Penicillamine protocol (based on Jaffe) for determining toxic and nutritional mineral status by provocation into the urine

Purpose: Determine the body's burden of mobilizable, potentially toxic minerals. Nutritional divalent mineral status may also be assessed.

Method: A short (3-day) course of d-penicillamine [Cupramine™, D-Pen™, dimethylcysteine, mercaptovaline] *or* Acetyl-d-penicillamine is prescribed.

Specimen for analysis: Collect a **24º urine** on the **2nd day**.

Protocol:

- Take 500 mg. (2 capsules of 250 mg. each) d-penicillamine or N-Acetyl-d-penicillamine with each meal and before bed for just three (3) days. This is a total of 2 grams each day for three (3) days for a typical 70 Kgm. adult. This is based on 30 mg./Kgm. body weight. If weight is under 100 pounds or over 300 pounds, calculation of dose is recommended.
  * For example, a 100-pound adult weighs 45.5 Kgms. A daily dose of 1,590 mg. (~1,500 mg.) is recommended. This would most easily be achieved by giving two (2) x 250 mg. capsules with breakfast, dinner, and at bedtime [two (2) capsules TID].
  * By comparison, a 350-pound person weighs 160 Kgm. At 30 mg./Kgm., this calculates to a daily dose of 4,800 mg. (~4,750 mg.). This means taking five (5) x 250 mg. capsules with each of three (3) meals plus four (4) x 250 mg. capsules at bedtime.
- **Starting** on the **morning of the second day**, collect in a heavy metal-free container (usually provided by the doctor or the laboratory) all urine output for the next day (a full 24-hour cycle). It is quite important to collect **ALL** the urine.
- If a urine sample is missed, the collection is incomplete. Start over with a new provocation one week later. Urine collected in an incomplete sample may be poured out and the same collection container reused. Take the entire urine collection to the laboratory as soon as possible after completion. **The total volume is an important part of the information to be sent to the analytic lab.** It is desirable, although not necessary, to keep the urine refrigerated during the collection period. **Note:** A third-day collection can not be compared with the standardized second-day collection results.

Because of short-term effects on other minerals, this specimen should *not* be used for calcium or other mineral balance studies. The specimen ***may*** also be used to check kidney function and to analyze for most hormones, neurotransmitter metabolites, etc.

This short course of d-penicillamine avoids the rare but important side effects of longer-term therapeutic doses of the drug as discussed in the *Physicians Desk Reference* (*PDR*). Of course, if you note any adverse response, discontinue taking the medication until otherwise instructed by your health professional.

Interpretation and substantiation of d-penicillamine protocol*:*

- Each laboratory has an applicable reference range for each mineral assayed. Elevation above the range reported by that laboratory is indicative of increased tissue stores of that heavy metal. Tissue status of nutritional minerals may also be assessed in this way. Typical d-penicillamine provocation reference ranges are included in the table at the end of this document.

- For modest amounts of provoked toxic minerals:

  Follow an'**alkaline way diet'** combined with therapeutic amounts of antioxidants plus minerals (potassium, calcium, magnesium, and zinc as their ascorbates, aspartates, citrates, glycinates, or other fully soluble, non-allergenic mineral salts) to displace the toxic minerals. Adequate herbal tea, mineral water, or spring water (eight (8) or more 8-ounce glasses each day) helps to 'wash out' these toxins. A repeat provocative heavy metal test after 30-60 days is recommended to confirm the reduction in available heavy metals.

  For more than modest amounts of provoked toxic minerals:

  Use d-penicillamine twice a week (e.g., Monday and Thursday) for 30-60 days at 7.5 mg./Kgm. taken QID (500 mg./QID for most adults) with supplemental calcium, magnesium, and zinc particularly on the non-penicillamine days to replace these minerals (which d-penicillamine will chelate along with the other divalent [double charged] minerals along with toxic or heavy metals). Therapeutic doses of antioxidants are beneficial as well as described. This includes:

