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35+ years of clinical & environmental laboratory diagnostics - worldwide

Updated protocols and research on Clinical Metal Toxicology,

Diagnosis and Treatment for beginning and experienced practitioners

(IBCMT approved)

Micro Trace Minerals Laboratory

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Chelation is

- NOT an ALTERNATIVE TREATMENT

Chelation is

main stream medicine

Summary: *Chelation therapy is the preferred medical treatment for reducing the toxic effects of metals (2010)*

PubMed Central
Search Journal List

MDPI International Journal of Environmental Research and Public Health

Journal List > Int J Environ Res Public Health > v.7(7); Jul 2010

Int J Environ Res Public Health. 2010 July; 7(7): 2745–2788. PMCID: PMC2922724
Published online 2010 June 28. doi: 10.3390/ijerph7072745.

Chelation in Metal Intoxication

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ROLE OF CHELATING AGENTS FOR PREVENTION, INTERVENTION, AND TREATMENT OF EXPOSURE TO TOXIC METALS

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1519187/pdf/envhper00359-0076.pdf

Environmental Health Perspectives Volume 103, Number 11, November 1995

Meeting Report

Role of Chelating Agents for Prevention, Intervention, and Treatment of Exposures to Toxic Metals

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The role of chelating agents for the prevention, intervention, and treatment of exposures to toxic metals was the topic of a conference held at the National Institute of Environmental Health Sciences, 22-23 September 1994. The objective of the conference was to review experimental and clinical studies concerned with the effectiveness and potential toxicity of chelating agents used to reduce the body burden of various metals and to identify research needs in the area of chelation. The conference was prompted by emerging evidence that low-level exposures to metals may result in toxic effects not previously recognized. For example, the recent interest in use of chelation as an intervention strategy to reduce blood lead levels followed the awareness that exposure to lead in infants and young children resulting in blood lead levels as low as 10-15 micrograms/dl may impair cognitive and behavioral development (*1*). The question increasingly

„Chelation therapy ***is the preferred medical treatment for reducing the toxic effects of metals****. Chelating agents are capable of binding to toxic metal ions to form complex structures which are easily excreted from the body removing them from intracellular or extracellular spaces.“*

Chem Rev. 1999 Sep 8;99(9):2683-710. **Principles and recent developments in chelation treatment of metal intoxication.** Andersen O. Department of Life Sciences and Chemistry, Roskilde University, Postbox 260 4000, Roskilde, Denmark.

AMERICAN CANCER SOCIETY STATEMENT

- Chelation therapy is a mainstream treatment used to treat heavy metal poisoning.
- EDTA, was first made in Germany in the 1930s. It is now widely accepted as an effective treatment for heavy metal poisoning

http://www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalternativemedicine/pharmacologicalandbiologicaltreatment/chelation-therapy

Diagnosing metal intoxication

1. Patient Evaluation
2. Laboratory Diagnostics

1. Patient Evaluation

- Patient History incl PB, CBC, liver panel, renal evaluation
- Symptoms

  acute vs chronic

- Work
- Hobbies
- Lifestyle

DETAILS see

PJvdSchaar: **IBCMT Textbook of Clinica Metal Toxicology**

ACUTE vs CHRONIC INTOXICATION

ACUTE POISONING

Acute poisoning is mainly related to occupational inhalation and foreign body ingestion.

Acute Symptoms may be life threatening

CHRONIC INTOXICATION

- Cause may be either environmental or occupational
- Symptoms may be severe or vague

2. Laboratory Diagnostics

ACUTE INTOXICATION

BLOOD METALS

SERUM OR WHOLE BLOOD

BASELINE URINE METALS

CHRONIC EXPOSURE

HAIR/NAIL METALS

PROVOCATION URINE

EDTA

DMPS

DMSA

DTPA

Example Mercury (Hg)

Mercury Intoxication

- **Mercury toxicity most commonly affects the neurologic, gastrointestinal (GI) and renal systems.**
- Poisoning can result from mercury vapor inhalation, mercury ingestion, mercury injection, and absorption of mercury through the skin.

Acute vs chronic

ACUTE POISONING

- Acute perioral and facial paresthesias
- Visual-field constriction
- Respiratory distress and nonspecific dermatitis
- Extremity numbness eventually appears, along with headache, fatigue, and tremor
- Ataxia and dysarthria can also be observed

CHRONIC EXPOSURE

- Tremors
- sensory loss
- Ataxia
- visual field constriction
- Hashimoto
- Infertility (Prof.Gebhardt, Uni Heidelberg)

http://emedicine.medscape.com/article/1175560-overview

Confusing Symptoms?
Blood test and unprovoced urine inconclusive?

Compare
unprovoked urine Hg-concentration
with
Test Hg-concentration after Provocation

Which CHELATING AGENT?

Provocation Test
- diagnostic test to determine chronic metal overexposure

- **NaEDTA** --- Lead, **Calcium, Iron** and other metals
- **NaCaEDTA**– Lead, **Iron** and other metals

- **DMSA** – Lead, **Mercury, Arsenic** and other metals
- **DMPS**- Lead, **Mercury, Arsenic, Copper** & others

For mobilization treatment

- **Deferoxamin**- **Iron** (Hemochromatosis)
  -**Aluminum** (Dialysis patients)

- **Prussian Blue- Thallium, Cesium**

Official German Antidota List

DMSA Dimercaptosuccinic acid; Succimer	Lead, Mercury, Arsenic and other metals
Na-EDTA (Ethylendiamintetraacetic acid), Na-EDTA (GPU Pharma)	Lead, Calcium, Iron and other metals
Iron(III)-hexacyanoferrat(II) (Berliner Blau, Antidotum Thallii Heyl®); Radiogardase-Cs Heyl®	Thallium, Cesium
***D*-Penicillamin**	Copper, Lead, Mercury, Zinc, Gold, Cobalt. Due to side effects, used only when other chelating agents are not an option
Zn-DTPA Trisodium-Zinc-diethylen triamin pentaacetate, DTPA-Zinc-Sodiumsalt	Like Ca-DTPA

German Official Antidota List (Synonym, Products)	Indication (appreviated information)
Aktive charcoal (Carbo medicinalis)	important for decontamination of intestinal tract with non specific binding of organic and inorganic toxins. Recommended oral use: 1g/kg body weight in approx 200ml fluid.
Ca-EDTA Calcium-disodium-EDTA, Calcium-edetat-Sodium	Lead, Chromium, Cobalt, Vanadium, Zinc, Cadmium, radioactive Metals
Ca-DTPA Calcium-Trisodium-DTPA; Ditripentate,	Decorporation of Cadmium, Lead, Zinc, Iron (also for Haemochromatosis), Manganese, Chromium, Plutonium u.a. radioactive Metals
Deferoxaminmethansulfonate (Desferal®); Desferrioxamin-B-mesylate	Iron and Haemochromatosis Aluminium (Dialysis patients)
Dimercaptoprol (BAL, British Anti-Lewisite, Sulfactin)	***Obsolete Chelating Agent.***
DMPS Dimercaptopropansulfonic acid, Dimaval® Na-(2,3)-dimercaptopropan(1)-sulfonate, Sulfactin	many heavy metal compounds. For example lead, organic und inorganic mercury and arsenic

