Basic Pharmacology of DMSA, DMPS and Ca-EDTA

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Doctor's Data, Inc.

Basic Toxicology

- Exposure→Assimilation→ Retention→Toxicity

Exposure ≠ Toxicity

“Low-level” Exposure & Retention

- 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

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

Assessment of Exposure: Blood

- Recent or ongoing exposure
- Kinetic models; blood pool shortest $T^{1/2}$
- **Relationship between blood Pb and post-EDTA urinary Pb is nonlinear:**

  arithmetic ↑ in blood Pb are associated with EXPONENTIAL ↑ in urinary lead

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

- Organic As rapidly excreted w/in 48 hrs. of consumption of **shellfish**
  (UAs up to 1500 µg/gm, normally <130)
- **PREVENT ALARMISM !**

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

Provoked Urinary Metals.gov

" The measurement of lead excreted in urine following an injection of the chelating agent, calcium disodium EDTA (*EDTA provocation*) 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 Metal Retention!

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

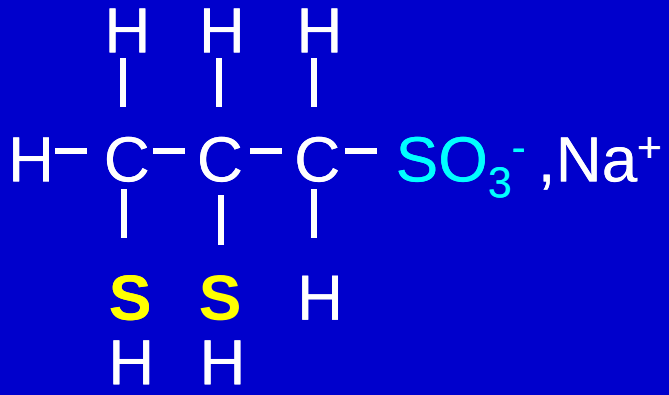
Pharmacological Detoxification

- Primarily **extracellular**, **aqueous** compartment
- Do NOT appreciably cross a healthy BBB !
- Rx **Pull**
- Concentration gradient
- Intracellular detoxification- **Push** (rGSH)
- Time for re-equilibration

Legal Status of Agents

- **<u>Ca-Na_2-EDTA</u>:** FDA approved in the 50s (Pb)
  Polyamine carboxylic acid (6 unpaired electrons)

- **<u>DMPS</u>**: NOT FDA approved

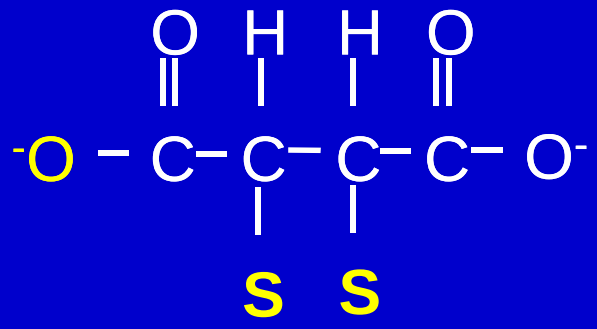


(Informed consent!)

Legal Status : DMSA

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

  2,3-meso-dimercapto-succinic acid



EDTA

- Slow iv drip Na_2-EDTA for CVD **(3 hrs.)**

NEVER PUSH Na_2- EDTA

- Introduction of **Ca-Na_2-EDTA** slow push iv
- No biotransformation *in vivo*
- $T^{1/2}$ about 30-45 minutes

Ca-Na_2-EDTA is Hypertonic

- 3 gm /10-30 ml; 800-2,400 (mOsm)
- 1-7X dilution (sterile H_2O, saline), **slow push (10 min.) or fast drip (15-30 min.)**
- 25-50 mg/kg (3 gm max), half dose initially
- **6 hour** urine collection
- Potential hypotension, hypoglycemia

Hydration, snack, reclining chair

Ca- Na_2-EDTA (cont'd)

