Chelation Therapy
&
Chelating Agents in Medicine

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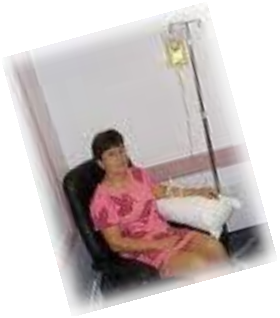
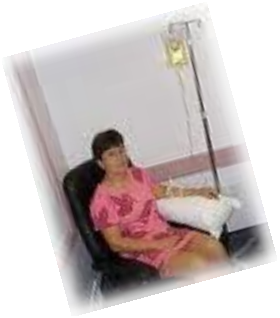
Chelation Therapy



http://www.freewebs.com/eclectives/messtoons.htm

Chelation Therapy



http://www.freewebs.com/eclectives/messtoons.htm

Chelation for Coronary Heart Disease: What You Need To Know

Heart disease is the leading cause of death among both men and women in the United States. Coronary heart disease is the most common type of heart disease and is responsible for more than 370,000 deaths each year. Treatments include lifestyle changes (such as following a heart-healthy diet and quitting smoking), medicines, and medical procedures such as angioplasty.

Some heart disease patients also seek out chelation therapy using disodium EDTA (ethylene diamine tetra-acetic acid), a controversial complementary health approach. This page describes chelation for coronary heart disease and the research done on it, including two large studies funded by the National Institutes of Health (NIH).

What is chelation?

Chelation is a chemical process in which a substance is used to bind metals or minerals so they can be excreted from the body. Chelation has uses in conventional medicine, such as treating iron overload or severe lead poisoning. When it’s used as a complementary treatment for heart disease, a health care provider administers a solution of disodium EDTA in a series of infusions through the veins. A course of treatment can require 20 to 40 weekly infusions lasting several hours each. Patients also typically take high-dose pills of vitamins and minerals.

Is chelation for heart disease approved by the U.S. Food and Drug Administration (FDA)?

No. The use of EDTA chelation for heart disease has not been approved by the FDA.

As discussed below, a large-scale study of EDTA chelation for heart disease in people who have had a heart attack and who also have diabetes is currently in progress. When the study is completed, the FDA may use its results to help make a decision about whether to approve the use of EDTA chelation therapy for this purpose.

What has research shown about chelation for coronary heart disease?

One large-scale study of chelation for coronary disease has been completed: the Trial to Assess Chelation Therapy (TACT), sponsored by the National Center for Complementary and Integrative Health (NCCIH) and the National Heart, Lung, and Blood Institute.

The 1,708 people who participated in TACT were age 50 or older and had had at least one heart attack. They were randomly assigned to receive 40 treatments with EDTA or a placebo, plus either high-dose vitamins and minerals or placebo pills, and they did not know which treatment they were receiving.

Overall, chelation therapy produced a modest reduction in cardiovascular events. However, further analysis showed that the beneficial effect occurred only in people with diabetes.

People with diabetes, who made up about one-third of the participants, had a 41 percent overall reduction in the risk of any cardiovascular event; a 40 percent reduction in the risk of death from heart disease, nonfatal stroke, or nonfatal heart attack; a 52 percent reduction in recurrent heart attacks; and a 43 percent reduction in death from any cause over a period of about 5 years.

The high-dose vitamins and minerals didn’t reduce cardiovascular events, but they appeared to be safe. However, the researchers couldn’t be completely certain about these conclusions because many people stopped taking their vitamin/mineral or placebo pills or dropped out of the study. When all four study groups (those receiving chelation treatments plus vitamins/minerals, chelation treatments plus placebo pills, placebo treatments plus vitamins/minerals, or placebo treatments plus placebo pills) were compared, the group receiving chelation plus vitamins/minerals had the fewest cardiovascular events and the group receiving placebo treatments and placebo pills had the most.

Further research is needed to fully understand the TACT results. Since this is the first clinical trial to show a benefit of chelation, these results are not, by themselves, sufficient to support the routine use of chelation as a post–heart attack therapy in people with diabetes.

History of Chelation Therapy

- EDTA the chelation agent developed in Germany during WW-II as a substitute for citric acid*, because supplies were scarce.
- Brought to the US in 1947.
- 1950s-Determined effective especially with lead detoxification
- 1960- current- toxicologists begin testing chelation therapy with CAD patients

*The development of deep-tank fermentation by Pfizer —– which enabled the mass production of penicillin for use in World War II —– was designated a National Historic Chemical Landmark by the American Chemical Society (ACS) in a special ceremony in Brooklyn, N.Y., on June 12, 2008.

