertebral arteries and evaluation of the external carotid arteries including assessment of stenosis in these vessels was performed.
Color Doppler images were recorded where appropriate.

Findings:

Carotid Arteries

Right side: The velocity measurement and ultrasound images are consistent with a **20-39%** stenosis. Moderate calcified plaque was seen in the right internal carotid artery. Mild plaque was seen in the right common carotid artery.

Left side: The velocity measurement and ultrasound images are consistent with a **20-39%** stenosis. Moderate calcified plaque was seen in the left internal carotid artery. Mild plaque was seen in the left common carotid artery.

Vertebral Arteries: Antegrade flow bilaterally.

Impression: **20-39%** stenosis of the Right ICA
20-39% stenosis of the Left ICA

Olivier Frankenberger, MD

Last Evaluation of Mrs. B by Dr Morrison

- After completion of 40 IV NaEDTA chelation treatments patient reported increased energy and had a visible improvement in color of skin.
- Patient is on maintenance IV NaEDTA 3.0gm 1x/month and still doing well.

Summary

- By understanding how EDTA chelation works you can safely and effectively administer treatment
  - Remember – first do no harm and be prepared
  - Replace minerals in between treatments
    - Zinc and Iron if needed
  - Be prepared for side effects
    - Low blood sugar, vein irritation, change in kidney function
  - Decrease pain during administration

The Science Behind Chelation Therapy

Jeffrey A. Morrison, M.D.

103 Fifth Avenue, 6th Floor

New York, NY 10003

Jeffrey A. Morrison, M.D.
Chelation Therapy
Bibliography

1. Chemet (Succimer), Thomson PDR, 60th Edition, 2006; 2480-2.
2. Calcium Disodium Versenate (edentate calcium disodium injection), Thomson PDR, 60th Edition, 2006; 1819-20.
3. DePalma A. The canaries had their coal mines; using songbirds to seek out mercury in the catskill watershed. In: The New York Times, August 8, 2005.
4. Hecky RE, Ramsey DJ, Bodaly RA, Strange NE. Increased methylmercury contamination in fish in newly formed freshwater reservoirs. In: Advances in Mercury Toxicology (Suzuki T, Imura N, Clarkson TW, eds). New York: Plenum Press, 1991;33-52.
5. Lorscheider FL, Vimy MJ. Evaluation of the safety issue of mercury release from dental fillings. FASEB J (Federation of American Societies for Experimental Biology Journal) 7:1432-1433 (1993).
6. Aposhian HV, Bruce DC, Alter W, Dart RC, Hurlbut KM, Aposhian MM. Urinary mercury after administration of 2,3-dimercaptopropane-1-sulfonic acid: correlation with dental amalgam score. FASEB J 6:2472-2476 (1992).
7. The trouble with mercury. Nature, New York. Winter 2006.
8. Clarkson TW, Friberg L, Hursh JB, Nylander M. The prediction of intake of mercury vapor from amalgams. In: Biological Monitoring of Toxic Metals (Clarkson TW, Friberg L, Nordberg GF, Sager PR, eds). New York: Plenum Press, 1988; 247-260.
9. Summers AO, Wireman J, Vimy MJ, Lorscheider FL, Marshall B, Levy SB, Bennett S, Billard L. Mercury released from dental "silver" fillings provokes an increase in mercury- and antibiotic-resistant bacteria in oral and intestinal floras of primates. Antimicrob Agents Chemother 37:825-834 (1993).
10. U.S. Centers for Disease Control. Preventing Lead Poisoning in Young Children. Atlanta, GA: U.S. Department of Health and Human Services, 1991.
11. National Health and Environmental Effects Research Laboratory. Workshop on Developing and Epidemiology Research Strategy for Arsenic in Drinking Water (Work Assignment 1-12, Contract no 68-D2-0187). Research Triangle Park, NC:National Health and Environmental Effects Research Laboratory, 1994.
12. Sancha AM, Vega F, Venturino H, Fuentes S, Salazar AM, Moreno V, Baron AM, Rodriguez D. The arsenic health problem in northern Chile evaluation and control. A case study preliminary report. In: Proceedings of the International Seminar. Arsenic in the Environment and Its Incidence on Health. Santiago, Chile:Universidad de Chile, 1992;187-202.
13. Aposhian HV, Arroyo A, Cebrian ME, Del Razo LM, Hurlbut KM, Dart RC, Gonzalez-Ramirez D, Kreppel H, Speisky H, Smith A, et al. DMPS-arsenic challenge test. I: Increased urinary excretion of monomethylarsonic acid in humans given dimercaptopropane sulfonate. J Pharmacol Exp Ther 277:938-944 (1997).
14. Hopenhayn-Rich C, Biggs ML, Smith AH, Kalman DA, Moore LE. Methylation study in a population environmentally exposed to high arsenic drinking water. Environ Health Perspect 104:1200-1207(1996).
15. Cebrian ME, Albores A, Aguilar M, Blakely E. Chronic arsenic poisoning in the north of Mexico. Hum Toxicol 2:121-133 (1983).

16. Vahter M, Concha G, Nermell B, Nilsson R, Duluot F, Natajaran A. A unique metabolism of inorganic arsenic in native Andean women. Eur J Pharmacol 293:455-462 (1995).
17. Guha Mazumder DN, Chakraborty AK, Ghose A, Gupta JD, Chakraborty DP, Dey SB. Chronic arsenic toxicity from drinking water in rural West Bengal. Bull World Health Org 66:499-506 (1988).
18. Chatterjee A, Das D, Mandal BK, Chowdhury TR, Samanta G, Chakraborty, D. Arsenic in ground water in six districts of West Bengal, India: the biggest arsenic calamity in the world. Part I: Arsenic species in drinking water and urine of the affected people. Analyst 120:643-650 (1995).
19. Luo ZD, Zhang YM, Ma L, Zhang ZY, He X, Wilson R, Byrd DM, Griffiths JG, Lai S, He L, et al. Chronic arsencism and cancer in Inner Mongolia - consequences of well-water arsenic levels greater than 50 µg/l. In: Arsenic: Exposure and Health Effects (Abernathy CO, Claderon RL, Chappell WR, eds). London:Chapman & Hall, 1997;55-68.
20. Chen CJ, Chuang YC, Lin TM, Wu HY. Malignant neoplasms among residents of a Blackfoot disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. Cancer Res 45:5895-5899 (1985).
21. Kemper FH, Jekat FW, Bertram HP, Eckard R. New chelating agents. In: Basic Science in Toxicology (Volans GM, Sims J, Sullivan FM, Turner P, eds). London:Taylor & Francis, 1990;523-546.
22. Maiorino RM, Barry TJ, Aposhian HV. Determination and metabolism of dithiol-chelating agents. Electrolytic and chemical reduction of oxidized dithiols in urine. Anal Biochem 160:217-226 (1987).
23. Maiorino RM, Aposhian HV. Determination and metabolism of dithiol chelating agents. IV: Urinary excretion of *meso*-2,3-dimercaptosuccinic acid and mercaptosuccinic acid in rabbits given *meso*-2,3-dimercaptosuccinic acid. Biochem Pharmacol 38:1147-1154 (1989).
24. Rivera M, Zheng W, Aposhian HV, Fernando Q. Determination and metabolism of dithiol chelating agents. VIII: Metal complexes of *meso*-dimercaptosuccinic acid. Toxicol Appl Pharmacol 100:96-106 (1989).
25. Maiorino RM, Dart RC, Carter DE, Aposhian HV. Determination and metabolism of dithiol chelating agents. XII: Metabolism and pharmacokinetics of sodium 2,3-dimercaptopropane-1-sulfonate in humans. J Pharmacol Exp Ther 259:808-814 (1991).
26. Aposhian HV, Maiorino RM, Dart RC, Perry DF. Urinary excretion of *meso*-2,3-dimercaptosuccinic acid in human subjects. Clin Pharmacol Ther 45:520-526 (1989).
27. Maiorino RM, Bruce DC, Aposhian HV. Determination and metabolism of dithiol chelating agents. VI: Isolation and identification of the mixed disulfides of *meso*-2,3-dimercaptosuccinic acid with l-cysteine in human urine. Toxicol Appl Pharmacol 97:338-349 (1989).
28. Hurlbut KM, Maiorino RM, Mayersohn M, Dart RC, Bruce DC, Aposhian HV. Determination and metabolism of dithiol chelating agents. XVI: Pharmacokinetics of 2,3-dimercapto-propanesulfonate after intravenous administration to human volunteers. J Pharmacol Exp Ther 268:662-668 (1994).
29. Gonzalez-Ramirez D, Maiorino RM, Zuniga-Charles M, Xu Z, Hurlbut KM, Junco-Munoz P, Aposhian MM, Dart RC, Diaz Gama JH, Echeverria D, et al. Sodium 2,3-dimercaptopropane-1-sulfonate challenge test for mercury in humans. II: Urinary mercury, porphyrins and neurobehavioral changes of dental workers in Monterrey, Mexico. J Pharmacol Exp Ther 272:264-274 (1995).

30. Maiorino RM, Gonzalez-Ramirez D, Zuniga-Charles M, Xu ZF, Hurlbut KM, Aposhian MM, Dart RC, Woods JS, Ostrosky-Wegman P, Gonsebatt ME, et al. Sodium 2,3-dimercaptopropane-1-sulfonate challenge test for mercury in humans. III: Urinary mercury after exposure to mercurous chloride. J Pharmacol Exp Ther 277:938-944 (1996).
31. Aaseth J, Jacobsen D, Anderson O, Wickstrom E. Treatment of mercury and lead poisonings with dimercapto succinic acid and sodium dimercaptopropanesulfonate: a review. Analyst 120:853-854 (1995).
32. Aposhian HV, Gonzalez-Ramirez D, Maiorino RM, Zuniga-Charles M, Xu ZF, Hurlbut KM, Junco-Munoz P, Aposhian MM, Dart RC. Mobilization of heavy metals by newer, therapeutically useful chelating agents. Toxicology 97:23-38 (1995).
33. Aposhian HV. DMSA and DMPS - water soluble antidotes for heavy metal poisoning. Annu Rev Pharmacol Toxicol 23:193-215 (1983).
34. Aposhian HV, Aposhian MM. *Meso*-2,3-dimercaptosuccinic acid: chemical, pharmacological and toxicological properties of an orally effective metal chelating agent. Annu Rev Toxicol 30:279-306 (1990).
35. Angle CR. Childhood lead poisoning and its treatment. Annu Rev Pharmacol Toxicol 33:409-434 (1993).
36. Klaassen CD. Heavy metals and heavy-metal antagonists. In: The Pharmacological Basis of Therapeutics (Gilman AG, Goodman LS, Rall TW, Murad F, eds). New York: Macmillan, 1985;1605-1627.
37. Enwonwu CO. Potential health hazard of use of mercury in dentistry: critical review of the literature. Environ Res 42:257-274 (1987).
38. Zheng W, Maiorino RM, Brendel K, Aposhian HV. Determination and metabolism of dithiol chelating agents. IV: Biliary excretion of dithiols and their interactions with cadmium and metallothionein. Fundam Appl Toxicol 14:598-607 (1990).
39. U.S. DHHS, PHS. Dental Amalgam: A Scientific Review and Recommended Public Health Service Strategy for Research. Washington: U.S. Department of Health and Human Services, Public Health Service, 1993.
40. Schiele R, Kroncke A. Mercury mobility through DMPS (Dimaval) in persons with and without amalgam fillings [German]. Zahnarztliche Mitteilungen 79:1866-1868 (1989).
41. Molin M, Schutz A, Skerfving S, Sallsten G. Mobilized mercury in subjects with varying exposure to elemental mercury vapour. Int Arch Occup Environ Health 63:187-192 (1991).
42. Vahter M. Species differences in the metabolism of arsenic compounds. Appl Organomet Chem 8:175-182 (1994).
43. Offergelt JA, Roels H, Buchet JP, Boeckx M, Lauwerys R. Relation between airborne arsenic trioxide and urinary excretion of inorganic arsenic and its methylated metabolites. Br J Ind Med 49:387 (1992).
44. Yamauchi H, Takahashi K, Mashiko M, Saitoh J, Yamamura Y. Intake of different chemical species of dietary arsenic by Japanese, and their blood and urinary arsenic levels. Appl Organomet Chem 6:383 (1992).
45. Hopenhayn-Rich C, Smith AH, Goeden HM. Human studies do not support the methylation threshold hypothesis for the toxicity of inorganic arsenic. Environ Res 60:161-177 (1993).
46. Aposhian HV. Methyltransferases of As species. Annu Rev Pharmacol Toxicol 37:397-419 (1997).

47. Vahter M, Marafante E, Lindgren A, Dencker L. Tissue distribution and subcellular binding of arsenic in marmoset monkeys after injection of ^{74}As-arsenite. Arch Toxicol 51:65-77 (1982).
48. Styblo M, Yamauchi H, Thomas DJ. Comparative *in vitro* methylation of trivalent and pentavalent arsenicals. Toxicol Appl Pharmacol 135:172-178 (1995).
49. Villanacci JF, Beauchamp R, Perrotta DM, Hendricks K, Rodriguez M, Dutton RJ, Sutton K, Simpson DM, Richards K, Nelson F, et al. Mercury poisoning associated with beauty cream - Texas, New Mexico, and California, 1995-1996. Arch Dermatol 132:1533-1534 (1996).
50. Pediatr Nurs. Arsenic in a Child's World, 30(3):215-218, 2004.
51. Aposhian HV. Mobilization of mercury and arsenic in humans by sodium 2,3-dimercapto-1-propane sulfonate (DMPS). Environ Health Perspect. 1998 Aug;106 Suppl 4:1017-25.
52. Aposhian H. DMSA and DMPS? Water-soluble antidotes for heavy metal poisoning. Ann Rev Pharmacol Toxicol 1983, 23:193-215.
53. Aposhian H, Maiorino R, Rivera M, et al. Human studies with the chelating agents, DMPS and DMSA. J Toxicol Clin Toxicol 1992, 30:505-528.
54. Maiorino R, Bruce D, Aposhian H. Determination and metabolism of dithiol chelating agents. VI. Isolation and identification of the mixed disulfides of meso-2,3-dimercdatosuccinic acid with L-cysteine in human urine. Toxicol Appl Pharmacol 1989, 97:338-349.
55. Marsden PA. Increased lead burden cause or consequence of chronic renal insufficiency? New England J Med 2003, 4:345-346.
56. Lustberg Mark, Silbergeld Ellen. Blood lead levels and mortality. Arch Intern Med 2002, 162:2443-2449.
57. Pinkle JL, Brody DJ, Gunter EW, et al. The decline in blood lead levels in the United States: the National Health and Nutrition Examination Surveys (NHANES). JAMA 1994, 272:284-291.
58. Winneke G, Kramer U. Neurobehavioral aspects of lead neurotoxicity in children. Cent Eur J Public Health 1997, 5:65-69.
59. Landrigan P, Baker E. Exposure of children to heavy metals from smelters: Epidemiology and toxic consequences. Environ Res 1981:25:204-224.
60. Perazella M. Lead and the kidney: Nephropathy, hypertension and gout. Conn Med 1996, 60:521-526.
61. Guallar E, Sanz-Gallardo I, Van Veer P, et al. Mercury, fish oils, and the risk of myocardial infarction. New England J Med 2002, 347:22, 1747-1754.
62. Bolger PM, Schwetz BA. Mercury and Health, New England J Med 2002, 347:22, 1735-1736.
63. Turner M, Marsh D, Smith J. Methylmercury in populations eating large quantities of marine fish. Arch Environ Health 1980, 35:367-377.
64. Wilhelm M, Muller F, Idel H. Biological monitoring of mercury vapor exposure by scalp hair analysis in comparison to blood and urine. Toxicol Lett 1996, 88:221-226.
65. Sandborgh-England G, Elinder C, Langworth S. Mercury in biological fluids after amalgam removal. J Dent Res 1998, 77:615-624.
66. Svare C, Peterson L, Reinhardt J, et al. The effect of dental amalgams on mercury levels in expired air. J Dent Res 1981, 60:1668-1671.
67. Derand, T. Mercury vapor from dental amalgams, an in vitro study. Swed Dent J 1989, 13:169-175.
68. Snapp K, Boyer D, Peterson L, Svare C. The contribution of dental amalgam to mercury in blood. J Dent Res 1989, 68:780-785.

69. Bluhm R, Bobbitt R, Welch I, et al. Elemental mercury vapour toxicity, treatment and prognosis after acute intensive exposure in chloralkali workers. Part I: History, neurophysical findings and chelator effects. Hum Exp Toxicol 1992, 11:201-210.
70. Low-Level Enviromental Exposure to Lead Unmasked as Silent Killer, Circulation, Sept 26, 2006;114(13):1347-49.
71. Blood Lead Below 0.48 µmol/L (10 µg/dL) and Mortality Among US Adults, Circulation, Sept 26, 2006;114:1388-94
72. Datzig, P, A New Cutaneous Sign of mercury poisoning?, J Am Acad Dermatol 2003;Vol 49, No 6:1109-11.
73. McKelvey, W, et al., A Biomonitoring Study of Lead, Cadmium, and Mercury in the Blood of New York City Adults., Environ Health Perspect, Oct 2007,115:1435-41.
74. Cranton, E., A Textbook on EDTA Chelation Therapy, 2nd ed., *Hampton Roads Publishing Co*., 2001.
75. Calcium Disodium Versenate (edentate calcium disodium injection), *Thomson PDR, 60th Edition*, 2006; 1819-20.
76. Low-Level Environmental Exposure to Lead Unmasked as Silent Killer, *Circulation*, Sept 26, 2006;114(13):1347-49.
77. Blood Lead Below 0.48 µmol/L (10 µg/dL) and Mortality Among US Adults, *Circulation*, Sept 26, 2006;114:1388-94
78. The Protocol for the Safe and Effective Administration of EDTA and Other Chelating Agents for Vascular Disease, Degenerative Disease, and Metal Toxicity, *Journal of Advancement in Medicine*, *Spring* 1997;10(1):5-100.
79. Chappell, T., Application of EDTA Chelation Therapy, *Alt Med Rev*1997;2(6):426-432.
80. Chappell, T., et al., Subsequent Cardiac and Stroke Events in Patients with Known Vascular Disease Treated with EDTA Chelation Therapy, *Evid Based Integrative Med* 2005;2(1):27-35.
81. Stadler, N., Direct Detection and Quantification of Transition Metal Ions in Human Atherosclerotic Plaques: Evidence for the Presence of Elevated Levels of Iron and Copper, *Arterioscler Thromb Vasc Biol* 2004;24:949-954.
82. Lin, J., et al., Environmental Lead Exposure and Progression of Chronic Renal Diseases in Patients without Diabetes, *N Engl J Med* 2003;348:277-286.

INFORMED CONSENT FOR Mg EDTA or Ca EDTA CHELATION THERAPY

I _____, hereby give consent to Dr._____, his associates, employees or staff, to perform intravenous EDTA chelation therapy ("Chelation Therapy") for the purpose of treatment of atherosclerotic disease and /or heavy metal toxicity, and /or prevention of treatment of degenerative diseases. I understand that Chelation Therapy is a standard therapy widely approved for the treatment of heavy metal toxicity , however, its usage is considered controversial for the generalized treatment of atherosclerotic vascular disease and other degenerative diseases, and the view that it is of benefit in the treatment of such disorders is accepted by a minority of the medical community and it is considered "experimental" by most physician, I am advised that my treating physician believes that Chelation Therapy does have positive clinical benefit. I have been informed that other treatment approaches have been used in these conditions, including but not limited to bypass surgery or angioplasty and these alternatives have been explained to my full satisfaction. As with any other medical procedure, a small percentage of patients do not respond to this therapy.

I understand that the benefits of Chelation Therapy are much greater if I follow a healthy lifestyle (non-smoking, weight control, proper exercise, proper diet, and nutritional supplementation). I understand that an initial series of treatment are anticipated, and that these treatments may be extended over a number of months. I have been informed that Chelation Therapy may need to be repeated from time to time in the future in order to maintain the benefits. I understand that it is my option to stop at any time this treatment protocol without incurring any further expenses after I have directed that such treatment be stopped.

I have been informed of possible risks and side effects including but not limited to discomfort at the injection site, thrombophelebitis, hypocalcemia, fatigue, muscle cramps, kidney problems including nephrotoxicity, allergic reaction, congestive heart failure, liver disease, anticoagulation, lower blood sugar levels and / or hypoglycemia, mineral loss and generalized complaints. If I have suffered from any previous kidney disease, I agree to execute a medical release so that all previous identified medical records of mine may be obtained from previous physicians, and I have disclosed openly any known previous disorders. I understand that this therapy should not be used if I am pregnant unless I have a severe life threatening disease. I understand that if I have a history of tuberculosis, Chelation Therapy may reactivate arrested tuberculosis and I agree to inform my physician of any occurrence of this disease. I understand the nature of the proposed procedure and the risks and dangers have been explained to me to my full satisfaction.

While I understand that there have been no warranties, assurances or guarantees of successful treatment made to me, I desire to undergo this treatment after having considered the information contained in this document, the information provided to me through my conversations with my treating physician and though materials provided to me by the office to educate me about the treatment. I acknowledge that I have had the opportunity to ask any questions of my physician with respect to the proposed therapy and the procedures to be utilized and all my questions have been answered to my full satisfaction. My Signature on this agreement will constitute a full and final release of any legal responsibility resulting from the administration of Chelation Therapy in my case and/or any other medical treatment that may be necessary as a result thereof.

I agree to have lab work performed and available to Dr. _____ when requested. I agree to schedule regular office visits with Dr. _____ at the requested intervals in order to continue my Chelation treatments and maintain an up-to-date health history and working relationship with physician.

Patient Name: _____ Date: _____

(Signature)

Patient Name: _____ Dr: _____

(Print or Typed Name)

David W. Quig, PhD

Appropriate laboratory tests for metal toxicity

Bio

David Quig received his Masters degree in Human Nutrition from Virginia Tech, and his Ph.D. in Nutritional Biochemistry from the University of Illinois. He was then a Post-Doctoral Fellow at Cornell University for five years, prior to serving as a Senior Cardiovascular Pharmacologist with a major pharmaceutical company for seven years. For the past 26 years, he has performed and published research pertaining to nutrition and chronic diseases. He regularly gives presentations at international and national biomedical conferences. Dr. Quig is currently Vice President, Scientific Support for Doctor's Data, Inc. where he conducts studies pertaining to the effects of heavy metal and chemical toxicity on nutrition and metabolism and advises medical practitioners about the interpretation of laboratory test results and treatment options for their patients.

Lecture Overview

The basic concepts of metal toxicology will be presented with emphasis on the scientific rational for "beyond the standard of care" lab tests that provide clinically relevant information regarding exposure to, and net retention of toxic metals. The pros and cons of direct measurement of toxic metals in hair, whole blood and urine will be discussed, as well as objective tests for metal-induced oxidative stress. For safe and efficacious urine provocation testing, prerequisite assessment of liver function, glomerular filtration and endogenous antioxidant protection/detoxification should be performed. Follow up testing to evaluate the efficacy of therapeutic metal detoxification will be addressed.

Contact Information

Doctor's Data, Inc.
3755 Illinois Ave.
St. Charles, IL 60174

dquig@doctorsdata.com

American College for Advancement in Medicine
Chelation Therapy Workshop
November 4-5, 2009
Las Vegas, Nevada

Appropriate Laboratory Testing for Metal Toxicity

David Quig, PhD

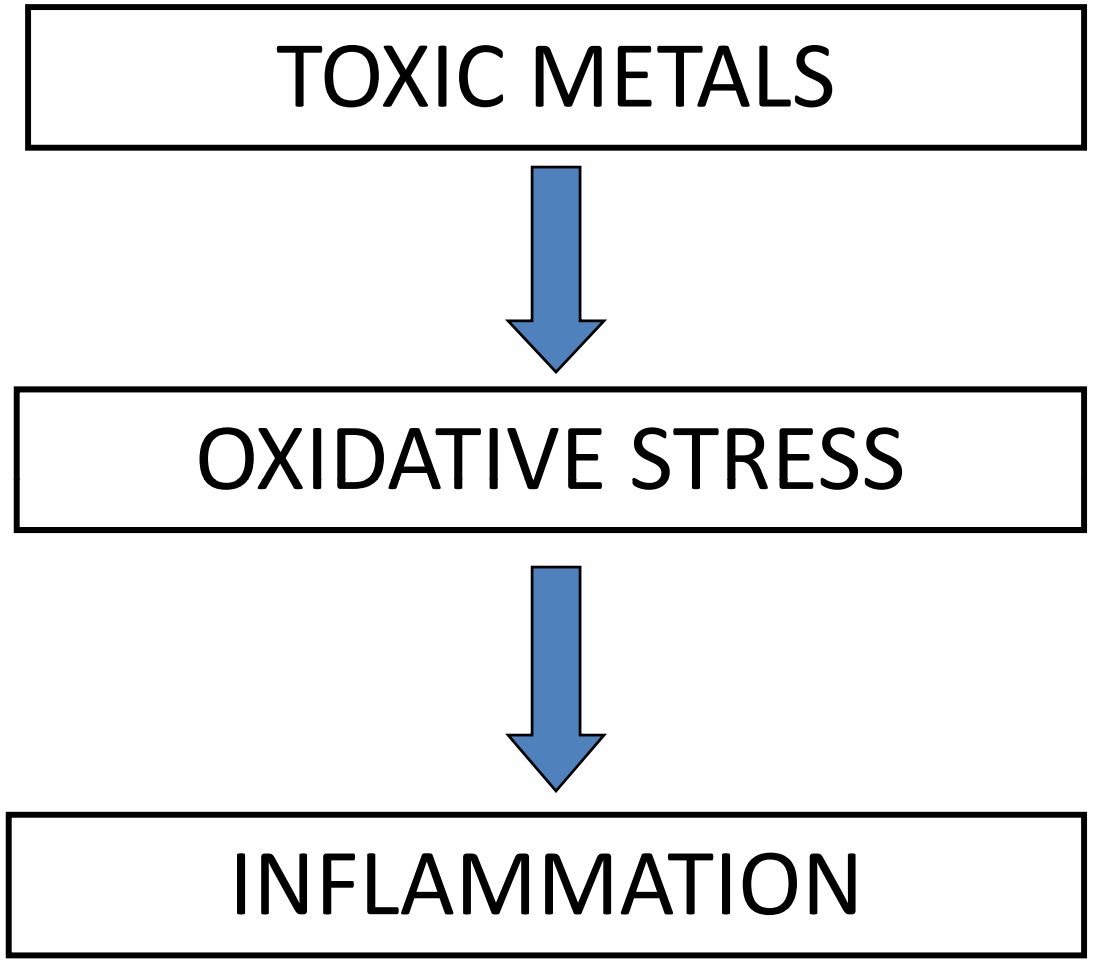
3755 Illinois Ave.

St. Charles, IL 60174

Environmental Toxins

- W.H.O. 30-40% of childhood illnesses associated with environmental toxins

- C.D.C. "The epidemic of epidemics of CVD and immunological and neurological disease is likely associated with environmental toxins"


TOXIC METALS
OXIDATIVE STRESS
INFLAMMATION

Oxidative Stress: Exposure to Pb or Cd

- NHANES III, n = 10,098
- Significant independent association of both BPb and UCd with oxidative stress

  (serum GGT, vit. C & E, carotenoids)
- **"Pb & Cd-induced oxidative stress should be considered among people with low exposure"**

  (means: BPb; 2.8 mg/dL, UCd; 0.37 µg/gm)

Environ Hlth Prosp (2006)114:350-54

Glutathione

- **λ glutamylcysteinylglycine**

  SH

- Intracellular Protective Functions

  Antioxidant (redox state)

  Conjugation of metals and chemicals

  Activation of immune function

  Inhibit replication of retroviruses

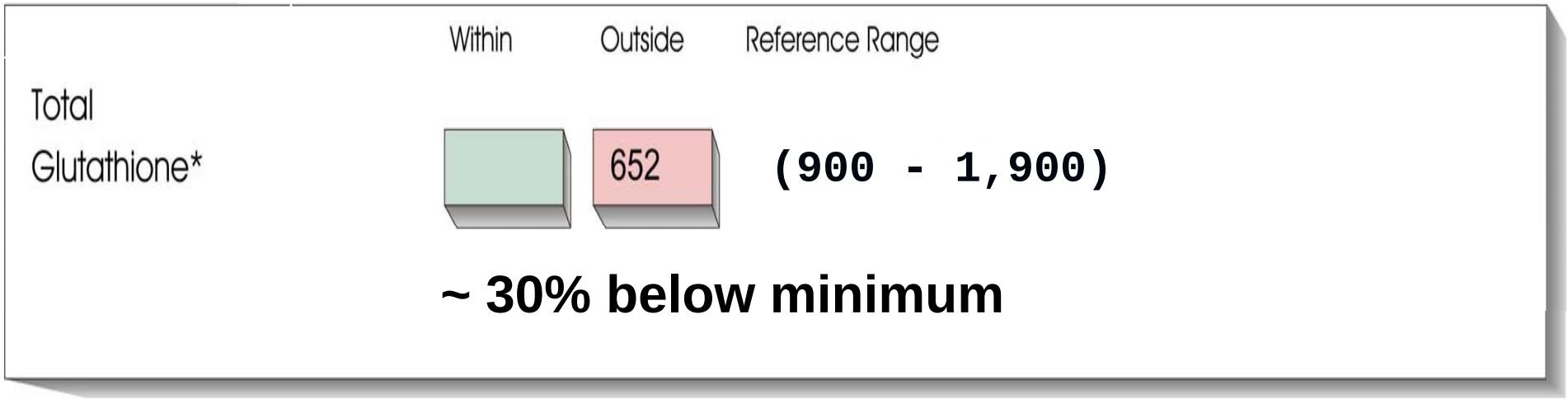
Proc. Nat. Acad. Sci. (1997) 94 AIDS Res. Hum. Retrovir. (1992) 8
Immunology (1967) 61

Depletion of GSH with:

- Metal Toxicity
- Chemical toxicity
- CVD
- Diabetes
- Cancer
- Neurological diseases
- *Extreme* exercise
- Aging
- Radiation Exposure
- *Chronic stress*
- *Anxiety*
- Chronic fatigue
- Autism
- Drugs

J Neurol Sci(2008)[Epub] AJCN(2004)80:1611 Prostaglandins Leukot Fatty Acids(2002)67:341 J Lab Clin Med(1992)120 Clin Chim Acta(2003)333:19

RBC Total Glutathione



- Find "source" of oxidative stress
- Support intracellular GSH (e.g. whey protein, oral liposomal GSH, iv GSH, N-AC)

DNA Oxidative Damage and Environmental As

- 10-12 yo students, 2 schools (n ≅ 50 each)
- School A: adjacent to, and downwind of 8 power plants, B: upwind, suburban areas

Urine	School A	School B
As (μg/gm)	**21** (4)	10 (1)
8-OHdG (ng/gm)	**19** (2)	8 (1)

Env. Hlth. Persp. (2005)113: 1186-90

Oxidative Damage to DNA: 8-OH-2'-deoxyguanosine (8OHdG)

DNA Oxidative Damage; Urine

	Within	Outside	Reference Range	
		**		
8-hydroxy-2'-deoxyguanosine* (8-OHdG)		26.1	< 8.5	ng/mg cr
Creatinine		33.0	45- 225	mg/dL

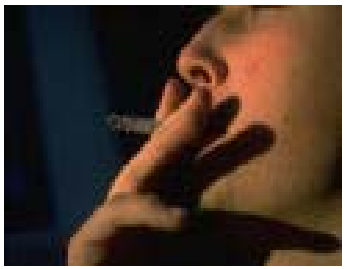
Urinary 8-OHdG is a sensitive biomarker of oxidative stress and has been associated with many diseases, including bladder and prostate cancer, cystic fibrosis, atopic dermatitis, rheumatoid arthritis, and a wide range of neurological conditions including Parkinson's disease, Alzheimer's disease and Huntington's disease.

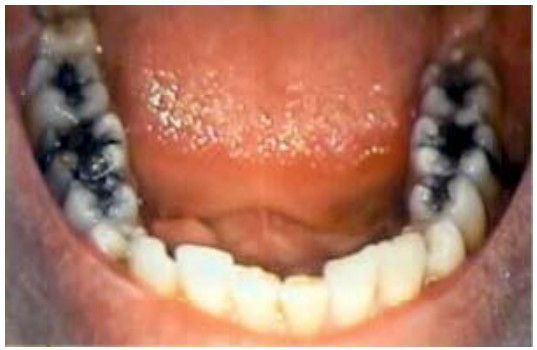
3X > oxidized DNA than average

Oxidative Stress, Metals Exposure

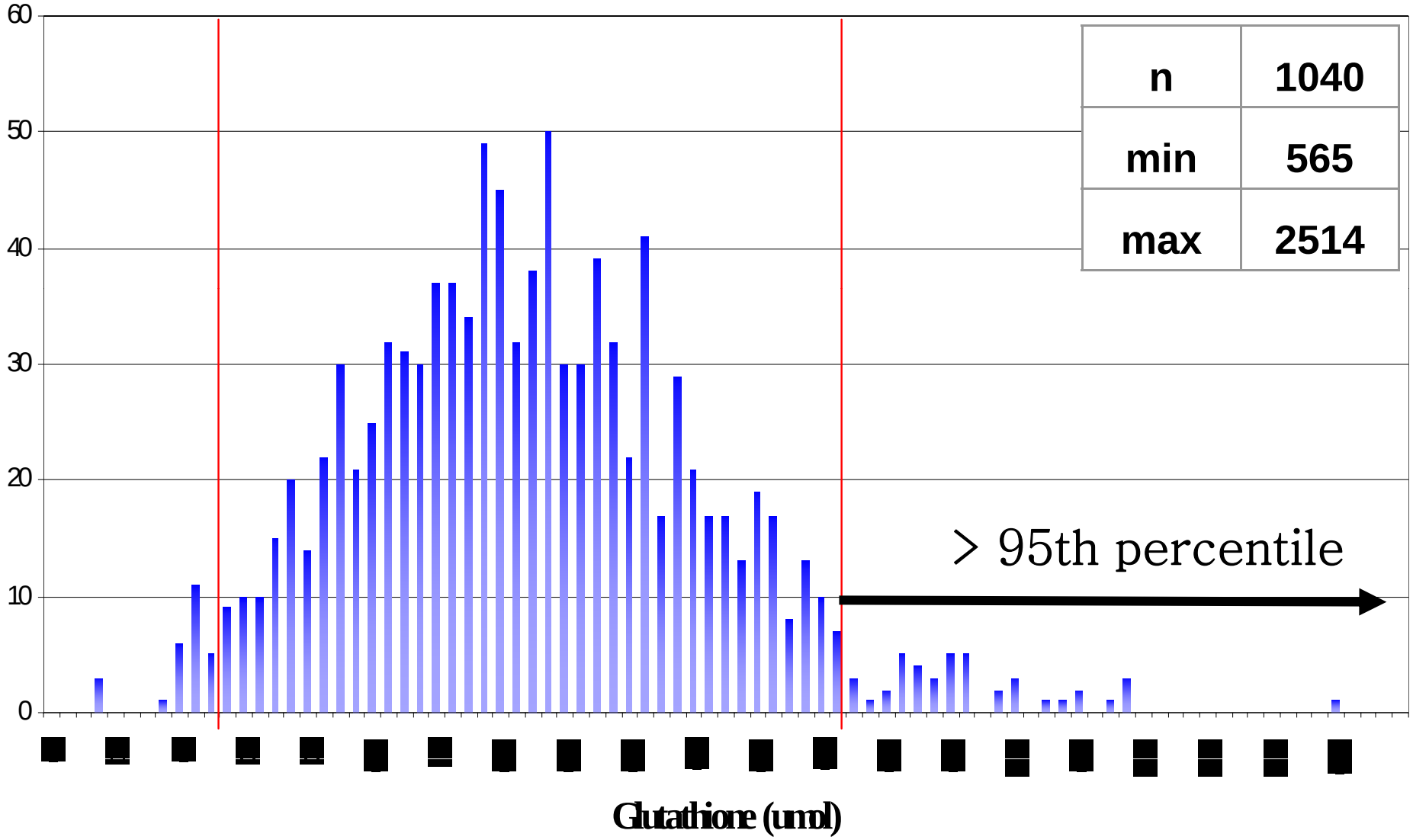
- 50 yo male, hypertension
- RBC GSH = **652** (900 -1,900 µmoles/L)
- 8-OHdG = **26.1** (< 8.5 ng/mg cr)
- Blood Metals

  Cd = **8.2** (< 4 µg/L) Hg = **3.6** (< 2 µg/L)
  Pb = 2.7 (< 2 µg/L)
- **Smoker, 18 amalgams**





RBC GSH Distribution



Basic Toxicology

Remove the source(s) of exposure!

ADHD / Tourette's Syndrome

- 10 y.o. male
- Learning problems, physical / verbal tics
- Hair lead: 10 μg/gm (99th percentile)
- Checked for neurotoxic metal retention

  40 mg/kg glycine (oral)

  DMSA (**10** mg/kg)

URINE TOXIC METALS

LAB#:
PATIENT: ADHD/TS
SEX:
AGE: 10 yo male

CLIENT#:
DOCTOR:

DMSA/glycine challenge

POTENTIALLY TOXIC METALS

METALS	RESULT µg/g CREAT	REFERENCE RANGE	WITHIN REFERENCE RANGE	ELEVATED	VERY ELEVATED
Aluminum	< dl	< 60			
Antimony	0.2	< 1.5			
Arsenic	24	< 130			
Beryllium	< dl	< 0.6			
Bismuth	0.4	< 20			
Cadmium	0.4	< 2			
Lead	110	< 5			
Mercury	2	< 5			
Nickel	1.7	< 15			
Platinum	< dl	< 1			
Thallium	0.4	< 1.1			
Thorium	< dl	< 0.5			
Tin	3.5	< 15			
Tungsten	< dl	< 1.5			
Uranium	< dl	< 0.2			

Pb = 110 µg/gm

The Source

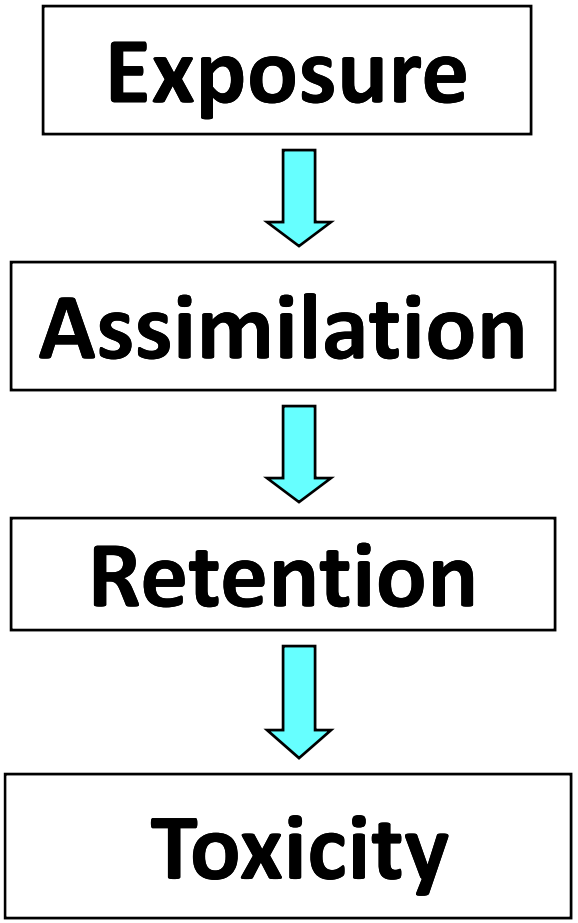
- Soil in the yard
- Lead level: **7,108** mg/kg
- E.P.A. safety level: **400** mg/kg
- $$ toxic real estate

Glycine : Assisting Agent

- 40 mg/kg glycine orally ~ about 2 hrs. before provocation test
- **Use in CONJUNCTION** with agents (logK- Hg; 9-13, Al; 8-10, Pb & Sb; 8-9)
- **Not** to be used alone

Envir Hlth Perspect (1986)65:363-411 Pangborn(1995), DDI/Bionostics Quig, Townsend Letter, June 2007

Basic Toxicology



Chronic Metal Toxicity

- Exposure→ Assimilation→ Retention→Toxicity
- NOT generally accepted as requiring treatment

" Sub clinical metal toxicity "

Chronic Metal Toxicity

- "Sub-clinical" metal toxicity = **sub-threshold**
- For a given **individual**, toxicity is exhibited when the level of **net retention** exceeds physiological tolerance.

Net Retention

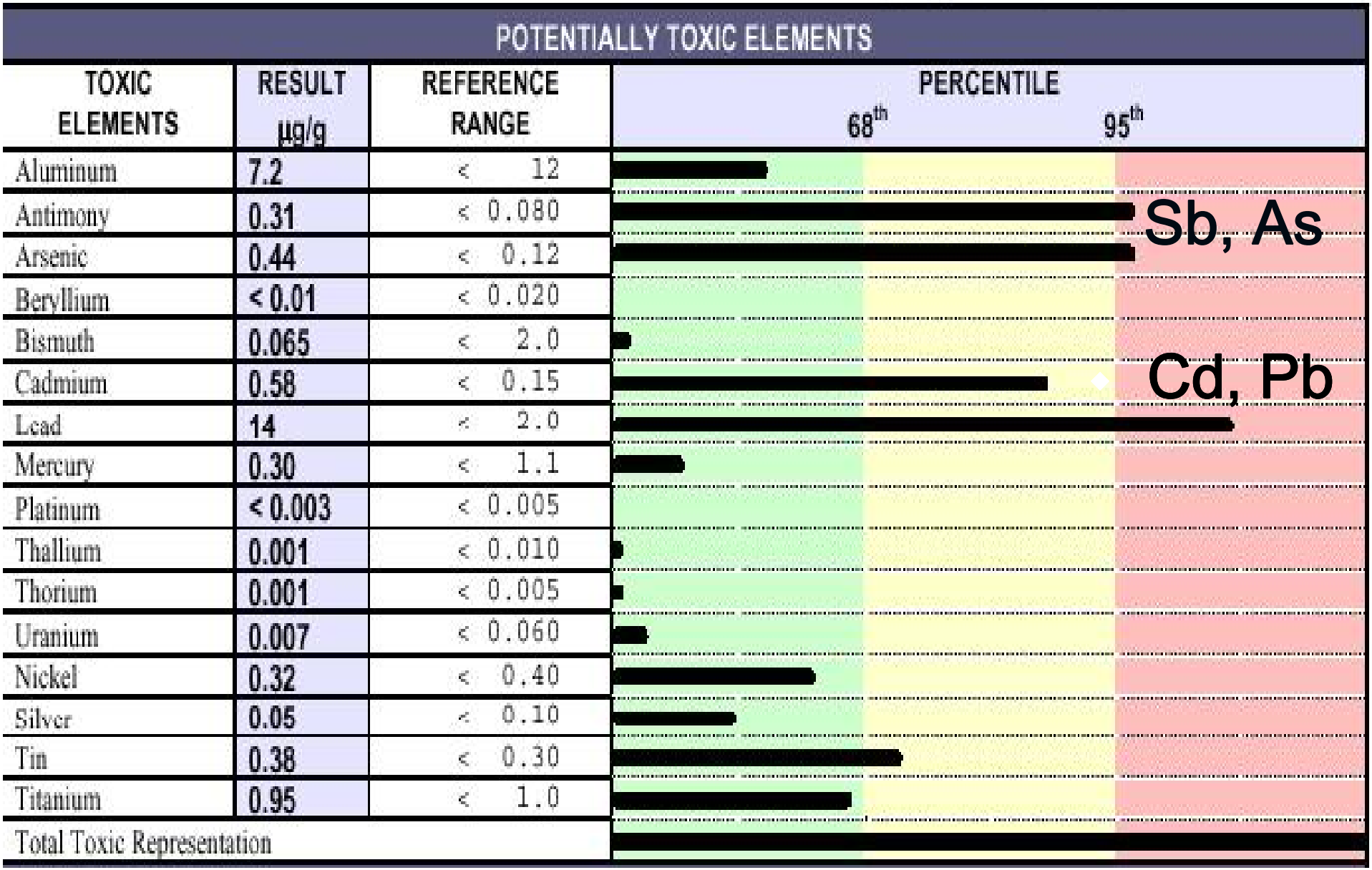
- Relative rates of ***assimilation*** and ***excretion***.
- Excretion is **highly variable** and determined by protein expression (GSH, MT), nutritional status, antibiotic use, life style, and **total toxic load.**

Assessment of Exposure: Hair

- Excretory tissue that binds **circulating** metals
- **Concentrates** metals cumulatively
- Hair Me-Hg 200-300X > than blood Hg
- Useful for recent/ongoing **EXPOSURE**
- Hair As, Tl, Hg, & Pb can provide firm evidence of cause of death

Arch Environ Hlth (1980) atsdr.cdc.gov/HAV/hairanalysis/6.2htm
Handbook on Metals in Clinical & Analytical Chemistry e. Seilier et al. (1994)

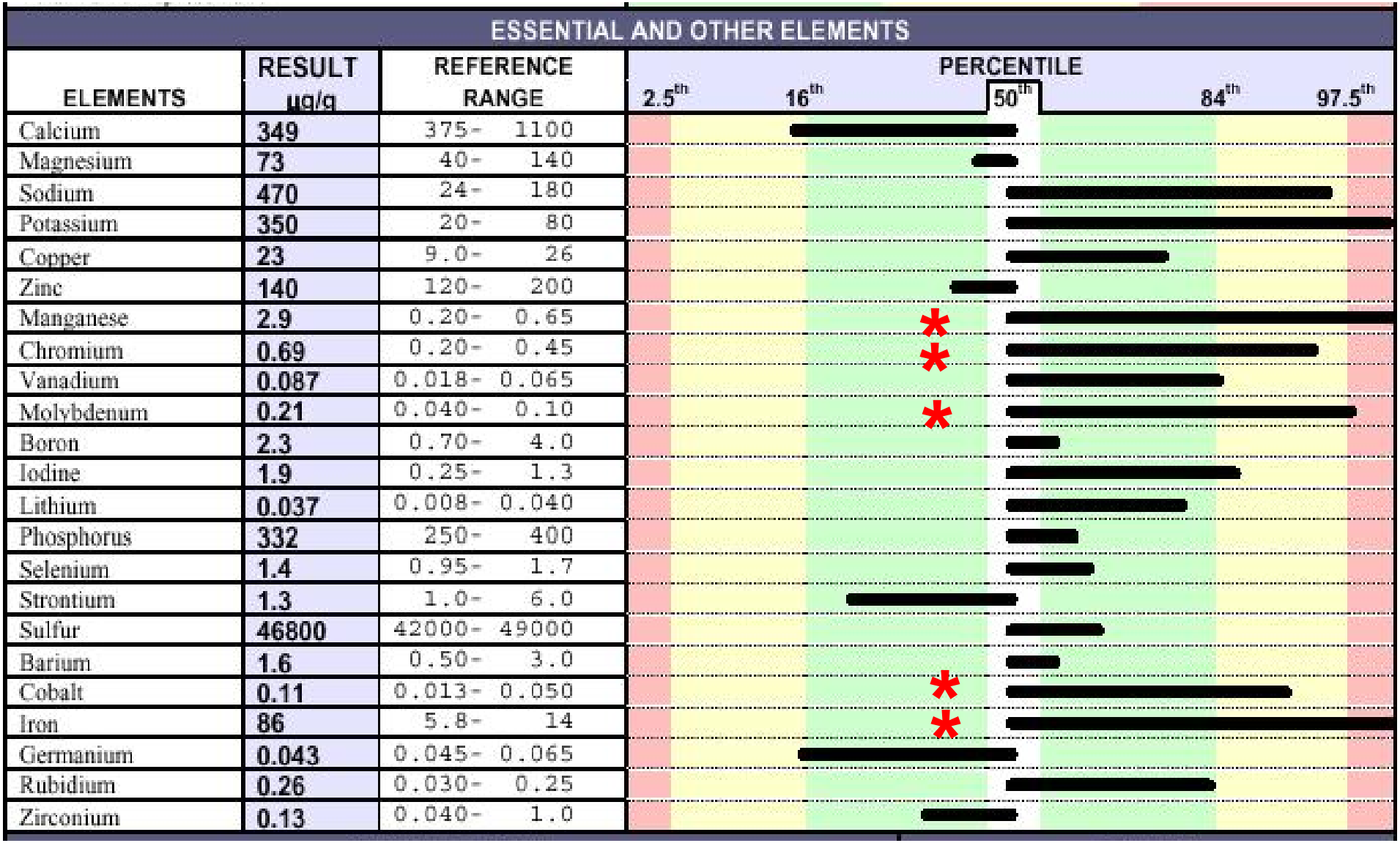
Pubic Hair Metals: Machinist / Welder



POTENTIALLY TOXIC ELEMENTS			
TOXIC ELEMENTS	RESULT µg/g	REFERENCE RANGE	PERCENTILE 68th 95th
Aluminum	7.2	< 12	
Antimony	0.31	< 0.080	Sb, As
Arsenic	0.44	< 0.12	
Beryllium	< 0.01	< 0.020	
Bismuth	0.065	< 2.0	
Cadmium	0.58	< 0.15	Cd, Pb
Lead	14	< 2.0	
Mercury	0.30	< 1.1	
Platinum	< 0.003	< 0.005	
Thallium	0.001	< 0.010	
Thorium	0.001	< 0.005	
Uranium	0.007	< 0.060	
Nickel	0.32	< 0.40	
Silver	0.05	< 0.10	
Tin	0.38	< 0.30	
Titanium	0.95	< 1.0	
Total Toxic Representation			

Machinist / Welder (cont'd)

(Mn, Cr, Mo, Co, Fe)



ESSENTIAL AND OTHER ELEMENTS

ELEMENTS	RESULT µg/g	REFERENCE RANGE
Calcium	349	375- 1100
Magnesium	73	40- 140
Sodium	470	24- 180
Potassium	350	20- 80
Copper	23	9.0- 26
Zinc	140	120- 200
Manganese	2.9	0.20- 0.65
Chromium	0.69	0.20- 0.45
Vanadium	0.087	0.018- 0.065
Molybdenum	0.21	0.040- 0.10
Boron	2.3	0.70- 4.0
Iodine	1.9	0.25- 1.3
Lithium	0.037	0.008- 0.040
Phosphorus	332	250- 400
Selenium	1.4	0.95- 1.7
Strontium	1.3	1.0- 6.0
Sulfur	46800	42000- 49000
Barium	1.6	0.50- 3.0
Cobalt	0.11	0.013- 0.050
Iron	86	5.8- 14
Germanium	0.043	0.045- 0.065
Rubidium	0.26	0.030- 0.25
Zirconium	0.13	0.040- 1.0

PERCENTILE

2.5th 16th 50th 84th 97.5th

Assessment of Exposure: Blood

- Recent or ongoing ***exposure***
- Toxicokinetic models; shortest $T^{1/2}$
- **NO** indication of net retention
- "Standard of care" is still blood Pb

Goyer RA et al. Environ Hlth Perspect (1995)103:1048-52

WHOLE BLOOD ELEMENTS

Fish 3X / week

NUTRIENT ELEMENTS

ELEMENTS	RESULT / UNIT	REFERENCE RANGE	PERCENTILE 2.5th 16th 50th 84th 97.5th
Calcium	5.0 mg/dL	4.4 - 6.9	
Magnesium	3.5 mg/dL	2.8 - 4.4	
Copper	70 µg/dL	61 - 128	
Zinc	679 µg/dL	420 - 810	
Manganese	9 µg/L	6 - 19	
Lithium	1.0 µg/L	0.3 - 20	
Selenium	362 µg/L	130 - 340	
Strontium	30 µg/L	8 - 38	
Molybdenum	0.8 µg/L	0.7 - 4.0	

POTENTIALLY TOXIC ELEMENTS

TOXIC ELEMENTS	RESULT / UNIT	REFERENCE RANGE	PERCENTILE 95th 99th
Arsenic	10 µg/L	< 20	
Barium	< 0.2 µg/L	< 10.0	
Cadmium	0.9 µg/L	< 4.0	
Cobalt	0.3 µg/L	< 4.0	
Lead	1.9 µg/dL	< 3.5	**
Mercury	18 µg/L	< 5.0	
Nickel	< 3 µg/L	< 15	
Platinum	< 0.2 µg/L	< 5.0	
Silver	0.1 µg/L	< 4.0	
Thallium	< 0.1 µg/L	< 1.0	
Uranium	< 0.1 µg/L	< 1.0	

Unprovoked Urine: As <u>Exposure</u>

- Organic As^{+5} rapidly excreted w/in 48 hrs. of consumption of **shellfish**
- **PREVENT ALARMISM !**

  Do **pre**- and **post** urinalysis initially, and abstain from fish and shellfish a week prior to provocative challenges.

Unprovoked 1st AM Urine

POTENTIALLY TOXIC METALS

METALS	RESULT µg/g CREAT	REFERENCE RANGE	WITHIN REFERENCE RANGE	ELEVATED	VERY ELEVATED
Aluminum	< dl	< 60			
Antimony	< dl	< 1.5			
Arsenic	1930	< 130			
Beryllium	< dl	< 0.6			
Bismuth	< dl	< 20			
Cadmium	0.4	< 2			
Lead	0.5	< 5			
Mercury	< dl	< 5			
Nickel	9.5	< 15			
Platinum	< dl	< 1			
Thallium	< dl	< 1.1			
Thorium	< dl	< 0.5			
Tin	0.4	< 15			
Tungsten	0.1	< 1.5			
Uranium	< dl	< 0.2			

As = 1,930 µg/gm

"All You Can Eat Crab Fest" night before

For Your Quiver

The measurement of lead excreted in urine following an injection of Ca-Na_2- EDTA has been used to detect elevated body burden of lead in adults (2,3,4,5) and children (6,7), and **is considered to be a reliable measure of the potentially toxic fraction of the lead body burden** (8).

www.atsdr.cdc.gov/toxprofiles/tp13.html#

Assessment of Retention

- **The precedent has been set**, assess the **net retention** of metals using **EDTA, DMPS or DMSA**
- **Pre- vs. Post provocation urinary metals**

  (1) objective assessment of body burden

  (2) legal/medical board considerations
- **Monitor efficacy with <u>identical</u> challenges after 5-10 treatments**

Pharmacological Provocations

- **Extracellular, aqueous** compartments
- Do **NOT** appreciably cross a *healthy* BBB
- Ca-EDTA, DMPS & DMSA provocations do not ***directly*** reflect retention in the CNS
- Significant kidney "flush"

J Pediatr(1997)130:966-71 Occup Environ Med (1995)52:13-19 Fund Appl Toxicol(1995)25:233-40 J Pharmacol Exp Ther (1987)243:804-3

Evaluations Prior to Provocation

- Blood chemistries (e.g.CBC w/ differential, creatinine, BUN, liver enzymes)
- Oral DMSA / DMPS

GI symptoms $\rightarrow$ Comprehensive Stool Analysis

DOCUMENT Assessment of Kidney Function!

- Many toxic metals are **nephrotoxic**
- Agent-metal complexes excreted primarily through the kidneys
- Dosage of agent proportional to relative efficiency of creatinine clearance
- Avoid acute renal failure!

Assessment of Glomerular Filtration

- Serum creatinine (Cockcroft-Gault Equation)
- Elderly and others with very low muscle mass, serum creatinine alone **inadequate/insensitive** for detection of compromised GF
- Creatinine clearance: timed urine (6 h), and blood draw

Arch Intern Med (2003)163:356-60

CREATININE CLEARANCE

	RESULT mL/min	REFERENCE RANGE	2SD LOW	1SD LOW	MEAN	1SD HIGH	2SD HIGH
Creatinine Clearance	**91.1**	80- 150					

URINE CREATININE

	RESULT mg/time	REFERENCE RANGE	2SD LOW	1SD LOW	MEAN	1SD HIGH	2SD HIGH
Urine Creatinine	**1400**	1100- 2800					

SERUM CREATININE

	RESULT mg/dL	REFERENCE RANGE	2SD LOW	1SD LOW	MEAN	1SD HIGH	2SD HIGH
Serum Creatinine	**1.1**	0.7- 1.5					

Dysbiosis and Sulfur Compounds

- N-AC, ALA and DMSA, DMPS (po) exacerbate GI symptoms
- Urease**+** bacteria (e.g. Citrobacter freundii) produce H_2S and NH_4 from cysteine (N-AC).
- Assess GI health/integrity: Clean up GI tract **BEFORE** using oral SH- compounds

Dial Transplant (1995); 10:696-8 Dr. S.Cave, ACAM 11/03 Manual of Clinical Microbiology, 6th edition. Washington, DC: ASM Press; 1995.

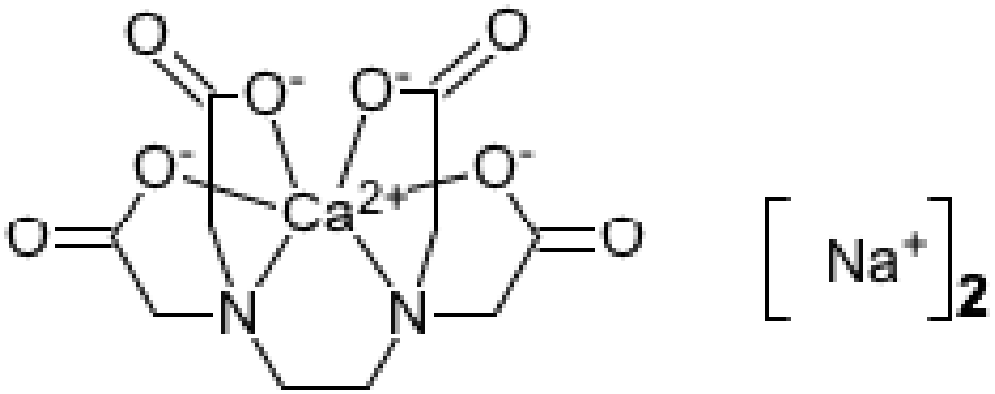
Fungal Methylation of Hg

- C. albicans and S. cerevisiae incubated with $HgCl_2$
- Both species transformed Hg to MeHg in proportion to Hg added
- **Survival mechanism for *yeast*, increased toxicity to *host***

Appl. Environ. Microbiol.(1991)57:245-7

FDA Status of Agents

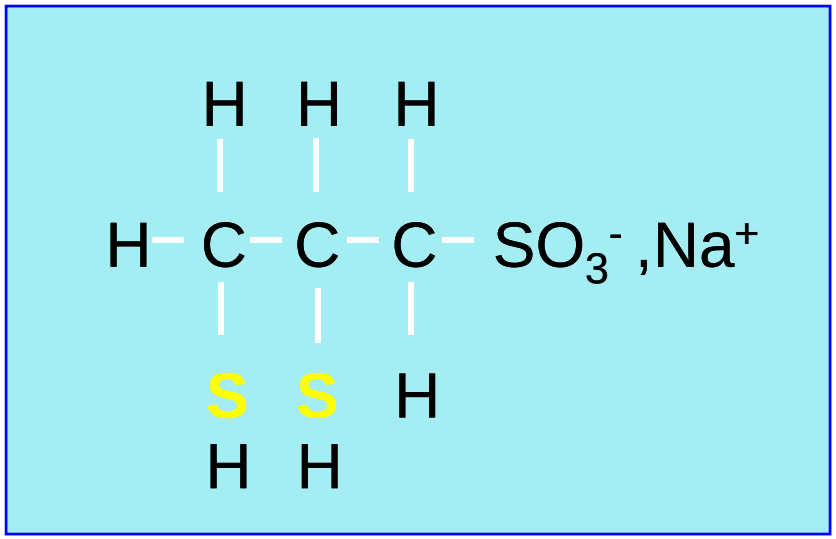
- **<u>Ca-Na_2-EDTA</u>:** FDA approved in the 50s (Pb)



DMPS

- DMPS: Not FDA approved, available from compounding pharmacies

  2,3-**d**i**m**ercapto**p**ropane-1-**s**ulfonic acid

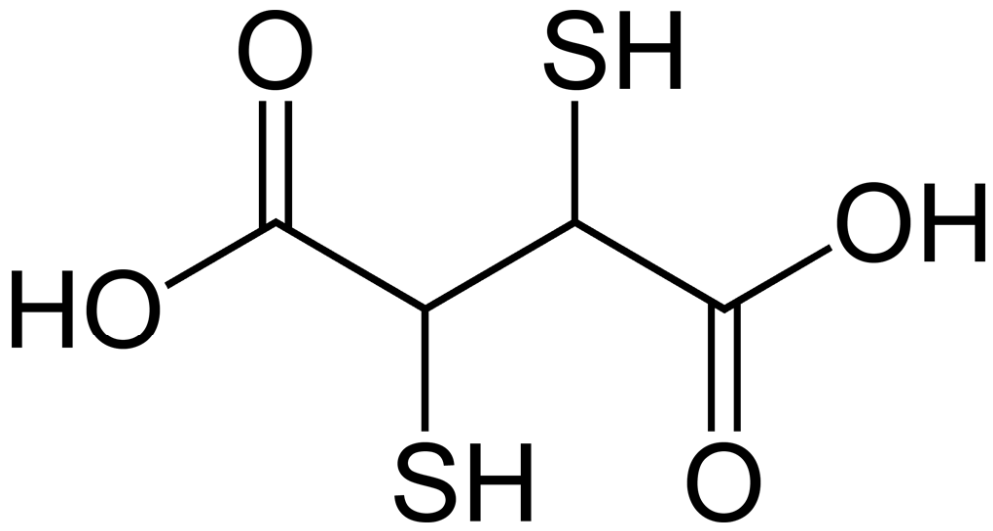


(Informed consent)

DMSA

- **Chemet**™: FDA approved for Pb "poisoning" in children in 1990

  2,3-meso-**dim**ercapto**s**uccinic **a**cid



Ca-Na_2-EDTA

- Ca-Na_2-EDTA: slow infusion/fast drip
- 50 mg/kg, not to exceed 3 gm
- $T^{1/2}$ about 30-45 minutes
- 6 hr. urine collection

Ca- Na_2-EDTA (cont'd)

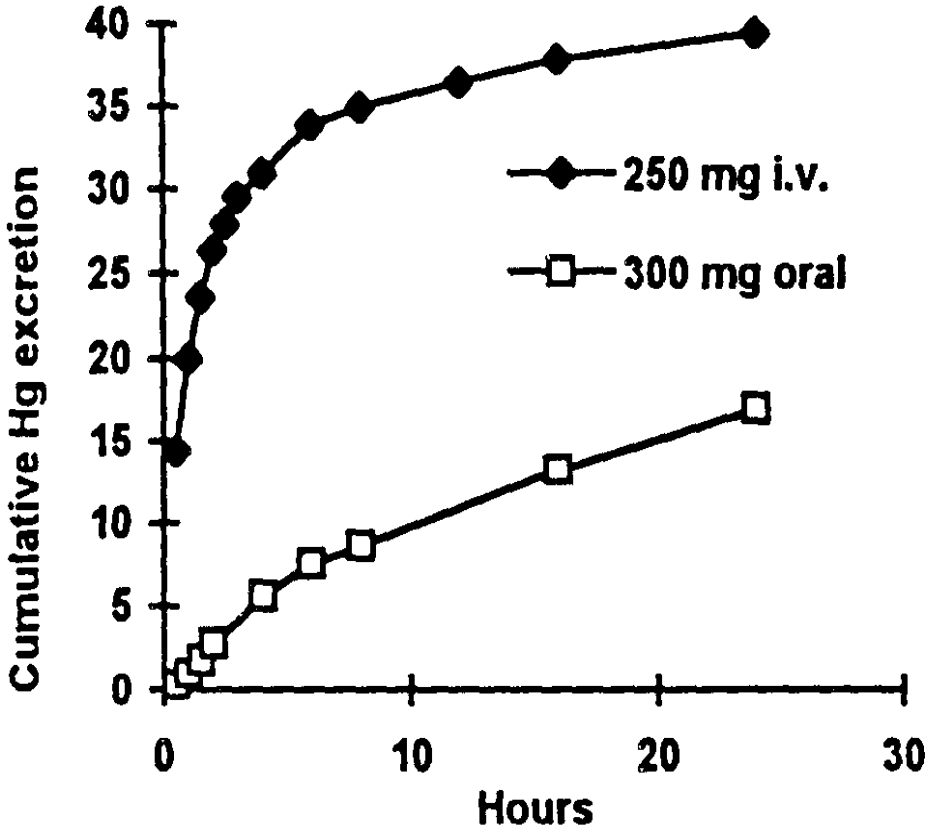
- No biotransformation
- Contraindicated when blood Pb > 80μg/dL*
- Different application vs **Mg-Na_2-EDTA** slow drip (1.5 – 3 hrs.)
- Orally 5-10 % absorbed

DMPS

- Intravenous: $T^{1/2\alpha}$ < **1 hr**.
- **Oral: $T^{1/2\alpha}$ ~ 9 hr.**
- ~ 55 % absorbed (peak at 2 hrs.)
- Forms dimers and, mixed disulfides (GSH, cysteine)
- Primarily urinary excretion, lesser biliary fecal
- Enterohepatic circulation- **not** blocked by charcoal but, 3X ↑ fecal As w/ **oral** DMPS & cholestyramine

Fund Appl. Toxicol (1990)14:598-607
Dimaval® Scientific Monograph (2008)

Urinary Hg Excretion Post DMPS



Dimaval® Scientific Monograph (1997)

Urinary Hg Before and After DMPS Challenge

ug Hg / 6h

	Before	After
Dental techs (10)	**5 ± 1**	**424 ± 85**
Dentists (5)	**3 ± 1**	**162 ± 52**
Controls (13)	**1 ± 0.2**	**27 ± 3**

(300 mg DMPS oral)

J Pharmacol Exp Ther (1995)272:264-74

DMPS Challenges

- **IV**: 3-5 mg/kg (250 mg max), **slow** push (5-10 min.)
- **Oral**: 10 mg /kg BW (5 mg/kg children), empty stomach (empty bladder)
- With hold food about 2 hrs.
- Encourage ~ 0.5L fluid over next few hrs.
- Collect all urine for 6 hrs.

DMPSbackfire.com

Bonnie's Report

…I never knew DMPS had **propane** in it either. This is very interesting because **I could no longer tolerate the steaks or meat cooked on the grill.**

DMPS "Frontfire.com"

- 31 y.o.f., ventricular tachycardia, demyelinating neuropathy with ↑ weakness
- DMSA 15 days, no ↑ urine As
- Progressive neuropathy (face, quadriplegic), ventilator dependent
- Started **iv** DMPS **@250mg q4hrs for 12 days**

J Toxicol Clin Toxicol (2000) 38:777-780

DMSA General

- Does **NOT** ↑ brain Pb or Hg levels
- ↓ brain Pb and Hg levels (animal studies)
- Increases urinary Pb, Hg and As in humans, **NOT Al, U or Tl**

Arch. Toxicol.(2002)76:437-31 Toxicol(1989)54:323-33 Toxicol (2002)177:186-97 Envir. Toxicol.(2001)9:173-84 Toxicol Appl Pharm(1999)161:283-93

URINE TOXIC METALS

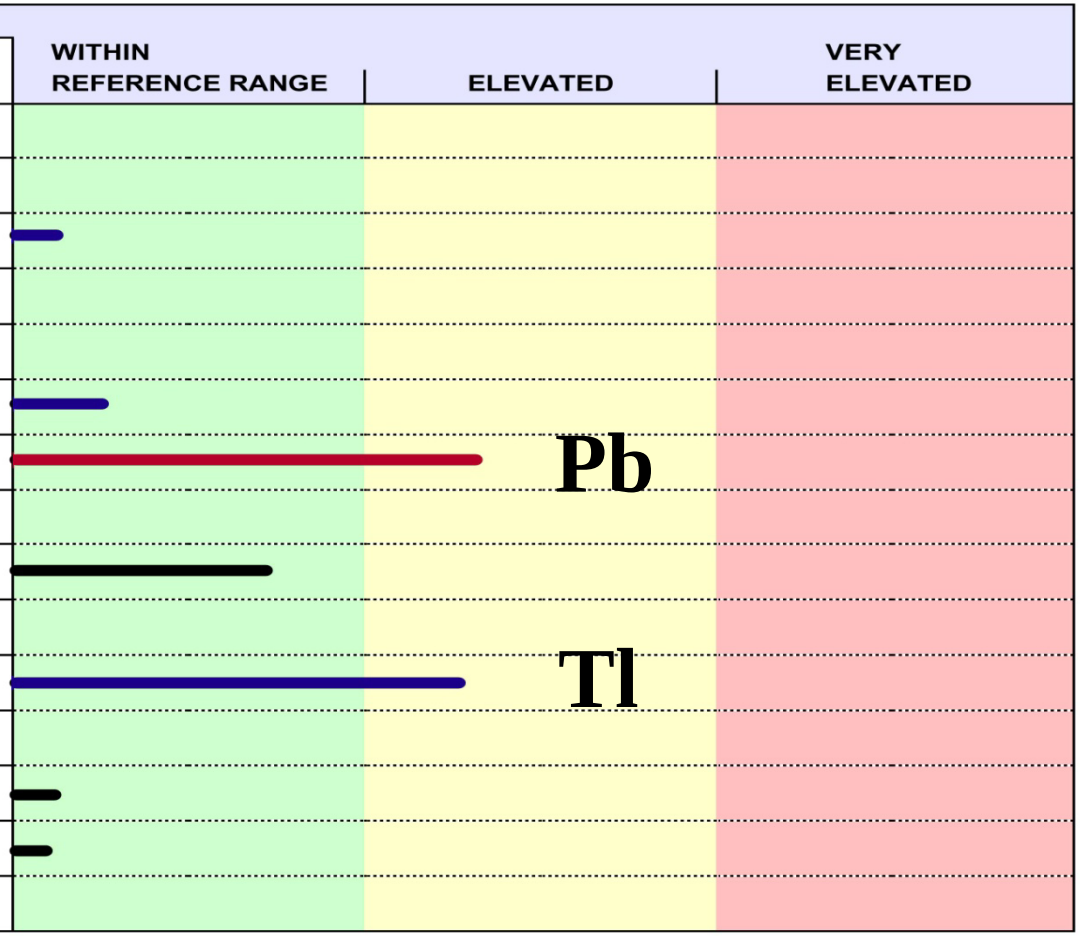
LAB#:
PATIENT:
SEX: Male
AGE: 68

CLIENT#:
DOCTOR:

Pre-Provocation

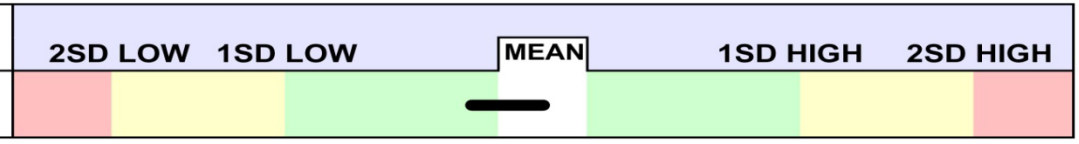
POTENTIALLY TOXIC METALS

METALS	RESULT µg/g CREAT	REFERENCE RANGE
Aluminum	< dl	< 25
Antimony	< dl	< 0.6
Arsenic	14	< 120
Beryllium	< dl	< 0.5
Bismuth	< dl	< 10
Cadmium	0.5	< 2
Lead	10	< 5
Mercury	< dl	< 3
Nickel	7.3	< 10
Platinum	< dl	< 1
Thallium	0.9	< 0.7
Thorium	< dl	< 0.3
Tin	1	< 9
Tungsten	0.06	< 0.7
Uranium	< dl	< 0.1



CREATININE

	RESULT mg/dL	REFERENCE RANGE
Creatinine	120	45- 225



URINE TOXIC METALS

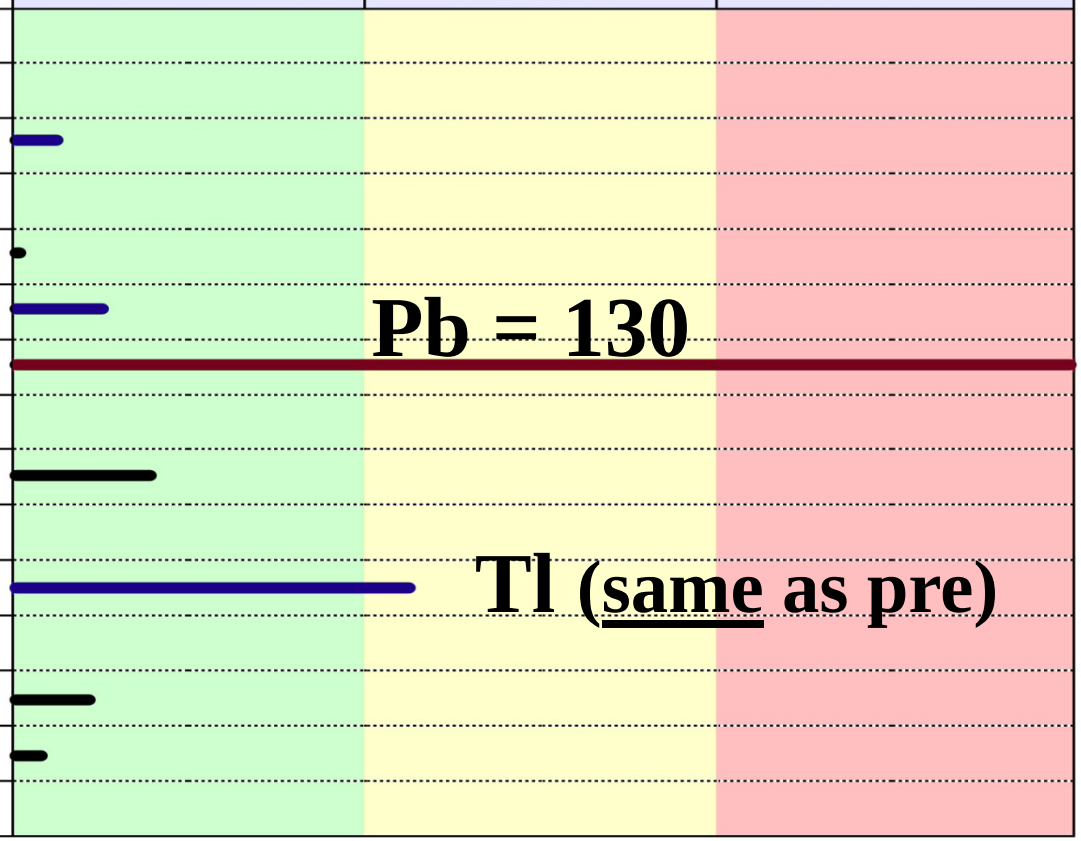
LAB#:
PATIENT:
SEX: Male
AGE: 68

CLIENT#:
DOCTOR:

Post-DMSA

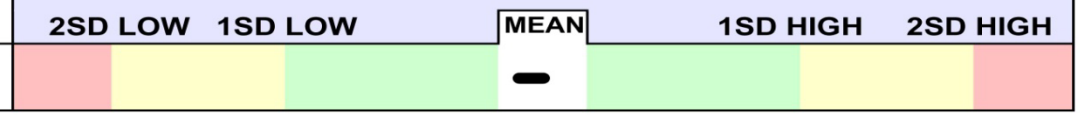
POTENTIALLY TOXIC METALS

METALS	RESULT µg/g CREAT	REFERENCE RANGE
Aluminum	< dl	< 25
Antimony	< dl	< 0.6
Arsenic	14	< 120
Beryllium	< dl	< 0.5
Bismuth	0.08	< 10
Cadmium	0.5	< 2
Lead	130	< 5
Mercury	< dl	< 3
Nickel	3.9	< 10
Platinum	< dl	< 1
Thallium	0.8	< 0.7
Thorium	< dl	< 0.3
Tin	1.9	< 9
Tungsten	0.05	< 0.7
Uranium	< dl	< 0.1



CREATININE

	RESULT mg/dL	REFERENCE RANGE
Creatinine	130	45- 225



Clinical Pharmacology: DMSA

- Oral: 20-25% absorbed, $T^{1/2\alpha}$ ~ 4 hrs.
- Peak plasma ~ 3 hrs., rate urinary excretion ~ 4 hrs.
- Urinary excretion: 90% as mixed disulfides with 2 cysteines (1:2)

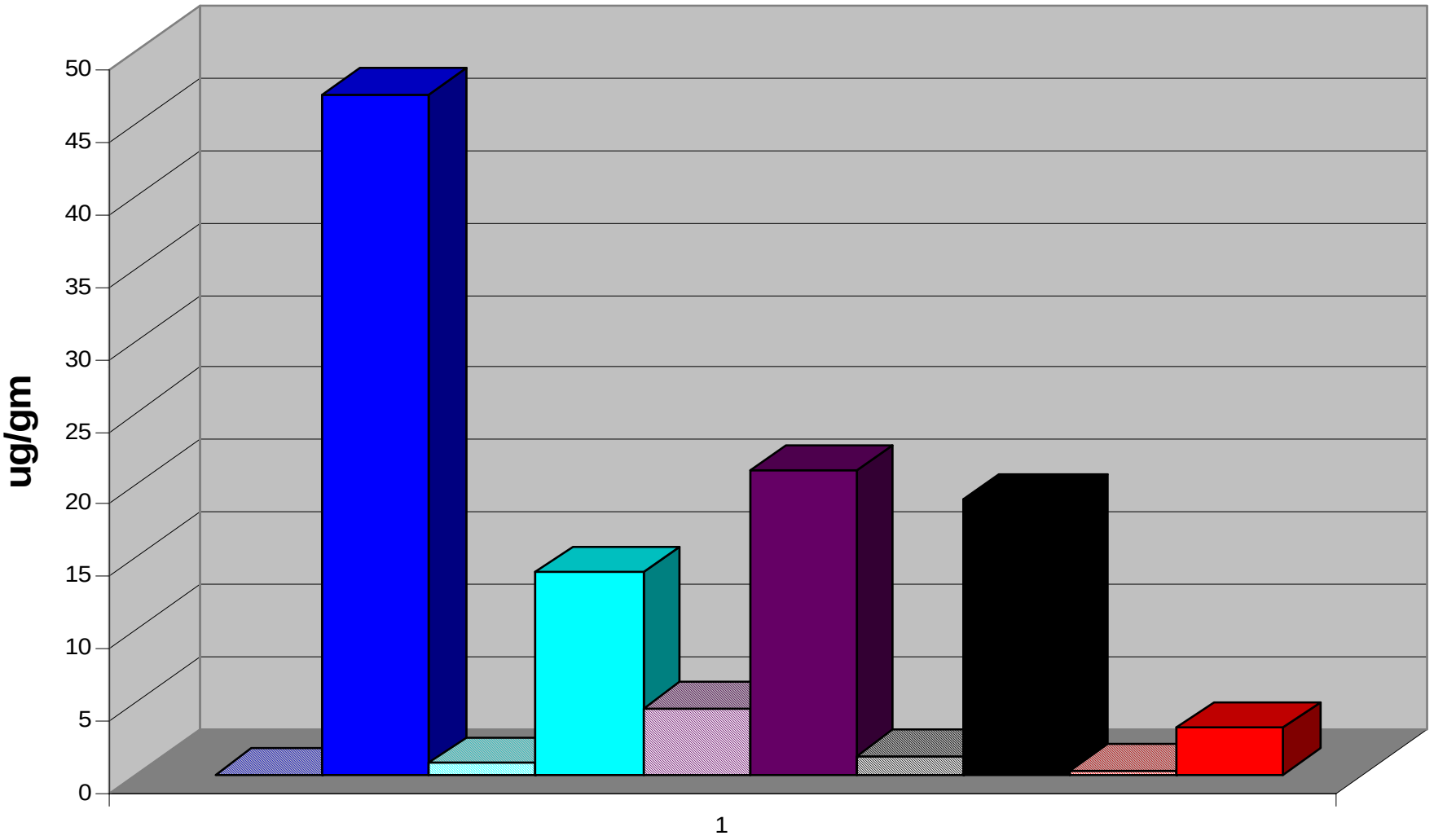
J Nutr Envir Med(1998)8:219-31 PDR(2005) Toxicol(1995)97:23-38
J Pharmacol Exp Therap(1993)267:12-21

Bolus DMSA Challenge

- **20-30** mg DMSA/kg BW as oral bolus on empty stomach ($\leq$ 2 gms)
- With hold food about 2 hrs.
- Encourage ~ 0.5L fluid over next few hrs.
- Collect all urine for 6 hrs.