  A. **Buffered ascorbate** based on ascorbate calibration to determine physiological ascorbate need[1]. **Flavonoid / flavanol combinations** (such as quercetin dihydrate and soluble OPC) potentiate the benefits of buffered ascorbate. Their need increases in proportion to buffered ascorbate need as noted in the ascorbate calibration document.
  B. **Natural vitamins E** (mixed tocopherols) 200-600 I.U./day with tocotrienols (polycosanols),
  C. A balanced, high-potency, **high-activity B complex including PABA**,
  D. A **comprehensive micromineral supplement** is recommended since micromineral deficits are pervasive. Selenomethionine is the most active mineral form for combining with and inactivating toxic minerals.
  E. Sulfhydryl-rich foods such as **garlic, ginger, and onions; eggs; and brassica vegetables** (*e.g.*, broccoli, cabbage, etc.). Make fresh ginger tea (with raw honey to taste) a staple beverage. A thumb-size piece of fresh ginger, finely chopped, and steeped in hot water for five minutes contains over 5,000 mcg. of toxic mineral-trapping sulfhydryl compounds. Ginger tea may be made up ahead of time and may be drunk cool or cold if preferred.
  F. Probiotics (10-20 Bn./day) containing multiple human strains that have been cultured, harvested, and lyophilized (freeze dried) for maximum activity and potency[2].

- d-penicillamine was found to bind copper in the urine of patients with Wilson's disease[3] for which it has remained the treatment of choice for almost half a century. Walsh has reported the safe and successful use of d-penicillamine in pregnant women, infants, the elderly and the infirm.

- In animal studies, lead in bone seems to be even more effectively mobilized by d-penicillamine than lead in soft tissues[4,5]. However, $CaNa_2EDTA$ is reported to be a more

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[1] Jaffe R. Determination of ascorbate physiologic need by calibration. *Health Studies Collegium Document 111*. Contact Client Services at 800-525-7372 for reprints.

[2] For information on PERQUE Digesta Guard Forté 10 (with or without FOS) call 800-525-7372 or Fax 703-450-2995 or email clientservices@PERQUE.com.

[3] Walshe JM. Penicillamine, a new oral therapy for Wilson's disease. *Am J Med* 1956;21:487-495.

[4] Russell JC, Griffin TB, McChesney EW, Coulston F. Metabolism of airborne particulate lead in continuously exposed rats: effect of penicillamine on mobilization. *Ecotoxicol Environ Safety* 1978;2:49-53.

[5] Hammond PB. The effects of d-penicillamine on the tissue distribution and excretion of lead. *Toxicol Appl Pharmacol* 1973;26:241-246.

effective lead chelator than d-penicillamine *in vitro* in tissue culture[6]. Questions have been raised about the safety of using any agent for low-level toxic mineral detoxification because some animal studies report that lead may redistribute into soft tissues such as the choroid plexus (where spinal fluid is produced) or the loop of Henle in the kidney after $CaNa_2EDTA$ therapy[7]. Concerns of this type have been raised about all oral chelators although less in regard to d-penicillamine than any other substance due to the tight bond between toxic minerals and d-penicillamine.

Mobilization of Lead, Mercury, Arsenic, Cadmium, and Nickel by d-penicillamine

- Clinical benefits of d-penicillamine are described by Sachs[8] *et al* and Vitale[9] *et al* yet not by Marcus[10] (who administered d-penicillamine while the study subjects continued to live in lead exposed environs). This may well explain the less dramatic decline in blood lead levels in the Marcus study. In Chisholm's study, children removed from further exposure and treated with d-penicillamine showed more rapid decline in blood lead levels and in the reversal of hematologic toxicity than the decline in toxicities resulting *solely* from eliminating the lead exposure sources[11]. In contrast, the study by Rogan[12] *et al* did not confirm these findings. This study has been criticized as flawed in method because the environment of the children studies was not mitigated for continued toxic mineral exposure during the study period[13].