Citric acid is a key ingredient in foods and beverages —– notably soft drinks. It is a natural preservative that adds a pleasantly acidic or sour taste. Charles Pfizer & Co had made citric acid the traditional way since 1880: from unripe citrus fruit, mainly imported from Italy, but World War I interfered with the supply. In 1917 Pfizer hired James Currie, a food chemist, who had the daring idea of producing citric acid without using citrus. Currie knew that fermentation of a fungus, or mold, called *Aspergillis niger* could convert sugar into citric acid. Currie also understood that *Aspergillis niger* is aerobic, meaning it needs air to grow.

Chelates help in:

- **Removing undesirable metals from the body**
- **Reversing the process of atherosclerosis**
- **Improves cerebro vascular arterial occlusion**
- **Improves memory, concentration, and vision**
- **Reversal of gangrene**
- **Restoration of memory**
- **Prevents and reverses problems of degenerative diseases**
- **Arthritis, scleroderma, and lupus**
- **Radiation toxicity**
- **Snake venom poisoning**
- **Digitalis intoxication**
- **Cardiac arthymia**

Freeman, S. K. (2007). *The Complete Guide to Autism Treatment.* Lynden, WA: SKF Books USA, Inc.

How a Chelating Agent Works

When there is a toxin in your body like mercury or lead a chelating agent is needed to bind to the toxin. Once the heavy metal has made an ionic bond with the chelating agent your body can eliminate it. It does this via the excretory system, generally the renal system. Basically you pee it out. There are a lot of things on the market claiming to be chelating agents when in fact they are very poor chelators.

Coordination Equilibria & Chelate effect

"The adjective chelate, derived from the great claw or chela (chely - Greek) of the lobster, is suggested for the groups which function as two units and fasten to the central atom so as to produce heterocyclic rings."

***J. Chem. Soc.*, 1920, 117, 1456**

The chelate effect or chelation is one of the most important ligand effects in transition metal coordination chemistry.

Coordination Equilibria & Chelate effect

$$[Fe(H_2O)_6]^{3+} + NCS^- \rightarrow [Fe(H_2O)_5(NCS)]^{2+} + H_2O$$

$$K_f = [Fe(H_2O)_5(NCS)]^{2+} / [Fe(H_2O)_6]^{3+}[NCS^-]$$

Equilibrium constant $K_f \Rightarrow$ formation constant

$$M + L \rightarrow ML \quad K_1 = [ML]/[M][L]$$

$$ML + L \rightarrow ML_2 \quad K_2 = [ML_2]/[ML][L]$$

$$ML_2 + L \rightarrow ML_3 \quad K_3 = [ML_3]/[ML_2][L]$$

$$ML_{n-1} + L \rightarrow ML_n \quad K_n = [ML_n]/[ML_{n-1}][L]$$

- $K_1, K_2 \ldots \Rightarrow$ Stepwise formation constant.
- To calculate concentration of the final product, use overall formation constant β_n:
  - $\beta_n = [ML_n]/[M][L]^n$
  - $= K_1 \times K_2 \times K_3 \times \ldots \times K_n$

Chelating agents

(1) Used to remove unwanted metal ions in water.

(2) Selective removal of Hg^{2+} and Pb^{2+} from body when poisoned.

(3) Prevent blood clots.

(4) Solubilize iron in plant fertilizer.

Common Uses of Chelation Therapy

- Chelation therapy has primarily been used as agent to detoxify heavy metals such as calcium, iron, magnesium, lead and zinc.
- EDTA binds to these metal ions because of its strong affinity for cations.
- The bound metal ions are then excreted in the urine.

Toxicities Related to Chelation Therapy

- Chelation therapy must be used with supplementation of calcium
- There have been a few deaths recorded related to hypocalcemia as a result of chelation therapy

  -stroke- calcium facilitates the conversion of prothrombin - > thrombin

  -heart attacks – calcium helps to regulate heartbeats

Chelating Agents in Medicine

Definition

A chelating agent is an organic compound in which two or more electron donor groups, themselves bound by a chemical linkage, co-ordinate with a polyvalent metal, the resultant co-ordination compound having a ring structure.