- Oral: poorly absorbed, only ~ 5-10 %

  Not appropriate for challenge test
- Suppositories

  Not appropriate for challenge test

  Appear to effective for long-term detoxification of lead

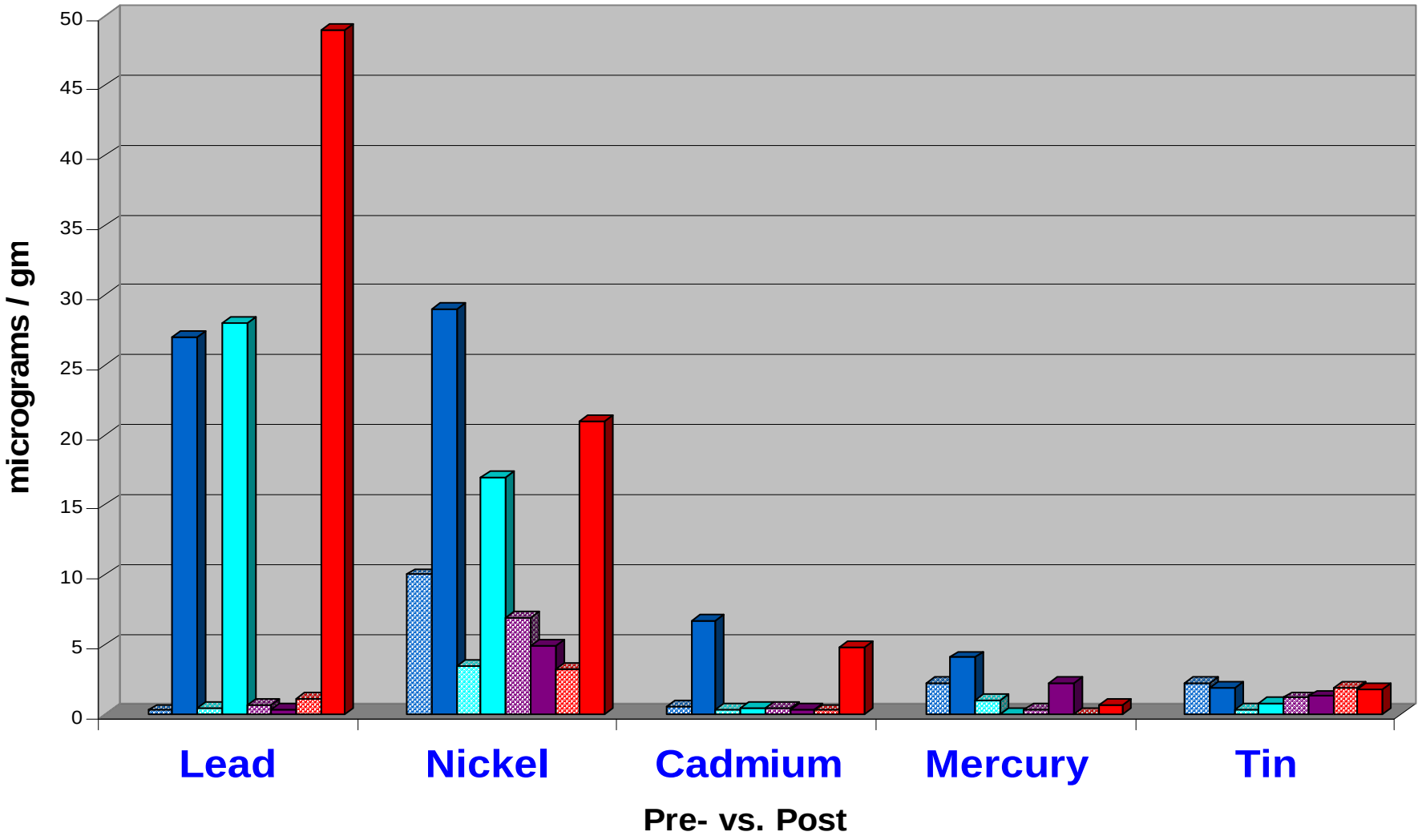
Urinary Metals After Intravenous $Ca\text{-}Na_2\text{-}EDTA$

	Increase*
Lead	147-X
Zn	32-X
Manganese	15-X
Iron	7.4-X
Cadmium	7-X
Antimony	4.4-X

*$p<0.05$, n=14

Quig, Filidei, Whitaker (2002)