- Penicillamine also mobilizes and facilitates the safer excretion of toxic minerals[14] including mercury[15,16,17,18,19,20,21,22] arsenic[23,24,25,26,27,28] cadmium[29,30,31] and nickel[32]. Inconsistent

[6] Rosen JF, Markowitz ME. d-penicillamine: its actions on lead transport in bone organ culture. *Pediatr Res* 1980;14:330-335.
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[8] Sachs HK, Blanksma LA, Murray EF, O'Connell MJ. Ambulatory treatment of lead poisoning: report of 1155 cases. *Pediatrics* 1970;46:389-396.
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[18] Rosenspire AJ, Bodepudi S, Mathews M, McCabe MJ Jr. Low levels of ionic mercury modulate protein tyrosine phosphorylation in lymphocytes. *Int J Immunopharmacol* 1998;20(12):697-707.

reports of efficacy have been published. On balance, these may reflect lack of attention to sufficient reducing substance (ascorbate) to enhance toxic mineral mobilization and excretion while maintaining the more effective reduced form of d-penicillamine rather than it's disulfide. An additional factor that reduces toxic mineral mobilization is metabolic cellular acidosis. Correction of magnesium buffering deficit aids directly (by displacement) and indirectly (by correcting cellular acidosis) the enhanced toxic mineral mobilization. Magnesium, as the second most prevalent mineral inside mammalian cells, is a major contributor to cellular acidosis[33].

- The toxicity of d-penicillamine has been described based on its use for several indications in both adults and children. Toxicity of the racemic mixture used years ago to treat chronic arthritis in adults may account for the severity of some of these symptoms and should never be used. In children, nausea and vomiting appear more often at doses exceeding **60** mg./Kgm. per day and may respond to a decrease in dosage[34]. This protocol uses 30 mg./Kgm. doses for just three (3) days for provocation.

- When given daily and for prolonged periods (which we never recommend) adverse blood and skin effects seem to be idiosyncratic hypersensitivity reactions and are not dose related. Reversible leukopenia or mild thrombocytopenia is reported in less than 10% of children in

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one study[35], but not with similar dosages in two other larger series[36]. This may have resulted from interaction between d-penicillamine and pyridoxine (B-6)[37]. Supplemental B-6 is now routinely recommended as part of d-penicillamine *therapy* (not provocation). Eosinophilia (defined as >18% eosinophils) has been noted in one-fifth of children treated daily for an extended duration[38]. Angioedema, urticaria, or maculopapular eruptions that require discontinuation of drug therapy are reported at a rate of 0.5-1%[39]. Still less commonly reported reactions are proteinuria, microscopic hematuria, and urinary incontinence[40]. All of these relate to increased tissue permeability due to inhibition of connective tissue cross links when d-penicillamine is given on a continuing daily basis and <u>not</u> when it is given in the pulsed manner recommended here.

- **Distribution in the body of d-penicillamine** is widespread. Like aminoacids such as cysteine (of which penicillamine is the dimethyl analogue), it freely moves inside cells, sub-cellular organelles like the mitochondria, and into deep tissue sites like the brain[41], [42], [43], [44], [45], [46], [47], [48]

- Food or ferrous sulfate[49] may reduce the peak level of d-penicillamine in blood by a third or more[50]. Antacids or functional hypochlorhydria[51] decrease d-penicillamine absorption by as

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much as two-thirds[52]. As with all amino acids, peak blood levels are achieved when the amino acid is given on an empty stomach. For provocation and for therapy, **mean** rather than **peak** blood levels are more important. Thus, taking the d-penicillamine with food is acceptable. Compliance with this regimen is high.

- **The recommended dose and duration of therapy with d-penicillamine have been empirically derived.** Doses have ranged from 100 mg./Kgm. per day (in earlier studies) to 20 to 40 mg./Kgm. per day (more recently). Far fewer side effects are reported at the lower dosage range. The duration of the pulse therapy herein recommended is typically on Monday and Thursday for 4 to 12 weeks, depending on the pretreatment provoked urine toxic mineral concentration. When used in this pulsed way, d-penicillamine has become a first line treatment of choice over the several decades of its increasingly widespread use.

- Finally, penicillamine has the added virtue of serving as a source for nitric oxide (NO), which facilitates cellular communication and improved vascular compliance[53].