Ideal chelating agents show:

- More affinity for metals than endogenous ligand
- High solubility in water
- Resistance to biotransformation
- Form non-toxic complexes with toxic metals
- Accelerate mobilization and/or removal of the metals
- Cheap and easy to administer
- Easy excretion of chelating complex

Chelating Agent (different metals)

Dimercaprol (British antilewisite) or BAL – As, Au, Bi, Ni, Sb and Hg poisoning

Dimercaptosuccinic acid (succimer) – Pb

Calcium disodium edetate (EDTA) – lead poisoning

Penicillamine – Cu, Pb, Hg, Zn

Desferrioxamine B – Iron overload

Deferiprone = Iron

Chelating Agent (different metals)

EDTA - Lead

Dimercaprol - Arsenic, Copper, Mercury

Succimer – Lead, Arsenic , Mercury

Trientine - Copper

Deferrioxamone - Iron

BAL or Dimercaprol

- World War-II as anti-Lewisite
- Oily, pungent smelling, viscous liquid, water insoluble

Pharmacological actions :

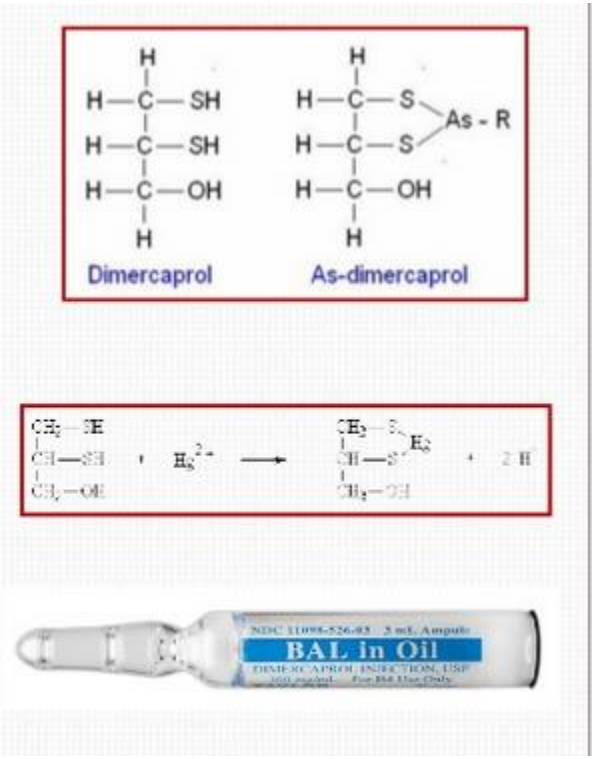
- Heavy metals like As, Hg, Au, Bi, Ni Sb and Cu etc. attacks (-SH) an important component of CoA and prevents formation of acetyl CoA leading to disaster- BAL binds with these Metals and protects CoA
- 1:1 Vs 2:1 Complex (more stability)- excess amount is required party metabolized in the body
- BAL is oxidized in the body
- Alkalinazation of urine is required –in acid urine complex dissociates faster
- However dose dependent toxicity – no large dose at time

BAL or Dimercaprol

Uses :

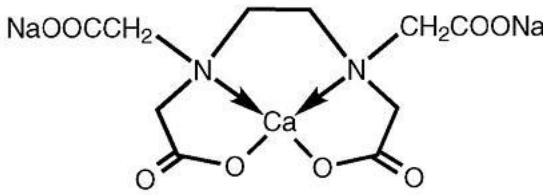
Poisoning by As, Hg, Au, Bi, Ni, and Sb etc.

- **Dose :** Given 1/M in 10 % solution in oil-Available as 2 ml ampoules (50 mg/ml)
- Given deep 1M 5mg/Kg stat every 4 Hrly for 2 days followed by increase in interval after 3 days



Calcium disodium edetate ($CaNa_2EDTA$)