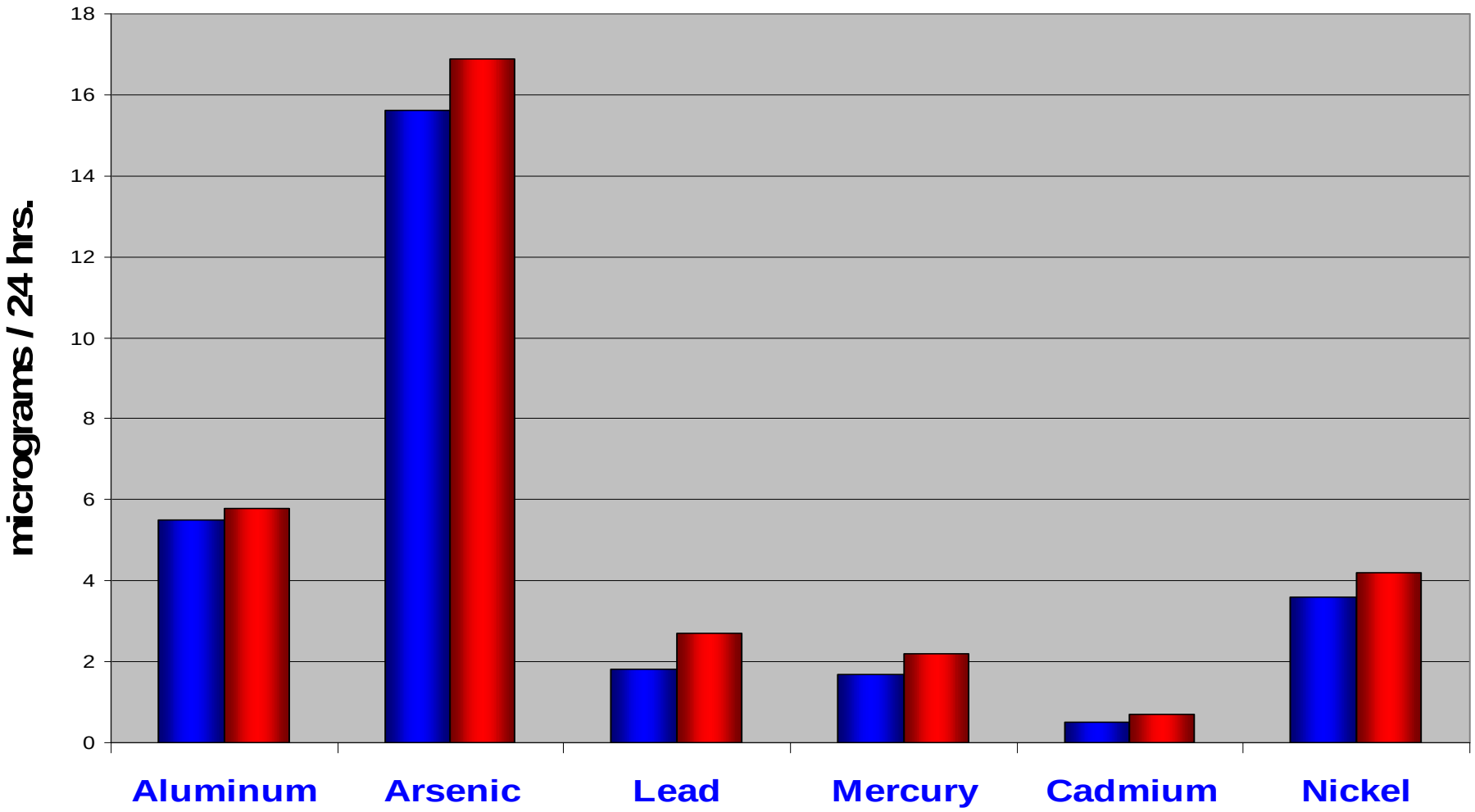
IV Ca-Na_2-EDTA Provocations: ASD



n = 4, ages 3-12, 