J Nutr Envir Med (1998) 8:219-231

DMSA SUPPOSITORY: LEAD



n = 5, 3-4 yo, 20 mg/kg

Quig,Usman (unpublished ’06)

Mobilization of Metals

- Determined by:
  1. Relative **affinities** (stabilty constants)
  2. **Mass competition**
  3. Competition with **endogenous ligands**

  (Hg^{++} binds protein-SH- at logK ~ $\mathbf{10^{40}}$)

Stability Constants: DMPS

	$\log K_1$	$\log K_2$
Hg^{2+}	27	36
Ag^{2+}	25	35
CH_3-Hg^{1+}	21	31
Cu^{2+}	18	29
Cd^{2+}	18	26
Pb^{2+}	17	25
Zn^{2+}	15	25

Dimaval Scientific Manual (2008)

Stability Constants: EDTA

	LogK
Hg^{2+}	21
Pb^{2+}	18.4
Cu^{2+}, Ni^{2+}	18.3
Cd^{2+}, Al^{3+}, Zn^{2+}	16.1
Fe^{2+}	14.4
Mn^{2+}	13.4

Chemistry of Metal Chelate Compounds (1978)

Efficacy of Agents to Remove Hg

- Rabbits exposed to $HgCl_2$
- Kidneys slices incubated with "chelators" at equivalent concentrations

Reduction in tissue Hg/μg DNA

DMPS	86%*	DTT	55%
DMSA	65%*	Lipoic acid	35%
D-Pen	60%	EDTA	20%

*($p<0.05$) Toxicol. (1997) 116: 67-75

Slow Push Ca-Na_2-EDTA

Urine Metals	Increase*
Lead	147-X
Zinc	32-X
Manganese	15-X
Iron	7.4-X
Cadmium	7-X
Antimony	4.4-X

n=14, *p<0.05

Quig, Filidei, Whitaker (2002)

Summary: Lab Tests

- **<u>Exposure</u>** (*very* recent or ongoing)

  Blood and unprovoked urine
  Hair (longer temporal window)

  (Elevated RBC GSH, induced)

- **<u>Net retention</u>**

  Comparison of **pre** and **post** provoked urine

  (Low RBC GSH)

  ↑ oxidized DNA damage (urine 8-OHdG)

Take Home Messages

- Assess status of liver & glomerular filtration.
- Apply pharmacokinetic **facts**.
- Do **pre** (1st AM) and **post** provocation urinalysis initially
- Remove **source(s)** of ongoing exposure.
- Monitor efficacy of detoxification:

  Repeat challenge after 5-10 treatments

Metal	1st Choice	2nd Choice
Hg, MeHg	DMPS or DMSA	
Pb	DMSA/EDTA	DMPS
As	DMPS/EDTA	DMSA
Cd	EDTA	EDTA
Sb, Sn	DMPS/DMSA	EDTA
Pt, Ti	DMPS	EDTA
Fe, Al	EDTA	DFO
Tl	Prussian Blue	

Toxicol (1995)97:23-38

Urinary Porphyrins: Biomarkers of Xenobiotic Toxicity

Porphyrins and Heme Biosynthesis

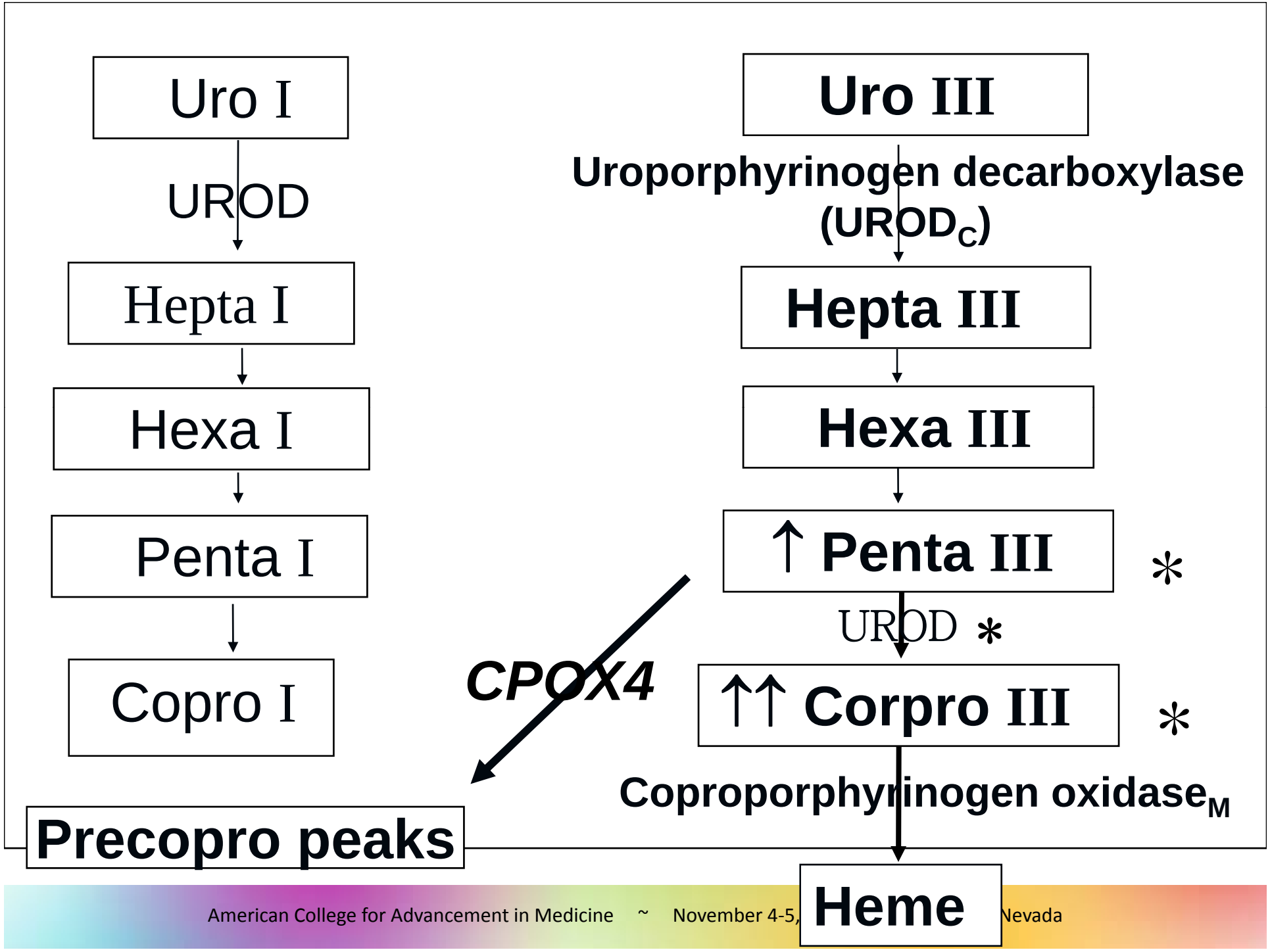
- Porphyrinogens: intermediates in heme biosynthesis (documented in 1934)
- Porphyrias are inherited or acquired (toxicants)
- Toxicants inhibit specific enzymes→ intermediates excreted
- **Very** high flux: rapid and large ↑ in intermediates
- Kidneys: high biosynthesis and, **accumulation** of toxicants

FLD1 A, Ex=395, Em=620 (Q:\1\DATA\CF081808\CF000008.D)
Uro I & II
Heptacarboxy
Hexacarboxy
Pentacarboxy
Unknown I
Unknown III
Copro I
15.203
Copro III
10
11
12
13
14
15
min

Mercury Specific Porphyrins

- Penta, precopro unknowns, copro III
- MeHg-fed rats: dose, duration, urine Hg. **↓ w/** DMPS dosing
- Correlated w/ severity of ASD & oxidative stress (not Asperger's)
- Dentists: UHg, neurological deficits. Most extreme w/ CPOX4 polymorphism

J Toxicol Env Hlth(1993)40:235 Can J Physiol Pharm(1996)74:210 Toxicol Sci(2001)61:234 Toxicol Appl Pharmacol(2006)214:99, (2005)206:113 Porphyrins(2005)14:93 J Neurol Sci(2008)Epub Toxicol Lett(2006)161:159


Uro I
UROD
Hepta I
Hexa I
Penta I
Copro I
Precopro peaks
Uro III
Uroporphyrinogen decarboxylase
(UROD$_C$)
Hepta III
Hexa III
↑ Penta III
*
UROD *
CPOX4
↑↑ Corpro III
*
Coproporphyrinogen oxidase$_M$
Heme

UROD

- 4 decarboxylations by the same enzyme (cytosol)

  uro → hepta → hexa→ penta → copro
- Complex dimeric protein with 2 active sites
- Decarboxylations ↓ polarity, more susceptible to Hg inhibition

Embo J (1998)17:2463-71

Mercury Poisoned Child

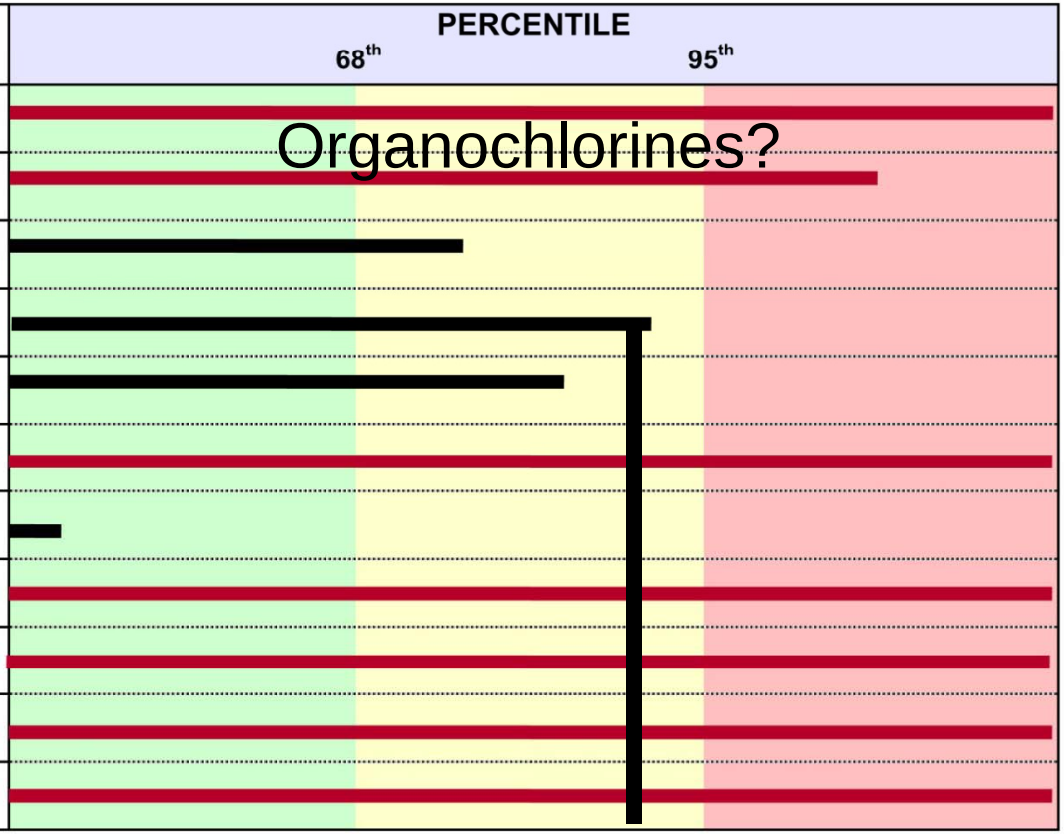
Specimen	Hg Level	Reference
Whole blood	**82** μg/L	< 5
Random urine	**15** μg/gm	< 5
Post-DMSA urine	**85** μg/gm	NA

PORPHYRINS; URINE

LAB#: 000000-0000-0
PATIENT: Sample Patient
ID: PATIENT-S-0001
SEX: M
AGE: 7

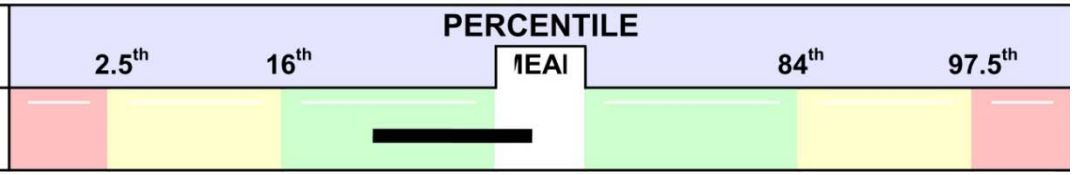
CLIENT#: 12345
DOCTOR:

PORPHYRINS	RESULT nmol/g creat	REFERENCE RANGE
Uroporphyrin I & III	73.1	< 18.5
Heptacarboxyporphyrin	8.1	< 5.0
Hexacarboxyporphyrin	2.9	< 5.0
Pentacarboxyporphyrin *	3.8	< 4.0
Coproporphyrin I	34.1	< 42.0
Coproporphyrin III	244	< 110
Copro I/Copro III	.14	< 0.8
Total Porphyrins	372	< 200
Unknown Peak I*	3.3	< 1.7
Unknown Peak III*	2.1	< 1.7
Total Unknown Peaks* *	5.4	< 3.4



CREATININE

	RESULT mg/dL	REFERENCE RANGE
Creatinine	58	25 - 180



Porphyrins Affected by Toxins

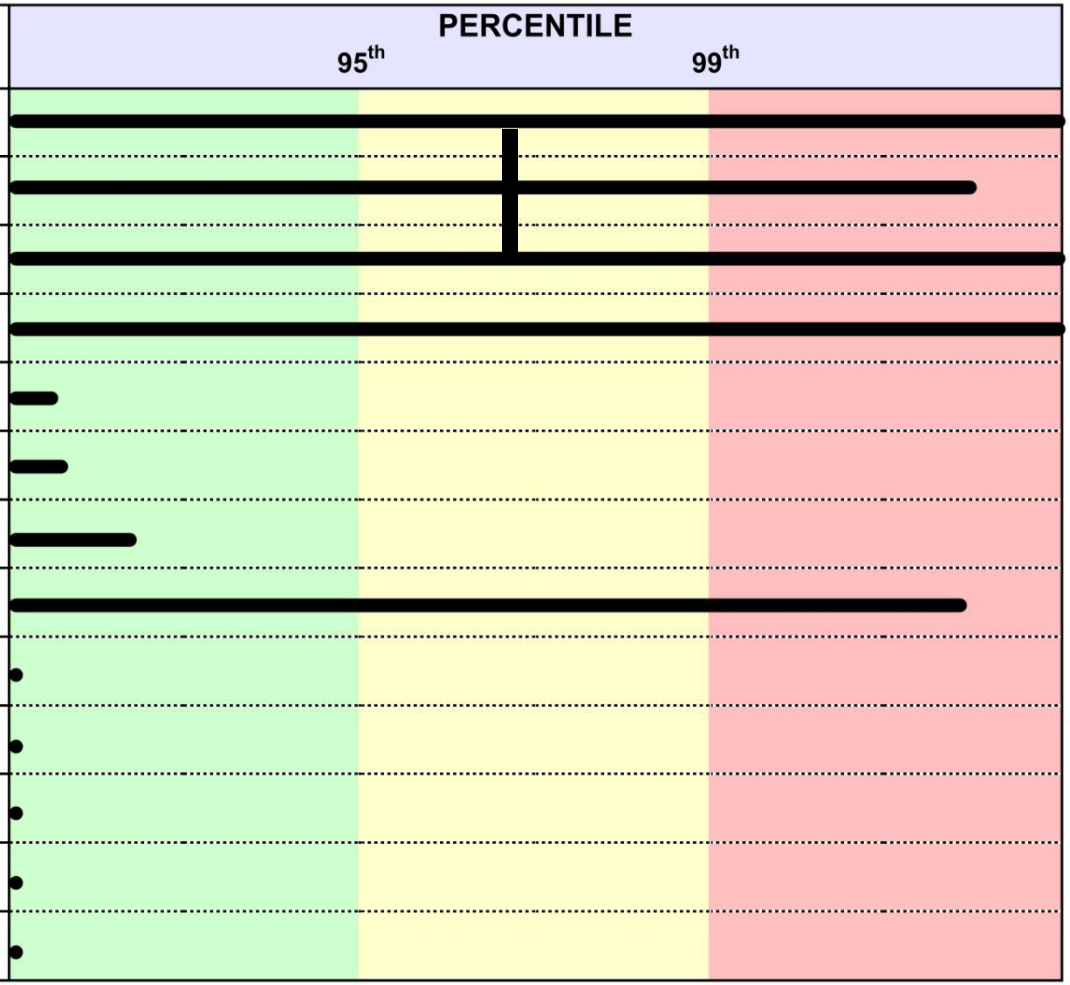
- As: Uros, high copro I : copro III ratio
- Hg: **Penta,, copro III**, precorpro unknowns I&III
- Pb: copro III, Zn-protoporphryn, (ALA)
- Hexachlorobenzene, dioxin: uros, hepta, hexa
- Methyl chloride, PVC, PBbiphenyl: copros

- Rule out ethanol, antibiotics, sedatives, analgesics, estrogens, oral contraceptives, liver dz, anemias

UROD Inhibition by Organochlorines

Porphyria Cutanea Profile (HCB)

PORPHYRINS	RESULT nmol/g creat	REFERENCE RANGE
Uroporphyrins	**240**	< 17
Heptacarboxylporphyrins	**12**	< 3
Hexacarboxylporphyrins	**30**	< 3
Pentacarboxylporphyrins	**13**	< 2.5
Coproporphyrin I	**2.1**	< 20
Coproporphyrin III	**8**	< 60
Copro I/Copro III	**0.27**	< 0.8
Total Porphyrins	**310**	< 90
Precoproporphyrin I*	**0**	< 2
Precoproporphyrin II*	**0**	< 1.2
Precoproporphyrins III*	**0**	< 1.2
Total Precoproporhyrins*	**0**	< 4
Precoproporphyrins*/Uro	**0**	< 0.1



Arch Dermatol (1999)135:400-4

Take Home Messages

- Urinary porphyrin profiles are valid biomarkers of inherited and toxicant-induced disruption of heme biosynthesis
- Toxicants include metals and chemicals that elicit specific profiles
- **High** levels of toxicants are required
- Porphyrin analysis DOES NOT replace provocations!
- May provide information about chemical toxicants

References for Quig, ACAM 04/09

1. Quig, DW "Chronic Metal Toxicity: Assessment of Exposure and Retention." In Textbook of Natural Medicine, ed. J.E.Pizzorno, Jr, Elsevier, 3rd edition, (2004)263-74
2. Goyer R. Chelation of toxic metals: Current interests. Env Health Persp 1995; 103: 988-989
3. www. Atsdr.cdc.gov/toxprofiles/tp13.html# (2007)
4. Agency for toxic Substances and Disease Registry (ATSDR). Toxicological profile for lead. Atlanta, GA: U.S. Department of health and Human Services, Public Health Service, 1993; p.131
5. Gonzalez-Ramirez D, Maiorino R M, Zuniga-Charles M. Sodium 2, 3-dimercaptopropane-1-sulfonate challenge test for mercury in humans: II. Urinary mercury, porphryns and neurobehavioral changes of dental workers in Monterrey, Mexico. J Pharmacol Exper Therapeutics 1995; 272: 264-274
6. Markowitz M E, Rosen J F. Assessment of lead stores in children: Validation of an 8-hour $CaNa_2EDTA$ provocative test. J Pediat 1984; 104: 337-341
7. Hibberd A R, Howard M A, Hunnisett A G. Mercury from dental amalgam fillings: Studies on oral chelating agents for assessing and reducing mercury burdens in humans. J Nutr Environ Med 1998; 8: 219-231
8. Aposhian H V, Bruce D C, Alter W et al. Urinary mercury after administration of 2,3-dimercaptopropane-1-sulfonic acid: correlation with dental amalgams. FASEB J 1992; 6: 2472-2476
9. Aposhian H V, Maiorino R M, Gonzalez-Ramirez D et al. Mobilization of heavy metals by newer, therapeutically useful chelating agents. Toxicol 1995; 97: 23-38
10. Aposhian H V. DMSA and DMPS - Water soluble antidotes for heavy metal poisoning. Ann Rev Toxicol 1983; 23; 193-215
11. Wax PM, Thorton CA. Recovery from severe arsenic-induced peripheral neuropathy with 2,3-dimercapto-1-propanesulphonic acid. Cinical Toxicol 2000; 38: 777-780
12. Grandjean P, Jacobsen I A, Jorgensen P J. Chronic lead poisoning treated with dimercaptosuccinic acid. Pharmacol Toxicol 1991; 68: 266-269
13. Lee B, Schwartz B S, Stewart W et al. Provocation chelation with DMSA and EDTA: evidence for differential access to lead storage sites. Occup Environ Med 1995; 52: 13-19
14. Besunder J B, Super D M, Anderson R L. Comparison of dimercaptosuccinic acid and calcium disodium ethylenediaminetetraacetic acid versus dimercaptoprpanol and ethylenediaminetetraacetic acid in children with lead poisoning. J Pediat 1997; 130: 966-971
15. Cory-Slecta DA, Weiss B, Cox C. Mobilization and redistribution of lead over the course of calcium disodium ethylenediamine tetraacetate chelation therapy. Pharmacol Exp Ther 1987; 243: 804-13
16. Cory-Slecta DA. Mobilization of lead over the course of DMSA chelation therapy and long-term efficacy. Pharmacol Exp Ther 1988; 246 :84-91

17. Flora SJ et al. Beneficial effect of combined administration of some naturally occurring antioxidants (vitamins) and thiol chelators in the treatment of chronic lead intoxication. Chem Biol Interact 2003; 15:267-80
18. Pastore A et al. Analysis of glutathione: implications in redox and detoxification. Clinica Chimica Acta 2003; 333: 19-39
19. Ruey-Hong W et al. Increased levels of 8-Hydroxy-2'-Deoxyguanosine attributable to carcinogenic metal exposure among schoolchildren. Environ Hlth perspect 2005; 113: 1386-1390
20. Duk-Hee L et al. Graded associations of blood lead and urinary cadmium concentrations with oxidative-stress-related markers in the U.S. population: results from the third National Health and Nutrition Examination Survey. Environ Hlth Prospect 2006; 114: 350-354
21. Ferguson LR et al. Oxidative DNA damage and repair: significance and biomarkers. J Nutr 2006; 136: 2687S-2689S
22. Swedko PJ et al. Serum creatinine is an inadequate screening test for renal failure in elderly patients. Arch Intern Med 2003; 163: 356-360
23. Woods JS and Miller HD. Quantitative measurement of porphyrins in biological tissues and evaluation of tissue porphyrins during toxicant exposures. Fund Appl Toxicol 1993; 21: 291-297
24. heyer NJ et al. A cascade analysis of the interaction of mercury and Coproporphyrinogen oxidase (CPOX) polymorphism on the heme biosynthetic pathway and porphyrin production. Toxicol Lett 2006; 161: 159-166

Reid L. Winick, DDS

The role of dentistry in causing and preventing heart disease

Bio

Reid L. Winick, D.D.S. is a graduate of New York University College of Dentistry. He has extensive experience in General Dentistry, as well as in TMD and Craniofacial Disorders. Dr. Winick is the founder and president of Dentistry for Health New York, a green and sustainable dental practice designed as a haven for overall wellness. He is committed to the environment and to the health and wellness of his patients' mind, body, and spirit. Dr. Winick is past co-founder and director of the Facial Pain/TMD Clinic at NY Eye & Ear Infirmary. He has completed numerous continuing education courses with an emphasis on TMD & cervical dysfunction, Neural Therapy and Biological Dentistry. Dr. Winick is a segment host for a nationally syndicated radio show called, "SafeKiss." Dr. Winick also lectures, writes, and teaches on Green Dentistry, TMD, head, neck & facial pain.

Lecture Overview

Years ago we have all been taught the prime focus of the oral cavity was to initiate the digestive process as food passes inside a 9m (30 ft) long duct called digestive tube. The tongue detects food's flavor, size, composition, texture and temperature. By chewing the food, the surface of the elements exposed to the action of the digestive juices is increased. Thus, the digestive process begins.

Over the past ten years of ongoing medical/dental research, Dentists have been inspired by the words of Charles Mayo who noted, over 90 years ago, that people who keep their teeth live an average of ten years longer than people who do not. There's been a huge paradigm shift in almost every aspect of periodontal diseases. Modern research has repeatedly demonstrated that the old traditional concepts of etiology and treatment were fundamentally flawed. The old simplistic concept that calculus caused periodontal disease has been replaced with a more scientific and accurate concept wherein specific bacterial infections trigger destructive immunological reactions.

Recently, the former Surgeon General Donna Shalala said in her address of 2000: "The terms oral health and general health should not be interpreted as separate entities. Oral health is integral to general health; this report provides important reminders that oral health means more than healthy teeth and that you cannot be healthy without oral health". "A thorough oral examination can detect signs of nutritional deficiencies as well as a number of systemic diseases, including microbial infections, immune disorders, injuries, and some cancers."

The goal of my presentation will be to inform and educate about the details of the systemic pathways that the oral cavity plays a role in, with regard to cardiovascular disease.

I will finish the presentation with natural wellness solutions to improve the environment of the oral cavity in order to support gastrointestinal health that the members of ACAM are pursuing for their patients. In addition, we will discuss how to foster a team relationship with their local dentist.

Contact Information

Dentistry for Health New York
120 East 56th Street, 12th Floor
New York, NY 10022
reid@dfhny.com

American College for Advancement in Medicine
Chelation Therapy Workshop
November 4-5, 2009
Las Vegas, Nevada

Dentistry for Health New York®

Innovative Dentistry for Optimal Health

The Role of Dentistry in Cardiovascular Disease

Reid Winick, D.D.S.

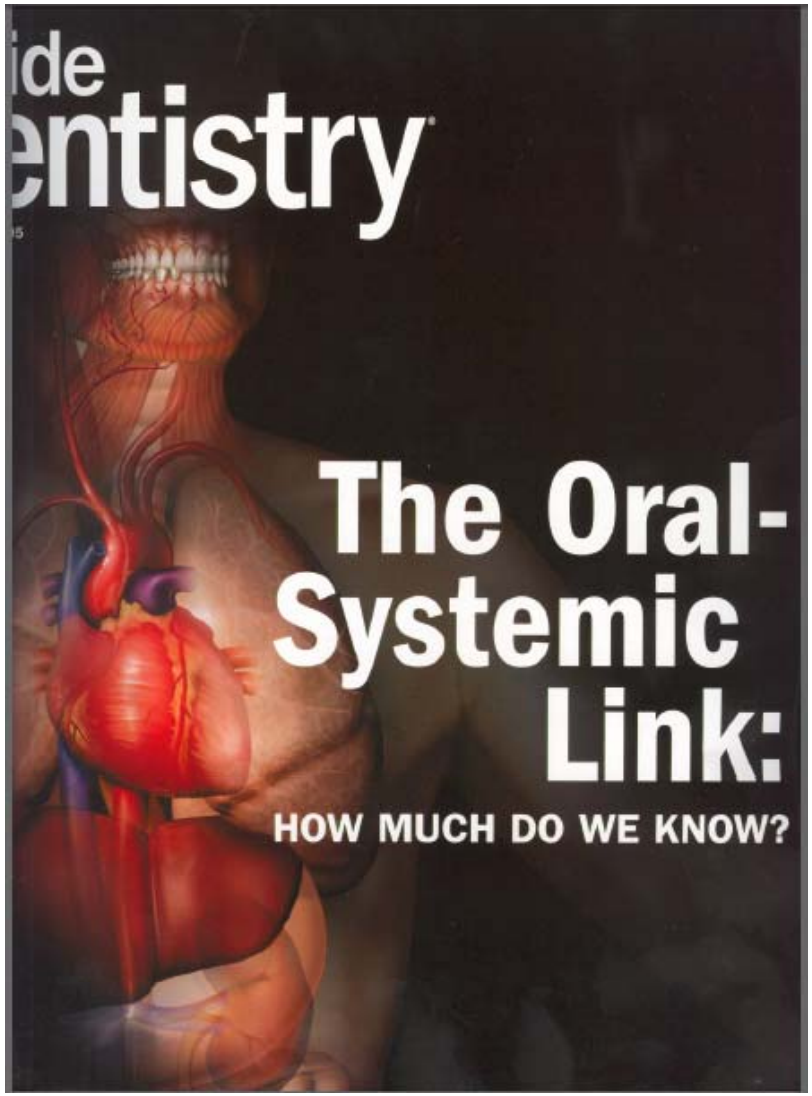
120 East 56th St., 12Th Fl. NY, NY 10022

November 5, 2009

American College for Advancement in Medicine

TEL 212 973 9425 FAX 212 973 1029 dentistryforhealthny.com

Dentistry for Health New York®



...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®

Oral Systemic History

- Charles H. Mayo 1865-1939
- Westin A Price, DDS 1870-1948
- Royal Lee, DDS, 1885-1967
- Perry A. Ratcliffe, DDS
- Donna Shalala- The Surgeon General's Report

Dentistry for Health New York®

Charles H. Mayo

- Co-founder of Mayo Clinic with brother William 1919
- World's first integrated group practice
- Pioneered medical specialization
- Mayo noted over 90 years ago, that "people who keep their teeth live an average of ten years longer than people who do not "

Dentistry for Health New York®

Weston Price, DDS

Weston A. Price

- Called the Charles Darwin of Nutrition
- Also the father of preventative dentistry
- Noticed overall health was related to the health of teeth & gums
- What is it in our diets that land so many people in my dental chair?
- Studied 14 primitive cultures
- The farther he got from civilization the fewer cavities he found
- Practiced nutrient dense, whole foods organic diet

Dentistry for Health New York®

Royal Lee, DDS

- DDS Marquette U. 1924
- Presented “Systemic causes of dental caries” written at age 16
- Hundreds of patents in electric field including motor speed controller for dentists
- Fought the FDA for whole, natural unadulterated food with vitamins in tact
- Founded Standard Process Vitamins
- Lee Foundation largest clearinghouse for nutritional information

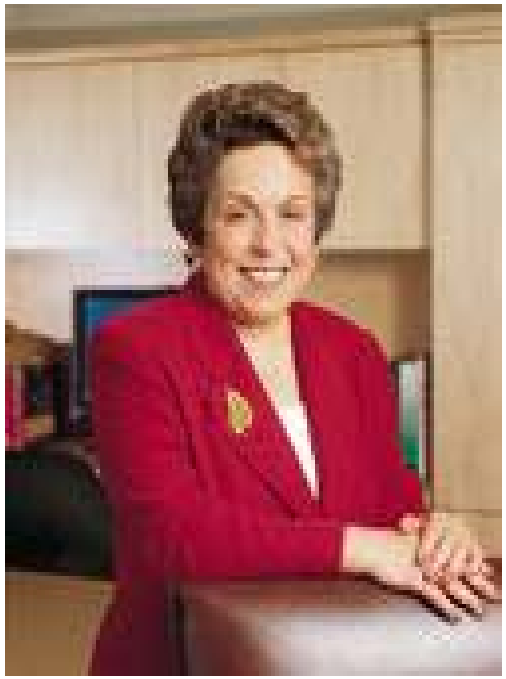
Dentistry for Health New York®

Perry A. Ratcliff, DDS

- 34th Person to receive Periodontal Specialty license
- Leader in non surgical periodontics
- Pioneer in Oral-Systemic Links- HIV, herpes, chlamydia
- Research in Volatile Sulfur Compounds chlorine dioxide and gram negative bacteria
- Founded Rowpar Pharmacueticals 1991
- 16 patients for CLO2 in dental products

Dentistry for Health New York®

A Growing Body of Evidence



- The former Surgeon General Donna Shalala who said in her address of 2000:
- "The terms oral health and general health should not be interpreted as separate entities. Oral health is integral to general health; this report provides important reminders that oral health means more than healthy teeth and that you cannot be healthy without oral health". .
- Periodontal disease is linked to diabetes, heart disease, stroke .. And pre-term birth

Dentistry for Health New York®

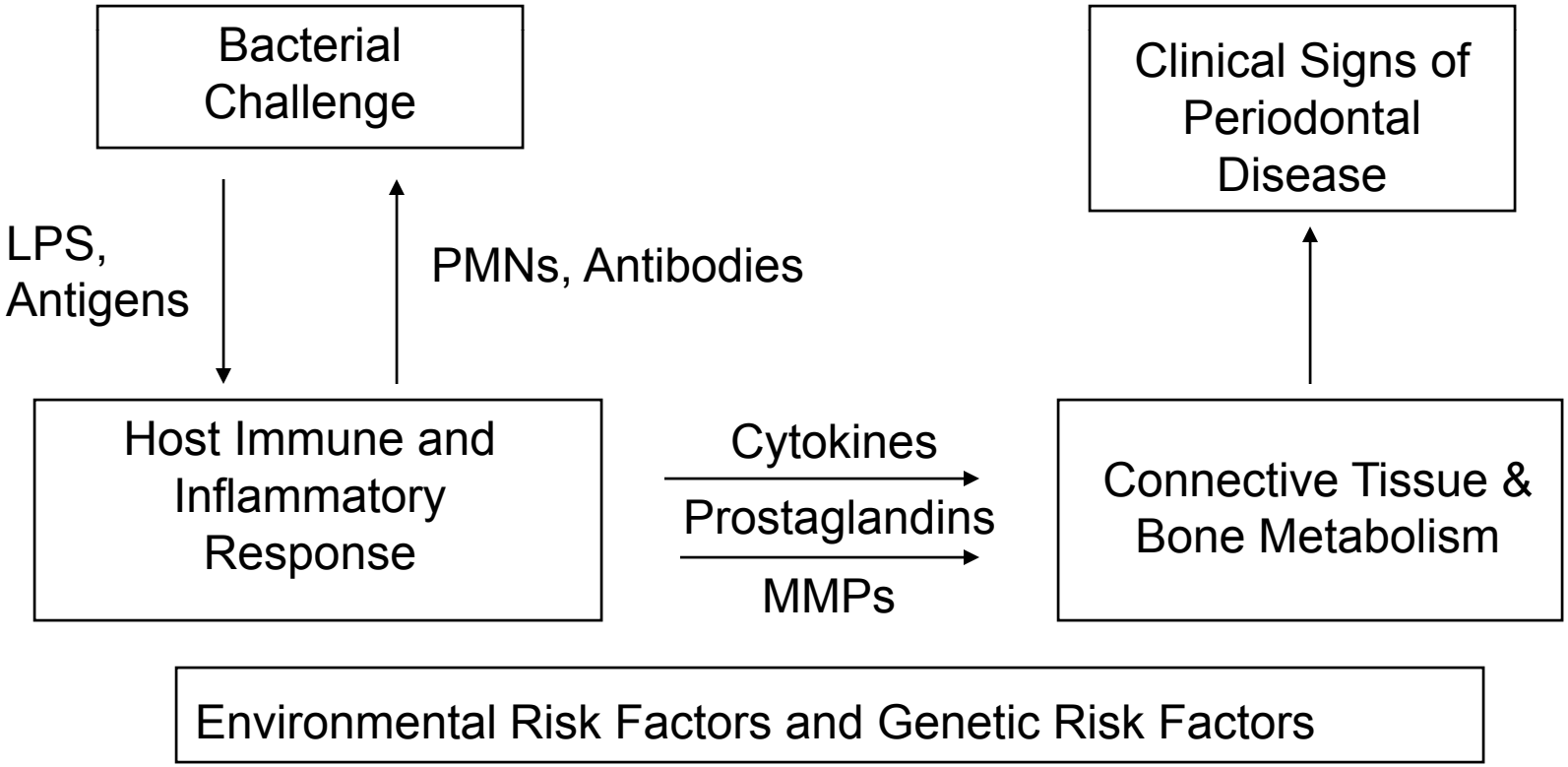
- **“If I needed to remove either the Medical or Dental component of my Clinic, I would keep the Dental because chronic problems will not resolve without Biological Dental care…”**

- Dr. Thomas Rau, Director of Paracelsus Clinic, Switzerland.

Dentistry for Health New York®

Pathogenesis of Periodontitis

Page RC. Ann Periodontol 1998



Dentistry for Health New York®

Pathogenesis of Periodontitis

- Current Concepts:

  - Bacteria are necessary for disease, but not sufficient to cause disease in all people

  - Disease initiation and progression also require susceptible host

  - Host factors play major role in pathogenesis of periodontal disease

  - **This is very similar to other inflammatory disease, where variability in host response is a major determinant of clinical disease**

Dentistry for Health New York®

Concepts of Periodontitis

- Periodontitis is an inflammatory disease
  - **It is not just about bugs**
- Periodontitis is a mucosal disease

Dentistry for Health New York®

Pathogenesis of Periodontitis

Risk factors and indicators for periodontitis:

- Smoking
- Systemic diseases
- Genetic factors
- Advancing age
- Race, ethnicity
- Male gender
- Past hx of periodontitis
- Compromised host defense
- Stress
- Poor oral hygiene
- Dental care status

Dentistry for Health New York®

Concepts of Periodontitis

- Periodontitis and periimplantitis are inflammatory mucosal diseases
- Presence of teeth/implants presents major challenge to host

Dentistry for Health New York®

The Presence of Toxicant Producing Microbes Within the Radicular Dentin of Vital and Non-vital Teeth: Implications for Systemic Diseases

By

BOYD E. HALEY, Ph.D.

PROFESSOR

DEPARTMENT OF CHEMISTRY

UNIVERSITY OF KENTUCKY

Dentistry for Health New York®

Questions

- Do toxicant producing microbes reside within the dentinal tubules of vital but periodontally diseased teeth?
- If so, what about non-vital, endodontically treated teeth?
  - In other words, are periodontally diseased teeth and endodontically treated teeth infected?
  - What do studies published in the dental literature have to say?

Dentistry for Health New York®

Occurrence of Invading Bacteria in Radicular Dentin of Periodontally Diseased Teeth: Microbiological Findings

- *Journal of Clinical Periodontology*, Vol. 24,
- pp.478-485, 1997
- [1]Giovanna Giuliana, [2]Pietro Ammatuna, Giuseppe Pizzo, [2]Francesca Capone, [1]Matteo D' Angelo

- [1]Department of Periodontology and [2]Departmentment of Hygiene and Microbiology, University of Palermo, Italy.

Dentistry for Health New York®

Giuliana et al., (1997) *J. Clin. Periodontol*. 24:478-485

- "Findings supported by laboratory studies have indicated that periodontal pathogens may penetrate connective tissue, epithelium and epithelial cells."
- "In a similar fashion, bacterial invasion of the cementum and radicular dentin was thought to be important in pathogenesis of periodontal disease in 1890, when Miller described bacteria invading the radicular dentin of periodontally diseased teeth."
- "More recently, observations using light microscopic, scanning electron microscopic and cultural studies have suggested that bacteria probably invade cementum and radicular dentin and dentinal tubules act as reservoirs of periodontal pathogens."

Miller, W.D. (1890). The microorganisms of the human mouth.
The local and general diseases which are caused by them.
S.S. White Dental Manufacturing. New York, NY.

Dentistry for Health New York®

Giuliana et al., (1997) *J. Clin. Periodontol*. 24:478-485

- "Invading bacteria were detected in 14 (53.8%) samples from periodontally diseased teeth."
- "The bacterial concentration ranged from 831 to 11,971 CFU/mg (mean ± standard deviation: 3043 ± 2763)."
- "Micro-organisms identified included putative periodontal pathogens such as *Prevotella intermedia*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Bacteroides forsythus*, *Peptostreptococcus micros* and *Streptococcus intermedius*."
- "These findings suggest that radicular dentin could act as bacterial reservoir from which periodontal pathogens can recolonize treated periodontal pockets, contributing to the failure of therapy and recurrence of disease."

Ultrastructural Observations on Bacterial Invasion in Cementum and Radicular Dentin of Periodontally Diseased Human Teeth

Journal of Periodontology, Vol. 59, pp.493-503, 1988

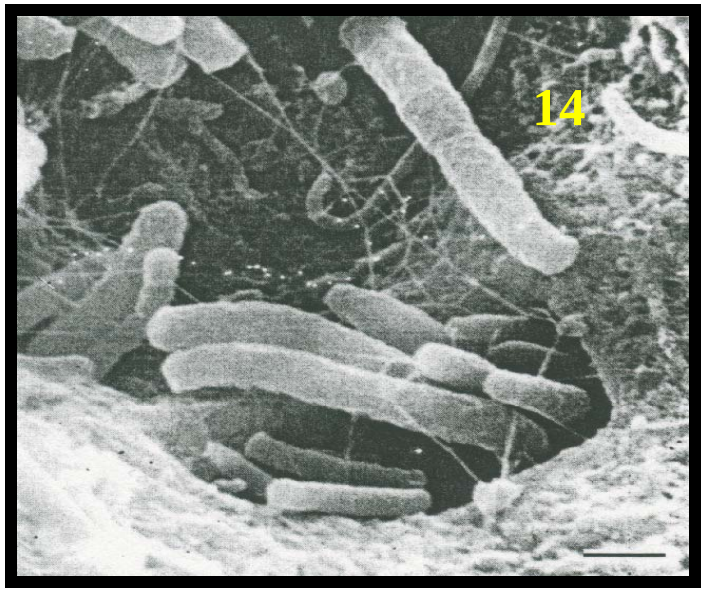
1Patrick A. Adriaens, 1Chris A. Edwards, 2Jan A. De Boever and 1Walter J. Loesche

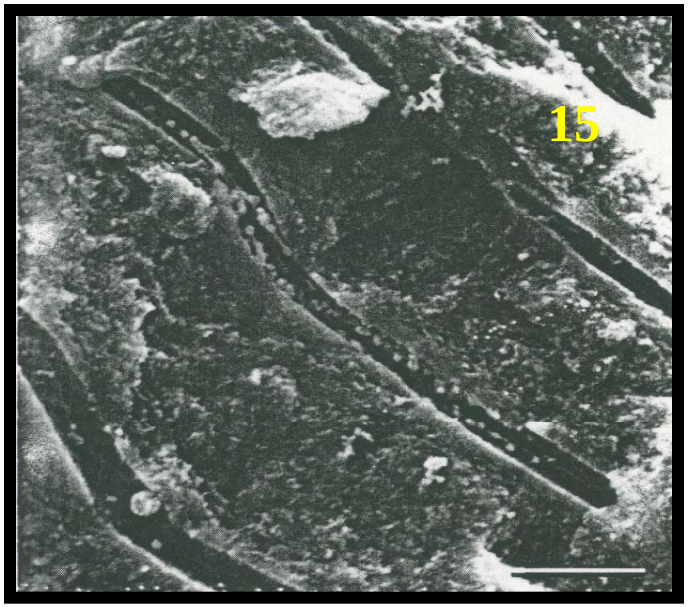
[1]University of Michigan, School of Dentistry, Department of Oral Biology and Dental Research Institute, Oral Bacteriology Laboratory, Ann Arbor, MI.

[2]State University of Ghent, School of Dentistry, Department of Fixed Prosthetics and Periodontology, University Hospital, Ghent, Belgium.

Dentistry for Health New York®

Adriaens et al., (1988). *J. Clin. Periodontol.* 59:493-503.





"Figure 14. Filamentous bacteria invading the dentinal tubules at their orifices in the bottom of a resorption lacuna."

"**Figure 15**. Longitudinally fractured dentinal tubules in the radicular dentin area corresponding to the exposed subgingival root surface. Bacteria are present in the dentinal tubules."

Dentistry for Health New York®

Bacterial Invasion in Root Cementum and Radicular Dentin of Periodontally Diseased Teeth in Humans: A Reservoir of Periodontopathic Bacteria

- *Journal of Periodontology*, Vol. 59, pp.222-230, 1988

- [1]Patrick A. Adriaens, [2]Jan A. De Boever and
- [1]Walter J. Loesche
- [1]University of Michigan, School of Dentistry, Department of Oral Biology and Dental Research Institute, Oral Bacteriology Laboratory, Ann Arbor, MI
- [2]State University of Ghent, School of Dentistry, Department of Fixed Prosthetics and Periodontology, University Hospital, Ghent, Belgium

Dentistry for Health New York®

Adriaens et al., (1988). *J. Periodontol.* 59:222

- "Bacterial growth was detected in 87% of the periodontally diseased teeth."
- "Fifty-nine percent of the diseased teeth contained bacteria in the pulp samples."
- "The mean bacterial concentration in the pulp and dentin layers from the diseased teeth was 259 to 7,190 times greater than the concentrations in the corresponding layers from healthy teeth."
- "These radicular structures are likely to serve as bacterial reservoirs from which bacterial recolonization of the mechanically treated root surfaces can occur."

Dentistry for Health New York®

Questions

- **Do bacteria reside within the dentinal tubules of vital but periodontally diseased teeth?**
  - **Answer: Yes**
- **Are these teeth infected?**
  - **Answer: Yes**
- **Does the cementum provide an impenetrable barrier that prevents the entry of bacteria into the dentinal tubules of vital teeth?**
  - **Answer: No**

Dentistry for Health New York®

The Implications of Intraradicular Bacteria

- Do bacteria remaining within the dentinal tubules of periodontally diseased teeth and the toxins they produce affect the successful outcome of periodontal disease treatment? Yes
- Can microbial factors such as bacterial cell-soluble and insoluble components, toxins, enzymes, and harmful metabolic by-products spread from these foci of infection to other sites in the mouth and cause problems? Yes
- Does the spread of these intraradicular bacteria and their toxins pose a potential risk to the systemic health of the individual. Yes
- Does the presence of toxicity and inflammatory proteins in the GCF indicate an infected tooth??? Only a competent dentist can decide this.

Dentistry for Health New York®

Cardiovascular Disease-

Periodontal Disease Connection

Atherosclerosis

...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®

Cardiovascular & Periodontal Diseases

- Overall, 28 of the 36 studies done show that periodontitis is an *independent risk factor* for CVD-related events (MI/ stroke)
  - Independent of other known risk factors such as diabetes, hypertension, BMI, smoking, age, cholestrol, etc
- The *degree* of risk is low to moderate (O.R. 1.2-2.0)
  - Not as strong a risk factor as smoking, cholesterol
- Degree of risk is higher for stroke than for heart attack
  - Odds ratios of 2.0-3.0

Beak et al. J. Periodontol 2005

Dentistry for Health New York®

Cardiovascular & Periodontal Diseases

- The more teeth that are affected by periodontal disease, the higher the risk.

Arbes et al. *J Dent Res 1999*

Dentistry for Health New York®

Cardiovascular and Periodontal Diseases

- How can this be? What mechanisms?
- Bacteremia (routine mastication, oral hygiene)
  - Exposure time to bacteremia over 1 month period 1000 times greater from routine chewing and brushing than from tooth extraction (Guntheroth *Am J Cardiol* 1984)
  - AHA guidelines clearly emphasize need for “best possible oral health to reduce potential sources of bacterial seeding” (Dajani et al. *JAMA* 1997)

Dentistry for Health New York®

Cardiovascular and Periodontal Diseases

- Blood drawn at baseline and after tx at 1.5, 5, 20, 40, and 60 minutes
- Incidence of bacteremia:
  - ext + placebo = 80%
  - ext + amoxicillin = 56%
  - tooth brushing = 32%
- Tooth brushing can induce bacteremia
- Bacteremia after ext is common, even with Ab prophylaxis

Dentistry for Health New York®

Cardiovascular and Periodontal Diseases

- Periodontal infection may lead to low-level bacteremia and intravascular LPS
  - Can result in altered coagulability, platelet function, endothelial/vessel wall integrity
- Infection is a known risk factor for acute thromboembolic events (stroke/MI)
  - MI/stroke often preceded by febrile illness

Mattila *J Int Med* 1989

Syrjanen et al. *Br Med J* 1988

Dentistry for Health New York®

Periodontal Medicine

- Examined *systemic dissemination* of bacterial endotoxin after chewing, using chromogenic limulus amoebocyte lysate assay
  - 42 moderate-to-severe periodontitis subjects
  - 25 periodontally healthy subjects
  - Blood samples before mastication, 5 & 10 minutes after mastication
    * Chewed gum 50 times on right side and 50 times on left side

Geerts et al. *J Periodontol* 2002

Dentistry for Health New York®

Periodontal Medicine

- Only 6 % of all subjects had endotoxemia before chewing (mean 0.89 pg/ml), vs. 24% after chewing (mean 3.0 pg/ml)…$p<0.001$
- After chewing, only 12% of the periodontally healthy subjects had endotoxemia (mean 1.17 pg/ml), vs. 40% of severe periodontitis patients (mean 5.58 pg/ml)…$p<0.05$

Geerts et al. *J Periodontol* 2002

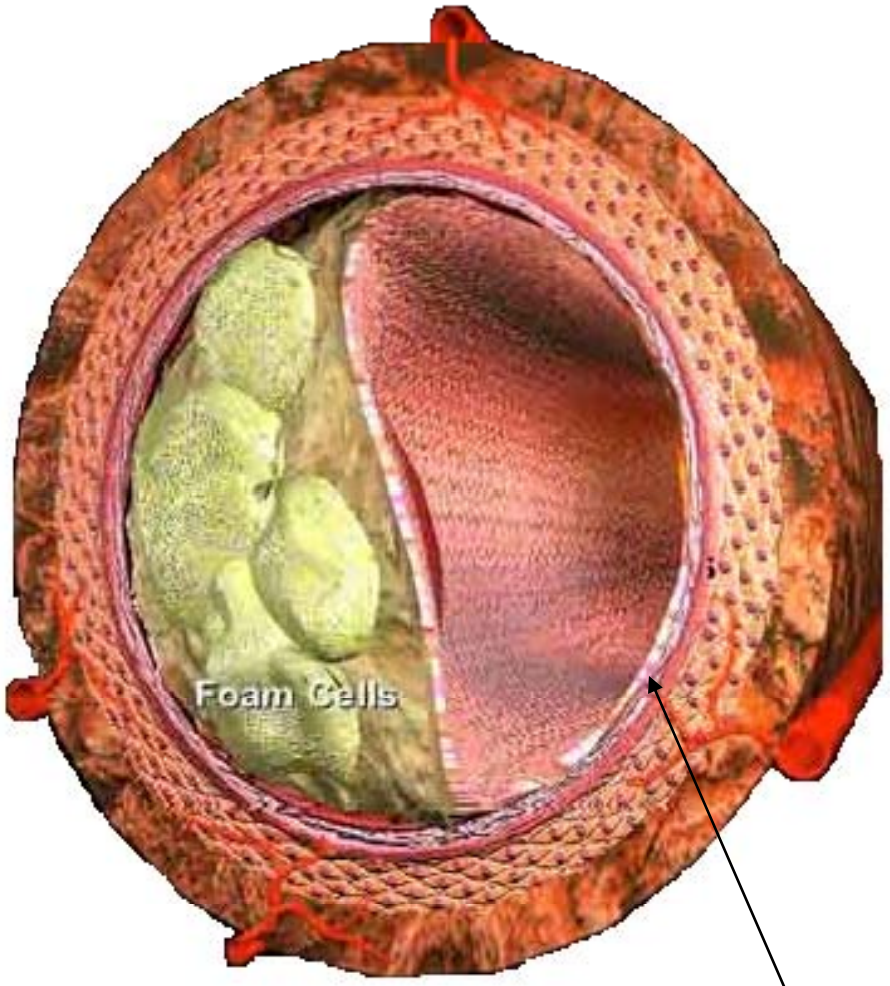
Dentistry for Health New York®

Periodontal Medicine

- Chewing may induce systemic dissemination of endotoxin
- Periodontal disease increases both the incidence of endotoxemia and the level of systemic endotoxin
- Oral cavity (GCF) is reservoir of endotoxin

Geerts et al. *J Periodontol* 2002

Dentistry for Health New York®



Endothelial Cells

...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®

Periodontal infections may affect cardiovascular/ cerebrovascular systems directly: Initial stages of atheroma formation are inflammatory in nature. Initiation and progression of atheroma formation involves:

1. Damage to vascular endothelium (bacterial, viral, chemical, shear forces, etc.)
2. **INFLAMMATION** - Adherence and penetration of monocytes into vessel wall
3. Production of chemotactic and pro-inflammatory cytokines by monocytes/macrophages
4. Monocytes become engorged with circulating LDL to form large foam cells

Dentistry for Health New York®

5. Chemotactic and pro-inflammatory factors stimulate smooth muscle cell proliferation
6. End result is formation of atheroma, thickening of vessel wall, narrowing of vessel lumen
7. Pro-inflammatory cytokines can result in rupture of fibrous cap over the atheroma, with formation of thromboembolis (stroke/MI)
8. Hematogenous spread of bacteria and bacterial products from other sites (e.g., oral cavity) may stimulate similar cascade of events or worsen existing condition. Periodontitis results in increased systemic bacterial endotoxin levels following normal chewing (Geerts et al. *J Periodontol* 2002)
9. Oral/periodontal pathogens have been found in carotid atheromas (Chiu *Am Heart J 1999*; Haraszthy et al. *J Periodontol 2000, 2001;* Zaremba et al. *J Periodontol 2007*)

Dentistry for Health New York®

Cardiovascular and Periodontal Diseases

- 50 patients (ages 56-82) with carotid stenosis
  - Surgical specimens obtained after carotid endarterectomy
- PCR & DNA probes used to detec DNA from
  - *Chlamydia pneumoniae*
  - Cytomegalovirus
  - *P. gingivalis, P. intermedia, B. forsythus, A. actinomycetemcomitans*

Haraszthy et al. *J Periodontol* 2000

Dentistry for Health New York®

Cardiovascular and Periodontal Diseases

- All 50 specimens had severe atheromatous plaques

C. pneumoniae	18%
CMV	38%
B. forsythus	30%
P. gingivalis	26%
A. actinomycetemcomitans	18%
P. intermedia	14%

Detected bacterial DNA; <u>not</u> intact or viable cells

•44% of atheromas had at least one perio pathogen

•59% of these had > 1 pathogen

Haraszthy et al. *J Periodontol* 2000

Dentistry for Health New York®

Periodontal and Cardiovascular Diseases

- Pathogenesis of thromboembolism (direct effect):
  - platelet aggregation forms thrombus
  - thrombus may break free to form embolus
  - oral organisms may increase platelet aggregation
  - hypercoagulability

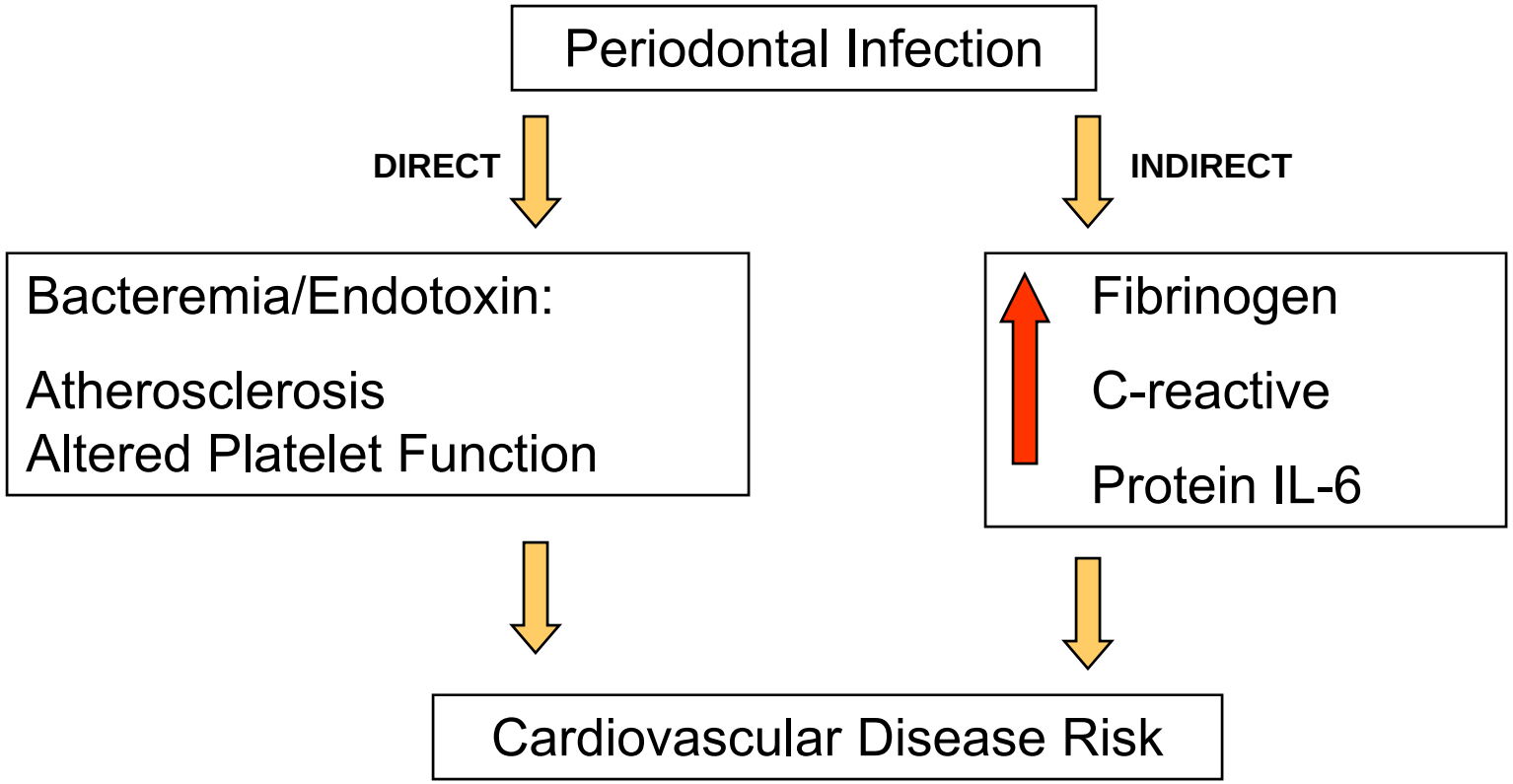
Dentistry for Health New York®

Cardiovascular and Periodontal Diseases

- Effect of periodontal infection may also be indirect
- Serum fibrogen and C-reactive protein levels are higher in patients with periodontitis
- Elevated fibrogen/ C-reactive protein are risk factors for ischemia/MI/stroke (increased coagulability)
- Cardiovascular risk factors (IL-6/fibrinogen/C-reactive protein) may be intermediate variables linking periodontal disease to increased CVD risk

Dentistry for Health New York®

Cardiovascular and Periodontal Diseases



Dentistry for Health New York®

Cardiovascular & Periodontal Diseases

- Periodontal *treatment* decreases serum inflammatory markers
  - 6 month prospective trial; 94 generalized periodontitis subjects; serum CRP and IL-6 measured before SCRP, then 2 and 6 months after
  - Significant reduction in serum CRP and IL-6 levels at 6 months
  - The better the clinical response to SCRP, the more likely there was a reduction in CRP and IL-6

D'Aiuto et al. *J.Dent Res* 2004

Dentistry for Health New York®

Three Phases of Research

- Phase 1- There is a correlation
  - But which came first….?
- Phase 2- Perio is a causal factor
  - But will treatment matter?
- Phase 3- Treating the perio reduces the risk of systemic disease
  - Time to do something about it!

Dentistry for Health New York®

YAHOO! NEWS Welcome, **learning61** [Sign Out, My Account]

News Home - Help

News Home | U.S. | Business | World | Entertainment | Sports | Tech | Politics | Science | Health | Most Popular | Index

Weight Loss | Sexual Health | Medications/Drugs | Parenting/Kids | Seniors/Aging | Diseases/Conditions

News Search Now with Blogs (BETA) Search: All News & Blogs Search Advanced

Got Gum Trouble? Your Heart Might Be Next

HealthDay

By E.J. Mundell
HealthDay Reporter
Tue Nov 29, 5:02 PM ET

TUESDAY, Nov. 29 (HealthDay News) -- There's mounting evidence that brushing, flossing and regular dental checkups may be at the heart of good cardiovascular health.

"People who have chronic infections -- and gum disease is one of the major chronic infections -- are at increased risk later in life for atherosclerosis [hardening of the arteries] and coronary heart disease," said **American Heart Association** spokesman Dr. Richard Stein, who is also director of preventive cardiology at Beth **Israel** Medical Center, in New York City.

Stein said he regularly counsels patients worried about their risk for heart

Dentistry for Health New York®

Out of the Closet!

- American Heart Association Statement : Gum disease >Heart disease- Nov 2005
- Consumer Articles Readers Digest, AZ Republic Web MD- Dec 2005 to date
- Colgate ADA Promotion Jan 2006
- CIGNA Oral Health Maternity Program- Jan 2006
- Joint ADA-AMA Conference Feb 2006
- Aetna Columbia- Treatment of Perio saves health$
- March 2006
- CIGNA Diabetes/Cardio Program- May 2006

Dentistry for Health New York®

Reader's Digest December 2005

How Your Dentist Can Save Your Life

The dentist may be the most important doctor you see this year.

By Dan Ferber

From Reader's Digest

December 2005

What Most People Don't Know

Ken Michener's tooth had been hurting off and on for months, and the pain was intense one Monday night in August. So Michener, 31, of Naperville, Illinois, who worked night shifts at a company that manufactures vitamins and dietary supplements, left at 3 a.m., halfway through his shift. At home, he tossed and turned. By the next afternoon, he'd found an oral surgeon to pull his sore molar, and started taking antibiotics to beat the bacterial infection and reduce the swelling. They did neither. By Friday, Michener was still hurting, and his left cheek bulged. At a local hospital, his oral surgeon removed another tooth, drained some pus, gave him painkillers and more antibiotics, and checked him into intensive care.

By the following Monday, when Michener was rushed by ambulance to Loyola University Medical Center, in suburban Chicago, his cheek was so swollen that he couldn't open his left eye. The infection had invaded the muscles that open the jaw, causing his jaw to clamp shut. It had also spread to Michener's neck and was squeezing his airway. He couldn't open his mouth, couldn't speak and, despite a breathing tube designed to help, struggled to draw each breath.

Few mouth infections grow as menacing as Michener's. But runaway dental infections can be treacherous. They have eaten through the skin in people's necks, choked off airways, migrated to the heart, burrowed into brains and, yes, even killed people.

Have we scared you enough yet? Here's the point: Everyone is vulnerable, because bacteria that routinely lurk in the mouth cause tooth decay and gum disease. The problem: Most people don't know they have these infections. They often cause no pain and few symptoms, but can lead to far worse. Gum disease may also heighten the risk for heart disease, diabetes, pneumonia and premature birth, according to recent clinical trials. But the good news is that with good old regular brushing and flossing, you may prevent all that. And by seeing your dentist often, you can nip most problems in the bud.

Regular dental checkups can pay off in other ways too. For example, dentists can spot signs of diabetes, heart disease and cancer, along with a variety of rare skin and autoimmune diseases. Since people typically visit their dentists more often than they visit other doctors, that can lead to early diagnosis and early treatment. All of which means that your dentist can do much more than save your teeth and gums. Your dentist can save your life.

An Oral Epidemic

Americans have brighter smiles than ever before, thanks to ubiquitous teeth-whitening systems. But behind those gleaming smiles, all is not well. Oral health has improved some in recent decades: More kids are being treated with dental sealants; the incidence of mild gum disease (gingivitis) has decreased about 40 percent since the 1960s; and untreated tooth decay in permanent teeth has decreased slightly since the late 1980s, according to an August report from the

Dentistry for Health New York®

WebMD with AOL Health SEARCH GO

- WebMD Main
- Condition Centers
- Drugs & Herbs
- Medical Library
- Health Tools
- Find a Doctor
- Clinical Trials
- Health Plans & More

Receive a FREE Newsletter! GO

- Women, Men, Lifestyle
- Pregnancy & Family
- Diet & Nutrition
- Chats & Boards
- About WebMD
- Sponsors
- Your Privacy
- Site Map

advertisement

Wednesday, May 24, 2006

You are in Condition Centers. Choose a Topic GO

sponsored

Featured Centers
- Cancer Support
- Migraine Headaches?
- Get Rx Savings Tips
- Bipolar Treatment

This article is from the WebMD Feature Archive

What Your Dentist Knows About Your Health

From predicting heart disease, diabetes, and premature birth to revealing leukemia, eating disorders, and vitamin deficiencies, your teeth and gums say a mouthful about your health.

By Sid Kirchheimer
WebMD Feature

Reviewed By Brunilda Nazario, MD

The eyes may be the window to your soul, but for a look into your physical health, open wide: Your teeth and gums say a mouthful.

Receding or inflamed gums, cavities, tooth loss, gingivitis, and other dental dilemmas in adults can indicate the presence of serious health problems -- including heart disease, diabetes, cancer, vitamin deficiencies, and even the risk of having a premature or low-birth-weight baby.

advertisement

Dentistry for Health New York®

Colgate Oral/Systemic Campaign

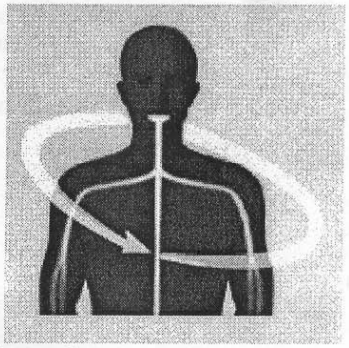
Colgate Professional.com News

Volume 5 November 2005

New Colgate patient education material for your practice, two new issues of the Colgate Oral Care Report and more.

Special Offers – Patient Education

ADA and Colgate partner on oral-systemic health campaign
Coming in 2006... The ADA/Colgate "Oral-Systemic Education Campaign" launches in early 2006. To help spread the word among dental and medical professionals and the public, the ADA and Colgate are developing a new campaign that demonstrates why the mouth is an integral part of the body.



Take advantage and pre-order materials for your office online. The kit includes: freebies

- A resource guide that dentists and hygienists can use to educate patients on chronic inflammation and the oral-systemic link
- A waiting room poster
- Patient education brochures
- A sample tube of Colgate Total® and instructions on ordering additional toothpaste samples online

Materials are available while supplies last. Will ship in January 2006.

Have a PIN or current online Colgate account? Click here.
Do not have a PIN or Account User Name? Register here.

Remember to visit each month to see what is available!

Dentistry for Health New York®

CIGNA
A Business of Caring.

Home > Health Care > Plan Members > Dental

Search go

◄ Return to CIGNA Home

Popular Links

- Log In/Register
- Provider Directory
- Drug Lists/Ordering
- Customer Service
- Important Forms

Dental Health & Wellness

- Dental Health
- Glossary of Dental Terms
- Keeping Teeth Healthy

CIGNA Dental Oral Health Maternity Program℠

CIGNA Dental has followed the research that shows women with periodontal (gum) disease may be at increased risk for pre-term babies. That's why we are launching our new CIGNA Dental Oral Health Maternity Program, which enhances benefits for pregnant members with CIGNA medical and fully-insured dental coverage.

We hope this will encourage pregnant members to have an oral health exam and to seek needed treatment for gum disease. Effective 1/1/06 CIGNA Dental will cover periodontal scaling and root planing performed during pregnancy at 100% for eligible members. In addition, for pregnant members not requiring scaling and root planing, we will cover an additional cleaning during pregnancy because we recognize the potential risk of "pregnancy gingivitis." We will also cover treatment for inflamed gums around wisdom teeth at 100% during pregnancy.

If you are pregnant and have CIGNA medical coverage, be sure to enroll in the CIGNA HealthCare Healthy Babies® program. Learn more.

Pregnancy and Oral Health

CIGNA Dental Oral Health Maternity Program℠

CIGNA HealthCare Healthy Babies® Program

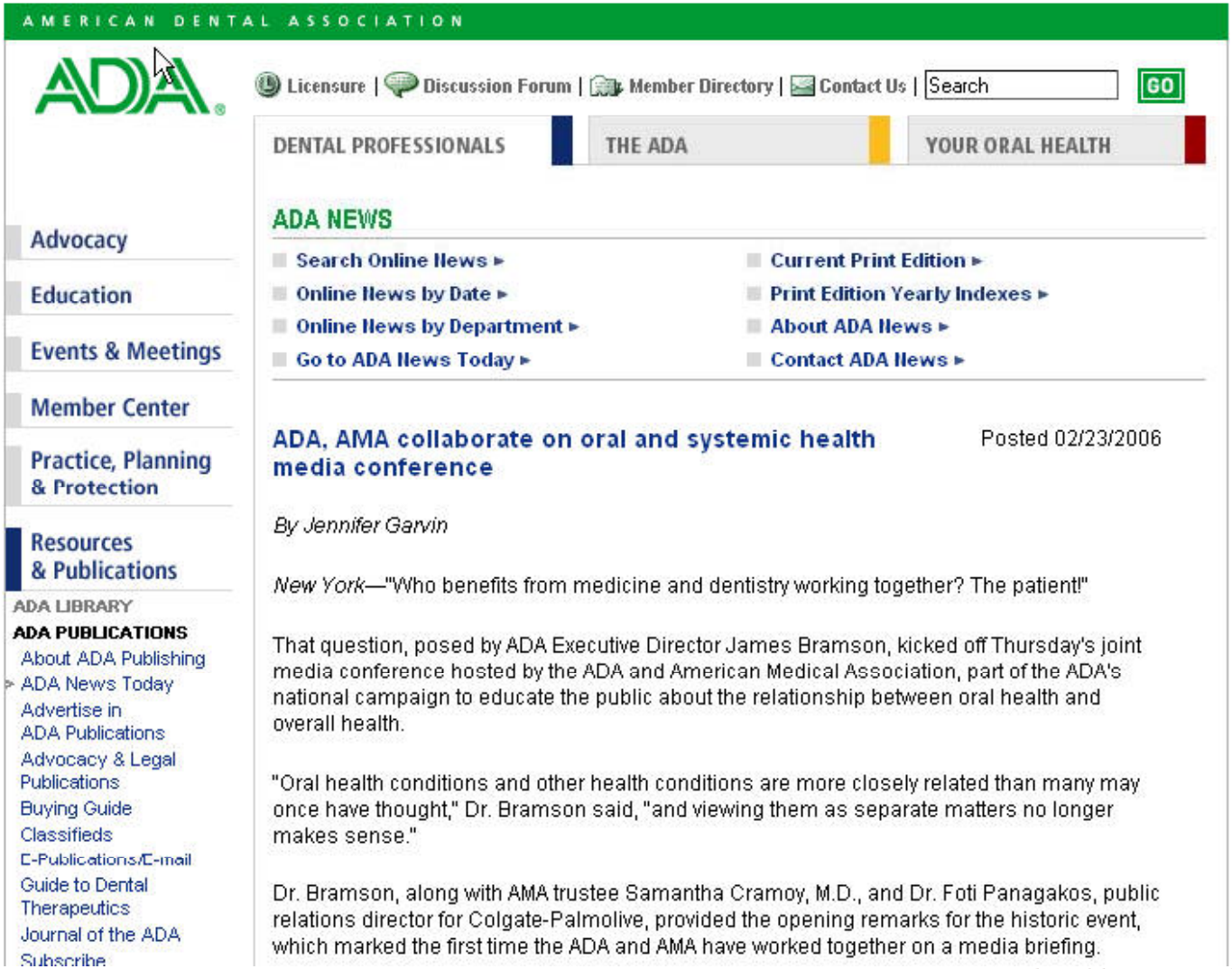
Good Oral Health Starts Early

Diabetes and Oral Health

Heart Disease and Oral

...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®



AMERICAN DENTAL ASSOCIATION

ADA

Licensure | Discussion Forum | Member Directory | Contact Us | Search GO

DENTAL PROFESSIONALS | THE ADA | YOUR ORAL HEALTH

- Advocacy
- Education
- Events & Meetings
- Member Center
- Practice, Planning & Protection
- Resources & Publications

ADA LIBRARY

ADA PUBLICATIONS

About ADA Publishing
ADA News Today
Advertise in ADA Publications
Advocacy & Legal Publications
Buying Guide
Classifieds
E-Publications/E-mail
Guide to Dental Therapeutics
Journal of the ADA
Subscribe

ADA NEWS

- Search Online News ▸
- Online News by Date ▸
- Online News by Department ▸
- Go to ADA News Today ▸
- Current Print Edition ▸
- Print Edition Yearly Indexes ▸
- About ADA News ▸
- Contact ADA News ▸

ADA, AMA collaborate on oral and systemic health media conference

Posted 02/23/2006

By Jennifer Garvin

New York—"Who benefits from medicine and dentistry working together? The patient!"

That question, posed by ADA Executive Director James Bramson, kicked off Thursday's joint media conference hosted by the ADA and American Medical Association, part of the ADA's national campaign to educate the public about the relationship between oral health and overall health.

"Oral health conditions and other health conditions are more closely related than many may once have thought," Dr. Bramson said, "and viewing them as separate matters no longer makes sense."

Dr. Bramson, along with AMA trustee Samantha Cramoy, M.D., and Dr. Foti Panagakos, public relations director for Colgate-Palmolive, provided the opening remarks for the historic event, which marked the first time the ADA and AMA have worked together on a media briefing.

Dentistry for Health New York®

We want you to know™ Aetna

Home

News | Press Center | Recent News | Executive Bios | Legal Issues | Media Contacts

Home > News > Press Center > Press Release

Aetna And Columbia Announce Results From Study Showing Relationship Between Periodontal Treatment And A Reduction In The Overall Cost Of Care For Three Chronic Conditions

HARTFORD, Conn., March 20, 2006 — Aetna (NYSE: AET) and Columbia University College of Dental Medicine conducted a study that found a relationship between periodontal (gum) treatment and the overall cost of care for several chronic diseases. The results of the study, which included approximately 145,000 Aetna members with continuous dental and medical coverage, indicate that periodontal care appears to have a positive effect on the cost of medical care, with earlier treatment resulting in lower medical costs for members with diabetes, coronary artery disease (CAD), and cerebrovascular disease (CVD) or stroke.

"The results of this study are encouraging because they show the connection between good oral health and overall well-being, as well as illustrating that the early treatment of periodontal disease can help reduce medical costs for these conditions," said Pat Farrell, head of Aetna Specialty Products. "We believe that in addition to lowering medical costs, we are also helping to improve members' quality of life. We will continue to work with Columbia to demonstrate ways that dental care can improve the overall health of our members."

"Systemic health is often associated with the condition of the oral cavity in that many systemic diseases manifest in the mouth; however, less is known about the connection between a diseased periodontium and the impact it may have on systemic health," said David A. Albert, D.D.S., M.P.H., Associate Professor of Dentistry at Columbia University. "The association between periodontal infection and systemic health has important implications for the treatment and management of patients."

The retrospective study of claims data included an examination of approximately 145,000 members participating in Aetna PPO plans with continuous dental and medical coverage over two years. Periodontal care appeared to have a positive effect on the cost of medical care in this two-year study (2001, 2002).

http://www.aetna.com/news/2006/pr_20060317.

Dentistry for Health New York®

CIGNA Dental Turns Evidence into Action; Builds on Industry Leading Oral Health Integration Program to Launch New Initiatives for Diabetes and Cardiovascular Disease

- PRNewswire
May 23, 2006

CIGNA Dental today announced the expansion of its Oral Health Integration Program to include new initiatives promoting the treatment of gum disease for members with diabetes and cardiovascular disease. In addition, CIGNA Dental has established a clinical advisory panel to provide advice on the creation of innovative coverage options addressing the emerging issues of medical/dental integration, evidence-based strategies, and new and developing dental technologies.

"The CIGNA Dental Oral Health Integration Program(SM) is the first enhanced benefit program of its kind to address diabetes, cardiovascular conditions and pre-term birth through improved oral health," said Karen Rohan, president of CIGNA Dental. "These programs combine CIGNA's integration and outreach capabilities to reinforce the connection between proper oral health and the overall health of an individual."

"The connection between periodontal ... end to pregnancy. However, studying such ... etes and cardiovascular disease is not as clea ... ntal Medicine, and CIGNA Dental Clinical ... diabetes and cardiovascular disease is a trem

Cigna will pay 100% of out of pocket perio expense for members with diabetes, cardiovascular disease- IADR study shows lower medical cost for diabetes & CDV patients when treated for periodontal disease

Under the new programs, beginning ... ease management programs for diabetes and cardiac care may receive 100% reimbursement for out-of-pocket costs associated with periodontal scaling and root planing, and periodontal maintenance.* The new initiatives expand upon the previously launched CIGNA Dental Oral Health Maternity Program(SM) (OHMP), which provides enhanced benefits during pregnancy for members with both CIGNA medical and dental coverage. The CIGNA Dental Oral Health Integration Programs are designed to help eliminate cost

http://fsnews.findlaw.com/articles/prnewswire/20060523/23may20061014.html

Dentistry for Health New York®

The Perio-Heart Disease Connection

- Generalized Observations
- Endothelial Function
- Small Dense LDL
- C-Reactive Protein

Dentistry for Health New York®

HEALTH & SCIENCE

CRP gains notice as key marker of cardiovascular health

Research on C-reactive protein has some experts saying cholesterol guidelines should be rewritten. Others caution it's too soon for routine CRP testing.

By Victoria Stagg Elliott, *AMNews* staff. Dec. 16, 2002. Additional information

---

Levels of C-reactive protein may be a stronger predictor of potential heart attack or stroke than cholesterol, according to a study published in the Nov. 14 *New England Journal of Medicine*.

The study, which involved more than 27,000 people, is by far the largest to date. It echoes what experts have suspected and smaller studies have been implying for years: Cholesterol is not the be-all and end-all in predicting cardiovascular health.

About half of people who have heart attacks have normal levels of cholesterol. CRP may be one of the missing links behind cardiovascular events for these people.

Dentistry for Health New York®

Phase III

Perio Treatment Reduces Systemic Risk

...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®

Treatment of Periodontal Disease Reduces CRP

- June 2003 – International Association for Dental Research Okayama University
- April 2004- State University NY, Buffalo
- 2004 IADR
- *J. Dent Res* 84(3):269-273, 2005 (and Cholesterol)

Dentistry for Health New York®

ADA NEWS

- Search Online News ►
- Online News by Date ►
- Online News by Department ►
- Go to ADA News Today ►
- Current Print Edition ►
- Print Edition Yearly Indexes ►
- About ADA News ►
- Contact ADA News ►

Periodontal therapy lowers levels of heart disease inflammation markers

Posted 04/21/2004

Treating periodontal disease with scaling and root planing combined with a topical antibiotic gel can significantly lower the levels of two inflammatory proteins associated with a heightened risk of heart disease, scientists from the State University of New York at Buffalo report.

Blood drawn from 102 subjects with periodontal disease showed elevated levels of both C-reactive protein and fibrinogen, proteins associated with increased risk for heart disease and blood clotting. All of the subjects were free of other conditions that could cause elevated levels of the proteins.

Scientists from the UB School of Dentistry's Department of Oral Biology divided the subjects into two groups to determine if periodontal therapy would be effective in lowering the levels of the heart disease markers. One group received scaling and root planing treatment while the second group received treatment with the topical antibiotic Atridox followed by scaling and root planing.

Dentistry for Health New York®

J Dent Res 83(2): 156-160, 2004

RESEARCH REPORT
Clinical

Periodontitis and Systemic Inflammation: Control of the Local Infection is Associated with a Reduction in Serum Inflammatory Markers

F. D'Aiuto[1,2], M. Parkar[1], G. Andreou[1,2], J. Suvan[1,2], P.M. Brett[1], D. Ready[3], and M.S. Tonetti[1,2,*]

[1] Department of Periodontology, Eastman Dental Institute and Hospital, University College London, 256 Gray's Inn Road, London WC1X 8LD, UK;
[2] Eastman Clinical Investigation Center, Eastman Dental Institute and Hospital, University College London; and
[3] Microbiology Unit, Eastman Dental Hospital, University College London Hospitals, NHS Trust;

[*] corresponding author, t.maurizio@eastman.ucl.ac.uk

ABSTRACT

Severe periodontitis is associated with elevated inflammatory markers in otherwise healthy populations. However, the nature of this association has not been determined. Our aim was to assess whether the degree of response to periodontal therapy was associated with changes in serological markers of systemic inflammation. Ninety-four systemically healthy subjects with severe generalized

Dentistry for Health New York®

Tx. Reduces CRP & Cholesterol

JOURNAL OF DENTAL RESEARCH® Featuring Critical Reviews in Oral Biology & Medicine

MOST CITED

HOME | HELP | FEEDBACK | SUBSCRIPTIONS | ARCHIVE | SEARCH | TABLE OF CONTENTS

QUICK SEARCH: [advanced]
Author: Keyword(s):
Go
Year: Vol: Page:

J Dent Res 84(3):269-273, 2005

RESEARCH REPORTS
Clinical

Short-term Effects of Intensive Periodontal Therapy on Serum Inflammatory Markers and Cholesterol

F. D'Aiuto, L. Nibali, M. Parkar, J. Suvan, and M.S. Tonetti*

Department of Periodontology and Eastman Clinical Investigation Center, Eastman Dental Institute and Hospital, University College London, 256 Gray's Inn Road, London WC1X 8LD, UK;

* corresponding author, m.tonetti@uchc.edu

Severe periodontitis has been associated with increased systemic inflammation. In a three-arm preliminary randomized trial, we investigated the impact of standard (SPT) and intensive periodontal therapy (IPT) on serum inflammatory markers and cholesterol levels. Medical and periodontal parameters, C-reactive protein (CRP), interleukin-6 (IL-6), total cholesterol, and LDL cholesterol were evaluated in 65 systemically healthy subjects suffering from severe generalized periodontitis. Two months after treatment, both SPT and IPT resulted in significant reductions in serum CRP compared with the untreated control (0.5 ± 0.2 mg/L for SPT, P = 0.030

...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®

A multiplex immunoassay demonstrates reductions in gingival crevicular fluid cytokines following initial periodontal therapy.
Source: J Periodontal Res. 2009 Jul 8. [Epub ahead of print]
Authors: Thunell DH, Tymkiw KD, Johnson GK, Joly S, Burnell KK, et al.

Our prediction is that one of the criteria to denote t*he end point of perio therapy* will be GCF and salivary tests for levels of periodontal pathogens and inflammatory mediators.

The relevance of this research is that in the near future, successful treatment outcomes will be measured not only by clinical improvement, but also by measuring the reduction of inflammatory mediators and bacterial levels as well.

Dentistry for Health New York®

Joint article from The American Journal of Cardiology and Journal of Periodontology Editor's Consensus: Periodontitis and Atherosclerotic Cardiovascular Disease

Find it at www.dentistryforhealthny.com under the section called “Oral Systemic Research”

...Because Optimal Health Begins With Oral Health

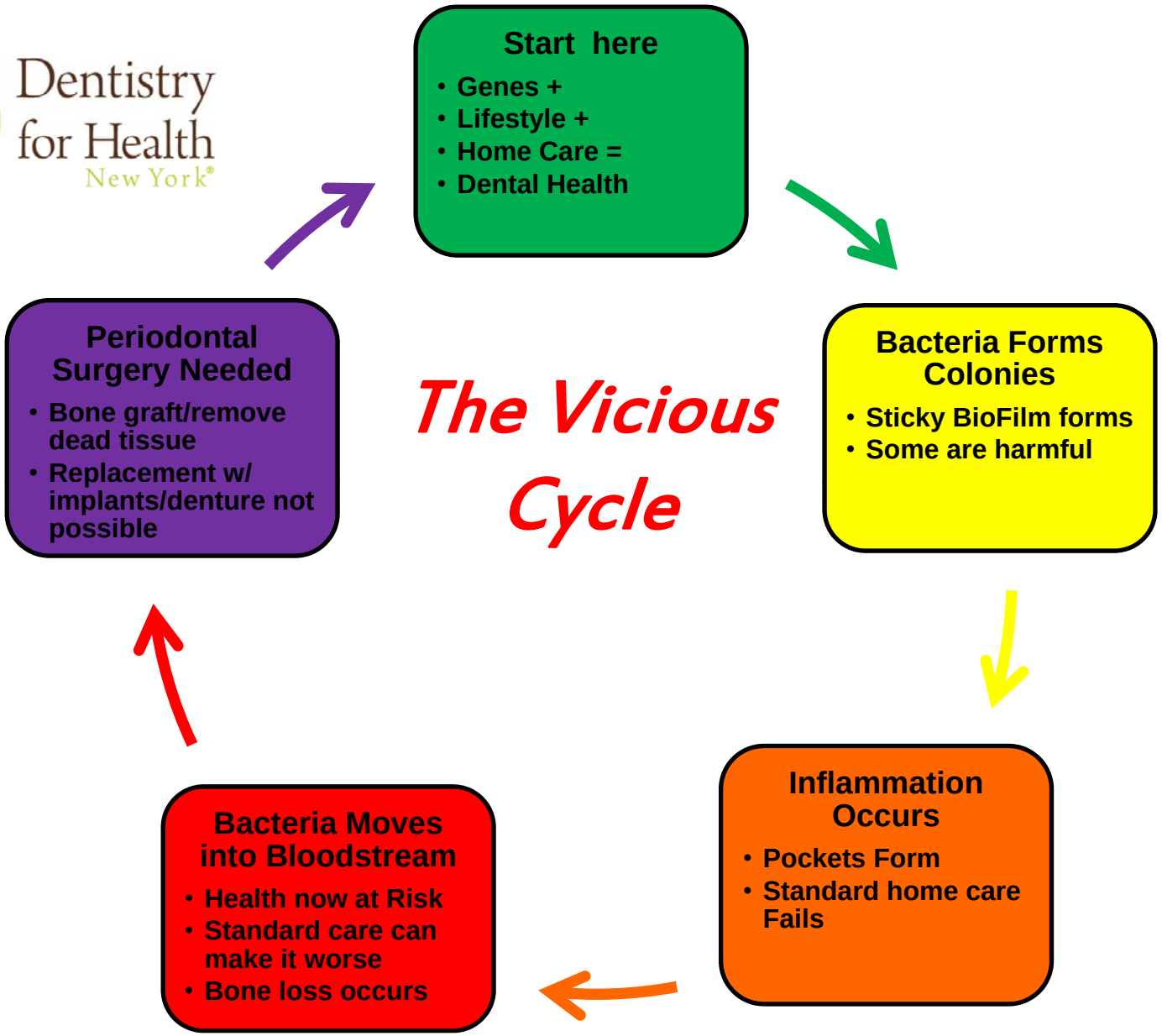
Dentistry for Health New York®

Unlike a cold, Periodontal Disease isn't going to go away on it's own

Let's take a look at the vicious cycle of Periodontal Disease and see where you fit in and what you can do about it.

