Labile and immobilized iron in neurodegenerative diseases

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3rd Int. Conference on Neurology and Therapeutics; September 6 2014

Iron

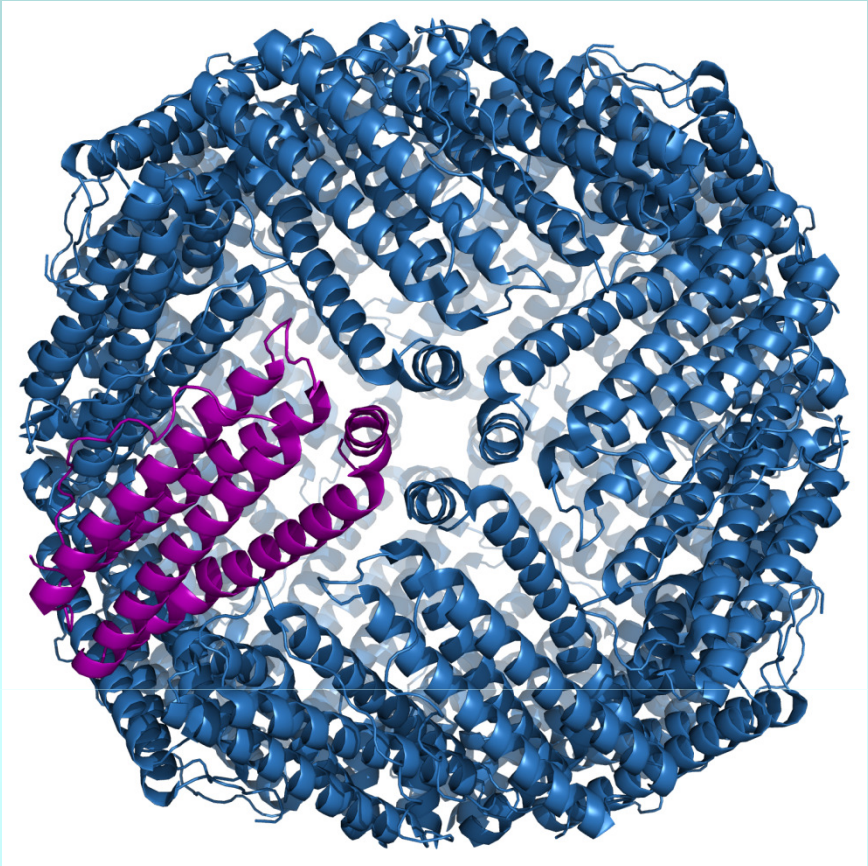
- *It's not what we don't know about nutrition that hurts us, it is what we know for sure that turns out to be dead wrong.*

- —attributed to Victor Herbert, MD, JD

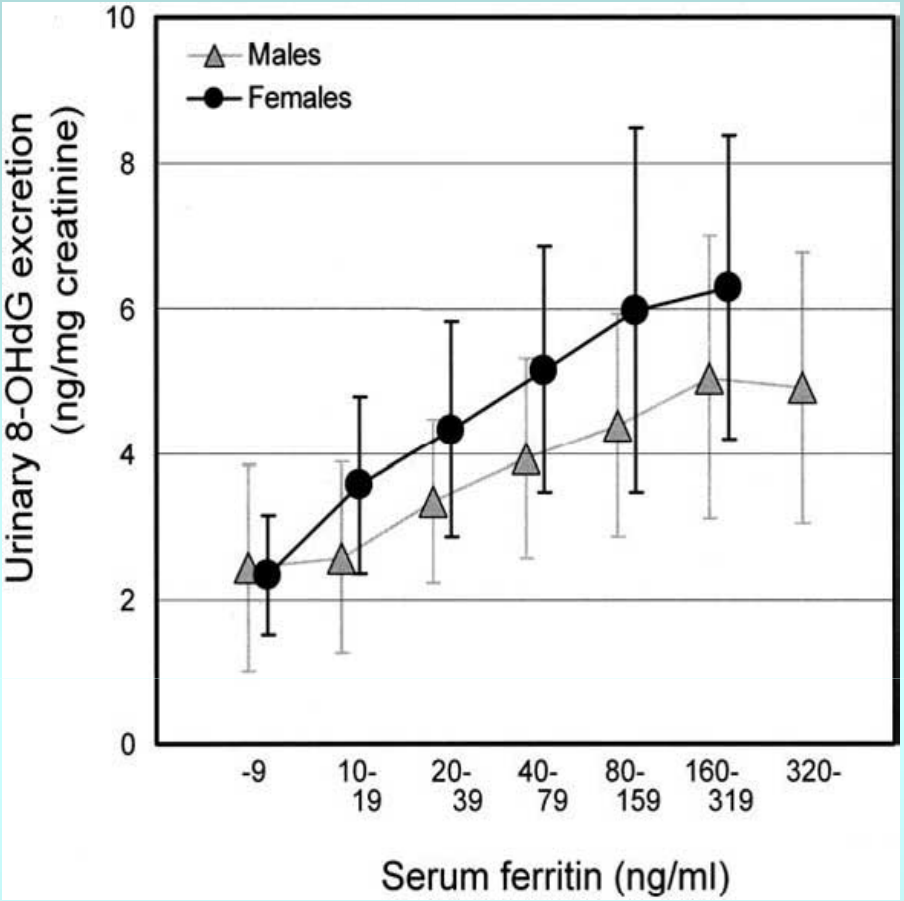
- Quoted by J. Sullivan in "Is stored iron safe?"
- J. L. Lab Clin Med 144 (6) p 280 (2004)