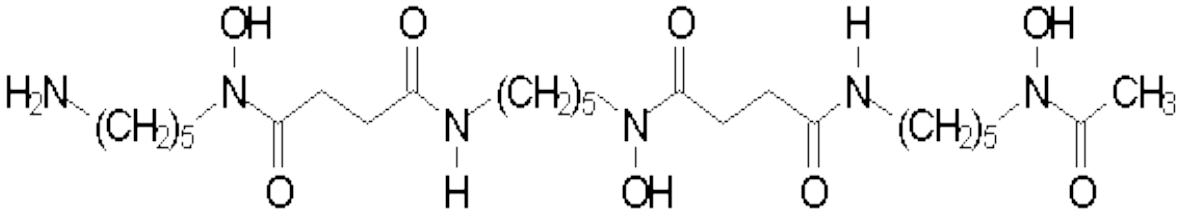
- **Calcium chelate of Na_2EDTA** is used clinically instead of Na_2EDTA – ethylene diamine tetracetic acid
- High affinity for Pb, Zn,Cd, Mn, Cu and some radioactive metals
- **MOA :** Removes the metals by exchanging with Ca^{++}
- Highly ionized – not absorbed orally and that's why acts extracellularly – rapidly excreated via kidney
- Given IV as not absorbed in gut – IM is painful
- No CSF penetration



Uses :

- Lead Poisoning – 1 gm is diluted in 200-300 ml of NS infused over 1 hr twice daily -2 course repeated after 1 week
- Fe, Zn, Cu and Mn poisoning – but not in Hg poisoning

Desferrioxamine (Acute Iron Poisoning)



- Ferrioxamine – an Iron containing compound – Actinomycetes
  - Chemical removal of Iron – desferrioxamine
  - 1gm = 85 mg of elemental iron

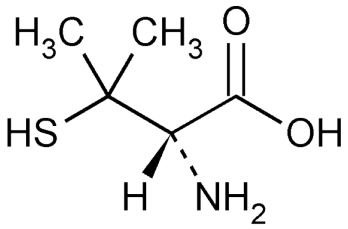
- **MOA :** Desferrioxamine binds with ferric Iron – stable non- toxic compound
  - Also removes Iron (loosely bound) from haemosiderin and ferritin, but not Hb and Cyt
  - Low Ca^{++} affinity

Uses: SC or IV (o.5 gm / vial)

1. **Acute Iron poisoning**
2. **Transfusion siderosis : -- 0.5- 1 gm/day SC or with Blood transfusion 2 gm / unit of blood**

Penicillamine

- Degraded product of Penicillin (beta dimethylcysteine)
- Prepared by alkaline hydrolysis of bezyl penicillin-d- penicillamine
- Strong Cu chelating property – useful in Cu poisoning
- MOA is same as others – selective chelating of Cu, Hg, Pb and Zn
- Absorbed orally – available as 250 mg capsules, metabolized in liver and excreted in urine



Uses:

- Wilson's disease hepatolenticular degeneration due to genetic deficiencty of ceruplasmin (Cu deposition in body) – life long therapy (0.5 – 1 gm daily)
- Cu and Hg (alternate) Poisoning
- Chromic Pb poisoning (adjuvant to edetate)
- Cystinuria and cystine stones