750-1,500 mg, 6 hr. collections

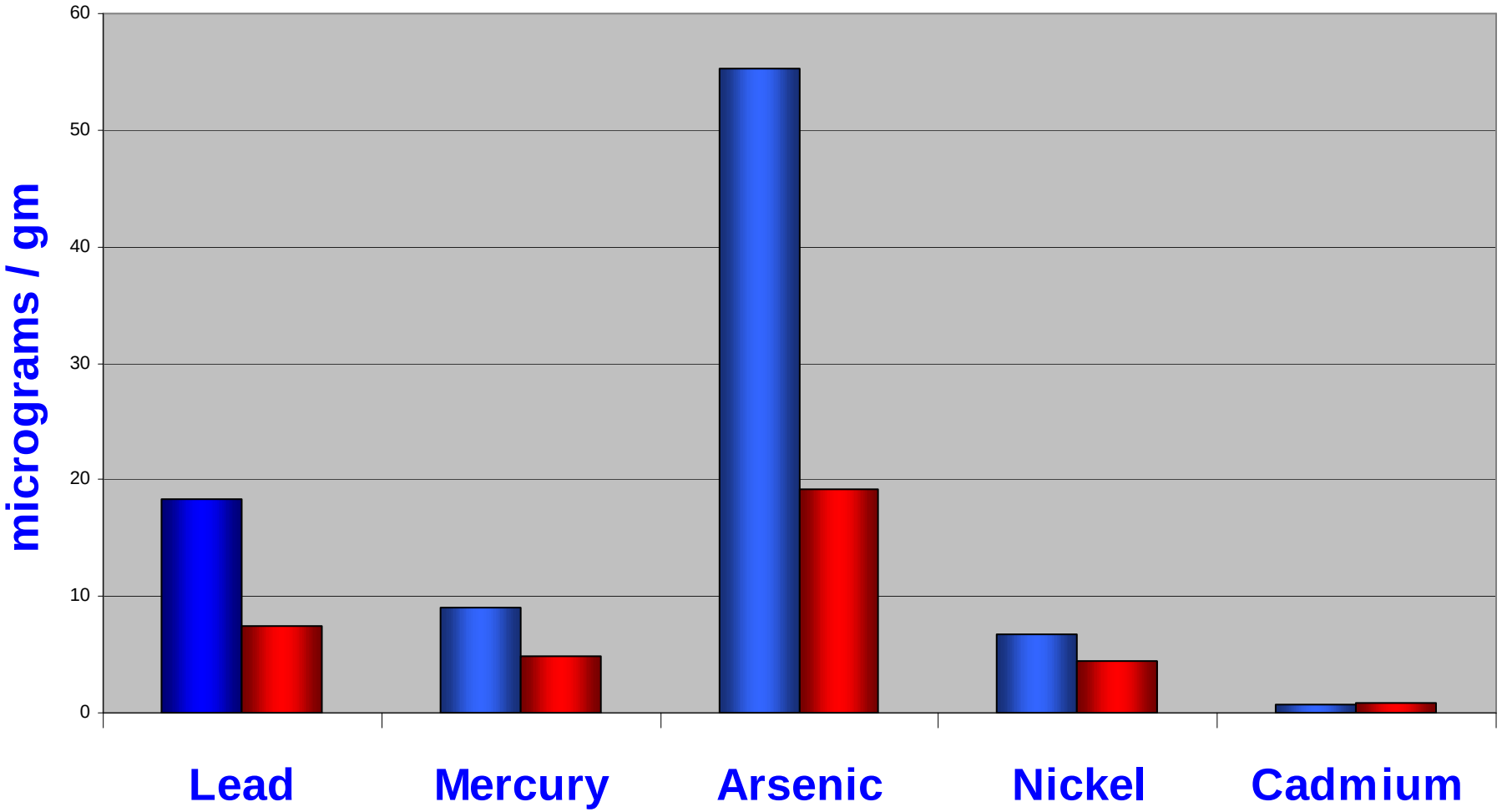
Usman and Quig (2006)