Iron distribution

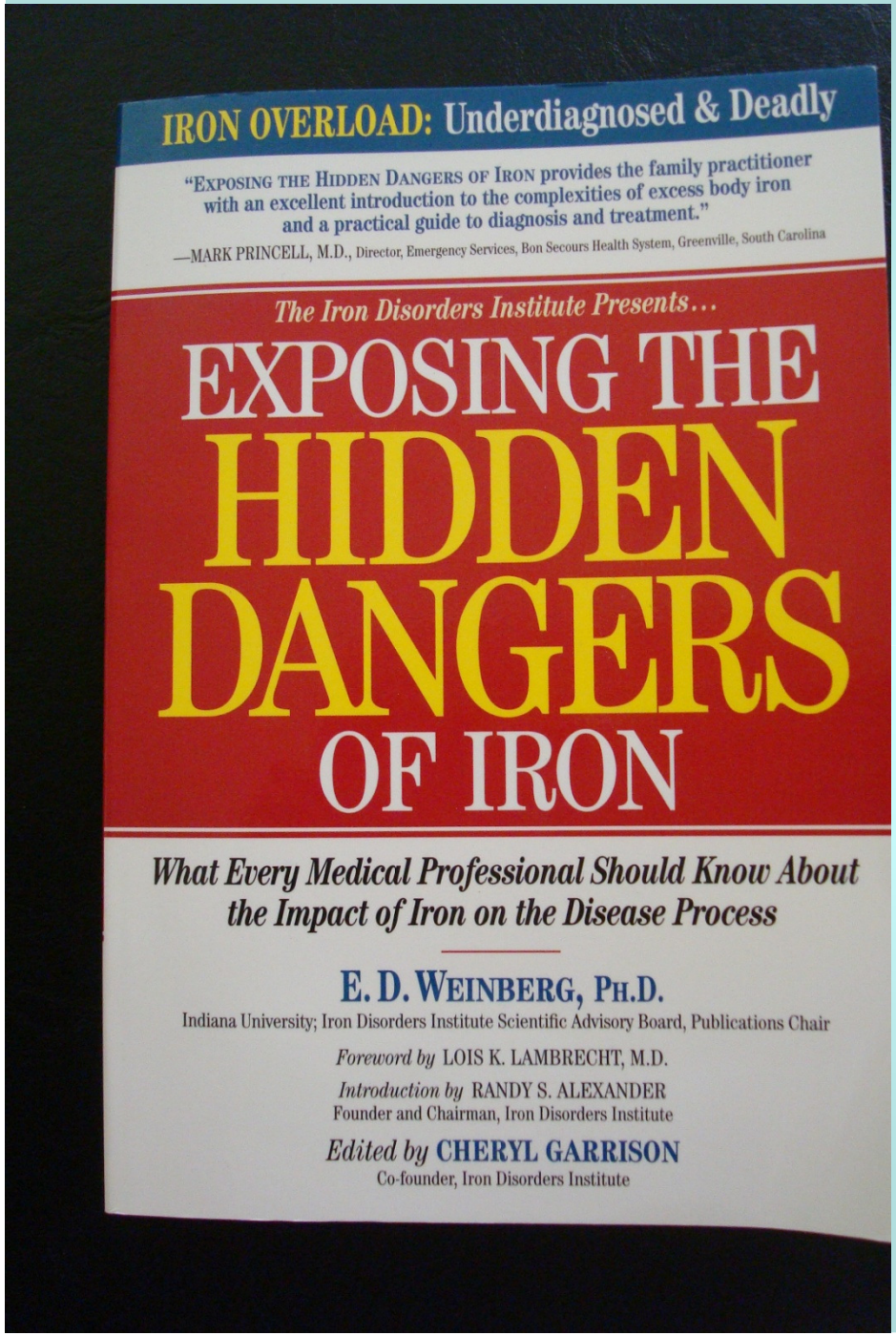
- "No" means of excretion, so all control is at absorption sites.
- Distribution (total 4 g males, 3.5 g females):
  - 70% in hemoglobin
  - 15% in myoglobin and enzymes
  - 14% in ferritin
  - 1% in transit in serum (mostly transferrin)
  - ? "free"/ labile/ reactive iron



"Ferritin… is a safe iron storage protein" (figure from wilkipedia)
…a nanoparticle 8 nm diameter



- **Fig on right:** Correlation between urinary 8-OHdG and serum ferritin concentrations, scaled to the logarithm. The urinary excretion of 8-OHdG correlated positively with serum ferritin (males ◆, $r = .32$; females ●, $r = .54$; $P < .05$). Reprinted from Free Radical Biology and Medicine. Copyright © 2003, Elsevier Inc.46



Growing recognition of problems with iron overload in a western diet (2004 book)

Iron deposits in aging brain tissue



On T2-weighted magnetic resonance images, the signal intensity is decreased in the pallidum and substantia nigra of aging mouse lemurs in comparison to young animals.

***Dhenain**, et al. Neurobiol Aging. 1998 Jan-Feb;19(1):65-9.*

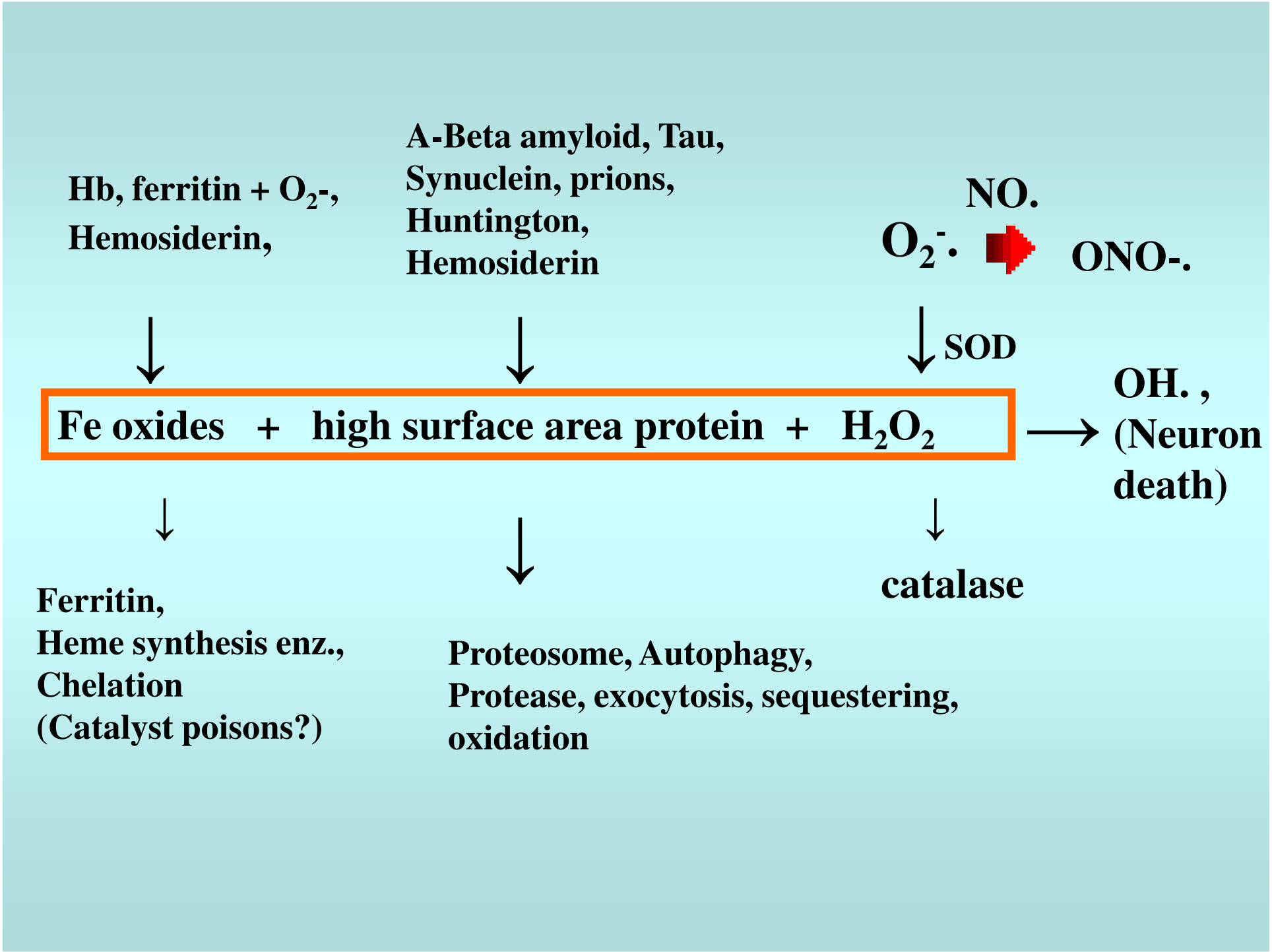
Iron can promote damaging oxidation in several ways:

- **"Fenton" chemistry (oxidative catalysis)**

$$Fe^{+2} + H_2O_2 \rightarrow Fe^{+3} + HO\cdot + HO^-$$

Homogeneous (solution)
Heterogeneous (on solid particles)

- **As well as possible magnetic field effects**


Hb, ferritin + O_2-,
Hemosiderin,
A-Beta amyloid, Tau,
Synuclein, prions,
Huntington,
Hemosiderin
NO.
O_2^-.
ONO-.
SOD
Fe oxides + high surface area protein + H_2O_2
OH. ,
(Neuron
death)
catalase
Ferritin,
Heme synthesis enz.,
Chelation
(Catalyst poisons?)
Proteosome, Autophagy,
Protease, exocytosis, sequestering,
oxidation

Removal of iron may improve cognitive function

Iron deposits in children with cerebral malaria were treated with an iron chelator, when in a coma. Measured hours to become conscious

untreated: 43 hours
treated: 20 hours

Gordeuk et al., *Effect of iron chelation therapy on recovery from deep coma in children with cerebral malaria.*
N Engl J Med. 1992 Nov 19;327(21):1473-7

Current state of the knowledge

"The physiological iron complex is unknown, consequently the rate constants for the …oxidation by hydrogen peroxide are unknown."