ANTIDOTE CHART

(Suggested Stocking Level is based on dose to treat a 70 kg patient for 24 hours)*

Updated: 3-11-2008

Generic/ Name Brand	Toxin	Notes	Suggested Stocking Level
Atropine	Organophosphate/Carbamate insecticide poisoning and other cholinesterase inhibitors (eg, warfare agents); bradycardia induced by a variety of toxins	May require large amounts in severe cholinesterase inhibitor poisoning. Also stocked in the Strategic National Stockpile but will need supplies for first 48 hours. Coordinate with local Homeland Security office.	1000 mg total (in vials) Use preservative free product
Antivenom, Crotalidae Polyvalent Immune-FAB(ovine)/ Cro-Fab®	Rattlesnake envenomation		24 vials
Antivenom, Black Widow Spider/ Antivenom (Latrodectus Mactans)®	Black Widow Spider envenomation		1 x 6000u vial
BAL(Dimercaprol)/ BAL in oil 10%®	Heavy Metal poisoning		6 x 3 mL (10% in oil) amps
Calcium Chloride injection	Calcium channel blocker poisoning; hypocalcemia induced by various agents	Can cause tissue necrosis if extravasation occurs – use large vein for infusion.	20 x 10mL (10%) vials
Calcium Gluconate Powder	Hydrofluoric Acid	For manufacture of topical gel	1 x 100gm powder bottle
Calcium Gluconate injection	Hydrofluoric Acid skin exposure or poisoning; hypocalcemia induced by various agents		20 x 10mL (10%) vials
Calcium Gluconate gel/Calgonate 2.5% gel®	Hydrofluoric Acid dermal burns	For topical burns	6 x 25 gm tubes
Carnitine (L-Carnitine)/ Carnitor®	Hyperammonemia from valproic acid toxicity		7 x 1gm vials
Cyanide Antidote Kit/ Taylor Cyanide Antidote Kit®	Cyanide poisoning	Thiosulfate component can be used separately. See also Hydroxocobalamin (Cyanokit®).	2 kits (or stock the Cyanokit® - see Hydroxocobalamin)
Deferoxamine/ Desferal®	Iron poisoning	IM administration is discouraged.	12 x 500mg vials
Digoxin Immune FAB (ovine)/ Digibind® or DigiFab®	Digoxin poisoning; Other cardiac glycosides (eg, oleander, foxglove)	Consult with poison center regarding dosing, especially for cardiac glycosides than digoxin.	15 vials of either product
DMSA (Succimer)/ Chemet®	Heavy metal poisoning		1 x 100 capsule bottle
DTPA-Calcium (Diethylenetriamine pentaacetate)/ Pentetate Calcium Trisodium injection)	Dirty bomb agents: Radioactive plutonium, americium and curium	Also stocked in the Strategic National Stockpile but will need supplies for first 48 hours. Coordinate with local Homeland Security office.	1 x 1gm vial
DTPA-Zinc (Diethylenetriamine pentaacetate)/ Pentetate Zinc Trisodium injection)	Dirty bomb agents: Radioactive plutonium, americium and curium	Also stocked in the Strategic National Stockpile but will need supplies for first 48 hours. Coordinate with local Homeland Security office.	1 x 1gm vial
EDTA-Calcium/ Versenate®	Heavy metal poisoning		18x 1000mg/5mL amps
Ethanol IV 10%	Ethylene glycol or Methanol poisoning	Note: Ethanol more difficult to obtain, dose and monitor than fomepizole.	Product no longer manufactured

California Poison Control System

Glucagon	Beta blocker/ Calcium channel blocker poisoning	Anticipate nausea and vomiting.	10 x 1 mg vials
Hydroxycobalamin/ Cyanokit®	Cyanide poisoning	Newer cyanide antidote, can be used instead of the conventional cyanide antidote kit from Taylor.	3 x 5gm kits (or stock the Taylor cyanide kit)
Methylene Blue	Methemoglobinemia		5 x 10mL (1%) amps (10mg/mL)
N-Acetylcysteine (NAC) Mucomyst® or generic	Acetaminophen poisoning (oral preparation)	Use orally. Dilute at least by a 3:1 ratio.	7 x 30mL (20%) vials
N-Acetylcysteine (NAC) Acetadote®	Acetaminophen poisoning (IV preparation)	Loading dose should be infused slowly over 45-60 minutes. Generic N-acetylcysteine can be used if Acetadote® is not available (consult with poison center and give via micropore filter).	1 carton of 4 x 30mL (20%) vials
Naloxone/ Narcan®	Opioid overdose	Use small initial dose to avoid abrupt awakening/ delirium.	20 x 0.4mg/2mL amps or 10 x 10mg/10mL vials
Octreotide acetate/ Sandostatin®	Oral sulfonylurea poisoning	Avoid long-acting depot products.	2 x 1mL (0.1mg/mL) amps 1 x 5ml 0.2mg/1ml MDV
Physostigmine/ Antilirium®	Anticholinergic poisoning, especially antimuscarinic delirium.	Administer slowly: May cause severe side effects including bradycardia, asystole and seizures	10 x 2mL (1mg/mL) vials
Pralidoxime(2-PAM)/ Protopam®	Cholinesterase Inhibitor poisoning (organophosphate or "nerve gas")	Also stocked in the Strategic National Stockpile but will need supplies for first 48 hours. Coordinate with local Homeland Security office.	12 x 1gm (20mL) vials
Prussian Blue/ Radiogardase®	Dirty bomb agents: radioactive cesium and thallium and non-radioactive thallium	Also stocked in the Strategic National Stockpile but will need supplies for first 48 hours. Coordinate with local Homeland Security office.	2 packs of thirty 500 mg capsules
Pyridoxine (Vitamin B_6)	Isoniazid (INH) poisoning	Large amounts needed for poisoning: 5 grams is the minimum antidotal dose used in an ingestion of an unknown amount. Note: the 100 mg in 1 ml vials contain the preservative chlorobutanol. A 5 gram dose requires 50 vials and will deliver a toxic dose of the preservative.	50 x 1mL (100 mg/mL) or the equivalent (Use preservative free product.)
Vitamin K_1(Phytonadione)/ Mephyton® or AquaMephyton®	Warfarin, warfarin-based anticoagulants and super-warfarin based rodenticide poisoning	If patient is actively bleeding use fresh frozen plasma or Factor VII concentrate.	20 x 5mg tabs 10 x 10mg/mL amps

Expert advice regarding use of antidotes is available 24 hours a day, 7 days a week from the California Poison Control System. Call us at

1-800-222-1222

*Adapted From Olson, KR (Ed): Poisoning & Drug Overdose. 5th Edition. McGraw-Hill. New York. 2007

Note: List is not all-inclusive but reflects agents used more exclusively as antidotes

UK Antidote Information for LEAD (Pb) exposure

- Parenteral chelators such as calcium disodium edetate given intramuscularly (IM) or IV.
- Dimercaptosuccinic acid (DMSA, or succimer) is an alternative oral agent.
- D-penicillamine is occasionally used but it is an unlicensed medication with adverse effects such as white cell and platelet count suppression.