Dentistry for Health New York®

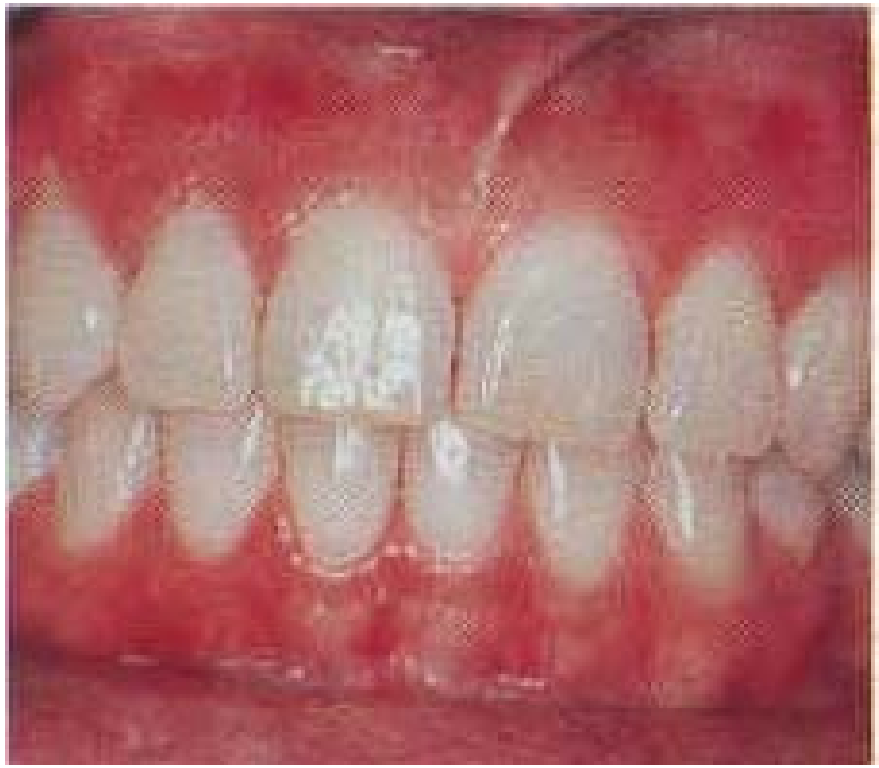
The Vicious Cycle

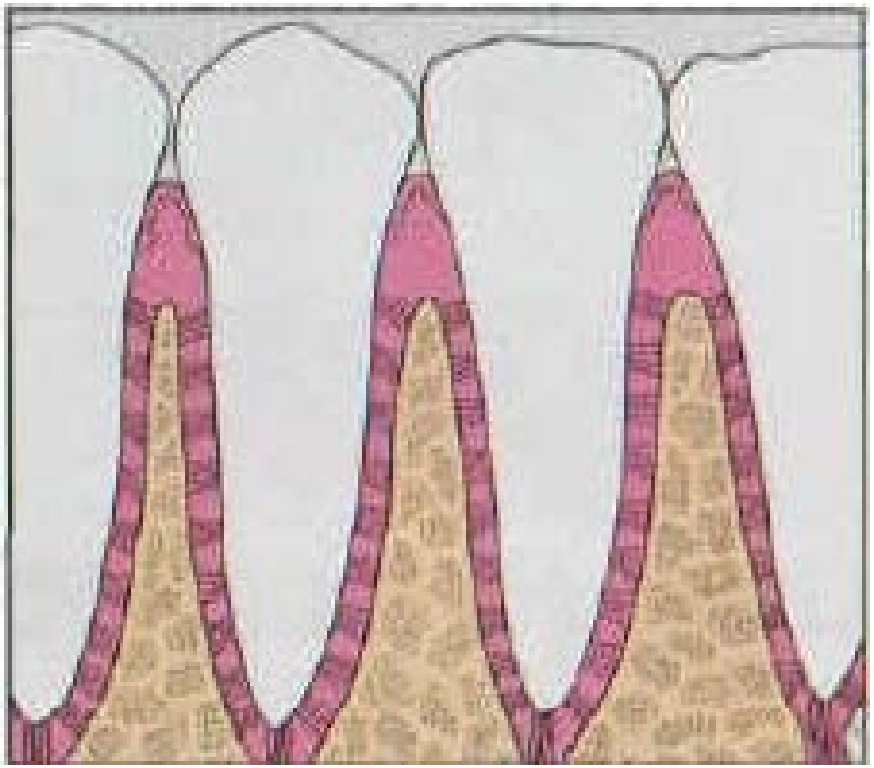


...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®

Normal Healthy Gums





...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®

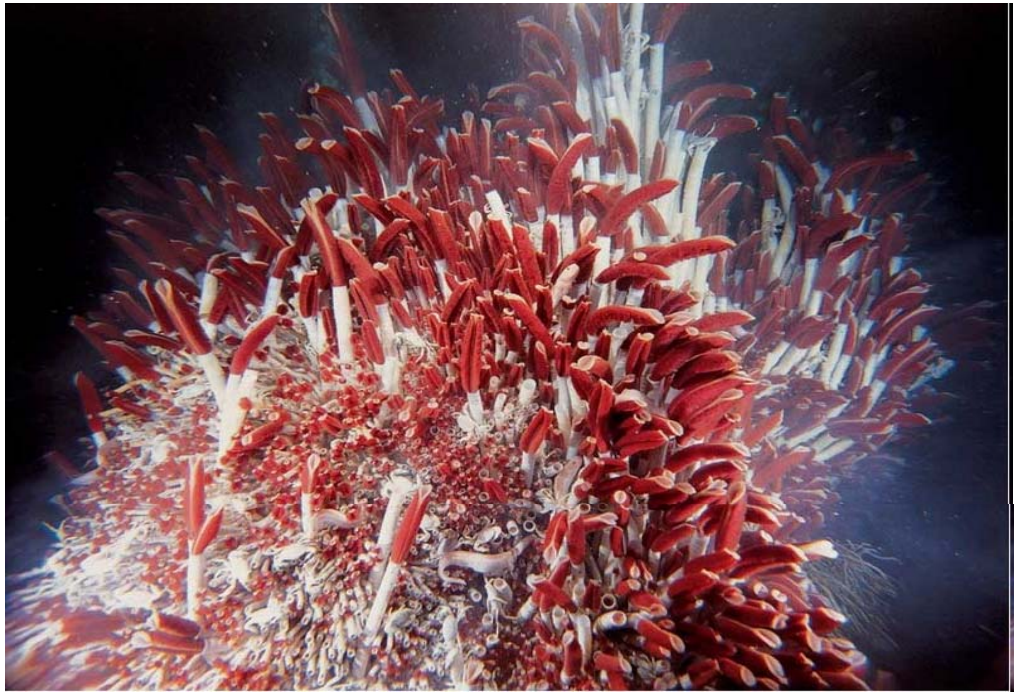
Start here

- **Genes +**
- **Lifestyle +**
- **Home Care =**
- **Dental Health**

Step 1: **Poor brushing and flossing are the most typical cause of periodontal disease,** allowing dental plaque and calculus to build up: the perfect home for bacteria. Other causes can be genetic pre-disposition, hormone changes, failing dental restorations or tooth crowding (mal-occlusion).

Dentistry for Health New York®

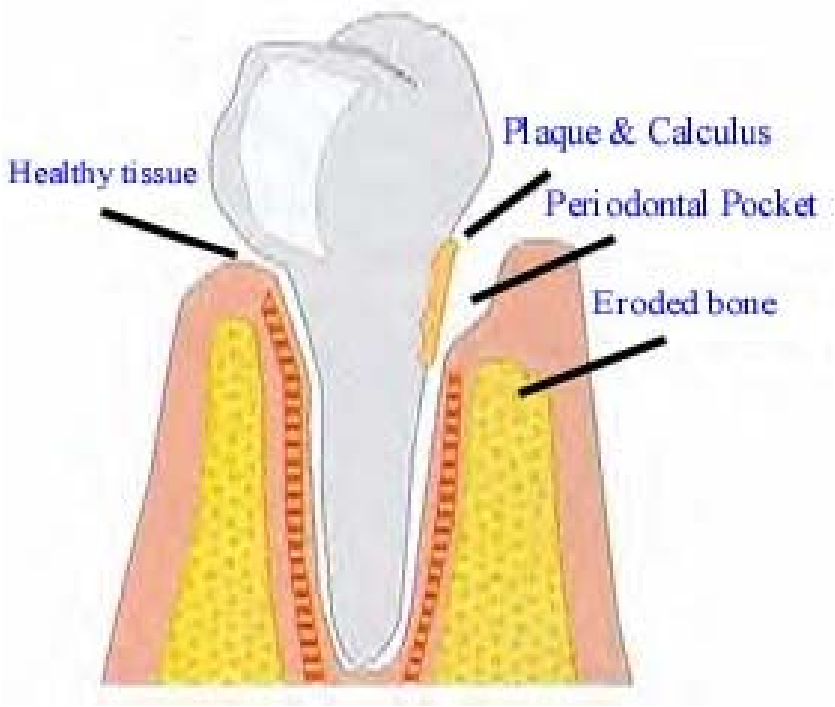
What has no mouth, eyes, or stomach yet can grow 3 meters tall… A Tubeworm!

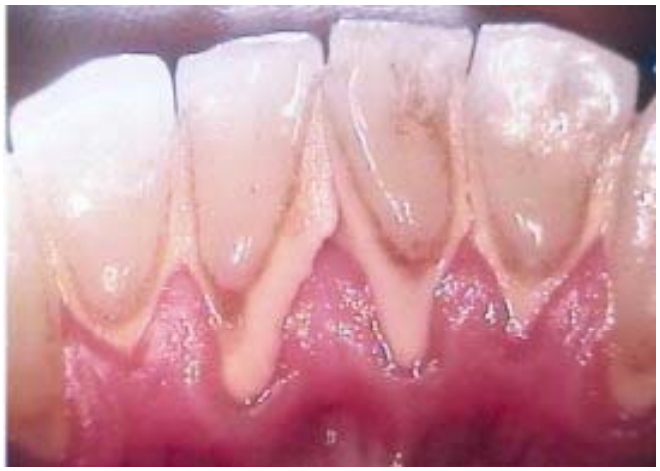


Tubeworms (Riftia pachyptila) may grow to about 3 meters (8 ft) tall. They have no mouth, eyes, or stomach (gut). They depend on bacteria living inside them for survival. The microbes convert chemicals spewing out of the vents into worm food.

Dentistry for Health New York®

Plaque & Calculus



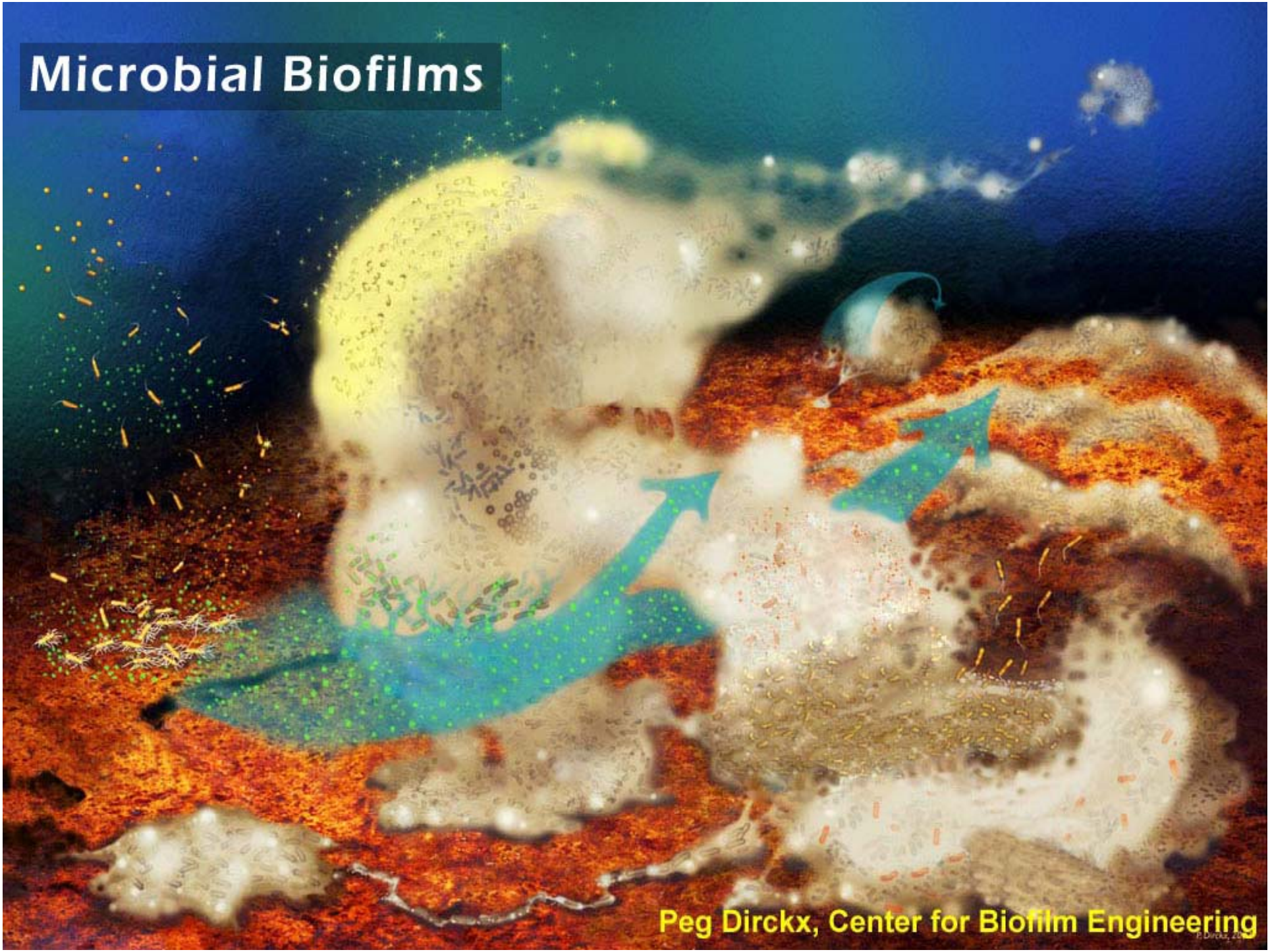


Dentistry for Health New York®

Bacteria Forms Colonies

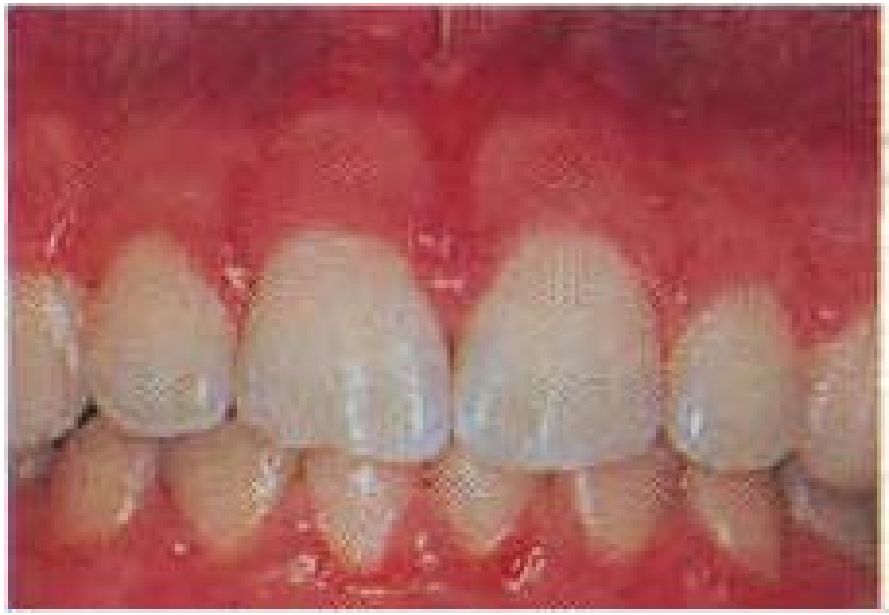
- **Sticky BioFilm forms**
- **Some are harmful**

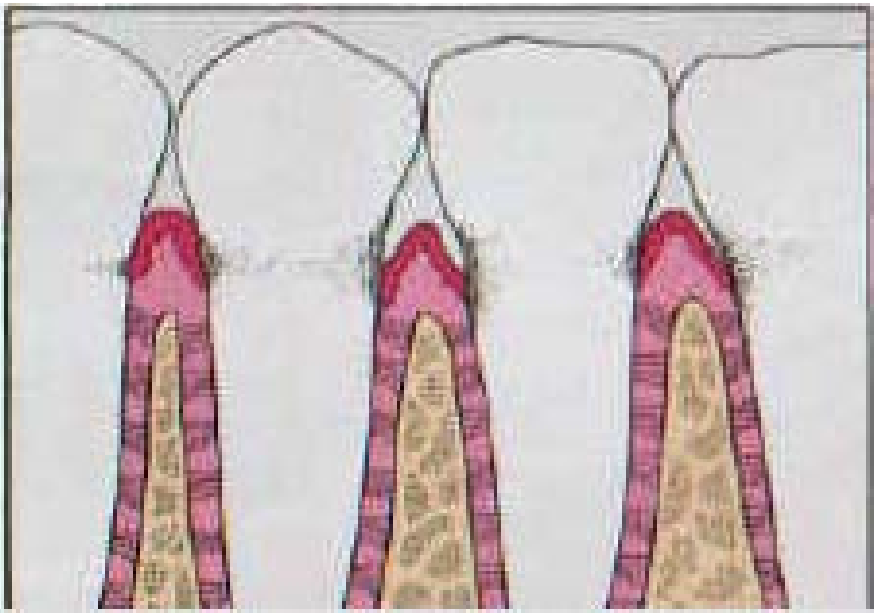
Step 2: The bacteria form colonies. The body's natural immune system comes to the rescue with inflammatory compounds to kill the bacteria. If the immune system becomes weakened due to poor nutrition, diseases such as diabetes, or even advancing age, **red** gums and **pink** toothbrush are the result. **This is a warning of the dangers to come.**


Microbial Biofilms
Peg Dirckx, Center for Biofilm Engineering

Dentistry for Health New York®

Gingivitis





...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®

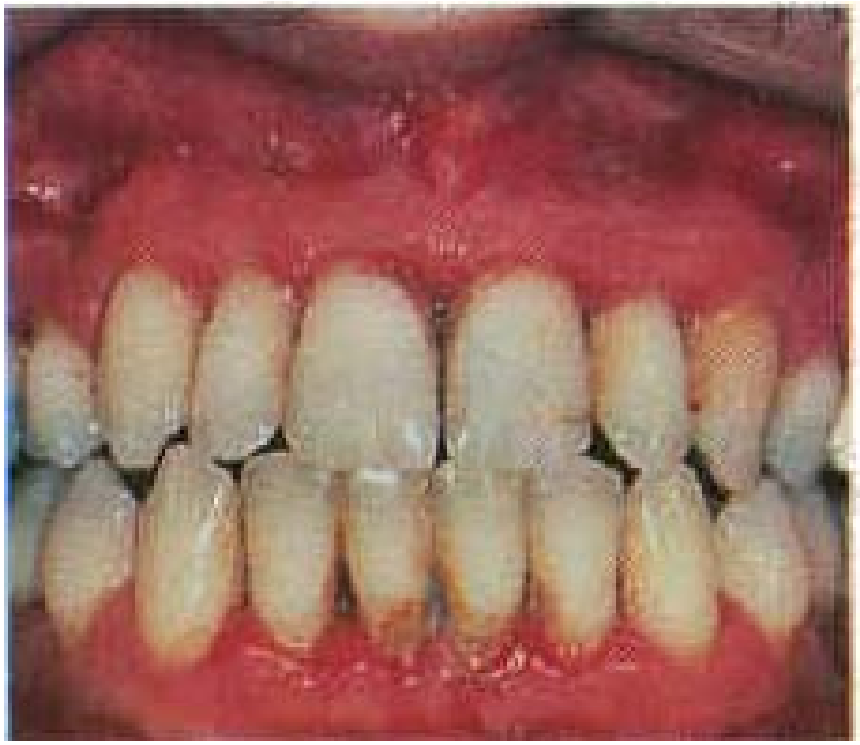
Inflammation Occurs

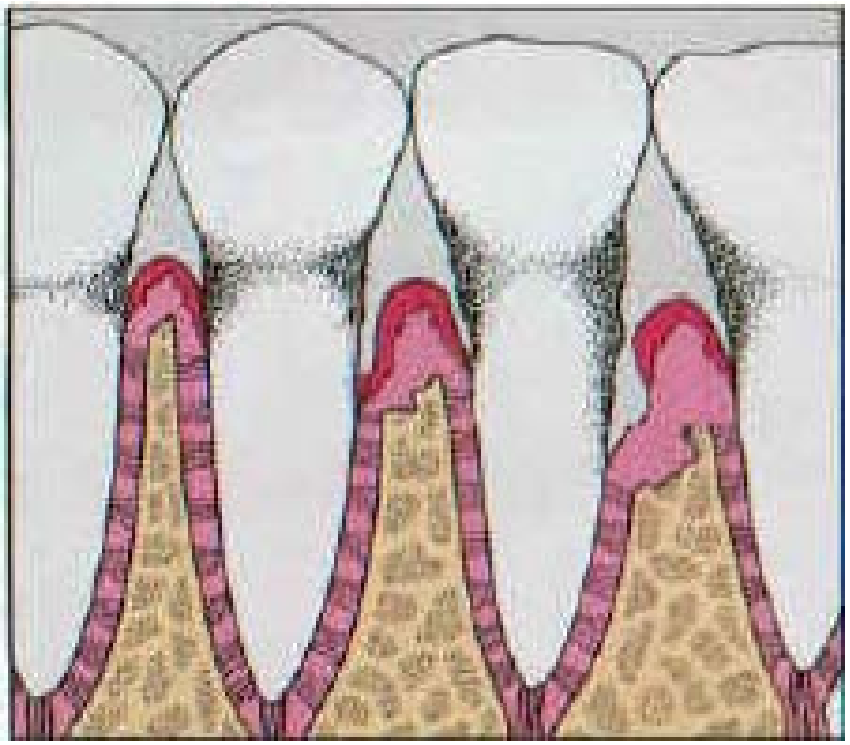
- **Pockets Form**
- **Standard home care Fails**

Step 3: The body's immune system starts to turn on itself and begins to form deep pockets. The bacteria transform from normal air breathing oral bacteria to dangerous pathogenic "anaerobic" bacteria which prefer an oxygen free environment. **Standard home care can no longer get into the deep pockets and keep you well.**

Dentistry for Health New York®

Periodontitis





...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®

Bacteria Moves into Bloodstream

- **Health now at Risk**
- **Standard care can make it worse**
- **Bone loss occurs**

Step 4: The pathogenic bacteria move into the bloodstream increasing the risk of heart disease, diabetes, pre-term birth and cancer.

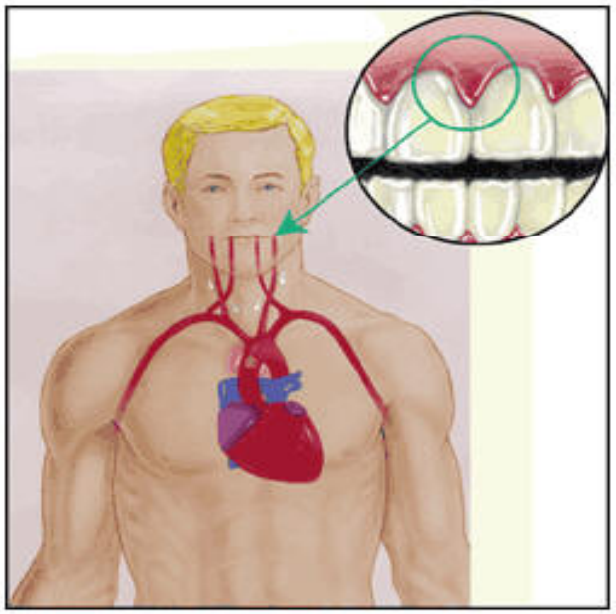
The disease has now put your overall health at risk.

At this point even normal tooth cleaning carries a risk of spreading bacteria to the **rest of the body called "bacteremia".**

The bone is now attacked by the autoimmune process, much like arthritis, causing eventual tooth loss. **70% of all tooth loss is because of periodontal disease.**

Dentistry for Health New York®

Heart Disease



Several theories exist to explain the link between periodontal disease and heart disease. One theory is that oral bacteria can affect the heart when they enter the blood stream, attaching to fatty plaques in the coronary arteries (heart blood vessels) and contributing to clot formation. Coronary artery disease is characterized by a thickening of the walls of the coronary arteries due to the buildup of fatty proteins. Blood clots can obstruct normal blood flow, restricting the amount of nutrients and oxygen required for the heart to function properly. This may lead to heart attacks.

Another possibility is that the inflammation caused by periodontal disease increases plaque build up, which may contribute to swelling of the arteries.

Researchers have found that people with periodontal disease are almost twice as likely to suffer from coronary artery disease as those without periodontal disease.

Periodontal disease can also exacerbate existing heart conditions. Patients at risk for infective endocarditis may require antibiotics prior to dental procedures. Your periodontist and cardiologist will be able to determine if your heart condition requires use of antibiotics prior to dental procedures.

Stroke

Additional studies have pointed to a relationship between periodontal disease and stroke. In one study that looked at the causal relationship of oral infection as a risk factor for stroke, people diagnosed with acute cerebrovascular ischemia were found more likely to have an oral infection when compared to those in the control group.

Dentistry for Health New York®

the DIABETIC in the DENTAL CHAIR

BY BRIAN L. MEALEY

CURRENTLY, 20.8 MILLION Americans have diabetes, according to the American Diabetes Association. About one third of those with the disease are unaware that they have it, and of those who have been diagnosed, only a little more than half have it under control.

Diabetes is a disease where the body does not produce or properly use insulin, a hormone made in the pancreas. Insulin "unlocks" cells, allowing sugars derived from carbohydrates and other food to enter. Sugar is the basic fuel for cells, providing energy for daily life.

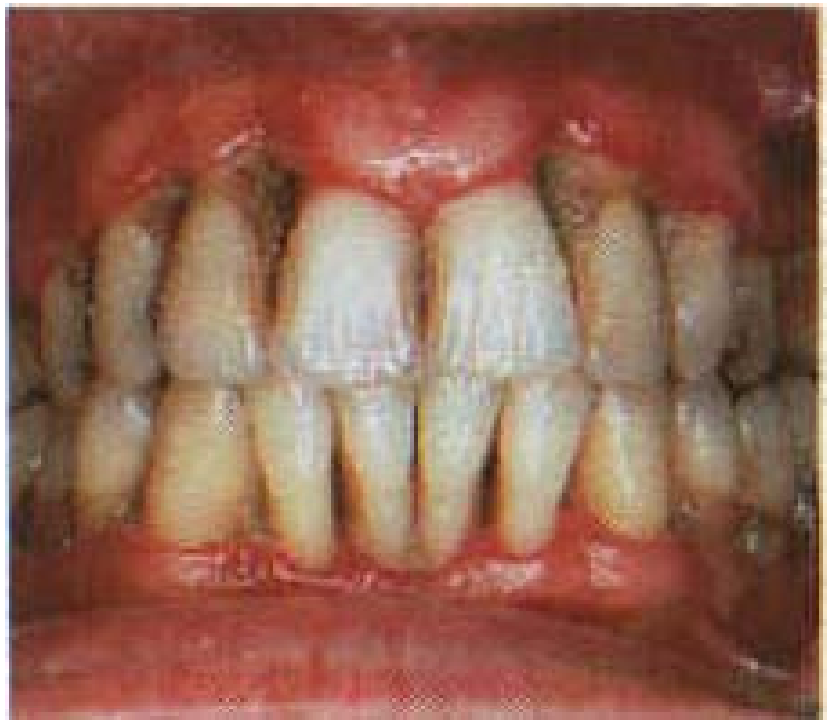
There are two types of diabetes: In type 1 diabetes, the pancreas no longer makes insulin. Sugar cannot enter the cells and builds up in the bloodstream. In

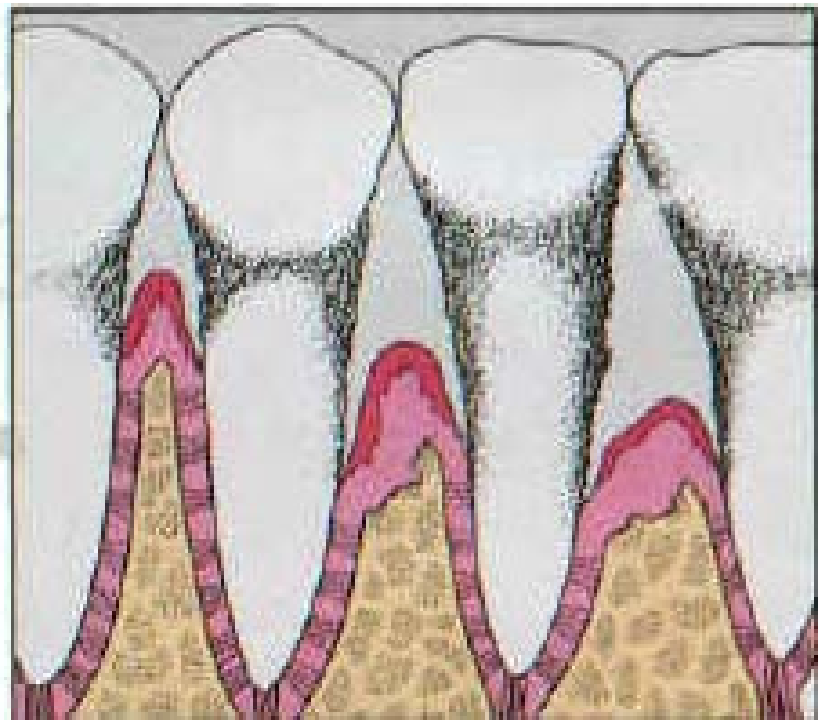
New research suggests that periodontal disease can also affect a diabetic patient's ability to control his or her blood sugar levels, and can contribute to diabetic complications such as heart and kidney disease. Inflammatory diseases of many kinds—including those that affect the mouth—can increase insulin resistance. In people with type 2, increased resistance caused by gum disease can make blood sugar harder to control. However, periodontal treatment reduces the level of inflammation in the tissues around the teeth, thereby improving blood sugar control in many diabetics.

Thus, care of patients with diabetes poses a particular challenge to dental professionals. Diabetes often worsens

Dentistry for Health New York®

Advanced Periodontitis





Dentistry for Health New York®

Periodontal Surgery Needed

- **Bone graft/remove dead tissue**
- **Replacement w/ implants/denture not possible**

Step 5: While often the answer to tooth loss is replacement by implants, at this stage **healing interference can result in implant failure. Significant bone loss makes implant/denture replacements impossible.**

At this point the only remedy may be **periodontal surgery with bone grafting to repair the damage that has been done.**

Dentistry for Health New York®

Traditional Diagnostic Tests

Traditional diagnostic tests: ***Legacy Techniques***.

- Disclosing Solution & Plaque Indices
- Bleeding on Probing
- Pocket Depth Measurements
- Radiographs

All developed prior to the discovery that periodontal diseases are infections.

Dentistry for Health New York®

Disclosing Solution & Plaque Indices

- Only measure supragingival plaque.
  (typically Gram (+) & aerobic → i.e. health)
- Cannot differentiate between
  pathogenic & non-pathogenic biofilms
- Mostly useful for patient motivation

Dentistry for Health New York®

Pocket Depth Measurements

- Cannot distinguish between high & low risk infections
- Not predictive
- Identify historical disease sites
- Fraught with measurement error

Dentistry for Health New York®

Pocket Depth Measurements

– The pocket is not the disease.
It is a ***result*** of disease, not the cause.

- Shallow sites are not protective!
Disease ***originates*** in shallow sites!
  - Deep pockets can be risk free & stable.

Dentistry for Health New York®

Radiographs

- Mostly ID historical damage
- Cannot identify pathogenic risk factors
- Intact *lamina dura*
  - Predictably protective
  - Not likely to break down for 12-18 months

Dentistry for Health New York®

The Health Cycle

...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®

Start Here

- Complete Periodontal Assessment

Step 1: The health cycle begins with a complete assessment of your current level of health.

Do you have pathogenic bacteria?

Do you have plaque/bio-film?

Do you have bleeding?

Do you have deep pockets forming?

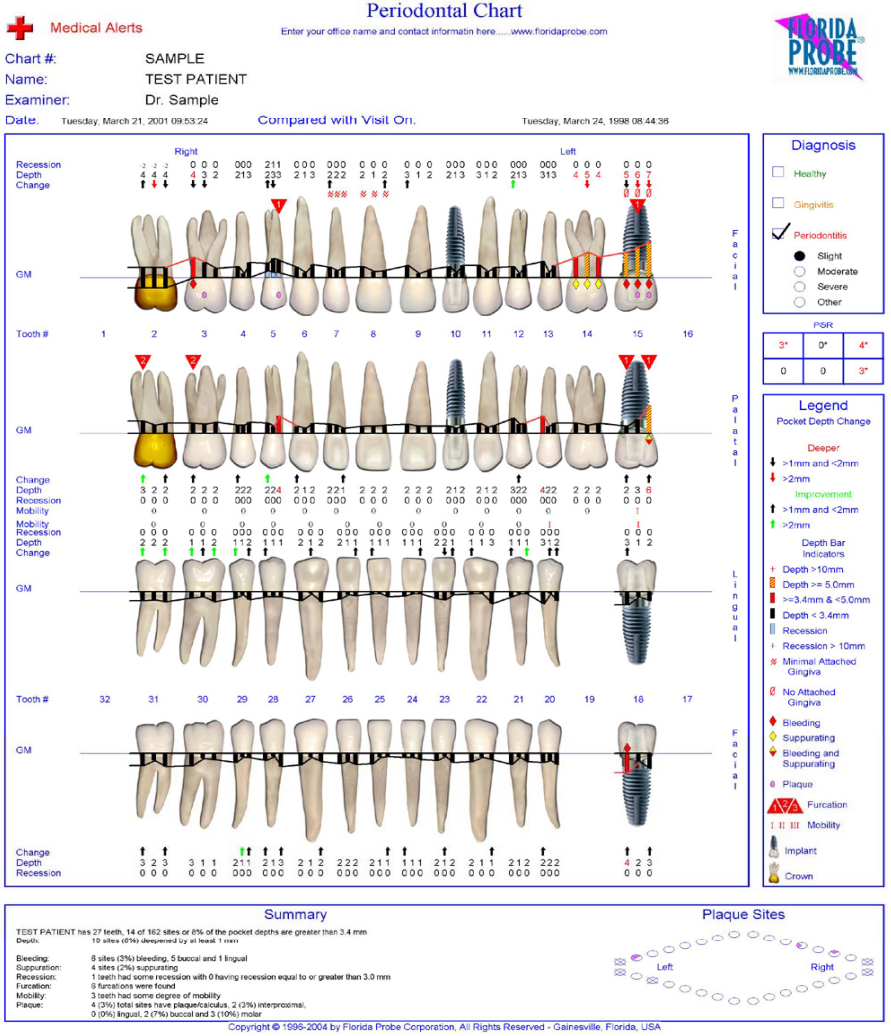
Do you have a high C-Reactive Protein Score

Do you have a high A1c (Average Blood Sugar)

Dentistry for Health New York®

Documentation

- Health History
- Family History
- Probing Scores
- Bleeding Scores
- CRP Levels
- HbA1c Levels
- Genetic Susceptibility
- Bacterial Infection



...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®

C-Reactive Protein

- Bodies' Response to Inflammation
- Periodontal Disease is Primary Cause of Inflammation in most people
- More Predictive of Heart Attacks than Cholesterol
- Causative Agent in Heart Disease Process
- May be Reduced Significantly by Anti-Microbial Periodontal Treatment

Health and Behavior

Posted 1/5/2005 11:00 PM Updated 1/6/2005 9:04 AM

New heart villain seen

By Steve Sternberg, USA TODAY

Two leading research groups independently reported today that lowering blood levels of a protein that promotes artery inflammation is just as important as reducing bad cholesterol for preventing heart attacks and strokes.

Their conclusions reflect a major shift away from the notion that bad cholesterol, or LDL, is the primary villain in heart disease. Levels of C-reactive protein (CRP) also must be reduced to halt the disease's progression, researchers said.

In that simple assertion lies the seed of a major debate among heart specialists. Revised just last year, current treatment guidelines reflect what studies then showed: the importance of lowering LDL to below 70 milligrams per deciliter of blood in high-risk patients.

Periodontal therapy lowers levels of heart disease inflammation markers

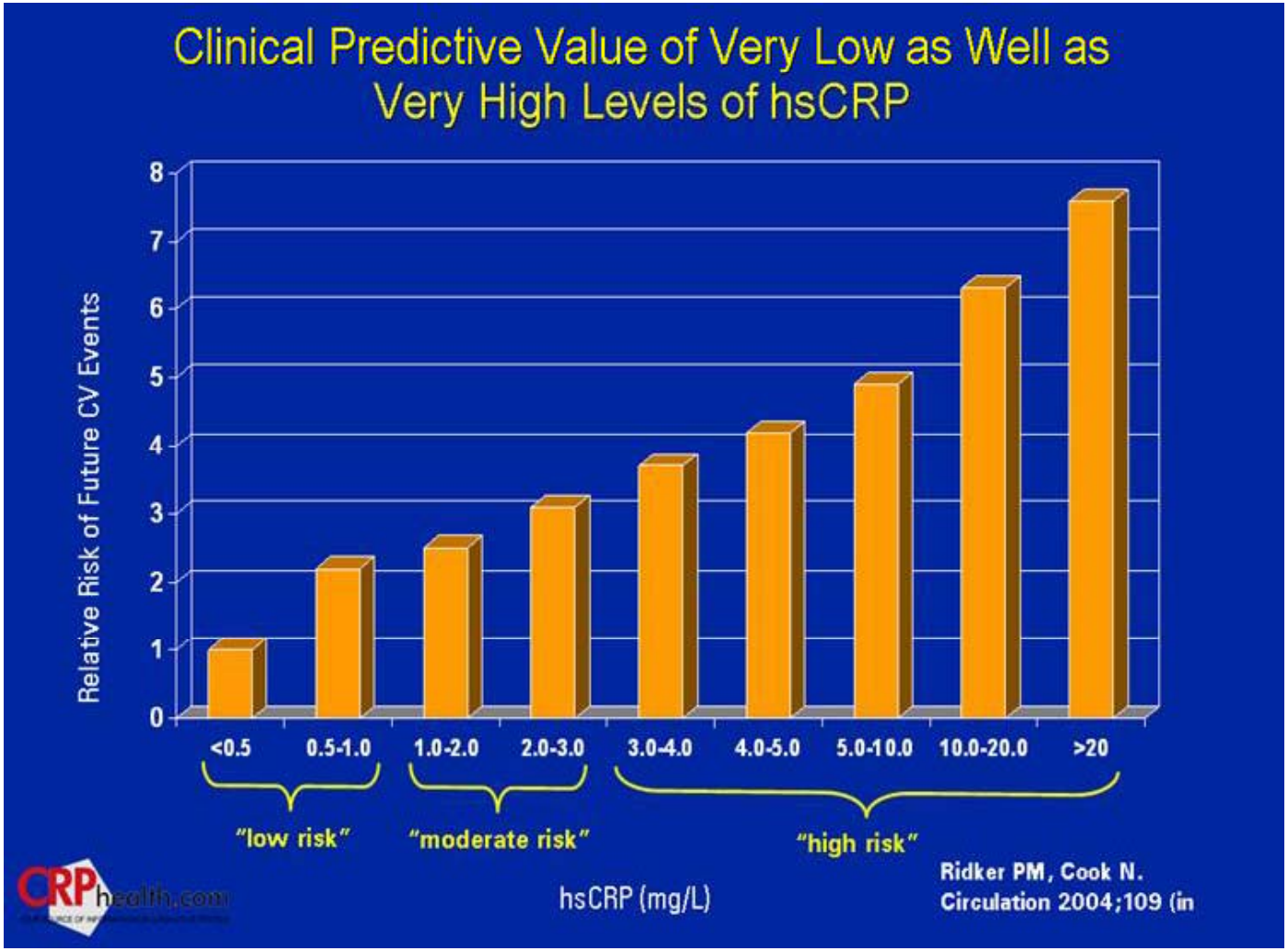
Posted 04/21/2004

Treating periodontal disease with scaling and root planing combined with a topical antibiotic gel can significantly lower the levels of two inflammatory proteins associated with a heightened risk of heart disease, scientists from the State University of New York at Buffalo report.

Blood drawn from 102 subjects with periodontal disease showed elevated levels of both C-reactive protein and fibrinogen, proteins associated with increased risk for heart disease and blood clotting. All of the subjects were free of other conditions that could cause elevated levels of the proteins.

Scientists from the UB School of Dentistry's Department of Oral Biology divided the subjects into two groups to determine if periodontal therapy would be effective in lowering the levels of the heart disease markers. One group received scaling and root planing treatment while the second group received treatment with the topical antibiotic Atridox followed by scaling and root planing.

Dentistry for Health New York®



...Because Optimal Health Begins With Oral Health

The Severity of Periodontal Disease is Associated with the Development of Glucose Intolerance in Non-diabetics: The Hisayama Study

T. Saito[1,*], Y. Shimazaki[1], Y. Kiyohara[2], I. Kato[2], M. Kubo[2], M. Iida[2], and T. Koga[1,3]

[1] Department of Preventive Dentistry, Kyushu University Faculty of Dental Science, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan;
[2] Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan;

[*] corresponding author, syt@dent.kyushu-u.ac.jp

ABSTRACT

TOP
ABSTRACT
INTRODUCTION
MATERIALS & METHODS
RESULTS
DISCUSSION
REFERENCES

Inflammation is hypothesized to play a significant role in the development of type 2 diabetes; however, reports on clinical inflammatory conditions are limited. Studies have suggested that periodontitis affects glucose control in diabetics. This community-based study examined the relationship between periodontitis and glucose tolerance status, including changes in status. The relationship between periodontal condition and the results of a 75-g oral glucose tolerance test was examined in 961 adults in 1998. Deep pockets (mean pocket depth > 2.0 mm) were significantly associated with impaired glucose tolerance and with diabetes as compared with shallow pockets (< 1.3 mm). In the subgroup with normal glucose tolerance 10 years previously, subjects who subsequently developed impaired glucose tolerance were significantly more likely to have deep pockets. Deep pockets were closely related to current glucose tolerance status and the development of glucose intolerance.

KEY WORDS: periodontal disease • diabetes • glucose tolerance • risk factor • epidemiology

JOURNAL OF Periodontology

August 1997 (Vol. 68, No. 8)

Treatment of Periodontal Disease in Diabetics Reduces Glycated Hemoglobin

Sara G. Grossi, Fred B. Skrepcinski, Thomas DeCaro, Don C. Robertson, Alex W. Ho, Robert G. Dunford, and Robert J. Genco

Abstract

Periodontal disease is a common infection-induced inflammatory disease among individuals suffering from diabetes mellitus. The purpose of this study was to assess the effects of treatment of periodontal disease on the level of metabolic control of diabetes. A total of 113 Native Americans (81 females and 32 males) suffering from periodontal disease and non-insulin dependent diabetes mellitus (NIDDM) were randomized into 5 treatment groups. Periodontal treatment included ultrasonic scaling and curettage combined with one of the following antimicrobial regimens: 1) topical water and systemic doxycycline, 100 mg for 2 weeks; 2) topical 0.12% chlorhexidine (CHX) and systemic doxycycline, 100 mg for 2 weeks; 3) topical povidone-iodine and systemic doxycycline, 100 mg for 2 weeks; 4) topical 0.12% CHX and placebo; and 5) topical water and placebo (control group). Assessments were performed prior to and at 3 and 6 months after treatment and included probing depth (PD), clinical attachment level (CAL), detection of *Porphyromonas gingivalis* in subgingival plaque and determination of serum glucose and glycated hemoglobin (HbA_{1C}). After treatment all study groups showed clinical and microbial improvement. The doxycycline-treated groups showed the greatest reduction in probing depth and subgingival *Porphyromonas gingivalis* compared to the control group. In addition, all 3 groups receiving systemic doxycycline showed, at 3 months, significant reductions (P less than or equal to 0.04) in mean HbA_{1C} reaching nearly 10% from the pretreatment value. Effective treatment of periodontal infection and reduction of periodontal inflammation are associated with a reduction in level of glycated hemoglobin. Control of periodontal infections should thus be an important part of the overall management of diabetes mellitus patients. *J Periodontol 1997;68:713-719.*

Key Words: Diabetes mellitus, non-insulin dependent/epidemiology; periodontal diseases/therapy; doxycycline/therapeutic use; chlorhexidine/therapeutic use; povidone-iodine/therapeutic use; *Porphyromonas gingivalis.*

(*Circulation.* 2003;108:2323.)

Clinical Investigation and Reports

Joint Effects of C-Reactive Protein and Glycated Hemoglobin in Predicting Future Cardiovascular Events of Patients With Advanced Atherosclerosis

Martin Schillinger, MD; Markus Exner, MD; Jasmin Amighi, MD; Wolfgang Mlekusch, MD; Schila Sabeti, MD; Helmut Rumpold, MD; Oswald Wagner, MD; Erich Minar, MD

From the Departments of Angiology and Laboratory Medicine (M.E., H.R., O.W.), Vienna General Hospital, Medical School, Vienna, Austria.

Correspondence to Martin Schillinger, MD, Department of Internal Medicine II, Division of Angiology, Vienna General Hospital, Medical School, Waehringer Guertel 18-20, A-1090 Vienna, Austria. E-mail martin.schillinger@akh-wien.ac.at

Received April 30, 2003; de novo received June 17, 2003; revision received August 11, 2003; accepted August 13, 2003.

Background— C-reactive protein (CRP) and glycohemoglobin (HbA1c) are established risk factors for the development of cardiovascular disease. We investigated the joint effects of these parameters on cardiovascular outcome of patients with advanced atherosclerosis.

Methods and Results— We studied 454 patients with advanced atherosclerosis (median age, 69 years; 2

Dentistry for Health New York®

Glycated Hemoglobin HbA1C- Average Glucose

- Average Glucose 2-3 months
- Extra Glucose links up with hemoglobin (glycates)
- The more glucose in the blood the more hemoglobin gets glycated
- Normal 5%- 100 blood Glucose
- Diabetic 7%- 150 blood glucose
- Is increased by periodontal pathogens in the bloodstream
- Is reduced by periodontal treatment

Result report

PST™ Periodontitis Susceptibility Test

Franklin, TN, 08/17/2006

Name of Patient	:	Patient Smith (05/08/2006)
Date of sample collection	:	05/07/2006
Receipt of sample	:	05/08/2006
Date and number of analysis	:	05/09/2006 (D 10078)

Dr. Michael Wirth, DDS

Gene locus 1	Interleukin 1α -889 Allele 1	Interleukin 1α -889 Allele 2
Result	negative	positive

Gene locus 2	Interleukin 1β +3953 Allele 1	Interleukin 1β +3953 Allele 2
Result	positive	positive

Gene locus 3	Interleukin 1 RN +2018 Allele 1	Interleukin 1 RN +2018 Allele 2
Result	positive	positive

Individual genetic periodontal risk	**Genotype 3**

Genotype 1: Patient with normal inflammatory reaction.
No increased risk for progressive development of periodontitis.

Genotype 2: Patient with increased inflammatory reaction.
Increased risk for progressive development of periodontitis.

Genotype 3: Patient with extremely high inflammatory reaction.
High risk for progressive development of periodontitis.

Genotype 4: Patient with reduced inhibition of inflammatory reaction.
Commonly present in periimplantitis.

Result report micro-IDent®*plus*

DNA test for periodontopathogenic marker bacteria

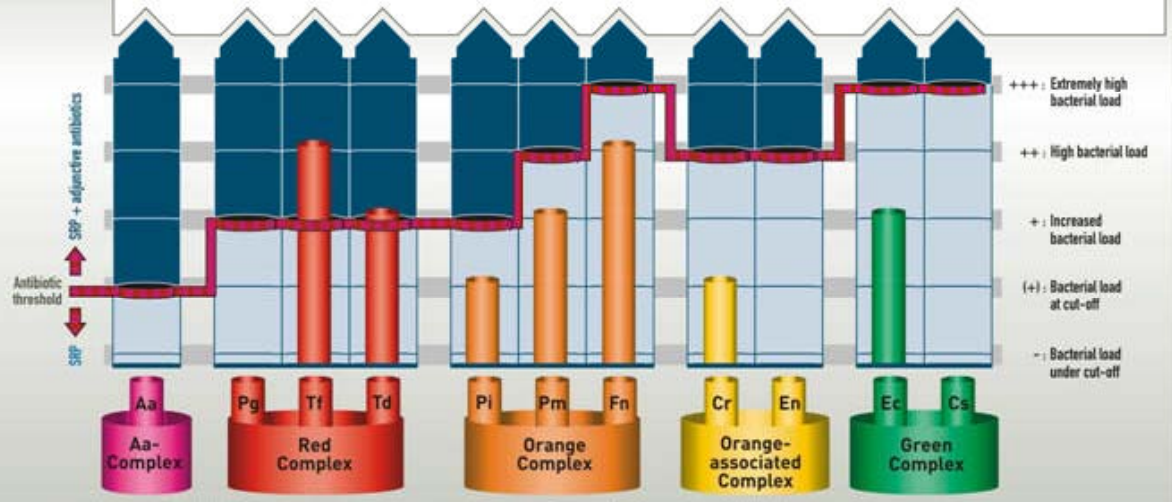
Advanced Dental Diagnostics, LLC | P.O. Box 680729 | Franklin, TN 37068-0729

Dr. Dennis Tree
100 Willowbrook Rd
Columbus, 39000, MS

Name of patient	**Sally Patient**
Date of birth	01/05/1954
Sample	Multi-site sample
Analysis	Initial analysis
Number of analysis	ANA182654/11767
Date of analysis	11/22/2006
Tooth / Teeth	2 / 14 / 19 / 21 / 30
Maximum pocket depth	7mm

Result

Microbiological analysis for patient Sally Patient resulted in a bacterial concentration requiring treatment due to the following complexes:Red Complex (Tf,Td). Depending on the clinical findings this requires, in addition to mechanica treatment (SRP), an adjunctive antibiotic administration (scenario 2, Metronidazole: 2 x 500 mg/day, 8 days). For evaluating therapy success a control analysis is recommended approx. 8 weeks after cessation of antibiotic intake.



Explanation of pathogen concentrations

-	= $<10^4$	[Exception Aa: $<10^3$]
[+]	= 10^4	[Exception Aa: 10^3]
+	= $<10^5$	[Exception Aa: $<10^4$]
++	= $<10^6$	[Exception Aa: $<10^5$]
+++	= $>10^7$	[Exception Aa: $>10^6$]

Abbreviations of bacteria names

Aa	= *Actinobacillus actinomycetemcomitans*	Fn	= *Fusobacterium nucleatum/periodonticum*
Pg	= *Porphyromonas gingivalis*	Cr	= *Campylobacter rectus*
Tf	= *Tannerella forsythia*	En	= *Eubacterium nodatum*
Td	= *Treponema denticola*	Ec	= *Eikenella corrodens*
Pi	= *Prevotella intermedia*	Cs	= *Capnocytophaga spec. (gingivalis, ochracea, sputigena)*
Pm	= *Peptostreptococcus micros*		

Smoking

Not specified. If your patient is smoker this risk factor should be considered in the individual therapy

Dentistry for Health New York®

BANA Enzyme Test

Advantages

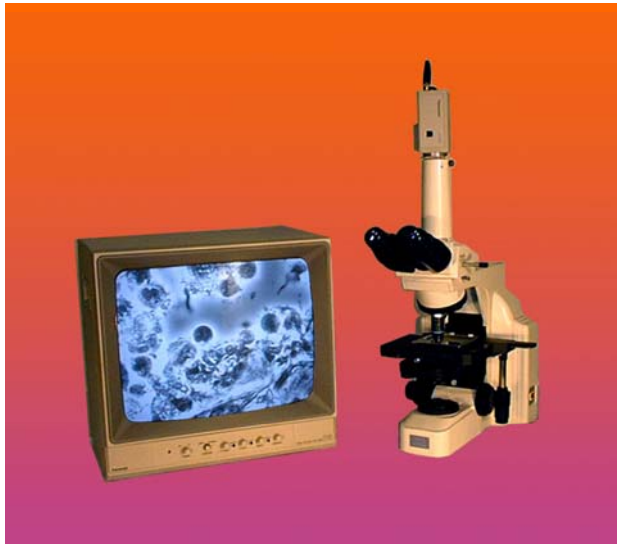
- Chairside
- Species specific
  - P. gingivalis
  - T. forsythus
  - T. denticola
- Fast: 5 minutes
- Inexpensive
  - $300 + $6 /test

Dentistry for Health New York®

Video Microscopy

Advantages

- Chairside
- Fast: 2 minutes
- Cheap: 25¢ / test
- ID's: <u>Morphotypes</u>
  Spirochetes
  Rods
  WBC's
  Trichomonads
  Amoebas
- Patient Motivation



Dentistry for Health New York®

Endo-PAT 2000

itamar MEDICAL

- Noninvasive - The PAT signal, recorded from the distal phalanx of a finger by the pneumatic finger probes
- Easy to use - user independent
- Automatic analysis - using proprietary advanced Digital Signal Processing algorithms.
- Supports both clinical and research applications
- Reliable and reproducible results
- FDA cleared and CE marked

Dentistry for Health New York®

[heartwire]

Intensive Treatment of Periodontal Disease Improves Endothelial Function

from Heartwire — a professional news service of WebMD

Michael O'Riordan

March 1, 2007 **(Farmington, CT)** - A new study appears to suggest that treating periodontal disease can improve endothelial dysfunction, with investigators showing that aggressively treating periodontal disease, a potential source of low-grade inflammation, results in a long-term improvement in vascular function [1].

"Local intensive mechanical treatment of periodontitis, without the use of systemic drug therapy, resulted in a transient acute inflammatory response and a transient impairment of endothelial function," write lead author **Dr Maurizio Tonetti** (University of Connecticut Health Center, Farmington, CT) and colleagues in the March 1, 2007 issue of the *New England Journal of Medicine*. "At six months, however, intensive treatment of the periodontitis, as compared with control treatment, was associated with reduced indexes of periodontal disease severity and significantly better endothelial function."

Dentistry for Health New York®

KODAK 9000C 3D Panoramic and Cephalometric System

- The Kodak 9000C system is the ideal and complete diagnostic tool, blending cutting edge “one-shot” cephalometric technology with high-quality panoramic imaging.
- “One-shot” cephalometric imaging
- Multiple cephalometric formats
- Upgradeable to low-dose, localized 3D imaging
- One built-in sensor per application, improved productivity
- and reduced chance of sensor damage
- High image quality due to the adjustable focal trough in panoramic mode
- Automatic landmark recognition saves time
- Less radiation and need for interpretation

Dentistry for Health New York®

Alpha-Stim 100

- Combined transcutaneous electrical nerve stimulator and cranial electrotherapy stimulator
- The Alpha-Stim® 100 uses microcurrent electrical therapy (MET) for those suffering from acute, chronic or postoperative pain.
- The Alpha-Stim® 100 treats anxiety, depression, and/or insomnia with microcurrent using a method called cranial electrotherapy stimulation (CES).

Dentistry for Health New York®

Use your test results to design the right plan for you

Step 2: Using your individual test results and your assessment, we will help you design a plan to become as healthy as you choose to be.

Dentistry for Health New York®

The Laser for Periodontal Therapy

- Decontaminates
- Reduces Discomfort
- Promotes tissue regeneration
- Saves Time
- Replaces Surgery in most cases

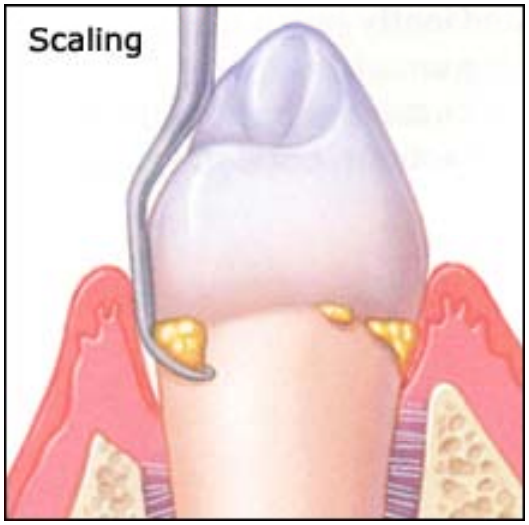
...Because Optimal Health Begins With Oral Health

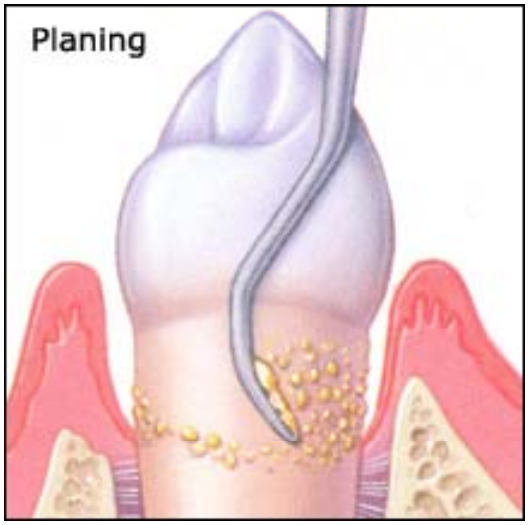
Dentistry for Health New York®

Ozone Generator

Dentistry for Health New York®

Scaling & Root Planning





Dentistry for Health New York®

Complete your Treatment Program to reach a higher level of health

Step 3: Once you complete your treatment plan for health, you will have reached a higher level of health. Your new assessments at each step of treatment will allow you see your own progress.

Dentistry for Health New York®

Improve your Home Care regime to keep bacteria from reforming

Step 4: Now that you know how to keep your mouth in a healthy state, it is important that you continue your new Home Care regime. Health isn't something you achieve once and have forever, it is a choice you make everyday and multiple times through out the day.

Dentistry for Health New York®

You Must Brush to Stop Bio Film Formation

Problems With the Typical Toothbrush

- People will only take 30 seconds to brush
- It is hard to learn proper method including angulations, motion, etc
- People brush their favorite places and never get to the others (lingual, etc.)

Dentistry for Health New York®

Plaque Removal by Worn Toothbrushes

- Oral B-35 brush
- 3 month study, University students
- Control group received new brush monthly
- No significant differences between groups for plaque or gingivitis.
- Efficiency of plaque control independent of toothbrush wear.

Sforza, J Clin Periodontology 27: 212-216;2000

Dentistry for Health New York®

Floss

"How many bacteria do you think
you can kill
with a piece of string?"

Paul H. Keyes

Dentistry for Health New York®

Floss Problems

- Surface concavities
- Technique sensitive
- It is used at all?
- Can the time be better spent?

Dentistry for Health New York®

Floss Problems

- And, as everyone knows floss is only used by …
- Dental Hygienists
  and …
- People who eat ***porkchops*** and ***popcorn!***

AAP Website 2005

Hydrofloss-Don't Bet Your Success On Your Ability To Floss

Dentistry for Health New York®

Hydrofloss

- Better and easier than flossing
- Ionizes water
- Prevents buildup of plaque
- Prevents buildup of Calculus
- Makes your mouth feel clean like you have just been to the dentist every day!

Dentistry for Health New York®

Closys II

- Chemically Neutralizes VSC's
- Kills Anaerobic Bacteria
- Eliminates Biofilm

...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®

You Must Stop the Sulfur Compounds that are Created Daily

- Skin contains sulfur
- Gum tissue constantly dies and is reborn
- Mixes with food debris
- Created by bacteria
- Allow the bacteria to penetrate the gum tissue
- Are Chemically eliminated by CLO2
- Are not removed by store brand toothpaste & mouthwash

Dentistry for Health New York®

You must also break up bacteria colonies where no toothbrush can reach (Closys & Hydrofloss) and prevent them from forming again.

Periodontal bacteria colonies double every 4 hours!! Dental plaque becomes calculus/tartar every 48 hours!!

Dentistry for Health New York®

THE Herbal DIFFERENCE,™ Inc.

- Perio-Care Dental Products that use only the highest quality, all-natural ingredients. The formulas are not just palliative, but actually contain herbs that have been proven to target the underlying causes of periodontal disease – infectious agents such as virus, bacteria, spirochetes, amoebas and fungus.
- Employing a three part (Powder, Rinse, Oral Capsule), three Stage system, Perio-Care Dental Products are designed to remove infectious agents in layers.
  - Stage I works to eliminate virus, bacteria and spirochetes.
  - Stage II works against amoebas (parasites) and fungus (Candida, etc.).
  - Stage III is designed to address resistant or “cross-over” organisms such as spirochetes, mycoplasma or mutant bacteria.

Dentistry for Health New York®

Fight Disease from the inside out with Nutritional Supplements

- Grape Seed Extract-
  - Prevents bacteria from colonizing,
  - Prevents destructive enzymes,
  - Destroys Free radicals
- COQ10- improves healing response
- Folic Acid-
  - Ensures normal epithelial development,
  - binds to endotoxins
- Olive Leaf Extract- natural antibiotic
- Bromelain- natural anti-inflammatory
- Alpha-Lipoic Acid- Blood Sugar Control

...Because Optimal Health Begins With Oral Health

Dentistry for Health New York®

Life Long Health- Physician's Formula

- Lowers Inflammation – CRP, Arthritis
- Improves Artery Function, Stamina
- Lowers Blood Pressure
- Anti Aging
- Antioxidant- 20 times more powerful than Vitamin C or E
- Natural Anti-Histamine
- Lowers Homocysteine
- Slows Onset of Senility

Dentistry for Health New York®

Physician's Periodontal Formula

- Pharmaceutical Grade Nutraceuticals
- Quality not found in store brands
- University Studies show these ingredients
  - Reduced pocket depth
  - Reduced bleeding
  - Reduced Plaque index

Dentistry for Health New York®

Loma Linda Study

Pocket Depth 5-7 mm

- 94% improved 1mm or more
- 80% improved to 4mm
- 68% improved to normal 3mm

Dentistry for Health New York®

Premier Research Labs- pH Trio

•**# 1 Coral Legend-** A unique marine coral powder, rich in naturally ionized calcium, magnesium and trace minerals (NOT colloidal minerals); an optimal 2 to 1 ratio (calcium to magnesium); 100% pure coral (no added sand or other fillers)

•**# 2 Quantum Aloe Powder-** Highly charged, concentrated organic aloe powder combined with pure organic pomegranate: the "gateway" transporter of the ionized coral minerals, a natural chelating agent bonding the minerals to the aloe's amino acids, thereby targeting them to the organs and endocrine glands.

•**# 3 Quantum Cod Liver Oil** (Capsules or Liquid) – Rich in natural vitamin D, an absolute requirement for absorbing calcium; * *best quality U.S.P. grade oil -- not animal feed-grade which is most commonly sold in health food stores.*

Dentistry for Health New York®

Begin Wellness Counseling to improve overall health

Step 5: Health does not stop at your mouth. When you begin Wellness Counseling, you will begin to discover other ways to improve your overall health from nutrition, to exercise, to changing some harmful habits, all geared to help you reach the level of health you choose.

Dentistry for Health New York®

Key is Managing INFLAMMATION

- So why not take out all the teeth to control the inflammation?
  - Extraction of all teeth with decrease systemic inflammatory & & thrombotic markers
    - 67 adults with severe periodontitis had full extraction
    - After 12 weeks serum CRP, fibrinogen, plasminogen activator inhibitor-1, white cell count and platelet count all decreased
- But is full extraction NEEDED?

Taylor BA, et al. *J Dent Res* 2006

Dentistry for Health New York®

Because the KEY is controlling INFLAMMATION, which can be done through periodontal therapy (with good diagnosis, treatment, and maintenance)

Lessons Learned from Scottsdale

By Casey Hein, BSDH, MBA†

This issue of *Grand Rounds in Oral-Systemic Medicine*™ is accompanied by a special supplement that features a landmark document entitled the *Report of the Independent Panel of Experts of 'The Scottsdale Project'*. The first of its kind, this report explores the exciting new frontier of medical-dental collaboration in guidelines development for intervention of diabetes, cardiovascular disease (CVD) and periodontal disease.

Consider the promise medical-dental collaboration might hold in reversing the pandemic trends in these interrelated chronic diseases. In the past decade, there has been substantial investigation of the potential interrelationship between oral and systemic diseases. Mounting evidence suggests there is a relationship between chronic inflammation associated with periodontal disease and increased risk for various systemic diseases. In spite of this evolving body of evidence, multiple institutional and attitudinal obstacles interfere with the diffusion of this body of science into contemporary healthcare. These hurdles have created a large and growing gap between what we know with reasonable certainty about oral-systemic connections, and what we actually do in the clinical practice of dentistry and medicine. This is precisely what the independent panel of experts from *The Scottsdale Project* sought to address in the report.

The independent panel of experts who served on The Scottsdale Project, and representatives from Colgate. Left to right: Walter Cohen, DDS; Casey Hein BSDH, MBA; Maurizio Trevisan, MD; Foti Panagakos, DMD, PhD (Colgate); Moïse Desvarieux, MD, PhD; Robert Ostfeld, MD, MS; Evanthia Lalla, DDS, MS; Louis Rose, DDS, MD; Shailesh Patel, BM, ChB, DPhil, FRCP; Maria Ryan, DDS, PhD; Steven Offenbacher, DDS, PhD, MMSc; Karen Williams, RDH, PhD; Anthony Iacopino, DMD, PhD; Lynnae Millar, MD; Charles Cobb, DDS, PhD; David Paquette, DDS, MPH, DMSc; Sheila Garris, MD, FACP; Seri Souvik, MD, MS, FAHA; Marsha Butler, DDS (Colgate); Carolyn Herrick, MBA (Colgate). Expert not pictured: Brian Mealey, DDS, MS.

The Scottsdale Project

Key Issue I: Is it appropriate to develop guidelines that assist dental providers in identifying patients who have or who are at risk for diabetes and cardiovascular disease, or screening patients for undiagnosed diabetes or cardiovascular disease who need to be referred to physicians?

Key Issue II: Is it appropriate to develop guidelines that assist medical providers in identifying patients who are at risk for periodontal disease, or screening patients who may have undiagnosed periodontal disease who need to be referred to dentists?

Re: Key Issue I

- Yes, it is appropriate to develop guidelines to assist dental providers in identifying patients who are at risk for diabetes and/or cardiovascular disease. A thorough search for patient provided information that may lead to a diagnosis to improve oral and systemic health should be conducted by dental providers.

Re: Key Issue II

- Yes, it is appropriate to develop guidelines to assist medical providers in identifying patients who are at risk for periodontal disease, or screening patients who may have undiagnosed periodontal disease who need to be referred to dentists. Medical providers' recognition of the signs and symptoms associated with periodontal disease may identify patients who are either at risk or are undiagnosed who should be referred to the dental provider.

Recommendations of Expert Panel

- red, sore, swollen, receding, or bleeding gums
- loose or sensitive teeth, separation of teeth
- presence or history of oral abscesses
- halitosis
- missing teeth
- accumulation of food debris or plaque around teeth

The expert panel recommended the following:

The physician should first ask the patient,
"Have you been to see the dentist in the last year?

NO

Refer to a Dentist

YES

Ask: Do you have any of the following?
- **B**leeding gums
- **U**nsteady teeth
- **G**um recession

BUG

and/or Oral exam

Refer to dentist as appropriate

The Scottsdale Project

Centers for Dental Medicine

Save Teeth!

Save Lives!

Make a difference!

CENTERS FOR DENTAL MEDICINE

Dentistry for Health New York®

Periodontal Medicine - Implications

Who else is interested in Periodontal Medicine besides dentists, dental, hygienists, patients, physicians, third party payers??...

Dentistry for Health New York®

Periodontal Medicine- Implications

- Recent studies have shown that periodontal treatment decreases Per Member Per Month (PMPM) costs within populations having DM, CAD, CVD
  - Aetna study: 144,225 enrollees with DM, CAD, CVD
  - Subjects receiving perio treatment had lower PMPM costs than those not receiving perio tx
  - Those receiving perio tx early in the 2-year study had lower PMPM costs than those receiving perio tx later in the study (sequecing effect)

Dentistry for Health New York®

Periodontal Medicine - Implications

- CIGNA Dental Oral Health Maternity Program
  - Covers 100% of SCRP when performed during pregnancy (no co-pay); covers an additional prophylaxis during pregnancy for women who don't need SCRP
  - "CIGNA dentists can now encourage a pregnant mom to seek further treatment of periodontal disease, knowing that hose services are covered."
    - *Managed Dental Care* 11(5), Jan 2006

Dentistry for Health New York®

Periodontal Medicine - Implications

- BC/BS of Massachusetts
  - Diabetic patients who received prophylaxis, SCRP or periodontal maintenance during the previous year had lower medical costs in the subsequent 12 months
  - Cover 100% of SCRP, periodontal maintenance, prophylaxis for patients enrolled in BC/BS's Preventive Health Program (targeted toward patients with DM and CAD/CVD, as well as women in "Healthy Babies/ Healthy Mothers" program)

Dentistry for Health New York®

Periodontal Medicine - Implications

Who else is interested in Periodontal Medicine besides dentists, dental, hygienists, patients, physicians, third party payers??...

Dentistry for Health New York®

"If you or someone you know had periodontal disease, diagnosed or undiagnosed, and either ignored or treated unsuccessfully, before or during the same time as any of the mentioned systemic diseases, you may be eligible for damages caused by these systemic diseases.

Please complete the contact information or phone my office for a free consultation. I am committed to providing you with the expertise necessary to meet your medical and dental malpractice needs.

At my law office, you, our client, comes first. We will do whatever is necessary to defend and uphold your legal rights."

Dentistry for Health New York®

Acknowledgements

Dentistry for Diabetics®

(877) 433-7342

www.DentistryForDiabetics.com

Brian L. Mealey, DDS, MS
Department of Periodontics
University of Texas Health Science Center
San Antonio, Texas

CENTERS FOR DENTAL MEDICINE

http://www.centersfordentalmedicine.com/

The Role of Dentistry in Cardiovascular Disease

Slide 10
Page RC. Ann Periodontol 1998

Slide 17-19
Journal of Clinical Periodontology, Vol. 24, pp.478-485, 1997
Giovanna Giuliana, 2Pietro Ammatuna, Giuseppe Pizzo, 2Francesca Capone, 1Matteo D' Angelo

Slide 18
Miller, W.D. (1890). The microorganisms of the human mouth. The local and general diseases which are caused by them. S.S. White Dental Manufacturing. New York, NY.

Slide 20
Journal of Periodontology, Vol. 59, pp.493-503, 1988
1Patrick A. Adriaens, 1Chris A. Edwards, 2Jan A. De Boever and 1Walter J. Loesche

Slide 21
Adriaens et al., (1988). *J. Clin. Periodontol.* 59:493-503.

Slide 22
Journal of Periodontology, Vol. 59, pp.222-230, 1988

Slide 23
Adriaens et al., (1988). *J. Periodontol.* 59:222

Slide 27
Beak et al. J. Periodontol 2005

Slide 28
Arbes et al. *J Dent Res 1999*

Slide 31
Mattila *J Int Med* 1989
Syrjanen et al. *Br Med J* 1988

Slide 32-34
Geerts et al. *J Periodontol* 2002

Slide 38-39
Haraszthy et al. *J Periodontol* 2000

Slide 43
D'Aiuto et al. *J.Dent Res* 2004

Slide 112
Sforza, J Clin Periodontology 27: 212-216;2000

Slide 116
AAP Website 2005

Slide 128
Taylor BA, et al. *J Dent Res* 2006

Slide 139
Managed Dental Care 11(5), Jan 2006

James Biddle, MD

Overview of heavy metal toxicity

Bio

Dr. Biddle graduated 1989 from University of Missouri-Columbia School of Medicine. He is Board-Certified in Internal Medicine after residency in Portland, OR at St. Vincent's Hospital. He is also certified in Chelation Therapy, Massage, Reiki, and Hypnotherapy. Dr. Biddle runs Asheville Integrative Medicine since 1997, and belongs to www.earthaven.org, a Permaculture community teaching sustainability for both humans and the Earth. Dr. Biddle served on the ACAM Board for six years.

Lecture Overview

Heavy-metal toxicity is a world-wide challenge contributing to increases in a wide variety of illnesses, disorders, syndromes, birth defects, and developmental abnormalities. Toxic heavy metals, including lead, mercury, cadmium, and arsenic, are generally overlooked in medicine, perhaps because they affect every cell and organ in the body, often subtly, and also affect many bodies in a population. This presentation will introduce the history and usage of toxic metals, the basics of why and how they are toxic, and the historical perspective of treating these toxicities.

Contact Information

832 Hendersonville Rd.
Asheville, NC 28803-1710
www.docbiddle.com
info@docbiddle.com

American College for Advancement in Medicine
Chelation Therapy Workshop
November 4-5, 2009
Las Vegas, Nevada

Vascular Risk Factors

James Biddle MD

Asheville Integrative Medicine

832 Hendersonville Road

Asheville NC 28803

www.docbiddle.com

Unified Theory of Athero-genesis:

Atherosclerosis is

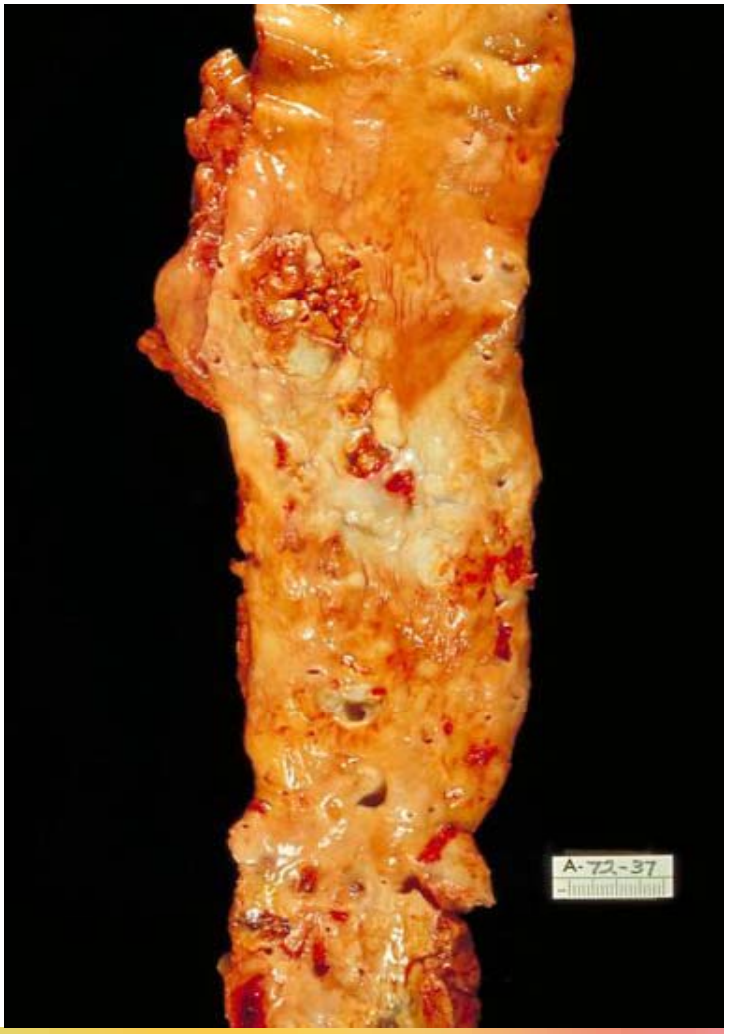
an INFLAMMATORY process.

Based on the presence of cytokines, growth factors, angiogenesis factors, and cellular recruitment to the site of intimal damage.

- Ross, R. *NEJM* Jan '99; 340:115-126. Atherosclerosis - An Inflammatory disease.

The Propagation of Atherosclerosis:

1. Endothelial Dysfunction & Injury.
2. Fatty Streak Formation.
3. Formation of an Advanced &/or Complicated Plaque.
4. Plaque Rupture & Clot Formation.



Endothelial Dysfunction:

Oxidative Stress: Free Radicals from various sources: e.g. cigarette smoke, radiation, transition metals, anti-oxidant deficiencies, and rancid fats.

- Oxidative Stress oxidizes LDL, increases endothelial permeability, and promotes a pro-thrombotic state.
- Chelation, as well as multiple antioxidants, can reduce the damage induced by free radicals.

Increased Permeability: to lipoproteins and other plasma constituents → mediated by nitric oxide, prostacyclin, PDGF, angiotensin-11, and endothelin.

Endothelial Dysfunction:

- Hyperlipidemia →
- **Modified Lipids and Lipoproteins**

  - **Modification occurs by** glycation (AGEs), oxidation, aggregation, proteoglycans, or incorporation into immune complexes.

  - **Internalization of LDL-m** by macrophages leads to lipid peroxidation, foam cells, and chemotaxis of monocytes.

Endothelial Dysfunction:

- **Up-Regulation of Leukocyte (WBC) Adhesion Molecules,** including ……. L-selectin and integrins.
- **Up-Regulation of Endothelial Adhesion Molecules**: E-selectin, P-selectin, ICAM-I, and VCAM-1.
- **Migration of Leukocytes** into the artery wall from oxidized-LDL, MCP-1, IL-8, PDGF, MCSF and osteopontin.

Fatty Streak Formation:

- **Foam Cell Formation** : mediated by ox-LDL, TNF-alpha and IL-1.
- **T-Cell Activation** : mediated by TNF-alpha and IL-2.
- **Smooth Muscle Migration** : stimulated by PDGF, Fibroblast Growth Factor 2, and Transforming Growth Factor-beta.
- **Platelet Adherence and Aggregation** : stimulated by Integrins, P-selectin, Fibrin, Thromboxane A2, and Tissue Factor.

Formation of an Advanced Complicated Plaque:

- **Macrophage Accumulation** is mediated by MCSF, MCP-1, and ox-LDL.
- A **Necrotic Core** is formed by apoptosis of cells, increased proteolytic activity, and lipid accumulation.
- A **Fibrous Cap** walls off the necrotic core. It is formed as a result of activity of PDGF, TFG-Beta, IL-1, and TNF-alpha.

Formation of an Advanced Complicated Plaque:

- The **Extra-Cellular Matrix** forms the bulk of an advanced plaque and contains **Collagen**, **Proteoglycans** and **Elastin**.
- **Collagen Synthesis** by smooth muscle is stimulated by PDGF and TGF-beta.
- The **Synthesis <-vs-> Breakdown** balance determines Stability-vs-Instability of a plaque.

‘Classical’ Risk Factors for Atherosclerosis in 75%:

1. Hyperlipidemia.
2. Hypertension.
3. Diabetes.
4. Smoking.

Magnus, P. The Real Contribution of the Major Risk Factors to the Coronary Epidemics. Time to End the “Only-50%” Myth. *Arch Intern Med* 2001:161;2657-60.

‘Emerging’ or ‘Novel’ Risk Factors for Atherosclerosis:

“Although **CRP, Lp(a), Fibrinogen**, and **Homocysteine** are associated with vascular disease risk, their **optimal use in routine screening and risk stratification remains to be determined.”**

- Hackman, D. *JAMA* 2003:290(7);891-904. Emerging Risk Factors for Atherosclerotic Vascular Disease. **A Critical Review of the Evidence.**

‘Under-Valued’ Risk Factors for Atherosclerosis:

1. Stress and Social Isolation.
2. Obesity and Sedentary Lifestyle.
3. Metabolic Syndrome X.
4. Chronic Infections.
5. Nutrition (i.e. high-calorie, trans-fat malnutrition).

More ‘Under-Valued’ Risk Factors for Atherosclerosis:

1. Gout.
2. PCOS.
3. Sleep Apnea.
4. Vitamin D Deficiency.
5. Auto-Immune Diseases.

‘Futuristic’ Risk Factors for Atherosclerosis:

1. Testosterone Deficiency.
2. Iron Overload.
3. Heavy Metal Toxicities: Lead, Mercury, Cadmium, Arsenic, etc.

Atherosclerosis Risk Factors:

- **Lack of Fitness**:

2478 pts aged 18-30 for 15 yrs: **Bottom Quintile in CV fitness had 3-6 times the risk** for later diabetes, HTN, or AMI.

➢ *JAMA* 2003 Dec 17;290(23): 3092-3100.
Carnethon, M. Cardiorespiratory Fitness in Young Adulthood and Development of Cardiovascular Risk Factors.

Atherosclerosis Risk Factors:

- Type A personality / **Stress:**

Studies are hard to do. Some worthwhile ones:

- 'Intensive Lifestyle change for reversal of CHD' Dean Ornish et al: *JAMA* 1998 Dec 16:280(23); 2001-7.
- 'Effect of psychological stress and psychological disorders on blood coagulation and fibrinolysis' : *PsychosomMed* 2001 July:63(4);531-44.

Atherosclerosis Risk Factors:

- **Insulin Resistance:**
  - Waist : Hip Ratio > 1 = strong predictive value.
  - Fasting Insulin costs <$30 ; should have result of <10 units.
  - Testosterone deficiency is increased in insulin resistance.

Atherosclerosis Risk Factors:

- Standard American Diet = **"SAD"**

= 145 lbs. sugar + 12 lbs. aspartame yearly

("high calorie malnutrition").

vs "Sustainable Nutrition"

= Adequate-Protein, Healthy-Fat, High-Fiber, and Lower-Glycemic Index.

Hydrogenated Fats = CAD Risk:

"Foods that are major sources of **trans**-isomers (margarine, cookies, biscuits, cake, and white bread) were each significantly associated with higher risks of CHD."

Diet Diary of 85,000 nurses over 10 yrs:

5th Quintile for reported intake of trans fats = **RR 1.5** for CHD.