W. Koppenol

The Oxygen Society Annual Meeting, San Diego (2000) pg. 19

"Needle in a Haystack" problem

Question: How to identify minute deposits in large samples?

Answer: Very sensitive synchrotron methods (XAFS, XANES), followed by Transmission Electron microscopy (TEM)

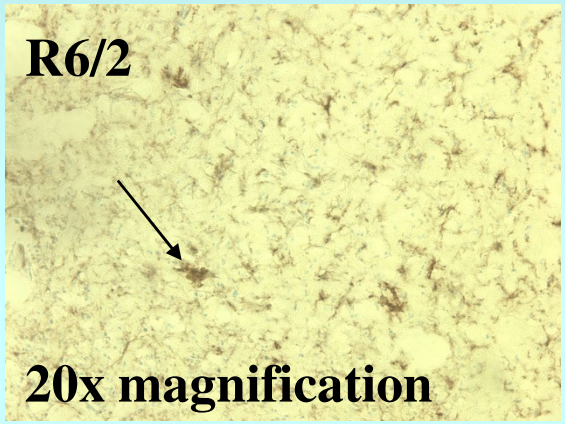
XAFS: X-ray Absorption Fine Structure
XANES: X-ray Absorption Near-edge Structure
TEM: transmission electron microscopy

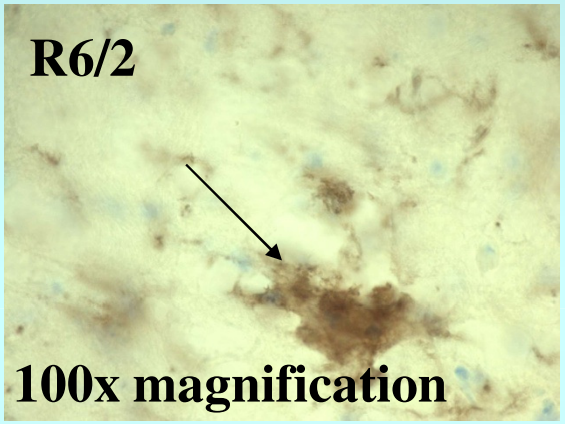
Iron containing brain specimens to develop techniques and understand the types of deposits:

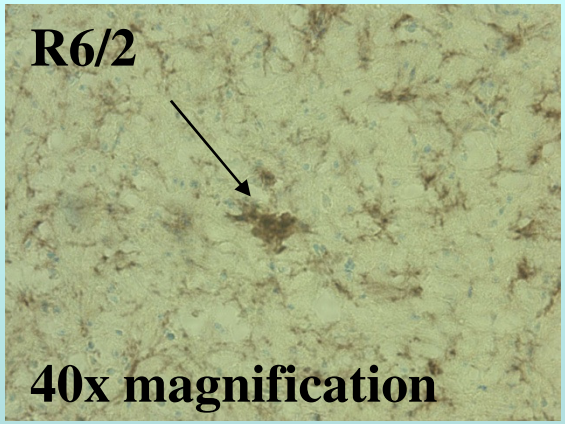
- **Pigeons**
- **Transgenic mouse models of accelerated aging: R6/2 mouse (Huntington's disease)**

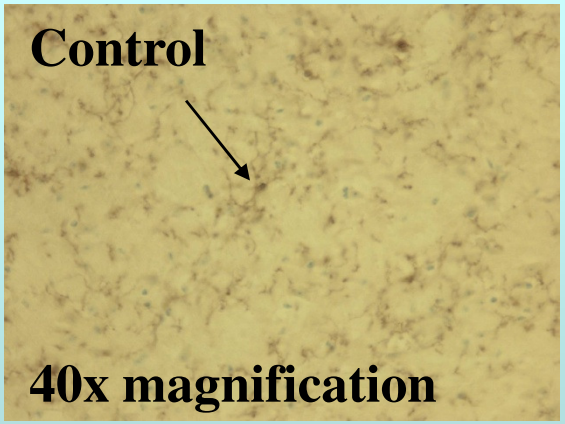
  GFAP-IL6 mouse (inflammatory model, planned)
- **Human brain tissue from Alzheimer's autopsy**