Iron Chelation Basics

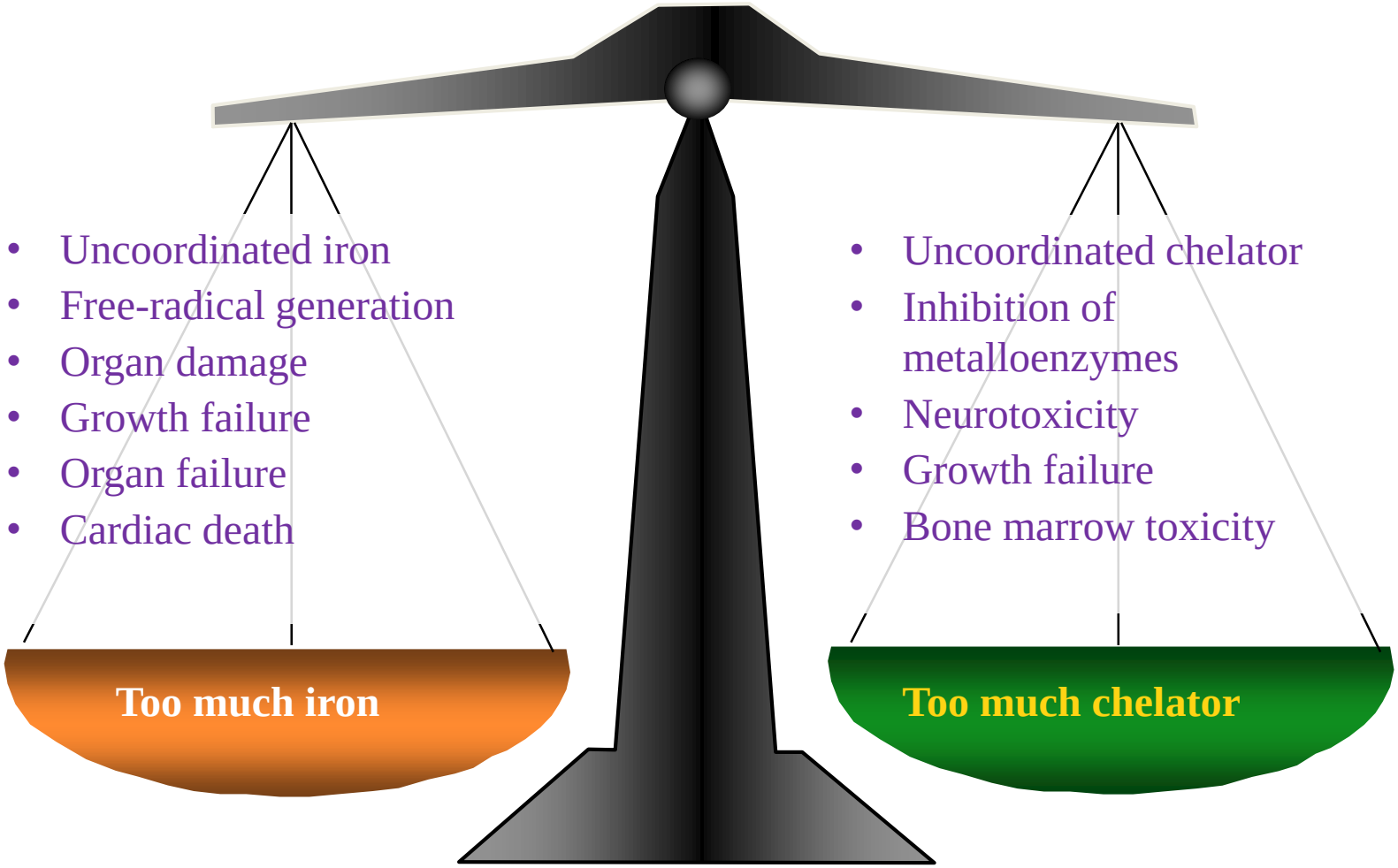
Goals of Chelation Treatment

- Iron balance with “safe” tissue iron levels
  - 0.4–0.5 mg/kg day excretion[1]
  - Slow process[2]
  - Finite chelatable iron pools[2]
  - Prevention of heart and endocrine damage
- Detoxification of iron
  - Extracellular (NTBI)
  - Intracellular (LIP)
  - Iron-chelate complex

NTBI = non–trasnsferrin-bound iron; LIP = labile iron pools.

1. Porter J. *Hematol/Oncol Clinics*. 2005;19:7.
2. Porter JB. *Am J Hematol*. 2007;82:1136.

The Challenge of Iron Chelation—A Question of Balance



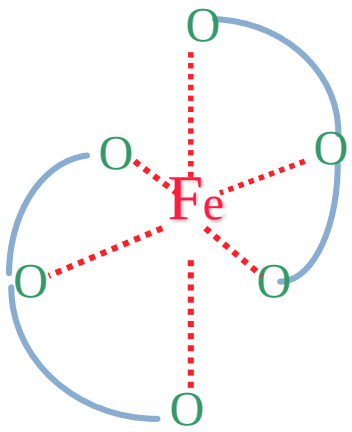
Properties of an Ideal Chelator

- To control body iron
  - High chelating efficiency
  - High and specific affinity for Fe3+
- To minimize iron toxicity
  - 24-hour coverage
  - Slow metabolism and elimination rate
  - Good tissue penetration with stable iron complex
- Acceptable toxicity-efficacy profile
  - Clear drug-dose relationship to efficacy and toxicity
  - No iron redistribution
- Simplicity and ease of monitoring
- Patient acceptance/compliance
  - Oral bioavailability
  - Suitable for monotherapy

How Chelators Bind Iron

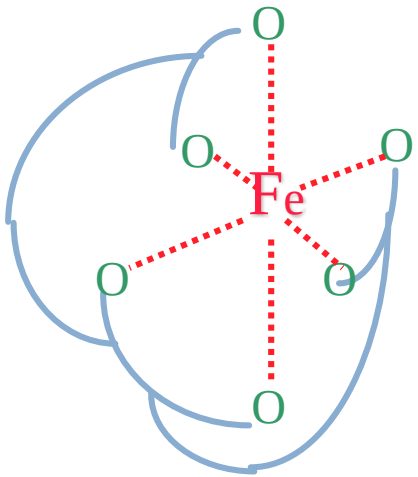
Deferasirox (DFS)