- Willett WC. *Lancet* 1993;341(8845):581-5. Intake of trans fatty acids and risk of CHD among women. Harvard.

Hydrogenated Fats = CAD Risk:

"Intake of margarine--the major source of trans-isomers--was significantly associated with risk of myocardial infarction." 239 CHD admits vs controls:

RR = 2.44 for 5th Q of trans-fats.

- Ascherio A. at Harvard Univ. *Circulation* 1994 Jan;89(1):94-101.

Hydrogenated Fats = CAD Risk:

Case Control with Fat Bx and Food Hx- 100 pts with AMI vs controls:

RR = 2.81 for 5th Q of trans fats.

- Pedersen JI. Univ of Oslo. Adipose tissue fatty acids and risk of myocardial infarction. *Eur J Clin Nutr* 2000 Aug;54(8):618-25.

Hydrogenated Fats = CAD Risk:

"The Danish Nutrition Council recommends that the addition of industrially-produced trans fatty acids to food stuffs ceases before 2005 and until then that declaration of the content in foodstuffs becomes mandatory."

- Stender S. [The importance of trans-fatty acids for health.][Article in Danish] *Ugeskr Laeger* 2001 Apr 23;163(17):2349-53.

Hydrogenated Fats = CAD Risk:

"There is no level of trans fatty acids that is safe to consume."

- Industry delayed labeling by 5-7 years.

➢ Institute of Medicine expert panel. Center for Science in the Public Interest; 2002 July 10.

No Safe Level of Trans Fats.

What to Eat?

"Frequent **nut consumption** reduced risk of both fatal coronary heart disease and non-fatal MI." Nurses Health Study – Prospective Cohort.

86 K women x 14 yrs, any MI:

RR = 0.65 for > 5 oz nuts/week.

- Hu FB, Harvard. *BMJ* 1998 Nov 14;317(7169):1341-5. Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study.

What to Eat?

"The inverse association between **nut consumption** and total CHD death is primarily due to a reduction in the risk of sudden cardiac death."

US Physician's Health Study –

21,000 men x 17 years; total CHD death:

RR = 0.53 for nuts > twice/week.

"Mechanism Unclear" → Magnesium, EFA's, fiber?

- Albert CM, Brigham & Women's Hosp. Nut consumption and decreased risk of sudden cardiac death in the Physicians' Health Study. *Arch Intern Med* 2002;162(12):1382-7.

What to Eat?

"Consumption of **fish** at least once per week may reduce the risk of sudden cardiac death in men."

US Physician's Health Study –

20,500 men x 11 years; sudden cardiac death:

RR = 0.48 for **fish > once/week**.

- Albert CM, Brigham and Women's Hosp. Fish consumption and risk of sudden cardiac death. *JAMA* 1998 Jan 7;279(1):23-8.

What to Eat?

"…an inverse association between **fish** consumption and death from coronary heart disease, especially non-sudden death from myocardial infarction." Chicago Western Electric Study –1822 men x 30 years: > 35 gms fish/day.

RR = 0.62 for sudden CHD death.

RR = 0.56 for non-sudden CHD death.

- Daviglus ML, Northwestern Univ. **Fish consumption and the 30-year risk of fatal myocardial infarction**. *N Engl J Med* 1997;336(15):1046-53.

What to Eat?

"The relative risk of sudden death was significantly lower among men with **Omega-3 levels** in the :

- third quartile (**RR 0.28**), and the
- fourth quartile (**RR 0.19**)."

➢ Albert CM. Blood levels of **long-chain n-3 fatty acids** and the risk of sudden death. ***N Engl J Med*** 2002;346(15):1113-8.

What to Drink?

"Men who consumed light-to-moderate amounts of **alcohol** (2 to 6 drinks/wk) had a significantly reduced risk of SCD (sudden cardiac death) compared with those who rarely or never consumed alcohol." >21K male docs over 12 years: "Unity" at > 2 drinks/day.

2-4 drinks/wk – **RR=0.40**

5-6 drinks/wk – **RR=0.21**

- Albert CM, Brigham and Women's Hosp. Moderate alcohol consumption and the risk of sudden cardiac death among US male physicians. *Circulation* 1999;100(9):944-50.

Atherosclerosis Risk Factors:

Hypertension:

- 9 studies = 420,000 pts x 10 years.
- For Diastolic BP 70-110 there is "No Threshold" for increased vascular events.
- **For Diastolic over 90, every 7 mm** Hg increases coronary vascular events **27%** and increases strokes **42%.**

  ➢ MacMahon S. *Lancet* 1990;335:1092-4.

Atherosclerosis Risk Factors:

- **Lp(a)** = Lipoprotein (a):
  - A dangerous lipoprotein genetic varient which occurs in 25% of the population.
    - Rhoads GG, Lp(a) as a risk factor for MI. JAMA 1986;256:2540-4.
    - Merz B, Is it time to include lipoprotein analysis in cholesterol screening? JAMA 1989;261(4);496-7.
    - Utermann G, The Mysteries of Lipoprotein (a). Science 1989;246:904-910.

Atherosclerosis Risk Factors:

- **Lipoprotein (a):**

  An LDL linked to a redundant Apo-a protein. Apo-a has homology with plasminogen but it does not cause fibrinolysis. When levels are high, it is associated with inability to break down clots.

Rx with Niacin, Co-Q10, Vitamin C, Natural HRT, and Lysine & Proline.

➢ Caplice NM. *Blood* 2001 Nov 15;98(10):2980-7.

Atherosclerosis Risk Factors:

- **Homocysteine**:
  - An amino acid that can build up due to genetics, renal insufficiency, or deficiencies of folate, B6, or especially B12.

➢ McCully KS, Vascular pathology of homocysteinemia. American Journal of Pathology **1969**;59:111-128.

➢ McCully KS, Homocysteine, folate, B6 and cardiovascular disease. JAMA **1998**;279:392-393.

Atherosclerosis Risk Factors:

- **Homocysteinemia:**

"Individuals with elevated **HCY > 12** demonstrated a mean increase in CC progression of **35% per year**, while those with HCY <12 (median) progressed at 17% per year (p = 0.0008)."

➢ Rasouli ML. *Atherosclerosis.* 2005 Jul;181(1):159-65. Plasma homocysteine predicts progression of atherosclerosis.

Is the Homocysteine Theory of Vascular Risk Dead?

- "In the era of folate fortification, B12 plays a key role in vitamin therapy for total homocysteine." Spence JD. *Stroke* 2005 Nov;36(11):2404-9.
- "…in the post-folic acid fortification era, low vitamin B(12) status has become the dominant nutritional determinant of hyperhomocysteinemia." Green R. *Clin Chem Lab Med* 2005;43(10):1048-51.

Atherosclerosis Risk Factors:

- **Chronic Infection:**
  - Helicobacter pylori, Chlamydia pneumoniae, or gum disease causing inflammation.
    - Grau AJ. Association of leukocytes, fibrinogen, and C-reactive protein with vascular risk factors and ischemic vascular diseases. *Thromb Res* 1996;82(3):245-55.
    - Ridker PM. C-Reactive Protein adds to predictive value of cholesterol in determining risk of first MI. *Circulation* 1998;97:2007-2011.

Atherosclerosis Risk Factors:

- **Inflammation -> CRP**: measures subtle inflammation and also induces adhesion molecule expression.
- CRP up-regulates ICAM-1 on endothelial cells; it induces TF expression by monocytes and activates the complement cascade of coagulation.

- Pasceri. *Circulation* 2000;102: 2165-8.
- Mulvihill. *Heart* 2002;87(3): 201-204.

Atherosclerosis Risk Factors:

- **CRP** – a proposed approach:

1. Test for H. pylori infection and treat if positive.
2. Look for dental infections.
3. Give 2-3 weeks of empiric antibiotics, e.g. doxycycline 100 mf BID, with probiotics.
4. Retest CRP in 2 – 3 months.

Exercise decreases CRP: RR = 0.53 for vigorous activity.
Epidemiology Sept 2002.

Atherosclerosis Risk Factors:

- **Fibrinogen:**

It critically influences platelet aggregation and blood viscosity, interacts with plasminogen binding, and (with thrombin) mediates the final step in clot formation.

↑fibrinogen seen with age, smoking, obesity, diabetes, and LDL-c.

↓fibrinogen with alcohol, exercise, HDL.

Atherosclerosis Risk Factors:

- **Testosterone:**

"…in men selected for coronary arteriography, age, HDL-C, **and FT** may be stronger predictors of degree of CAD than are blood pressure, cholesterol, diabetes, smoking, and BMI."

➢ Phillips GB. *Metabolism*. 2004 Mar;53(3):324-9

Vascular Risk & Iron Overload:

- Iron Overload:
  - Hemochromatosis in 1/250 adults; 1 in 10 whites are heterozygous carriers.
  - Increases “lipid peroxidation” causing atherosclerosis and liver damage.
  - Direct correlation with increased CAD.
  - Simple screening with **ferritin** (costs < $20.)
  - Treat by donating blood.

Vascular Risk & Iron Overload:

"An elevated serum ferritin was a strong risk factor for acute myocardial infarction in all multivariate models." 1931 men for 3 years.

Ferritin > 200 mcg/l = 2.2 RR of acute MI.

Dietary intake of Fe also showed a positive association with AMI.

- Salonen JT, Kuopio, Finland. *Circulation* 1992 Sep;86(3):803-11.

Vascular Risk & Iron Overload

>12,000 women, ages 51-69.

Heterozygote for hereditary hemochromatosis:

= **1.5 RR** for AMI.

= **2.4 RR** for CVA.

- Roest M, Utrecht Univ., The Netherlands. Heterozygosity for a hereditary hemochromatosis gene is associated with cardiovascular death in women. *Circulation* 1999 Sep 21;100(12):1268-73.

Iron Overload & Diabetes II Risk:

"Higher iron stores (reflected by an elevated ferritin…) are associated with an increased risk of type 2 diabetes in healthy women ..."

RR = 2.44 for 5th quintile.

- Jiang, R. Body Iron Stores in Relation to Risk of Type 2 Diabetes in Apparently Healthy Women. *JAMA* 2004 Feb 11;291(6):711-17. Harvard School of Public Health.

Desired Ferritin Level = 50-100.

Lead Toxicity & HTN:

HTN **RR = 3.4** for 4th Quartile in 'Normal' lead levels.

"These results provide support for continued **efforts to reduce lead levels** in the general population, especially women."

- Nash D. *JAMA* 2003 Mar 26;289(12):1523-32. Blood lead, BP, and HTN in perimenopausal and postmenopausal women.

Lead Toxicity & HTN:

Higher **Umbilical-Cord Blood Lead** levels (but still below 10 mcg/dl) were associated with increased SVR and decreased SV upon stress testing at age 9 ½, indicating clinically-significant increased cardiac afterload.

- Gump BB. *Neurotoxicol Teratal* 2005 27(4):655-65. Prenatal and early childhood blood lead levels and cardiovascular functioning in 9(1/2) year old children.

Lead Toxicity & Vascular Risk:

- Blood lead levels > 0.48 µmol/L (10 µg/dL) previously associated with increased risk of cardiovascular, cancer, and all-cause mortality.
- **Blood lead levels >0.10 µmol/L (2 µg/dL)** associated with total, myocardial infarction, and stroke mortality. 14,000 pts x 12 yrs.

➢ Menke A. American Heart Association, Inc. *Circulation* 2006;114:1388-1394.

Lead Toxicity & Vascular Risk:

A Prospective Study of Bone Lead Concentration and Death from All Causes, Cardiovascular Diseases, and Cancer in the Dept of VA Normative Aging Study.

"RR of lowest- vs highest-tertile of patella bone lead:

- All-Cause = 2.2; Cardiovascular = 5.63;
- Ischemic Heart Disease Mortality = **8.37**.
- Blood lead had no mortality associations."

Weisskopf, M. *Circulation* 2009; 120: 1056-64.

Cadmium Toxicity & Vascular Risk:

Comparing aged patients with HTN and CAD to aged healthy controls:

The cadmium content in serum of the diseased group were significantly higher than that of the healthy group ($p<0.01$).

- Yang YR, China. *Biological Trace Element Research* 2003 May;92(2):97-104. Studies of five microelement contents in human serum, hair, and fingernails correlated with aged hypertension and coronary heart disease.

Arsenic Toxicity & Vascular Risk:

"Arsenic has been identified as a major contributing risk factor for development of **blackfoot disease (BFD),** a unique peripheral vascular disease that was endemic to the southwestern coast of Taiwan. **CHD declined gradually** for approximately 17 - 20 yrs following cessation of consumption of high-arsenic artesian well water. "

- Chang CC, Taiwan. *J Toxicol Environ Health A.* 2004 Sep 10;67(17):1353-61.

Arsenic Toxicity & Vascular Risk:

"The odds ratios (95% confidence intervals) for IHD **were 1.60 and 3.60**, respectively, for those with Cumulative Arsenic Exposure of

0.1-14.9 and >15.0 mg/L-years, when compared with those lacking drinking water exposure to arsenic."

- Tseng CH, *Toxicol Lett.* 2003 Jan 31;137(1-2):15-21. Long-term arsenic exposure and ischemic heart disease in arseniasis-hyperendemic villages in Taiwan.

Mercury Toxicity & Vascular Risk:

"…a high intake of mercury … was associated with an excess risk of AMI (**RR=2.0** for highest tertile) as well as CV death (**RR=2.9** for highest tertile) … (which) may be due to the promotion of lipid peroxidation by mercury."

- Diet history (non-fatty fish), hair, and urine Hg prospectively over 7 years in 1833 men.
- **Increased Abs to oxidized cholesterol**.

➢ Salonen JT, Kuopio, Finland. *Circulation* 1995 Feb 1;91(3):645-55.

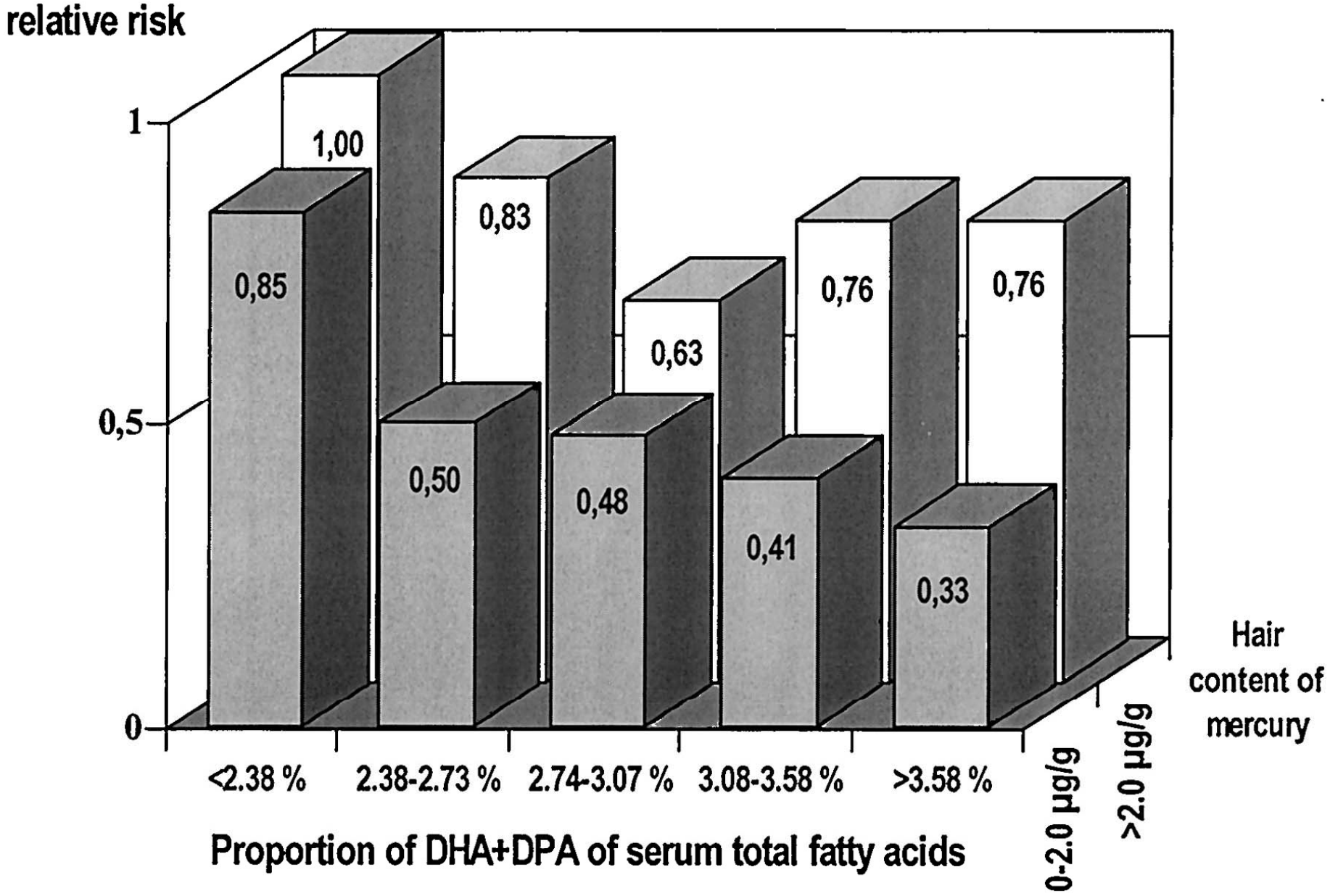
Mercury Toxicity & Vascular Risk:

Of men with the highest omega-3 levels, those with hair Hg in top 1/3 had twice the CAD risk as lowest 2/3:

RR = 0.76 vs 0.33

1871 prospective men in Finland.

- Rissanen T. *Circulation* 2000 Nov 28;102(22): 2677-9. Fish oil-derived fatty acids, DHA and EPA, and the risk of acute coronary events: the Kuopio ischaemic heart disease risk factor study.


relative risk
1
0,5
0
1,00
0,85
0,83
0,50
0,63
0,48
0,76
0,41
0,76
0,33
<2.38 %
2.38-2.73 %
2.74-3.07 %
3.08-3.58 %
>3.58 %
Proportion of DHA+DPA of serum total fatty acids
0-2.0 µg/g
>2.0 µg/g
Hair content of mercury

Mercury Toxicity & Vascular Risk:

Men with **hair Hg in top 1/3** had more CAD risk than lowest 2/3: - 1871 men prospectively x 13.9 years.

RR = 1.60 for AMI.

RR = 1.68 for CVD.

RR = 1.38 for any death.

Virtanen, JK et al. in eastern Finland. *Arterioscler Thromb Vasc Biol* 2005;25(1):228-33.

Mercury Toxicity & Vascular Risk:

Is Mercury as potent as smoking in CAD risk?

Toenail mercury level was directly associated with the risk of MI, with **RR=2.16** for highest vs lowest quintile.

(highest in dentists and fish eaters)

Case control, 684 men with 1st MI.

- Gualler E at Johns Hopkins. ***NEJM*** 2002 Nov 28;347(22):1747-54.

Mercury Toxicity & Vascular Risk:

"1,000 children from the Faroe Islands ... at age 7 years, **diastolic and systolic BP increased** by **13.9 and 14.6 mmHg** respectively when cord blood mercury increased from 1 to 10 mcg/liter."

- Sorensen N, Faroe Islands. *Epidemiology* 1999 Jul;10(4):370-5. Prenatal methylmercury exposure as a cardiovascular risk factor at seven years of age.

Mercury & Cardiomyopathy Risk:

Myocardial and muscle biopsies of 13 IDCM pts vs 25 controls with valvular or ASCVD:

- **Mercury x 22,000 times (178,400 vs 8 ng/g)**
- **Antimony x 12,000 times (19,260 vs 1.5 ng/g)**
- **Gold x 11 times (26 vs 2.3 ng/g)**
- **Chromium x 13 times (2,300 vs 177 ng/g)**
- **Cobalt x 4 times (86,5 vs 20 ng/g)**

"may adversely affect mitochondrial activity and myocardial metabolism and worsen cellular function."

➢ Frustaci A. *J Am Coll Cardiol* 2000;35(3):819-20.

Urine Toxic Element

Patient: **Jean A Biddle**

Doctor: **James R. Biddle, MD**

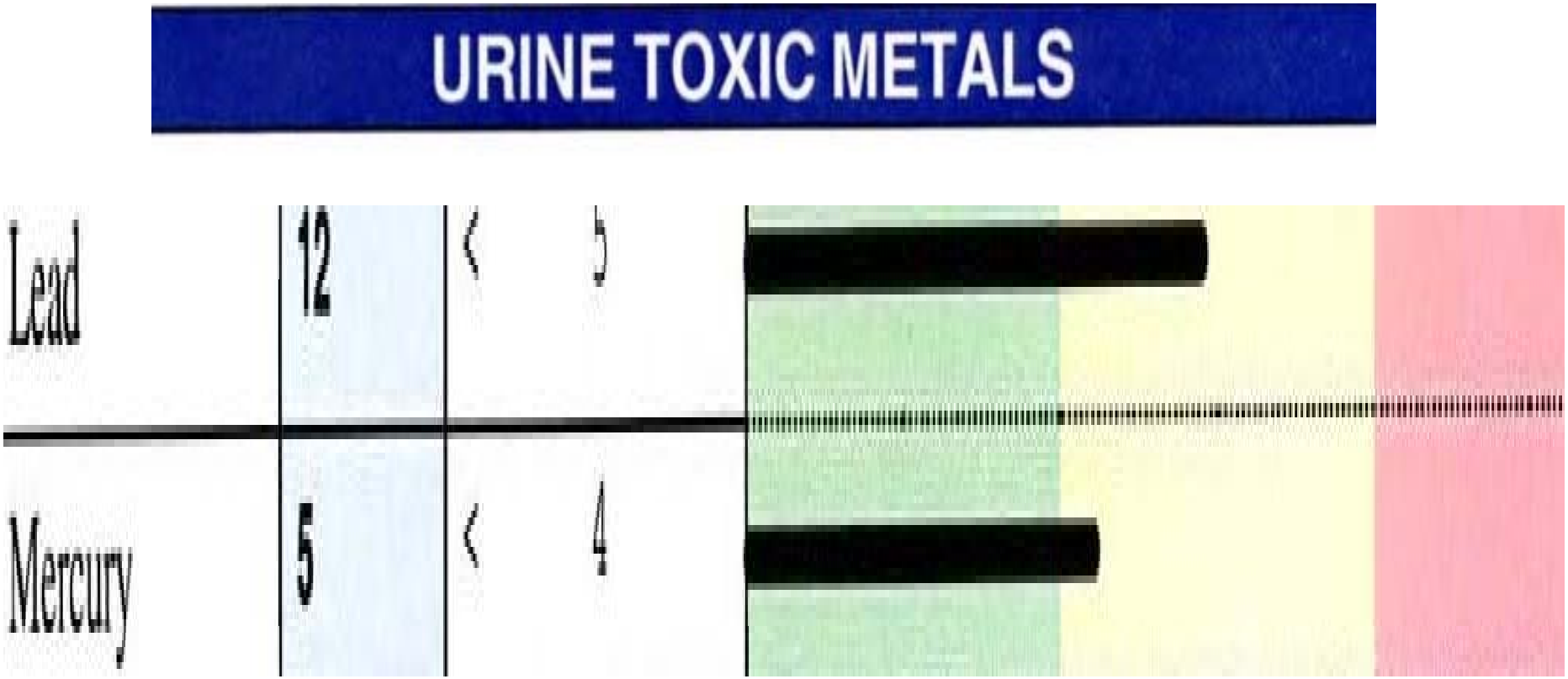
c/o: **Ashville Integrative Med**

Collection Date: **30 Jun 2000**

Date In: **5 Jul 2000**

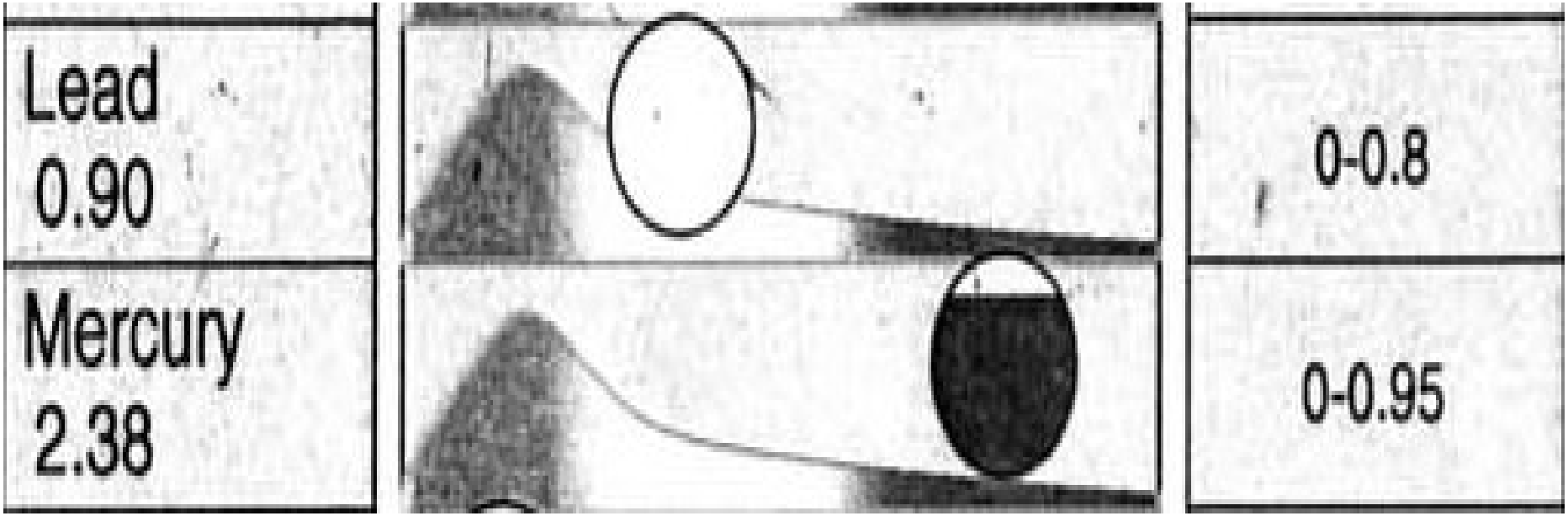
Lead	78	0 - 15	•••••••••••••	•••••••••••••	•••••••
Mercury	21	0 - 3	•••••••••••••	•••••••••••••	•••••••••••

Jean's Lab Results 2004



Provoking Agent: IV EDTA DMPS

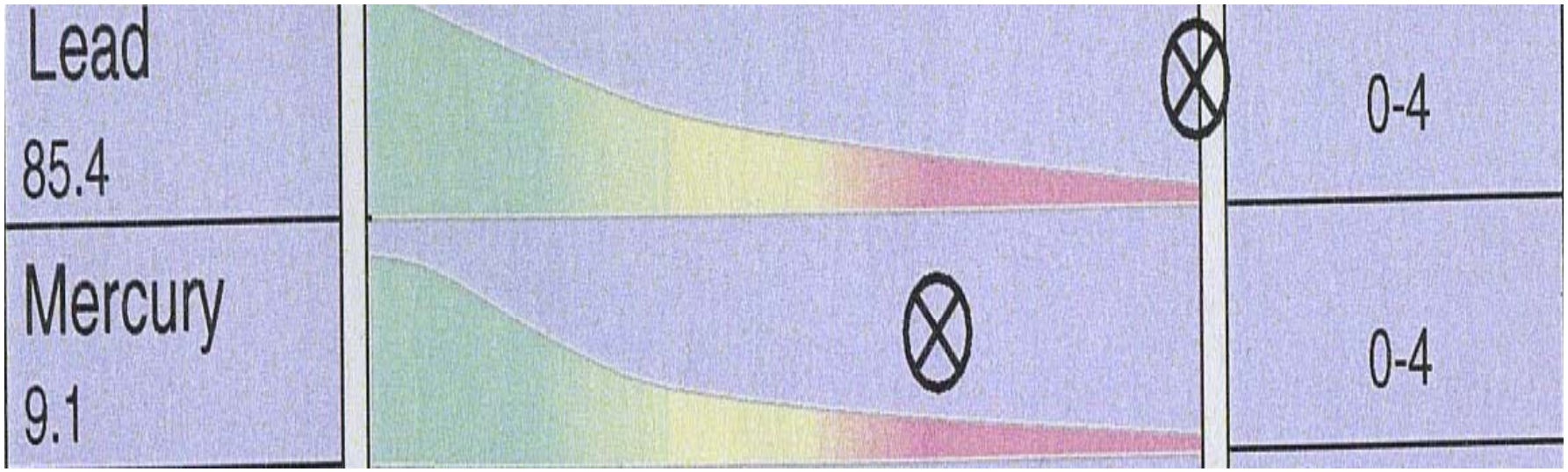
Elemental Analysis Hair



Patient: James Biddle

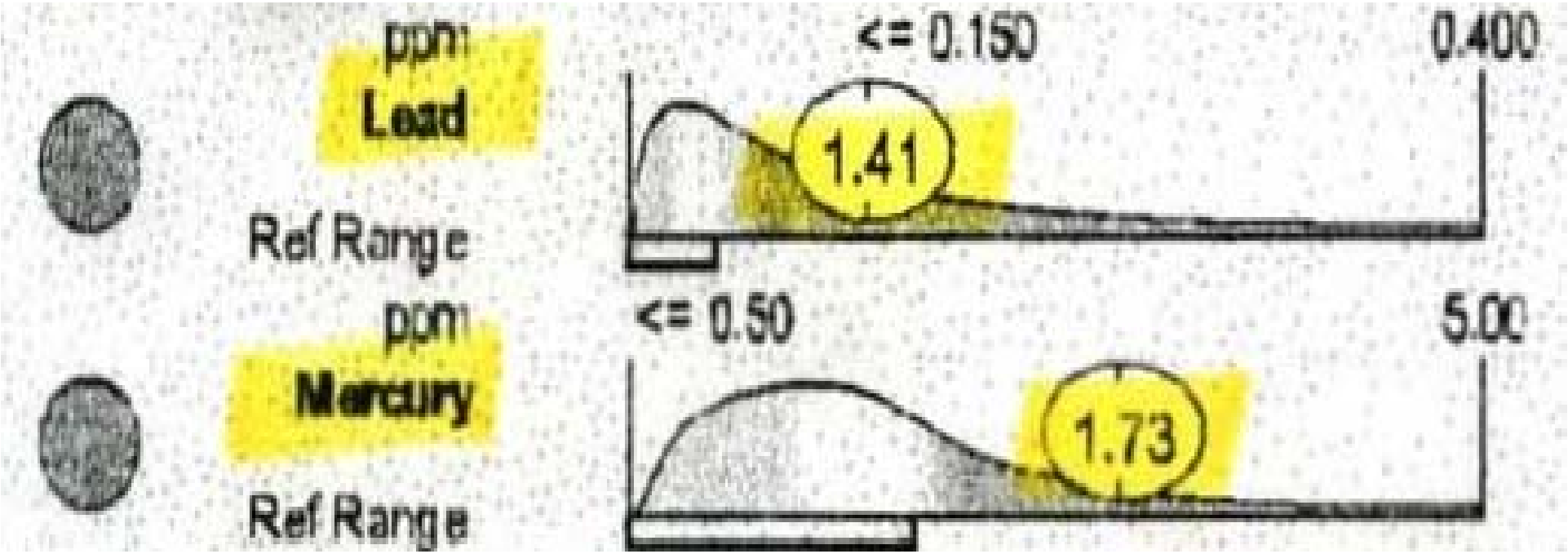
Collected: 10/17/1997

Analysis Urine (24 Hour)



Patient: James Biddle
Collected: 4/28/1998

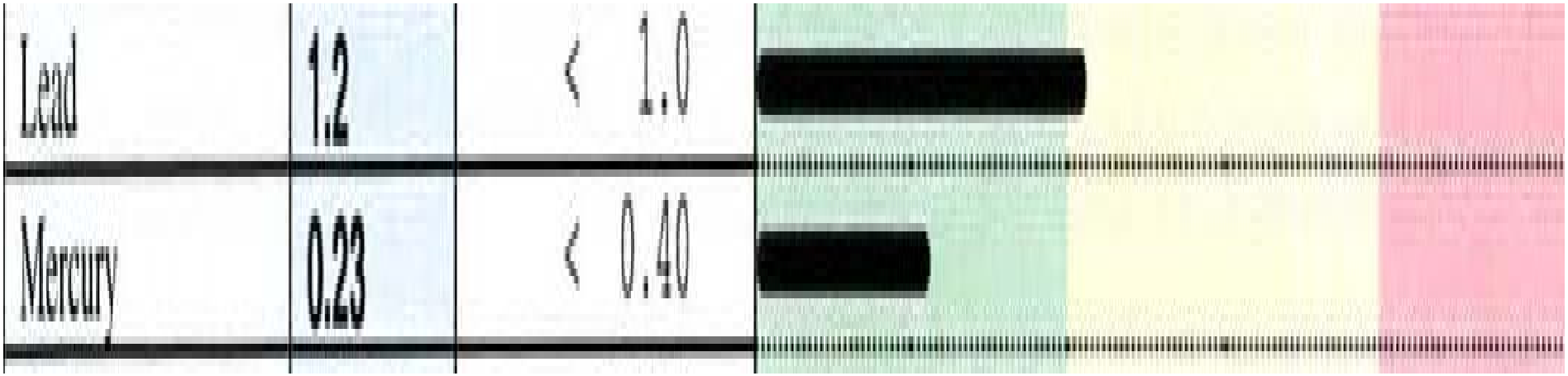
Elemental Analysis Hair



Patient: Mira Tieman

Age: 2 Collected: 3/2/2001

Elemental Analysis Hair



Patient: Mira Tieman

Age: 7 Collected: 6/27/2005

Interpretation of Abnormal Urinary Porphyrin Test Results:

Relationship to heme pathway defects and possible causes (with emphasis to toxic metals):

Abnormal Test Result -- Heme Pathway Defect -- Environmental Cause

- Uroporphyrin and Carboxyporphyrin -- Uroporphyrinogen decarboxylase –- **Arsenic**; organic chemicals.
- 5-carboxyporphyrin and Coproporphyrin- 6-carboxyporphyrin -- Uroporphyrinogen decarboxylase and Coproporphyrinogen oxidase -- **Mercury** ; organic chemicals.
- Precoproporphyrin4 (almost always accompanied by elevated coproporphyrin III) -- Uroporphyrinogen decarboxylase -- **Mercury** .
- Coproporphyrin III and Coproporphyrin I -- Coproporphyrinogen oxidase -- **Lead or Mercury**; Certain organic chemicals.
- Coproporphyrin I: Coproporphyrin III = Ratio > 1 -- Hepatobiliary dysfunction; PBG deaminase -- **Arsenic**.

Urine Porphyrins as Markers for Heavy Metals' Biological Effects:

- Woods JS, et al. Urinary porphyrin profiles as biomarkers of trace metal exposure and toxicity: studies on urinary porphyrin excretion patterns in rats during prolonged exposure to methyl mercury. *Toxicol Appl Pharmacol* 1991;110:464-76.
- Woods JS, et al. Porphyrin metabolism as indicator of metal exposure and toxicity. In: Goyer RA, Cherian MG, eds. *Handbook of Experimental Pharmacology.* Berlin: Springer-Verlag, 1995:19-52.
- Woods JS, et al. Urinary porphyrin profiles as a biomarker of mercury exposure: Studies on dentists with occupational exposure to mercury vapor. *Journal of Toxicology and Environmental Health* 1993;40:235-246.
- Woods JS, et al. Altered porphyrin metabolism as a biomarker of mercury exposure and toxicity. *Canadian Journal of Physiology and Pharmacology* 1996;74:210-215.

Coronary Artery Calcium Score:

"Hi There! What's your cardiac score?"

"Extensive coronary calcium detected by EBCT is associated with a significantly increased incidence of subsequent myocardial infarction, need for revascularization, and coronary death."

- Schermund, A. Unstable Coronary Plaque and its Relation to Coronary Calcium. *Circulation* 2001 Oct 2;104(14):1682-7.

Coronary Artery Calcium Score:

"Symptomatic males with extensive CSs carry an even higher risk for future events than other symptomatic males with advanced CAD."

- Mohlenkamp S, Essen, Germany. *Eur Heart J* 2003 May;24(9):845-54. Prognostic value of extensive coronary calcium quantities in symptomatic males-a 5-year follow-up study.

Coronary Artery Calcium Score:

"A high CS (> or = 1,000) on a screening EBT in an asymptomatic person portends a very high risk of an Hard Cardiac Event in the short term… greater than the risk associated with a severe perfusion abnormality on Myocardial Perfusion Imaging."

- Wayhs R, et al. High coronary artery calcium scores pose an extremely elevated risk for hard events. *J Am Coll Cardiol* 2002;39(2):225-30.

Coronary Artery Calcium Score:

"The EBT coronary calcium scores are greatly superior to the Framingham risk factors in predicting the measured proximal stenosis burden."

- Brown BG, U. of Washington, Seattle. *Am J Cardiol* 2001 Jul 19;88(2A):23E-26E.

CACS <u>vs</u> Stress Test: "Is this client's Chest Pain caused by Ischemia?"

Future Studies to see 'Vulnerable Plaque':

- **IVUS.**
- **Ultrafast "gated' MRI**.

"The disease of atherosclerosis is in the vessel wall, not the lumen."

"The disease process is far more dynamic than anybody ever realized."

➢ Steven Nissen MD, Cleveland Clinic.

Evaluating and Documenting the Risk and Extent of ASCVD

History and Physical Exam:

- Nutrition
- Lifestyle and Stress Management
- Nutraceuticals
- Pharmaceuticals
- Exercise
- Family history
- Risk factors as described

History and Physical Exam:

Nutrition:

- Have a standard form that looks at food for breakfast, lunch, dinner, and snack foods.
- Understand any special diets they have tried. Did it work, or why did it fail?
- Evaluate water and beverages.

History and Physical Exam:

Lifestyle:

- Are they work centered?
- Do they feel balanced between home responsibilities and career?
- Do they feel they have contributed to development of their kids?
- Do they have time for personal goals?
- How do they cope with stress?
- Understand their personality type.

Vascular Risk Factor Testing:

Blood Tests:

- Fasting Lipids, Glucose, Insulin, HbA1C.
- Lipoprotein (a).
- Cardio-CRP (high-sensitivity CRP).
- Homocysteine; Fibrinogen.
- Ferritin; 25-OH-Vitamin D level.
- Uric Acid; Rheumatology labs?
- Free Testosterone, E1/E2, DHT, etc.

Nocturnal Pulse-Oximeter to R/O Sleep Apnea!

Vascular Risk Factor Testing:

Lead, Cadmium, Arsenic, and Mercury:

1. Hair Analysis.
2. RBC Elements.
3. Chelation Challenge & Urine Elements.
4. Urine Porphyrins.

Coronary Artery Calcium Scoring:

"Should I be aggressive in managing this client's risk factors?"

Atherosclerosis Risk Factors:

Greenland, P. Major Risk Factors as Antecedents of Fatal and Nonfatal Coronary Heart Disease Events. *JAMA* 2003:290(7);891-904.

Hackman, D. Emerging Risk Factors for Atherosclerotic Vascular Disease: A Critical Review of the Evidence. *JAMA* 2003:290(7);891-904.

Magnus, P. The Real Contribution of the Major Risk Factors to the Coronary Epidemics: Time to End the "Only-50%" Myth. *Arch Intern Med* 2001:161;2657-60.

Ross R. Atherosclerosis-an inflammatory disease. *N Engl J Med* 1999 Jan 14;340(2):115-26.

Hypertension References:

He J. Long-term effects of **weight loss and dietary sodium** reduction on incidence of hypertension. *Hypertension* 2000 Feb;35(2):544-9. "The odds of hypertension was reduced by 77% (odds ratio 0.23) in the weight loss group and by 35% (odds ratio 0.65) in the sodium reduction group."

Stevens VJ. Long-term **weight loss** and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II. *Ann Intern Med* 2001 Jan 2;134(1):1-11. "Significant long-term reductions in blood pressure and reduced risk for hypertension can be achieved with even modest weight loss."

Witlin AG, meta-analysis. **Magnesium sulfate therapy** in preeclampsia and eclampsia. *Obstet Gynecol* 1998 Nov;92(5):883-9. "The evidence to date confirms the efficacy of magnesium sulfate therapy for women with eclampsia and severe preeclampsia."

Exercise:

Carnethon, M. Cardiorespiratory Fitness in Young Adulthood and Development of Cardiovascular Risk Factors. *JAMA* 2003 Dec 17;290(23): 3092-3100. "Bottom Quintile in CV fitness had 3-6 times the risk for later diabetes, HTN, or AMI."

Franklin B. Effects of a contemporary, exercise-based rehabilitation and cardiovascular risk-reduction program on coronary patients with abnormal baseline risk factors. *Chest* 2002 Jul;122(1):338-43. "Patients with the worst coronary risk factor profiles at baseline demonstrated the greatest improvements."

Lp(a):

Boonmark NW. The lysine-binding function of Lp(a). *Clin Genet.* 1997 Nov;52(5):355-60.

Caplice NM, Mayo Clinic. Lipoprotein (a) binds and inactivates tissue factor pathway inhibitor: a novel link between lipoproteins and thrombosis. *Blood* 2001 Nov 15;98(10):2980-7. "These data suggest a novel mechanism whereby Lp(a) through its apo(a) moiety may promote thrombosis by binding and inactivating TFPI."

Carlson LA. Pronounced lowering of serum levels of lipoprotein Lp(a) in hyperlipidaemic subjects treated with nicotinic acid. *J Intern Med.* 1989 Oct;226(4):271-6.

Gurakar A. Levels of lipoprotein Lp(a) decline with neomycin and niacin treatment. *Atherosclerosis.* 1985 Nov;57(2-3):293-301.

Lawn R. Lipoprotein(a) in Heart Disease *Scientific American* 1992 June, 54-60. Stanford.

Rath M, Niendorf. Detection and quantification of lipoprotein(a) in the arterial wall of 107 coronary bypass patients. *Arteriosclerosis.* 1989 Sep-Oct;9(5):579-92. "Lp(a) accumulates in the arterial wall,

partly in the form of lipoprotein-like particles, predominantly located extracellularly, therefore contributing to plaque formation."

Rath M, Pauling L. Hypothesis: lipoprotein(a) is a surrogate for ascorbate. *Proc Natl Acad Sci.* 1990 Aug;87(16):6204-7. "Properties of Lp(a) that are shared with ascorbate, are the acceleration of wound healing and other cell-repair mechanisms, the strengthening of the extracellular matrix (e.g., in blood vessels), and the prevention of lipid peroxidation."

Rath M, Pauling L. Solution to the Puzzle of Human Cardiovascular Disease: Its Primary Cause is Ascorbate Deficiency Leading to the Deposition of Lipoprotein(a) and Fibrinogin/Fibrin in the Vascular Wall. *J Orthomolecular Med* 1991; 6(3&4):125-134 & 139-143.

Singh RB. Serum concentration of lipoprotein(a) decreases on treatment with hydrosoluble coenzyme Q10 in patients with coronary artery disease. *Int J Cardiol.* 1999 Jan;68(1):23-9.

Homocysteine:

Li H, Stony Brook, NY. Homocysteine induces 3-hydroxy-3-methylglutaryl coenzyme a reductase in vascular endothelial cells: a mechanism for development of atherosclerosis? *Circulation* 2002 Mar 5;105(9):1037-43. "an unexpected link between Hcy and cholesterol dysregulation … the possible role of Hcy-induced oxidative stress."

Spence JD. Vitamin Intervention For Stroke Prevention trial: an efficacy analysis. *Stroke* 2005 Nov;36(11):2404-9. "In the era of folate fortification, B12 plays a key role in vitamin therapy for total homocysteine."

Green R. Vitamin B-12 deficiency is the dominant nutritional cause of hyperhomocysteinemia in a folic acid-fortified population. *Clin Chem Lab Med* 2005;43(10):1048-51. "…in the post-folic acid fortification era, low vitamin B(12) status has become the dominant nutritional determinant of hyperhomocysteinemia."

Rasouli ML. Plasma homocysteine predicts progression of atherosclerosis. *Atherosclerosis* 2005 Jul;181(1):159-65. "Individuals with elevated HCY (> or =12 micromol/L) demonstrated a mean increase in CC progression of 35% per year, while those with HCY <12 micromol/L (median) progressed at 17% per year (p = 0.0008)."

Inflammation and CRP:

Pasceri V. Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation* 2000;102:2165-8. "CRP induces adhesion molecule expression in human endothelial cells … CRP may play a direct role in promoting the inflammatory component of atherosclerosis.

Mulvihill NT. Inflammation in acute coronary syndromes. *Heart* 2002;87(3): 201-204. "Extensive evidence supports a pathogenic role for both local and systemic inflammation in acute coronary syndromes."

Ford ES, CDC, Atlanta, GA. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. *Epidemiology* 2002;13(5)561-8. "Exercise decreases CRP…RR = 0.53 for vigorous activity."

Zhu J. Prospective study of pathogen burden and risk of myocardial infarction or death. *Circulation* 2001 Jan 2;103(1):45-51. "The results suggest that infection plays an important role in incident MI or death and that the risk posed by infection is independently related to the pathogen burden."

George J, Sheba Medical Center, Israel. The prediction of coronary atherosclerosis employing artificial neural networks. *Clin Cardiol* 2000 Jun;23(6):453-6. "The most effective parameters predictive of coronary vessel involvement were (in decreasing order of importance) antibodies to oxLDL, to cardiolipin, to CMV, to Chlamydia pneumonia, and to beta 2-glycoprotein I (beta 2GPI). Although important in the prediction of vessel occlusion, hyperlipidemia, hypertension, CRP levels, and diabetes were less accurate."

Testosterone:

Phillips GB. Are major risk factors for myocardial infarction the major predictors of degree of coronary artery disease in men? *Metabolism.* 2004 Mar;53(3):324-9. "…in men selected for coronary arteriography, age, HDL-C, and FT may be stronger predictors of degree of CAD than are blood pressure, cholesterol, diabetes, smoking, and BMI."

Trans-Fats & Vascular risk:

Ascherio A. Harvard . **Trans-fatty acids** intake and risk of myocardial infarction. *Circulation* 1994 Jan;89(1):94-101. "Intake of margarine--the major source of trans-isomers--was significantly associated with risk of myocardial infarction. These data support the hypothesis that intake of partially-hydrogenated vegetable oils may contribute to the risk of myocardial infarction."

Baylin A. Harvard. High 18:2 **trans-fatty acids** in adipose tissue are associated with increased risk of nonfatal acute myocardial infarction in costa rican adults. *J Nutr* 2003 Apr;133(4):1186-91. "High 18:2 trans-FA in adipose tissue are associated with increased risk of MI. Because the use of hydrogenated oils is increasing worldwide, consumers should be aware of the harmful effects of products containing partially hydrogenated oils."

Institute of Medicine expert panel. **No Safe Level of Trans Fats**. Center for Science in the Public Interest 2002 July 10; "There is no level of trans fatty acids that is safe to consume."

Pedersen JI.. Univ of Oslo. Adipose tissue fatty acids and risk of myocardial infarction--a case-control study. *Eur J Clin Nutr* 2000 Aug;54(8):618-25. "**Trans fatty acids**, linoleic and alpha-linolenic acid were intercorrelated and associated with increased risk. It is suggested that the increased risk may be connected to trans fatty acids or to some other factor associated with margarine consumption."

Stender S. [The importance of trans-fatty acids for health. Update 2001][Article in Danish] *Ugeskr Laeger* 2001 Apr 23;163(17):2349-53. "The Danish Nutrition Council recommends that the addition of industrially-produced trans fatty acids to food stuffs ceases before 2005 and until then that declaration of the content in foodstuffs becomes mandatory."

Tavani A. Milano, Italy. **Margarine intake** and risk of nonfatal acute myocardial infarction in Italian women. *Eur J Clin Nutr* 1997 Jan;51(1):30-2. "Medium or high intake of margarine was associated with an increased risk of AMI. The association with margarine could explain about 6% of AMI in this population of Italian women."

Willett WC. Harvard. Intake of **trans fatty acids** and risk of coronary heart disease among women. *Lancet* 1993 Mar 6;341(8845):581-5. "Intakes of foods that are major sources of trans isomers (margarine, cookies [biscuits], cake, and white bread) were each significantly associated with higher risks of CHD. These findings support the hypothesis that consumption of partially hydrogenated vegetable oils may contribute to occurrence of CHD."

Nuts, Legumes, Alcohol and Vascular Risk:

Albert CM, Brigham and Women's Hosp. **Nut consumption** and decreased risk of sudden cardiac death in the Physicians' Health Study. *Arch Intern Med* 2002 Jun 24;162(12):1382-7. "the inverse association between nut consumption and total coronary heart disease death is primarily due to a reduction in the risk of sudden cardiac death."

Albert CM, Brigham and Women's Hosp. Moderate **alcohol consumption** and the risk of sudden cardiac death among US male physicians. *Circulation* 1999 Aug 31;100(9):944-50. "Men who consumed light-to-moderate amounts of alcohol (2 to 6 drinks/wk) had a significantly reduced risk of SCD compared with those who rarely or never consumed alcohol."

Bazzano LA, Tulane Univ. **Legume consumption** and risk of coronary heart disease in US men and women: NHANES I. *Arch Intern Med* 2001 Nov 26;161(21):2573-8 "Our study indicates a significant inverse relationship between legume intake and risk of CHD."

Hu FB, Harvard. Frequent **nut consumption** and risk of coronary heart disease in women: prospective cohort study. *BMJ* 1998 Nov 14;317(7169):1341-5. "Frequent nut consumption was associated with a reduced risk of both fatal coronary heart disease and non-fatal myocardial infarction."

Fish-Flax and Lipids/Vascular Risk:

Albert CM, Brigham and Women's Hosp. **Fish consumption** and risk of sudden cardiac death. *JAMA* 1998 Jan 7;279(1):23-8. "consumption of fish at least once per week may reduce the risk of sudden cardiac death in men."

Albert CM, Brigham and Women's Hosp. Blood levels of **long-chain n-3 fatty acids** and the risk of sudden death. *N Engl J Med* 2002 Apr 11;346(15):1113-8. "The relative risk of sudden death was significantly lower among men with N-3 levels in the third quartile (RR 0.28) and the fourth quartile (RR 0.19)."

Daviglus ML, Northwestern Univ. **Fish consumption** and the 30-year risk of fatal myocardial infarction. *N Engl J Med* 1997 Apr 10;336(15):1046-53. "an inverse association between fish consumption and death from coronary heart disease, especially nonsudden death from myocardial infarction."

Iron Overload:

Baykan M, Trabzon, Turkey. Iron status and its relationship with lipid peroxidation in patients with acute myocardial infarction. *Acta Cardiol* 2001 Oct;56(5):277-81. "There was an association of higher iron status with increased lipid peroxidation in patients with myocardial infarction."

Jiang, R. Harvard School of Public Health. Body Iron Stores in Relation to Risk of Type 2 Diabetes in Apparently Healthy Women. *JAMA* 2004 Feb 11;291(6):711-17. "Higher iron stores (reflected by an elevated ferritin…) are associated with an increased risk of type 2 diabetes in healthy women ..." RR = 2.44 for 5th quintile.

Lakka TA, Kuopio, Finland. Higher levels of conditioning leisure time physical activity are associated with reduced levels of stored iron in Finnish men. *Am J Epidemiol* 1994 Jul 15;140(2):148-60. "a reduction in stored iron levels could be one mechanism through which … physical activity decreases the risk of coronary heart disease."

Roest M, Utrecht U., The Netherlands. Heterozygosity for a hereditary hemochromatosis gene is associated with cardiovascular death in women. *Circulation* 1999 Sep 21;100(12):1268-73. "inherited

variation in iron metabolism is involved in cardiovascular death in postmenopausal women especially in women already carrying classic risk factors."

Salonen JT, Kuopio, Finland. High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. *Circulation* 1992 Sep;86(3):803-11. "An elevated serum ferritin was a strong risk factor for acute myocardial infarction in all multivariate models."

Lead Toxicity:

Gump BB. *Neurotoxicol Teratal* 2005 27(4):655-65. Prenatal and early childhood blood lead levels and cardiovascular functioning in 9(1/2) year old children. "Higher Cord Blood Lead levels (but still below 10 mcg/dl) were associated with increased SVR and decreased SV upon stress testing at age 9 ½, indicating clinically-significant increased afterload."

Menke, A, *Circulation* 2006;114:1388-1394. Blood Lead Below 0.48 µmol/L (10 µg/dL) and Mortality Among US Adults.

Muntner P, Tulane-Johns Hopkins-Research Triangle Park. Blood lead and chronic kidney disease in the general U.S. population. *Kidney Int* 2003 Mar;63(3):1044-1050. "exposure to lead, even at low levels, is associated with CKD."

Nash D, U of Md School of Med. Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. *JAMA* 2003 Mar 26;289(12):1523-32. "These results provide support for continued efforts to reduce lead levels in the general population, especially women."

Vupputuri S, Research Triangle Park, NC. *Hypertension* 2003 Mar;41(3):463-8. Blood lead level is associated with elevated blood pressure in blacks. "Increased levels of blood lead remain an important environmental risk factor for elevated blood pressure in blacks."

Weisskopf, M. *Circulation* 2009; 120: 1056-64. A Prospective Study of Bone Lead Concentration and Death from All Causes, Cardiovascular Diseases, and Cancer in the Dept of VA Normative Aging Study. "RR of lowest- vs highest-tertile of patella bone lead: All-Cause = 2.2; Cardiovascular = 5.63; Ischemic Heart Disease Mortality = 8.37. No association with cancer. Blood lead had no mortality associations."

Cadmium Toxicity:

Luoma P, Finland. Antioxidants, infections and environmental factors in health and disease in northern Finland. *Int J Circumpolar Health* 1998 Jul;57(2-3):109-13. "Our earlier studies indicate that people living in northeastern Finland, west of smelters in Kola Peninsula may be exposed to heavy metals such as cadmium and mercury. Blood cadmium was related to blood pressure and was high in men with arterial hypertensive disease."

Voors AW. Liver cadmium levels in North Carolina residents who died of heart disease. *Bull Environ Contam Toxicol* 1977 Jun;17(6):692-6. "Using data from an autopsy series, we found a strong positive correlation between liver concentration of cadmium and death from heart disease. In view of recent experiments reported in the literature, the possibility that a low level of cadmium has a toxic effect on the cardiac conduction system is supported."

Yang YR, China. Studies of five microelement contents in human serum, hair, and fingernails correlated with aged hypertension and coronary heart disease. *Biol Trace Elem Res* 2003 May;92(2):97-104. "Comparing aged patients with HTN and CAD to aged healthy controls, the

cadmium contents in serum of the diseased group were significantly higher than that of the healthy group ($p<0.01$)."

Arsenic Toxicity:

Chang CC, Taiwan. Ischemic heart disease mortality reduction in an arseniasis-endemic area in southwestern Taiwan after a switch in the tap-water supply system. *J Toxicol Environ Health A.* 2004 Sep 10;67(17):1353-61. "Arsenic has been identified as a major contributing risk factor for development of blackfoot disease (BFD), a unique peripheral vascular disease that was endemic to the southwestern coast of Taiwan. CHD declined gradually for approximately 17 to 20 yr following cessation of consumption of high-arsenic artesian well water."

Tseng CH, Taiwan. Long-term arsenic exposure and ischemic heart disease in arseniasis-hyperendemic villages in Taiwan. *Toxicol Lett.* 2003 Jan 31;137(1-2):15-21. "The odds ratios (95% confidence intervals) for IHD were 1.60 (0.48, 5.34), and 3.60 (1.11, 11.65), respectively, for those with Cumulative arsenic exposure of 0.1-14.9 and >15.0 mg/L-years, when compared with those lacking drinking water exposure to arsenic."

Wang CH, Taiwan. Biological gradient between long-term arsenic exposure and carotid atherosclerosis. *Circulation* 1977 2002 Apr 16;105(15):1804-9. "Carotid atherosclerosis RR = 3.1 for a cumulative arsenic exposure of > 20 mg/L-years compared with those without exposure."

Mercury Toxicity:

Frustaci A, Rome, Italy. Marked elevation of myocardial trace elements in idiopathic dilated cardiomyopathy compared with secondary cardiac dysfunction. *J Am Coll Cardiol* 2000;35(3):819-20. "A large, significant increase of myocardial TE is present in IDCM but not in secondary cardiac dysfunction. The increased concentration of TE in pts with IDCM may adversely affect mitochondrial activity and myocardial metabolism and worsen cellular function."

Guallar E, Johns Hopkins. Mercury, fish oils, and the risk of myocardial infarction. *N Engl J Med* 2002 Nov 28;347(22):1747-54. ""Toenail mercury level was directly associated with the risk of myocardial infarction, with RR=2.16 for highest vs lowest quintile."

Rissanen T, Kuopio, Finland. Fish oil-derived fatty acids, DHA and EPA, and the risk of acute coronary events: the Kuopio ischaemic heart disease risk factor study. *Circulation* 2000 Nov 28;102(22):2677-9. "Fish-oil derived fatty acids reduce the risk of acute coronary events. However, a high mercury content in fish could attenuate this protective effect."

Salonen JT, Kuopio, Finland. Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men. *Circulation* 1995 Feb 1;91(3):645-55. "…a high intake of mercury … and the consequent accumulation … are associated with an excess risk of AMI as well as death (from) any cause … (which) may be due to the promotion of lipid peroxidation by mercury."

Sorensen N, Faroe Islands. Prenatal methylmercury exposure as a cardiovascular risk factor at seven years of age. *Epidemiology* 1999 Jul;10(4):370-5. "1,000 children from the Faroe Islands ... at 7 years, diastolic and systolic BP increased by 13.9 and 14.6 mmHg respectively when cord blood mercury increased from 1 to 10 mcg/liter."

Virtanen, JK et al. Kuopio, Finland. Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland. *Arterioscler Thromb Vasc Biol* 2005;25(1):228-33.

Porphyrins:

Woods JS, et al. Urinary porphyrin profiles as biomarkers of trace metal exposure and toxicity: studies on urinary porphyrin excretion patterns in rats during prolonged exposure to methyl mercury. *Toxicol Appl Pharmacol* 1991;110:464-76.

Woods JS, et al. Porphyrin metabolism as indicator of metal exposure and toxicity. In: Goyer RA, Cherian MG, eds. *Handbook of Experimental Pharmacology*. Berlin: Springer-Verlag, 1995:19-52.

Woods JS, et al. Urinary porphyrin profiles as a biomarker of mercury exposure: Studies on dentists with occupational exposure to mercury vapor. *Journal of Toxicology and Environmental Health* 1993;40:235-246.

Woods JS, et al. Altered porphyrin metabolism as a biomarker of mercury exposure and toxicity. *Canadian Journal of Physiology and Pharmacology* 1996;74:210-215.

Coronary Artery Calcium Scores:

Brown BG, U. of Washington, Seattle. *Am J Cardiol* 2001 Jul 19;88(2A):23E-26E. "The EBT coronary calcium scores are greatly superior to the Framingham risk factors in predicting the measured proximal stenosis burden."

Mohlenkamp S. *Eur Heart J* 2003 May;24(9):845-54. Prognostic value of extensive coronary calcium quantities in symptomatic males-a 5-year follow-up study. "Symptomatic males with extensive CSs carry an even higher risk for future events than other symptomatic males with advanced CAD."

Schermund, A, et al. Unstable Coronary Plaque and its Relation to Coronary Calcium. *Circulation* 2001 Oct 2;104(14):1682-7. "Extensive coronary calcium detected by EBCT is associated with a significantly increased incidence of subsequent myocardial infarction, need for revascularization, and coronary death."

Wayhs R, et al. High coronary artery calcium scores pose an extremely elevated risk for hard events. *J Am Coll Cardiol* 2002;39(2):225-30. "A high CS (> or = 1,000) on a screening EBT in an asymptomatic person portends a very high risk of an Hard Cardiac Event in the short term… greater than the risk associated with a severe perfusion abnormality on Myocardial Perfusion Imaging."

Less Angioplasties:

Am J Cardiol 2002 Mar 1;89(5):567-70. Need for a moratorium on percutaneous transluminal coronary angioplasty in stable coronary artery disease. Nash DT. PMID: 11867043.

Dietary Patterns and Vascular Health:

Amano Y. Correlation between dietary glycemic index and cardiovascular disease risk factors among Japanese women. *Eur J Clin Nutr.* 2004 Nov;58(11):1472-8. "Calculated dietary GI and GL were positively associated with CVD risk factors among the Japanese women who consumed white rice as a staple food."

Bazzano LA. Dietary intake of fruits and vegetables and risk of cardiovascular disease. *Curr Atheroscler Rep.* 2003 Nov;5(6):492-9. "Evidence-based strategies that reduce cardiovascular events in those with CVD include reduction in saturated fat and substitution with unsaturated fats. Individuals who have suffered a myocardial infarction may also benefit from adopting a Mediterranean type diet and increasing intake of omega 3 fats."

Beulens JW. High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: a population-based follow-up study. *J Am Coll Cardiol.* 2007 Jul 3;50(1):14-21. Epub 2007 Jun 18. "Among overweight women, glycemic load was associated with CVD (RR =1.78)."

Liu S. Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health Study. *Am J Clin Nutr.* 2000 Oct;72(4):922-8. (Higher fruit and vegetable intake for extreme quintiles had a RR = 0.68 lower risk for CVD and 0.62 lower risk of MI.)

Lockheart MS. Dietary patterns, food groups and myocardial infarction: a case-control study. *Br J Nutr.* 2007 Aug;98(2):380-7. Epub 2007 Mar 29. "A dietary pattern emphasising nutrient-rich plant foods and high-fat fish and low in trans-fatty acids was associated with decreased risk of MI among Norwegians."

Mead A. Dietetic guidelines on food and nutrition in the secondary prevention of cardiovascular disease - evidence from systematic reviews of randomized controlled trials (second update, January 2006). *J Hum Nutr Diet.* 2006 Dec;19(6):401-19. (supports Mediterranean diet, more omega-3s, less saturated fats.)

Trichopoulou A. Vegetable and fruit: the evidence in their favour and the public health perspective. *Int J Vitam Nutr Res.* 2003 Mar;73(2):63-9. "…the intake of vegetables and fruits reduces the risk of CVD."

Emotions and Stress:

Ornish D. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA* 1998 Dec 16;280(23):2001-7. "More regression of coronary atherosclerosis occurred after 5 years than after 1 year in the experimental group."

von Kanel R, Zurich. Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis: a biobehavioral pathway to coronary artery disease? *Psychosom Med* 2001 Jul-Aug;63(4):531-44. "psychological measures to varying extent are associated with characteristic patterns of coagulation and fibrinolysis activity."

Statins:

Ornish D. Statins and the Soul of Medicine. *Am J Cardiology* - Editorial: Jun 1, 2002; V89:1286-90.

Wright JM, "Are Lipid-Lowering Guidelines Evidenced-Based?" *Lancet.* 2007;369: 168-9.

F.T. Guilford, MD

Glutathione in metals detoxification

Bio

Dr. Guilford has been in clinical practice since 1979. He began using complementary medical approaches into his practice beginning in the early 1980's. The concept that chronic inflammation functions as a causative factor in illness became apparent while he was director of a laboratory specializing in in-vitro allergy and viral immunology testing (1982 -1992). He began using metal detoxification methods in 1995 and research into the toxicity of mercury lead to the observation that glutathione is a critical component of the defense against heavy metals. In 2002 he received ACAM's Norman C Clark Award for Innovation and presented a lecture, "Mercury, the Great Imitator: Perspectives on the Various Presentations Related to Mercury, Methods of Diagnosis and an Approach to Therapy." In 2004, his interest in glutathione led to the formulation of a liposomal glutathione product, whose antioxidant and anti-atherogenic properties have been reviewed in an article published in the journal Atherosclerosis, Dec 2007.

Lecture Overview

Glutathione is part of the basic design pattern for cell protection. The advantage of glutathione over other antioxidants is that it works with enzymes. For example, the enzyme glutathione peroxidase has been found to be imbedded naturally in LDL and HDL cholesterol and serves a major role in the prevention of the oxidation of these lipoproteins as well as the lipoproteins associated with cell membranes. Glutathione also plays a key role in detoxification. The ability of glutathione to conjugate with toxins such as mercury has been shown to be a major component of the mechanism for removal of metals from cells. As glutathione also functions as a cell signal in the immune system, it may serve as a critical component linking toxicity from sources such as metals to immune dysfunction. The relationships of heavy metals such as mercury to immune function and diseases disease states will also be reviewed.

Contact Information

F.T. Guilford, MD
555 Bryant St. #305
Palo Alto, CA 94301

drg@readisorb.com

American College for Advancement in Medicine
Chelation Therapy Workshop
November 4-5, 2009
Las Vegas, Nevada

The Role of Glutathione in Metal Related Vascular Disease

Tim Guilford, MD

Your Energy Systems, llc

www.readisorb.com

Liposomal Glutathione: Anti-oxidant, Anti-atherogenic Properties

Rosenblat M, Volkova N, Coleman R, Aviram M. Anti-oxidant and anti-atherogenic properties of liposomal glutathione: studies in vitro, and in the atherosclerotic apolipoprotein E-deficient mice. Atherosclerosis. 2007;195(2):e61-8. PubMed; 17588583.

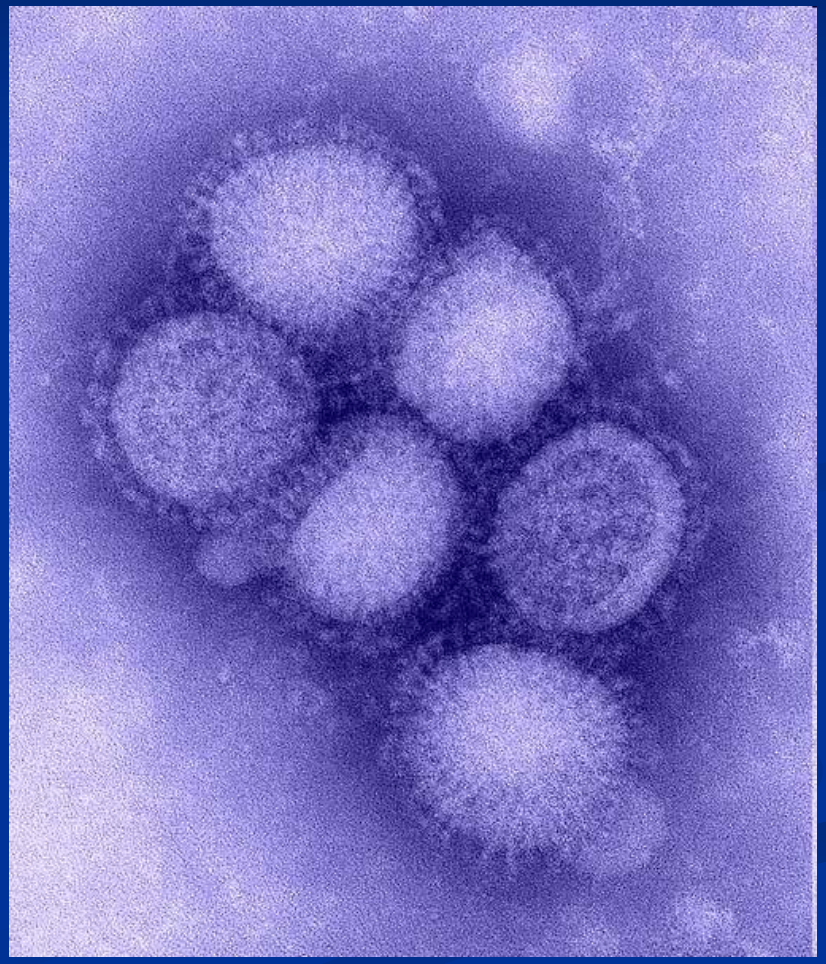
Glutathione Functions

- Antioxidant
- Detoxifying
  - Binds to toxins to facilitate removal
  - Uses enzyme Glutathione-s-transferase (GST)
    - Mercury PMID: 18560528
    - Mycotoxins PMID: 8910329
- Cell Signal

  Immune cells

Influenza and Cardiac Disease

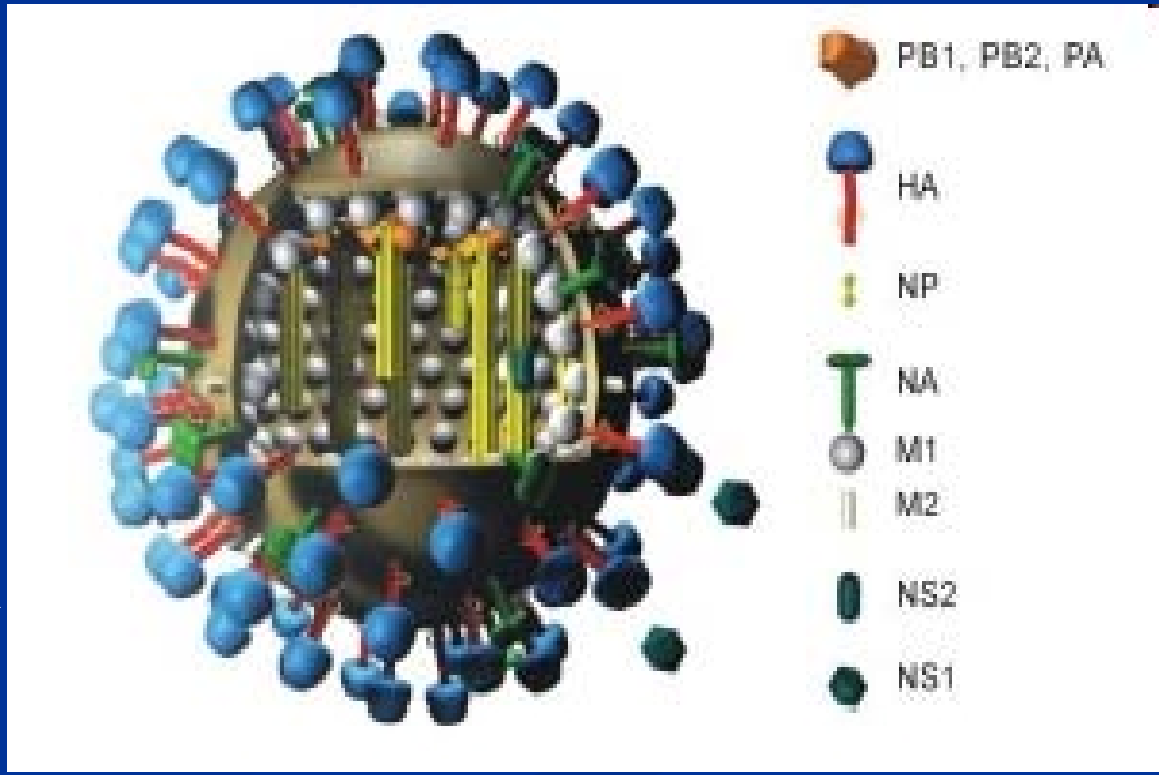
- It has been estimated that during more virulent influenza episodes roughly twice as many individuals die of cardiac causes than from influenza pneumonia.
- Influenza as an Oxidation Stress Disease



Madjid M, Casscells SW. Of birds and men: cardiologists' role in influenza pandemics. Lancet. 2004;364(9442):1309. Cited in PubMed; 15474125.

Glutathione Prevents Influenza Virus Replication

- Maintaining glutathione in cells prevents viral replication



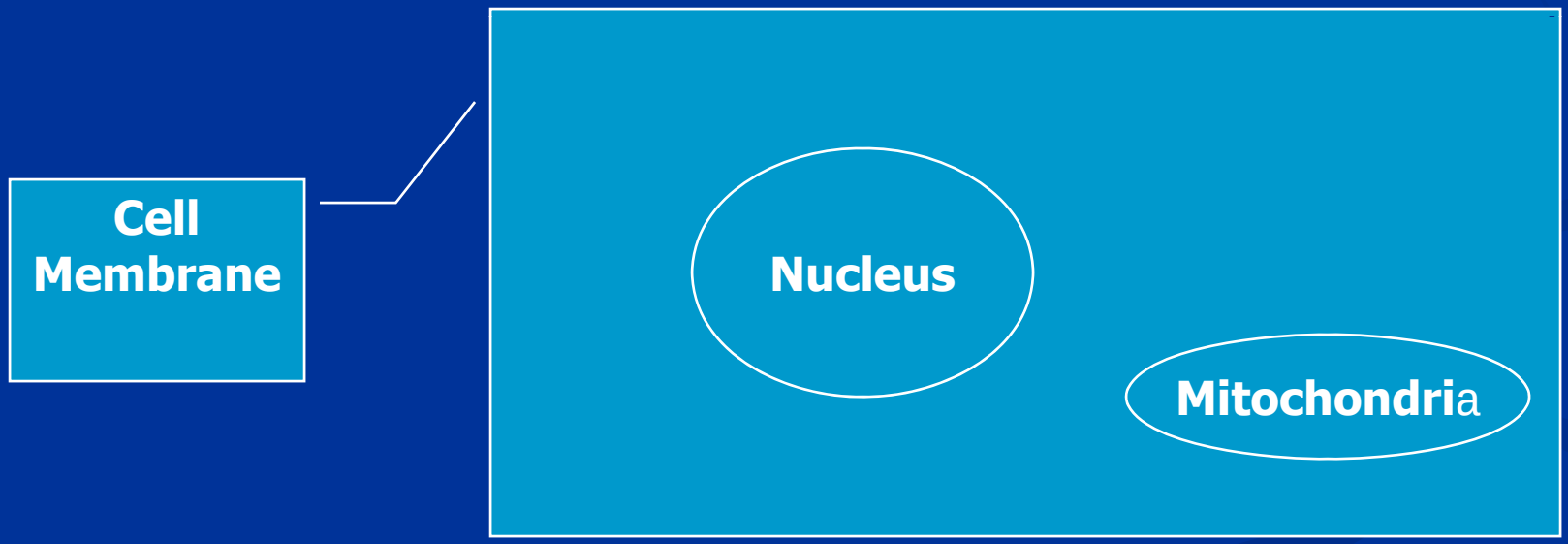
Cai J, Chen Y, Seth S, Furukawa S, Compans RW, Jones DP. Inhibition of influenza infection by glutathione. Free radical biology & medicine. 2003;34(7):928-36. Cited in PubMed; 12654482.

Diseases Associated with Low Glutathione

- Autism
- Cystic fibrosis &Lung disease (asthma)
- Liver disease
- Parkinson's disease
- Alzheimer's disease
- Atherosclerosis: Heart attack and Stroke
- Diabetes
- Viral disease both chronic and acute

Body and Cell Function: Role of Mitochondria -

Uses O_2 In the Production of Energy

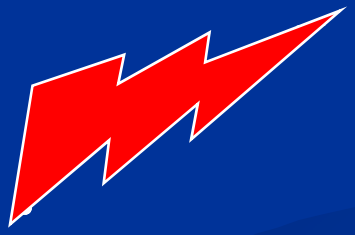


Vital Dust, De Duve, 1995

ISBN 0-465-0944-3

However,…
Energy Production also Makes Free Radicals of Oxygen which are Reactive Oxygen Species (ROS)

- And ROS Cause …
  - Oxidative Stress



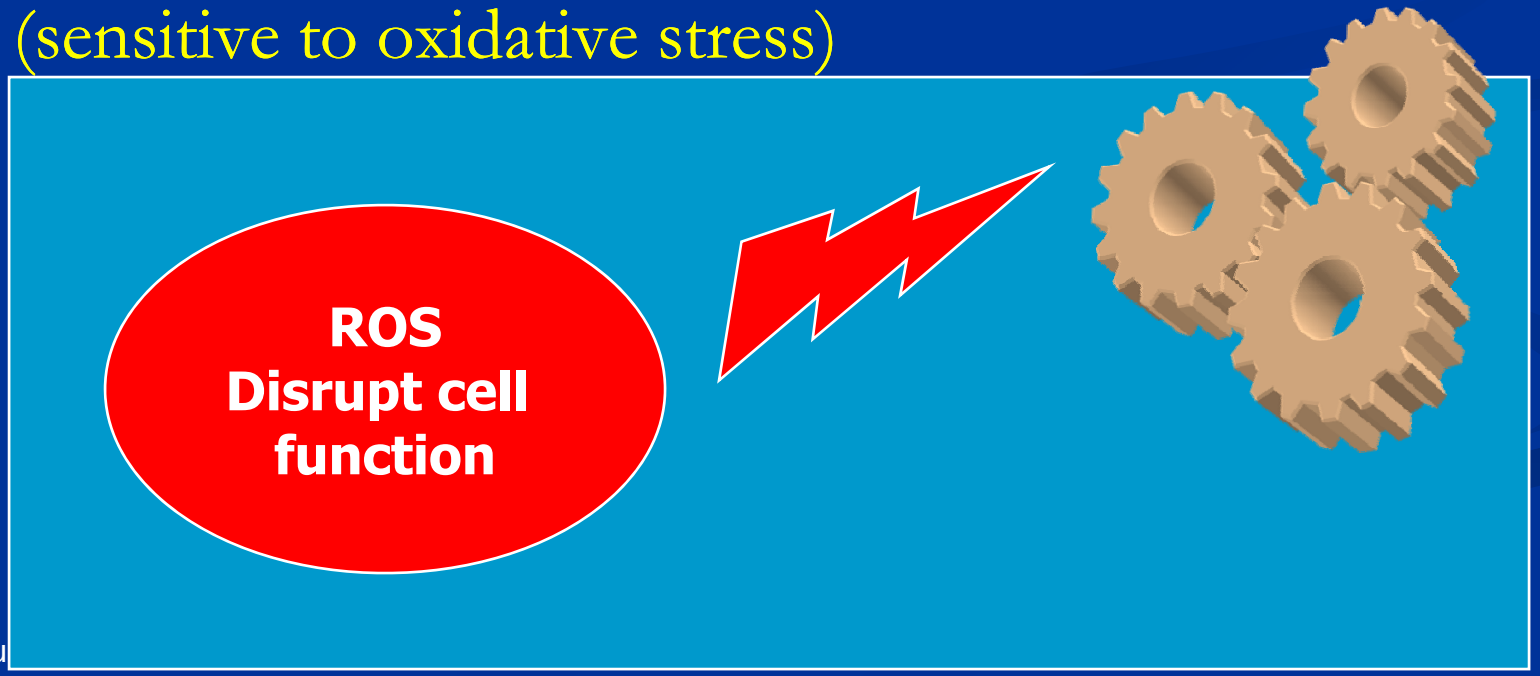
Oxidative Stress Occurs in Cells

- Membranes of cells and of the organelles inside cells are damaged by oxidative stress
- Membranes are made of lipids (fatty acid chains, phospholipids, and cholesterol)

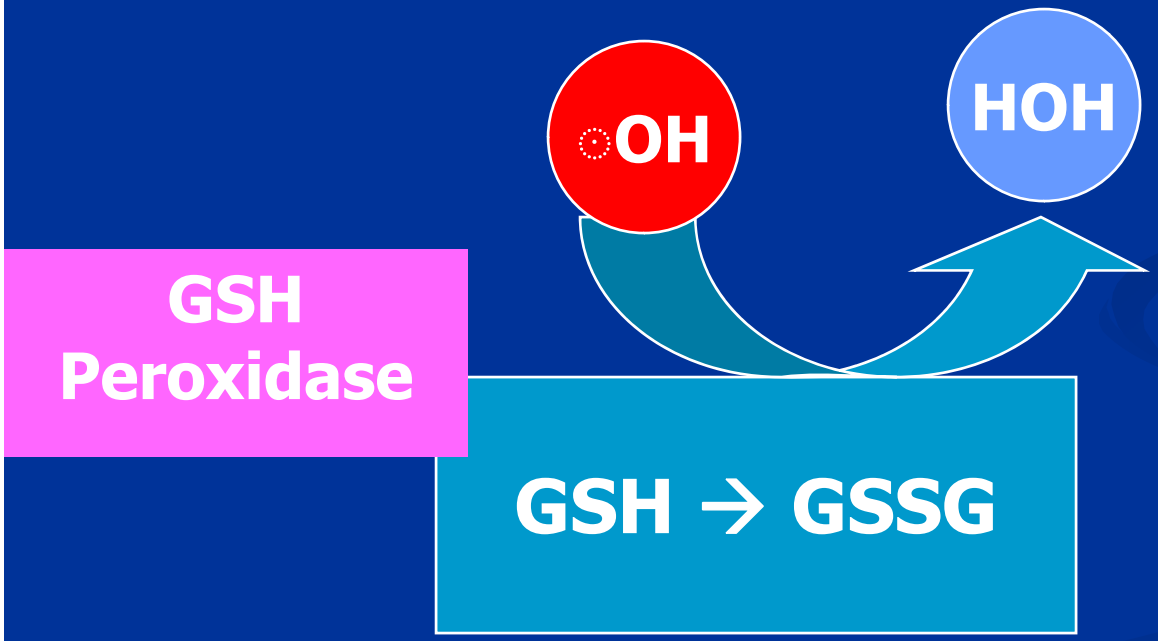
Lipid Peroxidation

- Saturated Fatty Acid C-C-C-C-C-C
- Unsaturated Fatty Acid C-C=C-C=C-C

(sensitive to oxidative stress)



Glutathione the key player in removing free radicals in human cells



Membrane Peroxidation

Membrane Disruption

Altered Structure **Altered Function**

Redox-Active Transition Metal Ions and Atherosclerosis

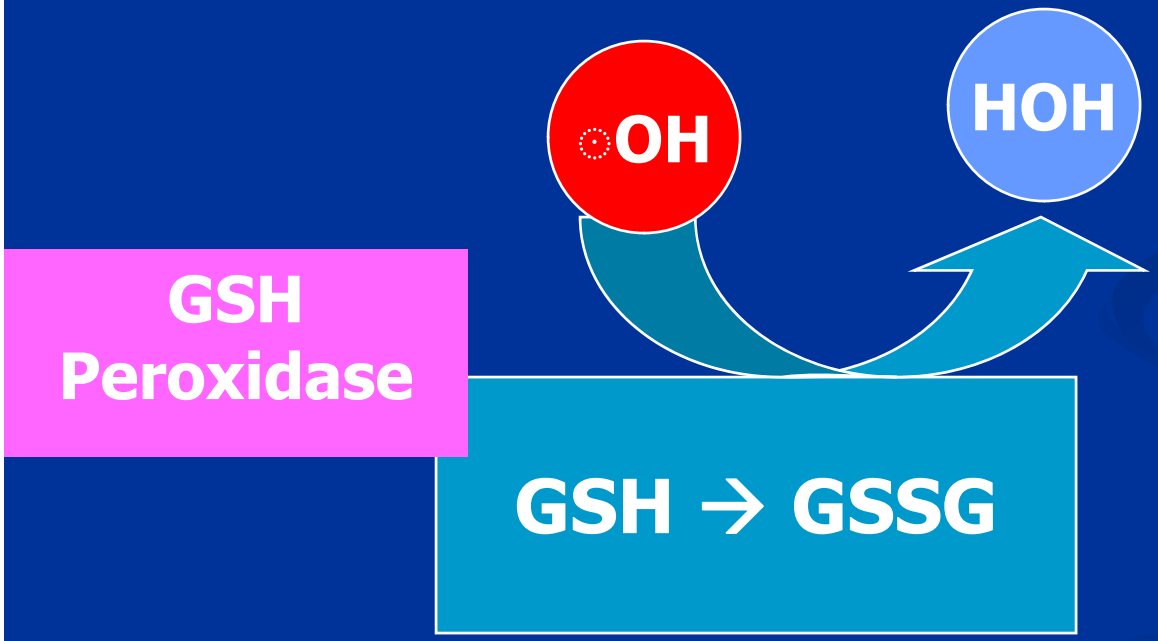
- Iron
- Copper
- Lead
- Mercury

- Increase oxidation stress

Iron: Metal Catalyzed Fenton Reaction

- the Fenton Reaction
- $$Fe_2^{+} + H_2O_2 \rightarrow Fe_3^{+} + OH\cdot + OH^{-}$$
- Because it is involved in the generation of free radicals, H2O2 is included in the general term reactive oxygen species.