Demonstration of Neuropathological changes in brain tissue of R6/2 mice

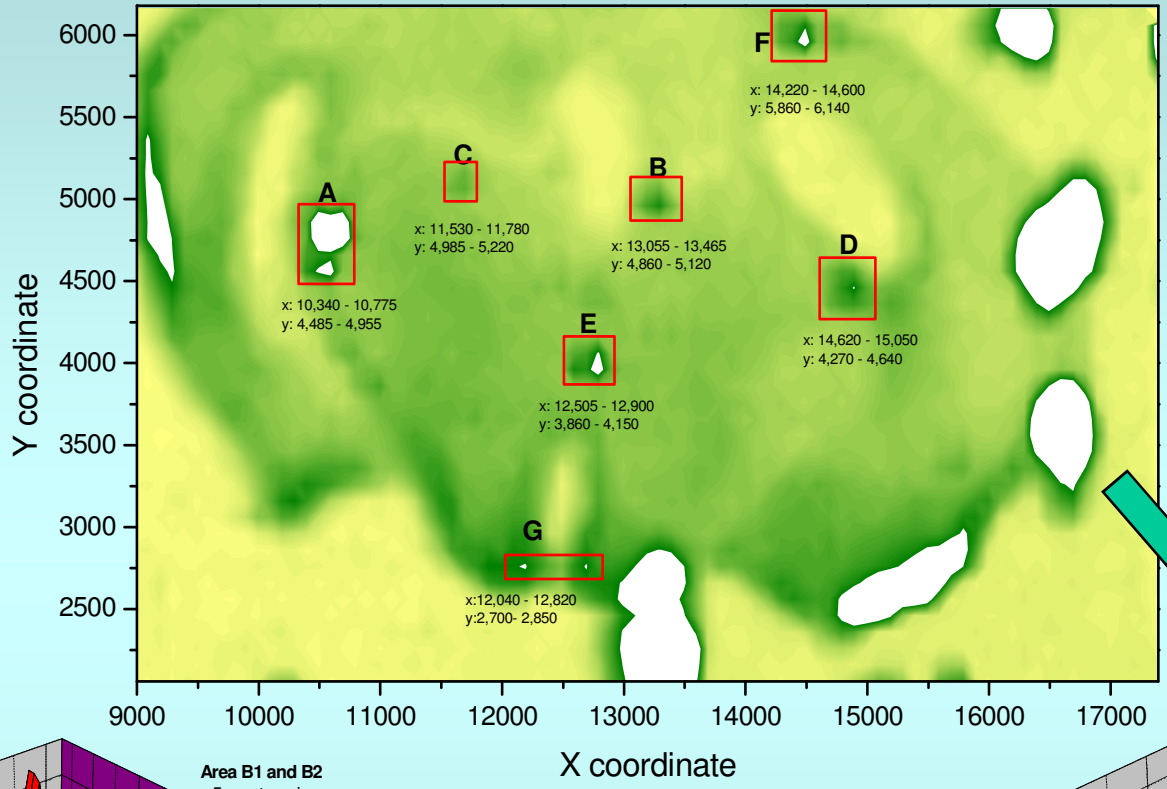




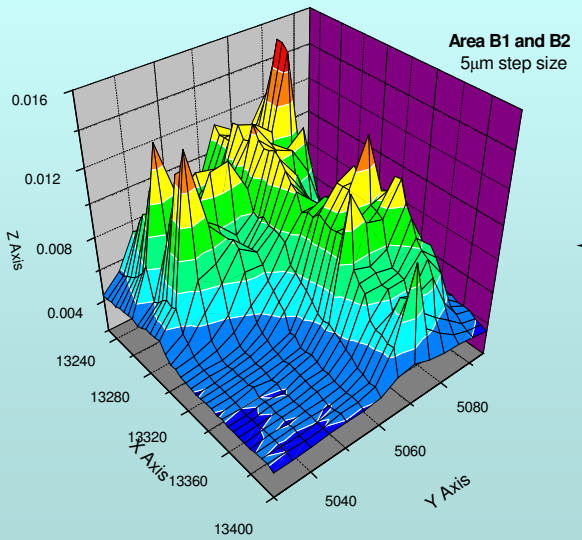


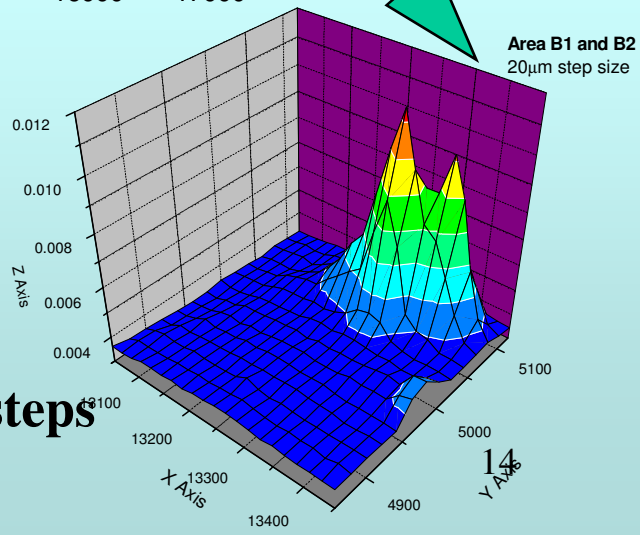


Transgenic R6/2 mouse brain tissue



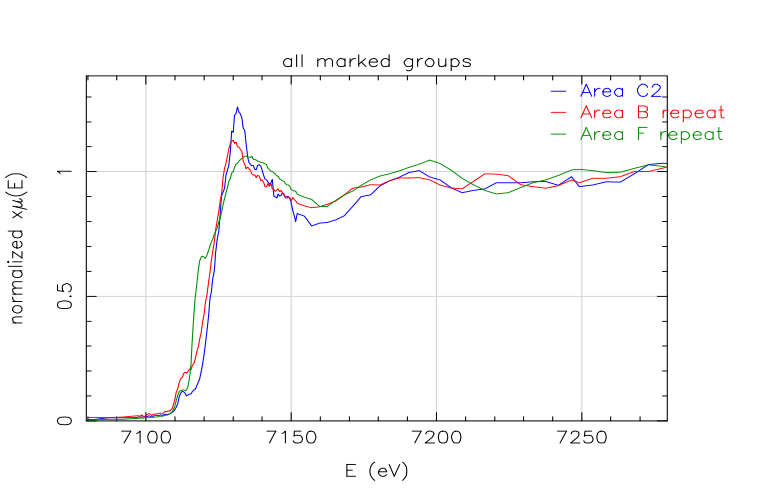
100µm steps

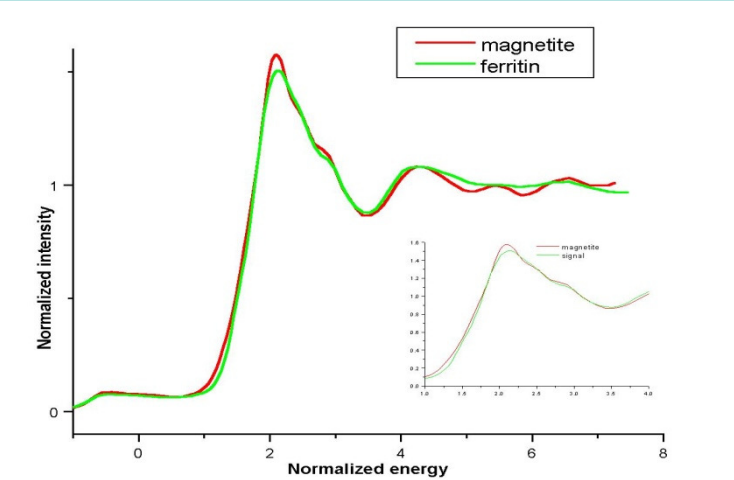