Ca-EDTA Suppositories: Pre- vs. Post



n=35 adults, 750 mg

Post DMSA Before and After Ca-EDTA Suppository Treatment



n=35, 90 days, 750 mg/night

DMPS

- Official drug in Soviet Union since 1958, registered with German health authorities (Dimaval®)
- $T^{1/2}$ oral ~ **9 hr.** (~ 50 % absorbed)
- $T^{1/2}$ iv < **1 hr**.

Fund Appl. Toxicol (1990)14:598-607

Urinary Mercury Before and After DMPS Challenge

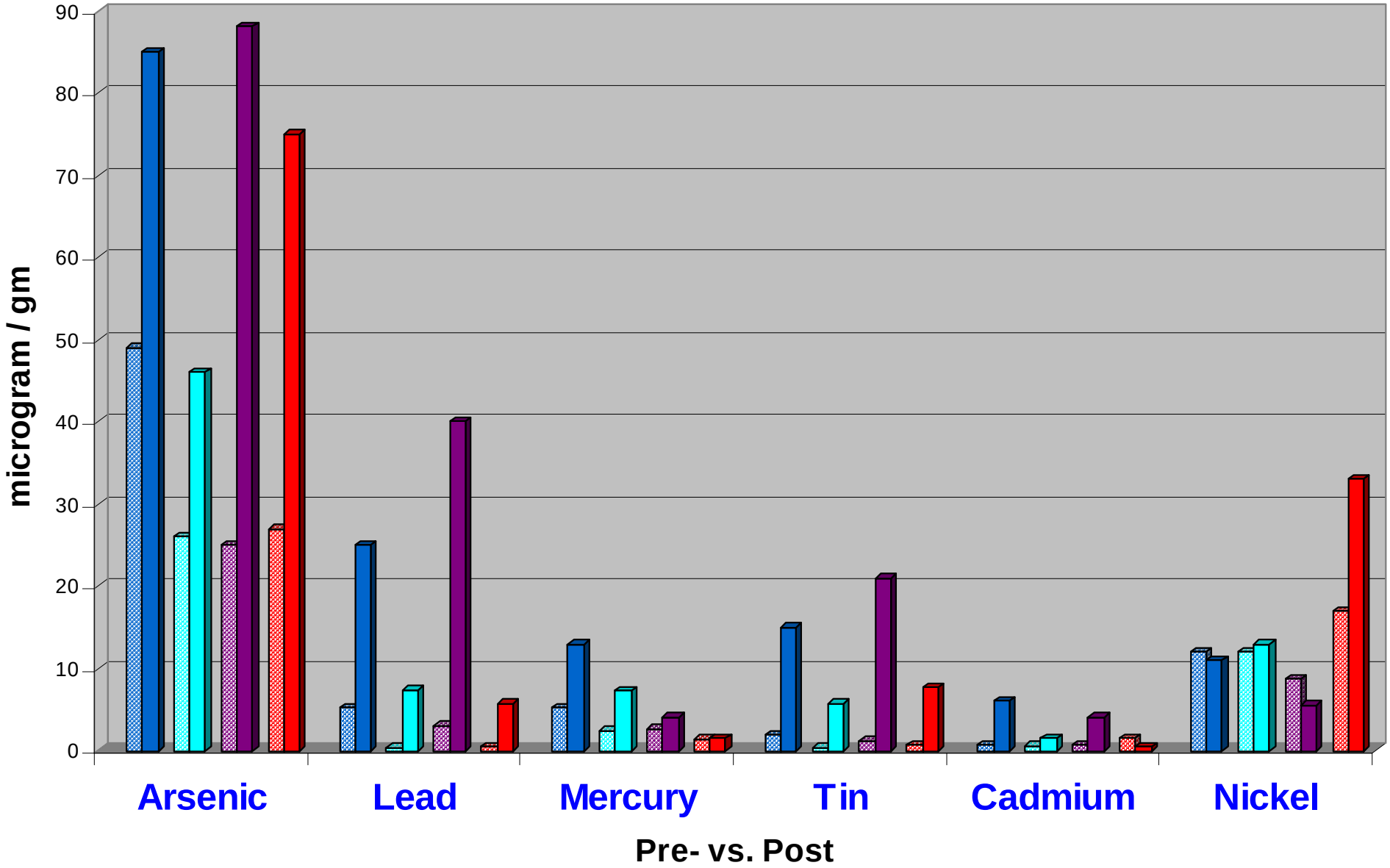
μg Hg / 6h

	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

IV DMPS Provocations: ASD



n = 4, 50-80 mg, 6 hr. collections, ages 2-6

Usman and Quig (2006)

DMPS: Possible Side Effects

- Severe reaction **(rare):** mucocutaneous eruptions
- Chills, fever, itching, skin rash --presumably mild allergic reactions
- Elevated transaminase levels (ALT)
- Hypotension, nausea, dizziness and weakness (usually i.v.), depression, “brain fog,” fatigue
- Cu, Zn and Mo deficiencies
- **NO DOCUMENTED** Stevens-Johnson Syndrome

(V. Aposhian, 2004)

DMSA General

- Does **NOT** cross healthy BBB
- Does **NOT** ↑ brain Pb or Hg levels
- Increases urinary Pb, Hg and As, but **NOT** aluminum or uranium

Toxicol(1995)97:23-38 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

DMSA and Brain Metals

DMSA *decreased* brain Pb, Hg in:

- Animals *pre-loaded* with Hg or Pb
- Rats pre-loaded or **ongoing** Pb exposure

  Normalized CNS levels of GFAP

  Normalized behavioral hyperactivity

Toxicol 89 (1994) Toxicol Appl Pharm 133 (1995)
Free Radic Biol Med 21 (1996) Pharm Toxicol 80 (1997)
Chem Res Toxicol 1 (1996) Toxicol Appl Pharm 144 (1997)