Glutathione the key player in removing free radicals in human cells



Toxic metals deplete GSH

- Metals, including iron, copper, chromium, and vanadium undergo redox cycling, while cadmium, mercury, and nickel, as well as lead, deplete glutathione, resulting in the production of ROS as $\bullet O^-$, H_2O_2, and $\bullet OH$ radicals. As a consequence, enhanced lipid peroxidation, DNA damage, and altered calcium and sulfhydryl homeostasis occur.

Oxidative mechanisms in the toxicity of metal ions.
Stohs SJ, Bagchi D.
Free Radic Biol Med. 1995 Feb;18(2):321-36. Review.
PMID: 7744317

Lead and Vascular Disease

- **In vivo and in vitro (animal) studies have shown that chronic lead exposure causes HTN and cardiovascular disease by promoting oxidative stress, limiting nitric oxide availability, impairing nitric oxide signaling, augmenting adrenergic activity, increasing endothelin production, altering the renin-angiotensin system, raising vasoconstrictor prostaglandins, lowering vasodilator prostaglandins, promoting inflammation, disturbing vascular smooth muscle Ca(2+) signaling, diminishing endothelium-dependent vasorelaxation, and modifying the vascular response to vasoactive agonists. Moreover, lead has been shown to cause endothelial injury, impede endothelial repair, inhibit angiogenesis, reduce endothelial cell growth, suppress proteoglycan production, stimulate vascular smooth muscle cell proliferation and phenotypic transformation, reduce tissue plasminogen activator, and raise plasminogen activator inhibitor-1 production. Via these and other actions, lead exposure causes HTN and promotes arteriosclerosis, atherosclerosis, thrombosis, and cardiovascular disease.**

Mechanisms of lead-induced hypertension and cardiovascular disease. Vaziri ND.
Am J Physiol Heart Circ Physiol. 2008 Aug;295(2):H454-65.
PMID: 18567711

Lead and Vascular Disease

- lead exposure causes
- HTN
- and promotes
- arteriosclerosis, atherosclerosis, thrombosis, and cardiovascular disease.

Mechanisms of lead-induced hypertension and cardiovascular disease. Vaziri ND.
Am J Physiol Heart Circ Physiol. 2008 Aug;295(2):H454-65.
PMID: 18567711

Hg and Vascular disease

- Salonen et al.
- Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men. Circulation, 1995 PMID: 7828289

- Mercury accumulation and accelerated progression of carotid atherosclerosis: a population-based prospective 4-year follow-up study in men in eastern Finland. Atherosclerosis 2000.

Salonen JT, Seppänen K, Lakka TA, Salonen R, Kaplan GA. Atherosclerosis. 2000 Feb;148(2):265-73. PMID: 10657561

Hg and Vascular Disease

- A simultaneous exposure to high inorganic mercury, copper, and iron and low selenium concentrations can lead to a condition in which mercury promotes lipid peroxidations (oxLDL). This mechanism provides a plausible molecular-level explanation for the observed association between high body mercury content and atherosclerosis. - 2004

Does mercury promote lipid peroxidation? An in vitro study concerning mercury, copper, and iron in peroxidation of low-density lipoprotein. Seppänen K, Soininen P, Salonen JT, Lötjönen S, Laatikainen R. Biol Trace Elem Res. 2004 Nov;101(2):117-32. PMID: 15557676

Hg & MeHg has been shown to exit as a complex with GSH

- Hg & MeHG have been shown to exit from liver cells into bile as a complex of glutathione on the endogenous carriers of glutathione.
- Clarkson TW, Vyas JB, Ballatori N. Mechanisms of mercury disposition in the body. Am J Ind Med. 2007;50(10):757-64.
- PubMed 17477364

Osawa and Magos, 1974; Refsvik and Norseth, 1975; Ballatori and Clarkson, 1982, 1985

Infants may not excrete meHG

- Suckling rats do not secrete glutathione into bile and neither do they secrete methylmercury [Ballatori and Clarkson, 1982].
- Data on human infants have not been published.

Mercury (HG) excretion liver to fecal excretion as a complex with glutathione (GSH)

2 glutathione molecules used for each molecule of mercury

Out of cell and into the blood stream

To the liver

Fecal excretion

Excreted from the liver in bile fluid

Clarkson TW, Vyas JB, Ballatori N. Mechanisms of mercury disposition in the body. Am J Ind Med. 2007;50(10):757-64. PubMed; 17477364.

Methylmercury (meHG) excretion liver to fecal excretion as a complex with glutathione (GSH)

1 glutathione molecule used for each molecule of me-mercury

Out of cell and into the blood stream

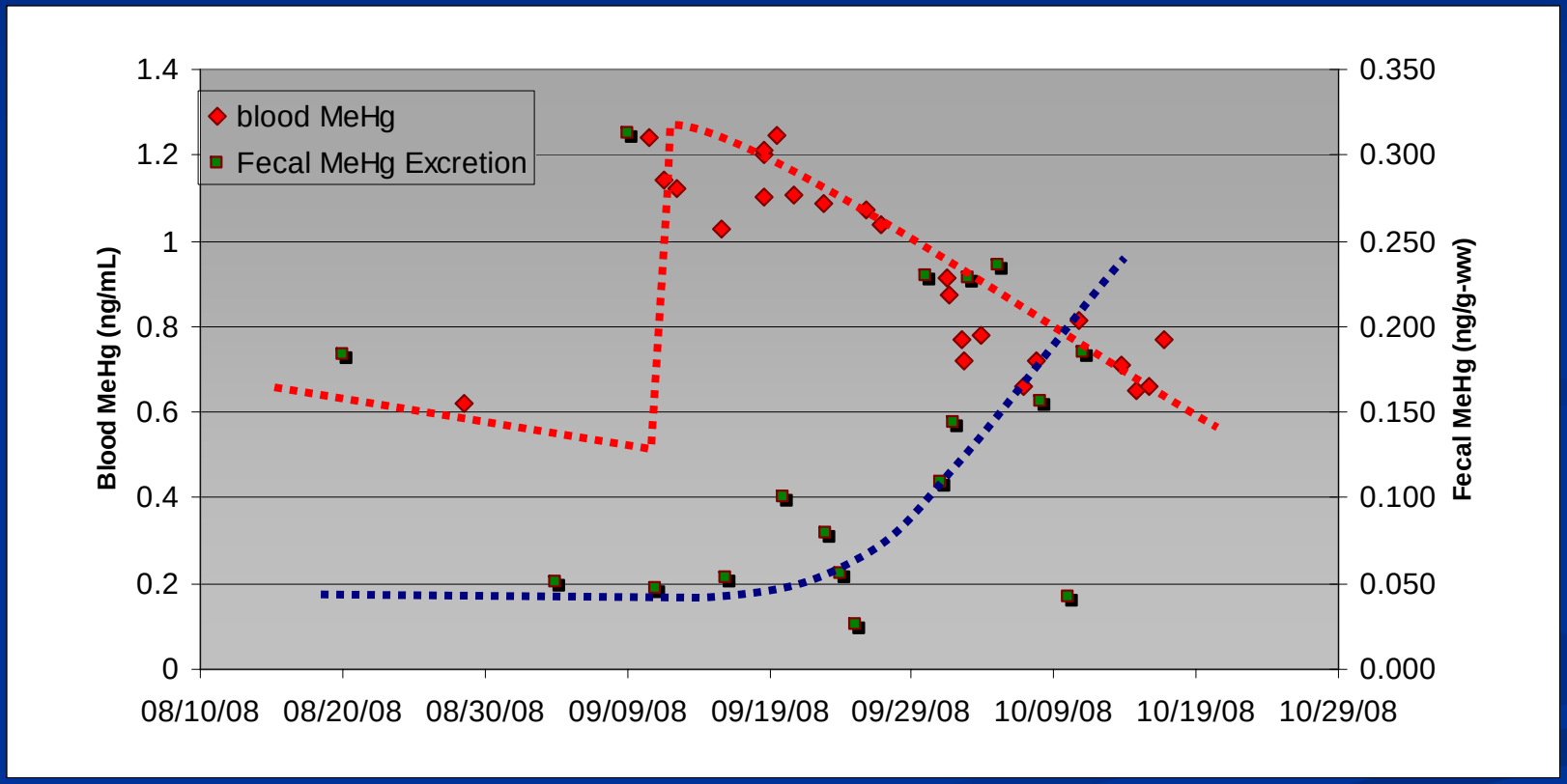
To the liver

Fecal excretion

Excreted from the liver in bile fluid

Clarkson TW, Vyas JB, Ballatori N. Mechanisms of mercury disposition in the body. Am J Ind Med. 2007;50(10):757-64. PubMed; 17477364.

Excretion Rates
Liposomal GSH Supplementation



QUICKSILVER SCIENTIFIC

Aflatoxin B1(AFB1)-glutathione(GSH) conjugation via glutathione-S-transferase (GST) is the major pathway for the detoxification of aflatoxin and metabolites.

Out of cell and into the blood stream

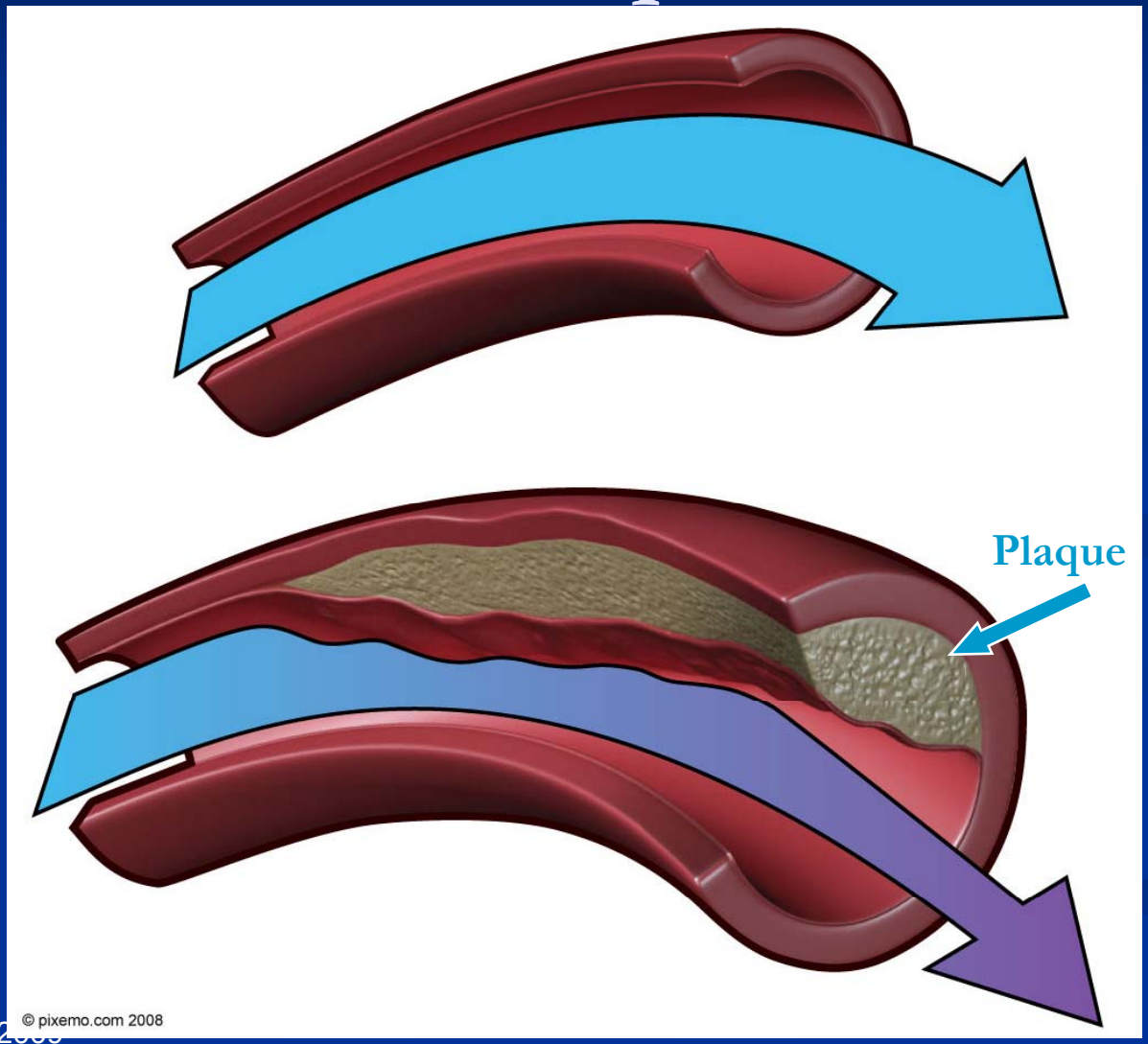
To the kidney and liver

Urine & Fecal excretion

Excreted in urine and the liver in bile fluid

Kinetic studies of aflatoxin B1-glutathione conjugate formation in liver and kidneys of adult and weanling rats. Allameh A, et al Mech Ageing Dev. 2000 May 18;115(1-2):73-83. PMID: 10854630 ALSO see Science 1981 212: 541

Atherosclerosis – from Fatty Streak to Plaque



Atherosclerosis Lesions

- Atherosclerotic lesions are first characterized by the presence of inflammatory cells, mainly lipid-filled macrophages, forming fatty streaks in the neointima of the vessel.

J. Clin. Invest. **107**(10): 1227-1234 (2001).

Foam Cells Form the Fatty Streak

- Faggiotto et al, 1984
- A study of diet-induced hypercholesterolemia
- 12 days: monocytes became adherent to the surface of the endothelium
- 30 days: a "serofibrinous insudate" formed together with variable numbers of subendothelial lipid-laden macrophages.

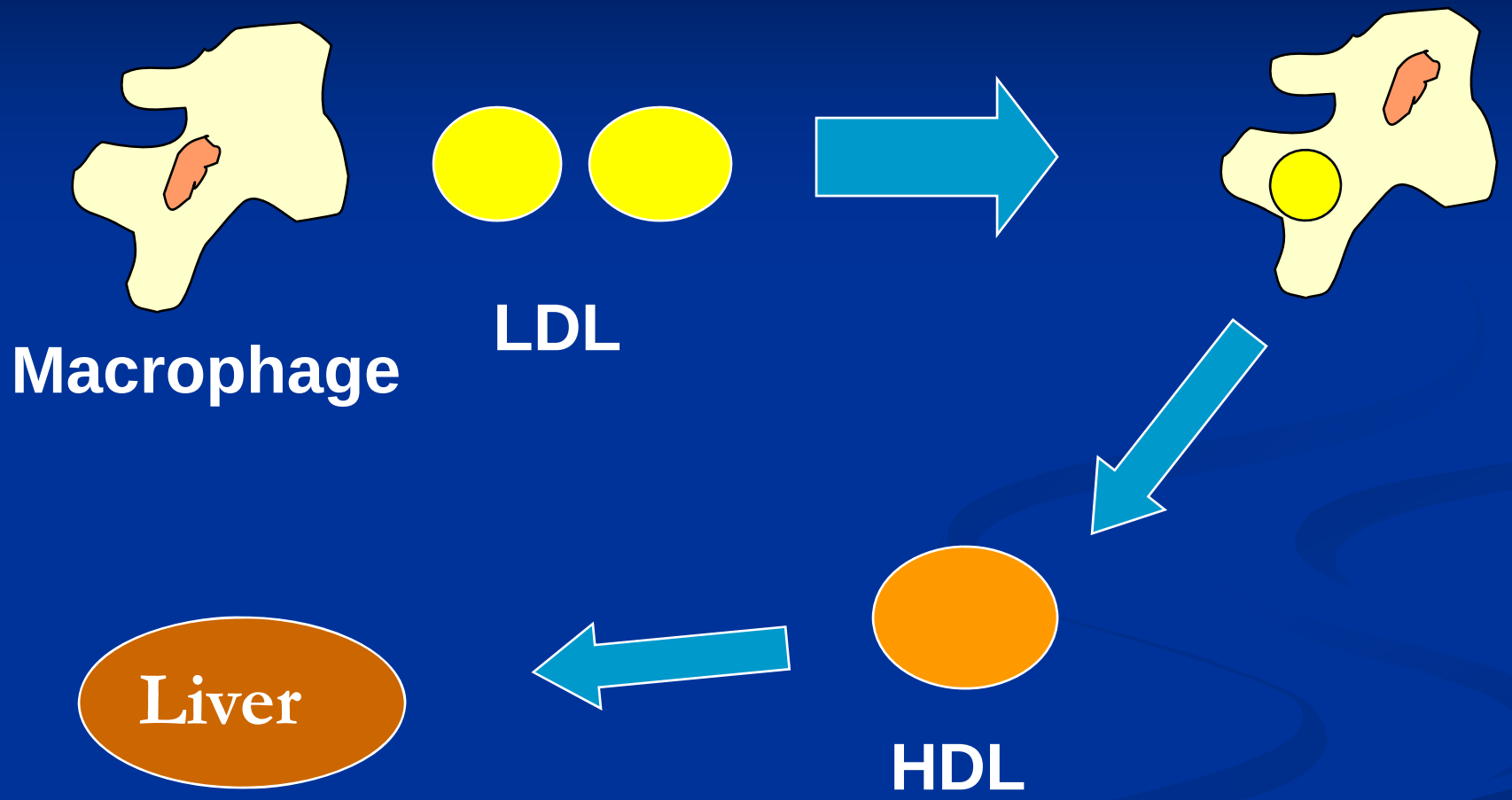
Arteriosclerosis. 1984 Jul-Aug;4(4):323-40 PMID: 6466191

Foam Cells

- Because the expression of scavenger receptors (CD36) is not down-regulated by cholesterol, macrophages expressing scavenger receptors can internalize substantial quantities of cholesteryl ester from oxidized LDL and HDL, leading to foam cell formation.

Macrophage scavenger receptors and foam cell formation.
J Leukoc Biol. 1999 Nov;66(5):740-6. PMID: 10577503

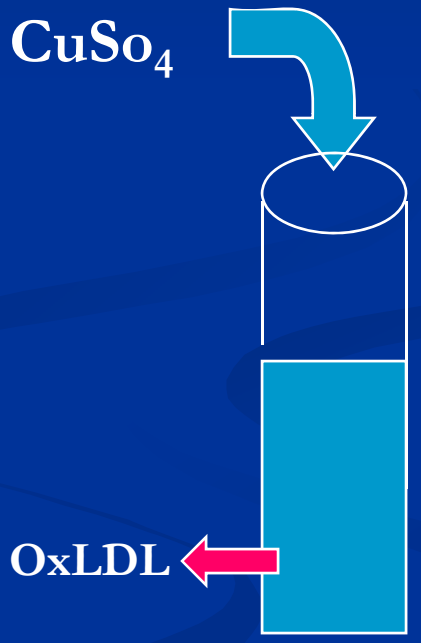
LDL - HDL Cholesterol transport



Johnson, et al, 1991. Cholesterol transport between cells and high-density lipoproteins. *Biochim. Biophys. Acta.* **1085**:273-298 PMID: 1911862

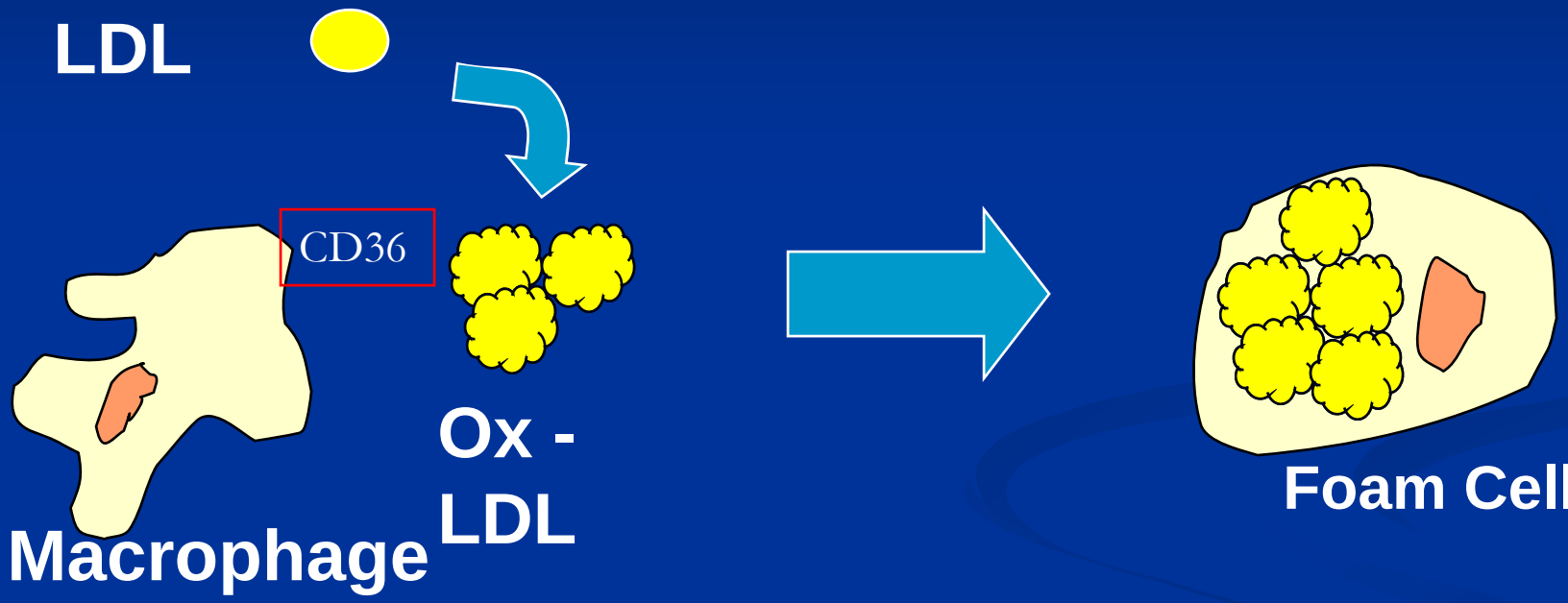
Oxidation of LDL Cholesterol

Metals catalyze the oxidation of LDL Cholesterol



Anti-oxidant and anti-atherogenic properties of liposomal glutathione: studies in vitro, and in the atherosclerotic apolipoprotein E-deficient mice.
Rosenblat M, Volkova N, Coleman R, Aviram M.
Atherosclerosis. 2007 Dec;195(2):e61-8.
PMID: 17588583

Oxidized LDL cholesterol



Macrophage scavenger receptors and foam cell formation.
J Leukoc Biol. 1999 Nov;66(5):740-6. PMID: 10577503

OxLDL

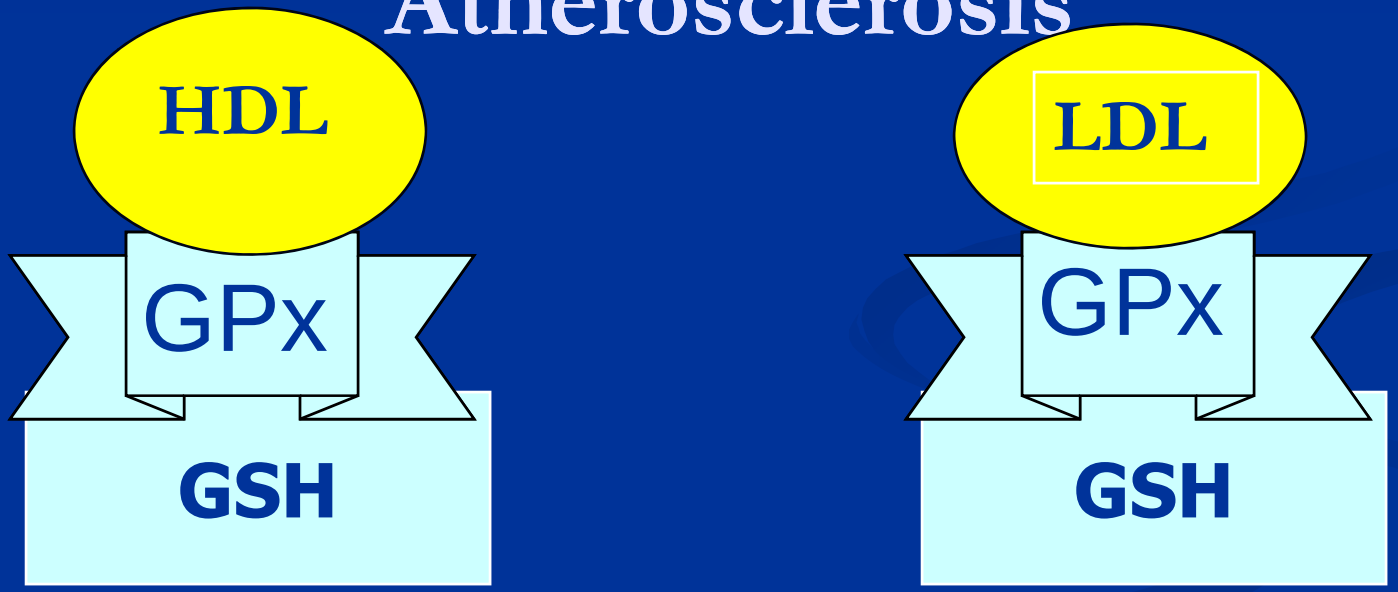
- Oxidized LDL has also been shown to stimulate the proliferation of smooth muscle cells and to be immunogenic by eliciting the production of autoantibodies and the formation of immune complexes that can also facilitate macrophage internalization of LDL. The recruitment of inflammatory cells may result in the continued oxidation of LDL, setting the stage for catalytic expansion of the atherosclerotic lesion and the full-blown spectrum of atherosclerosis.

Stocker, R. et al. Physiol. Rev. 84: 1381-1478, 2004

Liposomal Glutathione Prevents Ox - LDL formation which occurs with low GSH

Atherosclerosis. 2007 Dec;195(2):e61-8.
PMID: 17588583

Liposomal Glutathione Provides the Substrate for the Enzyme GPx to Protect Both HDL & LDL from Oxidation and to Prevent Atherosclerosis



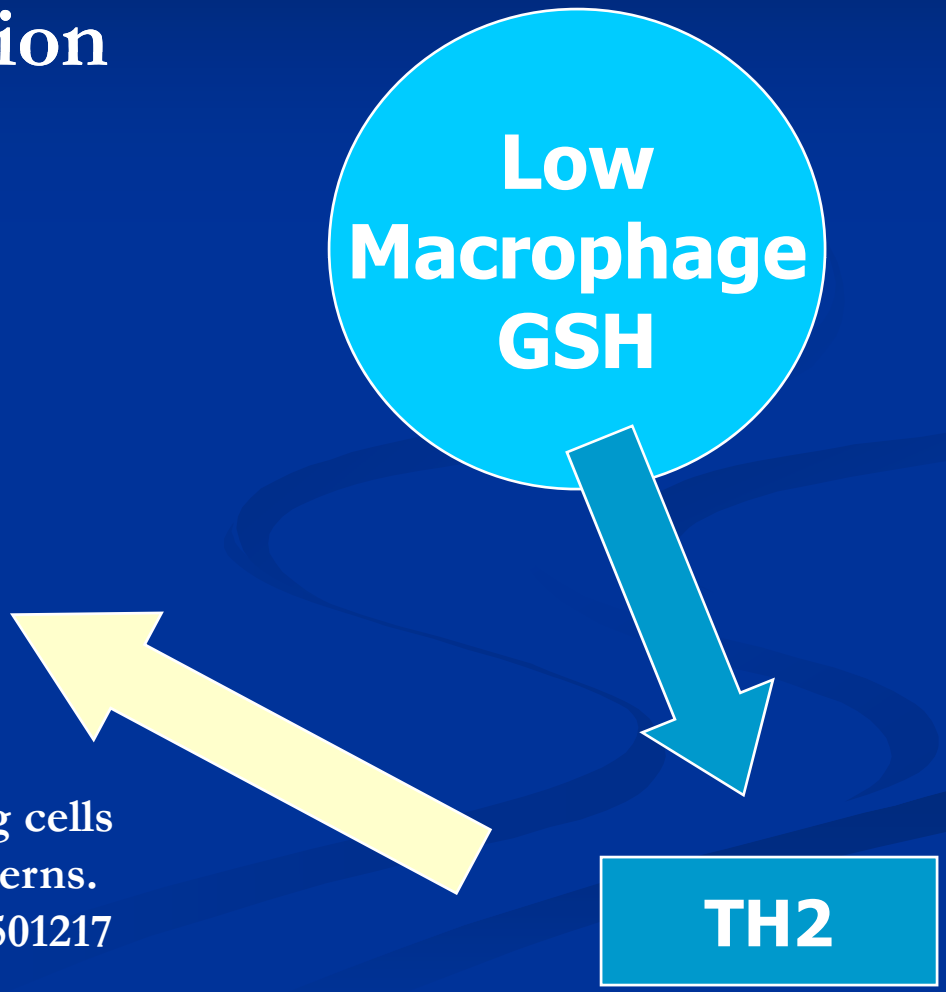
Atherosclerosis. 2007 Dec;195(2):e61-8.
PMID: 17588583

Low GSH in Macrophage and Antigen Presenting Cells (APC)

Results in TH2 expression

Allergy

Chronic Inflammation



Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns. PNAS 1998 Mar 17;95(6):3071 PMID: 9501217

Low Glutathione a Risk Factor for Coronary Artery Disease and Influenza Infection

- It is interesting to note that AMI activity may precede the peak in influenza infection in the population, suggesting that individuals with coronary disease may be more susceptible to influenza, although other stressors could be possible present.

Madjid M, Miller CC, Zarubaev VV, Marinich IG, Kiselev OI, Lobzin YV, et al. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34,892 subjects. European heart journal. 2007;28(10):1205-10. Cited in PubMed; 17440221.

W.A. Shrader, Jr., MD

The nuts and bolts of EDTA chelation therapy

Bio

Dr. Shrader is Board-certified in Environmental Medicine and Director of the Santa Fe Center for Allergy & Environmental Medicine in Santa Fe, New Mexico. He is a Past President of the American Academy of Environmental Medicine (AAEM) and the current CME Director for the AAEM. Dr. Shrader has been a member of ACAM for 20 years and also serves on the Board of Directors of ACAM and AAEM.

Lecture Overview

This lecture will cover the actual mechanics of the office administration of chelation therapy (NaMgEDTA). This will include the calculation of the dose of EDTA to administer, how to mix a complete chelation infusion and how to start and finish a chelation infusion. We will also cover the purpose for the nutrients in chelation and calculation of "safe" osmolarity for any IV. At the end the session, there will be an actual hands-on IV workshop where attendees will be administering a commonly used IV "Push" protocol.

Contact Information

Santa Fe Center for Allergy
141 Paseo de Perlata
Santa Fe, NM 87501

wshradermd@aol.com

DISCLOSURE

No Disclosure

American College for Advancement in Medicine 2009 Las Vegas, Nevada Fall

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

American College for Advancement in Medicine

The Nuts and Bolts of EDTA Chelation Therapy:

Safe EDTA Dose Calculation, Mixing & Administration, Potential Problems, Pre- & Post-treatment Evaluation, Osmolarity Calculation

W.A. ("Butch") Shrader, Jr., MD

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Nutrients We Use for Chelation

(discussed in syllabus)

Vitamins

Vitamin C
Pantothene
B-12
Folic Acid
Pyridoxine

B-complex: thiamin (B_1) riboflavin (B_2), niacin (B_3) pantothene (B_5) and pyridoxine (B_6)

Minerals

Magnesium (MgCl), Potassium (KCl) and Sodium Bicarbonate ($NaHCO_3$)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Nutrients We *Don't* Use

Vitamins

Vitamin A

Vitamin D

Vitamin E

Vitamin K

Minerals

Calcium or trace minerals

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

A brief Biochemistry diversion

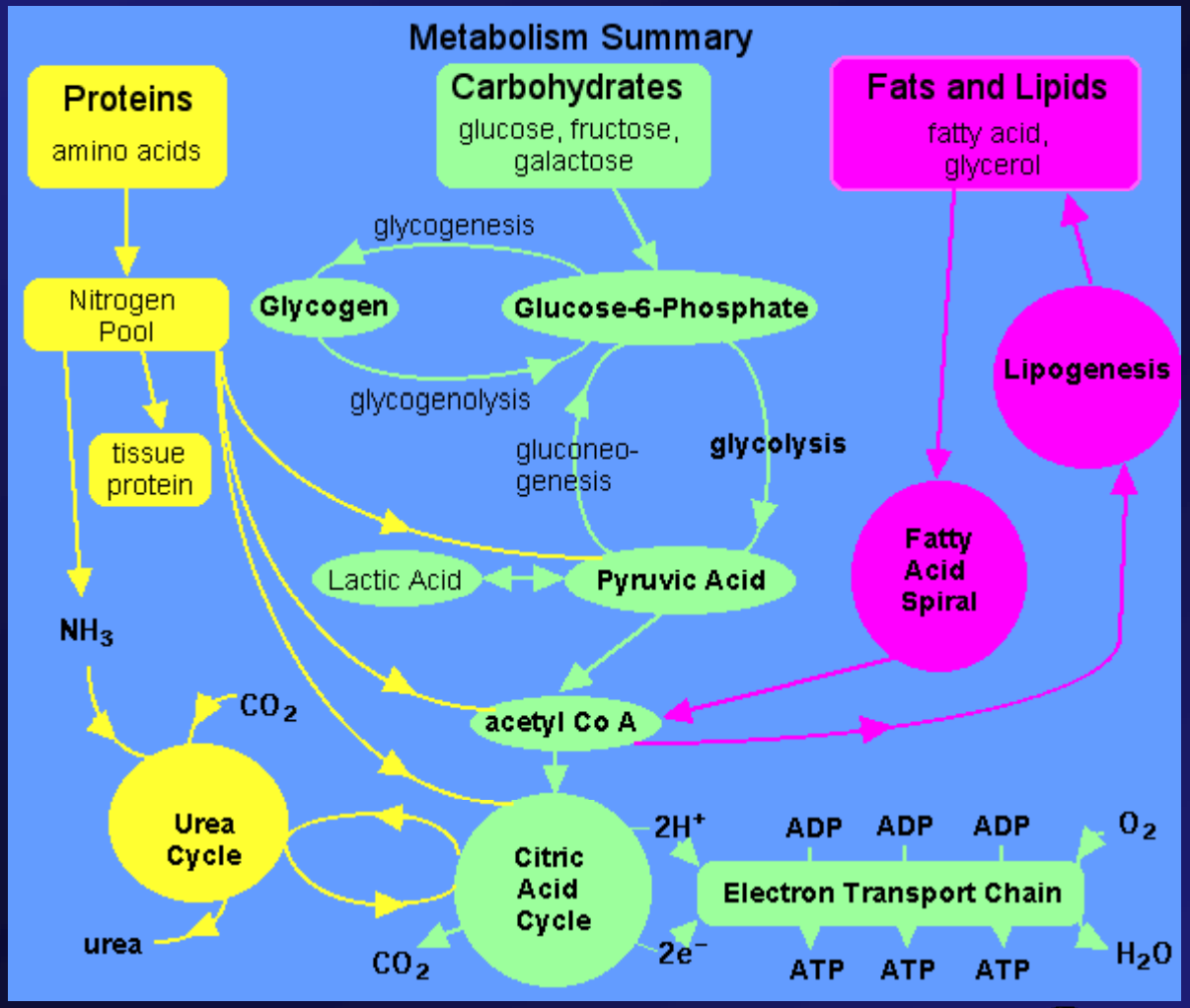
About those vitamins and minerals . . . . .

Vitamins are incorporated into cofactors, enzymes and coenzymes for thousands of cellular processes – life as we know it.

Minerals act as catalysts and cofactors in most enzymatic reactions

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Overall Human Metabolic Summary



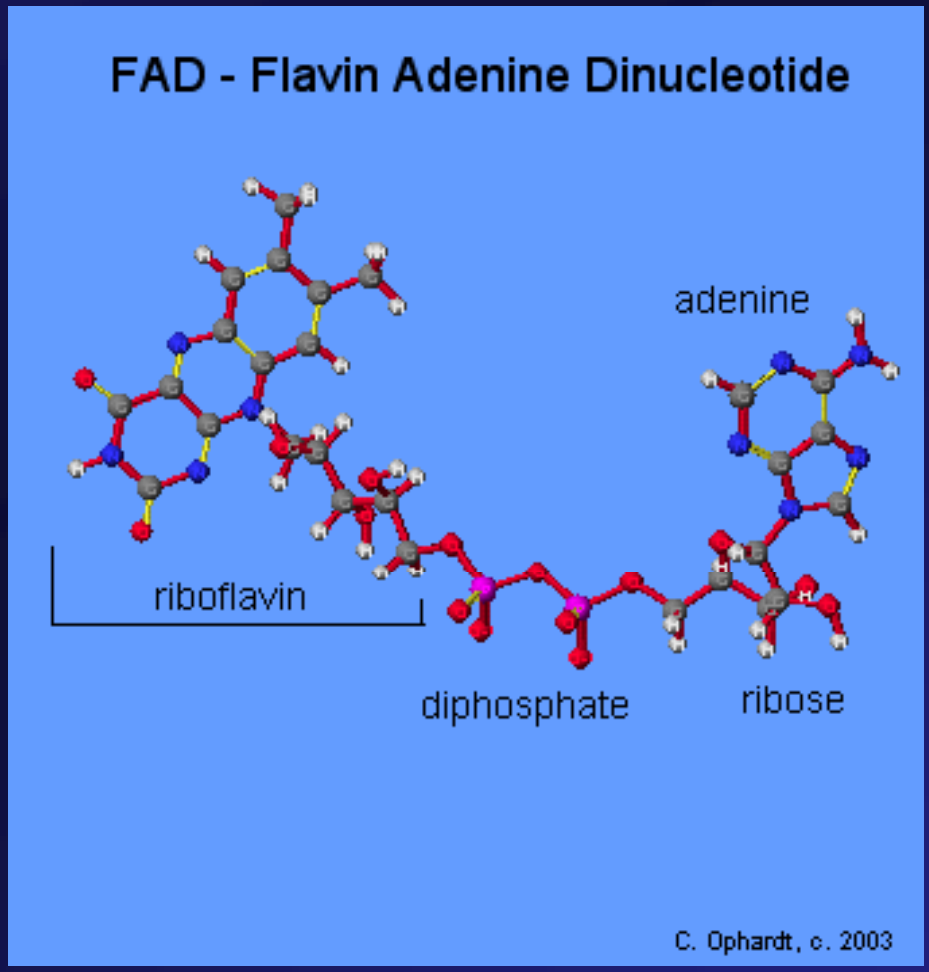
W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Example: Niacin, Riboflavin and Pantothenic Acid (most B – vitamins)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Riboflavin (B_2)

Riboflavin is the precursor for several enzymes, including flavin adenine dinucleotide (FAD). FAD is a coenzyme for monoamine oxidase, glucose oxidase, xanthine oxidase and others. Many are metalloflavoproteins and detoxicants.

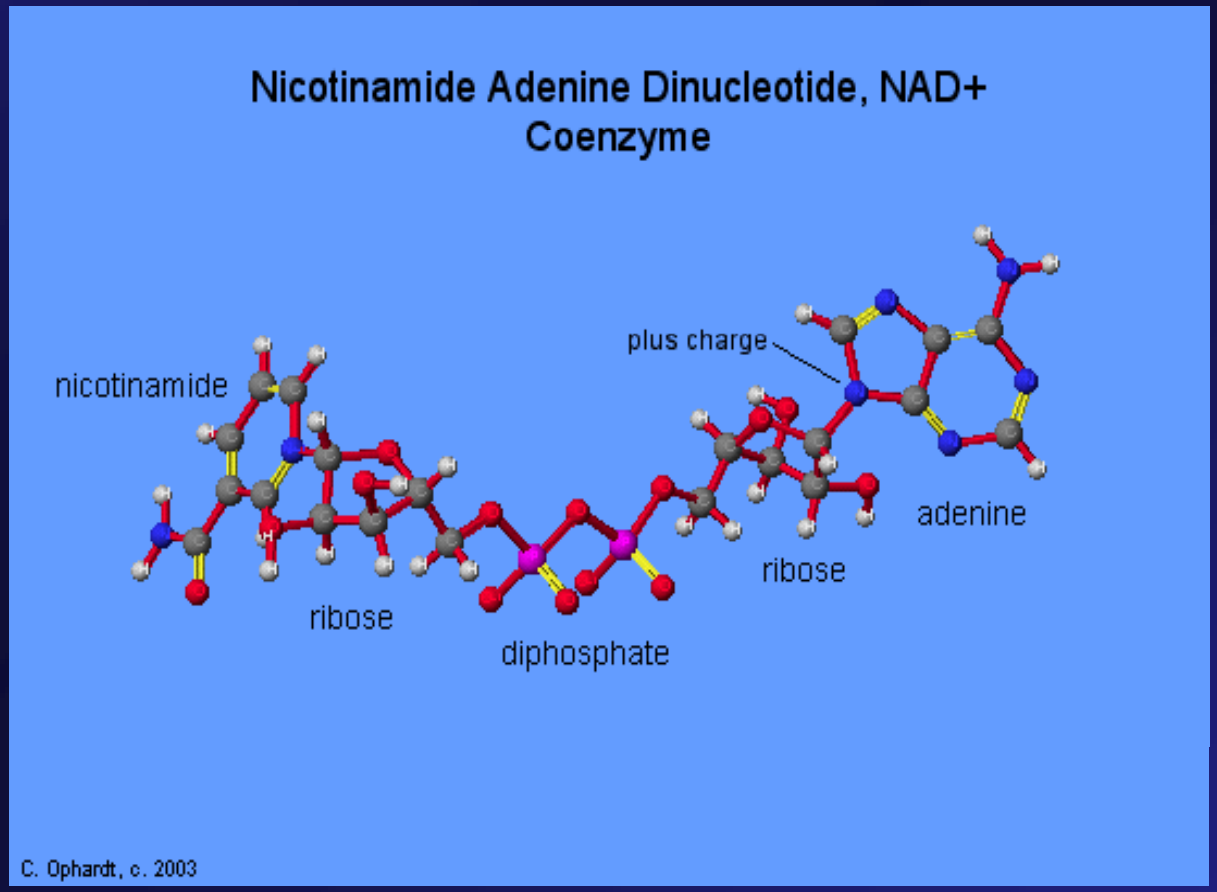


Detox

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

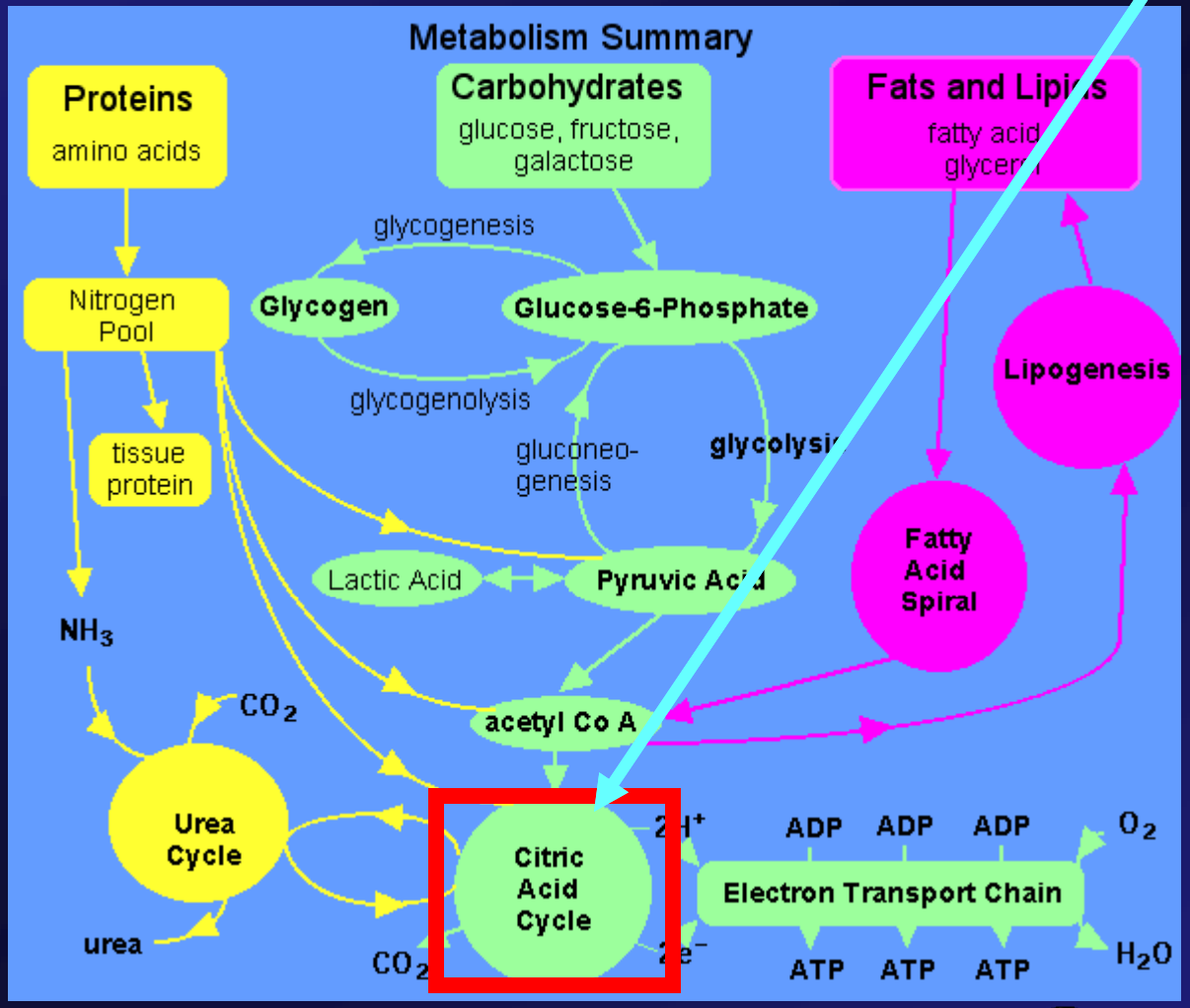
Niacin (B_3)

Known also as nicotinic acid and nicotinamide, niacin is required for synthesis of the active forms of B_3, nicotinamide adenine dinucleotide (NAD) and NADP



W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

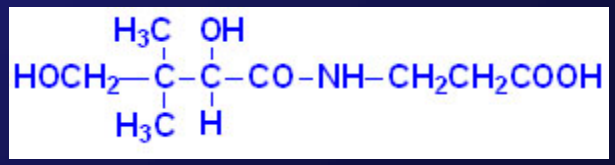
NAD and FAD both fit here



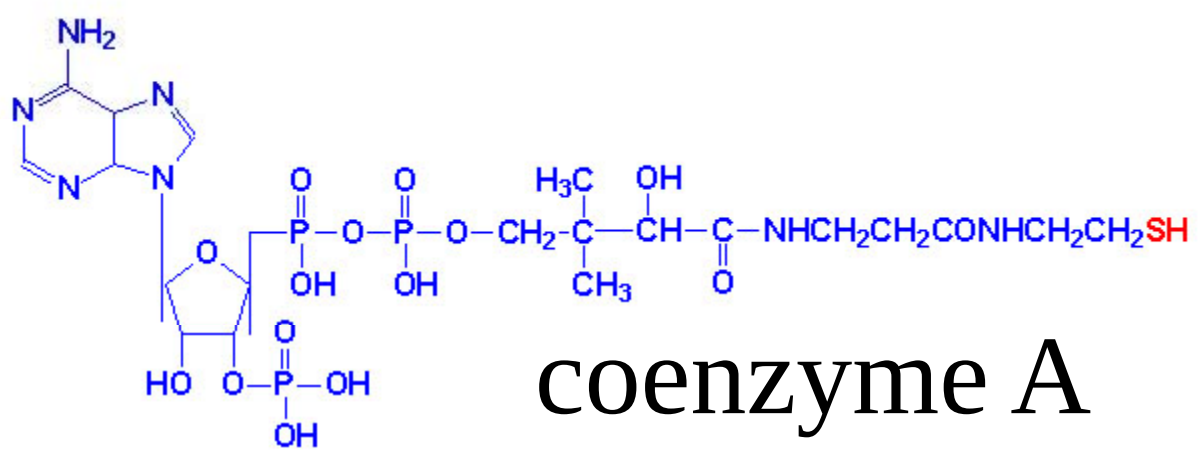
there, and everywhere

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Pantothenic acid



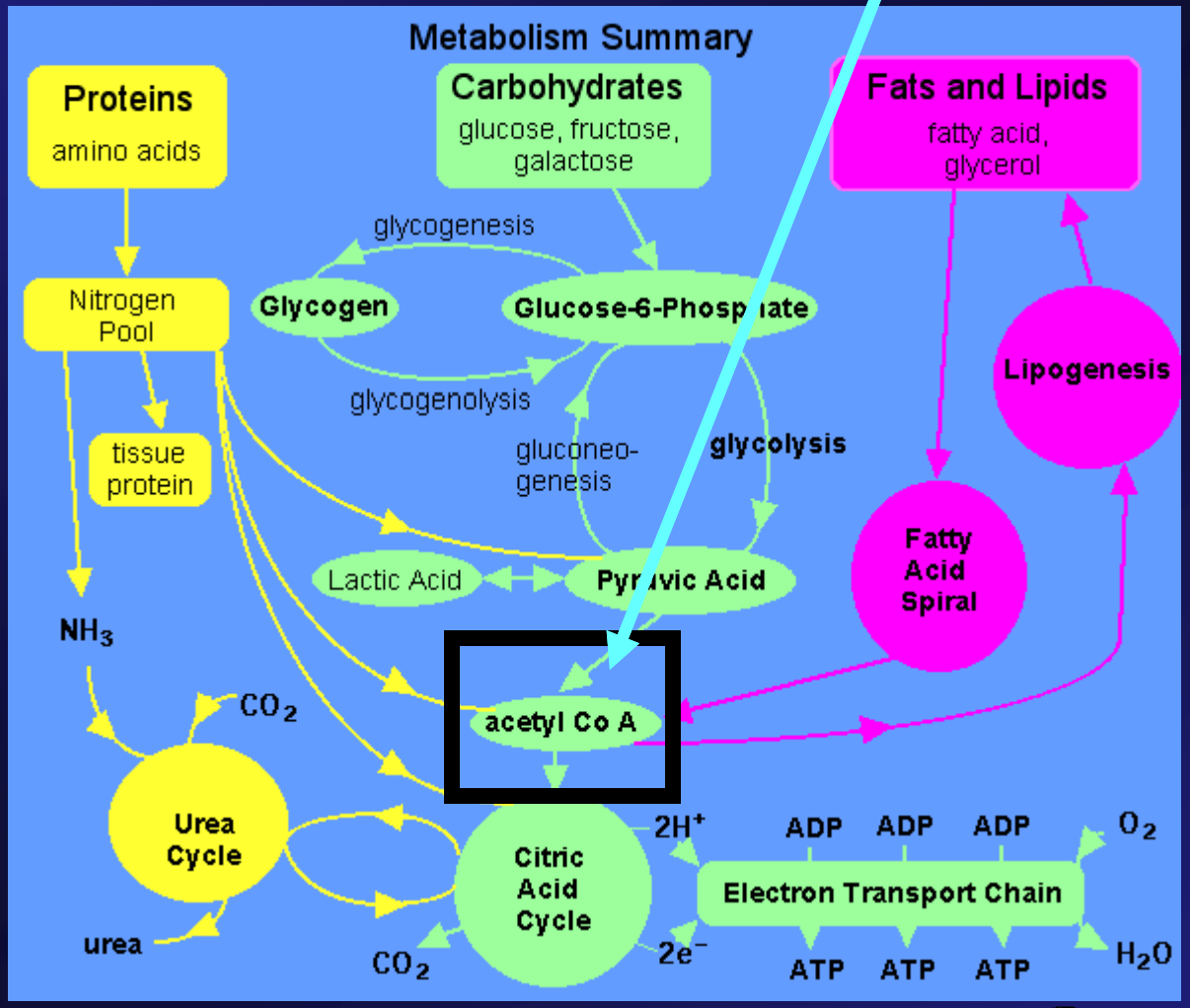
Required for the synthesis of coenzyme A (CoA), which is required in over 70 enzymes



coenzyme A

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

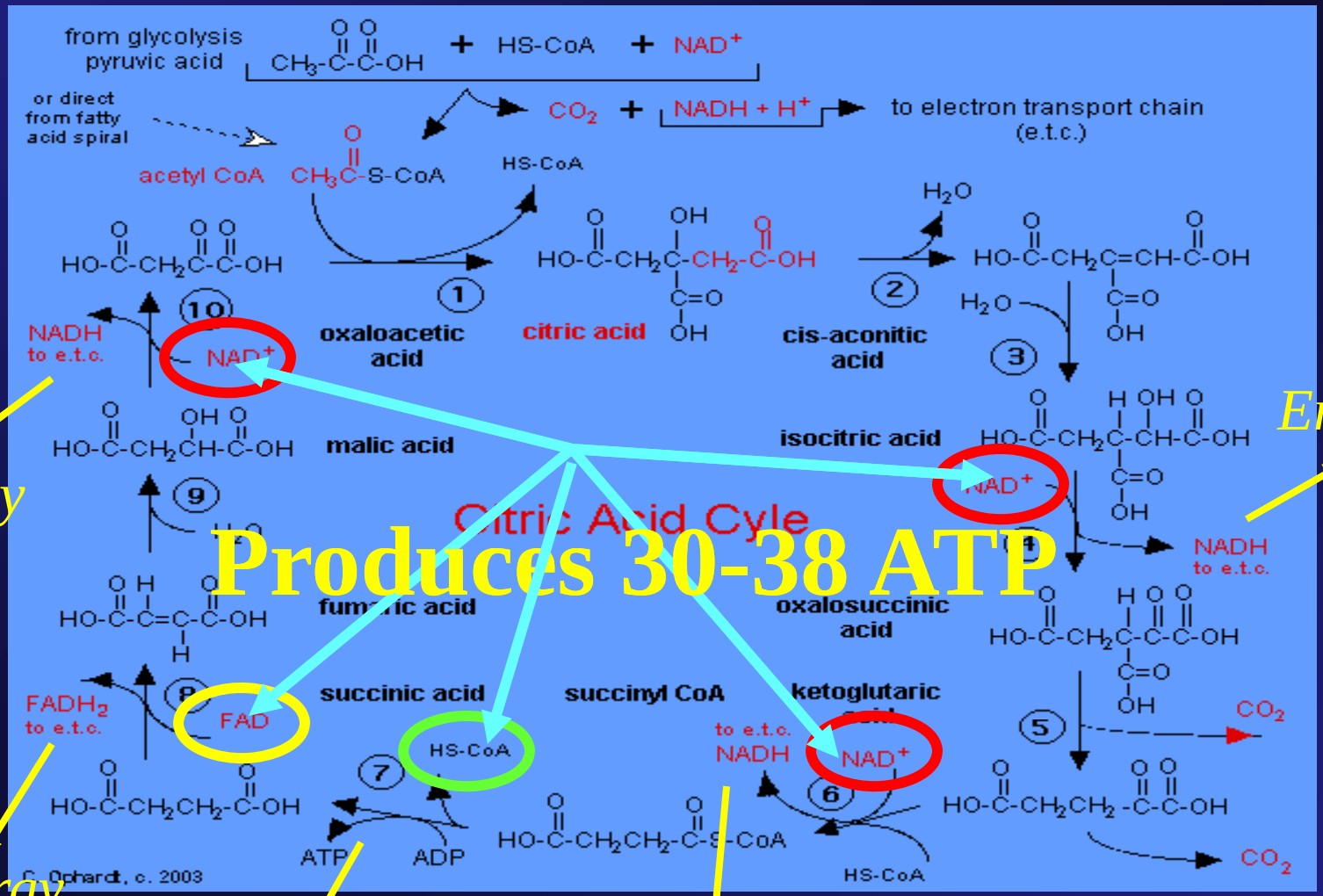
CoA fits here



there, and everywhere!

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Citric Acid Cycle (TCA cycle)



Produces 30-38 ATP

Energy

Energy

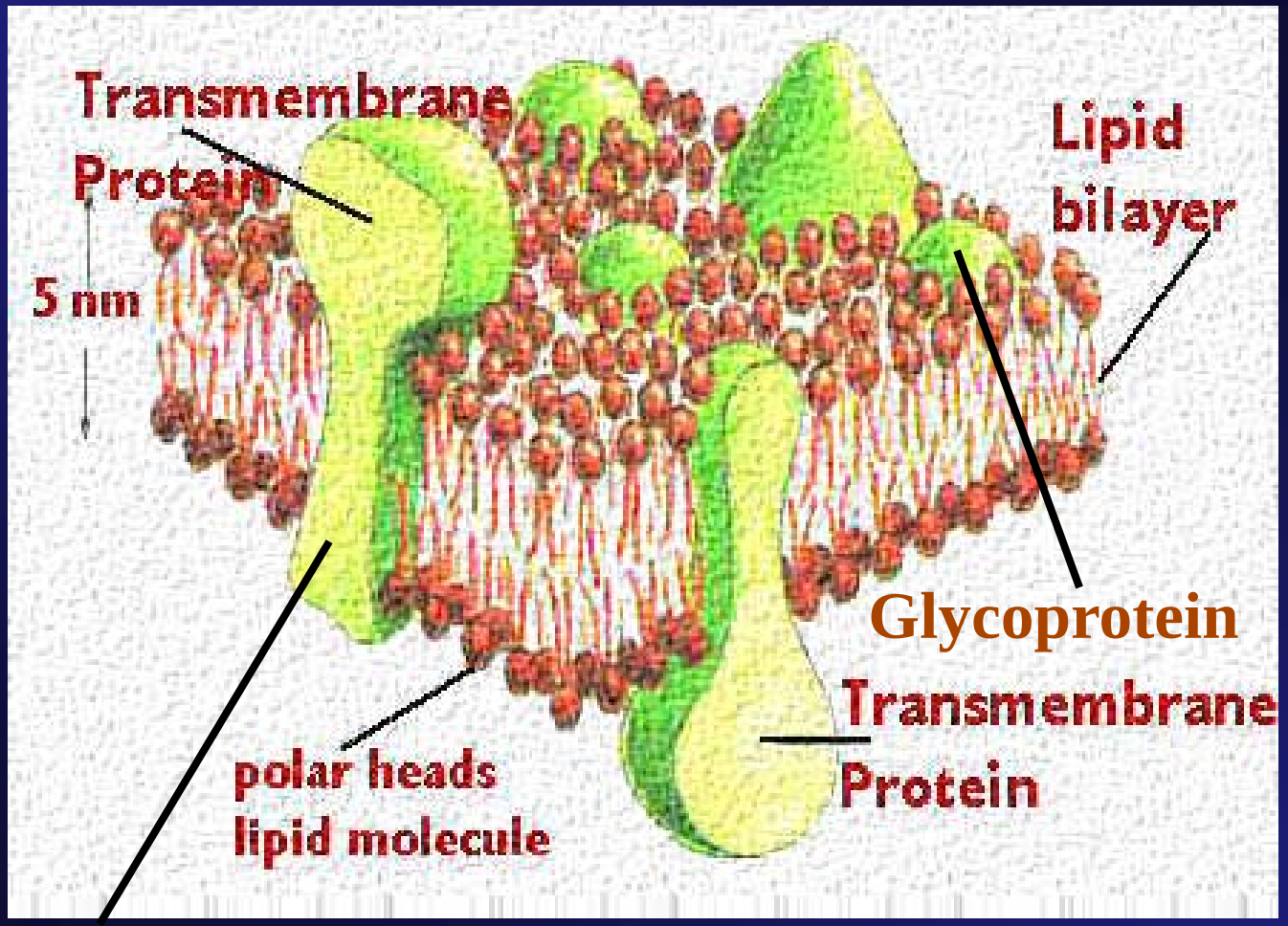
Energy

Energy

Energy

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Cell Membranes



Channel Protein (Ca^{++}, amino acid transport, Na^{++}, anion, etc.)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Channel Proteins

Channel proteins channel many cations (+) with and against the cellular osmotic gradient

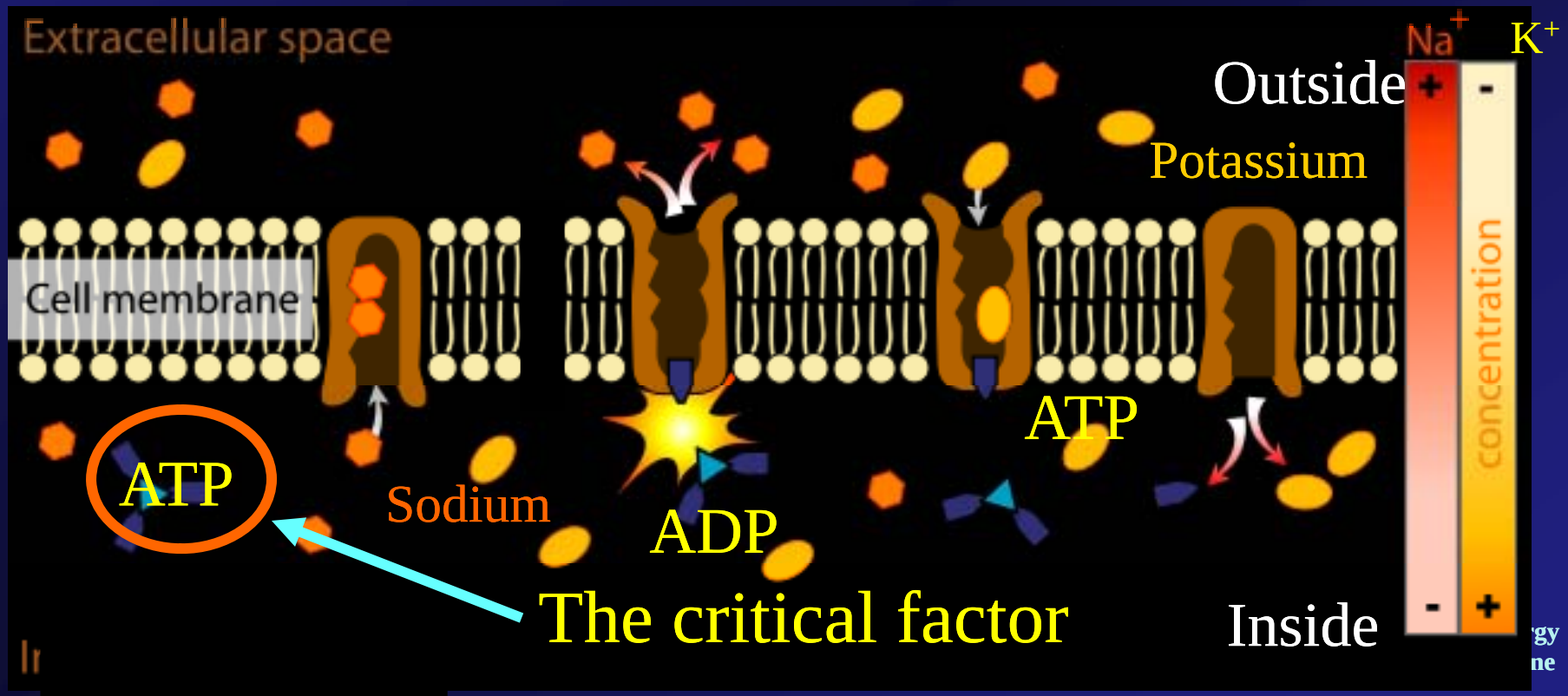
Most channels require ATP to function

Channel proteins include metallothionein, which may carry zinc, copper, selenium, cadmium mercury, silver and other metals

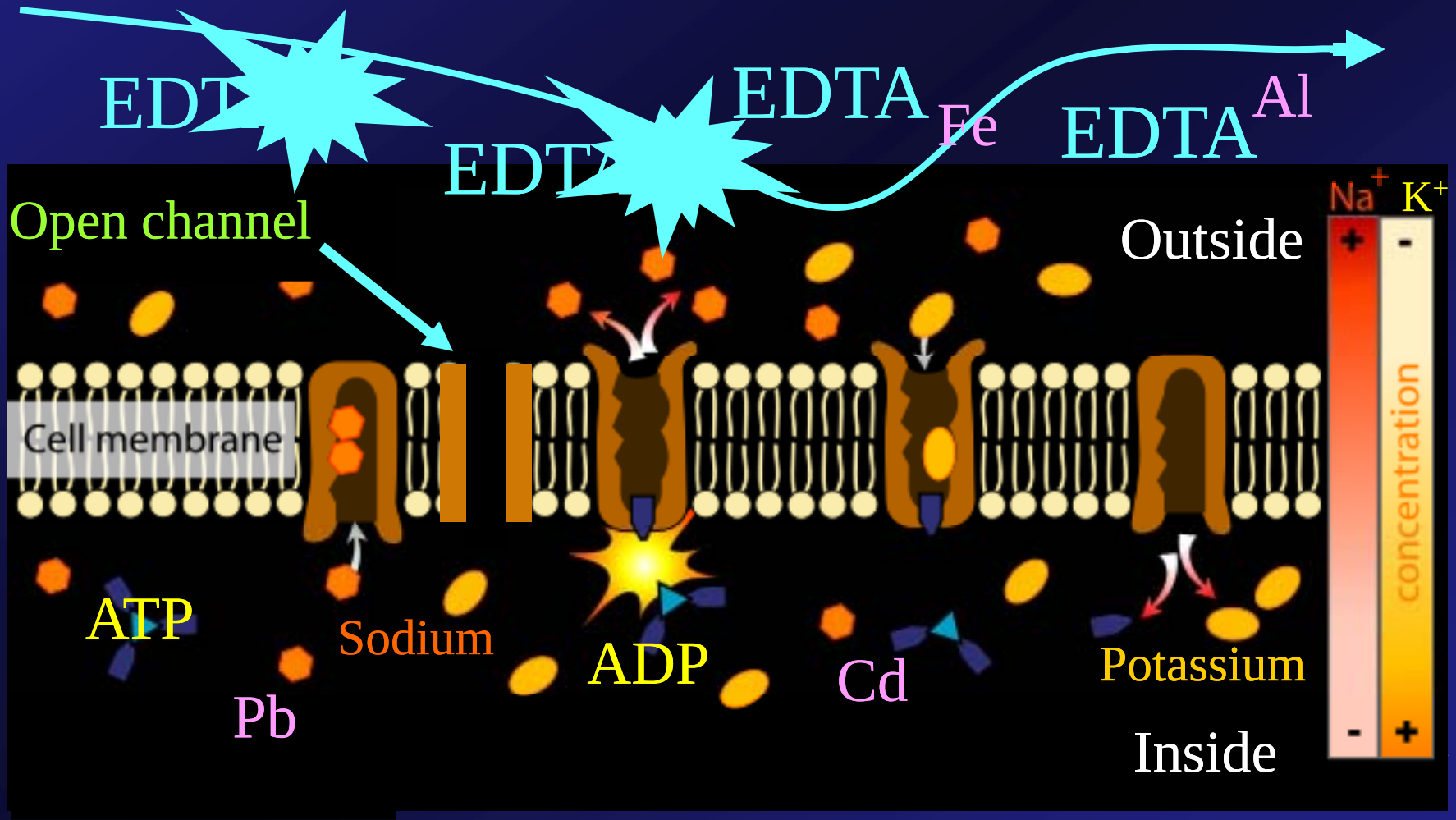
Channels and “open channels” take heavy metals out of the cell so that EDTA can grab it

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Active transport uses ATP: Transports ions *against* concentration gradient – *all* cells



Passive transport uses open channels
Transports ions *in any direction*, using concentration gradient



Nutrients: General Caveats

Use only preservative-free nutrients

Use IV solutions only in glass (sterile water for chelation) – never in plastic bags

Observe the rules for safe osmolarity

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

The nutrients we add to EDTA chelation therapy are essential, not just window dressing.

(see syllabus)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Consent Forms

Remember, CYA:

Use
Appropriate consent forms
Release forms
Medicare forms

(see syllabus)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Cockcroft-Gault Equation for EDTA Dosage Calculation

$$\text{EDTA Dose (in mg.)} = 50 \text{ mg./kg.} \times \text{LBW} \times \frac{\text{CrCl}}{100}$$

$$\text{CrCl} = \frac{(140 - \text{Age}) \times (\text{LBW})}{54 \times \text{Cr (mg./dl)}}$$

Finally, you must divide this calculated EDTA dose (mg.) by 1000 to obtain grams of EDTA

Maximum dose = 3.0 grams

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Cockcroft-Gault Equation for Dose Calculation of EDTA

Lean Body Weight (LBW) in kg. for computations
LBW for males is 50 kg plus 2.3 kg / inch
of height over 5 feet.

LBW for females is 45.5 kg plus 2.3 kg / inch of height over 5 feet.

Use Actual Weight whenever it is less than computed lean body weight.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Cockcroft-Gault Equation for EDTA

1. $CrCl = \frac{(140 - Age) \times (LBW)}{54 \times Cr\ (mg./dl)}$

2. $EDTA\ Dose\ (mg.) = 50\ mg./kg. \times LBW \times \frac{CrCl}{100}$

For 60 y.o. male 5'10", creatinine 0.8

LBW

1. $CrCl = \frac{(140 - 60) \times (50 + 23)}{54 \times Cr\ (mg./dl)}$, or $\frac{80 \times 73}{54 \times 0.8}$, or $\frac{5840}{43.2}$

So, CrCl is 135

$EDTA\ Dose\ (in\ mg.) = (50 \times 73) \times \frac{135}{100}$, or 3650×1.35

Which is: 4927 mg

Divided by 1000 = 4.927 grams

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Cockcroft-Gault Equation for EDTA Dosage Calculation

Final dose = 4.927 grams

However, Maximum Dose for any patient is 3 grams

Disodium EDTA is usually 150 mg./cc, so dose would be 20 ccs (for IV infusion)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Drawing Up the Chelation Solution

See syllabus for sample chelation protocol

Step-by-step instructions appear in syllabus

Line up nutrients in order you'll draw them up and de-pressurize all bottles with a needle

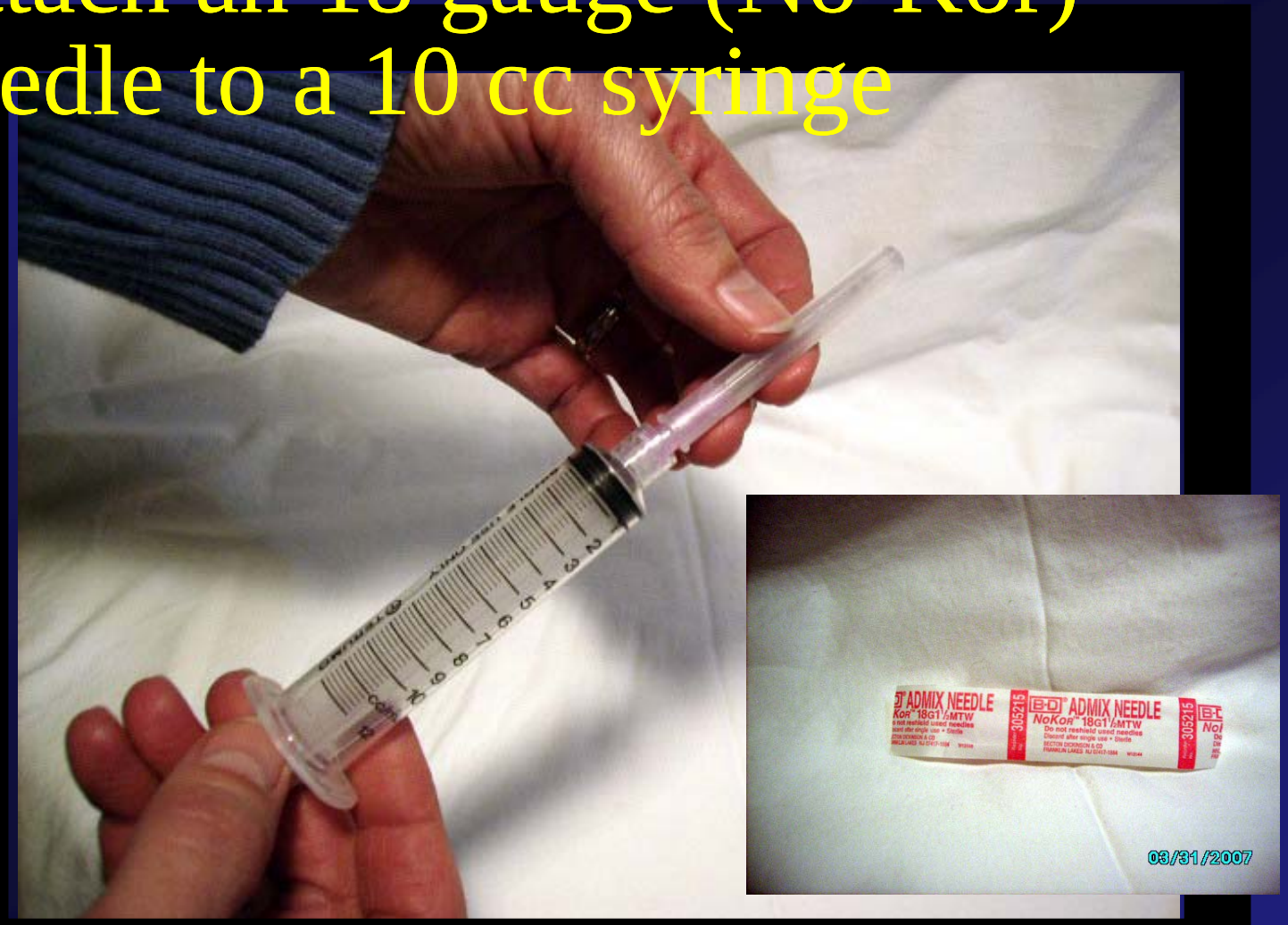
Use sterile procedure

Draw up nutrients separately and inject them in the IV bottle (sterile water)

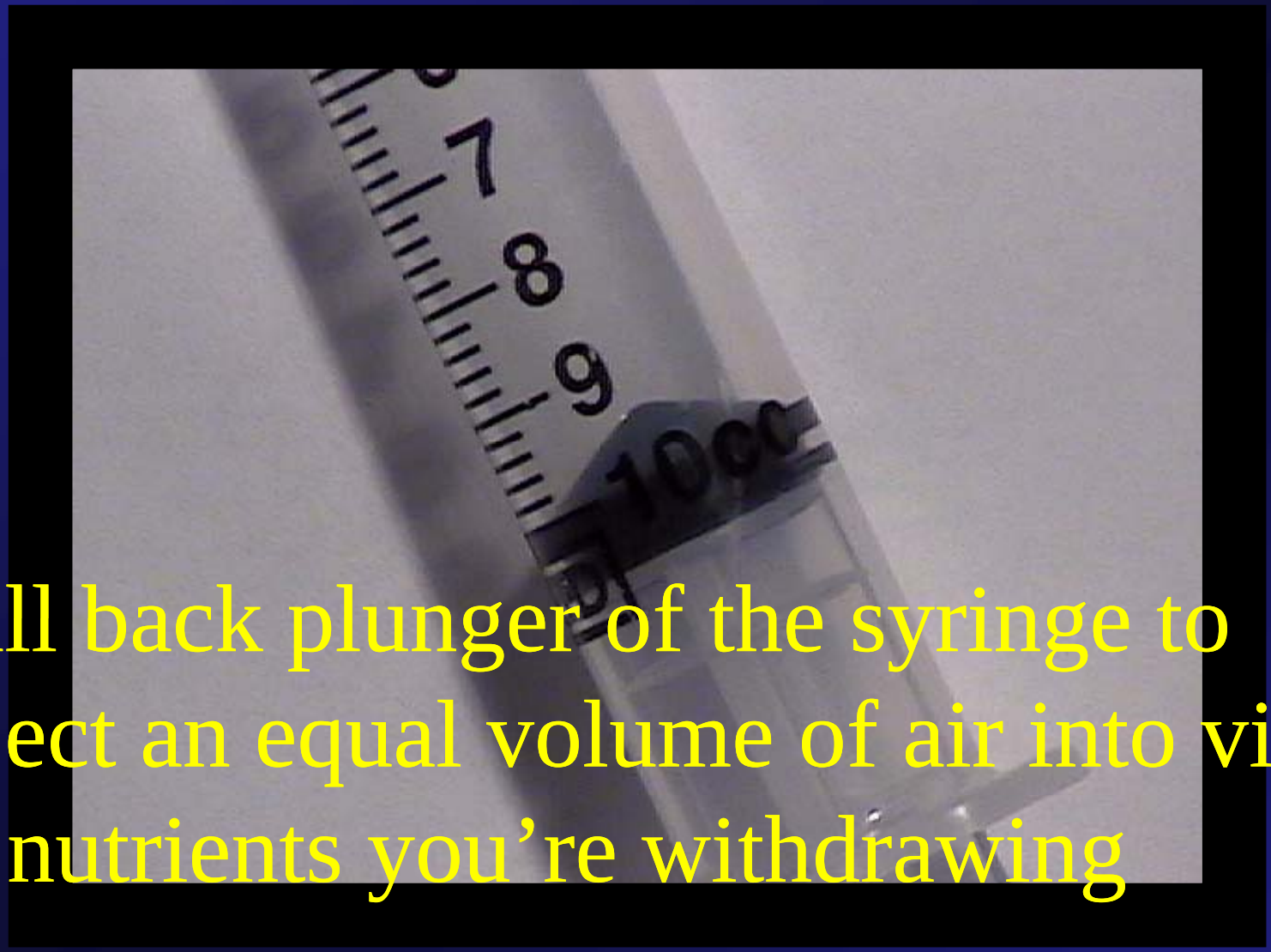
Draw up colored nutrients last

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Attach an 18 gauge (No-Kor) needle to a 10 cc syringe



W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine



Pull back plunger of the syringe to inject an equal volume of air into vials as nutrients you're withdrawing

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Insert the needle of the syringe into the vial, *invert the bottle* (you do this with all of the vials of nutrients and EDTA as you use them) and inject the air.

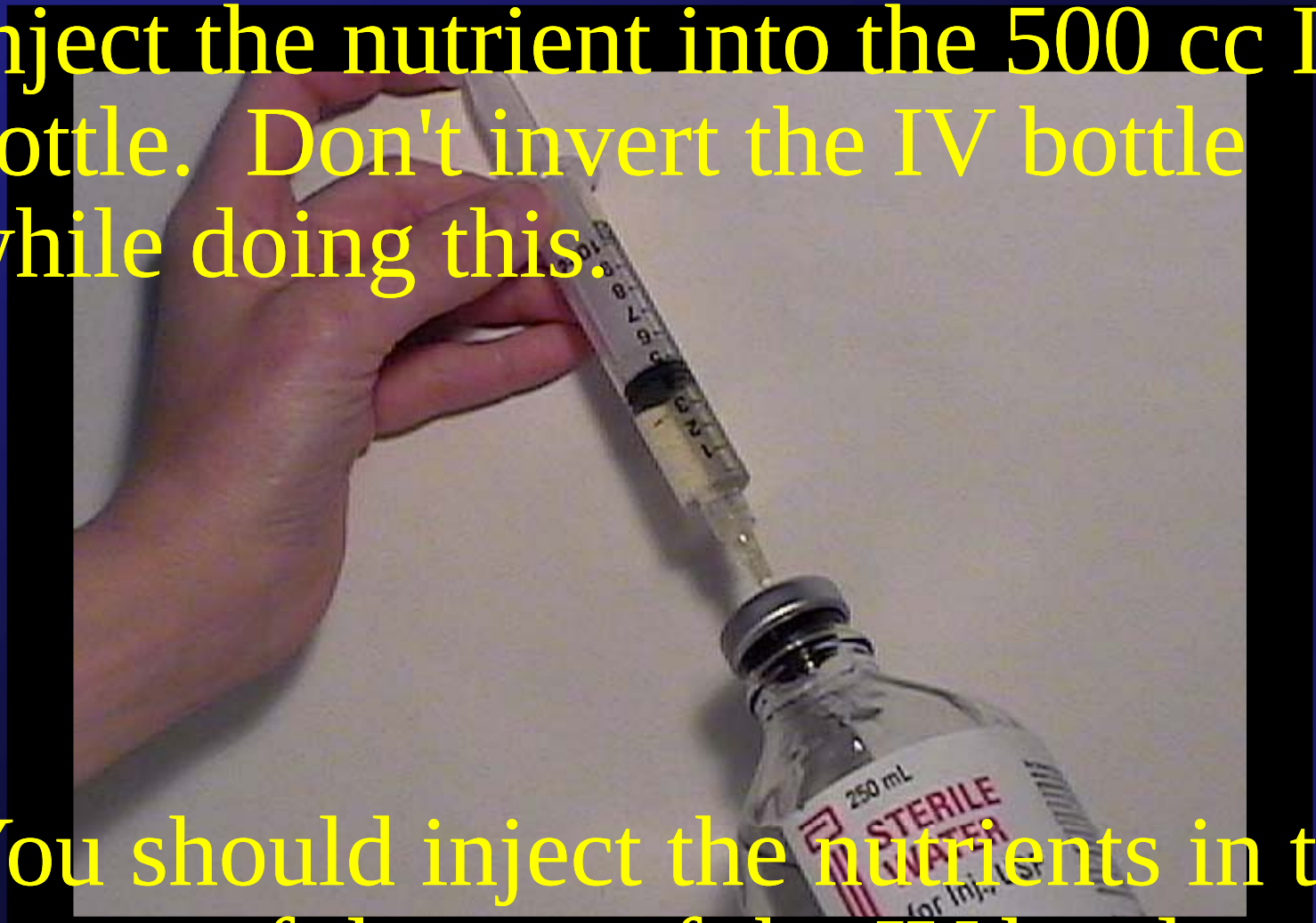
W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Withdraw nutrient from the vial into the syringe.

When you are done with a nutrient, *push the vial back.*

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Inject the nutrient into the 500 cc IV bottle. Don't invert the IV bottle while doing this.