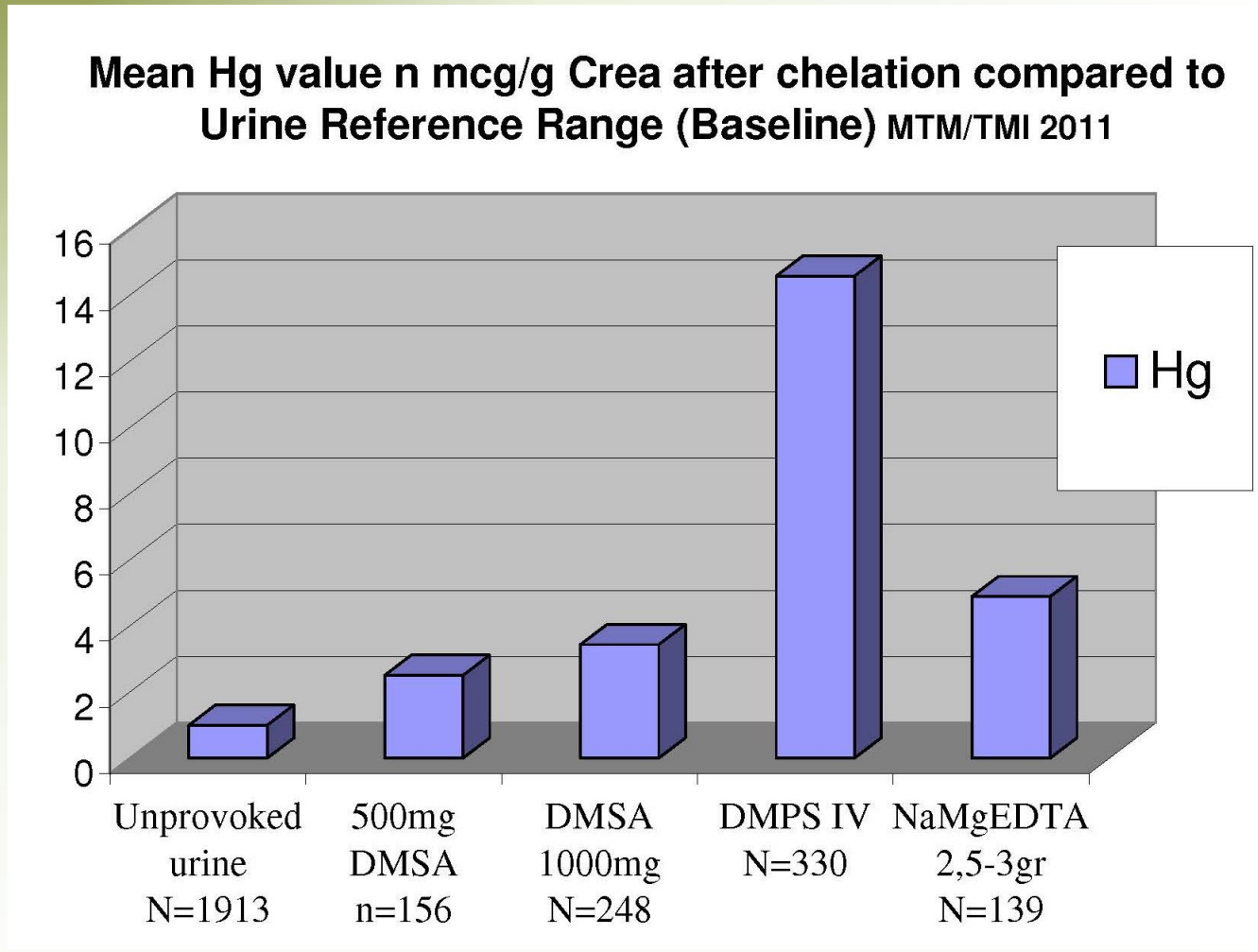
Select the chelator of choice, depending on the type of metal intoxication

Consider patient age, condition and symptoms (i.e. sclerotic disease may warrant a different chelation approach than neurological disease)