DMSA: Clinical Pharmacology

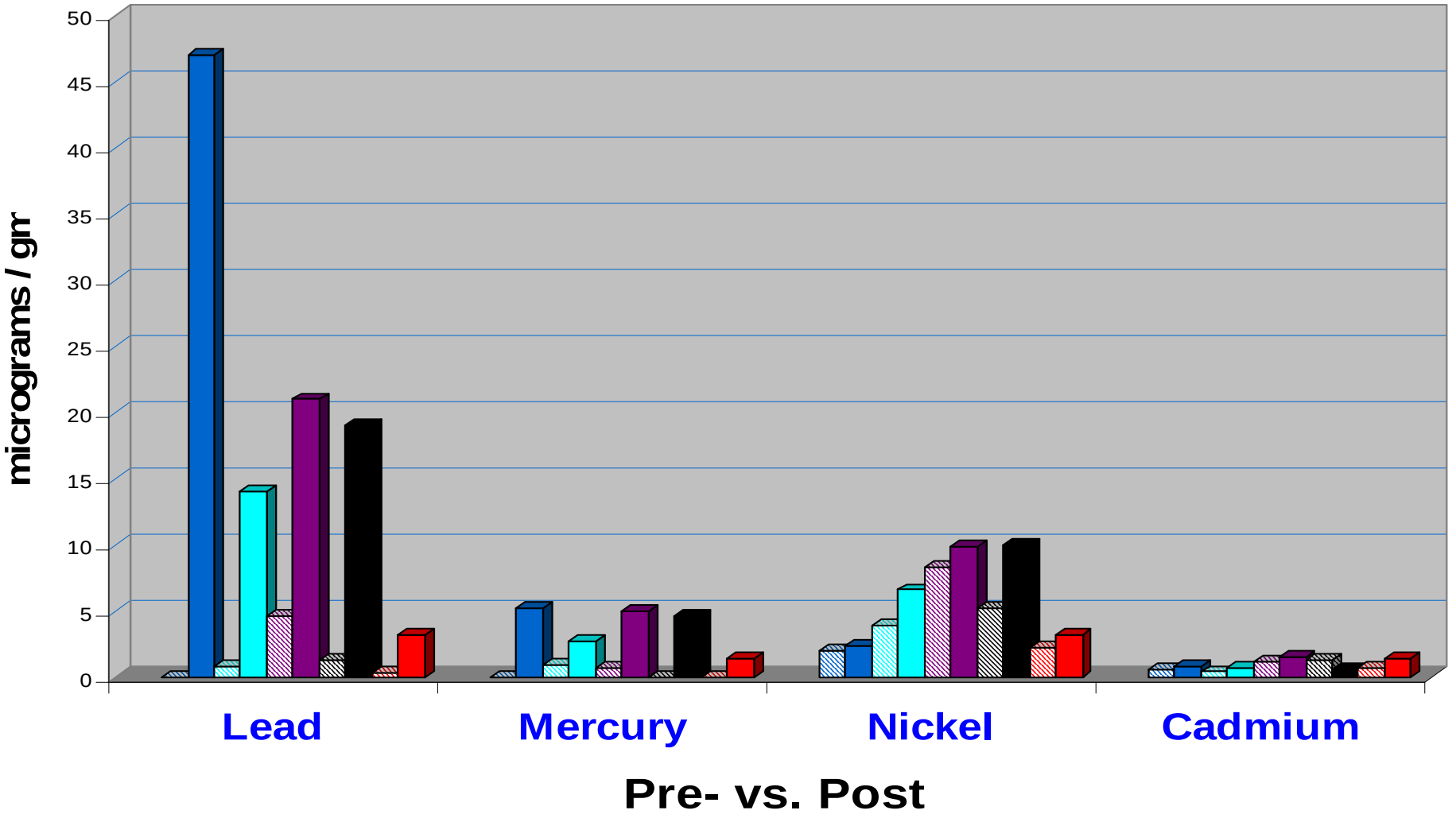
- 20-25% absorbed (orally)
- Peak plasma ~ 3 hrs., rate U excretion ~ 4 hrs.
- Urinary excretion: **90% as mixed disulfides with 2 cysteines (1:2)**

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

Dysbiosis and Sulfur Compounds

- N-AC, ALA and DMSA exacerbate GI symptoms, and apparently the growth of undesirable bacteria/yeast.
- Urease+ bacteria produce H_2S and NH_4 from cysteine (N-AC).
- Clean up GI tract **BEFORE** starting metal detoxification with oral SH- compounds