You should inject the nutrients in the center of the top of the IV bottle.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Setting up the IV

The IV administration set – always use *vented* administration sets

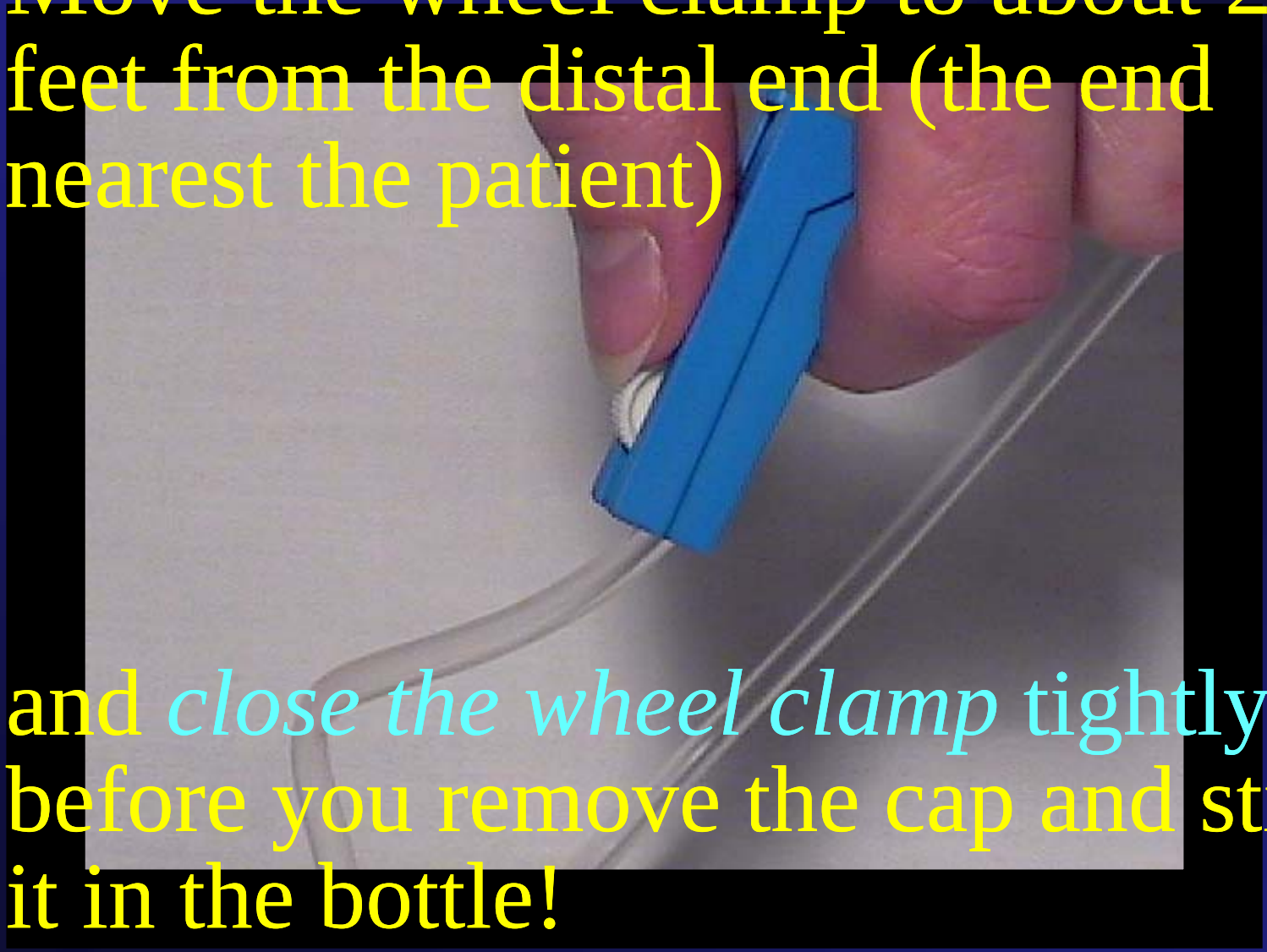
W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

This is what's in there

The sharp end is stabbed through the middle of the top of the IV bottle

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Move the wheel clamp to about 2 feet from the distal end (the end nearest the patient)



and *close the wheel clamp* tightly before you remove the cap and stick it in the bottle!

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Insert the spiked end of the IV set through the top of the sterile water

Check that the clamp is closed!

Hang the bottle on the IV stand

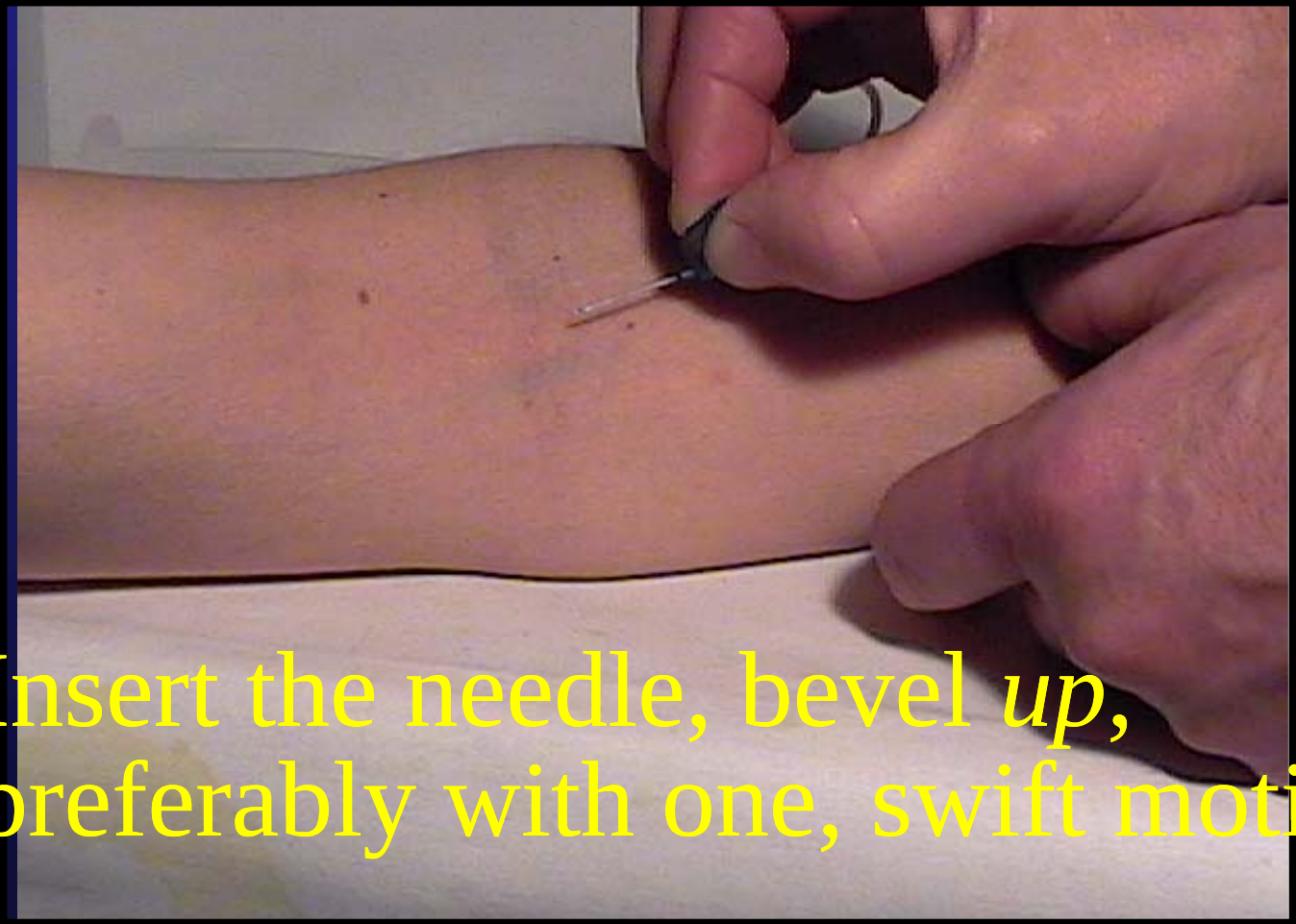
Squeeze the reservoir a few times to fill it about half-way with the IV solution

Flush the tubing, attach butterfly (usually 25 ga. needle)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

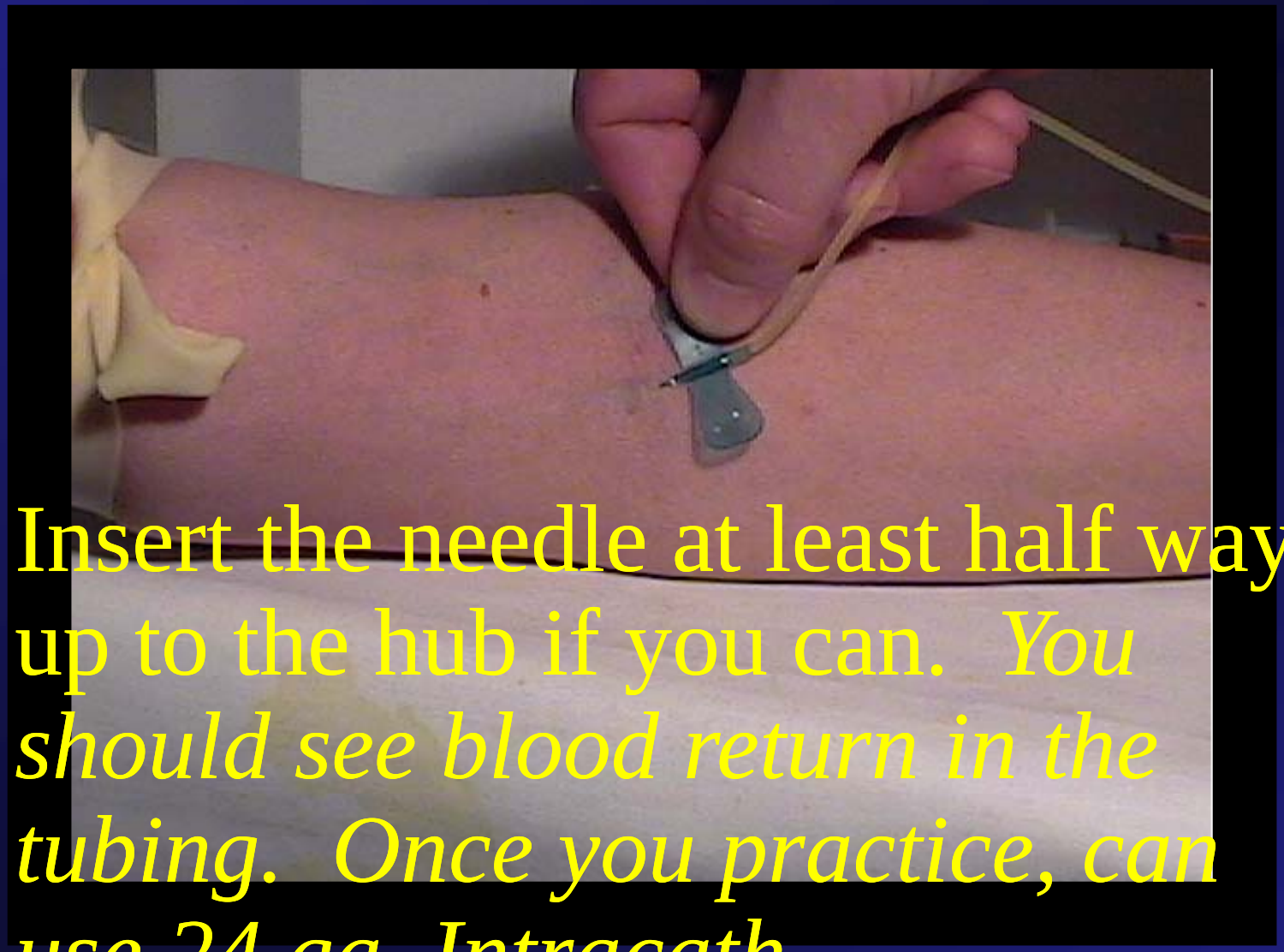
Put on the tourniquet and *get somebody to hold the patient down!*

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine



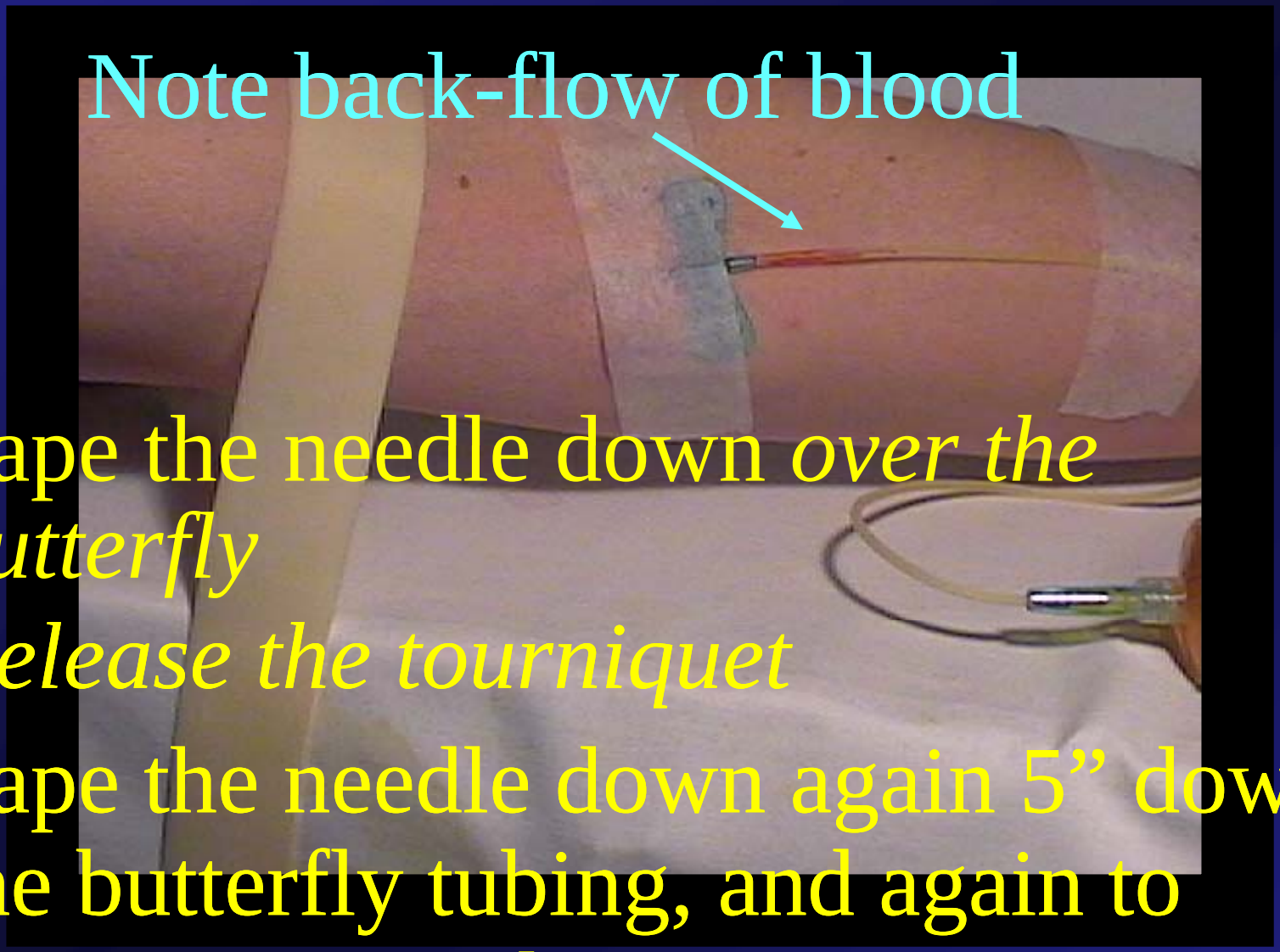
Insert the needle, bevel *up*, preferably with one, swift motion

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine



Insert the needle at least half way up to the hub if you can. *You should see blood return in the tubing. Once you practice, can use 24 ga. Intracath.*

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine



Tape the needle down *over the butterfly*

Release the tourniquet

Tape the needle down again 5” down the butterfly tubing, and again to your patient’s sleeve

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Open the wheel clamp *slowly* and observe the IV site to be sure the solution is going *into* the vein

Set the drip rate to about 10-15 drops per minute. If you patient experiences discomfort, stop the IV right away (? adjust the needle)

Once your patient is comfortable, you may open the wheel clamp and set the drip rate to approx. 65 drops per minute.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Infusion rate: 1 gm EDTA/hr. – slightly over 1 drop per second

This IV will run about 3 hours.

Anything between 2-1/2 and 3 hours is OK. The IV can run out completely before it is discontinued.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

When this IV is done, *carefully* peel back the tape over the needle while holding down the butterfly. Press the 2” x 2” *lightly* to the skin where the needle is inserted and remove the needle with a quick, smooth action. As the needle is removed, *increase* the pressure on the gauze pad for about a minute and then apply a strip of tape tightly over the gauze.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Pre-treatment Evaluation for Potential Problems

Pre-existing congestive heart failure

Pre-existing *hypo*calcemia

Pre-existing diabetes

Pre-existing renal failure/anemia

So:

Do a complete history and physical exam

Check creatinine (Chem 24), CBC, serum cholesterol, HDL

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Post-Treatment Evaluation

Repeat serum creatinine q. 3-6 months, depending on the patient's original creatinine and the patient's general health problems. Adjust the EDTA dose accordingly.

Evaluate patient's Chem-24 q. 6-12 months

Evaluate patient's cardiac functional ability

Some physicians evaluate heavy metals

Ultra fast CT scans not helpful

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Side Effects and Adverse Reactions

EDTA administration has *very few* side effects.

True “allergy” to the specific nutrients we use is basically impossible. However, if there are any problems, first take out the vitamin B complex.

Some patients experience pain, no matter what IV they receive. For those few patients, once you determine the pain has no other origin, you may add 8 cc of 1% preservative-free xylocaine to the IV

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Side Effects and Adverse Reactions

Venous irritation/inflammation

Fatigue

Headache

Nausea

Joint pain

Hypoglycemia (pts. on zinc bound insulin)

Death

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Chelation Deaths

- 4-6 deaths reported due to EDTA in early 50's
  - Used 10 grams of EDTA
  - Due to lead poisoning – renal tubules
  - Cardiac arrhythmias (hypocalcemia)
- 3 deaths between 2003 – 2005 (OR, TX, PA)
  - Disodium EDTA given as a "push" in two patients
  - Hypocalcemia present in the other patient; type of EDTA undetermined

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Precautions

Patients should *eat* before/during chelation

Use nearly isotonic solutions

Use appropriate dose of EDTA

Give oral vitamins and minerals between chelation, especially calcium and zinc

Avoid minerals *on day of* chelation

May need to change patient's type of insulin

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Osmolarity

Molarity is determined the molecular weight of the compound.

The *osmolarity* or osmotic pressure is determined by the dissociation of the compound.

The *heavier* a compound and the *higher* the dissociation, the greater the osmolarity.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Osmolarity

$$\text{Osmolarity} = \frac{\text{Osmoles}}{\text{Volume}}$$

We refer to osmolarity in *milli*osmoles

$$\text{mOsm/L} = \frac{\text{Milliosmoles}}{\text{Liter}}$$

$$\text{mOsm/mL} = \frac{\text{Milliosmoles}}{\text{Milliliter}}$$

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Calculating Osmolarity for all IVs

Plasma Osmolarity averages from about
.280 to .310 mOsm/ml, or
280 – 310 mOsm/L

Most IVs are slightly to moderately hypertonic

*Hypo*tonic IVs can be dangerous

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Plasma Osmolarity

Compounding pharmacies give you the osmolarity of all their nutrients

When making your IV solutions, it is safer to use the higher side of osmolarity (.310), since hypotonic solutions can be a problem

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Safe Osmolarity Limits

IV Push (mOsm/ml)	
Large vein	1.40
Medium vein	.950
Any vein	.400

IV Infusion (mOsm/ml)	
Large vein	1.20
Medium vein	.700
Any vein	.400

The longer the infusion and the smaller the vein, the more conservative you should be with the osmolarity

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Osmolarity Calculation Formula to make any IV you can think of

You usually need to calculate the water you must add to make a solution isotonic

$$\frac{\text{Total mOsm of Additives}}{.310} - (\text{Total ccs of additives}) = \text{ccs of water to add}$$

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Osmolarity Calculation

To determine the total osmolarity of each nutrient in your solution, multiply the osmolarity of the nutrient by the number of ccs of the nutrient you add

See Table I: Osmolarity Calculation Worksheet (in syllabus)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Osmolarity Calculation - *EDTA*

Agent or Nutrient	ccs	times	mOsm/cc	Total mOsm
Disodium EDTA (150 mg./ml)	20	X	1.34	26.80
Vitamin C, 500 mg./ml	15	X	5.80	87.00
$NaHCO_3$ (8.4%)	20	X	1.79	35.80
MgCl, 500 mg./ml	5	X	7.13	35.65
Pantothene (250 mg./ml)	1	X	.85	.85
Potassium Chloride (2 mEq./ml)	1	X	4.00	4.00
B-6, 100 mg./ml	1	X	1.11	1.11
Heparin (5000 U/cc)	1	X	.46	.46
Folic acid 10 mg./ml	1	X	.20	.20
B-Complex 100 mg./ml	2	X	2.14	4.28
B-12 (1000 mcg./ml)	1	X	.31	.31
Total cc/mOsm	**68**			**196.46**

How much water do we add to make this *isotonic*?

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Osmolarity Calculation - *EDTA*

$$\frac{\text{Tot. mOsm of addit.}}{.310} - (\text{Tot. ccs of addit.}) = H_2O \text{ to add}$$

From the previous calculations:

Total mOsm of additives = 196.46

Total ccs of additives = 68 cc

So: $\frac{196.46}{.310} - 68 = X$

$633.74 - 68 = X$

X = about 566 ccs of water to add to make this isotonic (.310)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Osmolarity Calculation - *example*

We have only 500 cc bottles of sterile water

$$\frac{\text{Tot. mOsm of addit.}}{.310} - (\text{Tot. ccs of addit.}) = H_2O \text{ to add}$$

So: $\frac{196.46}{X} - 68 = 500$

$196.46 - 68 = 500\ X$

$196.46 = 568\ X$

$X = \frac{196.46}{568}$, or $X = .345$ mOsm/ml

(345 mOsm/L)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Last

If you use NSS instead of H_2O, the osmolarity almost doubles (see syllabus)

However, if the calculated osmolarity of your IV is *less than* .280, put it in NSS

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

The IV Push Workshop

Our special thanks
to
McGuff Pharmacy
for providing all materials
used in this session

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

DISCLOSURE

No Disclosures

American College for Advancement in Medicine 2009 Las Vegas, Nevada Fall

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

The IV "Push" Workshop

Special packets of nutrients

Sterile water – we'll share it

Read each step *all the way through* before you do it and check-mark each step as you complete it

Please do NOT skip ahead!

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

IV Push Protocol

Nutrient	mOsm/ml		ml's in protocol	Total mOsm
B-6 (100 mg/ml)	1.11	x	1	1.11
Calcium gluconate (100 mg./ml)	.72	x	2	1.44
Mag. chloride (200 mg./ml)	2.95	x	5	14. 75
Pantothenic acid (250 mg./ml)	.85	x	1	.85
Ascorbate (500 mg/ml)	5.80	x	4	23.20
B-Complex (100 mg./ml)	2.14	x	1	2.14
B-12 (1000 mcg./ml)	.30	x	2	.60
TOTALS			16	44.99

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

IV Push Protocol

Both partners will receive the IV and draw up the nutrients, one after the other

Each vial of nutrients is to be shared

Both partners should do the sample osmolarity calculation for this IV (syllabus)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Calculations

For your calculations:

You'll be adding 19 ccs of sterile water. The osmolarity is the unknown this time.

The answer you should get is:

1.28 mOsm/ml (1280 mOsm/L)

This IV is moderately *hyper*tonic

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Precautions

Give the IV slowly - magnesium can cause a drop in BP. Your partner could even *faint (OOOOoooops!)*

If there is any intense burning or significant aching sensation at the needle site, *stop the IV immediately and call an instructor*

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Detailed instructions appear in the syllabus, numbered.

Please do NOT skip ahead and start the administration of the IV before we complete these steps together

Please put all used needles in the sharps container provided. Do NOT put them in with your *other trash*.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Materials you will have

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Line up the vials – left to right – in the same order you will be drawing them up:

B-6 (pyridoxine)

Calcium gluconate

Magnesium chloride

Pantothene (dexpanthenol)

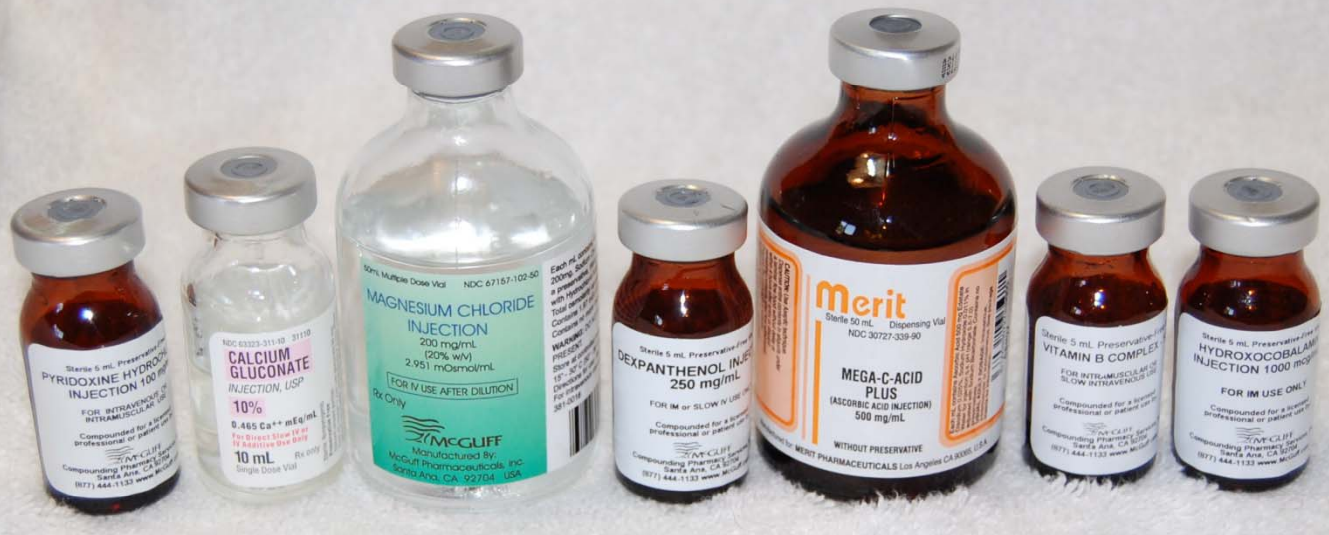
Ascorbic acid

B-complex

B-12 (hydroxocobalamine)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Like this



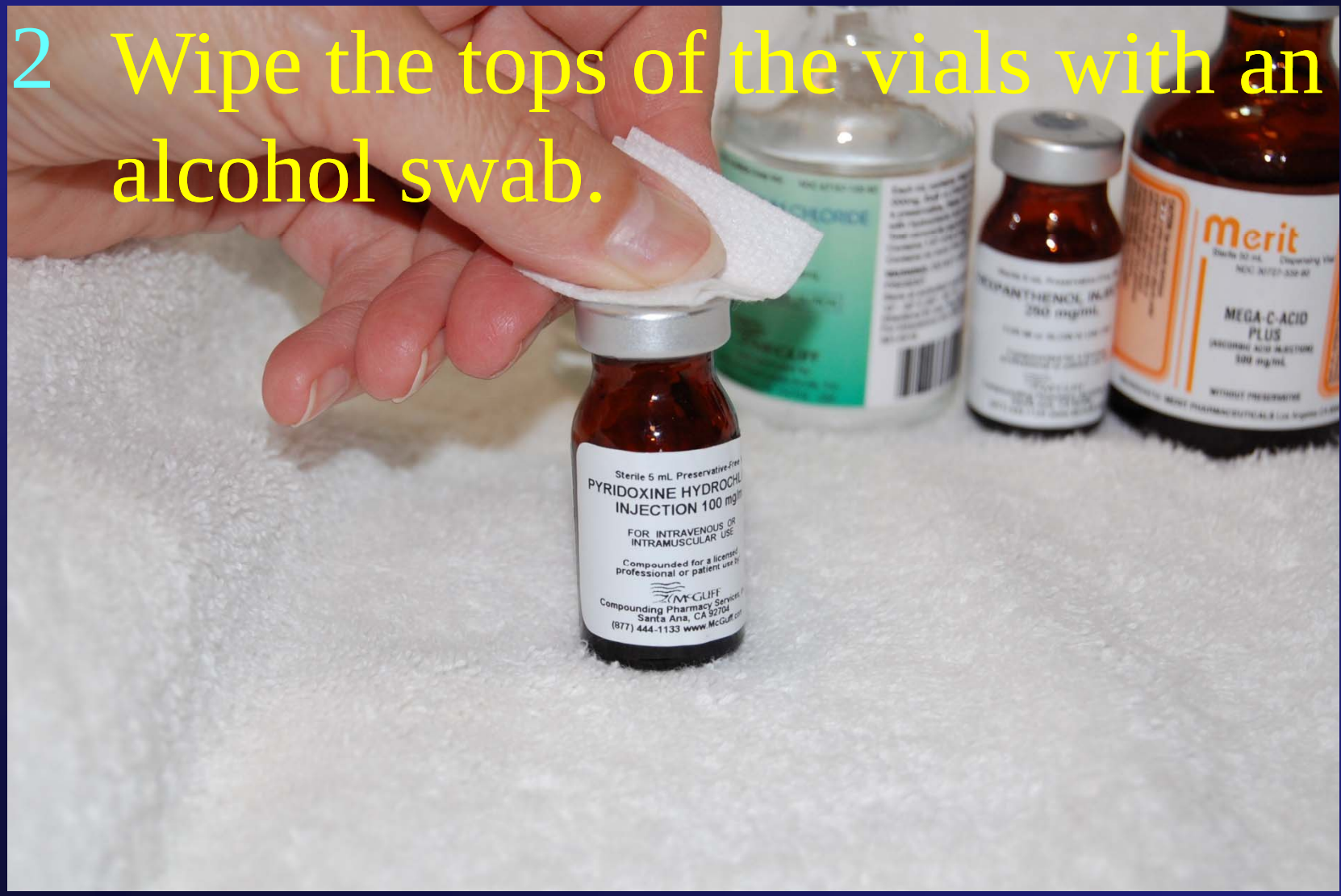
B6 Ca Mg B5 C B B_{12} Complex

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

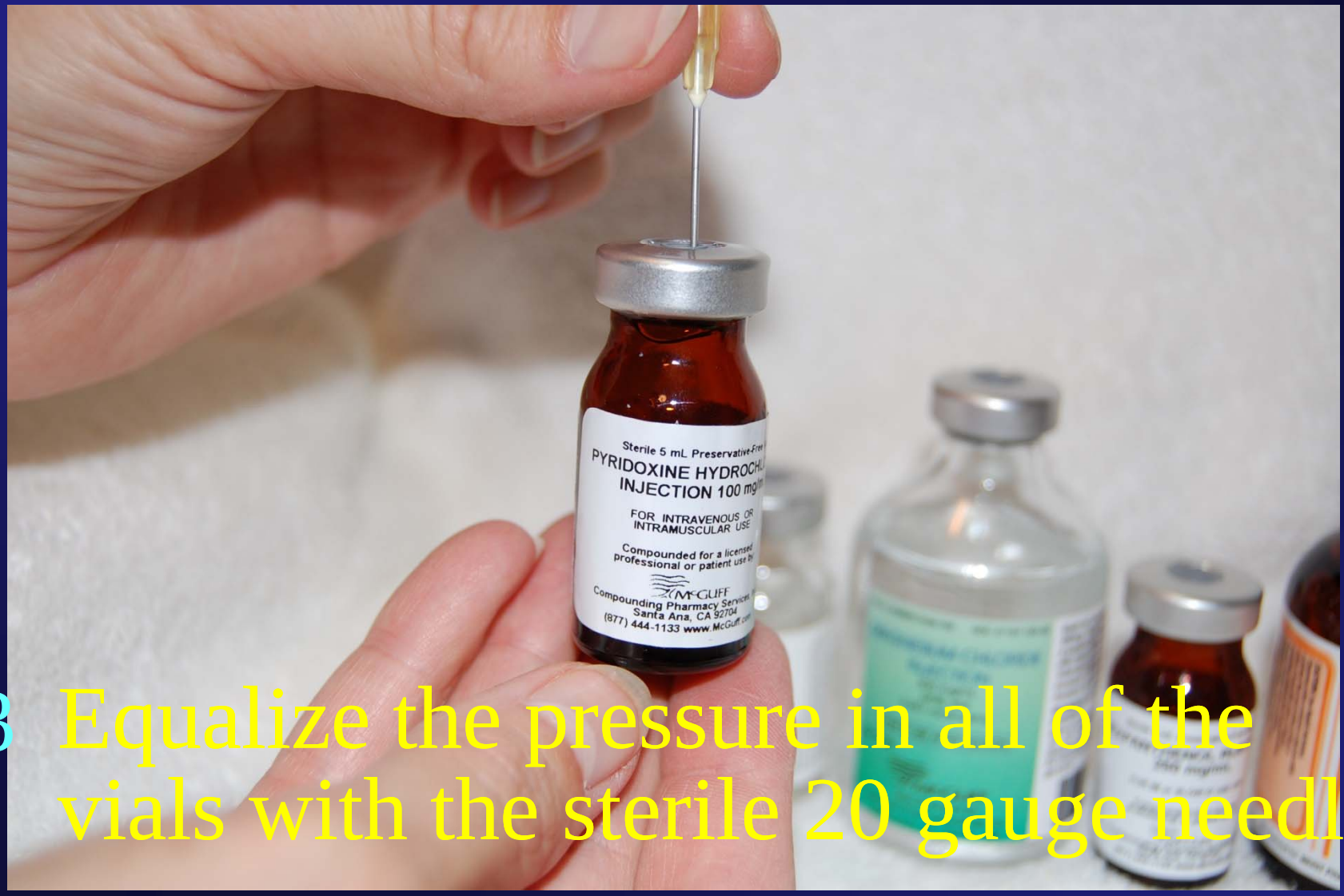
1 Remove the plastic caps from the nutrients

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

2 Wipe the tops of the vials with an alcohol swab.



W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine



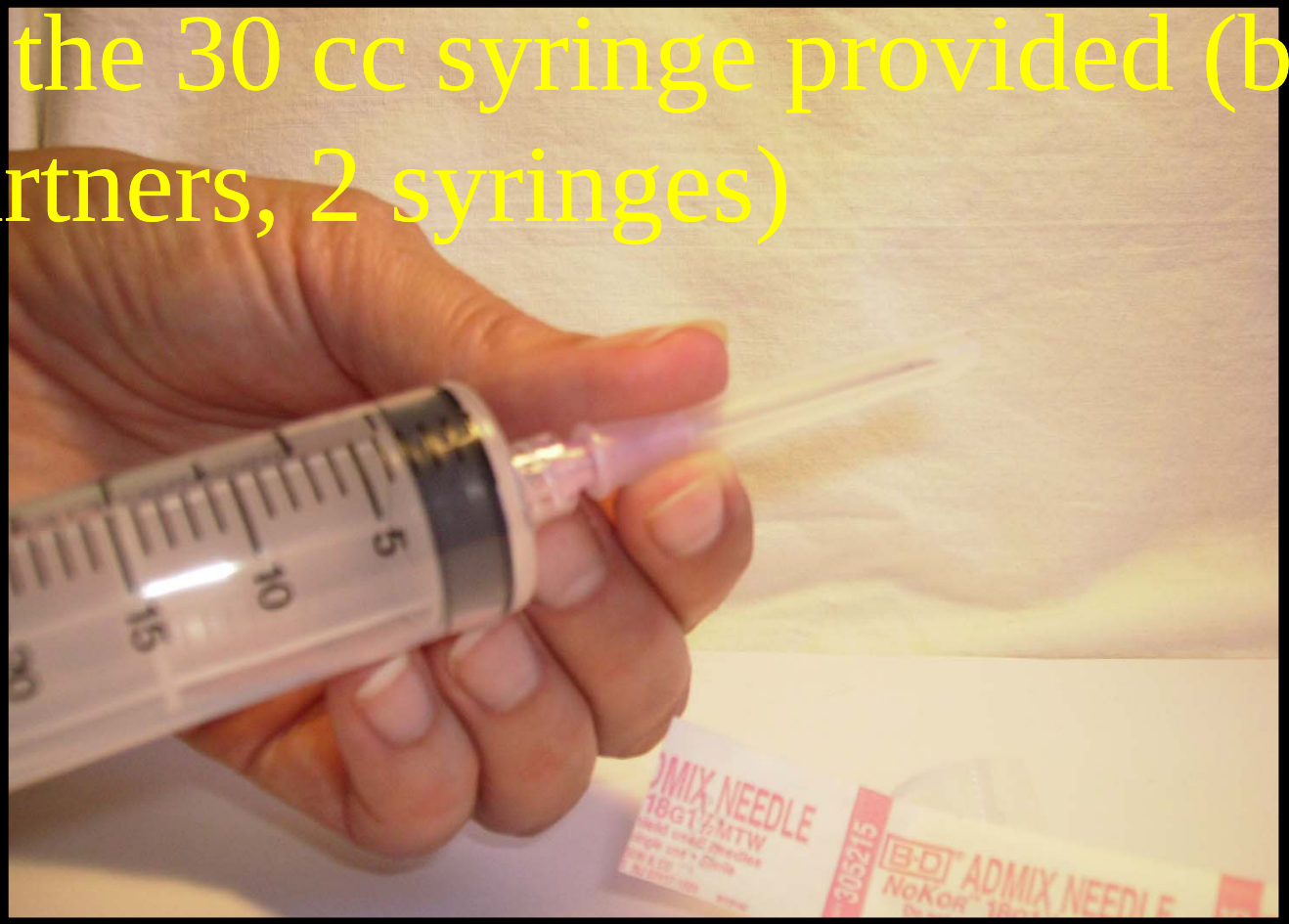
3 Equalize the pressure in all of the vials with the sterile 20 gauge needle

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Put the needle back into the needle cap CAREFULLY (not good medical practice, mind you), but for today's purpose, your partner will use this needle to de-pressurize the vials when he/she uses them.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

4 Attach the 18 gauge No-Kor needle to the 30 cc syringe provided (both partners, 2 syringes)



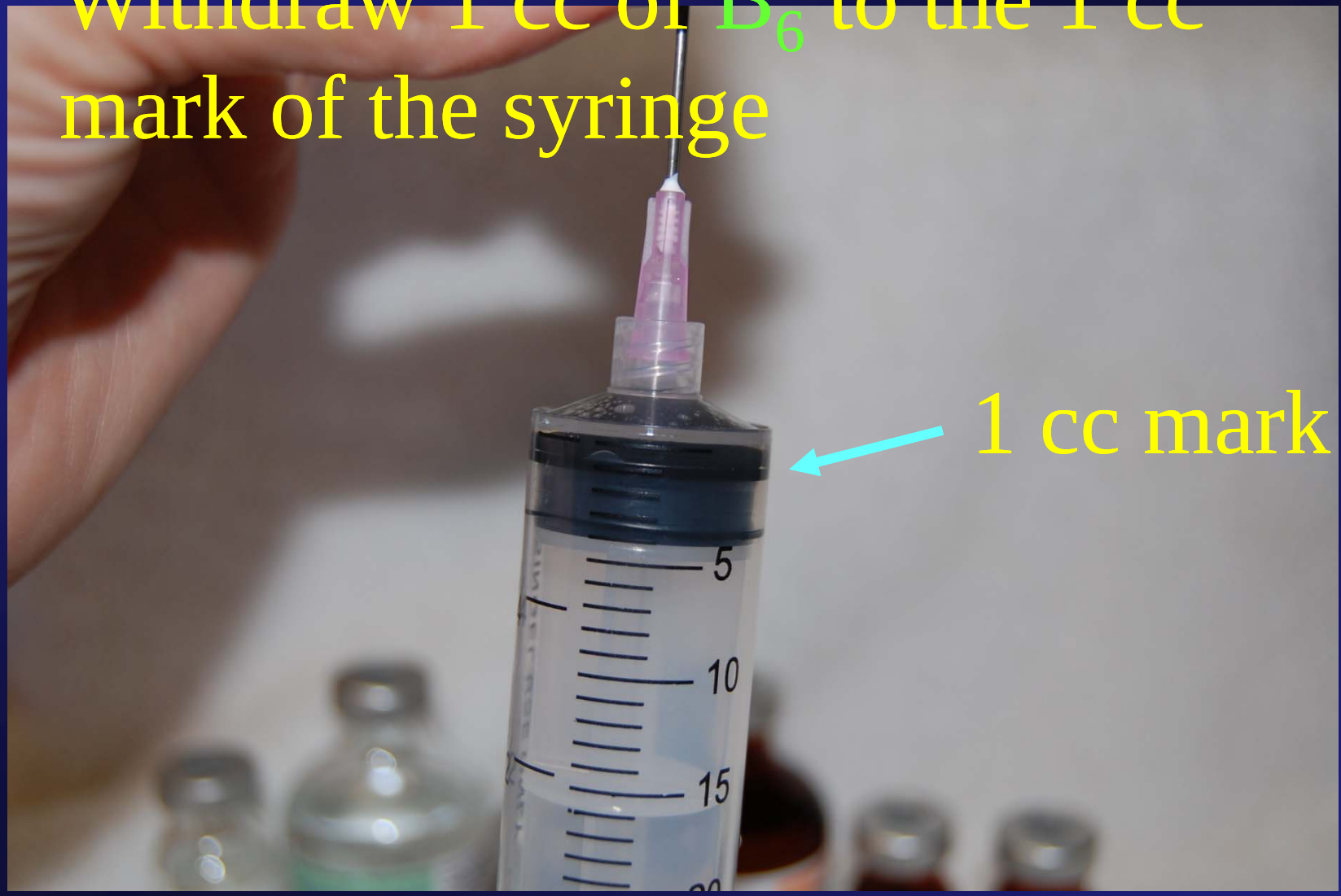
W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

5 Invert the vial of B_6 (you'll do this with each vial) and

6 insert the needle into the vial

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

7 Withdraw 1 cc of B_6 to the 1 cc mark of the syringe



W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

7 Remove the needle from the B_6 and hand the vial to your partner

Your partner should then equalize the pressure in the vial with the 20 gauge needle and withdraw the nutrient, repeating the previous steps with his/her syringe.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

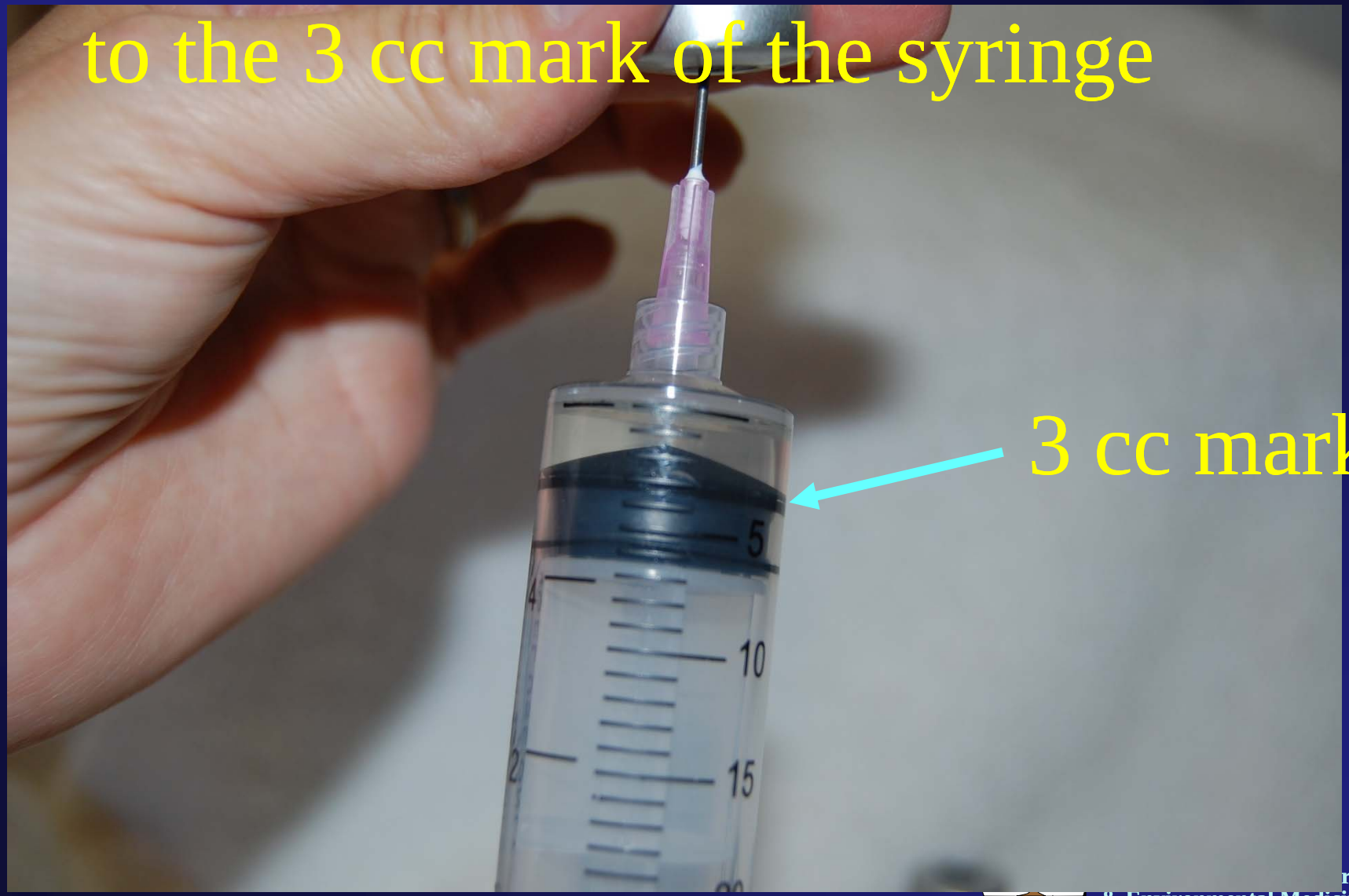
1 cc of B_6 to the 1 cc mark of the syringe.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

9 Insert the needle into the vial of calcium gluconate

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

10 Withdraw 2 cc of calcium gluconate to the 3 cc mark of the syringe



11 Remove the needle from the calcium gluconate and hand the vial to your partner

Your partner should then equalize the pressure in the vial with the 20 gauge needle and withdraw the nutrient, repeating the previous steps with his/her syringe.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

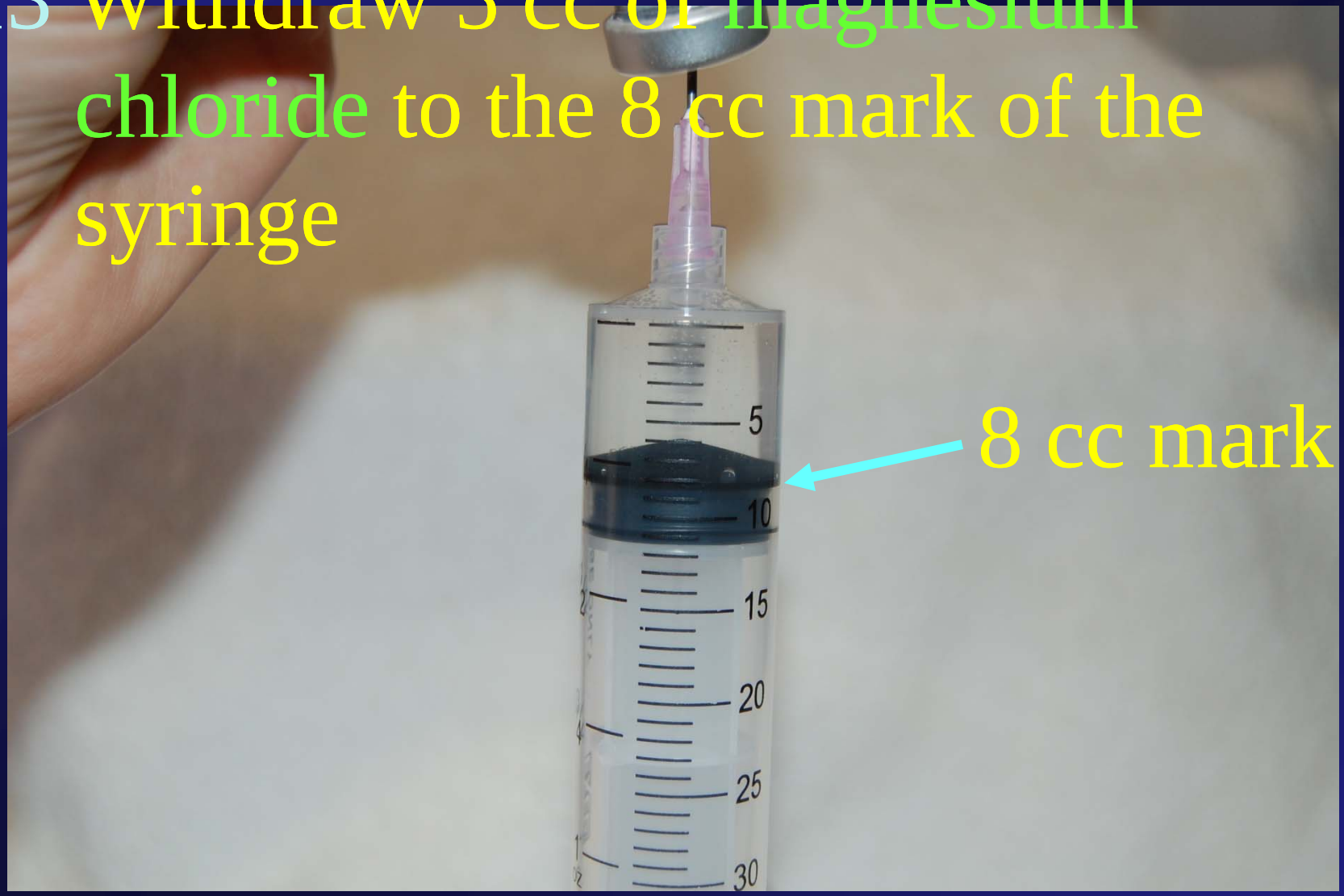
2 cc of calcium gluconate to the 3 cc mark of the syringe.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

12 Insert the needle into the vial of magnesium chloride

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

13 Withdraw 5 cc of magnesium chloride to the 8 cc mark of the syringe



W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

14 Remove the needle from the magnesium chloride and hand the vial to your partner

Your partner should then equalize the pressure in the vial with the 20 gauge needle and withdraw the nutrient, repeating the previous steps with his/her syringe.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

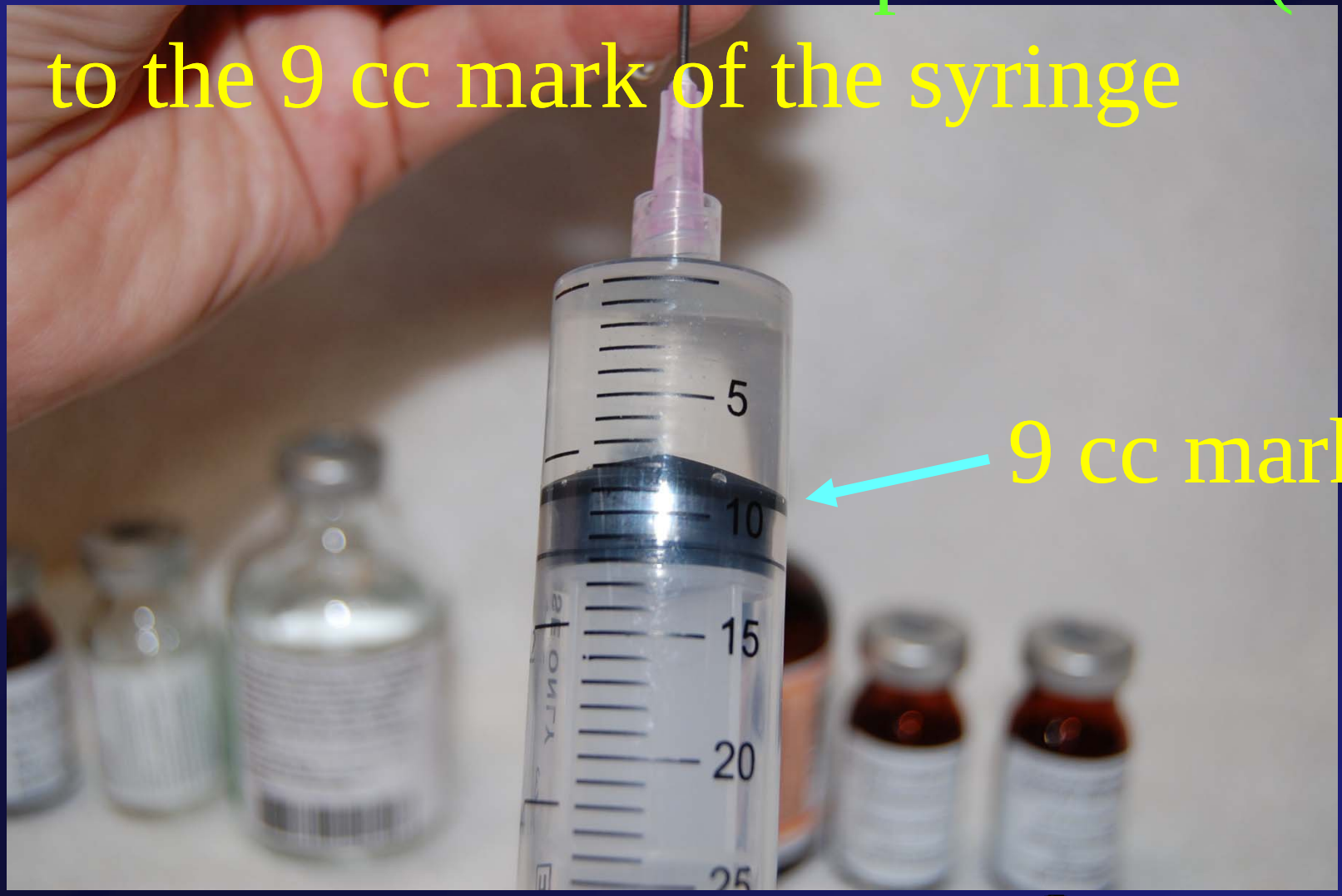
5 cc of magnesium chloride to the 8 cc mark of the syringe.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

15 Insert the needle into the vial of dexpantothene (B_5)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

16 Withdraw 1 cc of dexpanthenol (B_5) to the 9 cc mark of the syringe



W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

17 Remove the needle from the dexpantothene (B_5) and hand the vial to your partner

Your partner should then equalize the pressure in the vial with the 20 gauge needle and withdraw the nutrient, repeating the previous steps with his/her syringe.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

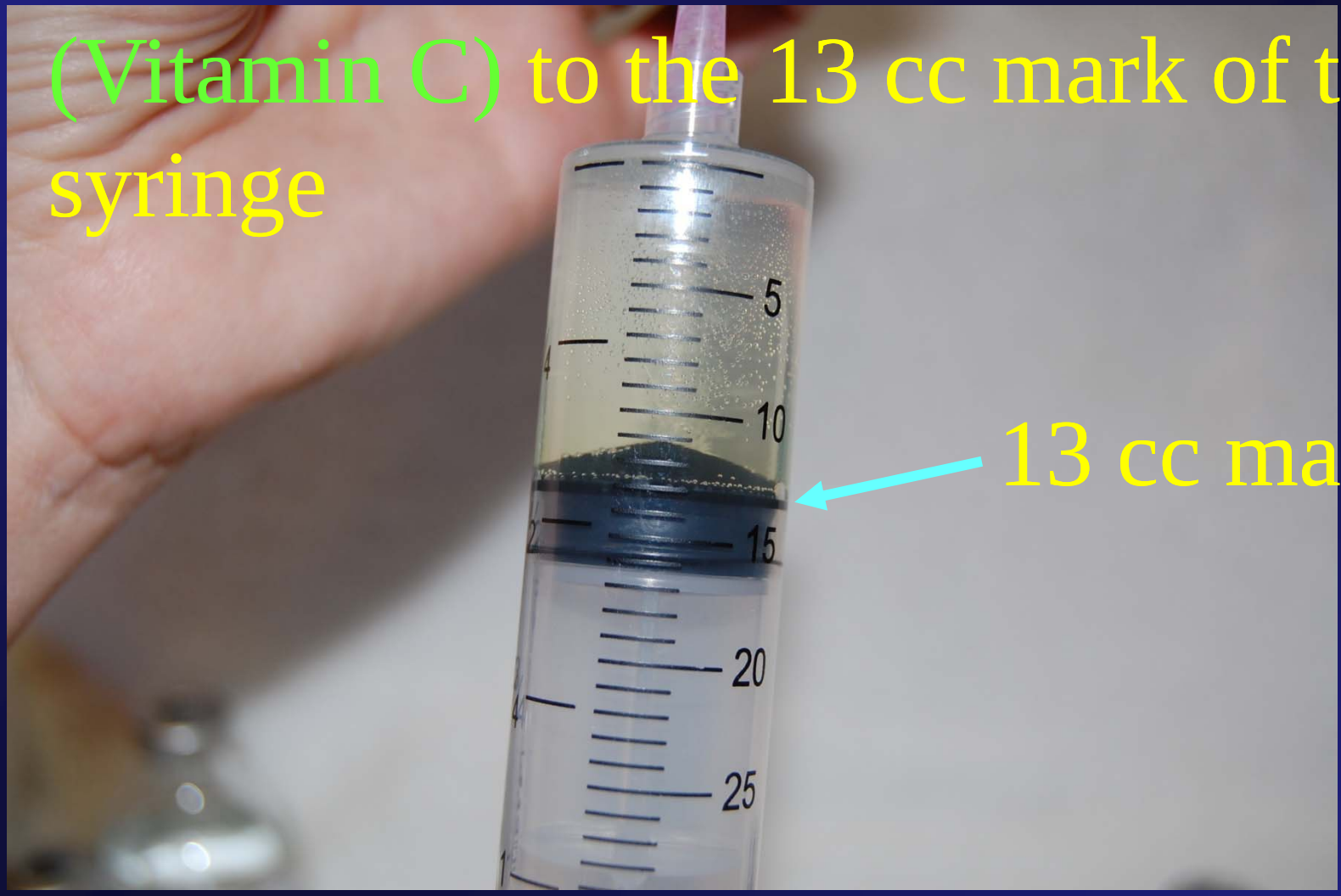
1 cc of dexpanthenol to the
9 cc mark of the syringe.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

18 Insert the needle into the vial of ascorbic acid (Vitamin C)

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

19 Withdraw 4 cc of ascorbic acid (Vitamin C) to the 13 cc mark of the syringe



W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

20 Remove the needle from the Vitamin C and hand the vial to your partner

Your partner should then equalize the pressure in the vial with the 20 gauge needle and withdraw the nutrient, repeating the previous steps with his/her syringe.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

4 cc of vitamin C to the
13 cc mark of the syringe.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

21 Insert the needle into the vial of B-complex

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

22 Withdraw 1 cc of B-complex to the 14 cc mark of the syringe

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

23 Remove the needle from the B-complex and hand the vial to your partner

Your partner should then equalize the pressure in the vial with the 20 gauge needle and withdraw the nutrient, repeating the previous steps with his/her syringe.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

1 cc of B-complex to the
14 cc mark of the syringe.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

24 Insert the needle into the vial of hydroxocobalamine (B_{12})

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

25 Withdraw 2 ccs of B_{12} to the 16 cc mark of the syringe

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

26 Remove the needle from the B_{12} and hand the vial to your partner

Your partner should then equalize the pressure in the vial with the 20 gauge needle and withdraw the nutrient, repeating the previous steps with his/her syringe.

You're now done with the nutrients

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

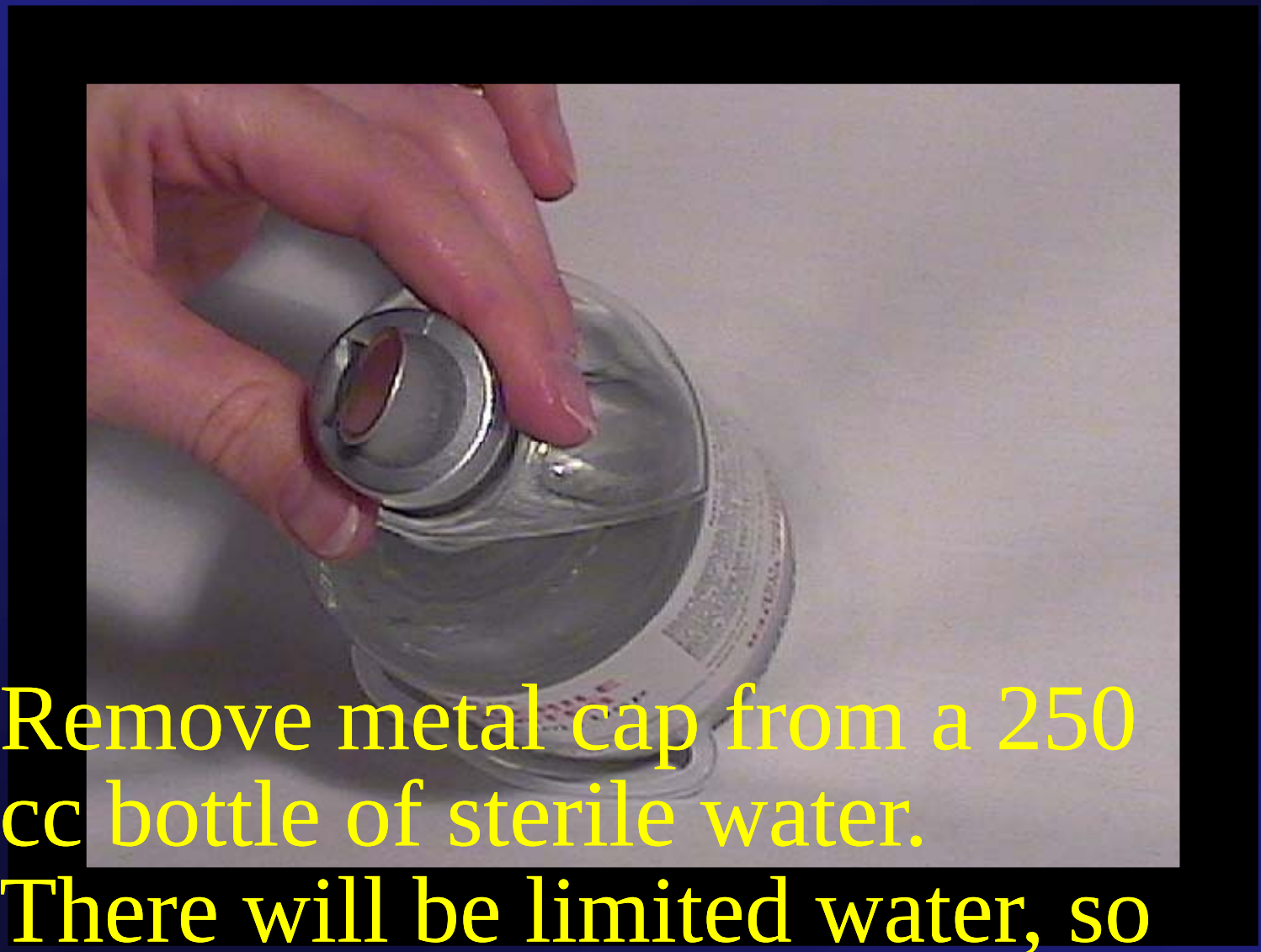
2 cc of B_{12} (hydroxocobalamine) to the16 cc mark of the syringe.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

That’s it for the nutrients

Everyone can do the next steps – up to administering the IV - together

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine



1 Remove metal cap from a 250 cc bottle of sterile water. There will be limited water, so everyone must share.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Insert the 20 gauge needle through the stopper to equalize the pressure!

1

Critical:

If you leave a vacuum in the bottle, your nutrients will get "sucked" in

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

2 Pull the plunger of the syringe back to the 35 cc mark

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

2 Invert the 250 cc bottle of sterile water

and insert the needle into the bottle

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

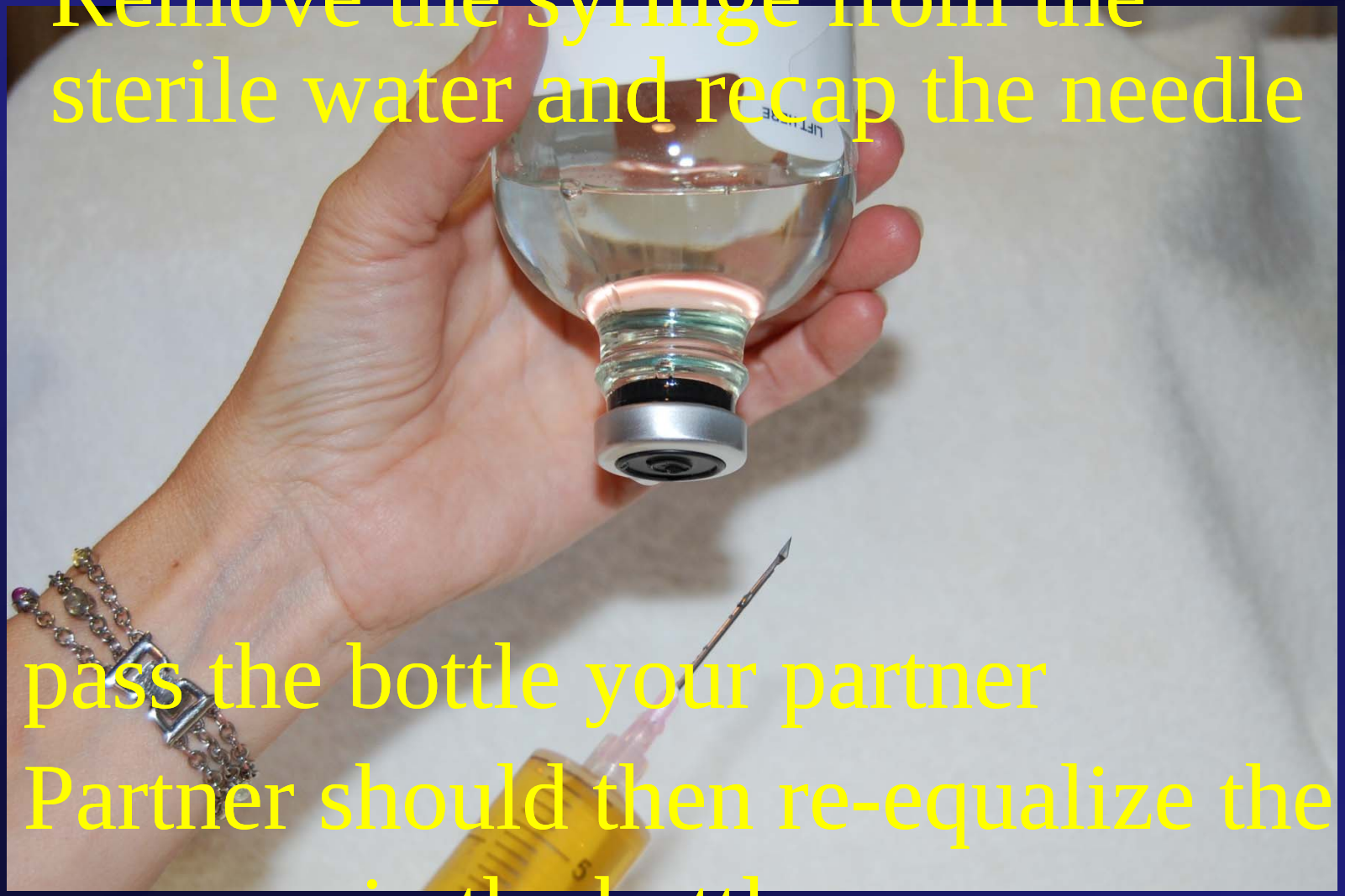
3 Inject most of the air into the bottle. Be careful not to inject the nutrients

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

4 Draw up 19 ccs of sterile water

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

5 Remove the syringe from the sterile water and recap the needle

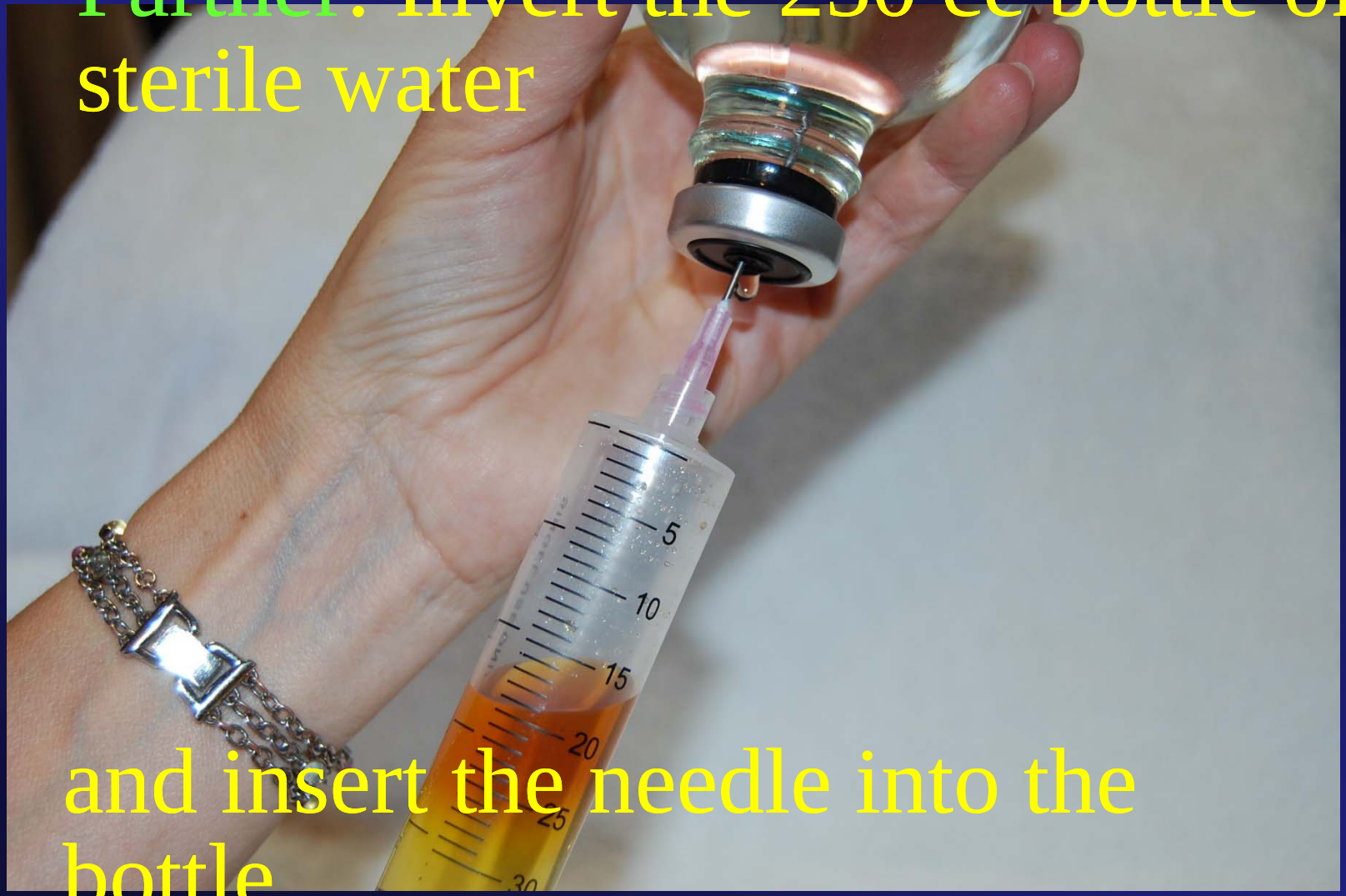


pass the bottle your partner

Partner should then re-equalize the pressure in the bottle

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

2 Partner: Invert the 250 cc bottle of sterile water



and insert the needle into the bottle

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

3 Partner: inject most of the air into the bottle. Be careful not to inject the nutrients

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

4 Partner: draw up 19 ccs of sterile water

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

6 All participants: draw up a few cc's of air into the syringe

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

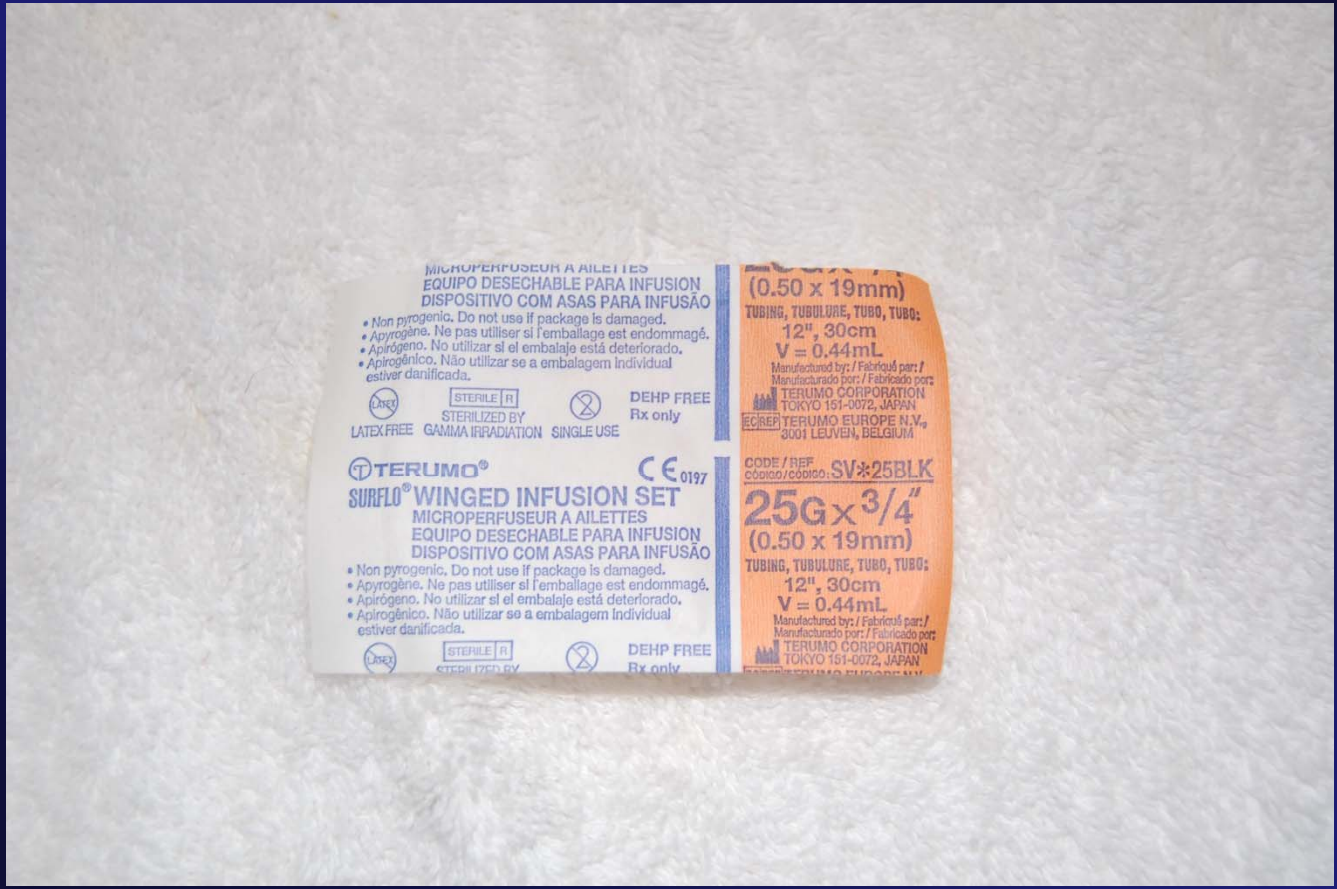
7 Mix the nutrients by rocking the syringe back and forth

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

8 Remove the capped needle from the syringe

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

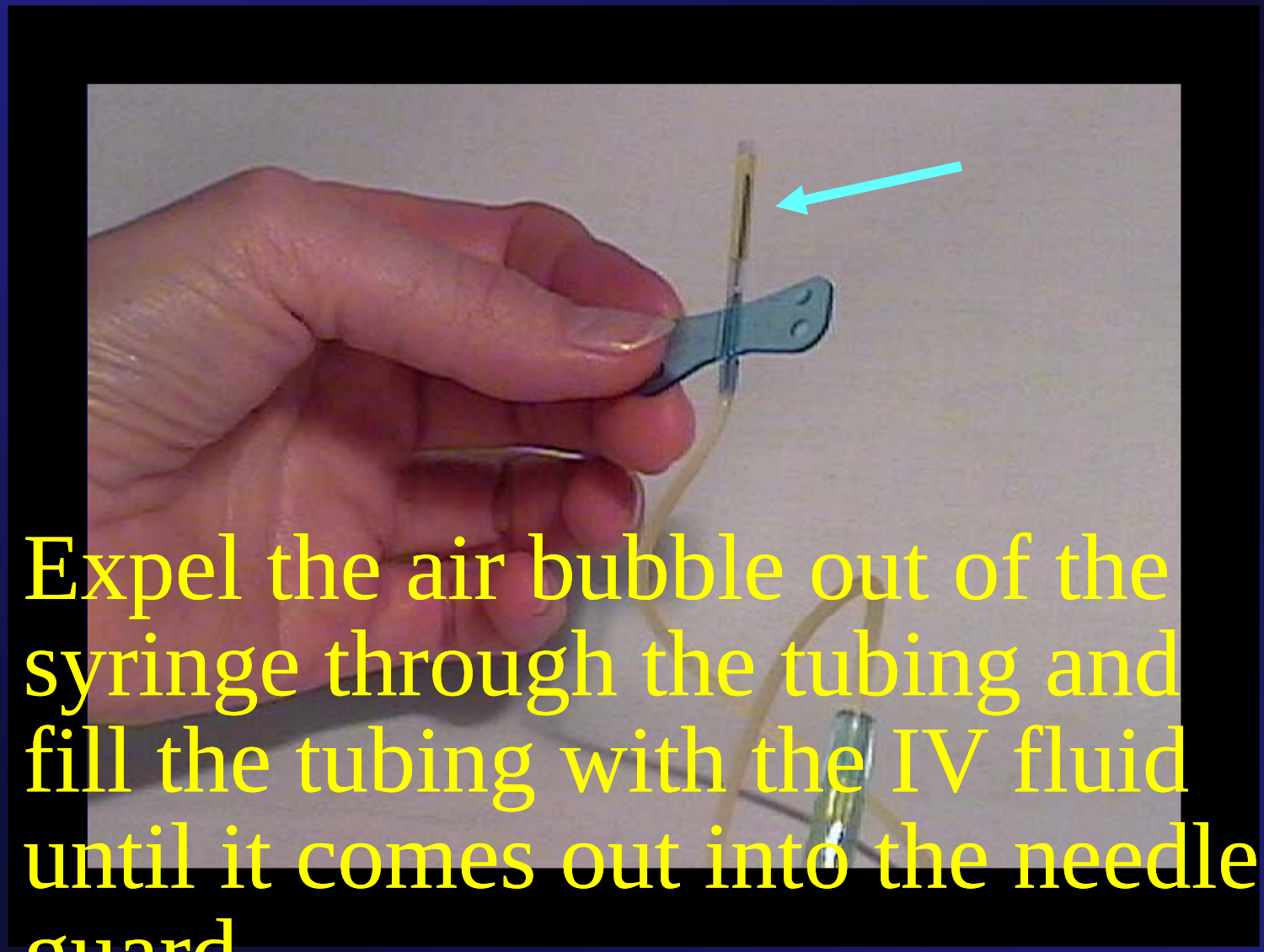
9 Winged infusion set, 25 gauge needle – you gotta open it



W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

10 Attach the infusion set to the syringe

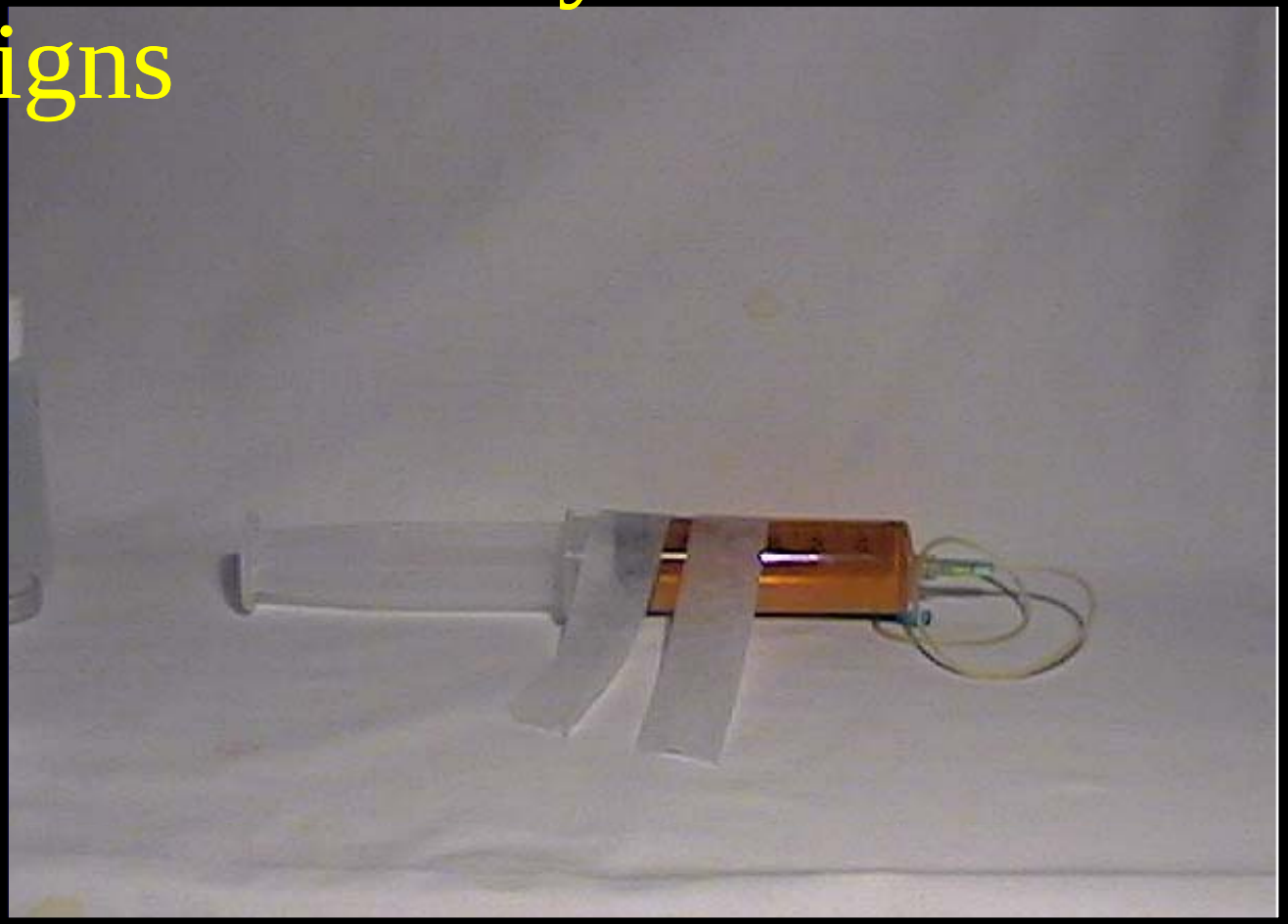
W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine