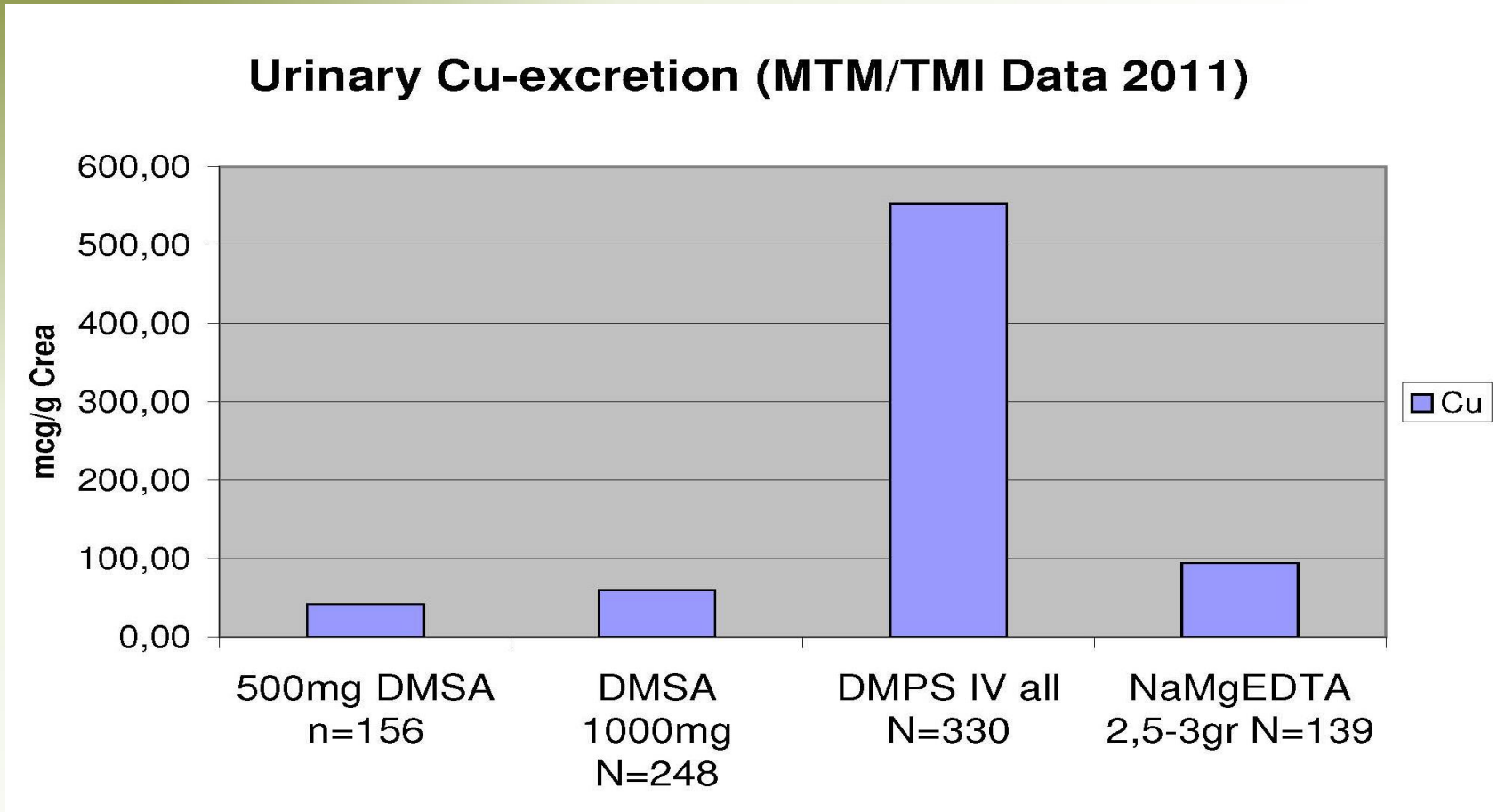
DMPS- Chelator of Choice for

- Arsenic
- Mercury (organic and inorganic)
- Lead and many other heavy metals

MERCURY (Hg)


Mean Hg value n mcg/g Crea after chelation compared to Urine Reference Range (Baseline) MTM/TMI 2011
16
14
12
10
8
6
4
2
0
Hg
Unprovoked urine N=1913
500mg DMSA n=156
DMSA 1000mg N=248
DMPS IV N=330
NaMgEDTA 2,5-3gr N=139

Alternative: DMPS (mean values in mcg/g crea)



DMPS – Few side effects

i.v. injection

- Local reactions may appear on injection site
- Usually after the 3rd or 4th treatment

Oral

- Gastrointestinal spasms

(mostly as a result of a ‚toxic' gastrointestinal tract)

DMPS Heyl Protocol

Chronic exposure:

DMPS iv (usually 1Amp = 5ml, inject slowly over 10min
Urine collection time = 1hr

DMPS oral, 100-400mg/d
Oral bioavailability = between 40 and 60%*
Urine collection time = 3hrs

Treatment schedule depends on exposure, generally not more than once/wk

*http://www.ncbi.nlm.nih.gov/pubmed/8113976
http://www.fda.gov/ohrms/dockets/dockets/98n0182/nom005b.pdf

DMPS & Wilson‘s Disease

Unithiol, 200mg twice daily was used successfully to treat cupriuresis in a 13-year-old boy with Wilson’s disease after he developed systemic lupus during treatment with penicillamine urd with trientine dihydrochloride, which are two of the agents used in Wilson’s disease.

Walshe JM. Unithiol in Wilson’s disease.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1417642

DMSA- Chelator of Choice for

- Arsenic
- Mercury (organic and inorganic)
- Lead and many other heavy metals

- Similar function (oral bioavailability rate 20-50%*)
- Fewer side effects

*http://pharmacycode.com/DMSA.html

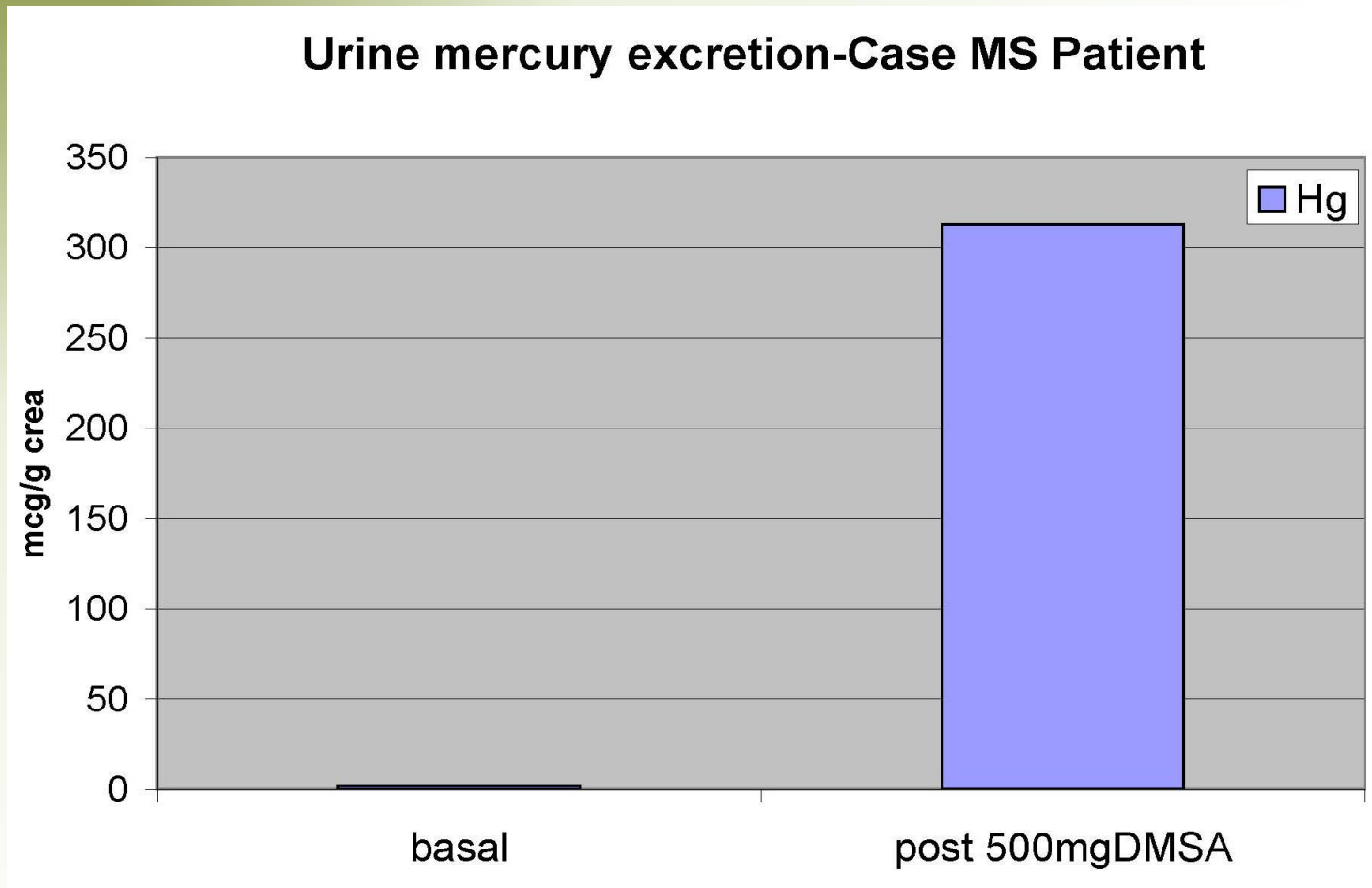
DMSA Protocol

Chronic exposure:

DMSA, 10-30mg/kg BW/d
Urine collection: 4hrs

Treatment schedule depends on exposure. For chronic exposure generally not more than once/wk

Oral DMSA & Multiple Sclerosis



EDTA

NaEDTA

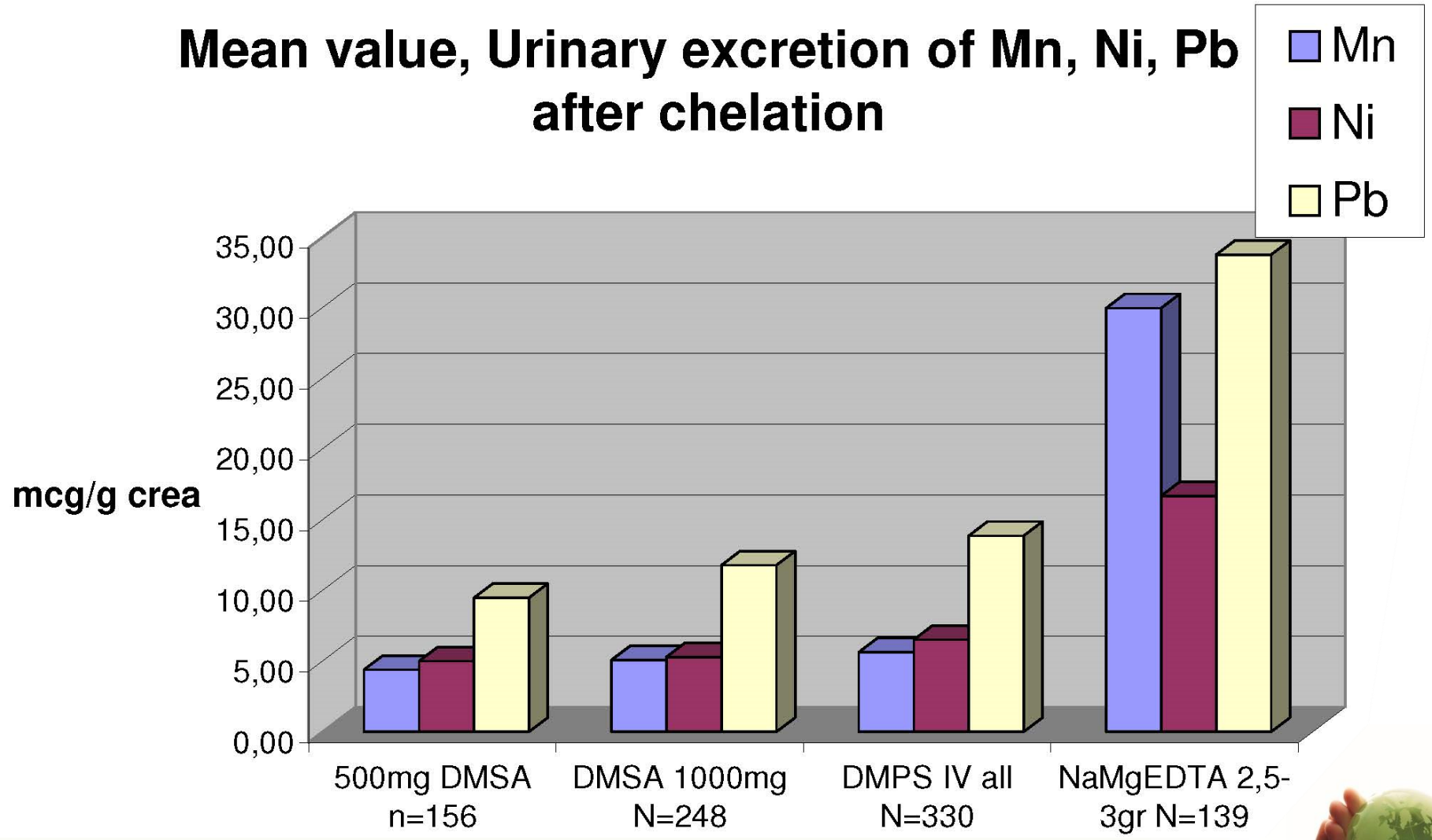
- Calcium
- Cadmium
- Iron
- Lead
- Manganese
- and other metals

CaNaEDTA

- Cadmium
- Iron
- Lead
- Manganese
- and other metals

NO CALCIUM

Mean value, Urinary excretion of Mn, Ni, Pb after chelation



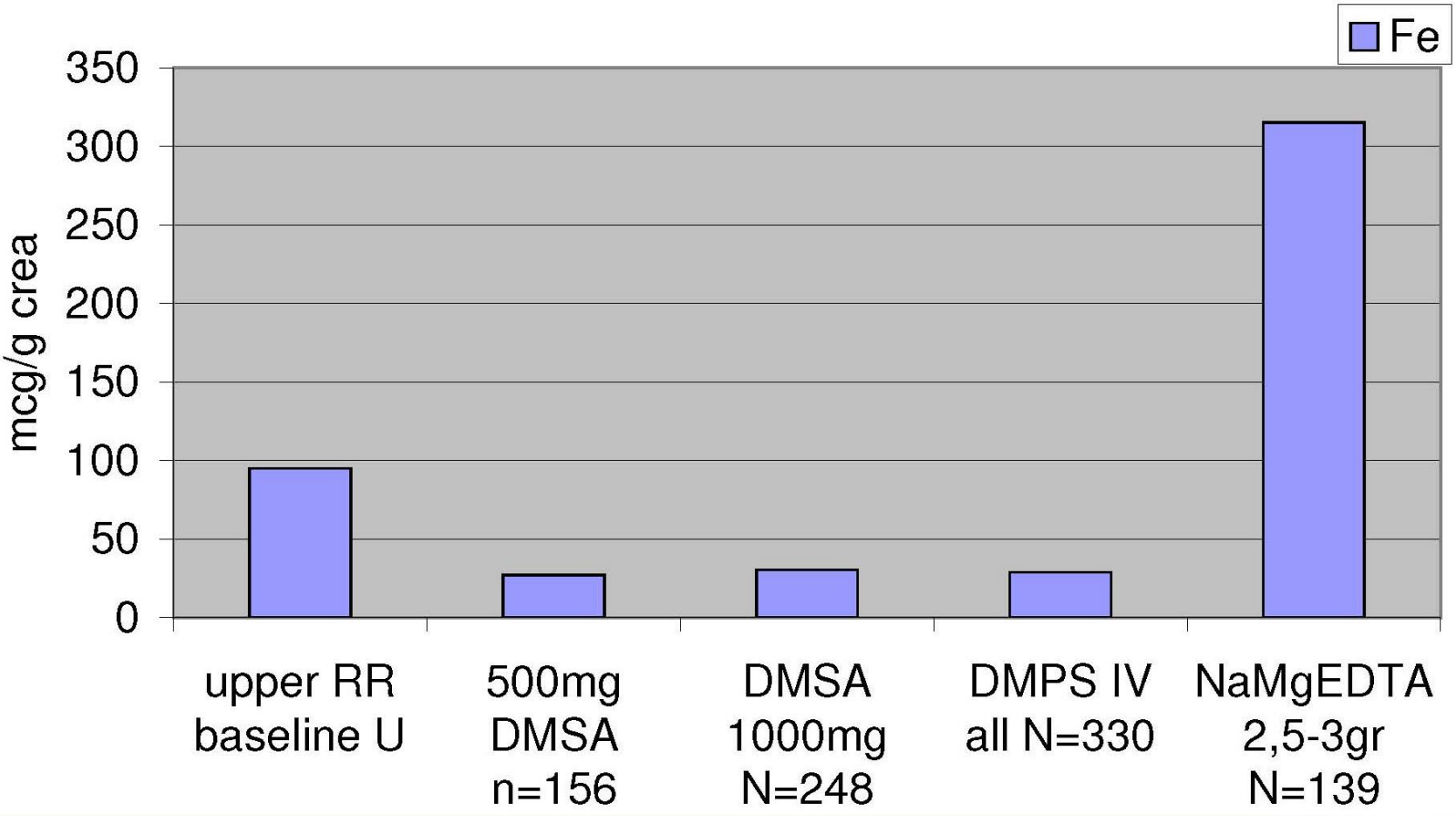
„Iron is intimately tied to the inflammatory response“