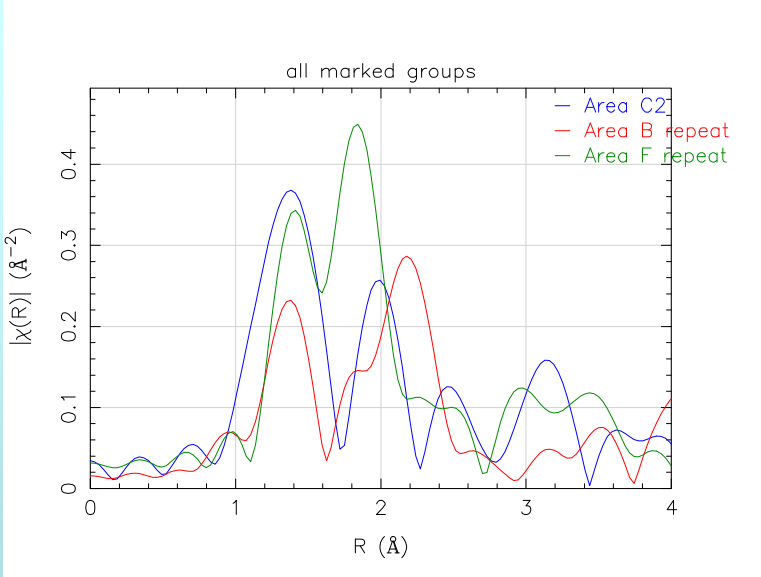


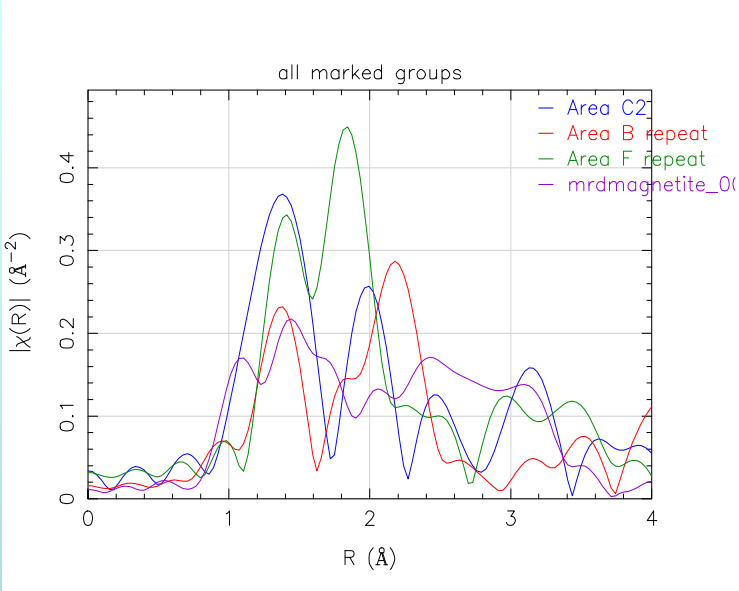
5µm steps 20µm steps

XAFS Collected Spectra Comparison with Magnetite

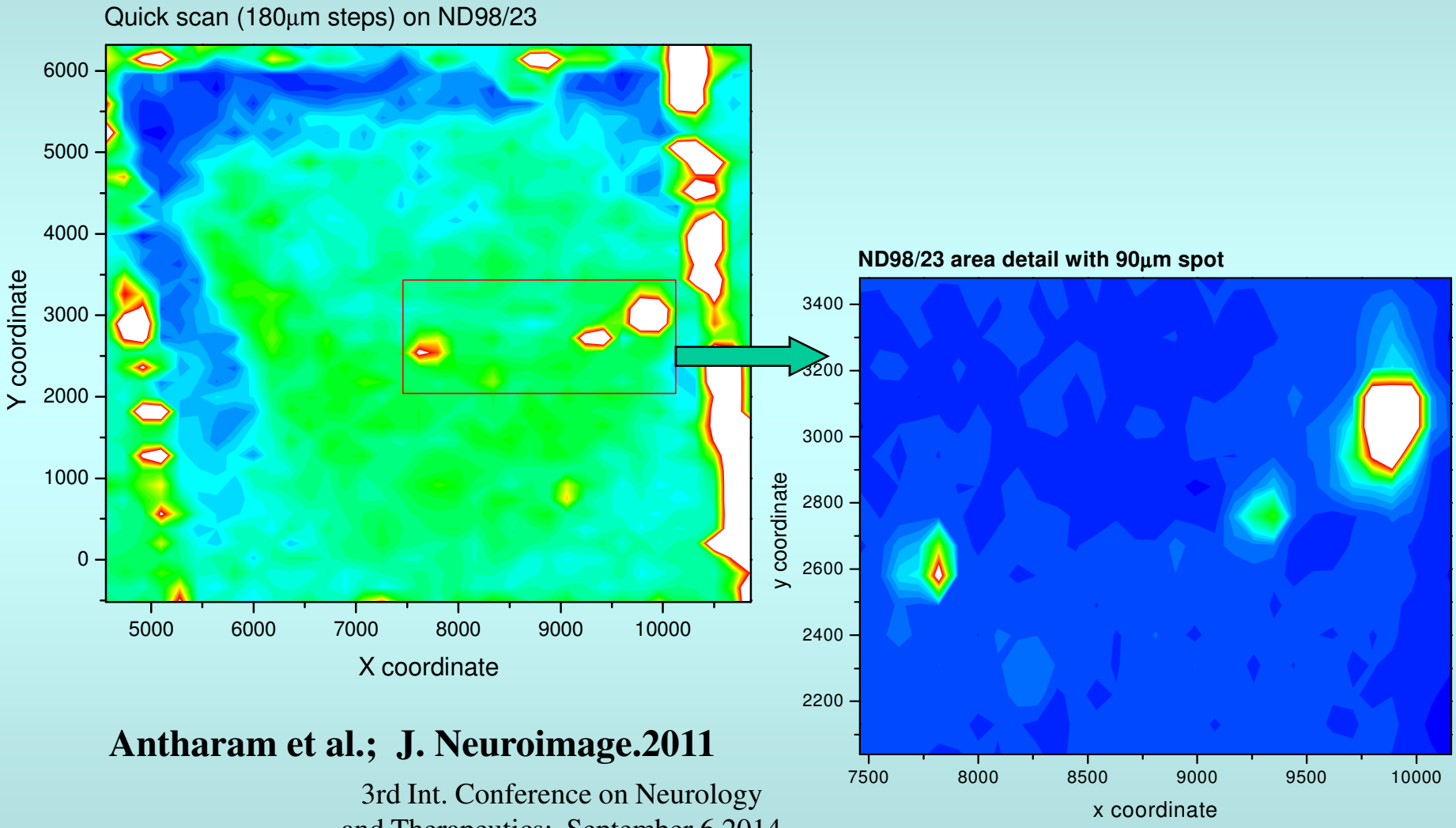








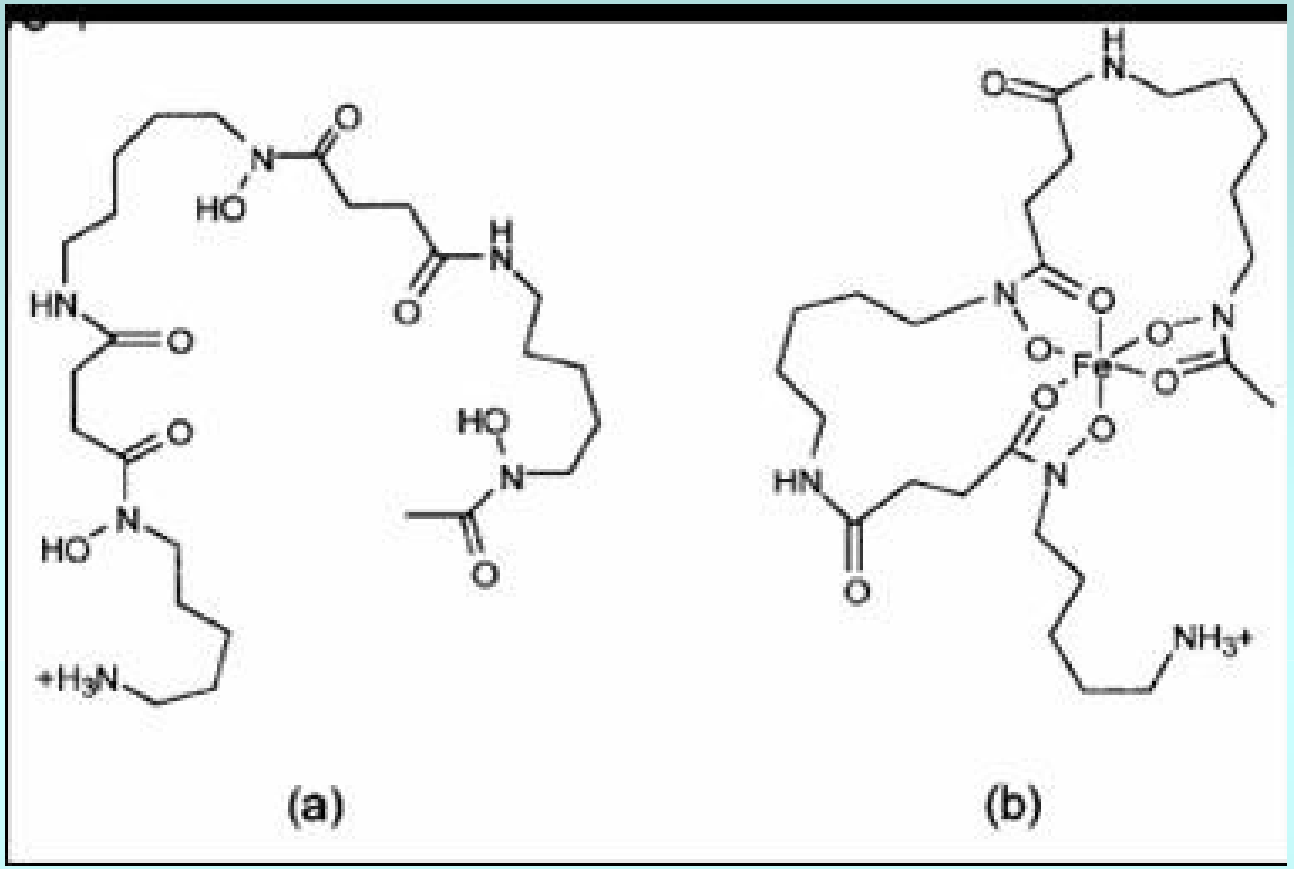
Human non-demented brain tissue



Antharam et al.; J. Neuroimage.2011

Use chelation to remove or deactivate?