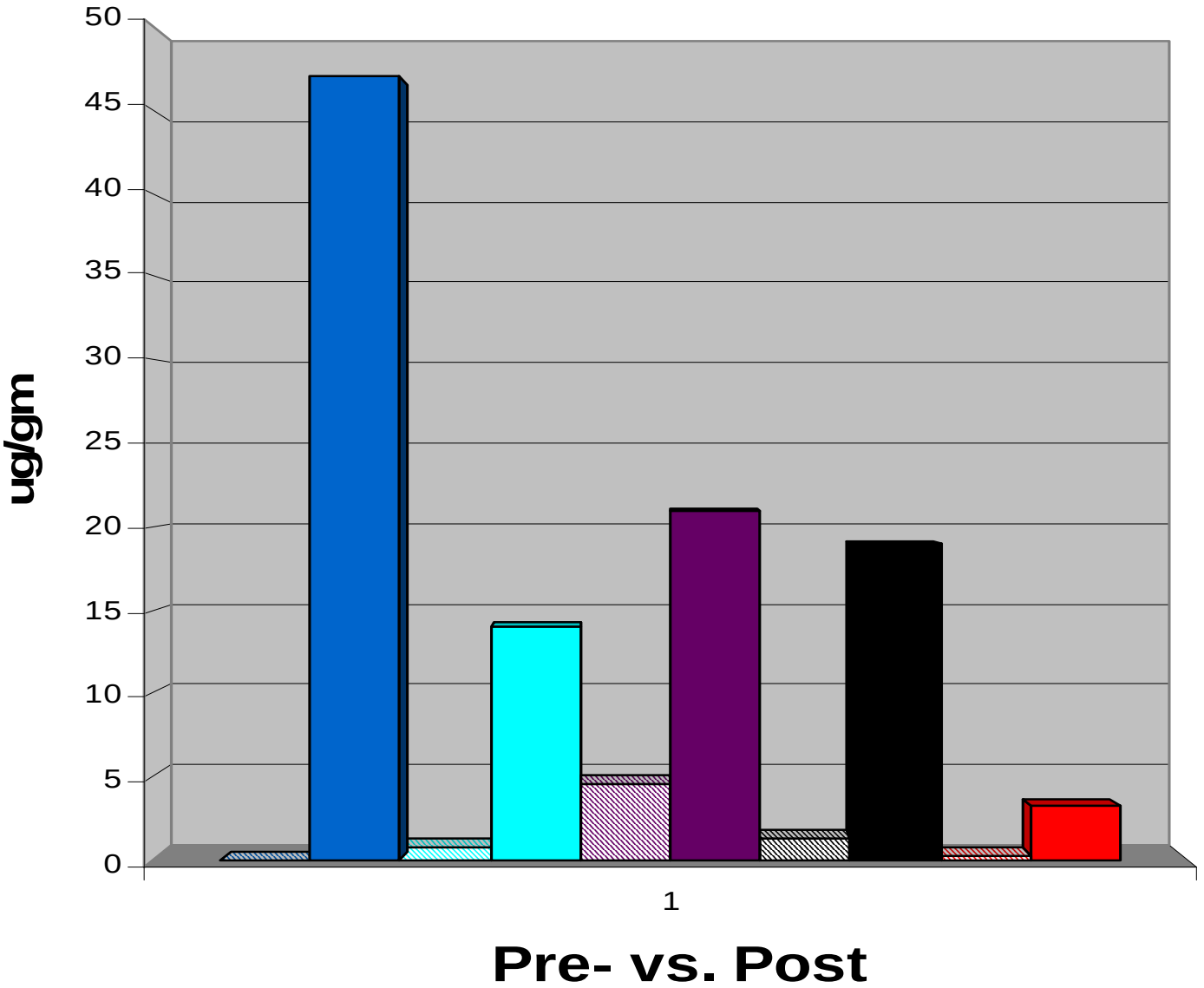
DMSA Suppository Challenge



n = 5, 20 mg/kg, 6 hr collections, age 3-4 yrs.

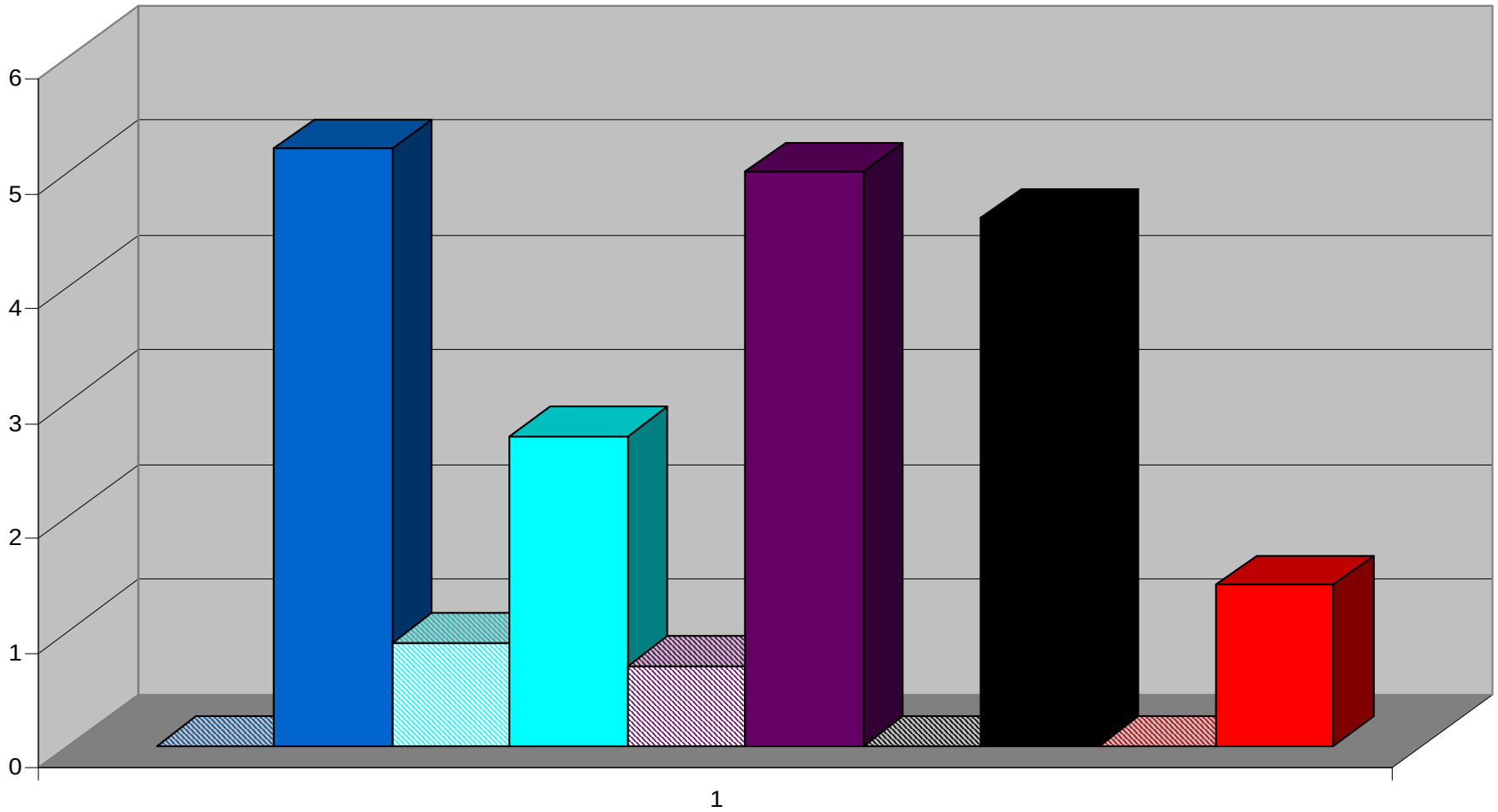
Quig (2006)