Tridentate



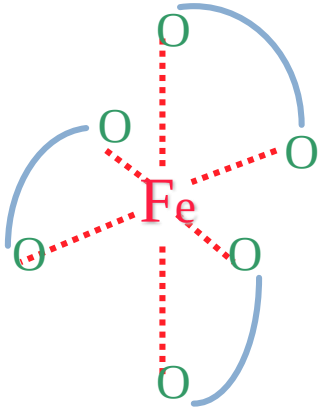
Desferrioxamine (DFO)

Hexadentate



Deferiprone (DFP)

Bidentate



Adapted from Porter JB, et al. *Baillieres Clin Haematol*. 1989;2:257.

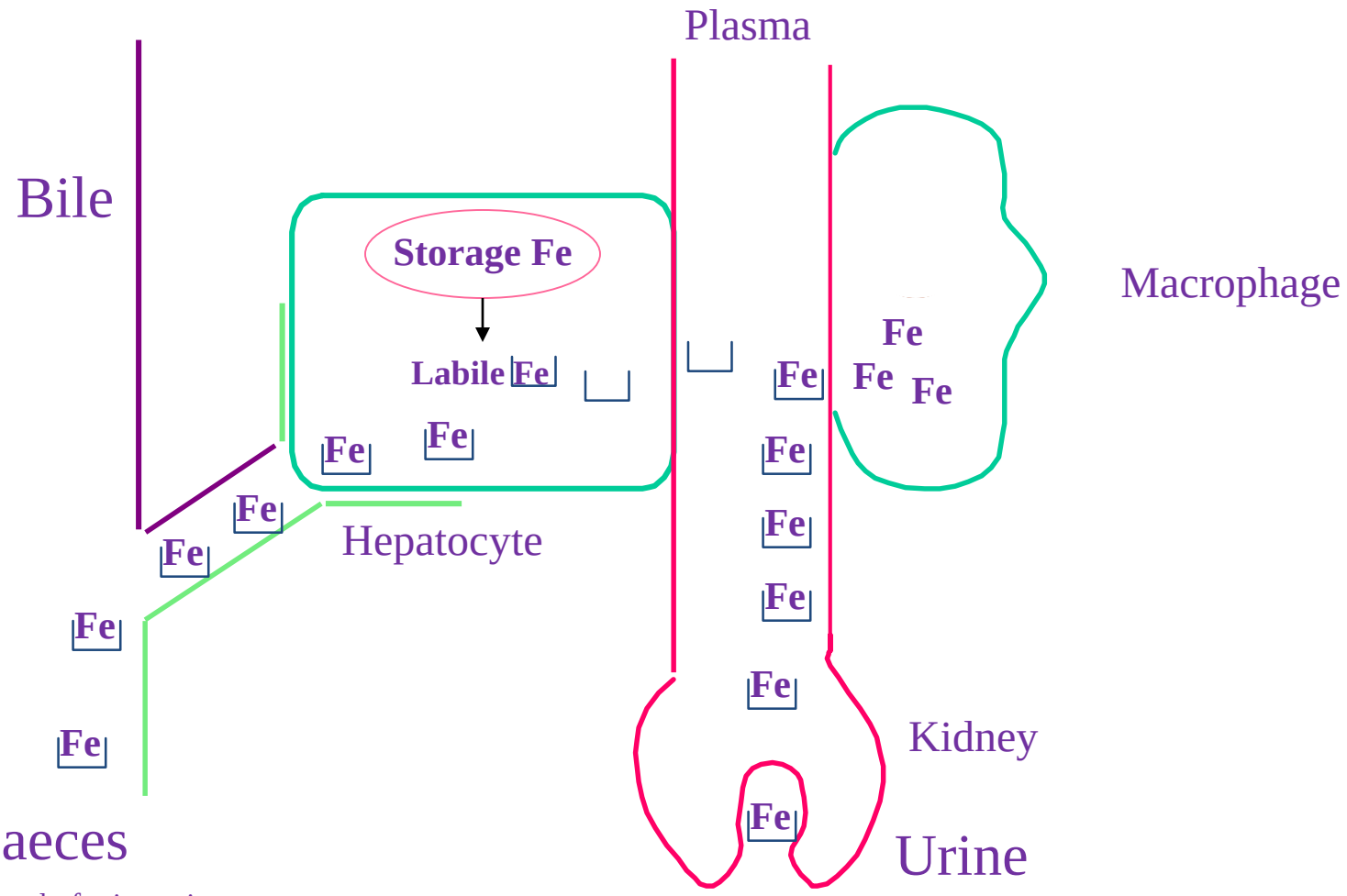
Chelatable Iron Pools

- For iron balance
  - Plasma iron turnover pools