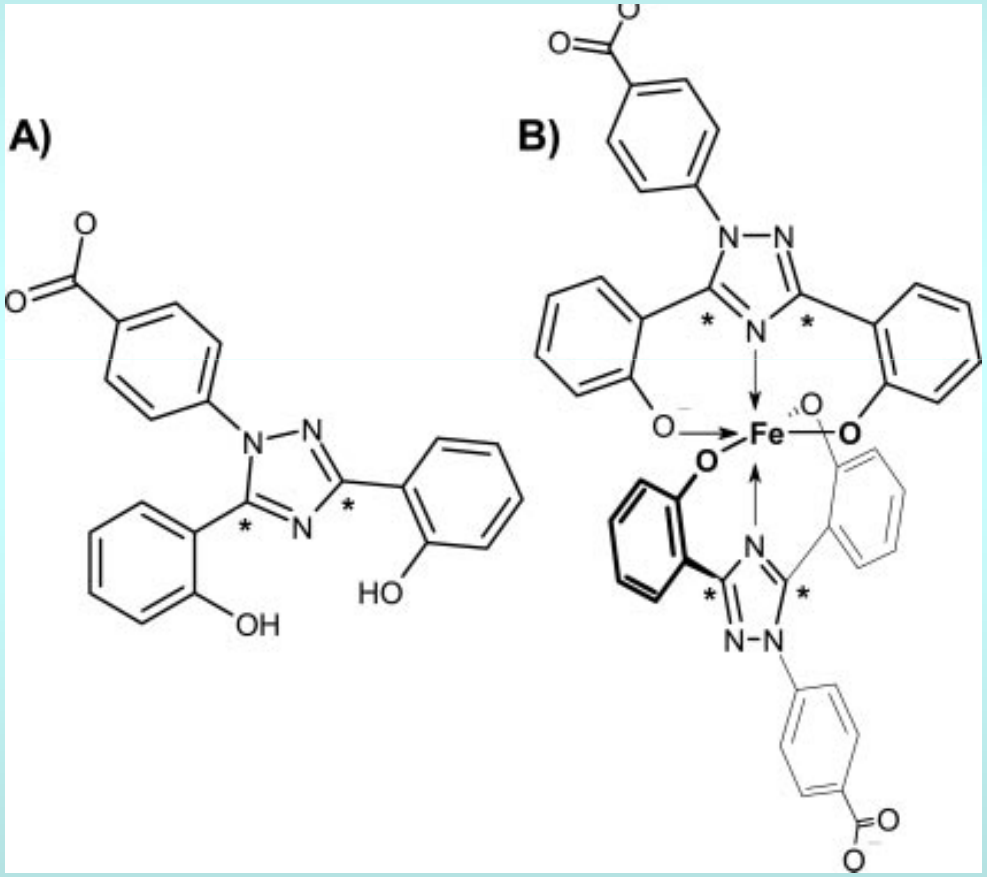
- i.v.
- Oral medications?
- Dietary?



Deferoxamine (injectable)

http://blog.daum.net/shchang425/17042100

Exjade (Novartis' desferisirox)

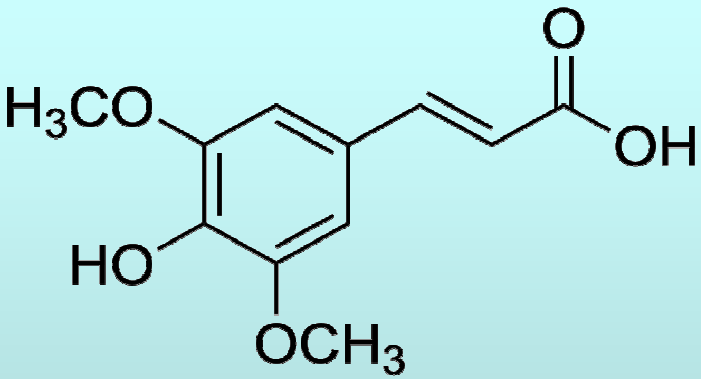


FDA cleared In 2005. First oral iron chelator for daily use.

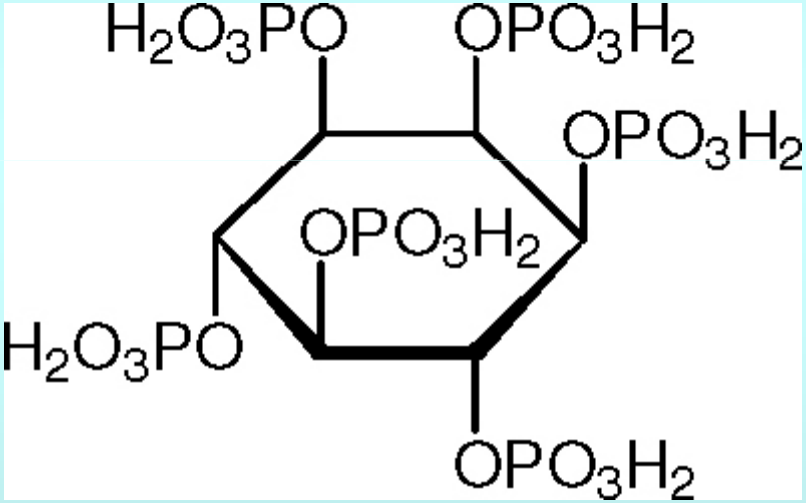
Weiss et al. DRUG METABOLISM AND DISPOSITION 34:971–975, 2006

Natural dietary products?