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Mineral value ranges for nutritional and toxic minerals in 2nd day 24º urine after d-penicillamine provocation, 7.5 mg./Kgm. QID for three days [N=200]

Mineral element	Reference Range µg/gm Creatinine	Reference Range mg./24º sample
Nutritional		
Calcium	**310 - 620**	**400 - 900**
Magnesium	**250 - 550**	**350 - 700**
Zinc	**0.8 - 1.3**	**1.1 - 1.5**
Copper	**0.04 - 0.06**	**0.06 - 0.08**
Iron	**0.20 - 0.30**	**0.24 - 0.36**
Manganese	**0.005- 0.007**	**0.006- 0.008**
Molybdenum	**0.11 - 0.14**	**0.13 - 0.19**
Boron	**4.1 - 5.6**	**5.8 - 6.7**
Chromium	**0.19 - 0.30**	**0.21 - 0.33**
Cobalt	**0.04 - 0.06**	**0.05 - 0.07**
Selenium	**0.25 - 0.31**	**0.24 - 0.35**
Vanadium	**0.02 - 0.03**	**0.03 - 0.04**

Note: Values lower than the reference range in provoked specimens suggest deficiency of the above needed essential minerals. Adequacy of supplemental intake to replenish deficits can be monitored by repeat d-penicillamine provocation every three months.

Toxic		
Lead	**< 20**	**< 25**
Mercury	**< 7**	**< 9**
Arsenic	**<120**	**<175**
Nickel	**< 16**	**< 25**
Cadmium	**< 4**	**< 6**

Summary of suggested treatment guide to reduce total toxic mineral tissue burden (TTMTB):

1. An '**alkaline way'** energized, high-fiber diet with 80% of what is eaten being alkaline forming when metabolized. Assessment of first morning urine pH (after a six or more hour rest and equilibration period) to assess net acid excess (NAE) to clinically evaluate metabolic acidosis is recommended.
2. **Ginger tea** (with raw honey to taste) is rich in beneficial thiols (active sulfur sources) and recommended as a beverage of choice. Ginger tea may be taken warm, cool or cold. Other sources of **'sulfur rich toxic mineral detoxifiers'** include:
   • Onions and garlic
   • Brassica vegetables like broccoli and cabbage (especially their sprouts)
   • Eggs (especially organic, free range)
   Note: These sulfur rich detoxifying foods are interchangeable (as long as no immune delayed allergy to them exists) in terms of their toxic mineral binding benefits. **Include the preferred ones liberally for a healthier diet.**
3. **PERQUE Potent C Guard** intake based on the ascorbate calibration protocol to determine individual ascorbate intake need.
   PERQUE Pain Guard Forté flavonoid and flavanol **1-4 tabs QID <u>OR</u>**
   PERQUE Repair Guard **1-2 tabs BID**
   PERQUE2 Life Guard comprehensive formula **2 tabs TID**
   PERQUE1 Detox IN Guard neuro-immune support **1-2 tabs TID**
   [start slow and build up with this potent formula]
   PERQUE Digesta Guard Forté 10 active probiotics **3 caps BID**
   PERQUE Magnesium (Mg) Plus Guard **2 caps BID**
   PERQUE Choline Citrate (taken in juice or water) **1 tsp. BID** taken along with **PERQUE Mg Plus Guard** to facilitate magnesium uptake while building acetylcholine neurotransmitter, cholinergic bile salts, and cell acid buffering / ATP production from citrate.
   The above supplements are given together to gain the cumulative benefit of the following free radical trapping antioxidant detoxification mechanisms in:
   A. Flowing blood
   B. Metabolically and hormonally active cells
   C. The blood brain barrier and the choroid plexus
   D. The enterocytes in the digestive tract
   E. Brain cells
   F. Immune active cells and systems
   G. Healthy skin look and function

4. In addition, if substantial total toxic mineral tissue burdens are documented, oral pulse therapy (two (2) days per week) with d-penicillamine is recommended. Use 7.5 mg./Kgm. QID, on the two (2) days each week for three (3) months is given. After three (3) months, retest the urine by the d-penicillamine provocation test to determine residual toxic mineral being eliminated as well as comparison of nutritional mineral status. For example, are they assimilating what is being given? Do they have particularly high need for particular minerals for their unique metabolic type or metabolic condition?