  - Intrahepatic pools
- For iron detoxification
  - Plasma iron toxic pools (NTBI)
  - Intraparenchymal iron toxic pools

    eg, heart, liver, endocrine, joints

NTBI = non–transferrin-bound iron.

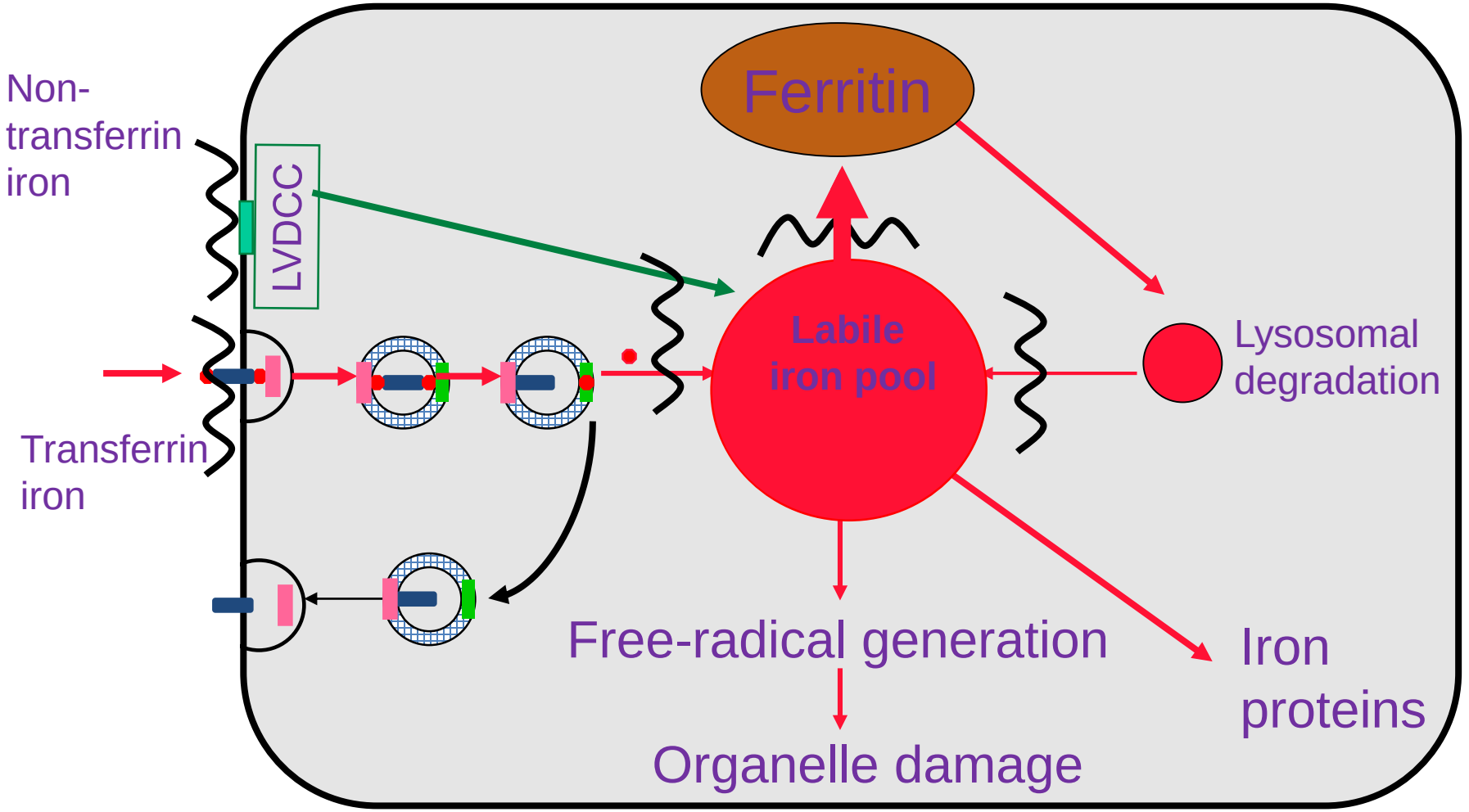
Chelatable Pools and Excretion Pathways with DFO



DFO = desferrioxamine.