- Curcumin (curry)
- Tannins (apples)
- Resveratrol (wine)
- Phytic acid (brown rice)
- Sinapic acid (wine)

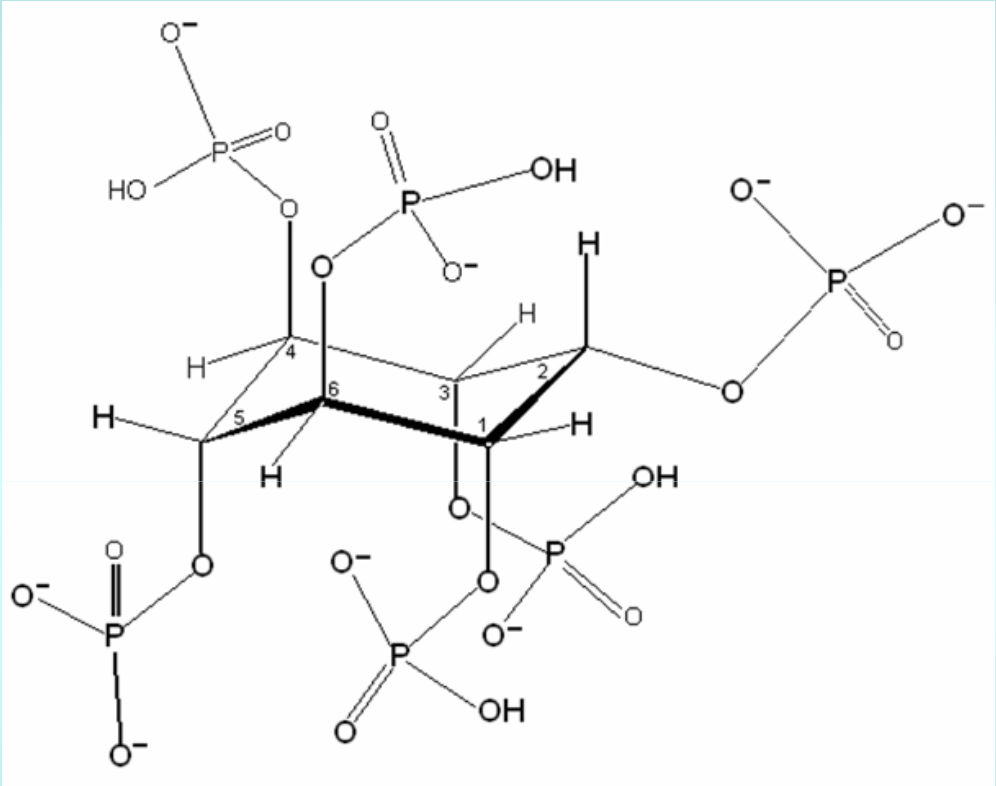


Myo-Inositol hexaphosphate (IP-6, phytic acid)



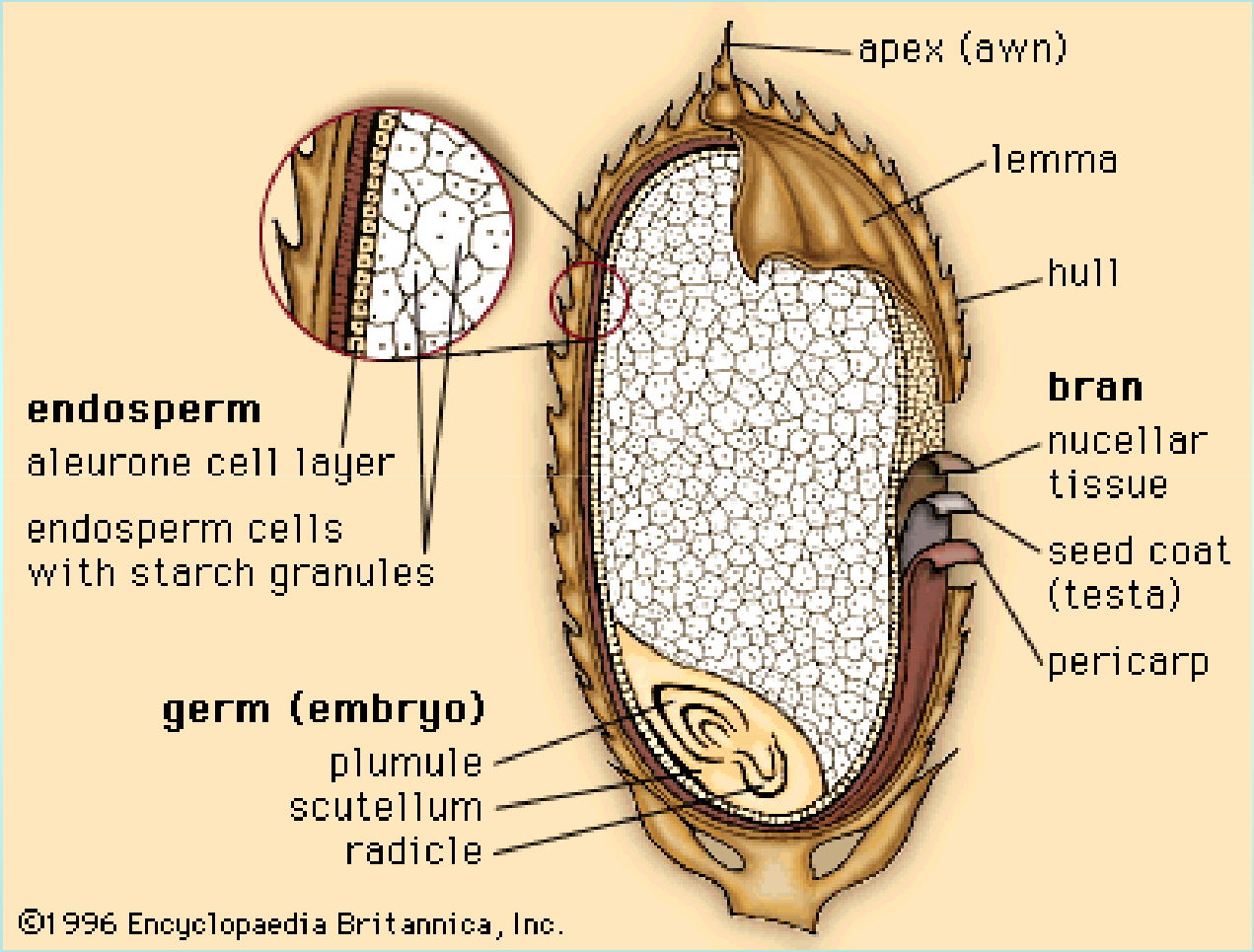
http://www.answers.com/topic/phytic-acid

Can have axial conformation



http://www.kitchenstewardship.com/2010/02/18/exploring-soaking-grains-what-are-phytates-and-phytic-acid/

common in brown rice (1-3%)



Most IP-6 is removed making white rice



http://projectfidgetyfingers.blogspot.com/2010/10/brown-rice-vs-white-rice.html

Two often mentioned problems:

- “Phytic Acid is an anti-nutrient and removes ions such as zinc, and causes nutritional deficiency.”