Iron Homeostasis and the Inflammatory Response

Annual Review of Nutrition. Vol. 30: 105-122 (Volume publication date August 2010)

- **Marianne Wessling-Resnick**, Department of Genetics and Complex Diseases, Harvard School of Public Health, Boston, MA

Ironbinding & excretion after chelation (NO supplementation before or after) MTM/TMI 2011

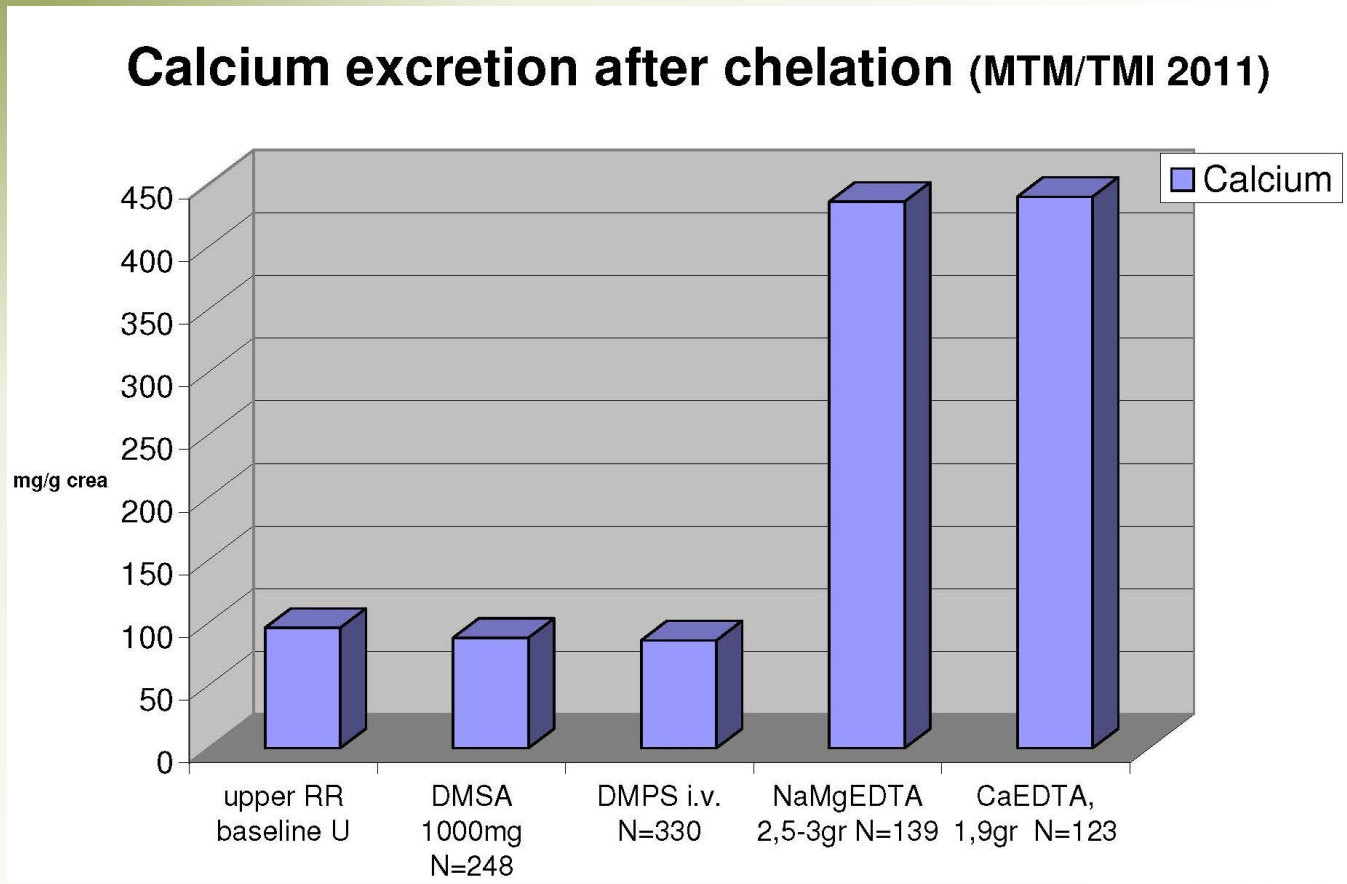


In the 1950s,
scientists theorized that NaEDTA
could **remove calcium** from the body

IT DOES!

CaEDTA does NOT. It is already bound to Calcium.
CaEDTA ADDS CALCIUM
(exchanging it with other metals)
see Table

CaEDTA adds Calcium
NaEDTA or NaMgEDTA binds & removes



Protocol for EDTA (NaEDTA or CaNaEDTA)

- Infusion time: 1gr/hr
- Urine collection time = infusion time + 45min

NOTE:

NaEDTA binds calcium & excretes it

CaEDTA is added to system (exchanged with metals such as lead)

Example Lead (Pb)

- High affinity for bone
- Overexposure affects bone marrow

Acute LEAD POISONING

Symptoms

The severity of symptoms often correlates with blood levels and at high levels the following may be seen:

- Lethargy (due to haemolytic anaemia).
- Abdominal pain - moderate-to-severe, usually diffuse but may be colicky.
- Vomiting.
- Encephalopathy - more common in children, characterised by seizures, mania, delirium and coma, death.
- Jaundice (due to hepatitis).

DIAGNOSING PB INTOXICATION

- **Whole blood lead levels:**

  <10 µg/dL - normal.

  >10 µg/dL - may cause impaired cognitive development in children.

  >45 µg/dL - GI symptoms in adults and children.