Expel the air bubble out of the syringe through the tubing and fill the tubing with the IV fluid until it comes out into the needle guard.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

12 Here's where you'd take vital signs



13 Tear off one piece of tape, 3-4" long

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

Reminder

You'll take turns giving the IV

Use the largest vein you can find

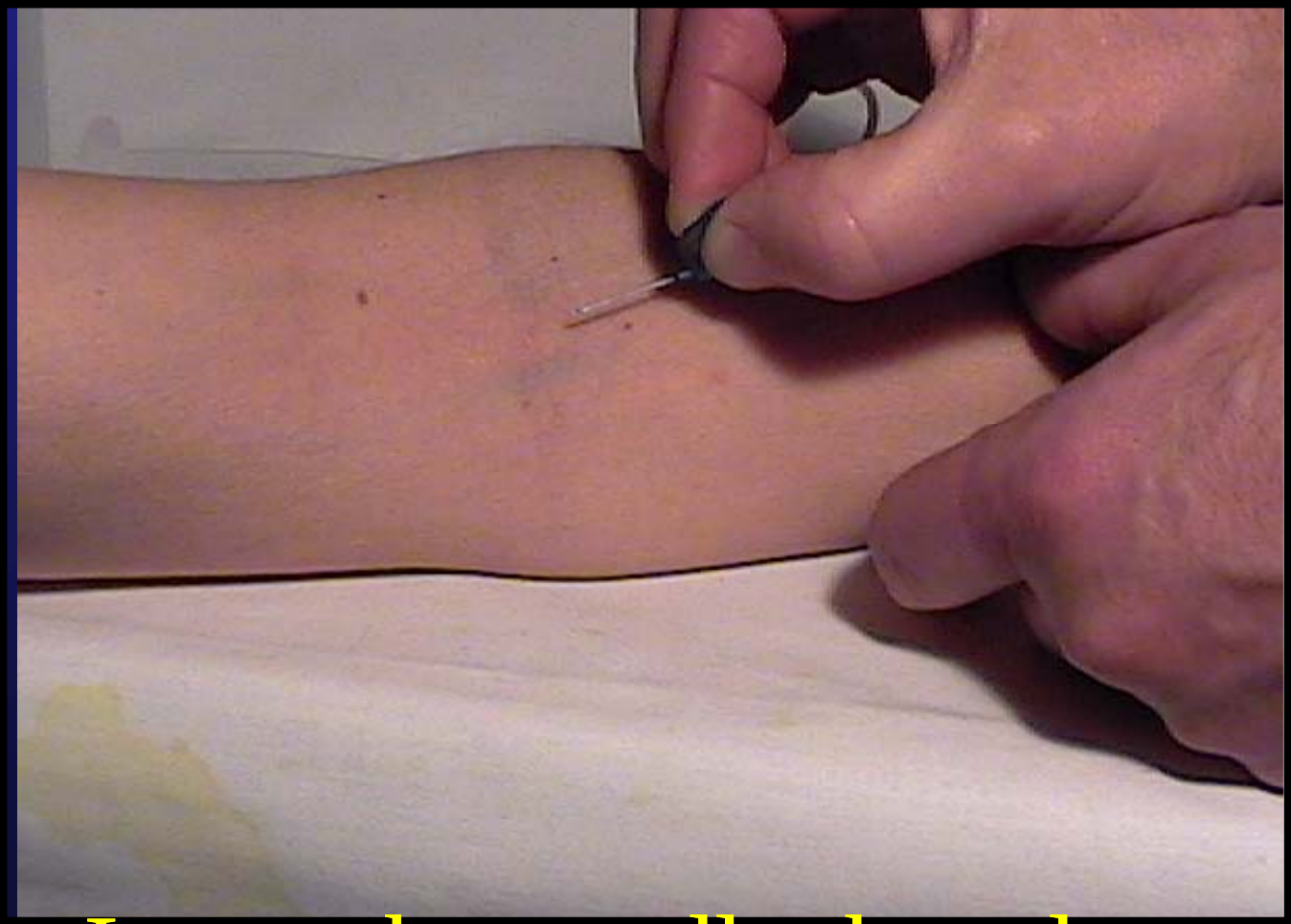
Give the IV slowly - magnesium can cause a drop in BP. Your partner could even *faint. Be careful.*

If there is any intense burning or significant aching sensation at the needle site, *stop the IV immediately and be sure there is no extravasation.*

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

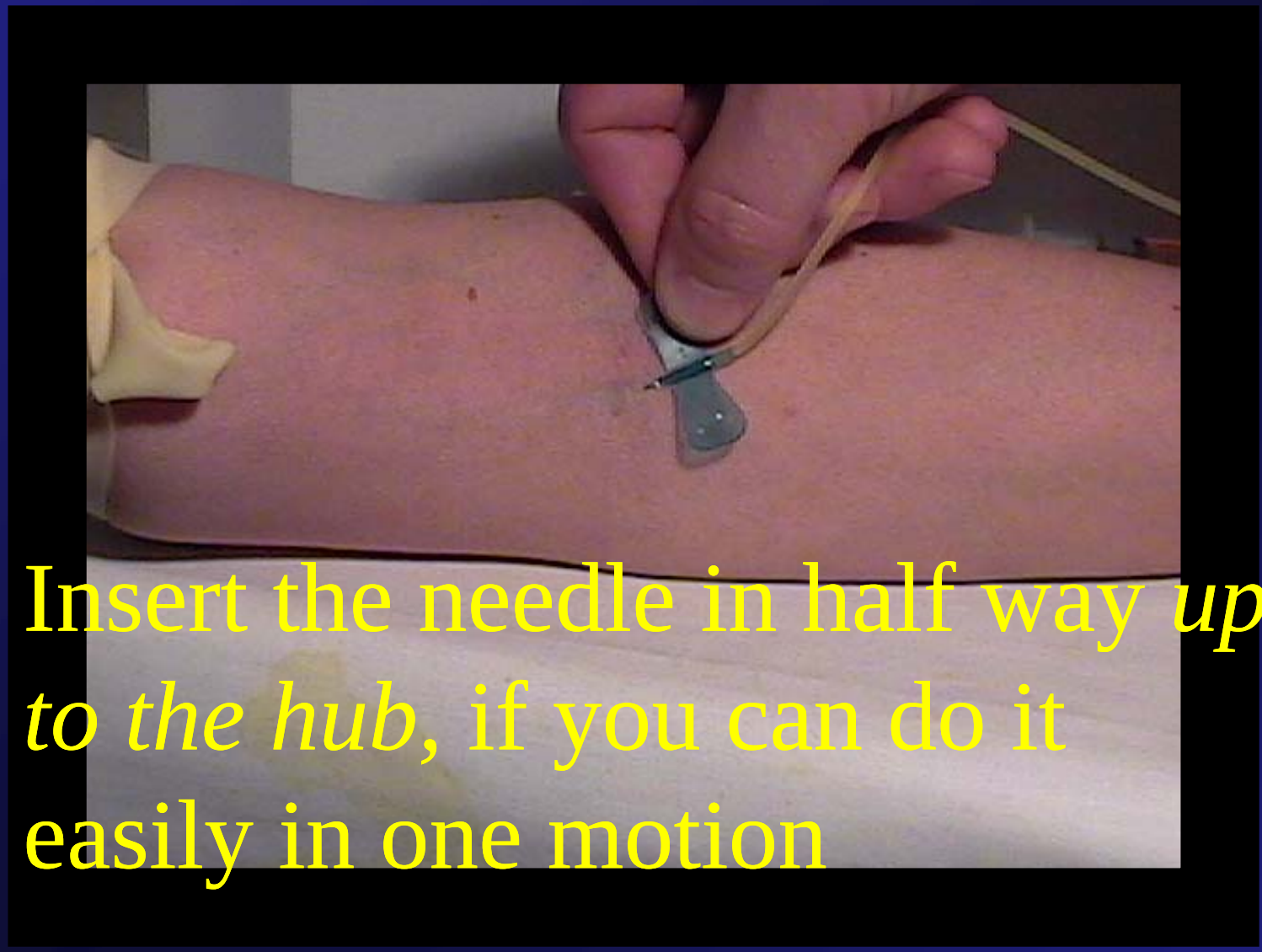
14 Put on the tourniquet and get somebody to *hold the patient down*

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine



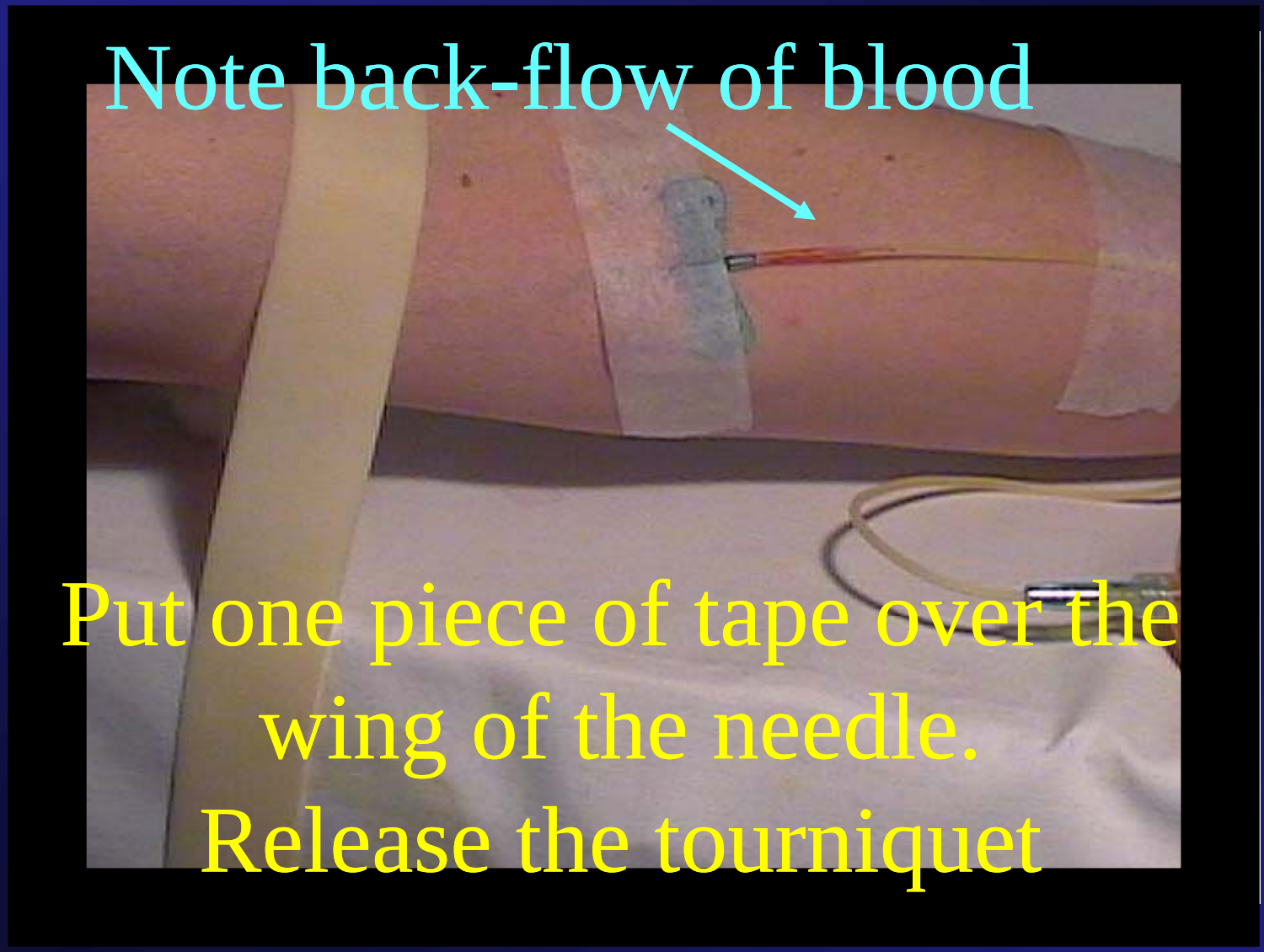
15 Insert the needle, bevel up

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine



Insert the needle in half way *up to the hub*, if you can do it easily in one motion

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine



16 Put one piece of tape over the wing of the needle.

17 Release the tourniquet

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

18 Slowly inject 1-2 cc's of the solution and be sure to watch the site carefully and observe your patient.

19 If he or she experiences any discomfort or other symptoms, stop the push and call for help

20 If not, continue slowly (10-15 minutes) if all seems OK

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

21 Proceed with the IV. If your partner feels too warm or becomes lightheaded, stop the IV until the symptoms pass.

22 Once the IV is complete, fold the 2” x 2” in quarters, place it lightly over the needle, remove the needle and put firm pressure on the 2” x 2”.

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy
& Environmental Medicine

23

The other partner should then go back to step # 14 and give the IV

Reminder: please put all needles in the sharps containers – do NOT put them in with your trash!

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

End of the Formal “Push” Instructions

QUESTIONS?

W.A. Shrader, Jr., MD
Santa Fe Center for Allergy & Environmental Medicine

Nuts and Bolts of Chelation Therapy

Mixing and Administration, Added Nutrients, Safe EDTA Dose Calculation and Osmolarity Calculation

This session will teach you the practical aspects of chelation therapy and the "hands-on" things you need to know before you begin actual chelation therapy on patients in your office. At the end of this session you should know how to:

1. Recognize the importance of nutrients added to chelation therapy
2. Mix a chelation solution
3. Initiate and terminate a disodium or disodium/magnesium EDTA infusion
4. Evaluate your patients pre- and post-treatment
5. Calculate the dosage of EDTA to use for specific patients
6. Calculate the osmolarity of a chelation (or any other) IV solution

You will also learn some of the reasons we use nutrients with chelation IVs, and finally, we'll have a workshop so you can get the actual hands-on experience with IV administration, by way of giving an actual IV "push" protocol (the Meyer "cocktail").

Nutrients in Chelation Therapy

I will not have time in the slide portion of this presentation to discuss all of the reasons we add nutrients when we use chelation. Therefore, most are discussed here, if you would like further discussion.

Some Reasons Chelation Works

EDTA's *only* action is to alter the distribution of metals in the body. Metals can be extremely toxic, of poisoning enzyme systems and acting as pro-oxidants. EDTA both removes and moves metals. Many of the natural metals present in the body are present in the metalloenzymes, including metallothionein. Metallothionein is responsible for transporting many metals in an out of the cell. EDTA removes the catalysts of free radical proliferation (e.g. iron), and these free radicals damage all cells and the vascular endothelium. EDTA also removes circulating extracellular heavy metals and creates a strong cellular gradient to pull metals out of cells through the cell membrane.

All of these actions require the presence of specific nutrients.

The nutrients we use both augment the action of EDTA and have specific activities of their own. Some have their own independent actions that enhance the overall performance of EDTA.

In the body, vitamins are incorporated into cofactors, enzymes and coenzymes for thousands of cellular processes. Minerals act as catalysts and cofactors in most enzymatic reactions that take place in the body.

Riboflavin: riboflavin is the precursor for several enzymes, including flavin adenine dinucleotide (FAD). FAD is the precursor for monoamine oxidase, glucose oxidase, xanthine oxidase and others. Many of these are metalloflavoproteins and detoxicants. FAD

is essential in the citric acid cycle for energy production (ATP), and ATP is essential for all cellular activity, including the transport of metals.

Niacin (Vitamin B_3): also known as nicotinic acid and nicotinamide, niacin is required for synthesis of all of its active forums, nicotinic acid dinucleotide (NAD) and an NADP. Again these are both essential in the citric acid cycle for energy production.

Pantothene (pantothenic acid): pantothene is primarily responsible for the synthesis of acetyl CoA. Acetyl CoA is required for the synthesis of over 70 enzymes in the body and is used, once again, in the citric acid cycle for energy production.

Folic acid (folate): must first be converted to tetrahydrofolate (THF), which transfers one-carbon units during biosynthesis, primarily for protein metabolism. These reactions are required for the production of serine, methionine, glycine, choline, purine dinucleotides and thymidine monophosphate. The value of added folic acid is primarily to aid in treatment of neurological problems such as Alzheimer's, and many patients on chelation have these conditions.

All active cells in the body contain channel proteins. These channel proteins allow the transport of many cations in and out of the cell. Channel proteins include metallothionein, which may carry copper, zinc, cadmium, mercury, silver and many other metals out of the cell. Channel proteins all require ATP to function, which is the reason ATP is so important in this discussion. *Most of the B-vitamins we add to our chelation solutions enhance the production of ATP*.

Some nutrients are added to chelation protocols because they have their own independent actions. These include:

Potassium chloride: KCl is added primarily because it regulates intracellular electrolyte exchange. This is important especially for patients on diuretics or other medications that alter potassium balance.

Sodium bicarbonate: sodium bicarbonate is added primarily to balance the acid pH produced by the added vitamin C. Additionally, EDTA (and all nutrients) work best in an alkaline environment.

Vitamin C: Vitamin C is required for the maintenance and repair of connective tissue (for the hydroxylation of proline), and aids in the repair of damaged endothelium in large and medium arteries. Additionally, vitamin C is a mild chelating agent in its own right and has an additive effect with EDTA.

Magnesium: magnesium acts as a cofactor in most enzymatic reactions in the body. This includes, of course, the citric acid cycle, and magnesium aids in the production of ATP and enhancement of channel protein activity to excrete metals. Magnesium helps maintain vascular tension, and in quantities used with chelation protocols is a mild vasodilator. This helps to transport the IV solution to more cells.

Magnesium also stabilizes nerve conduction and prevents arrhythmias, which is important, especially in older patients. Further, magnesium acts to help to lower blood pressure. I have found in practice that IV chelation, over time, and especially using magnesium/disodium EDTA, will indeed lower blood pressure for patients with mild to moderate hypertension. This effect is not seen until patients have had 15-18 treatments.

Calculation of Creatinine Clearance: Cockroft-Gault Equation

The most important concept when treating patients with EDTA chelation is the calculation of the proper amount of EDTA to administer. EDTA is excreted primarily by the kidneys, so kidney function must be evaluated in all patients by way of creatinine. There is evidence in the literature that EDTA can be harmful or fatal if too much is administered to be handled properly by the kidneys.*

* Oliver LD, Mehta MB, Sarles HE. Acute renal failure following administration of ethylenediamine tetraacetic acid (EDTA). *Texas Medicine.* 1984;80:40-41.

The formula we use was developed by DW Cockroft and MH Gault, and published in 1976. So it's called the Cockroft-Gault formula (equation).

To calculate creatinine clearance (CrCl), you must take into account the patient's creatinine, sex, age, height and *lean body weight* (LBW).

LBW for males = 50 kg + 2.3 kg/inch over 5 feet

LBW for females = 48.5 kg + 2.3 kg/inch over 5 feet.

If the patient's *actual weight* if it is less than their LBW, *use the actual weight*.

The formula to use is: **CrCl = $\frac{\text{(140 – age) times LBW}}{\text{(Age) times (creatinine)}}$**

To calculate the dose of EDTA, the formula is:

EDTA dose = 50 mg./kg of LBW X $\frac{\text{CrCl}}{100}$

For example, say you have a male who is 65 years old, is 5 feet 7 and weighs 175 lbs, and his creatinine is 1.0. **Note: the example here is a *different* one than I will use in the lecture, so you have two examples from which to work and compare).**

For his **LBW**, it's: 50 + (2.3 X 7"), or 50 + 16.1 = **66.1**

So, his **CrCl** is $\frac{(140 - 65)\ (66.1)}{(65)\ (1.0)}$ or $\frac{(75)\ (66.1)}{65}$ or $\frac{4957.5}{65}$ or **76.27**

So his **EDTA dose** is (50 mg./kg.) (66.1) X $\frac{76.27}{100}$

or (3305 mg.) X 0.7627, which equals 2520 mg., or **2.5 grams**. At 150 mg./cc (standard concentration of EDTA), you'd put **16.8 cc of EDTA** in the IV (2.5 divided by 150).

This formulation is used primarily to avoid overdosages for patients who have an abnormal creatinine, to make sure you're giving a safe dose of EDTA. In any case, you never give more than 3 grams of EDTA for males and 2.8 grams for females, and do the calculation for all patients.

This IV is generally given over a period of 2-1/2 to 3 hours (slightly over 1 drop per second with a 25 gauge needle), once weekly for 30-40 treatments. I then give it once

every two weeks awhile, depending on a patient's symptoms, and then monthly. Most patients with significant cardiovascular disease and risk factors continue to do this indefinitely, some going to every 2-4 months, though we recommend they continue about monthly. It can be a remarkable treatment for some patients.

Mixing the chelation solution

In my office, we use only magnesium disodium EDTA via IV infusion, since I primarily treat cardiovascular disease, not heavy metal toxicity. I use a 2-1/2 to 3-hour infusion, mixed in 500 cc of sterile water (not saline). Some physicians use *calcium* EDTA via IV push. We do not do this, primarily because old habits die hard.

Please note: if you decide to use *both* types of EDTA in your office (IV push and the infusion), it is *absolutely critical* you keep your *calcium* EDTA *separate* from your *disodium/magnesium* EDTA, and that your disodium/magnesium EDTA is clearly labeled "IV DRIP ONLY". NEVER USE DISODIUM OR DISODIUM/MAGNESIUM EDTA VIA IV PUSH, as *this can cause fatal hypocalcaemia*.

Sample EDTA Chelation Protocol (additives and osmolarity)

Agent or Nutrient	ccs	Times	mOsm/cc	Total mOsm
Disodium EDTA (150 mg./ml)	20	X	1.34	26.80
Vitamin C, 500 mg./ml	15	X	5.80	87.00
$NaHCO_3$ (8.4%)	20	X	1.79	35.80
MgCl, 500 mg./ml	5	X	7.13	35.65
Pantothene (250 mg./ml)	1	X	.85	.85
Potassium Chloride (2 mEq./ml)	1	X	4.00	4.00
B-6, 100 mg./ml	1	X	1.11	1.11
Heparin (5000 U/cc)	1	X	.46	.46
Folic acid 10 mg./ml	1	X	.20	.20
B-Complex 100 mg./ml	2	X	2.14	4.28
B-12 (1000 mcg./ml)	1	X	.31	.31
Total	68			196.46

Note: You may not be using this amount (20 ccs) of EDTA. The amount you will use is calculated by a specific method you will be taught in this session (Cockroft-Gault).

A similar protocol appears in Table II, and you may use either, or one of your own creation. It would probably be wise to use a protocol similar to one of these, as they are both fairly "typical" chelation protocols. If you want to deviate significantly from these, be sure to consult with an ACAM physician who has had many years of experience first.

Drawing Up the Chelation Infusion

Method: Exact, step-by-step instructions appear in the material that follows, and you can refer to the slides from the lecture that will graphically illustrate some of these steps.

An IV *Infusion* is easier to draw up and administer than an IV *Push* (which is why we're giving you hands-on experience with the more difficult of the two). So during the lecture, I

won't spend much time on the actual infusion process, but it all appears here so you can follow it step by step when you get home.

The Chelation Protocol: General comments

Note: In our office, we cover our EDTA infusion bottles with a black bag (you can make some out of plastic trash bags) to protect the lability of the Vitamin C (it's very light-sensitive). **NOTE: DO NOT USE NUTRIENTS OR IV SOLUTIONS CONTAINING PRESERVATIVE. NEVER USE PLASTIC BAGS.** Plastic bags all contain plasticizers that have leached into the solution, and many are associated with cancer in both animals and humans.

Drawing up the Nutrients

It's best to start by drawing up each nutrient and the EDTA separately, using a 10 cc syringe, and injecting them separately into the IV bottle. As you (or your nurse) get more proficient, you may draw up several nutrients at once, using a single large (20-30 cc) syringe (much like we'll teach you in the workshop with the IV push protocol). It saves time. We have done this in our office since 1986, and have not seen a problem. Use of multiple syringes – one for each nutrient – is quite costly and unnecessary.

For the chelation infusion protocol here, you will use one syringe for all the additives, and they will be drawn up one at a time. When one syringe is used, e.g. 10 cc, a minimal but measurable amount of "cross-contamination" between vials of nutrients is bound to occur. However, the effects of this are negligible if the procedure is done carefully and as directed.

This cross-contamination is only noticeable if a small amount of a "colored" nutrient (such as B-12) is inadvertently introduced into a vial of a "clear" nutrient, such as magnesium chloride. *Therefore, we usually draw up the clear, or non-colored nutrients first, followed by the nutrients that have any color.*

When drawing up nutrients in our office, we use an 18 ga., 1-½ inch BD Admix needle (called "No-Kor"), BD # 305215. This needle does not produce "coring", or removing little cores of the rubber stoppers. We do this because these cores can end up in your IVs, which is not a good thing.

NOTE: You may draw up a chelation IV up to 24 hours ahead of time, as long as you place it in the fridge as soon as it is drawn up. However, if you do this, DO NOT add the EDTA or the Vitamin C into the IV until the patient *appears in your office* and is ready to receive it, since these are both labile and will lose potency if they are mixed into the solution ahead of time.

DRAWING UP THE CHELATION IV

1. Line up the vials in front of you (cross-wise from *left to right*) from which you will draw the nutrients and EDTA, in the same order they appear down the list in the protocol: EDTA, Vitamin C, $NaHCO_3$, MgCl, pantothene, B_6 (pyridoxine), potassium chloride, heparin (optional), folic acid, B-complex, B-12 and the 500 cc bottle of sterile water.
2. Wipe the tops of all vials with an alcohol swab. *Leave the **sterile water** capped for now.*

3. *Equalize the pressure in all of the vials* with a No-Kor sterile needle (stick the needle briefly through tops of all vials, *except for the IV bottle*). Put the needle back into the needle cap *carefully* (not good medical practice, mind you), but you will use this needle to attach to the syringe to draw up the nutrients and EDTA).
4. Attach the above 18 gauge No-Kor needle to a 10 cc syringe.

   4 a. Carefully uncap the 500 cc bottle of sterile water, pulling the metal tab straight out and then down towards the bottom of the bottle. Then remove the outer metal rim of the cap (be careful, the edges are sharp) and the top cover, and **w**ipe the top with an alcohol swab**. Do NOT equalize the pressure in the bottle**.

EDTA (150 mg./cc, usually in a 100 cc vial)

Note: You may not be using this amount (20 ccs) of EDTA. The amount you will use is calculated by a specific method you will be taught in this session (Cockroft-Gault).

Remember, if you are drawing this IV up ahead of time, skip steps 1-18 until your patient arrives in your office for the IV.

5. Pull back plunger of the syringe to the *10 cc mark*
6. Insert the needle of the syringe into the 10 cc vial of **EDTA** and **invert the vial. (You will do this with all of the vials of additives as you use them.)**
7. Inject the 10 ccs of air into the **EDTA** vial. Note: the full volume of air may not all go in *at once*, so release pressure on the syringe and allow some **EDTA** to flow into the syringe, push in some more air, back and forth, and so on.
8. Withdraw 10 ccs of **EDTA** from the vial into the syringe and remove the needle from the vial of **EDTA**.
9. *Leave the bottle of water on the table*, and inject the 10 ccs of **EDTA** into the IV bottle. You should inject the nutrients in the center of the top of the IV bottle. If you have not depressurized the bottle, it will "suck" the nutrient out of the syringe.
10. Repeat steps 5-9, for a total dose of 20 ccs (not always the dose – see above)
11. Push the vial of **EDTA** back, so you'll know you've used it. This may seem silly, but occasionally you get interrupted during this process, and if you've pushed the vials back as you've used them, you'll remember where you are.

Vitamin C (500 mg./cc, 50 cc vial)

12. Pull back plunger of the syringe to the *10 cc mark*
13. Insert the needle of the syringe into the 10 cc vial of **Vitamin C** and invert the vial**.**
14. Inject the 10 ccs of air into the **Vitamin C** vial. Note: the full volume of air will not all go in *at once*, so release pressure on the syringe and allow some **Vitamin C** to flow into the syringe, push in some more air, back and forth, and so on.
15. Withdraw 10 ccs of **Vitamin C** from the vial into the syringe and remove the needle from the vial of **Vitamin C**.
16. Inject the 10 ccs of **Vitamin C** into the IV bottle
17. **Repeat steps 12-16*, but with 5 ccs,* for a total of 15 ccs**
18. Push the vial of **Vitamin C** back

$NaHCO_3$ (8.4%, 50 cc vial)

19. Pull back plunger of the syringe to the *10 cc mark*
20. Insert the needle of the syringe into the 10 cc vial of **$NaHCO_3$** and invert the vial**.**
21. Inject the 10 ccs of air into the **$NaHCO_3$** vial. Note: the full volume of air may not all go in *at once*, so release pressure on the syringe and allow some **$NaHCO_3$** to flow into the syringe, push in some more air, back and forth, and so on.
22. Withdraw 10 ccs of **$NaHCO_3$** from the vial into the syringe and remove the needle from the vial of **$NaHCO_3$**.
23. Inject the 10 ccs of **$NaHCO_3$** into the IV bottle
24. **Repeat steps 19-16, for a total of 20 ccs**
25. Push the vial of **$NaHCO_3$** back.

Magnesium Chloride (500 mg./cc – vial size variable)

26. Pull back the plunger of the 10 cc syringe to the *5 cc mark* of the syringe.
27. Insert the needle into the vial of **magnesium chloride** and invert the vial.
28. Inject the air into the **magnesium chloride**.
29. Withdraw 5 ccs of **magnesium chloride.**
30. Remove the needle from the vial of **magnesium chloride**, and *push the vial back*.
31. Inject the contents of the syringe into the IV bottle.

Pantothene (Vitamin B-5, 250 mg./cc – vial size variable)

32. Draw back the plunger to the *1 cc mark* of the syringe.
33. Insert the needle into the vial of **pantothene** (pantothenic acid) and invert the vial.
34. Inject the air into the vial of **pantothene**.
35. Withdraw 1 cc of **pantothene**.
36. Remove the needle from the vial, and *push the vial back*.
37. Inject the contents of the syringe into the IV bottle.

Potassium Chloride – (2 mEq./cc, 20-30 cc plastic vial from the manufacturer)

38. Draw back the plunger to the *1 cc mark* of the syringe.
39. Insert the needle into the vial of **potassium chloride** and invert the vial.
40. Inject the air into the vial of **potassium chloride**.
41. Withdraw 1 cc of **potassium chloride**.
42. Remove the needle from the vial, and *push the vial back*.
43. Inject the contents of the syringe into the IV bottle.

B_6 (pyridoxine, 100 mg./cc– vial size variable)

44. Draw back the plunger to the *1 cc mark* of the syringe.
45. Insert the needle into the vial of **B_6** and invert the vial.
46. Inject the air into the vial of **B_6**.
47. Withdraw 1 cc of **B_6**.
48. Remove the needle from the vial, and *push the vial back*.
49. Inject the contents of the syringe into the IV bottle.

Heparin (optional, 5000 U/cc – usually 10 cc vial from the manufacturer)

50. Draw back the plunger to the *1 cc mark* of the syringe.
51. Insert the needle into the vial of **heparin** and invert the vial.
52. Inject the air into the vial of **heparin**.
53. Withdraw 1 cc of **heparin**.
54. Remove the needle from the vial, and *push the vial back*.
55. Inject the contents of the syringe into the IV bottle.

Folic Acid (10 mg./cc – vial size varies)

56. Draw back the plunger to the *1 cc mark* of the syringe.
57. Insert the needle into the vial of **folic acid**
58. Inject the air into the vial of **folic acid**.
59. Withdraw 1 cc of **folic acid.** You will often note that folic acid turns cloudy when you draw it up. This is normal, as in low volume it needs an alkaline solution to dissolve, and will temporarily partially precipitate. Don't worry about it – it will re-dissolve as soon as you inject it into the IV solution.
60. Remove the needle from the vial, and *push the vial back*.
61. Inject the contents of the syringe into the IV bottle.

B-complex (100 mg./cc – vial size varies)

62. Draw back the plunger to the *2 cc mark* of the syringe.
63. Insert the needle into the vial of **B-complex** and invert the vial.
64. Inject the air into the vial of **B-complex**.
65. Withdraw 2 ccs of **B-complex**.
66. Remove the needle from the vial, and *push the vial back*.
67. Inject the contents of the syringe into the IV bottle.

B-12 (hydroxocobalamine or methyl cobalamine, 1000 mcg./cc – vial size varies)

68. Draw back the plunger to the *1 cc mark* of the syringe.
69. Insert the needle into the vial of **B-12**
70. Inject the air into the vial of **B-12**.
71. Withdraw 1 cc of **B-12**
72. Remove the needle from the vial, and *push the vial back*.
73. Inject the contents of the syringe into the IV bottle (250 cc).

You're now done drawing up the IV.

Setting up the IV

You'll need vented IV administration sets (the plastic tubing for the IV) and 25 gauge butterfly-type needles to administer IVs in your office. These may be ordered from Merritt or another supplier.

Note: When you administer IV therapy at your office, advise patients to *eat before they come in*, whenever possible. Most patients do much better with IVs of any kind if they've eaten *beforehand*.

1. Pull apart "Bubble Pak" containing a vented IV administration set, and remove the tubing.
2. **Move the wheel clamp on the IV tubing distally to about 2 feet from the distal end (the end opposite the "spiked" end, which will be the end closest to the patient) and *close the wheel clamp tightly***.
3. Remove sterile cap from the "spiked" end of the IV tubing (administration set).
4. Insert the spiked end of the IV tubing firmly through the *center* of the stopper of the IV bottle (you have to push firmly -- there is no "pre-drilled" hole, and, uh, don't forget to take the metal cap off of the IV bottle, if you haven't removed it yet).
5. *Be sure the wheel clamp is closed tightly*! Hang the IV bottle on an IV pole (we use a hook over the sink in our office). This is so any IV solution can go into the sink while the IV line is flushed.
6. *(Be sure the wheel clamp is closed tightly*!) Squeeze the drip chamber a few times to get the IV solution to fill the reservoir about *half full*.

   NOTE: The administration set will have a "vent" valve near or on the reservoir. *THE VENT IS ALREADY OPEN*.
7. Slowly open the clamp and slowly let the solution run through the tubing of the administration set *until it comes out of the end*. Most of the air bubbles will come out of the tubing as you let the solution flow through it (tiny bubbles won't cause any harm to the patient).
8. Open the winged infusion set, unscrew the cap and connect it to the administration tubing (you have to also remove the cap from the end of the administration tubing). *Leave the needle guard on the butterfly in place*. Allow the IV solution to flow into the butterfly until it comes out of the needle.
9. Once this is done, again close the wheel clamp tightly and move the IV to the patient's IV stand.
10. In your offices, you would take the patient's vital signs -- blood pressure and pulse, before you begin *any* IV therapy on *any* patient.
11. Tear off three 3" pieces of hypoallergenic tape (we use 3M Micropore hypoallergenic surgical tape), and stick them just by their ends somewhere within easy reach (the IV pole is usually convenient), so you can reach up and grab them when you need to.
12. Apply the tourniquet to your patient's arm.
13. Insert the butterfly needle, **preferably in the antecubital space** (crook of the arm) of your patient, and preferably in one, swift motion. As soon as the needle enters the vein, you will note a small amount of a back-flow of blood appear in the butterfly tubing. Put a piece of tape over the flexible plastic butterfly where it enters the skin, covering it and the spot where the needle enters the skin. (This solution is tolerated by most people in a peripheral vein, but large veins – for most purposes – are best and will avoid problems.)
14. **Release the tourniquet**.
15. Tape the butterfly tubing again *proximally* to the skin with another piece of tape, and with the third piece of tape, tape the *administration tubing* to the patient's *clothing* (shirt or dress sleeve).

16. Open the wheel clamp, very gradually at first, to be certain your patient has no adverse response to the solution, and to best prevent the vein from "blowing out." Watch the tubing and the site carefully as you do this to be certain the solution is running into the patient's *vein* and not the *subcutaneous tissue* (it burns)!
17. Set the drip rate at about 10-15 drops per minute (count them) for the first 2-3 minutes (usually you need to do this for the first chelation only – after that, you can set the drip rate at the required rate immediately). **Watch the site, watch the patient, and** s**top the IV** if your patient has *any* sensation of *severe burning, pain or discomfort*. Some "aching" of the upper arm could occur – the patient can massage it – but this is not infiltration: infiltration burns at the needle site).
18. Once several ccs have been administered and if your patient has no discomfort or other unusual symptoms, you may then speed the rate up to *about 65 drops per minute – a bit faster than one drop per second*. This will usually get a 500 cc IV into your patient in about three hours. You will get into the habit of checking the level of the IV as it's being given to calibrate the time in which you want it administered. Anywhere between 2 ½ to 3 hours is fine.
19. The IV may be allowed to run ***completely*** *out* before it is disconnected. Air will *not* flow into a patient's vein.
20. Once the IV is finished, fold a 2" X 2" gauze pad in quarters. *Carefully* peel back the tape covering the needle where it enters the arm, while holding down the plastic butterfly portion. Press the 2" X 2" *lightly* to the skin where the needle is inserted and at the same time remove the needle with a quick, smooth action. As the needle is removed, *increase* the pressure on the gauze pad for about a minute and then apply tape tightly over the gauze. The patient may remove the tape and gauze in about 10-15 minutes.

Billing Codes Used for IV Therapy

You must check these codes yearly, as they tend to change. We never bill insurance for chelation, though some physicians do. We bill only for nutritional IVs.

1. 99211 – Minimal office visit, and
2. 90784 – for the IV for a patient with asthma – if you want to justify you've given magnesium for acute asthma, refer to multiple references in the literature and included here. *Insurance companies in our area have not been covering this code*. Also, see my article with mixed nutrients, mentioned previously.
3. 90765 – used for any other IV (you may have to justify the IV for insurance), and you may add:
4. 90766 – for each extra hour, per hour (unit)
5. 90799 – "unlisted" therapeutic or diagnostic injection (asking for trouble, likely)

If you specify that the substances you are using are nutrients, insurance often will ask you to justify what you're doing, and they will end up not paying in the end, anyway. The FDA considers nutrients given parentally to be drugs, and so should you (for these purposes), but insurance companies usually may not.

If you bill for this type of therapy, be prepared to be challenged. It's even possible, whether you receive payments directly from insurance or not, a company could challenge this retrospectively, refute it as a legitimate treatment, and demand you return any money

they paid you or your patient in the past. This is absolutely true with Medicaid, Champus and Medicare, and I would *very strongly advise you not to bill these providers* for **any** IV you administer.

Waiver Forms for IV and other "non-conventional" therapy

Whenever you are using other than what is termed "standard of practice" methodology in your office, you should advise your patients. We do this in writing, and have patients sign forms. At the end of this section, I've included most of our "standard forms" we use in my office. Please feel free to use them if you wish.

It's always smart to have your patients well informed by giving them, *in writing*, everything you're planning, in the form of something they can sign and keep a copy. The forms we use in our office (waivers, consent, Medicare, other) have been included on the following pages. Please feel free to copy and use them. Jonathan Emord and Associates provided most of these; *however*, laws in this arena can change rapidly, and before you rely totally on them, you might want to double-check with your own attorney or consult Jonathan to see whether the forms are up-to-date.

CONSENT FOR NON-CONVENTIONAL TREATMENT

1. I, _____, hereby authorize the following procedure: use of _____ a testing modality for diagnosis of _____, or _____ treatment, a treatment for _____ _____.
2. I understand that the procedure will involve _____ _____, possibly combined with diet and lifestyle modifications.
3. I understand that _____ is not a currently medically accepted procedure for testing or treating _____ and, thus, that its use for this purpose may be considered by some insurance companies to be "medically unnecessary" or "experimental". The procedure has some risks. Dr. _____ has explained to me verbally the short and long-term risks, which may include temporary worsening of my current symptoms or headache, tachycardia (increased heart rate), syncope (fainting), visual difficulties, shortness of breath, joint pains, red eyes, itchy eyes, nasal congestion, numbness, gastrointestinal disturbances and a very rare but serious reaction called anaphylaxis. Also, further side-effects or complications could be: _____
4. By signing this form, I accept those risks. Moreover, I understand and accept that because this procedure may be considered "medically unnecessary" or "experimental", it may not mitigate, alleviate, or cure my condition (s). Its possible benefits may not be apparent immediately. The possible benefits include mitigation or improvement of my current symptoms, improvement of respiratory function, decreased skin reactions, increased stamina, improved metabolism, decrease in frequency or severity of headaches, improved concentration, and others.
5. I understand the nature of the treatment, which has been explained to me by Dr. _____.
6. I understand that the currently "standard" medically indicated treatment(s) for my condition is/are _____ _____. I understand that the risks of those treatments include: no improvement or worsening of my condition; headache, tachycardia (increased heart rate), syncope (fainting), visual difficulties, shortness of breath, joint pains, red eyes, itchy eyes, nasal congestion, numbness, gastrointestinal disturbances and a very rare but serious reaction called anaphylaxis and others.
7. Based on the risks and potential benefits of the currently medically indicated treatment(s) and of the proposed treatment, I have elected to forego or supplement the indicated treatment(s) and receive the proposed treatment from Dr. _____.
8. I further understand and agree to adhere to the treatment schedule and attend the follow-up visitations set by Dr. _____ to permit observation and study of my progress. I also agree to comply with the recommended lifestyle modifications in order to provide optimum opportunities for the beneficial effects of chelation therapy.
9. I understand that I may suspend or terminate my treatment at anytime by informing Dr. _____
10. I assume full liability for any adverse effects that may result from the non-negligent administration of the proposed treatment. I waive any claim in law or equity for redress of any grievance that I may have concerning or resulting from the procedure, except as that claim pertains to negligent administration of this procedure.
11. I hereby confirm that the nature and purpose of the aforementioned treatment may be considered medically unnecessary or experimental and not currently indicated treatments. The risks involved and the possibilities of complications have been explained to me. I fully understand that the treatment to be provided may be considered experimental and unproven by scientific testing and peer-reviewed publication.

Signature of Patient _____ DATE:_____ TIME:_____

Signature of Witness _____

AGREEMENT BY MEDICARE BENEFICIARY
FOR MEDICAL SERVICES by Physician Opted Out of Medicare

Date: _____ Time: _____

_____ , a patient and Medicare Part B beneficiary ("Patient"), and _____, M.D. (Physician"), a physician licensed to practice medicine in _____ enter into this agreement for the provision of medical services specified herein ("Services") in accordance with the provisions of Section 4507 of the Balanced Budget Act of 1997. Wherefore, in exchange for consideration, the receipt and sufficiency of which the Parties hereby acknowledge, Patient and Physician agree as follows:

1. Patient acknowledges and agrees that this Agreement has been entered into, and that Patient has received a copy of this Agreement, before Physician has provided the services specified herein to Patient.
2. Patient acknowledges and agrees that this Agreement has not been entered into at a time when Patient is facing an emergency or urgent health care situation.
3. The services to be provided Patient are: _____
_____
_____
_____ (collectively referred to hereinafter as "Services")
4. Patient agrees not to submit a claim (or request that Physician submit a claim on Patient's behalf) under the Social Security Act, as amended (42 U.S.C. § 1395a), for the Services, even if such Services are otherwise covered under Medicare Part B.
5. Patient agrees to be personally responsible, whether through private insurance or otherwise, for the payment of Services.
6. Patient acknowledges that Medicare will not provide reimbursement for the Services and that no Medicare fee limits (including those specified in 42 U.S.C. §§ 1395a; 1848(g)) will apply to the amount Physician charges for Services.
7. Patient acknowledges that Medigap plans under 42 U.S.C. § 1882 do not, and other supplemental insurance plans may not, make payments for the Services.
8. Patient acknowledges that, as a Medicare beneficiary, Patient has the right to have the Services provided by other physicians or practitioners for whom payment would be made under Medicare, 42 U.S.C. § 1395a.
9. Physician has informed Patient that Physician is not excluded from participating in Medicare Part B under 42 U.S.C. § 1128.
10. By signing this contract Patient understands that Patient is forgoing his or her right to receive Medicare benefits for the Services from Physician, but that Patient is not forfeiting all Medicare benefits for other services from other Medicare providers.
11. Physician filed an affidavit with Medicare effective on _____. That affidavit expires on _____. This Agreement expires on _____.

Signature of Patient _____ Date: _____

Witness: _____

Signature of Physician: _____ Date:_____

Witness: _____

NOTICE IN ADVANCE OF SERVICE TO PATIENT THAT SERVICE MAY NOT BE COVERED BY INSURANCE

PHYSICIAN NOTICE:

Your insurance plan will only pay for services that it determines to be "reasonable and necessary" under its coverage policy. If your insurance plan determines that a particular service, although it would otherwise be covered, is "not reasonable and necessary" under its coverage policy standards, the plan will deny payment for that service. I believe that, in your case, your insurance may deny payment for EPD immunotherapy because it is not considered the "standard of care" in the USA and possibly because it is not FDFA-approved.

BENEFICIARY AGREEMENT:

I have been notified by _____ that he/she believes that, in my case, my insurance may deny payment for the service identified above, for the reasons stated. I agree to be personally and fully responsible for payment.

Signed,

_____ _____

Beneficiary (or Representative) Signature *Date*

_____ _____

Witness Date

NOTICE IN ADVANCE OF SERVICE TO PATIENT THAT SERVICE MAY NOT BE COVERED BY MEDICARE

NOTICE TO MY PATIENTS:

Medicare will only pay for services that it determines to be "reasonable and necessary" under Section 1862 (a)(1) of the Medicare law. If Medicare determines that a particular service, although it would otherwise be covered, is "not reasonable and necessary" under Medicare program standards, Medicare will deny payment for that service. I believe that, in your case, Medicare is likely to deny payment for _____ for the following reasons:
_____
_____
_____

BENEFICIARY AGREEMENT:

I have been notified by my physician that he or she believes that, in my case, Medicare is likely to deny payment for the services identified above, for the reasons stated. If Medicare denies payment, *I agree to be personally and fully responsible for payment.*

Signed,

_____ _____

Beneficiary (or Representative) Signature *Date*

_____ _____

Witness Date

IV Therapy for Asthma/Cardiovascular Disease/Other Health Problems -- Signature Form

Dr. _____ treats a number of illnesses using IV therapy (parenteral therapy) with various nutrients or chelation therapy. This is because, for most patients with significant health problems, IV therapy has been shown in his practice to be effective in the long term, and because Dr. _____ feels it is far safer than giving you powerful and potentially dangerous drugs which often have significant adverse side effects.

Parenteral therapy with nutrients or chelation therapy are not yet considered to be "traditional" therapy in this country. More and more physicians are finding the benefits from this approach, but it will take quite some time before it is considered the "standard" of care. For this reason -- because it is a non-traditional approach -- Dr. _____ wants you to understand the risk verses benefit ratio of this important approach to helping solve your health problems.

IV therapy with nutrients must be considered "investigational" in this country and *does not benefit all patients*. Some of the IV nutrients in the form or dosage used by this office are not yet approved by the FDA. If you have asthma or another serious illness, *IV therapy could even make you considerably worse after the first (or even the first few) treatment(s)*, so you must be aware of this eventuality. We generally ask our patients to commit to 3 treatments at a minimum, as it sometimes takes 3 treatments to see a significant effect. However, if satisfactory subjective or clinical results are not noted by the time the first 3 treatments are complete, we generally discontinue therapy and move on to another approach.

IV therapy is generally administered once or even twice weekly until you are able to go longer between treatments without loss of benefit. Generally speaking, should you note an improvement with IV therapy, you should find that the periods of improvement last longer and longer as time goes on. IV therapy with nutrients is often combined with other treatment modalities in this office, and it is hoped and somewhat expected that IV therapy can be discontinued without loss of benefit when the other treatment modalities take effect. Chelation therapy is usually administered long-term.

The general risks of IV or chelation therapy include, with decreasing frequency: fatigue; headache; worsening of symptoms after the first 1-3 treatments (lessening with each, if it happens): discomfort during the infusion; irritation of the vein, causing eventual closure of the vein; inflammation at the site of an IV (phlebitis); failure to achieve a substantial benefit; renal failure; death. All except the first 3 are *extremely* rare, and there has never been a reported death from IV therapy with any of the nutrients (or EDTA) used in our office unless used contrary to our explicit instructions (I include it here because it must be included in any disclaimer form).

By signing this form, you acknowledge that you understand all of the above information, and that you are consenting to parenteral therapy with nutrients with such knowledge.

Thanks very much.

Signed: _____ Dated: _____

[note: this is my form, not from J. Emord]

Calculating Osmolarity

A Critical Factor When You Use IV Therapy

The mathematics of preparing solutions and calculating osmolarity when customizing IV nutrient protocols

A. Definition:

The *molarity* of a substance is determined by the molecular weight of a substance. For example, the molecular weight of NaCl is about 58. One (1) mole of NaCl is therefore 58 grams. If 58 grams of NaCl is dissolved in 1 liter of water, this creates a 1 molar solution.

Osmolarity – or osmotic pressure – on the other hand, is primarily determined by the dissociation of any particular substance. Since NaCl dissociates into Na ions and chloride ions in solution, the osmolarity of a mole of NaCl dissolved in 1 liter of water is not one osmole, but *two*.

Fortunately, we don't have to suffer through this chemical enigma to determine the osmolarity of our solutions; the osmolarity of everything we use is known and appears in Table I.

B. Basic Formula

$$\frac{\textbf{Osmoles}}{\textbf{Volume}} = \textbf{Osmolarity}$$

or

$$\frac{\textbf{Milliosmoles}}{\textbf{Liters}} = \textbf{mOsm/}\textit{\textbf{L}} \quad \textbf{or} \quad \frac{\textbf{Milliosmoles}}{\textbf{mL}} = \textbf{mOsm/}\textit{\textbf{mL}}$$

Normal *osmolarity of plasma* is generally between .280 and .310 mOsm/mL.

To avoid problems, the optimal osmolarity of any IV solution would be within these ranges.

*For our purposes, I'll always talk in terms of milliosmoles per milliliter (***mOsm/*mL*.*).*

For osmolarity of all the common IV agents we use, please see Table I (Osmolarity calculation sheet); for osmolarity of specific protocols, see Table II. I have included several of our nutritional protocols as well.

B. Example of calculation of osmolarity of solutions:

1. Let's say you want to know the osmolarity of the following solution:
   10 mL of Ascorbate, 500 mg./mL (osmolarity **5.8 mOsm/mL** - see Table I), and
   2 mL of calcium gluconate, 100 mg./mL (osmolarity **.72 mOsm/mL** - see Table I)

10 mL	X	5.8 mOsm/mL =	58 .00 mOsm
2 mL	X	.72 mOsm/mL =	1.44 mOsm
Totals: **12 mL**			**59.44 mOsm**

Using the previous formula, we get: $\frac{59.44 \text{ mOsm}}{12 \text{ mL}} =$ **4.95 mOsm/mL**

C. DERIVATION OF THE FORMULA TO DETERMINE THE AMOUNT OF DILUENT TO ADD TO A SOLUTION TO MAKE IT ISOTONIC

It isn't critical you learn the actual derivation of the formula to follow by heart. The important thing is that you know how to use the formula, once it's derived. The derivation is for you geeks out there.

The solution just calculated is far too hyperosmolar to inject "straight." **We need to know how we can make this solution fall in the range of that of plasma** (.28 - .31 mOsm/mL), or to be **isosmolar/isotonic**, so we can inject it without discomfort or venous irritation.

To do this, we need to add something with a *lower osmolarity* to dilute this solution. Also, we usually want to add as *little diluent as possible*, so the resultant solution can be fit into a syringe or reasonably-sized IV bottle. Therefore, **sterile water is best, as it has an osmolarity of 0 (zero).**

Using the numbers we calculated in the previous example, let's represent the quantity of diluent we're going to add (in mLs) as **Q**. Its total osmolarity (in milliosmoles) will equal **O**, and we will use the formula above to calculate the osmolarity to be the same as that of plasma, (.280 - .310 mOsm/mL):

$$\frac{\textbf{mOsm}}{\textbf{mL}} = \textbf{mOsm/mL (= osmolarity)}$$

so, $$\frac{59.44 + \textbf{O} \text{ (mOsm of added agent)}}{12 + \textbf{Q} \text{ (ccs of added agent)}} = \textbf{.310 mOsm/mL (310 mOsm/L)}$$

(We use .310 mOsm/mL (310 mOsm/L) so that if we slightly miscalculate, it will be on the "safe" (higher) side, rather than on the lower side, as hypotonic solutions can cause hemolysis in certain unusual conditions.

Using some basic (but easily forgettable) math, we can *exchange* the (12 + Q) and the .310 without affecting the equation, which gives us:

$$\frac{59.44 + \textbf{O} \text{ (mOsm of added agent)}}{.310} = 12 + \textbf{Q} \text{ (ccs of added agent)}$$

We can then bring the 12 to the other side of the equation, but must change its sign:

$$\frac{59.44 + \textbf{O} \text{ (mOsm of added agent)}}{.310} - 12 = \textbf{Q} \text{ (ccs of added agent)}$$

Since the osmolarity of sterile water (**O**) for injection is 0 (zero), we can simply eliminate it from the equation, which finally gives us:

$$\frac{59.44 - 12}{.310} = \textbf{Q} \text{ (ccs of added agent)} \quad \text{or} \quad \textbf{191.74 - 12 = 179.74}$$

So, we'd have to add 179.74 (or about 180) mL of *plain sterile water for injection* to make this IV solution (10 mL of ascorbate & 2 mL of calcium gluconate) isotonic.

*So, as derived above, the **Formula** to Determine amount of **Sterile Water** to add to any IV to make it **isotonic** (.310 mOsm/mL) is therefore***:**

$$\frac{\textbf{Total } \textbf{\textit{mOsm}} \textbf{ of Additives}}{\textbf{.310}} - (\textbf{ Total } \textbf{\textit{mLs}} \textbf{ of Additives }) = \textbf{Water to Add (mLs)}$$

Using this formula, you can calculate the amount of plain sterile water to add to *any* IV solution you might produce in your office to make it isotonic. Solutions may be given which are slightly or even significantly hypertonic, but the more hypertonic an infusion is, the greater the likelihood of damage to veins (sclerosis) and patient discomfort. More hypertonic solutions should be given in larger veins, while isotonic or very near-isotonic solutions may easily be given in smaller veins. *NEVER GIVE HYPOTONIC SOLUTIONS.*

The preceding formula is easy to check. For example, if you were to take one mL of magnesium sulfate (500 mg./mL), whose osmolarity is 4.06 mOsm/mL, and added 1 mL of water for injection (osmolarity zero), you would expect the resulting osmolarity (**Os**) to be exactly half, or 2.03 mOsm/mL. Let's see if the formula works:

$\frac{4.06}{\textbf{Os}} - 1 = 1$; $\frac{4.06}{\textbf{Os}} = 2$; $2\ \textbf{Os} = 4.06$; $\textbf{Os} = \frac{4.06}{2}$; so **Os** = 2.03!

If you get a *negative* value in the calculation above, this indicates a *hypotonic* solution. To calculate the amount of **Normal Saline** solution (.9% NaCl) to add, you have to *divide this absolute number (convert the negative number to a positive one) by* ***.031***.

You will only end up with a hypotonic solution if most or all of the agents you're using have an osmolarity of less than .280, such as multiple trace minerals. If you are giving an IV of strictly minerals, give them in NSS (.31 mOsm/mL).

The rule for *safe upper limits of osmolarity* of IV solutions we follow in our office is approximately:

	Large vein	Medium vein	Any vein
IV Push (mOsm/L)	**1400**	**950**	**400**
IV Infusion (mOsm/L)	**1200**	**700**	**400**

Note: these are *general* guidelines. The exception is our protocol (IV infusion) for high dose Vitamin C given for cancer, where the osmolarity is 1362 mOsm. Some patients will not tolerate osmolarity this high.

Another general rule to consider when administering IV therapy is:

The *longer* the infusion and the *smaller* the vein,
the more *conservative* the *osmolarity* should be.

Here's an example of the calculation process for an IV Protocol:

PLEASE NOTE: This is *not* the same protocol we will be using in the workshop

Nutrient	mOsm/cc	ccs in protocol	Total mOsm of additive
Vitamin C (ascorbate, ascorbic acid)	5.80	12	69.60
B-6	1.11	5	5.55
B-complex	2.14	2	4.28
B-12	.31	5 cc (but not included in calculations, as it is given IV "push" at end of the IV)	
Calcium gluconate	.72	2	1.44
Magnesium Sulfate	4.06	5	20.30
Mineral mix	.57	1	.57
Molybdenum	.80	1	.80
Pantothene	.85	2	1.70
Water you'll need to add	0	(TO CALCULATE)	0
	TOTALS:	**30** (you don't include the B-12	**103.74**

Formula: $\frac{\textbf{Total mOsm of Additives}}{\textbf{.310}} - \textbf{Total mLs of Additives} = \textbf{mLs of water to add}$

thus, $\frac{103.74}{.310}$ - (30) = mLs of water to add,

(We don't count the B-12 because it's given separately at the end, and not mixed with the IV. B-12 should not be mixed with an IV containing copper (in the mineral mix), since copper inactivated the ring structure of B-12))

$\frac{103.74}{.310}$ - (30) = *mLs of water to add*

334 - 30 = *304 mLs of water to add*

However, Sterile Water doesn't come in bottles of 304 ccs – it comes in 250 cc bottles (or larger). So we solve this dilemma by adding 250 ccs of Sterile Water for Injection, simply because that's how it is supplied. But if we add 250 ccs, then the osmolarity won't be .310. Since we'll be adding less water, the osmolarity will become higher. To calculate the osmolarity of this new solution, we now have to make the osmolarity the "unknown" (X), and re-calculate:

$\frac{103.74}{\text{"X"}}$ – (30) = 250 (since we want to add this much water now)

"X" equals the osmolarity that will result when we add 250 mLs of water, because we're *not* going to add 304 mLs. Now move the 30 cc's of additives to the other side of the equation, and

$\frac{103.74}{X}$ = 280, 280 X = 103.74, so X = $\frac{103.74}{280}$ or **.371**

The resultant osmolarity is not .310, but *.371 mOsm/mL*, still well within safe limits for a small vein.

Problems with Normal Saline: Osmolarity of IV's

I can't tell you how many patients we see who have virtually "no veins" because of multiple previous IV's which have been given in NSS with hypertonic nutrients, rather than sterile water for infusion. This is because osmolarity had not been calculated, and/or nutrients or medications have just been "dumped" into an IV, especially in hospital situations. In many cases, nutrients or drugs are just added to NSS without regard to osmolarity. This is especially a problem with Vitamin C and magnesium, as they have a very high osmolarity.

These patients are usually *desperately* in need of IV therapy, and – because previous IV's have been given improperly at other offices – often it is extremely difficult for us to do it without a central venous catheter.

Following is an example of how osmolarity changes significantly by using NSS instead of sterile water.

Sample EDTA Chelation Protocol

Agent or Nutrient	ccs	mOsm/cc	Total mOsm
Disodium EDTA	20	1.34	26.80
Vitamin C, 500 mg./cc	15	5.80	87.00
Folic acid 10 mg./cc	1	.20	
MgCl, 500 mg./cc	5	7.13	35.70
$NaHCO_3$	20	1.79	17.90
Pantothene	1	.85	.85
Potassium Chloride	1	4.00	4.00
Heparin	1	.46	.46
B-12, 1 mg./cc	1	.31	.31
B-6, 100 mg./cc	1	1.11	1.11
B-Complex 100	2	2.14	4.28
Total:	**68**		**200.7**

A. Calculations, using *Sterile Water* (500 cc) as the diluent (osmolarity of 0):

$$\frac{200.7}{X} - (68) = 500 \text{ (cc } H_2O)$$

$$\frac{200.7}{X} = 568, \text{ so } 568X = 200.7, \text{ so } X = \frac{\mathbf{200.7}}{568}$$

and **X = .353 mOsm/mL**

B. Calculations, using *Normal Saline Solution* (500 cc) as diluent instead of water:

NSS has an osmolarity of .31 mOsm/L. So, when using NSS, you have to count it as an *additive* on both sides of the equation. Therefore, 500 cc of NSS contains .31 times 500, or 155 mOsm. This must be added to the milliosmoles of "additives" and to the additives themselves.

Using the previous example, adding saline instead of water:

$$\frac{200.7 + \mathbf{155.0}}{X} - (68 + \mathbf{500}) = 0 \text{ (no water is added)}$$

$$\frac{355.7}{\mathbf{X}} - (568) = 0, \text{ then } \frac{\mathbf{355.7}}{\mathbf{X}} = 568, \text{ and } 568X = 568,$$

$$X = \frac{341.42}{568} \quad \text{so,} \quad \mathbf{X = .601 \text{ mOsm/mL}}$$

Although this latter solution would be tolerated in a larger vein, it could be a problem if infused into a smaller vein.

The rule of thumb is that infusions diluted with NSS have a bit less than twice the osmolarity as do those in sterile water.

Conclusion:

When administered according to these protocols and guidelines, chelation therapy is extremely safe, and can be tremendously beneficial. Chelation infusion protocols are easy to administer and patients rarely have side effects. If they do, these will usually consist of fatigue, feeling “wiped out”, and occasionally a headache, occurring mostly on the day of the IV, and usually for only the first one to three treatments. Even then, patients will often feel extremely well for several days after a chelation treatment, and after several treatments, they will only feel well.

If you’re treating patients with symptoms such as angina or claudication, patients should write down what their symptoms are, how often they occur, how far they can walk without pain, etc. *before* you begin treatment. This way you have a barometer to monitor how well patients do as they receive treatment, and benefits are consistent.

There is also no doubt that IV (parenteral) therapy with selected nutrients can be tremendously beneficial for patients with many different illnesses. Moderate to high dose nutrients, when given IV, bypass the intestinal tract and resultant "first pass" detoxification by the liver. Considering this, they usually have a drug-like effect rather than the effect the nutrient would have if take orally. There is a great deal we have to learn about IV administration of nutrients, as the field is in its infancy (although many of our members and Fellows have used it for 25 years or more), and more outcome studies of specific disorders are needed.

Additionally, IV therapy must be done correctly: solution concentration (osmolarity) must be in tolerable and comfortable ranges to prevent structural harm to a patient's veins, and to prevent dangerous reactions from hypotonic solutions.

Table I: OSMOLARITY CALCULATION WORKSHEET FOR COMMONLY USED NUTRIENTS

IV Additives	mOsm/mL	(multiply times:)	nutrient added (mLs)		Total mOsm
Amino Acids (FreAmine III 8.5%)	0.81	X	cc	=	
Ascorbic Acid 500 mg/mL	5.80	X	cc	=	
B-6 (Pyridoxine) 100 mg/mL	1.11	X	cc	=	
B-12 (hydroxycobalamine) 1000 mcg.*	0.31	X	cc	=	
B-Complex 100 mg/mL	2.14	X	cc	=	
Sodium Bicarbonate 8.4%	2.00	X	cc	=	
Calcium Gluconate 10% 100 mg./mL	0.72	X	cc	=	
Disodium EDTA 150 mg./mL	1.34	X	cc	=	
Folic Acid 10 mg./mL	0.20	X	cc	=	
Germanium 100 mg./mL **	0.25	X	cc	=	
Glutathione 100 mg./mL ***	0.38	X	cc	=	
Heparin 5,000 U/mL	0.46	X	cc	=	
HCl (hydrochloric acid) 2 mg./mL)	0.11	X	cc	=	
Lactated Ringer's	.28	X	cc	=	
Magnesium Sulfate 500 mg./mL	4.06	X	cc	=	
Magnesium Chloride 200 mg./mL	2.95	X	cc	=	
Magnesium Chloride 500 mg./mL.	7.13	X	cc	=	
Mineral Mix (Dr. Shrader's)**	0.57	X	cc	=	
Molybdenum 500 mcg./mL **	0.80	X	cc	=	
Pantothenic acid 250 mg./mL	0.85	X	cc	=	
Potassium chloride 2 mEq/mL	4.00	X	cc	=	
Selenium 200 mcg./mL **	0.09	X	cc	=	
Taurine 50 mg./mL.	0.50	X	cc	=	
Zinc 10 mg./mL **	0.50	X	cc	=	
TOTALS FOR ADDITIVES:			**cc**	=	

* Do not mix with copper (becomes deactivated)

** Do not ever give IV push

*** Do not mix with vitamin C. Not effective if given by infusion. Give IV Push for appropriate effect.

DESIRED OSMOLARITY RANGE = 280 to 310 mOsm/L (.280 - .310 mOsm/mL)

DILUENTS	**mOsm/mL**
Water, sterile	0.00
NaCl (.9%)	.31
Lactated Ringer's	.28

To figure the number of ccs of Sterile Water to add to create a desired osmolarity of .310 mOsm/mL (upper range of plasma):

$$\frac{\textbf{Total mOsm of Additives}}{\textbf{.310}} - (\textbf{Total ccs of additives}) = \textbf{ccs of water to add}$$

*A *negative* number for the answer indicates a *hypo*-osmolar (hypotonic) solution. To figure the number of ccs of NSS (.9% NaCl) to add to bring the hypotonic solution to the desired osmolarity, *divide* this *absolute* number by .031, and add that amount of NSS. If NSS is used as the IV solution, you must calculate the NSS as you would **an additive,** and **ccs of water to add as 0 (zero).** Do the same if you were to use lactated Ringer's.

Table II – Dr. Shrader's Office IV Protocols (selected) – 2008

⇓ **IV Push Protocols** ⇓ ⇐ **All IV Infusion protocols**

⇒

Protocols ⇨ **Nutrients ⇩**	**mOsm per mL**	**Meyer (rev.)**	**Acute Asthma**	**Headache Migraine, muscle spasm**	**Glutathione Protocol**	**Chronic Asthma**	**Chronic Illness CFIDS, etc.**	**Acute Viral Illness**	**Super - Immuno**	**Chelation**	**Chelation Nutritional**
Amino Acids (FreAmine III 8.5%) *	0.81						50				
Ascorbic Acid 500 mg/mL	5.80	4	3			12	20	200	50	15	5
B-6 (Pyridoxine) 100 mg/mL	1.11	1	3	4		5	2	1	2	1	1
B-12 (hydroxocobalamine) 1000 mcg. **	0.31	2	5		1	5 **	5 **	1	15 **	1	1
B-Complex 100 mg/mL	2.14	1	2		1	2	2	1	2	2	2
Bicarbonate Sodium 8.4%	2.00					17	15	60	20	20	10
EDTA (magnesium/disodium) 150 mg./mL	1.34									20 ❦	
Calcium Gluconate 10% 100 mg./mL	0.72	2	2			2	2	40	20		5
Folic Acid 10 mg./mL †^	0.20					1 ^	1 ^	1 ^	1 ^	1 ^	1 ^
Germanium 50 mg./mL †	0.25								10		
Glutathione 100 mg./mL **†	0.38				6 to 25						
Heparin 5,000 U/mL	0.46	Optional								0.5	
Magnesium Chloride 200 mg./mL	2.95	5	10-15	15	5	10	5	5	5	5	10
Magnesium Chloride 500 mg./mL	7.13										
Mineral Mix *** †	0.57					1	2		2		1
Molybdenum 500 mcg./mL †	0.80					1					
N-acetyl cysteine 100 mg./mL	1.91				2						
Pantothenic acid 250 mg./mL	0.85	1	2			2	3	3	3	1	
Potassium chloride 2 mEq/mL	4.00	**NO**	**NO**	**NO**	**NO**	1	1	1	1	1	1
Selenium 200 mcg./mL	0.09										2
Taurine 50 mg./mL. †	0.50						6		10		5
Zinc sulfate (5 mg./mL)	0.11								1		1
Additives		16	26-32	19	15 to 34	54	103	313	125	67.5	45
mOsm Additives		*44.1*	*59.2-73.9*	*48.7*	*23.3 to 30.5*	*151.6*	*217.1*	*1334*	*377*	*179.5*	*95.4*
Sterile Water	0	17	27	16	15	250	500	800 Ÿ	450 º		250
Normal Saline, .9%	.31										
Syringe or IV bottle, in mL		35	60	35	35-60	250	500.0	1000	500	500	250
Osmolarity (mOsm/L)		**1336**	**1095-1253**	**1391**	**776 to 623**	**499**	**360**	**1198**	**655**	**316**	**323**

* Caution: contains preservative (may be compounded preservative-free)

** Given IV push at end of infusion (not counted in volume or osmolarity calculations).

† Not FDA-approved nutrients/mixtures

*** "Shrader's Mineral Mix": the formulation is *boron* 1 mg./mL., *zinc* 5 mg./mL., *copper* 1 mg./mL, *molybdenum* 250 mcg./mL., *selenium* 200 mcg./mL., *chromium* 100 mcg./mL., *manganese* 100 mcg./mL., *vanadium* 100 mcg./mL., *lithium* 5 mg./mL. and *strontium* 1 mg./mL. (College has this formula, and other pharmacies may have this and different formulations available also)

Ÿ Remove 200 mL of water from the IV bottle before adding additives

º Remove 50 mL of water from IV bottle before adding additives

❦ EDTA dose must be calculated before this solution is given! (see text)

^ Add folic acid *last* to all protocols – use a separate syringe

Protocols developed by W.A. Shrader, Jr., MD, except "Meyer" protocol. All have received extensive therapeutic use. Chelation protocol is similar to that of other physicians who employ chelation.

Vitamin C Protocols for the Adjunctive Treatment of Cancer

	Vitamin C						
	15 grams	**30 grams**	**45 grams**	**50 grams**	**60 grams***	**60 grams**	**100 grams**
			500 cc bottle			1000 cc bottle	
				Amounts to add (cc)			
Ascorbic Acid 500 mg/ml	30	60	90	100	120	120	200
B-6 (Pyridoxine) 100 mg/ml	1	1	1	1	1	1	1
B-12 (hydroxocobalamine) 1000 mcg.	1	1	1	1	1	1	1
B-Complex 100 mg/ml	1	1	1	1	1	1	1
Sodium Bicarbonate 8.4%	18	18	28	45	50	50	60
Calcium Gluconate 10% 100 mg./ml	10	10	15	25	40	40	40
Folic Acid 10 mg./ml †	1	1	1	1	1	1	1
Magnesium Chloride 200 mg./ml	5	5	5	5	5	5	2
Pantothenic acid 250 mg./ml	1	1	1	1	1	1	1
Additives	68	98	143	180	220	220	307
Milliosmoles of additives	213	411	608	707	844	844	1308.9
Sterile Water (bottle size)	500	500	500	500	*500*	*1000*	1000
Remove:			**40**	**80**	**100**	**300**	**200**
Total Volume	568	598	603	600	620	920	1020
Osmolarity (mOsm/L)	**385**	**687**	**1009**	**1179**	**1362***	**918**	**1182**
Infusion rate (drops/min.):	*120*	*130*	*130*	*130*	*130*	*180*	*185*

Note: this solution is quite hypertonic and some patients will tolerate it only in a large vein, if then. It may easily and very safely be given via an implanted central venous IV port.

If you have questions about this material, or IV therapy in general, please feel free to contact me. If you send a fax, just ask your question and leave space for my answer – this is usually the quickest way.

W.A. Shrader, Jr., MD
141 Paseo de Peralta, Suite A
Santa Fe, NM 87501

FAX: 505-820-7315
E-mail: wshradermd@aol.com

My complete set of instructional IV articles (originally they appeared as a "series" in the AAEM *Newsletter*) was compiled into a manual that has been revised, updated and is available from our office above. The manual contains step-by-step instructions how you would set up IV therapy in your office, the supplies needed, etc., and the further details about IV therapy which we were not able to include here, including how you can make IV nutrients in your office for far less than the cost anywhere else.

Included with the above are instructions I wrote specifically to teach physicians how to make their own *preservative-free* allergens and nutrients for testing and treatment. We're happy to share these with you. According to current FDA regulations, physicians are permitted by law to compound medicinal substances in their offices.

Our Favorite Suppliers for Materials:

Miscellaneous standard supplies:

Darby Drug Co., Inc.: 800-247-4768
Moore Drug Exchange: 800-678-8678
McGuff Co.: 800-854-7220

Suppliers for IV Nutrients

Abrams Royal Pharmacy (compounding)
8220 Abrams Rd.
Dallas, TX 75231
800-458-0804, 214-341-7966

American Biologics
1180 Walnut Ave.
Chula Vista, CA 91911
800-227-4473, 619-429-8200

Apothecure (compounding)
13720 Midway Rd., Suite 109
Dallas, TX 75244
800-969-6601, 214-960-6601

College Pharmacy (compounding)
833 N. Tejon St.
Colorado Springs, CO 80903
800-888-9358

Harvard Drugs
31778 Enterprise Dr.
Lavonia, MI 48150
800-875-0123

McGuff Co.
3524 West Lake Center Dr.
Santa Ana, CA 92704
800-854-7220, FAX 714-540-5614

McGuff Compounding Pharmacy
3524 West Lake Center Drive
Santa Ana, CA 92704
800-854-7220, 714-546-2941

Merit Pharmaceuticals
2611 San Fernando Rd.
Los Angeles, CA 90065
800-421-9657

Wellness Pharmacy
2800 South 18th St.
Birmingham, AL 35209
800 227-2627

References

Please note: There references are *important to you*.

You can use them to justify your IV therapy with nutrients if you are challenged by *anyone*. Each year I take considerable time to update them to include the most important articles published over the past year. Latest update complete through December 2007.

IV References, not categorized (pre-1998 – alphabetical by author). Note: intravenous vitamin references did not appear in the medical literature until about 1989, except for some general references of multivitamins used in TPN. The references that appeared between 1989 and 1998 – about 47 of them – were the "ground-breakers", so I've listed them separately here. After about 1992, IV vitamin references have increased steadily. My article (2004) is the only one justifying multiple nutrients (54).

1. Anibarro B. Asthma with sulfite intolerance in children: a blocking study with cyanocobalamin. *J. Aller. Clin. Immunol*. 90: 103-9, 1992 Jul.
2. Beasley R. Nishima S. Pearce N. Crane J. Beta-agonist therapy and asthma mortality in Japan [letter]. Lancet. 351(9113): 1406-7, 1998 May 9.
3. Bernstein W. Khastgir T. Khastgir A. Hernandez E. Miller J. Schonfeld S. Nissim J. Chernow B. Lack of effectiveness of magnesium in chronic stable asthma. A prospective, randomized, double-blind, placebo-controlled, crossover trial in normal subjects and in patients with chronic stable asthma. *Arch. Int. Med*. 155(3): 271-6, 1995 Feb 13.
4. Bloch H. Silverman R. Mancherje N. Grant S. Jagminas L. Scharf S. Intravenous magnesium sulfate as an adjunct in the treatment of acute asthma [see comments]. Comment in: *Chest* 1996 May, 109(5): 1411-2; *Chest* 107(6): 1576-81, 1995 Jun.
5. Bone R. Burch S. Management of status asthmaticus. *Ann. Allerg*. 67(5): 461-9, 1991 Nov.
6. Bucca C. et al. Effect of vitamin C on histamine bronchial responsiveness of patients with allergic rhinitis. *Ann. of Allergy*. 65:311-14, 1990 Oct.
7. Bucca C. et al. Effect of Vitamin C on transient increase of bronchial responsiveness in conditions affecting the upper respiratory airways. Beyond Deficiency: New Views on the Function and Health Effects of Vitamins, *New York Academy of Sciences*. Abstract 16, 1992 Feb 9-12.
8. Campbell M. Low levels of manganese in bronchial biopsies from asthmatic subjects. *J. Aller. Clin. Immunol*. 89: (1, Part II): 332/749, 1992 Jan.
9. Ciarallo L. Sauer A. Shannon M. Intravenous magnesium therapy for moderate to severe pediatric asthma: results of a randomized, placebo-controlled trial [see comments]. Comment in: *J. Ped*. 129(6): 783-51996 Dec; *J. Ped*. 129(6): 809-14, 1996 Dec.
10. Devi P. Kumar L. Singhi S. Prasad R. Singh M. Intravenous magnesium sulfate in acute severe asthma not responding to conventional therapy. *Indian Ped*. 34(5): 389-97, 1997 May.
11. Downey P. Cox R. Update on the management of status asthmaticus. *Cur. Opin. Ped.* 8(3): 226-33, 1996 Jan.
12. Ertle A. London M. Insights into asthma prevalence in Oregon. *J. Asthma*. 35(3): 281-9, 1998.
13. Frakes M. Richardson L 2nd. Magnesium sulfate therapy in certain emergency conditions. *Amer. J. of Emer. Med*. 15(2): 182-7, 1997 Mar.
14. Freeland-Graves J. *Nutrition Today* 13-19, 1988 Nov/Dec.
15. Green S. Rothrock S. Intravenous magnesium for acute asthma: failure to decrease emergency treatment duration orneed for hospitalization [see comments]. Comment in: Ann. Emerg. Med. 1993 Mar 22(3): 616-17, discussion 618-19, Comment in: *Ann. Emerg. Med*. 1993 Mar 22(3): 617, discussion 618-19, Comment in: *Ann. Emerg. Med*. 1993 Mar, 22(3): 617-8, discussion 618-9, Comment in: *Ann. Emerg. Med.* 1993 Mar 22(3): 618; discussion 618-19; *Ann. Emerg. Med*. 21(3): 260-5, 1992 Mar.
16. Hill J. Britton J. Effect of intravenous magnesium sulpfate on airway calibre and airway reactivity to histamine in asthmatic subjects. *Br. J. Clin. Pharmacol*. 42(5): 629-31, 1996 Nov.

17. Johnson K. Klingman E. Preventative nutrition: disease-specific dietary interventions for older adults. *Geriatrics* 47: 39-49, 1992 Oct.
18. Johnston C. Antihistamine effect of supplemental ascorbic acid in neutrophil chemotaxis. *J. Amer. Coll. Nutr*. 11(2): 172-4, 1992.
19. Kanazawa H. The role of free radicals in airway obstruction in asthmatic patients. Chest 100: 1319-22, 1991 Nov.
20. Keen J. Intravenous magnesium sulfate for acute asthma. *J. Emer. Nursing* 21(1): 44-6, 1995 Feb.
21. Keistinen T. Saynajakangas O. Tuuponen T. Kivela S. Ostro B. Chestnut L. Assessing the health benefits of reducing particulate matter air pollution in the United States. *Environ. Research* 76(2): 94-106, 1998 Feb.
22. Kuitert L. Kletchko S. Intravenous magnesium sulfate in acute, life-threatening asthma [published erratum appears in *Ann. Emerg. Med*. 1992 Oct, 21(10): 1272]. *Ann. Emerg. Med*. 20(11): 1243-5, 1991 Nov.
23. Lang D. Trends in US asthma mortality: good news and bad news [editorial; comment]. Comment on: *Ann. Aller. Asthma Immunol*. 1997 Apr: 78(4): 347-54 *Ann. Aller. Asthma Immunol*. 78(4): 333-7, 1997 Apr.
24. Lemesle F. High-dose intravenous magnesium sulfate in the management of life-threatening status asthmaticus [letter; comment]. Comment on: *Intensive Care Med*. 1993, 19(8): 467-71; *Intensive Care Med*. 21(1): 94-5, 1995 Jan.
25. Lieberman J. Kane G. Asthma mortality: the worldwide response. *J. Royal Soc. Med.* 90(5): 265-7, 1997 May.
26. Mannino D. Homa D. Pertowski C. Ashizawa A. Nixon L. Johnson C. Ball L. Jack E. Kang D. Surveillance for asthma--United States 1960-1995. *MMWR CDC Surveillance Summaries* 47(1): 1-27, 1998 Apr 24.
27. McClain C. et al. Minerals and inflammatory response. *J. Amer. Coll. Nutr*. 11(5): 598 Abstract 4, 1992 Oct.
28. McClain, C. et al. Trace minerals in liver disease [zinc, selenium, copper, chromium and iron]. *Seminars in Liver Disease* 11(4): 321-37, 1991.
29. McNamara R. Spivey W. Skobeloff E. Jacubowitz S. Intravenous magnesium sulfate in the management of acute respiratory failure complicating asthma. *Ann. Emerg. Med*. 18(2): 197-9, 1989 Feb.
30. Mills R. Leadbeater M. Ravalia A. Intravenous magnesium sulphate in the management of refractory bronchospasm in a ventilated asthmatic. *Anaesthesia* 52(8): 782-5, 1997 Aug.
31. Moan M. Fanta C. Bronchodilator therapy in the management of acute asthma. *Comprehensive Ther*. 21(8):421-7, 1995 Aug.
32. Nakazawsa T. Kawakami Y. Sudo M. Kobayashi S. Suetsugu S. Nakajima S. Yamakido M. Nagano H. [Trends of asthma death among adults in Japan 1992-1994. Analysis of 313 cases reported questionnaires sent to hospitals with more than 100 beds]. *Arerugi – Jap. J. Allergology* 47(1): 41-7, 1998 Jan.
33. Noppen M. Vanmaele L. Impens N. Schandevyl W. Bronchodilating effect of intravenous magnesium sulfate in acute severe bronchial asthma [see comments]. Comment in: *Chest* 1991 Feb, 99(2): 525-6; *Chest*. 97(2): 373-6, 1990 Feb.
34. Odeh M. The role of zinc in acquired immunodeficiency syndrome. *J. Int. Med*. 231: 463-69, 1992.
35. Okayama H. Aikawa T. Okayama M. Sasaki H. Mue S. Takishima T. Bronchodilating effect of intravenousmagnesium sulfate in bronchial asthma. *JAMA* 257(8): 1076-78, 1987 Feb 27.
36. Prasad A. Zinc and lymphocyte immune function. *J. Am. Coll. Nutr*. 11(5): 597 Abstract 3, 1992, Oct.
37. Rolla G. Bucca C. Brussino L. Colagrande P. Effect of intravenous magnesium infusion on salbutamol-induced bronchodilatation in patients with asthma. *Magnesium Research*. 7(2): 129-33, 1994 Jun.