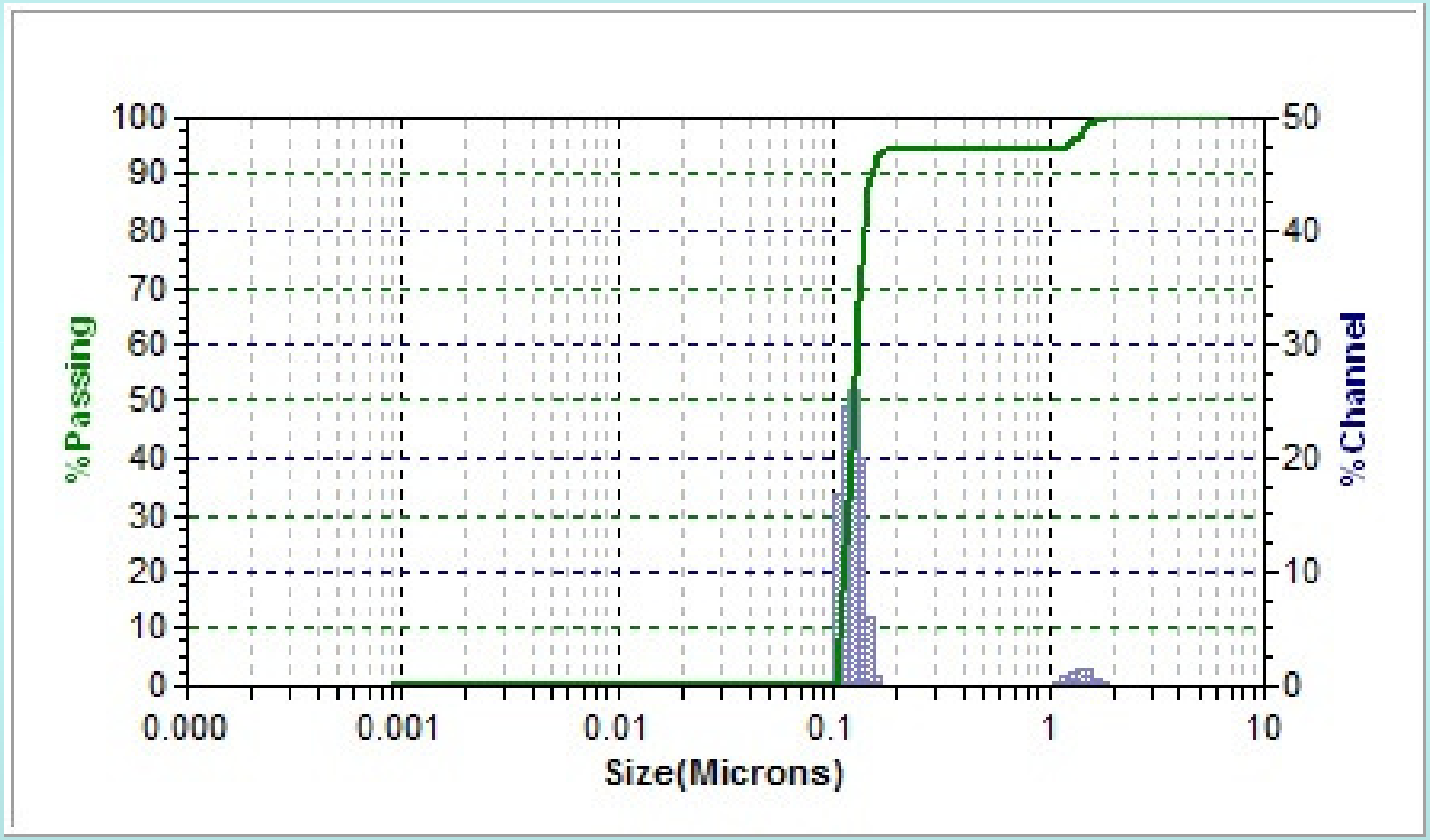
- “A highly ionic molecule such a phytic acid will not be absorbed in the gut.”

However…

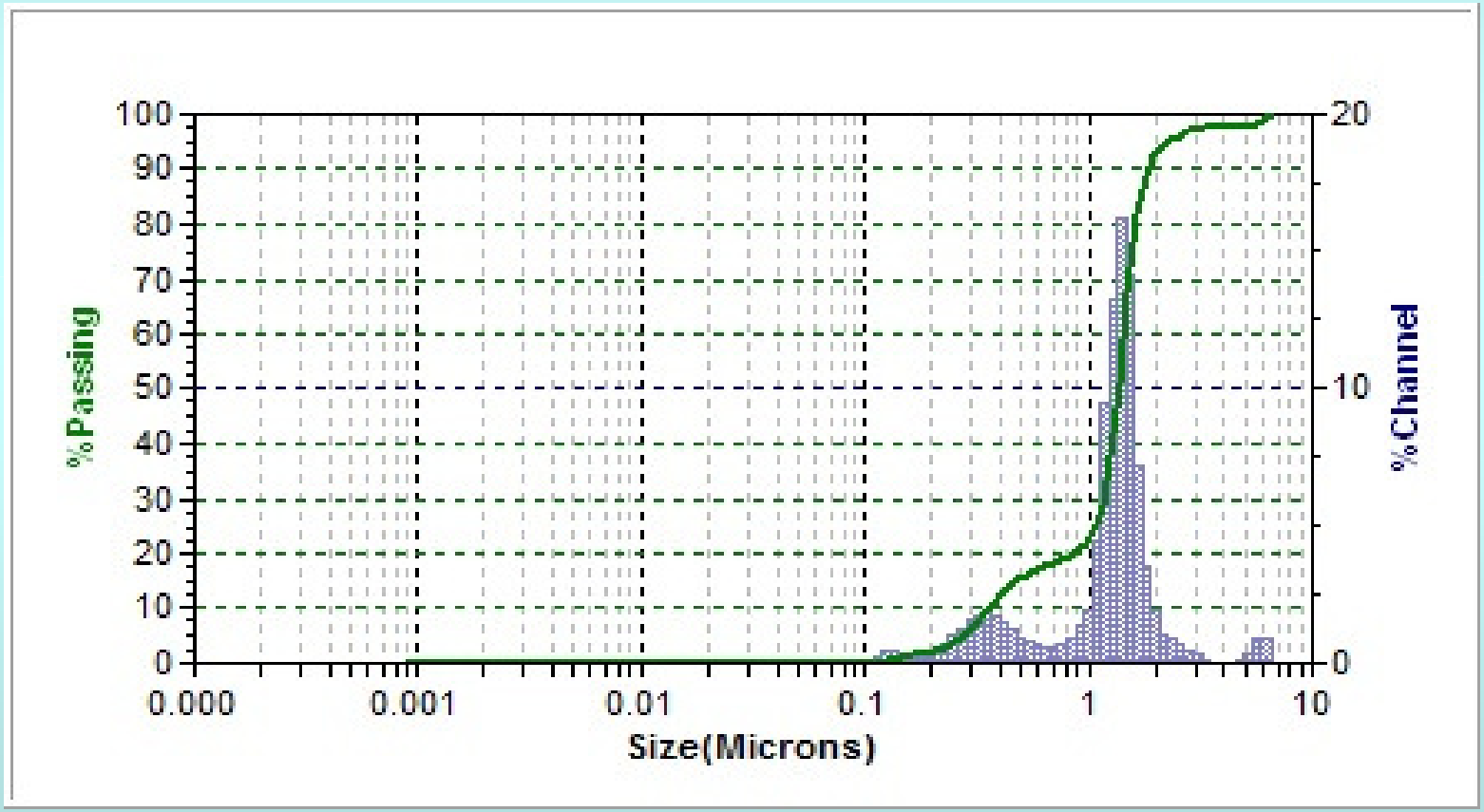
- Only in areas with very poor mineral nutrition is removal of Zn or other metal ions a problem, and not in the US.

- Several studies have shown phytic acid can cross cell membranes by complexion with lipids or other ions. Nanoparticles?

Particle size of PA (number average)



Particle size of PA (Weight average)



2011 paper by Anekonda et al.

- Cell culture, PA reduced A-beta oligomer damage.
- Murine model of AD showed no change in Cu, Fe or Zn levels with PA in water
- Improved
  - Oxidative damage (less)
  - Mitochondrial function (more)
  - Autophagy
  - A-beta plaques (reduced)

“Need to do a clinical study”

- CTSI goal is to promote clinical studies.
- PA is available at health food stores over the counter.
- Not expensive (c. $20/month)

Bottom lines….

- IND application should go to the FDA "approved"
- Six month study of 20 patients
- Outcomes: mental test decline (vs. historical control)
- Will include MCI (mild cognitive impairment)

Thank you!

- Questions?