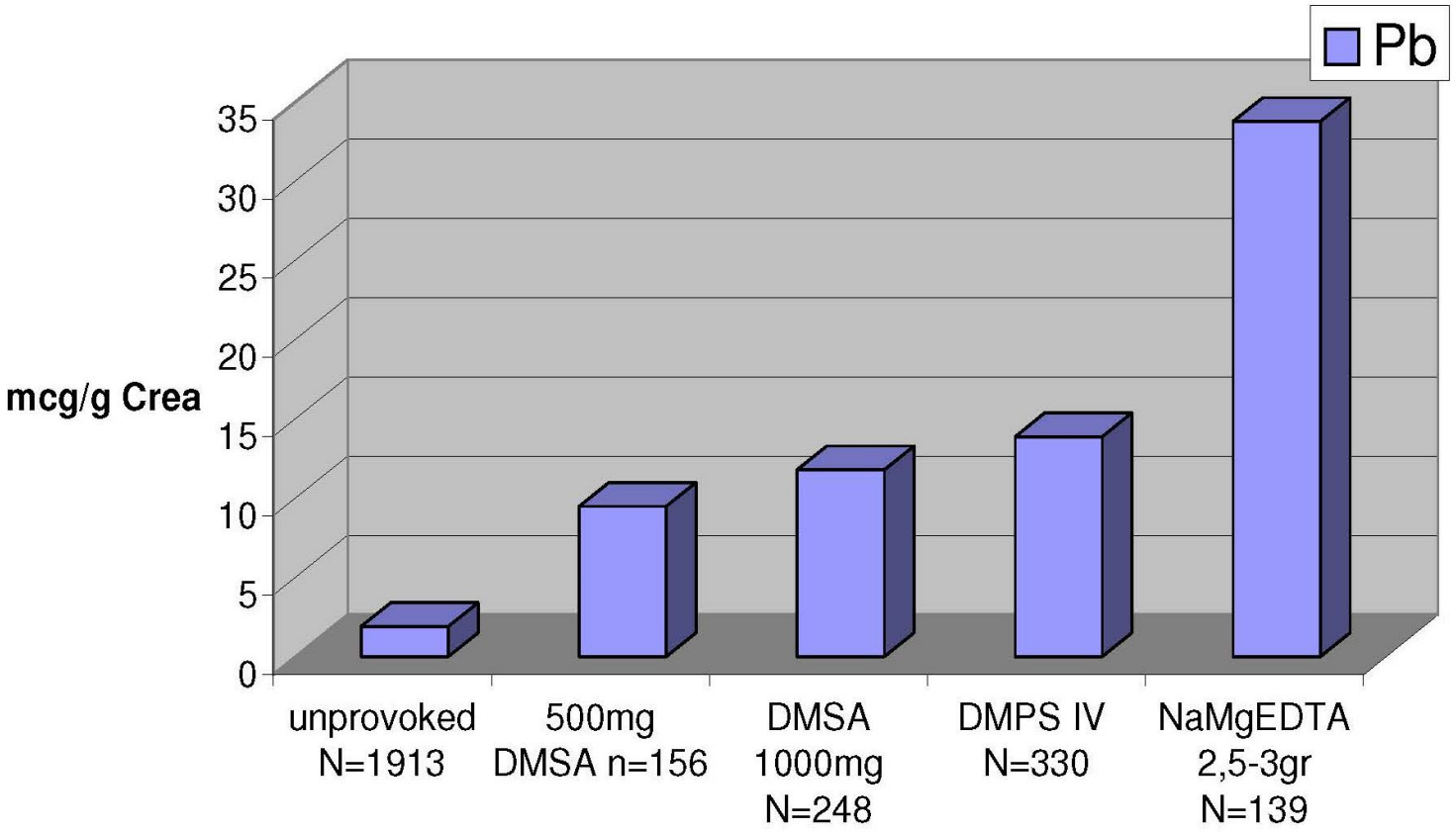
  >70 µg/dL - high risk of acute CNS symptoms.

  >100 µg/dL - may be life-threatening.

CHRONIC LEAD INTOXICATION

- Mild abdominal pain.
- Constipation.
- Aggression.
- Antisocial behaviour.
- Headaches.
- Hearing loss.
- Subfertility.
- Foot drop - due to motor peripheral neuropathy.
- Wrist drop - this is a late sign.
- Carpal tunnel syndrome.
- Gout.
- Autonomic dysfunction.

Pb-Mean Concentration in Urine, before and after chelation (MTM/TMI 2011)



Chelation Treatment Schedule

- How frequent?
- How effective are repeated treatments?
- Can laboratory tests prove effectiveness?

Acute vs chronic

- **Acute Poisoning** = emergency situation that needs immediate and aggressive antidote treatment.
- Poison is generally known
- Symptoms are typical
- **Emergency treatment important**

- **Chronic Overexposure** = situation that has continued over time (often years)
- **Type of toxin mostly unknown**
- Symptoms atypical, diffuse
- Diagnosis crucial to treatment success
- **Treatment timing should consider internal regulation mechanism**

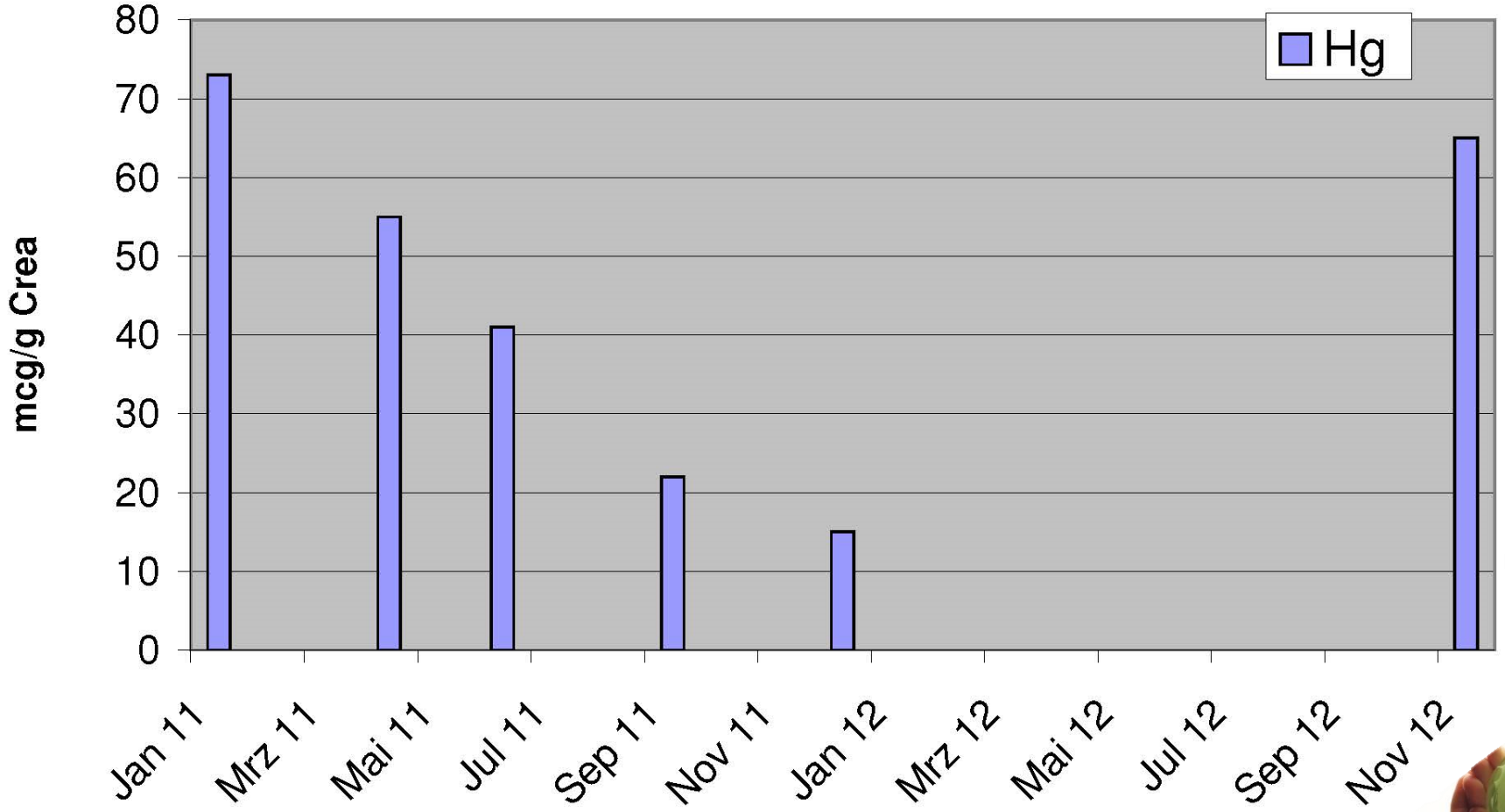
  (Metal Homeostatis)