38. Rolla G. Bucca C. Caria E. Arossa W. Bugiani M. Cesano L. Caropreso A. Acute effect of intravenous magnesium sulfate on airway obstruction of asthmatic patients. Ann. Allerg. 61(5): 388-91, 1988 Nov.
39. Ruffman R. Wendel A. GSH rescued by N-acetyl cysteine, *Klin. Wochenschr* 69:857-62, 1991.
40. Schiermeyer R. Finkelstein J. Rapid infusion of magnesium sulfate obviates need for intubation in status asthmaticus. *Amer. J. Emer. Med*. 12(2): 164-6, 1994 Mar.
41. Sly R. O'Donnell R. Stabilization of asthma mortality [See comment]. Comment in *Ann. Aller. Asthma Immunol.* 78 (4): 333-7, 1997, Apr. *Ann. Aller. Asthma & Immunol.* 78 (4): 347-54, 1997.
42. Sydow M. Crozier T. Zielmann S. Radke J. Burchardi H. High-dose intravenous magnesium sulfate in the management of life-threatening status asthmaticus [see comments]. Comment in: *Intensive Care Med*. 1995, Jan 21(1): 94-5; *Intensive Care Med*. 19(8): 467-71, 1993.
43. Tiffany B. Berk W. Todd I. White S. Magnesium bolus or infusion fails to improve expiratory flow in acute asthma exacerbations. *Chest* 104(3): 831-4, 1993 Sep.
44. Turnlund J. Vitamin B6 depletion followed by repletion with animal or plant source calcium and magnesium in young women. *Amer. J. Clin. Nutr*. 56: 905-10, 1992.
45. Wright J. Littleton K. Defects in sulfur metabolism. *Internatl. Clin. Nut. Rev.* 9 (3): 118-19, 1989 Jul.
46. Wright J. *Vitamin B-12:* Powerful protection against childhood asthma. *Internatl. Clin. Nutr. Rev.* 9(4): 185-8, 1989.
47. Zidenberg-Cherr S. Essential trace elements in antioxidant processes. *Trace Elements, Micronutrients and Free Radicals* 107-27, 1992.

IV References, categorized, most recent to oldest by subject (Dec. 31 1998 - Dec., 2007)

Magnesium references

Anesthesia

48. Arcioni R, Palmisani S, Tigano S, Santorsola C, Sauli V, Romanò S, Mercieri
49. M, Masciangelo R, De Blasi RA, Pinto G. Combined intrathecal and epidural magnesium sulfate supplementation of spinal anesthesia to reduce post-operative analgesic requirements: a prospective, randomized, double-blind, controlled trial in patients undergoing major orthopedic surgery. Acta Anaesthesiol Scand. 2007 Apr;51(4):482-9.
50. Cizmeci P, Ozkose Z. Magnesium sulphate as an adjuvant to total intravenous anesthesia in septorhinoplasty: a randomized controlled study.
51. Aesthetic Plast Surg. 2007 Mar-Apr;31(2):167-73.
52. Gupta K, Vohra V, Sood J. The role of magnesium as an adjuvant during general anaesthesia. Anaesthesia. 2006 Nov;61(11):1058-63.
53. Elsharnouby NM, Elsharnouby MM. Magnesium sulphate as a technique of hypotensive anaesthesia. Br J Anaesth. 2006 Jun;96(6):727-31. Epub 2006 May 2.

Asthma: *multiple nutrients*

54. Shrader, W.A. Jr. Short and long term treatment of asthma with intravenous nutrients. Nutr J. 2004 May 14; 3(1): 6.

Asthma: *magnesium*

55. Mannix R, Bachur R. Status asthmaticus in children.
56. Curr Opin Pediatr. 2007 Jun;19(3):281-7. Review.
57. Beasley R, Aldington S. Magnesium in the treatment of asthma. Curr Opin Allergy Clin Immunol. 2007 Feb;7(1):107-10. Review.
58. Behbehani N, Fitzgerald JM. The assessment and management of patients with acute asthma *Int J Tuberc Lung Dis*. 2006 Apr;10(4):356-64. Comment in: *Int J Tuberc Lung Dis*. 2006 Oct;10(10):1182-3.
59. Cheuk DK, Chau TC, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. Arch Dis Child. 2005 Jan;90(1):74-7. Review.

60. Blitz M, Blitz S, Beasely R, Diner BM, Hughes R, Knopp JA, Rowe BH. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev. 2005 Jul 20;(3): CD003898. Review.
61. Sellers WF. Intravenous magnesium sulphate and salbutamol for asthma. Anaesthesia. 2004 Feb;59(2):198.
62. Silverman RA, Osborn H, Runge J, Gallagher EJ, Chiang W, Feldman J, Gaeta T, Freeman K, Levin B, Mancherje N, Scharf S; Acute Asthma/Magnesium Study Group. IV magnesium sulfate in the treatment of acute severe asthma: a multicenter randomized controlled trial. Chest 2002 Aug;122(2):489-97. Erratum in: Chest 2002 Nov;122(5):1870. Comment in: Chest. 2002 Aug;122(2):396-8.
63. Singh M. Management of acute asthma. Indian J Pediatr 2001 Sep;68 Suppl 4:S23-30.
64. Rowe BH, Edmonds ML, Spooner CH, Camargo CA. Evidence-based treatments for acute asthma. Respir Care 2001 Dec;46(12):1380-90; discussion 1390-1.
65. Schenk P, Vonbank K, Schnack B, Haber P, Lehr S, Smetana R. Intravenous magnesium sulfate for bronchial hyperreactivity: a randomized, controlled, double-blind study. Clin Pharmacol Ther 2001 May;69(5):365-71.
66. Rowe BH, Edmonds ML, Spooner CH, Camargo CA. Evidence-based treatments for acute asthma. Respir Care 2001 Dec; 46(12): 1380-91
67. Schenk P, Vonbank K, Schnack B, Haber P, Lehr S, Smetana R. Intravenous magnesium sulfate for bronchial hyperreactivity: a randomized, controlled, double-blind study. Clin Pharmacol Ther 2001 May;69(5):365-71.
68. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo CA Jr. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Cochrane Database Syst Rev 2000;(2):CD001490.
69. Ciarallo L, Brousseau D, Reinert S. Higher-dose intravenous magnesium therapy for children with moderate to severe acute asthma. Arch Pediatr Adolesc Med 2000 Oct;154(10):979-83.
70. Gurkan F, Haspolat K, Bosnak M, Dikici B, Derman O, Ece A. Intravenous magnesium sulphate in the management of moderate to severe acute asthmatic children non-responding to conventional therapy. Eur J Emerg Med 1999 Sep;6(3):201-5.
71. Swain R, Kaplan-Machlis B. Magnesium for the next millennium. South Med J 1999 Nov;92(11):1040-7.
72. Alter HJ, Koepsell TD, Hilty WM. Intravenous magnesium as an adjuvant in acute bronchospasm: a meta-analysis. Ann Emerg Med 2000 Sep;36(3):191-7. Comment in: Ann Emerg Med. 2000 Sep;36(3):234-6.

Magnesium, Cardiovascular:

73. Stiles MK, Sanders P, Disney P, Brooks A, John B, Lau DH, Shashidhar, Wilson
74. L, Mackenzie L, Young GD. Differential effects of intravenous magnesium on atrioventricular node conduction in supraventricular tachycardia. Am J Cardiol. 2007 Oct 15;100(8):1249-53. Epub 2007 Aug 6.
75. Onalan O, Crystal E, Daoulah A, Lau C, Crystal A, Lashevsky I. Meta-analysis of magnesium therapy for the acute management of rapid atrial fibrillation.
76. Am J Cardiol. 2007 Jun 15;99(12):1726-32. Epub 2007 Apr 26.
77. Ho KM, Sheridan DJ, Paterson T. Use of intravenous magnesium to treat acute onset atrial fibrillation: a meta-analysis. Heart. 2007 Nov;93(11):1433-40. Epub 2007 Apr 20. Review.
78. Li J, Zhang Q, Zhang M, Egger M. Intravenous magnesium for acute myocardial infarction. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD002755. Review.
79. Hoshino K, Ogawa K, Hishitani T, Isobe T, Etoh Y. Successful uses of magnesium sulfate for torsades de pointes in children with long QT syndrome Pediatr Int. 2006 Apr;48(2):112-7..
80. Brackbill ML, Moberg L. Magnesium sulfate for prevention of postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting. Am J Health Syst Pharm. 2005 Feb 15;62(4):397-9.

81. Kohno H, Koyanagi T, Kasegawa H, Miyazaki M. Three-day magnesium administration prevents atrial fibrillation after coronary artery bypass grafting. Ann Thorac Surg. 2005 Jan;79(1):117-26. Review.
82. Henyan NN, Gillespie EL, White CM, Kluger J, Coleman CI. Impact of intravenous magnesium on post-cardiothoracic surgery atrial fibrillation and length of hospital stay: a meta-analysis. Ann Thorac Surg. 2005 Dec;80(6):2402-6.
83. Nakashima H, Katayama T, Honda Y, Suzuki S, Yano K. Cardioprotective effects of magnesium sulfate in patients undergoing primary coronary angioplasty for acute myocardial infarction. Circ J. 2004 Jan;68(1):23-8.
84. Coleman CI, Kalus JS, White CM, Spencer AP, Tsikouris JP, Chung JO, Kenyon KW, Ziska M, Kluger J, Reddy P. Cost effectiveness of ibutilide with prophylactic magnesium in the treatment of atrial fibrillation. Pharmacoeconomics. 2004;22(13):877-83.
85. Rukshin V, Santos R, Gheorghiu M, Shah PK, Kar S, Padmanabhan S, Azarbal B, Tsang VT, Makkar R, Samuels B, Lepor N, Geft I, Tabak S, Khorsandhi M, Buchbinder N, Eigler N, Cercek B, Hodgson K, Kaul S. A prospective, nonrandomized, open-labeled pilot study investigating the use of magnesium in patients undergoing nonacute percutaneous coronary intervention with stent implantation. J Cardiovasc Pharmacol Ther. 2003 Sep;8(3):193-200.
86. Shechter M, Hod H, Rabinowitz B, Boyko V, Chouraqui P. Long-term outcome of intravenous magnesium therapy in thrombolysis-ineligible acute myocardial infarction patients. Cardiology. 2003;99(4):205-10.
87. Smetana R, Stuhlinger HG, Kiss K, Glogar DH. Intravenous magnesium sulphate in acute myocardial infarction--is the answer "MAGIC"? Magnes Res. 2003 Mar;16(1):65-9.
88. Caron MF, Kluger J, Tsikouris JP, Ritvo A, Kalus JS Effects of intravenous magnesium sulfate on the QT interval in patients receiving ibutilide. Pharmacotherapy. 2003 Mar;23(3):296-300.
89. Nel L, Hatherill M, Davies J, Andronikou S, Stirling J, Reynolds L, Argent. Organophosphate poisoning complicated by a tachyarrhythmia and acute respiratory distress syndrome in a child. J Paediatr Child Health 2002 Oct;38(5):530-2.
90. Hoshino K, Ogawa K, Hishitani T, Kitazawa R. Studies of magnesium in congenital long QT syndrome. Pediatr Cardiol 2002 Jan-Feb;23(1):41-8.
91. Ohtsuka S, Oyake Y, Seo Y, Eda K, Yamaguchi I. Magnesium sulphate infusion suppresses the cardiac release of noradrenaline during a handgrip stress test. Can J Cardiol 2002 Feb;18(2):133-40.
92. Chang KH, Uchikoba K, Obara M, Chinzei M, Sumida T, Arita E, Hanaoka K. [Marked reduction of life-threatening ventricular tachyarrhythmias in a critically ill patient by intravenous administration of magnesium sulfate] [Article in Japanese]. Masui 2002 Jan;51(1):56-60.
93. Toraman F, Karabulut EH, Alhan HC, Dagdelen S, Tarcan S. Magnesium infusion dramatically decreases the incidence of atrial fibrillation after coronary artery bypass grafting. Ann Thorac Surg 2001 Oct; 72(4):1256-61; discussion 1261-2.
94. Chiladakis JA, Stathopoulos C, Davlouros P, Manolis AS. Intravenous magnesium sulfate versus diltiazem in paroxysmal atrial fibrillation. Int J Cardiol 2001 Jul;79(2-3):287-91.
95. Christiansen EH, Frost L, Andreasen F, Mortensen P, Thomsen PE, Pedersen AK. Dose-related cardiac electrophysiological effects of intravenous magnesium. A double-blind placebo-controlled dose-response study in patients with paroxysmal supraventricular tachycardia. Europace 2000 Oct; 2(4):320-6.
96. Chiladakis JA, Stathopoulos C, Davlouros P, Manolis AS. Patras. Intravenous magnesium sulfate versus diltiazem in paroxysmal atrial fibrillation. Int J Cardiol 2001 Jul;79(2-3):287-91.
97. Thiele R, Protze F, Winnefeld K, Pfeifer R, Pleissner J, Gassel M. Effect of intravenous magnesium on ventricular tachyarrhythmias associated with acute myocardial infarction. Magnes Res 2000 Jun;13(2):111-22.
98. GyamLani G, Parikh C, Kulkarni AG. Benefits of magnesium in acute myocardial infarction: timing is crucial. Am Heart J 2000 Apr;139(4):703.

99. Dorman BH, Sade RM, Burnette JS, Wiles HB, Pinosky ML, Reeves ST, Bond BR, Spinale FG. Magnesium supplementation in the prevention of arrhythmias in pediatric patients undergoing surgery for congenital heart defects. Am Heart J 2000 Mar; 139(3): 522-8.

100. Ceremuzynski L, Gebalska J, Wolk R, Makowska E. Hypomagnesemia in heart failure with ventricular arrhythmias. Beneficial effects of magnesium supplementation. J Intern Med 2000 Jan;247(1):78-86.

101. Shechter M. The role of magnesium as antithrombotic therapy. Wien Med Wochenschr 2000;150(15-16):343-7.

102. Ravn HB, Lassen JF, Bergenhem N, Kristensen AT. Intravenous magnesium does not influence the activity of the coagulation cascade. Blood Coagul Fibrinolysis 2001 Jun;12(4):223-8.

103. Raghu C, Peddeswara Rao P, Seshagiri Rao D.Protective effect of intravenous magnesium in acute myocardial infarction following thrombolytic therapy. Int J Cardiol 1999 Dec 1;71(3):209-15. Comment in: Int J Cardiol. 1999 Dec 1;71(3):217-8.

104. O'Brien JM, Rockwood RP, Suh KI. Haloperidol-induced torsade de pointes. Ann Pharmacother 1999 Oct; 33(10): 1046-50.

105. Falck G, Lundgaard H, Jareld T, Skarra S, Arbo I, Gunnes S, Jynge P. Effect of magnesium infusion on bleeding time in healthy male volunteers. Scand J Clin Lab Invest 1999 Oct;59(6):425-30.

106. Kobusiak-Prokopowicz M, Mysiak A. Katedry i Kliniki Kardiologii AM we Wroclawiu. [The effect of intravenous magnesium on the arrhythmias in patients after electrical cardioversion] [Article in Polish]. Pol Merkuriusz Lek 1999 Aug;7(38):51-3.

107. Shibata M, Ueshima K, Harada M, Nakamura M, Hiramori K, Endo S, Sato N, Mukaida H, Suzuki T, Suzuki T, Inada K. Effect of magnesium sulfate pretreatment and significance of matrix metalloproteinase-1 and interleukin-6 levels in coronary reperfusion therapy for patients with acute myocardial infarction. Angiology 1999 Jul;50(7):573-82.

108. Datta S, Nasr NF, Khorasani A, Datta R. Current concepts in cardiopulmonary resuscitation in adults. J Indian Med Assoc 1999 Jul;97(7):259-64, 270.

109. Parikka H, Toivonen L, Verkkala K, Jarvinen A, Nieminen MS. Ventricular Arrhythmia Suppression by Magnesium Treatment after Coronary Artery Bypass Surgery. International Journal of angiology 1999 Jun;8(3):165-170.

110. Ravn HB, Moeldrup U, Brookes CI, Ilkjaer LB, White P, Chew M, Jensen L, Johnsen S, Birk-Soerensen L, Hjortdal VE. Intravenous magnesium reduces infarct size after ischemia/reperfusion injury combined with a thrombogenic lesion in the left anterior descending artery. Arterioscler Thromb Vasc Biol 1999 Mar;19(3):569-74.

111. Parikka HJ, Toivonen LK. Acute effects of intravenous magnesium on ventricular refractoriness and monophasic action potential duration in humans. Scand Cardiovasc J 1999;33(5):300-5.

Magnesium: Neurology/Neurosurgery:

112. Dorhout Mees SM, Rinkel GJ, Feigin VL, Algra A, van den Bergh WM, Vermeulen M, van Gijn J. Calcium antagonists for aneurysmal subarachnoid haemorrhage.

113. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD000277. Review.

114. Wong GK, Poon WS, Chan MT, Boet R, Gin T, Lam CW. The effect of intravenous magnesium sulfate infusion on serum levels of sodium and potassium in patients with aneurysmal subarachnoid hemorrhage. Magnes Res. 2007 Mar;20(1):37-42.

115. Aslanyan S, Weir CJ, Muir KW, Lees KR; IMAGES Study Investigators. Magnesium for treatment of acute lacunar stroke syndromes: further analysis of the IMAGES trial. Stroke. 2007 Apr;38(4):1269-73. Epub 2007 Mar 8.

116. Natale JE, Guerguerian AM, Joseph JG, McCarter R, Shao C, Slomine B,

117. Christensen J, Johnston MV, Shaffner DH. Pilot study to determine the hemodynamic safety and feasibility of magnesium sulfate infusion in children with severe traumatic brain injury. Pediatr Crit Care Med. 2007 Jan;8(1):1-9.

118. Stippler M, Crago E, Levy EI, Kerr ME, Yonas H, Horowitz MB, Kassam A. Magnesium infusion for vasospasm prophylaxis after subarachnoid hemorrhage. J Neurosurg. 2006 Nov;105(5):723-9. Lancet. 2006 Oct 21;368(9545):1436-43.

119. Wong GK, Chan MT, Boet R, Poon WS, Gin T. Intravenous magnesium sulfate after aneurysmal subarachnoid hemorrhage: a prospective randomized pilot study Neurosurg Anesthesiol. 2006 Apr;18(2):142-8.

120. Wong GK, Chan MT, Poon WS, Boet R, Gin T. Magnesium therapy within 48 hours of an aneurysmal subarachnoid hemorrhage: neuro-panacea Neurol Res. 2006 Jun;28(4):431-5.

121. Schmid-Elsaesser R, Kunz M, Zausinger S, Prueckner S, Briegel J, Steiger HJ. Intravenous magnesium versus nimodipine in the treatment of patients with aneurysmal subarachnoid hemorrhage: a randomized study. Neurosurgery. 2006 Jun;58(6):1054-65; discussion 1054-65.

122. Turan A, Memis D, Karamanlioglu B, Guler T, Pamukcu Z. Intravenous regional anesthesia using idocaine and magnesium. Anesth Analg. 2005 Apr;100(4):1189-92.

123. van Norden AG, van den Bergh WM, Rinkel GJ. Dose evaluation for long-term magnesium treatment in aneurysmal subarachnoid haemorrhage. J Clin Pharm Ther. 2005 Oct;30(5):439-42.

124. Saver JL, Kidwell C, Eckstein M, Starkman S; FAST-MAG Pilot Trial Investigators. Prehospital neuroprotective therapy for acute stroke: results of the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) pilot trial. Stroke. 2004 May;35(5):e106-8. Epub 2004 Mar 11.

125. Muir KW, Lees KR, Ford I, Davis S. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. Lancet. 2004 Feb 7;363(9407):439-45. Comment in: Lancet. 2004 Feb 7;363(9407):414-5.

126. Enya M, Kanoh Y, Mune T, Ishizawa M, Sarui H, Yamamoto M, Takeda N, Yasuda K, Yasujima M, Tsutaya S, Takeda J. Depressive state and paresthesia dramatically improved by intravenous MgSO4 in Gitelman's syndrome. Intern Med. 2004 May;43(5):410-4. Comment in: Intern Med. 2004 May;43(5):351-2.

127. Barile M, van De Wyngaert F, Mbia JJ, Jativa M, Grandin C, Rooijakkers H, Hantson P. Intravenous magnesium sulfate administration in a patient with refractory vasospasm following subarachnoid hemorrhage. Intensive Care Med. 2003 Jul;29(7):1182-5. Epub 2003 Apr 16.

128. van den Bergh WM, Albrecht KW, Berkelbach van der Sprenkel JW, Rinkel GJ. Magnesium therapy after aneurysmal subarachnoid haemorrhage a dose-finding study for long term treatment. Acta Neurochir (Wien). 2003 Mar;145(3):195-9; discussion 199.

129. Brill S, Sedgwick PM, Hamann W, Di Vadi PP. Efficacy of intravenous magnesium in neuropathic pain. Br J Anaesth 2002 Nov;89(5):711-4.

130. Gordin A, Goldenberg D, Golz A, Netzer A, Joachims HZ. Magnesium: a new therapy for idiopathic sudden sensorineural hearing loss. Otol Neurotol 2002 Jul;23(4):447-51.

131. Chia RY, Hughes RS, Morgan MK. Magnesium: a useful adjunct in the prevention of cerebral vasospasm following aneurysmal subarachnoid haemorrhage. J Clin Neurosci 2002 May;9(3):279-81.

132. Sahin N, Ulusan V, Aydogdu T. Magnesium infusion reduces perioperative pain. Kara H, Eur J Anaesthesiol 2002 Jan;19(1):52-6.

133. Demirkaya S, Vural O, Dora B, Topcuoglu MA. Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. Headache 2001 Feb;41(2):171-7.

134. Ko SH, Lim HR, Kim DC, Han YJ, Choe H, Song HS. Magnesium sulfate does not reduce postoperative analgesic requirements. Anesthesiology 2001 Sep; 95(3):640-6.

135. Corbo J, Esses D, Bijur PE, Iannaccone R, Gallagher EJ. Randomized clinical trial of intravenous magnesium sulfate as an adjunctive medication for emergency department treatment of migraine headache. Ann Emerg Med 2001 Dec;38(6):621-7.

136. Heath DL, Vink R. Subdural hematoma following traumatic brain injury causes a secondary decline in brain free magnesium concentration. J Neurotrauma 2001 Apr;18(4):465-9.

137. Demirkaya S, Vural O, Dora B, Topcuoglu MA. Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. Headache 2001 Feb;41(2):171-7.

138. Lampl Y, Gilad R, Geva D, Eshel Y, Sadeh M. Intravenous administration of magnesium sulfate in acute stroke: a randomized double-blind study. Clin Neuropharmacol 2001 Jan-Feb;24(1):11-5.

139. Ginder S, Oatman B, Pollack M. A prospective study of i.v. magnesium and i.v. prochlorperazine in the treatment of headaches. J Emerg Med 2000 Apr;18(3):311-5.

140. Crosby V, Wilcock A, Corcoran R. The safety and efficacy of a single dose (500 mg or 1 g) of intravenous magnesium sulfate in neuropathic pain poorly responsive to strong opioid analgesics in patients with cancer. J Pain Symptom Manage 2000 Jan; 19 (1):35-9.

141. Heiden A, Frey R, Presslich O, Blasbichler T, Smetana R, Kasper S. Treatment of severe mania with intravenous magnesium sulphate as a supplementary therapy. Psychiatry Res 1999 Dec 27;89(3):239-46.

142. Sanders GM, Sim KM. Is it feasible to use magnesium sulphate as a hypotensive agent in oral and maxillofacial surgery? Ann Acad Med Singapore 1998 Nov;27(6):780-5.

Magnesium, obstetrics:

143. Lyell DJ, Pullen K, Campbell L, Ching S, Druzin ML, Chitkara U, Burrs D,

144. Caughey AB, El-Sayed YY. Magnesium sulfate compared with nifedipine for acute tocolysis of preterm labor: a randomized controlled trial. Obstet Gynecol. 2007 Jul;110(1):61-7.

145. Marret S, Marpeau L, Zupan-Simunek V, Eurin D, Lévêque C, Hellot MF, Bénichou

146. J; PREMAG trial group. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial*. BJOG. 2007 Mar;114(3):310-8. Epub 2006 Dec 4.

147. Schauf B, Becker S, Abele H, Klever T, Wallwiener D, Aydeniz B. Effect of magnesium on red blood cell deformability in pregnancy. Hypertens Pregnancy. 2005;24(1):17-27.

148. Zygmunt M, Heilmann L, Berg C, Wallwiener D, Grischke E, Munstedt K, Spindler A, Lang U. Local and systemic tolerability of magnesium sulphate for tocolysis. Eur J Obstet Gynecol Reprod Biol. 2003 Apr 25;107(2):168-75.

149. Amon E, Midkiff C, Winn H, Holcomb W, Shumway J, Artal R. Tocolysis with advanced cervical dilatation. Obstet Gynecol 2000 Mar;95(3):358-62.

150. Yamaguchi K, Fukuuchi Y, Nogawa S, Dembo T, Tomita Y, Tanaka K. Recovery of decreased local cerebral blood flow detected by the xenon/CT CBF method in a patient with eclampsia. Keio J Med 2000 Feb;49 Suppl 1:A71-4.

151. Duley L, Henderson-Smart D. Magnesium sulphate versus phenytoin for eclampsia. Cochrane Database Syst Rev 2000;(2):CD000128.

152. Duley L, Henderson-Smart D. Magnesium sulphate versus diazepam for eclampsia. Cochrane Database Syst Rev 2000;(2):CD000127.

153. Vigil-De Gracia P, Simiti E, Lora Y. Intrapartum fetal distress and magnesium sulfate. Int J Gynaecol Obstet 2000 Jan;68(1):3-6.

154. El-Sayed YY, Riley ET, Holbrook RH Jr, Cohen SE, Chitkara U, Druzin ML. Randomized comparison of intravenous nitroglycerin and magnesium sulfate for treatment of preterm labor. Obstet Gynecol 1999 Jan;93(1):79-83.

Magnesium, general:

155. Thwaites CL, Yen LM, Loan HT, Thuy TT, Thwaites GE, Stepniewska K, Soni N, White NJ, Farrar JJ. Magnesium sulphate for treatment of severe tetanus: a randomised controlled trial. Comment in: Lancet. 2006 Oct 21; 368(9545):1398-9.

156. Gathwala G, Khera A, Singh I. Magnesium therapy in birth asphyxia. Indian J Pediatr. 2006 Mar;73(3):209-12.

157. Guler A, Satilmis T, Akinci SB, Celebioglu B, Kanbak M. Magnesium sulfate pretreatment reduces myoclonus after etomidate. Anesth Analg. 2005 Sep;101(3):705-9, table of contents.

158. Canavese C, Petrarulo M, Massarenti P, Berutti S, Fenoglio R, Pauletto D,Lanfranco G, Bergamo D, Sandri L, Marangella M. Long-term, low-dose, intravenous vitamin C leads to plasma calcium oxalate supersaturation in hemodialysis patients. Am J Kidney Dis. 2005 Mar;45(3):540-9.

159. Brousseau DC, Scott JP, Hillery CA, Panepinto JA. The effect of magnesium on length of stay for pediatric sickle cell pain crisis. Acad Emerg Med. 2004 Sep;11(9):968-72.

160. Bhatia A, Kashyap L, Pawar DK, Trikha A. Effect of intraoperative magnesium infusion on perioperative analgesia in open cholecystectomy. J Clin Anesth. 2004 Jun;16(4):262-5.

161. Dumont L, Lysakowski C, Tramer MR, Junod JD, Mardirosoff C, Tassonyi E, Kayser B. Magnesium for the prevention and treatment of acute mountain sickness. Clin Sci (Lond). 2004 Mar;106(3):269-77.

162. Gulhas N, Durmus M, Demirbilek S, Togal T, Ozturk E, Ersoy MO. The use of magnesium to prevent laryngospasm after tonsillectomy and adenoidectomy: a preliminary study. Paediatr Anaesth. 2003 Jan;13(1):43-7.

163. Gourgoulianis KI, Chatziparasidis G, Chatziefthimiou A, Molyvdas PA. Magnesium as a relaxing factor of airway smooth muscles. J Aerosol Med 2001 Fall; 14(3):301-7.

164. Papazachariou IM, Martinez-Isla A, Efthimiou E, Williamson RC, Girgis SI. Magnesium deficiency in patients with chronic pancreatitis identified by an intravenous loading test. Clin Chim Acta 2000 Dec;302(1-2):145-54.

165. Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium: An update on physiological, clinical and analytical aspects. Clin Chim Acta 2000 Apr;294(1-2):1-26.

166. Po SS, Wang DW, Yang IC, Johnson JP Jr, Nie L, Bennett PB. Modulation of HERG potassium channels by extracellular magnesium and quinidine. Cardiovasc Pharmacol 1999 Feb;33(2):181-5.

Vitamin C

167. Shinke T, Shite J, Takaoka H, Hata K, Inoue N, Yoshikawa R, Matsumoto H, Masai

168. H, Watanabe S, Ozawa T, Otake H, Matsumoto D, Hirata K, Yokoyama M. Vitamin C restores the contractile response to dobutamine and improves myocardial efficiency in patients with heart failure after anterior myocardial infarction. Am Heart J. 2007 Oct;154(4):645.e1-8.

169. Stephenson CM, Levin RD, Lis CG. Phase 1 trial of high-dose intravenous vitamin C treatment for patients with cancer. J Am Osteopath Assoc. 2007 Jun;107(6):212-3. No abstract available.

170. McCarty MF, Barroso-Aranda J, Contreras F. A two-phase strategy for treatment of oxidant-dependent cancers. Med Hypotheses. 2007;69(3):489-96. Epub 2007 May 14.

171. Briguori C, Airoldi F, D'Andrea D, Bonizzoni E, Morici N, Focaccio A, Michev I, Montorfano M, Carlino M, Cosgrave J, Ricciardelli B, Colombo A. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. Circulation. 2007 Mar 13;115(10):1211-7. Epub 2007 Feb 19.

172. McNulty PH, Robertson BJ, Tulli MA, Hess J, Harach LA, Scott S, Sinoway LI. Effect of hyperoxia and vitamin C on coronary blood flow in patients with ischemic heart disease. J Appl Physiol. 2007 May;102(5):2040-5. Epub 2007 Feb 15.

173. Moreau KL, DePaulis AR, Gavin KM, Seals DR. Oxidative stress contributes to chronic leg vasoconstriction in estrogen-deficient postmenopausal women. J Appl Physiol. 2007 Mar;102(3):890-5. Epub 2006 Nov 16.

174. Yeom CH, Jung GC, Song KJ. Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration. J Korean Med Sci. 2007 Feb;22(1):7-11.

175. Muran PJ. Mercury elimination with oral DMPS, DMSA, vitamin C, and glutathione: an observational clinical review. Altern Ther Health Med. 2006 May-Jun; 12(3):70-5.

176. Kodama M, Kodama T. Four problems with the clinical control of interstitial pneumonia, or chronic fatigue syndrome, using the megadose vitamin C infusion system with dehydroepiandrosterone-cortisol annex. In Vivo. 2006 Mar-Apr;20(2):285-91.

177. Padayatty SJ, Riordan HD, Hewitt SM, Katz A, Hoffer LJ, Levine M. Intravenously administered vitamin C as cancer therapy: three cases. CMAJ. 2006 Mar 28;174(7):937-42. Comment in: CMAJ. 2006 Mar 28;174(7):956-7.

178. Bailey DM, Raman S, McEneny J, Young IS, Parham KL, Hullin DA, Davies B, McKeeman G, McCord JM, Lewis MH. Vitamin C prophylaxis promotes oxidative lipid damage during surgical ischemia-reperfusion. Free Radic Biol Med. 2006 Feb 15;40(4):591-600.

179. Grebe M, Eisele HJ, Weissmann N, Schaefer C, Tillmanns H, Seeger W, Schulz R. Antioxidant vitamin C improves endothelial function in obstructive sleep apnea. Am J Respir Crit Care Med. 2006 Apr 15;173(8):897-901. Epub 2006 Jan 26.

180. Gonzalez MJ, Miranda-Massari JR, Mora EM, Guzman A, Riordan NH, Riordan HD, Casciari JJ, Jackson JA, Roman-Franco A. Orthomolecular oncology review: ascorbic acid and cancer 25 years later. Integr Cancer Ther. 2005 Mar;4(1):32-44. Review.

181. Sturm B, Laggner H, Ternes N, Goldenberg H, Scheiber-Mojdehkar B. Intravenous iron preparations and ascorbic acid: effects on chelatable and bioavailable iron. Kidney Int. 2005 Mar;67(3):1161-70.

182. Kodama M, Kodama T. The clinical course of interstitial pneumonia alias chronic fatigue syndrome under the control of megadose vitamin C infusion system with dehydroepiandrosterone-cortisol annex. Int J Mol Med. 2005 Jan;15(1):109-16.

183. Intravenous ascorbic acid as a treatment for severe jellyfish stings. Kumar S, Miranda-Massari JR, Gonzalez MJ, Riordan HD. P R Health Sci J. 2004 Jun;23(2):125-6.

184. Intravenous vitamin C as a chemotherapy agent: a report on clinical cases. Riordan HD, Riordan NH, Jackson JA, Casciari JJ, Hunninghake R, Gonzalez MJ, Mora EM, Miranda-Massari JR, Rosario N, Rivera A.P R Health Sci J. 2004 Jun;23(2):115-8.

185. Intravenous ascorbic acid: protocol for its application and use. Riordan HD, Hunninghake RB, Riordan NH, Jackson JJ, Meng X, Taylor P, Casciari JJ, Gonzalez MJ, Miranda-Massari JR, Mora EM, Rosario N, Rivera A. P R Health Sci J. 2003 Sep;22(3):287-90.

186. Taji Y, Morimoto T, Okada K, Fukuhara S, Fukui T, Kuwahara T. Effects of intravenous ascorbic acid on erythropoiesis and quality of life in unselected hemodialysis patients. J Nephrol. 2004 Jul-Aug;17(4):537-43.

187. Tarng DC, Liu TY, Huang TP. Protective effect of vitamin C on 8-hydroxy-2'-deoxyguanosine level in peripheral blood lymphocytes of chronic hemodialysis patients. Kidney Int. 2004 Aug;66(2):820-31.

188. Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, Wesley RA, Levine M. Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med. 2004 Apr 6;140(7):533-7.Comment in: Ann Intern Med. 2004 Apr 6;140(7):I61.

189. Du WD, Yuan ZR, Sun J, Tang JX, Cheng AQ, Shen DM, Huang CJ, Song XH, Yu XF, Zheng SB. Therapeutic efficacy of high-dose vitamin C on acute pancreatitis and its potential mechanisms. World J Gastroenterol. 2003 Nov;9(11):2565-9.

190. Schindler TH, Nitzsche EU, Munzel T, Olschewski M, Brink I, Jeserich M, Mix M, Buser PT, Pfisterer M, Solzbach U, Just H. Coronary vasoregulation in patients with various risk factors in response to cold pressor testing: contrasting myocardial blood flow responses to short- and long-term vitamin C administration. J Am Coll Cardiol. 2003 Sep 3;42(5):814-22.

191. Drisko JA, Chapman J, Hunter VJ. The use of antioxidants with first-line chemotherapy in two cases of ovarian cancer. J Am Coll Nutr. 2003 Apr;22(2):118-23.

192. Lin CL, Hsu PY, Yang HY, Huang CC. Low dose intravenous ascorbic acid for erythropoietin-hyporesponsive anemia in diabetic hemodialysis patients with iron overload. Ren Fail. 2003 May;25(3):445-53.

193. Nightingale AK, Blackman DJ, Field R, Glover NJ, Pegge N, Mumford C, Schmitt M, Ellis GR, Morris-Thurgood JA, Frenneaux MP. Role of nitric oxide and oxidative stress in baroreceptor dysfunction in patients with chronic heart failure. Clin Sci (Lond). 2003 May;104(5):529-35.

194. Deng YB, Li TL, Xiang HJ, Chang Q, Li CL. Impaired endothelial function in the brachial artery after Kawasaki disease and the effects of intravenous administration of vitamin C. Pediatr Infect Dis J. 2003 Jan;22(1):34-9.

195. Tomiyama H, Watanabe G, Yoshida H, Doba N, Yamashina A. Reduction of oxidative stress augments natriuretic effect of furosemide in moderate heart failure. Am Heart J. 2003 Jan;145(1):E2.

196. Schindler TH, Lewandowski E, Olschewski M, Hasler K, Solzbach U, Just H. [Effect of vitamin C on platelet aggregation in smokers and nonsmokers] [Article in German] Med Klin (Munich). 2002 May 15;97(5):263-9. German.

197. Gonzalez MJ, Miranda-Massari JR, Mora EM, Jimenez IZ, Matos MI, Riordan HD, Casciari JJ, Riordan NH, Rodriguez M, Guzman A. Orthomolecular oncology: a mechanistic view of intravenous ascorbate's chemotherapeutic activity. P R Health Sci J 2002 Mar;21(1):39-41.

198. Richartz BM, Werner GS, Ferrari M, Figulla HR. Reversibility of coronary endothelial vasomotor dysfunction in idiopathic dilated cardiomyopathy: acute effects of vitamin C. Am J Cardiol 2001 Nov 1;88(9):1001-5.

199. Rossig L, Hoffmann J, Hugel B, Mallat Z, Haase A, Freyssinet JM, Tedgui A, Aicher A, Zeiher AM, Dimmeler S. Vitamin C inhibits endothelial cell apoptosis in congestive heart failure. Circulation 2001 Oct 30;104(18):2182-7.

200. Shen CT, Wang NK. Antioxidants may mitigate the deterioration of coronary arteritis in patients with Kawasaki disease unresponsive to high-dose intravenous gamma-globulin. Pediatr Cardiol 2001 Sep-Oct;22(5):419-22.

201. Yamada T, Minohara M, Imaiso Y, Sakae N, Hara H, Tanaka K, Yamamoto T, Taniwaki T, Furuya H, Kira J. High-dose vitamin C therapy for inclusion body myositis. Artif Organs 2001 Jun;25(6):430-6. Fukuoka Igaku Zasshi 2001 Apr;92(4):99-104.

202. Casciari JJ, Riordan NH, Schmidt TL, Meng XL, Jackson JA, Riordan HD. Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fibre in vitro tumours. Br J Cancer 2001 Jun 1;84(11):1544-50.

203. Hamabe A, Takase B, Uehata A, Kurita A, Ohsuzu F, Tamai S. Impaired endothelium-dependent vasodilation in the brachial artery in variant angina pectoris and the effect of intravenous administration of vitamin C. Am J Cardiol 2001 May 15;87(10):1154-9.

204. Ellis GR, Anderson RA, Chirkov YY, Morris-Thurgood J, Jackson SK, Lewis MJ, Horowitz JD, Frenneaux MP. Acute effects of vitamin C on platelet responsiveness to nitric oxide donors and endothelial function in patients with chronic heart failure. J Cardiovasc Pharmacol 2001 May;37(5):564-70.

205. Grossmann M, Dobrev D, Himmel HM, Ravens U, Kirch W. Ascorbic acid-induced modulation of venous tone in humans. Hypertension 2001 Mar;37(3):949-54.

206. Chambers JC, Haskard DO, Kooner JS. Vascular endothelial function and oxidative stress mechanisms in patients with Behcet's syndrome. J Am Coll Cardiol 2001 Feb;37(2):517-20.

207. Mak S, Newton GE. Vitamin C augments the inotropic response to dobutamine in humans with normal left ventricular function. Circulation 2001 Feb 13;103(6):826-30. Comment in: Circulation. 2001 Feb 13;103(6):782-3. UI: 21112918.

208. Hamabe A, Takase B, Uehata A, Kurita A, Ohsuzu F, Tamai S. Impaired endothelium-dependent vasodilation in the brachial artery in variant angina pectoris and the effect of intravenous administration of vitamin C. Am J Cardiol 2001 May 15;87(10):1154-9.

209. Mak S, Newton GE. Vitamin C augments the inotropic response to dobutamine in humans with normal left ventricular function. Circulation 2001 Feb 13;103(6):826-30. Comment in: Circulation. 2001 Feb 13;103(6):782-3.

210. Chambers JC, Haskard DO, Kooner JS. Vascular endothelial function and oxidative stress mechanisms in patients with Behcet's syndrome J Am Coll Cardiol 2001 Feb;37(2):517-20

211. Halimi JM, Mimran A. Systemic and renal effect of nicotine in non-smokers: influence of vitamin C. J Hypertens 2000 Nov;18(11):1665-9.

212. Ellis GR, Anderson RA, Lang D, Blackman DJ, Morris RH, Morris-Thurgood J, McDowell IF, Jackson SK, Lewis MJ, Frenneaux MP. Neutrophil superoxide anion--generating capacity, endothelial function and oxidative stress in chronic heart failure: effects of short- and long-term vitamin C therapy. J Am Coll Cardiol 2000 Nov 1;36(5):1474-82.

213. Sakagami H, Satoh K, Hakeda Y, Kumegawa M. Apoptosis-inducing activity of vitamin C and vitamin K. Cell Mol Biol (Noisy-le-grand) 2000 Feb;46(1):129-43.

214. Volchegorskii IA, Vasil'kov AY. Effects of ascorbic acid on lipid peroxidation and functional state of neutrophils at the early period after transurethral resection of the prostate. Bull Exp Biol Med 2000 Nov;130(11):1055-7.

215. Giancaspro V, Nuzziello M, Pallotta G, Sacchetti A, Petrarulo F. Intravenous ascorbic acid in hemodialysis patients with functional iron deficiency: a clinical trial. J Nephrol 2000 Nov-Dec;13(6):444-9.

216. Yamada T, Minohara M, Imaiso Y, Sakae N, Hara H, Tanaka K, Yamamoto T, Taniwaki T, Furuya H, Kira J. High-dose vitamin C therapy for inclusion body myositis. Fukuoka Igaku Zasshi 2001 Apr;92(4):99-104.

217. Casciari JJ, Riordan NH, Schmidt TL, Meng XL, Jackson JA, Riordan HD. Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fibre in vitro tumours. Br J Cancer 2001 Jun 1;84(11):1544-50

Vitamin A:

218. Darlow BA, Graham PJ.. Vitamin A supplementation for preventing morbidity and mortality in very low birthweight infants. Cochrane Database Syst Rev 2000;(2):CD000501

Vitamin B-12:

219. Borron SW, Baud FJ, Barriot P, Imbert M, Bismuth C. Prospective study of hydroxocobalamin for acute cyanide poisoning in smoke inhalation. Ann Emerg Med. 2007 Jun;49(6):794-801, 801.e1-2. Epub 2007 May 4.

220. Uhl W, Nolting A, Golor G, Rost KL, Kovar A. Safety of hydroxocobalamin in healthy volunteers in a randomized, placebo-controlled study.Clin Toxicol (Phila). 2006;44 Suppl 1:17-28.

221. Hoffer LJ, Saboohi F, Golden M, Barre PE. Cobalamin dose regimen for maximum homocysteine reduction in end-stage renal disease. Metabolism. 2005 Jun; 54(6):835-40.

222. Bugarin Gonzalez R, Portela Romero M, Martinez Varela F, Galego Feal P. [Intravenous administration of vitamin B12a in cases of cyanide poisoning] Aten Primaria. 2005 Apr 30; 35(7):382-3. Spanish.

223. Tremblay R, Bonnardeaux A, Geadah D, Busque L, Lebrun M, Ouimet D, Leblanc M. Hyperhomocysteinemia in hemodialysis patients: effects of 12-month supplementation with hydrosoluble vitamins. *Kidney Int* 2000 Aug;58(2):851-8.

224. Henning BF, Zidek W, Riezler R, Graefe U, Tepel M. Homocyst(e)ine metabolism in hemodialysis patients treated with vitamins B6, B12 and folate. *Res Exp Med* (Berl) 2001 Mar;200(3):155-68.

225. Collins DA, Hogenkamp HP, O'Connor MK, Naylor S, Benson LM, Hardyman TJ, Thorson LM. Biodistribution of radiolabeled adenosylcobalamin in patients diagnosed with various malignancies. *Mayo Clin Proc* 2000 Jun;75(6):568-80.

226. Kuwabara S, Nakazawa R, Azuma N, Suzuki M, Miyajima K, Fukutake T, Hattori T. Intravenous methylcobalamin treatment for uremic and diabetic neuropathy in chronic hemodialysis patients. Intern Med 1999 Jun;38(6):472-5.

227. Herzlich BC, Schiano TD. Reversal of apparent AIDS dementia complex following treatment with vitamin B12. J Intern Med 1993 Jun;233(6):495-7.

228. Dierkes J, Domrose U, Ambrosch A, Schneede J, Guttormsen AB, Neumann KH, Luley C. Supplementation with vitamin B12 decreases homocysteine and methylmalonic acid but also serum folate in patients with end-stage renal disease. Metabolism 1999 May;48(5):631-5.

229. Houeto P, Borron SW, Sandouk P, Imbert M, Levillain P, Baud FJ. Pharmacokinetics of hydroxocobalamin in smoke inhalation victims. Toxicol Clin Toxicol 1996;34(4):397-404.

230. Houeto P, Hoffman JR, Imbert M, Levillain P, Baud FJ. Relation of blood cyanide to plasma cyanocobalamin concentration after a fixed dose of hydroxocobalamin in cyanide poisoning. Lancet 1995 Sep 2;346(8975):605-8. Comment in: Lancet. 1995 Dec 23-30;346(8991-8992):1706-7

231. Forsyth JC, Mueller PD, Becker CE, Osterloh J, Benowitz NL, Rumack BH, Hall AH. Hydroxocobalamin as a cyanide antidote: safety, efficacy and pharmacokinetics in heavily smoking normal volunteers. J Toxicol Clin Toxicol 1993;31(2):277-94.

232. Ikeda T, Yamamoto K, Takahashi K, Kaku Y, Uchiyama M, Sugiyama K, Yamada M. Treatment of Alzheimer-type dementia with intravenous mecobalamin. Clin Ther 1992 May-Jun;14(3):426-37.

233. Kurabayashi H, Kubota K, Kawada E, Tamura K, Tamura J, Shirakura T. Complete cure of urinary and faecal incontinence after intravenous vitamin B12 therapy in a patient with post-gastrectomy megaloblastic anaemia. J Intern Med 1992 Mar;231(3):313-5.

Vitamin B-6 and folate

234. Sheehan P. Hyperemesis gravidarum--assessment and management.

235. Aust Fam Physician. 2007 Sep;36(9):698-701. Review.

236. Teune LK, vd Hoeven JH, Maurits NM, Bos AF, Alffenaar JW, Reijngoud DJ,

237. Brouwer OF, Sival DA. Pyridoxine induces non-specific EEG alterations in infants with therapy resistant seizures. Seizure. 2007 Jul;16(5):459-64. Epub 2007 Apr 3.

238. Leathem AM, Dorran TJ. Poisoning due to raw Gyromitra esculenta (false morels) west of the Rockies. CJEM. 2007 Mar;9(2):127-30.

239. Hasegawa S, Oda Y, Ichiyama T, Hori Y, Furukawa S. Ginkgo nut intoxication in a 2-year-old male. Pediatr Neurol. 2006 Oct;35(4):275-6.

240. Wang HS, Kuo MF, Chou ML, Hung PC, Lin KL, Hsieh MY, Chang MY. Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy. Arch Dis Child. 2005 May;90(5):512-5.

241. Gonella M, Calabrese G, Mengozzi A, Aleo AG, Vagelli G, Mazzotta A, Deambrogio P. The achievement of normal homocysteinemia in regular extracorporeal dialysis patients. J. Nephrol. 2004 May-Jun;17(3):411-3.

242. Gonella M, Calabrese G, Mengozzi A, Aleo AG, Vagelli G, Mazzotta A, Deambrogio P. The achievement of normal homocysteinemia in regular extracorporeal dialysis patients. J Nephrol. 2004 May-Jun;17(3):411-3.

243. de Gomez Dumm NT, Giammona AM, Touceda LA. Variations in the lipid profile of patients with chronic renal failure, treated with folic acid. Int J Vitam Nutr Res. 2003 May;73(3):215-20.

244. Kuo MF, Wang HS. Pyridoxal phosphate-responsive epilepsy with resistance to pyridoxine. Pediatr Neurol 2002 Feb;26(2):146-7.

245. Citak A, Kaya O, Ucsel R, Karabocuoglu M, Uzel N. Acute isoniazid neurotoxicity in childhood. Turk J Pediatr 2002 Jan-Mar;44(1):54-7.

246. Gupta VK, Mishra D, Mathur I, Singh KK. Pyridoxine-dependent seizures: a case report and a critical review of the literature. J Paediatr Child Health 2001 Dec;37(6):592-6.

247. Henning BF, Zidek W, Riezler R, Graefe U, Tepel M. Homocyst(e)ine metabolism in hemodialysis patients treated with vitamins B6, B12 and folate. Res Exp Med (Berl) 2001 Mar;200(3):155-68.

248. Henning BF, Zidek W, Riezler R, Graefe U, Tepel M. Homocyst(e)ine metabolism in hemodialysis patients treated with vitamins B6, B12 and folate. *Res Exp Med* (Berl) 2001 Mar;200(3):155-68.

249. Tremblay R, Bonnardeaux A, Geadah D, Busque L, Lebrun M, Ouimet D, Leblanc M. Hyperhomocysteinemia in hemodialysis patients: effects of 12-month supplementation with hydrosoluble vitamins. *Kidney Int* 2000 Aug;58(2):851-8.

250. Touam M, Zingraff J, Jungers P, Chadefaux-Vekemans B, Drueke T, Massy ZA. Effective correction of hyperhomocysteinemia in hemodialysis patients by intravenous folinic acid and pyridoxine therapy. Kidney Int 1999 Dec;56(6):2292-6.

251. Goto T, Matsuo N, Takahashi T. CSF glutamate/GABA concentrations in pyridoxine-dependent seizures: etiology of pyridoxine-dependent seizures and the mechanisms of pyridoxine action in seizure control. Brain Dev 2001 Mar;23(1):24-9.

252. Hauser AC, Hagen W, Rehak PH, Buchmayer H, Fodinger M, Papagiannopoulos M, Bieglmayer C, Apsner R, Koller E, Ignatescu M, Horl WH, Sunder-Plassmann G. Efficacy of folinic versus folic acid for the correction of hyperhomocysteinemia in hemodialysis patients. *Am J Kidney Dis* 2001 Apr;37(4):758-65.

253. Henning BF, Zidek W, Riezler R, Graefe U, Tepel M. Homocyst(e)ine metabolism in hemodialysis patients treated with vitamins B6, B12 and folate. *Res Exp Med* (Berl) 2001 Mar;200(3):155-68

254. Tremblay R, Bonnardeaux A, Geadah D, Busque L, Lebrun M, Ouimet D, Leblanc M. Hyperhomocysteinemia in hemodialysis patients: effects of 12-month supplementation with hydrosoluble vitamins. *Kidney Int* 2000 Aug;58(2):851-8

255. Touam M, Zingraff J, Jungers P, Chadefaux-Vekemans B, Drueke T, Massy ZA. Effective correction of hyperhomocysteinemia in hemodialysis patients by intravenous folinic acid and pyridoxine therapy. Kidney Int 1999 Dec;56(6):2292-6.

Thiamine

256. Moonen M, Lancellotti P, Betz R, Lambermont B, Piérard L. [Beriberi]

257. Rev Med Liege. 2007 Jul-Aug;62(7-8):523-30. French.

258. Ueda K, Takada D, Mii A, Tsuzuku Y, Saito SK, Kaneko T, Utsumi K, Iino Y, Katayama Y. Severe thiamine deficiency resulted in Wernicke's encephalopathy in a chronic dialysis patient. Clin Exp Nephrol. 2006 Dec;10(4):290-3. Epub 2006 Dec 20.

259. Wilson RK, Kuncl RW, Corse AM. Wernicke's encephalopathy: beyond alcoholism. Nat Clin Pract Neurol. 2006 Jan;2(1):54-8; quiz 58.

260. Harrison RA, Vu T, Hunter AJ. Wernicke's encephalopathy in a patient with schizophrenia J Gen Intern Med. 2006 Dec;21(12):C8-C11. Epub 2006 Aug 22.

261. Chotmongkol V, Limpawattana P. Wernicke's encephalopathy: report of a case. J Med Assoc Thai. 2005 Jun;88(6):855-8.

262. Cho YP, Kim K, Han MS, Jang HJ, Kim JS, Kim YH, Lee SG. Severe lactic acidosis and thiamine deficiency during total parenteral nutrition--case report. Hepatogastroenterology. 2004 Jan-Feb;51(55):253-5.

263.. Diltoer MW, Troubleyn J, Lauwers R, De Wijngaard S, Vercammen MJ, Hubloue I, Huyghens LP. Ketosis and cardiac failure: common signs of a single condition. Eur J Emerg Med. 2004 Jun;11(3):172-5

264. Ishimaru T, Yata T, Hatanaka-Ikeno S. Hemodynamic response of the frontal cortex elicited by intravenous thiamine propyldisulphide administration. Chem Senses. 2004 Mar;29(3):247-51.

Carnitine:

265. Makino Y, Sugiura T, Ito T, Sugiyama N, Koyama N. Carnitine-associated encephalopathy caused by long-term treatment with an antibiotic containing pivalic acid. Pediatrics. 2007 Sep;120(3):e739-41. Epub 2007 Aug 27.

266. Russell S. Carnitine as an antidote for acute valproate toxicity in children.

267. Curr Opin Pediatr. 2007 Apr;19(2):206-10. Review.

268. Loffredo L, Pignatelli P, Cangemi R, Andreozzi P, Panico MA, Meloni V, Violi F. Imbalance between nitric oxide generation and oxidative stress in patients with peripheral arterial disease: effect of an antioxidant treatment. J Vasc Surg. 2006 Sep;44(3):525-30.

269. Signorelli SS, Fatuzzo P, Rapisarda F, Neri S, Ferrante M, Oliveri Conti G,Fallico R, Di Pino L, Pennisi G, Celotta G, Anzaldi M. Propionyl-L-carnitine therapy: effects on endothelin-1 and homocysteine levels in patients with peripheral arterial disease and end-stage renal disease. Kidney Blood Press Res. 2006;29(2):100-7. Epub 2006 Jun 30.

270. Rathod R, Baig MS, Khandelwal PN, Kulkarni SG, Gade PR, Siddiqui S. Results of a single blind, randomized, placebo-controlled clinical trial to study the effect of intravenous L-carnitine supplementation on health-related quality of life in Indian patients on maintenance hemodialysis. Indian J Med Sci. 2006 Apr;60(4):143-53.

271. Silvestro A, Schiano V, Bucur R, Brevetti G, Scopacasa F, Chiariello M. Effect of propionylcarnitine on changes in endothelial function and plasma levels of adhesion molecules induced by acute exercise in patients with intermittent claudication.Angiology. 2006 Mar-Apr;57(2):145-54.

272. Siciliano M, Annicchiarico BE, Lucchese F, Bombardieri G. Effects of a single, short intravenous dose of acetyl-L-carnitine on pattern-reversal visual-evoked potentials in cirrhotic patients with hepatic encephalopathy. Clin Exp Pharmacol Physiol. 2006 Jan-Feb;33(1-2):76-80.

273. Vernez L, Dickenmann M, Steiger J, Wenk M, Krahenbuhl S. Effect of L-carnitine on the kinetics of carnitine, acylcarnitines and butyrobetaine in long-term haemodialysis. Nephrol Dial Transplant. 2006 Feb;21(2):450-8. Epub 2005 Nov 11. Erratum in: Nephrol Dial Transplant. 2006 Apr;21(4):1141.

274. Ferrari R, Merli E, Cicchitelli G, Mele D, Fucili A, Ceconi C. Ann N Y. Therapeutic Effects of l-Carnitine and Propionyl-l-carnitine on Cardiovascular Diseases: A Review. Ann N Y Acad Sci. 2004 Nov;1033:79-91.

275. Calvani M, Benatti P, Mancinelli A, D'Iddio S, Giordano V, Koverech A, Amato A, Brass EP. Carnitine replacement in end-stage renal disease and hemodialysis. Acad Sci. 2004 Nov;1033:52-66.

276. Ragozzino G, Mattera E, Madrid E, Salomone P, Fasano C, Gioia F, Acerra G, del Guercio R, Federico P. Effects of propionyl-carnitine in patients with type 2 diabetes and peripheral vascular disease: results of a pilot trial. Drugs R D. 2004;5(4):185-90.

277. Brass EP, Adler S, Sietsema KE, Hiatt WR, Orlando AM, Amato A. Intravenous L-carnitine increases plasma carnitine, reduces fatigue, and may preserve exercise capacity in hemodialysis patients. Am J Kidney Dis 2001 May;37(5):1018-28.

278. Winter S, Birek L, Walker T, Phalin-Roque J, Chandler MJ, Field C, Zorn E. Therapy of metabolic disorders with intravenous (IV) access ports and long term intravenous L-carnitine therapy. Southeast Asian J Trop Med Public Health 1999;30 Suppl 2:152-3.

Vitamin K-1:

279. Dezee KJ, Shimeall WT, Douglas KM, Shumway NM, O'malley PG Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. Arch Intern Med. 2006 Feb 27;166(4):391-7.

280. Chambrier C, Bannier E, Lauverjat M, Drai J, Bryssine S, Bouletreau P. Replacement of long-chain triglyceride with medium-chain triglyceride/long-chain triglyceride lipid emulsion in patients receiving long-term parenteral nutrition: effects on essential fatty acid status and plasma vitamin K1 levels. JPEN J Parenter Enteral Nutr. 2004 Jan-Feb;28(1):7-12.

281. Shields RC, McBane RD, Kuiper JD, Li H, Heit JA.. Efficacy and safety of intravenous phytonadione (vitamin K1) in patients on long-term oral anticoagulant therapy. Mayo Clin Proc 2001 Mar;76(3):260-6.

282. MacLaren R, Wilson SJ, Campbell A, Anderson D, Rocker G. Evaluation and survey of intravenous vitamin K1 for treatment of coagulopathy in critically ill patients. Pharmacotherapy 2001 Feb;21(2):175-82.

Molybdenum:

283. Novotny JA, Turnlund JR.

284. Molybdenum intake influences molybdenum kinetics in men. J Nutr. 2007 Jan;137(1):37-42.

285. Werner E, Roth P, Heinrichs U, Giussani A, Cantone MC, Zilker TH, Felgenhauer N, Greim H. Internal biokinetic behaviour of molybdenum in humans studied with stable isotopes as tracers. Isotopes Environ Health Stud 2000;36(2):123-32.

286. Friel JK, MacDonald AC, Mercer CN, Belkhode SL, Downton G, Kwa PG, Aziz K, Andrews WL. Molybdenum requirements in low-birth-weight infants receiving parenteral and enteral nutrition. JPEN J Parenter Enteral Nutr 1999 May-Jun;23(3):155-9.

N-acetyl cysteine

287. Poletti PA, Saudan P, Platon A, Mermillod B, Sautter AM, Vermeulen B, Sarasin

288. FP, Becker CD, Martin PY. I.v. N-acetylcysteine and emergency CT: use of serum creatinine and cystatin C as markers of radiocontrast nephrotoxicity.

289. AJR Am J Roentgenol. 2007 Sep;189(3):687-92.

290. Lawlor DK, Moist L, DeRose G, Harris KA, Lovell MB, Kribs SW, Elliot J, Forbes

291.TL. Prevention of contrast-induced nephropathy in vascular surgery patients.

292.Ann Vasc Surg. 2007 Sep;21(5):593-7.

293.Schaller G, Pleiner J, Mittermayer F, Posch M, Kapiotis S, Wolzt M. Effects of N-acetylcysteine against systemic and renal hemodynamic effects of endotoxin in healthy humans. Crit Care Med. 2007 Aug;35(8):1869-75.

294.Godber IM, Jarvis SJ, Maguire D. Hypokalaemia following paracetamol overdose in two teenage girls. Ann Clin Biochem. 2007 Jul;44(Pt 4):403-5.

295.Recio-Mayoral A, Chaparro M, Prado B, Cózar R, Méndez I, Banerjee D, Kaski JC,

296.Cubero J, Cruz JM. The reno-protective effect of hydration with sodium bicarbonate plus N-acetylcysteine in patients undergoing emergency percutaneous coronary

297.intervention: the RENO Study. J Am Coll Cardiol. 2007 Mar 27;49(12):1283-8. Epub 2007 Mar 12.

298.Briguori C, Airoldi F, D'Andrea D, Bonizzoni E, Morici N, Focaccio A, Michev

299.I, Montorfano M, Carlino M, Cosgrave J, Ricciardelli B, Colombo A. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a

300.randomized comparison of 3 preventive strategies. Circulation. 2007 Mar 13;115(10):1211-7. Epub 2007 Feb 19.

301.White ML, Liebelt EL. Update on antidotes for pediatric poisoning.Pediatr Emerg Care. 2006 Nov;22(11):740-6; quiz 747-9. Review.

302.Schultz MJ, Baas MC, van der Sluijs HP, Stamkot GA, Smit W. N-acetylcysteine and other preventive measures for contrast-induced nephropathy in the intensive care unit. Curr Med Chem. 2006;13(21):2565-70. Review.

303.Kanter MZ. Comparison of oral and i.v. acetylcysteine in the treatment of acetaminophen poisoning. Am J Health Syst Pharm. 2006 Oct 1;63(19):1821-7. Review.

304.Calello DP, Osterhoudt KC, Henretig FM. New and novel antidotes in pediatrics. Pediatr Emerg Care. 2006 Jul;22(7):523-30. Review.

305.Moling O, Cairon E, Rimenti G, Rizza F, Pristera R, Mian P. Severe hepatotoxicity after therapeutic doses of acetaminophen.Clin Ther. 2006 May;28(5):755-60.

306.Marenzi G, Assanelli E, Marana I, Lauri G, Campodonico J, Grazi M, De Metrio M, Galli S, Fabbiocchi F, Montorsi P, Veglia F, Bartorelli AL. N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. N Engl J Med. 2006 Jun 29;354(26):2773-82.

307.Leow, Melvin [corrected to Leow, Melvin Khee-Shing]. Sule AA, Tai DY, Tze CC, Deepa B, Leow MK. Potentially fatal paracetamol overdose and successful treatment with 3 days of intravenous N-acetylcysteine regime--a case report. Ann Acad Med Singapore. 2006 Feb;35(2):108-11. Erratum in: Ann Acad Med Singapore. 2006 Jun;35(6):446.

308.Desai A, Kadleck D, Hufford L, Leikin JB. N-acetylcysteine use in ischemic hepatitis. Am J Ther. 2006 Jan-Feb;13(1):80-3.

Sodium bicarbonate

309.Patel NP, Pugh ME, Goldberg S, Eiger G. Hyperinsulinemic euglycemia therapy for verapamil poisoning: case report. Am J Crit Care. 2007 Sep;16(5):520, 518-9.

310.Wetzels JF. Letter by Wetzels regarding article, "Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies". Circulation. 2007 Aug 21;116(8):e310; author reply e311. No abstract available.

311.Woolf AD, Erdman AR, Nelson LS, Caravati EM, Cobaugh DJ, Booze LL, Wax PM,

312.Manoguerra AS, Scharman EJ, Olson KR, Chyka PA, Christianson G, Troutman WG.

313.Tricyclic antidepressant poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila). 2007;45(3):203-33.

314.Recio-Mayoral A, Chaparro M, Prado B, Cózar R, Méndez I, Banerjee D, Kaski JC,

315.Cubero J, Cruz JM. The reno-protective effect of hydration with sodium bicarbonate plus N-acetylcysteine in patients undergoing emergency percutaneous coronary

316. intervention: the RENO Study. J Am Coll Cardiol. 2007 Mar 27;49(12):1283-8. Epub 2007 Mar 12.

317. Schultz MJ, Baas MC, van der Sluijs HP, Stamkot GA, Smit W. N-acetylcysteine and other preventive measures for contrast-induced nephropathy in the intensive care unit. Curr Med Chem. 2006;13(21):2565-70. Review.

318. Ganesh R, Suresh N, Ramesh J. Diabetic ketoacidosis in children.Natl Med J India. 2006 May-Jun;19(3):155-8. Review.

319. Rojas Vega S, Struder HK, Wahrmann BV, Bloch W, Hollmann W. Bicarbonate reduces serum prolactin increase induced by exercise to exhaustion. Med Sci Sports Exerc. 2006 Apr;38(4):675-80.

320. Kidney Int Suppl. 2006 Apr;(100):S16-9. Review. Mueller C. Prevention of contrast-induced nephropathy with volume supplementation.

321. DePalo VA, Mailer K, Yoburn D, Crausman RS. Lactic acidosis. Lactic acidosis associated with metformin use in treatment of type 2 diabetes mellitus. Geriatrics. 2005 Nov;60(11):36, 39-41.

322. Brucculeri M, Kaplan J, Lande L. Reversal of citalopram-induced junctional bradycardia with intravenous sodium bicarbonate. Pharmacotherapy. 2005 Jan;25(1):119-22.

323. Buysse CM, de Jongste JC, de Hoog M. Life-threatening asthma in children: treatment with sodium bicarbonate reduces PCO2. Chest. 2005 Mar;127(3):866-70.

324. Agarwal P, Agrawal PK, Sharma D, Baghel KD. Intravenous infusion for the treatment of diabetic and ischaemic non-healing pedal ulcers. J Eur Acad Dermatol Venereol. 2005 Mar;19(2):158-62.

325. Donmez O, Cetinkaya M, Canbek R. Hemoperfusion in a child with amitriptyline intoxication.Pediatr Nephrol. 2005 Jan;20(1):105-7. Epub 2004 Oct 26.

326. Shadnia S, Moiensadat M, Abdollahi M. A case of acute strychnine poisoning. Vet Hum Toxicol. 2004 Apr;46(2):76-9.

327. Odegard KC, Schure A, Saiki Y, Hansen DD, Jonas RA, Laussen PC. Anesthetic considerations during caval inflow occlusion in children with congenital heart disease. J Cardiothorac Vasc Anesth. 2004 Apr;18(2):144-7.

328. Yanagawa Y, Kiyozumi T, Hatanaka K, Itoh T, Sakamoto T, Okada Y. Reversible blindness associated with alcoholic ketoacidosis. Am J Ophthalmol. 2004 Apr;137(4):775-7.

329. Sarin B, Chugh PK, Kaushal D, Soni NL, Sawroop K, Mondal A, Bhatnagar A. Sodium bicarbonate-augmented stress thallium myocardial scintigraphy. Eur J Nucl Med Mol Imaging. 2004 Apr;31(4):475-81. Epub 2003 Dec 12.

330. Sharma AN, Hexdall AH, Chang EK, Nelson LS, Hoffman RS. Diphenhydramine-induced wide complex dysrhythmia responds to treatment with sodium bicarbonate. Am J Emerg Med. 2003 May;21(3):212-5.

Coenzyme Q10:

331. Zhou M, Zhi Q, Tang Y, Yu D, Han J. Effects of coenzyme Q10 on myocardial protection during cardiac valve replacement and scavenging free radical activity in vitro. J Cardiovasc Surg (Torino) 1999 Jun;40(3):355-61.

Phosphatidyl Choline

332. Keil C, Zeisig R, Fichtner I. Effect of surface modified liposomes on the aggregation of platelets and tumor cells. Thromb Haemost. 2005 Aug; 94 (2):404-11.

333. Pownall HJ, Ehnholm C. Enhancing reverse cholesterol transport: the case for phosphatidylcholine therapy. Curr Opin Lipidol. 2005 Jun; 16 (3):265-8.

General IV Vitamin references (1980-present):

334. Kirkemo AK, Burt ME, Brennan MF. Serum vitamin level maintenance in cancer patients on total parenteral nutrition. Am J Clin Nutr 1982 May;35(5):1003-9.

335. Inculet RI, Norton JA, Nichoalds GE, Maher MM, White DE, Brennan MF. Water-soluble vitamins in cancer patients on parenteral nutrition: a prospective study. JPEN J Parenter Enteral Nutr 1987 May-Jun;11(3):243-9.

336. Silvers KM, Sluis KB, Darlow BA, McGill F, Stocker R, Winterbourn CC. Limiting light-induced lipid peroxidation and vitamin loss in infant parenteral nutrition by adding multivitamin preparations to Intralipid. Acta Paediatr 2001 Mar;90(3):242-9.

ACAM IV THERAPY WORKSHOP – THE IV "PUSH"

W.A. Shrader, Jr., MD

General Comments:

The IVP protocol we are using for this session is basically a Meyer's IV. There are several variations of this protocol, but this is the one we've ended up with over the years.

All of the steps are listed below, similarly to the ones in the preceding section for a chelation IV. We will be using a 35 cc syringe to draw up the nutrients. The major thing that makes an IV "Push" different from an infusion is that all of the nutrients and the sterile water are *drawn into the same syringe and administered to the patient using that syringe*.

The IV Push (Meyer) Protocol:

Nutrient	mOsm/ml	mls in protocol	Total mOsm
B-6 (100 mg/mL)	1.11	1	1.11
Calcium gluconate (100 mg./mL)	.72	2	1.44
Mag. Chloride (200 mg/mL)	2.95	5	14.75
Pantothenic acid (250 mg/mL)	.85	1	0.85
Ascorbate (500 mg/mL)	5.80	4	23.20
B-Complex (100 mg/mL)	2.14	1	2.14
B-12 (1000 mcg./mL)	.30	2	1.50
TOTALS		**16**	**44.99**
"ccs of water to add" (at the end)		**19**	
Osmolarity of IV *(to calculate)* =			?

NOTE: If you don't have a fairly large (e.g. antecubital) vein available for a hypertonic IV, it would be best not to receive this one, as it may be uncomfortable or harm a small vein. If you don't have an available large vein, the IV *may* be given SLOWLY in a medium vein. The partner with the best veins should go first.

- **Important exercise for participants**: At some point, calculate the osmolarity of the "push" IV being used, using the Osmolarity Calculation Worksheet, which appears in the syllabus but also you should have as a hand-out. If you have problems getting the right answer, now is the time to speak, as we can walk you through it. Once you

know how to do this, you'll be able to administer *any* combination of nutrients safely in your offices.

For the *Total ccs of additives* in the formula, you need to use "16" in the calculation. The *ccs of water to add* is 19 - we need to fill up the 35 cc syringe. **The "unknown" you're trying to find in this case is the *osmolarity* of the solution**, so you must *substitute "X" for the .310* in the general calculation equation, because the osmolarity is *not* going to be .310. Don't read the next paragraph until you've tried to get the answer. So for the ccs of additives, you use 16, and for the ccs of sterile water, you use 19. The total mOsm of additives is 44.99.

If you can't remember your algebra, the formula is thus:

$$\frac{\textbf{44.99}\ \text{(Total mOsm)}}{\textbf{X}\ \text{(osmolarity)}} - (16\ \text{(ccs of additives)}) = 19\ \text{(water to add)}$$

So, $\frac{44.99}{X} = 35$

and $35X = 44.99$

so $X = 1.28$

OK? So the answer is that the osmolarity of this solution is going to be 1.28 mOsm/ml (1280 mOsm/L), but *you need to understand how to do this* if you plan to create some of your own protocols in your office.

NOTE! This solution is rather hypertonic, so the IV push needs to be done in the *largest vein you can find* in your partner's arm.

- **BEFORE we start this infusion, there are a few precautions to note:**

- Rapid infusion of magnesium could cause the participant (or patient) to become "flushed," with a sensation of "heat," often in the face, skin, trunk or groin area, followed by hypotension, "cold" sweating and even fainting. Once the first "warm" sensations are noted, *the push should be slowed until the sensation is less intense, mild, or stops*. (Note: if you're treating acute asthma or a headache, it is *desirable* to create some flushing, as those IVs are given to produce vasodilatation or bronchodilatation.)
- A vitamin "taste" from the B-vitamins will be noted by most.
- Since the solution is hypertonic, some of you may note an "aching" sensation proximal or distal to the IV site. This can usually be relieved by rubbing the area of discomfort with your hands, slowing the infusion, or both.
- Be sure to watch carefully as you give the infusion, and pull back on the syringe frequently to make sure the blood is free-flowing. **You *really* want to avoid extravasation into the soft tissue**, as it will produce an *intense* burning sensation that may last an hour or considerably longer. The best way to avoid this is to insert the needle *at least half way* into the vein when you start the IV.

- The most severe systemic reaction possible could be a feeling of light-headedness or faintness. Unless the IV is slowed at this point, the patient may become nauseated or possibly even faint.
- **Repeat: If there is an intense "burning" sensation at the needle site, *stop the IV immediately*, as it could indicate infiltration due to improper placement of the needle. Call an instructor if you're not sure.**
- **Repeat**: Draw back very slightly on the syringe frequently to get a blood return during the injection, to be certain needle placement remains correct.

- ***Please do not "skip" ahead*! Every year somebody does this, and is shocked to find they've ruined the IV somewhere during the instructions. *Please* resist this temptation. Wait until the step is *stated* until you do it**. Look around, and if your solution is a *weird color* or a *different color* from **everybody else's**, you've probably done something terribly wrong, and you will be removed from the room and immediately executed (well, OK, not this year).
- CHECK OFF *EACH STEP* AS IT'S COMPLETED.
- READ EACH STEP *ALL THE WAY THROUGH* BEFORE YOU DO IT.
- **Both participants will be drawing up this IV. Participants will take turns giving the IV to each other. Participants with the largest veins should get the IV first. We ask that no participants begin administration until both partners have drawn up the nutrients and the sterile water.**

  With an IV 'push", you draw up all nutrients into the same syringe. In your office you may be using a few multi-dose vials from which to draw, because if you do a significant number of IVs daily in your office, you may use larger vials of individual nutrients than you might use for a single dose. This is fine, as long as you plan to draw up the nutrients from multi-dose vials in a single day or so and the remainder is refrigerated.

Since all of the nutrients are going to go into one syringe, we have to give you all of the specific measurements so you get the proper amounts of each nutrient. It may be a little confusing at first, since you're not just using one syringe and immediately injecting each nutrient someplace right after you draw it up, as you do for a chelation protocol. You'll get the hang of this after the first two nutrients or so.

DRAWING UP THE IV

1. Remove the plastic tops or foil stickers (if any) from the tops of the vials from which you will draw the nutrients, and line them up in front of you *left to right*, in the same order they appear in the protocol. A bottle of sterile water will be shared among several participants and added at the end. Order of vials: B-6, calcium gluconate, magnesium chloride, pantothene (dexpanthenol), Vitamin C (ascorbic acid), B-complex and B-12 (hydroxocobalamine), followed by the sterile water to be shared. ***Don't touch the water until the end of these steps*.**

2. Wipe the tops of all vials with an alcohol swab.

3. Equalize the pressure in the vials with the 20 gauge sterile needle (stick the needle briefly through tops of all vials). **Put the needle back into the needle cap without contaminating it**. Your partner will use it when it's his or her turn.
4. Attach an 18 gauge No-Kor needle to the **30 cc syringe**

B-6 – (10 cc vial with about 5 cc nutrient inside)

5. Invert the vial of **B-6** (you draw up all of the following nutrients with each nutrient vial **inverted**)
6. Insert the needle into the vial of **B-6** (pyridoxine).
7. Withdraw 1 cc of **B-6** into the syringe. In doing this, the plunger should be pulled back to the *1 cc mark*.
8. Remove the needle from the vial of **B-6**, and hand the vial to your partner. Your partner will go back to step #3. IMPORTANT: In the office, you would *push the vial of **B-6** back* so you know you've used it.

IMPORTANT NOTE: the second partner who draws up the nutrients must equalize the pressure in the vials again before drawing up the nutrient. Otherwise, any vacuum in the vial could "suck" nutrients from the syringe back into the vial.

Calcium gluconate – (10 cc vial with about 5 cc nutrient inside)

9. Insert the needle into the vial of **calcium gluconate** *without injecting any of the **B-6** already in the syringe into the vial of* **calcium gluconate. This is the major reason vials are de-pressurized before you draw up any nutrient in your office, and several times during the day. Drawing up a nutrient from any vial without replacing the volume drawn up with air creates a small vacuum in the vial. This may "suck" nutrients in a syringe back into the vial and cross-contaminate the nutrient, *especially if the nutrient has been drawn up several times without the air being replaced*.**
10. Withdraw 2 ccs of **calcium gluconate** to the *3 cc mark* on the syringe.
11. Remove the needle from the vial of **calcium gluconate**, and *push the vial back*.

Magnesium chloride (10 cc vial with about 10 cc nutrient inside)

12. Insert the needle into the vial of **magnesium chloride**.
13. Withdraw 5 ccs of **magnesium chloride**, back to the 8 *cc mark* of the syringe
14. Remove the needle from the vial, and *push the vial back* (hand it to your partner).

Pantothenic Acid (B_5) (10 cc vial with about 5 cc nutrient inside)

15. Insert the needle into the vial of **Vitamin B-5** (dexpanthenol)
16. Withdraw 1 cc of **Vitamin B-5**, to the 9 *cc mark* of the syringe.
17. Remove the needle from the vial, and *push the vial back* (hand it to your partner).

Vitamin C – (50 cc vial – we may be sharing this among several participants)

18. Insert the needle of the syringe into the vial of **Vitamin C** (ascorbic acid).
19. Withdraw 4 ccs of **Vitamin C** to the *13 cc mark* of the syringe.
20. Remove the needle from the **Vitamin C** and *push the vial back* (hand it to your partner).

B-Complex – (10 cc vial with about 5 cc nutrient inside)

21. Insert the needle into the vial of **B-Complex**
22. Withdraw 1 cc of **B-Complex**, back to the *14 cc mark* of the syringe
23. Remove the needle from the vial, and *push the vial back* (hand it to your partner).

B-12 – (10 cc vial with about 5 cc nutrient inside)

24. Insert the needle into the vial of **B-12**
25. Withdraw 2 ccs of **B-12**, to the *16 cc mark* of the syringe
26. Remove the needle from the vial, and *push the vial back* (hand it to your partner).

Okay, you're done drawing up the nutrients!

Preparation of the IV

The nutrients you have drawn into the 35 cc syringe will be given IV "push," using only a butterfly set. However, before the IV can be given, ***sterile water must be added to the nutrients in the 35 cc syringe to dilute them to a reasonable osmolarity***.

1. Remove the metal seal from the bottle of sterile water if you're using an unopened one, but you will probably share the same bottle among several of you. **NOTE: if you're first in line to use the unopened bottle of sterile water, you *must* equalize the air pressure in this bottle** (unlike an infusion, where it's best not to do this) with a needle. Remove the needle when the pressure is neutral. Otherwise the bottle of sterile water will "suck" the nutrients from your syringe into the bottle. Wipe the top with alcohol (although this cap should be sterile).
2. Pull back the plunger of the syringe of nutrients to the 35 cc mark. Invert the 250 cc bottle and insert the needle of the **syringe containing your nutrients** into the center of the bottle of sterile water for injection.
3. Inject *most of the air* from the syringe – leave an air bubble. Be careful not to inject any of the nutrients or you'll contaminate the water.
4. Draw 19 ccs of water into the syringe to fill the syringe to the 35 cc mark.
5. Remove the syringe from the sterile water, re-cap the needle and pass the water to your partner. The partner should then re-equalize the pressure in the sterile water, just to be sure!

   The partner will then repeat steps 2-4.
6. Draw a few ccs of air into the syringe.
7. Rock the syringe a few times to mix the nutrients and the water.
8. Remove the capped needle from the syringe.
9. Open the wrapper of the **25 gauge winged infusion set**.
10. Attach the **winged infusion set** (butterfly) supplied to the syringe. **DO NOT REMOVE THE NEEDLE GUARD from the butterfly YET.**
11. **Expel the air bubble out of the syringe and through the butterfly tubing. Fill the tubing of the winged infusion set with the IV solution until the solution comes out of the needle, *into the needle guard*. Leave the needle guard on.**
12. You would normally take your patient's vital signs before administering this or any other IV.

13. Tear off a 3-4” piece of tape and have it handy to tape the needle to the skin (1" 3M Micropore tape) and to use once the needle is removed.
14. Put on the tourniquet.
15. Insert the butterfly needle, **bevel up is easiest,** *at least half way into a large vein,* preferably in the antecubital space (crook of the arm) of your ~~victim~~ partner, and preferably in one, swift motion, so that the needle is inserted at least half way *to the flexible plastic butterfly part of the needle*. As soon as the needle enters the vein, you will note a small amount of a back-flow of blood appear in the butterfly tubing.
16. Put a piece of tape over the flexible plastic butterfly where it enters the skin, covering it and the spot where the needle enters the skin. If in doubt, ask one of the instructors.
17. **Release the tourniquet**.
18. *Slowly* inject about 1-2 ccs of the solution, then *stop* for about 30 seconds to be certain your partner is experiencing no adverse reaction. Watch the tubing and the site *carefully* as you do this to be certain the solution goes into the patient’s vein and *not* the subcutaneous tissue!
19. Be sure to watch carefully as you give the push, and pull back on the plunger of the syringe frequently to make sure the blood is free-flowing. Remember, **stop immediately** if your partner has **any** sensation of *severe burning, pain or discomfort, or if you recognize there is any infiltration*.
20. Once all appears to be OK, continue the IV injection.
21. You may proceed with the injection at a speed your "patient" will tolerate. If he or she experiences any of the symptoms as noted previously, *stop the push for a moment*. As the symptoms abate, you may resume. This IV may be given to most patients over a period of 10-15 minutes without problems.
22. Once the IV is finished, fold a 2" X 2" gauze pad in quarters. *Carefully* peel back the tape covering the needle where it enters the arm, while holding down the plastic butterfly portion. Press the 2” X 2” *lightly* to the skin where the needle is inserted and at the same time remove the needle with a quick, smooth action. As the needle is removed, *increase* the pressure on the gauze pad about a minute and then apply the last piece of tape tightly over the gauze. The patient may remove the tape and gauze in about 10-15 minutes.
23. **The other partner should then go back to step #12 and administer the IV.**

Hopefully, all of you and your partners have survived, feel well, and everybody can now get a good night’s sleep after a long day!

We would very much again like to thank McGuff Compounding Pharmacy for providing the nutrients **and Merritt Laboratories for supplying most of the other materials used in this workshop. These companies are both an excellent source where you can purchase materials for any IVs you do in your offices and for other compounded agents.**

Abrams Pharmacy, College Pharmacy and McGuff Compounding and have most of the protocols we routinely use in our office *pre-mixed*, and at very reasonable prices. These can be ordered “as is” if you don’t want to get into mixing IVs in your office, and they will send them to patients’ homes, etc. You can possibly find these also at other

compounding pharmacies as well, and you can certainly ask your local compounding pharmacy if they would make up these protocols (except keep the Vitamin C separate) for you to use in your office or if they would send them to patients.

Some nutrients (questionable FDA status) are often not carried by these pharmacies and perhaps can be ordered from one of the other suppliers listed and added at the time you administer the IV, should you choose to use them. Since it is labile, Vitamin C needs to be stored in the dark and added to any of the pre-mixed protocols available from compounding pharmacies *immediately before the IV is given*.