DMSA SUPPOSITORY: LEAD



Quig (2006)

DMSA SUPPOSITORY: MERCURY



Pre- vs. Post

Quig (2006)

DMSA: Potential Side Effects (oral)

- Potential side effects listed in PDR: mucocutaneous reactions, nausea, fatigue, ↑ liver enzymes, leucopoenia, neutropenia, thrombocytopenia
- **Clinically observed side effects (transient):**

  Dizziness, weakness, G.I. distress (gas, loose stools, bloating), occasional ↑ ALT

Toxic Metals are Pro-oxidative

- Promote lipid peroxidation
- Inhibit antioxidative enzymes
  SOD, GSH-Px, catalase
- Deplete glutathione (rGSH)
  Direct binding/irreversible excretion
  Inhibit GSH reductase/GSH S-transferase

Antioxidant Effects of Agents

- EDTA, DMPS, and DMSA are free radical scavengers
- ↓ oxidative stress
- EDTA, DMPS and DMSA increase hepatic GSH in lead-exposed animals

J Biochem Mol Toxicol(2004)18:221 Chem Biol Interact(2003)145:267
Comp Biochem Physiol C Toxicol Pharmacol(2003)134:319
Dimaval Scientific Monograph(Heyltech)1997

Antioxidants Are a Must: Cellular Protection

- DMSA, EDTA, ALA, N-AC, E, C, melatonin and taurine improve redox state of cells, ↑ GSH and ↓ biomarkers of oxidative damage
- **Greater** urinary **metal excretion with DMSA PLUS antioxidants**

Chem Biol Interact(2003)145:267 Arch Toxicol(2002)76:437
Toxicology(2002)177:186 Envir Toxicol.(2001)9:173
Arch Envir Contam Toxicol(2001)41:397

Glycine : Assisting Agent for Challenges

- 40 mg/kg glycine orally about 2 hrs. before a challenge
- **Use in CONJUNCTION** with EDTA, DMSA, or DMPS
- **Not** to be used alone
- Contraindication: hyperammonemia

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

Take Home Messages

- Apply pharmacokinetic **facts.**
- IV Ca-EDTA is very effective for Pb, Cd and Al.
- Rectal Ca-EDTA appears effective over time therapeutically.
- **Rectal DMSA** is effective for **challenges** and **detox**.
- IV and oral DMPS is very effective; need **pre-/post** rectal DMPS data.

Take Home Messages

- Ca-EDTA, DMSA and DMPS have **dual actions:** antioxidative (immediate), **and** metal detoxification
- The agents work best when **combined** with natural antioxidants
- DMSA is **NOT** a nutritional supplement

Equilibrium Constants for DMPS-Metal Complexes

	$\log K_1$	$\log K_2$
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

Heyltex Corp

EDTA Stability Constants

	Log K
Pb^{2+}	**18.4**
Cu^{2+}, Ni^{2+}	**18.3**
Cd^{2+},Zn^{2+},Co^{2+}	**16.1**
Fe^{2+}	**14.4**
Mn^{2+}	**13.4**
Ca^{2+}	**10.6**
Sr^{2+}	**8.6**

Chemistry of Metal Chelate Compounds (1978)

Metal	1st Choice	2nd Choice
Inorg. Hg	DMPS	DMSA
Org. Hg	DMSA/ DMPS	
Pb	DMSA/EDTA	DMPS
As	DMPS	DMSA
Cd	EDTA	DMPS*
Sb	DMPS/DMSA	EDTA
Sn	DMPS,DMSA	EDTA
Tl	Prussian Blue	DMSA

(K ferric cyanoferrate II)

Toxicol (1995)97:23-38