Timing of Treatment and Metal Homeostatis

Hypothesis:

Aggressive schedule
for treatment of chronic intoxication
=
initially detoxification of soft tissue
(liver, renal pathway, thyroid etc)

Hg in Urine after 1Amp DMPS i.v. (RA patient)



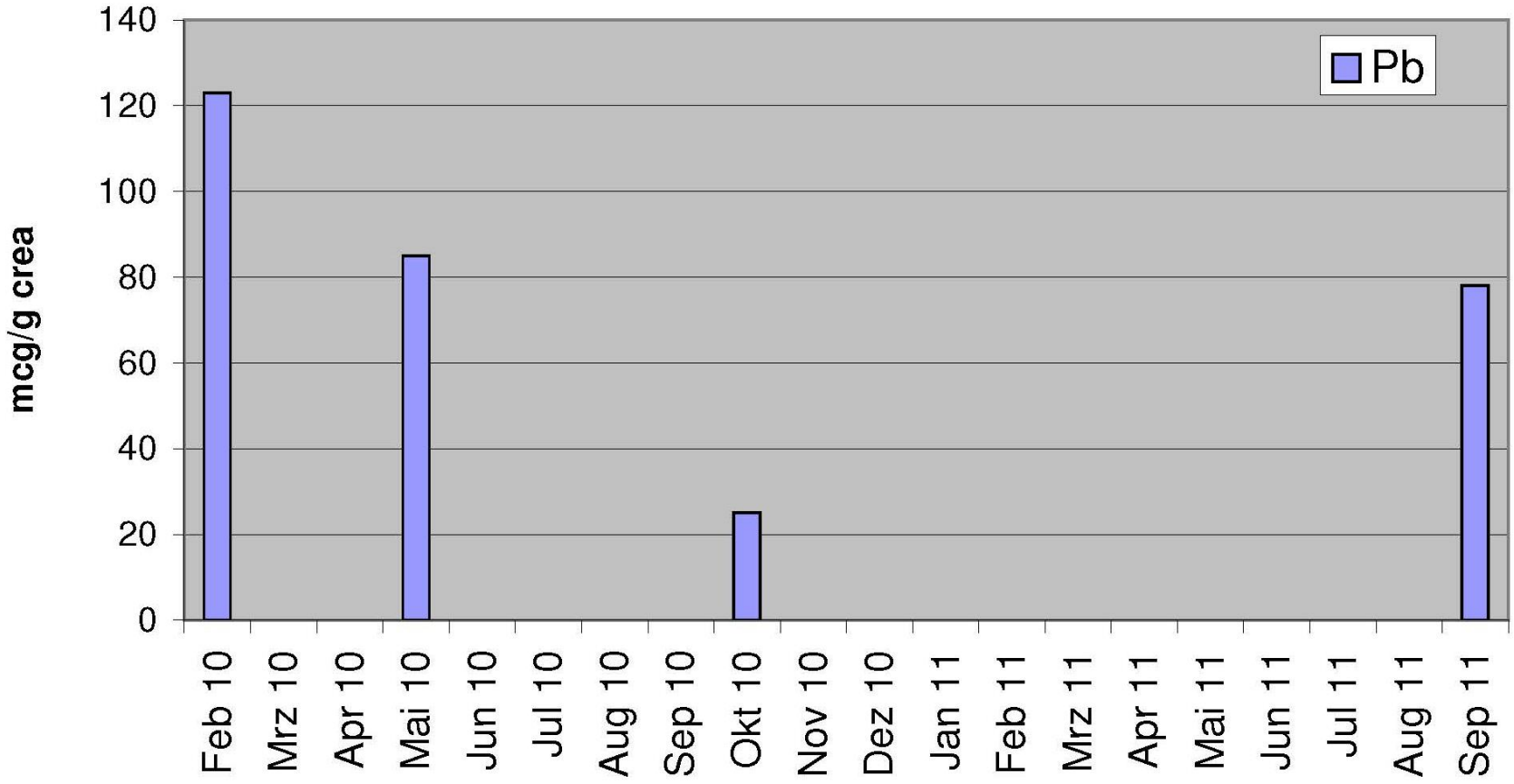
Metal Homeostatis, NaEDTA Bone Metabolism, and Timing of Treatment

Facts about NaEDTA & Bone Metabolism (not CaEDTA)

- NaEDTA or NaMgEDTA bind Calcium,
- Resulting in temporary (mild) hypocalcemia
- Resulting in activated Osteoclast activity
- Resulting bone loss continues for approx 6 wks
- Resulting in release of Lead & other metals stored in bone

Osteoblast Activity & new bone formation follows

EDTA treatment -Rifleman with severe muscle & sceletal pain, noticeably less after 1st treatment



Treatment pause supports metal homeostasis

- Treatment pause can be used to improve biochemical (nutritional) balance
- Which in turn supports metal homoestasis
- Levels may rise after pause due to distribution of metals from difficult-to-reach-compartments into soft tissue

Nutrients & Chelation

- …micronutrients can modifying metal toxicity, ..and also act as complementary chelating agents (adjuvants) increasing the efficacy of a known chelator, or by acting independently.

Flora S.J.S. Nutritional Components Modify Metal Absorption, Toxic Response and Chelation Therapy 2002, Vol. 12, No. 1 , Pages 53-67

Thank you!

www.ibcmt.com www.microtrace.de