With permission from Cohen AR, Porter JB. In: Steinberg MH, et al, editors. *Disorders of hemoglobin: genetics, pathophysiology, and clinical management*. Cambridge: Cambridge University Press; 2001.

Decreasing Cellular Toxicity with Chelators



LVDCC = L-type voltage-dependent calcium channel.

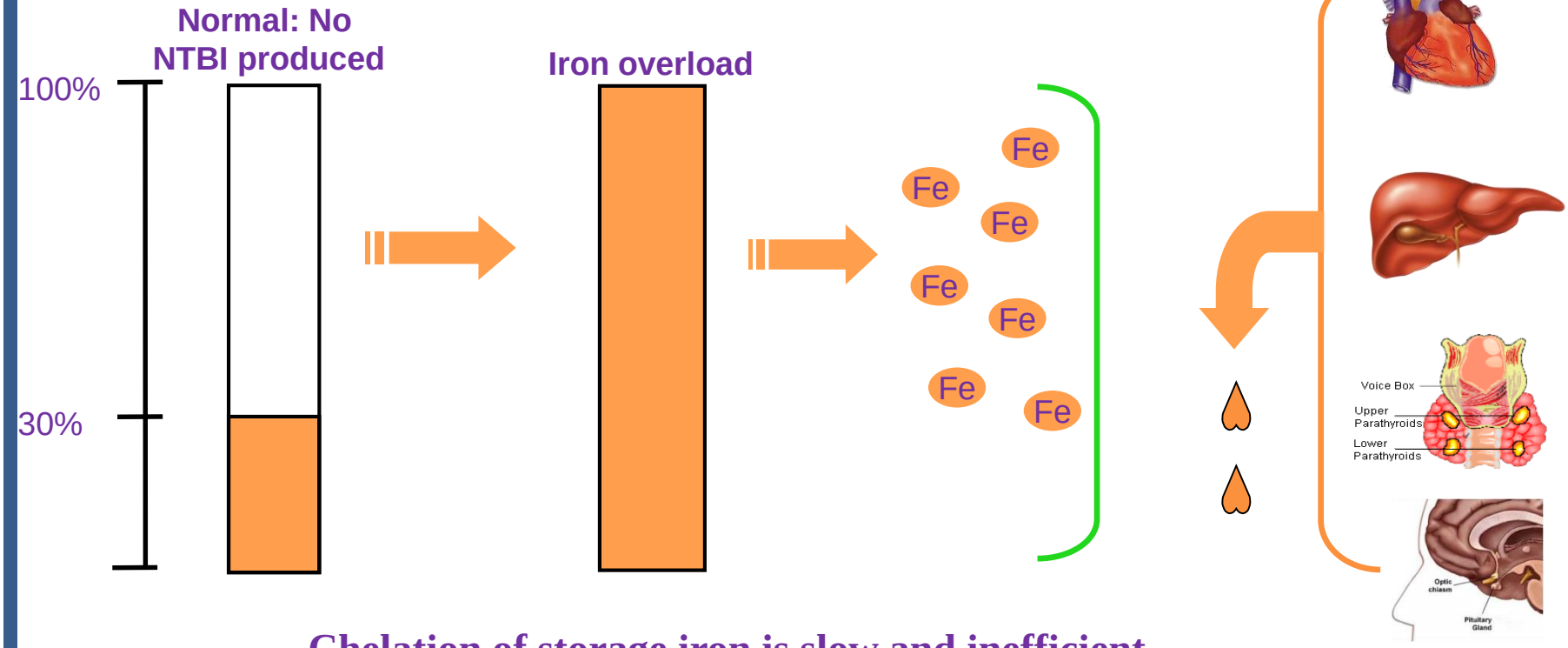
With permission from Porter JB. *Am J Hematol*. 2007;82:1136.

Chelatable Iron Pools *Prevention of Accumulation More Efficient than Removal of Stored Iron*

Transferrin saturation occurs due to frequent blood transfusions

Subsequent formation of NTBI in plasma

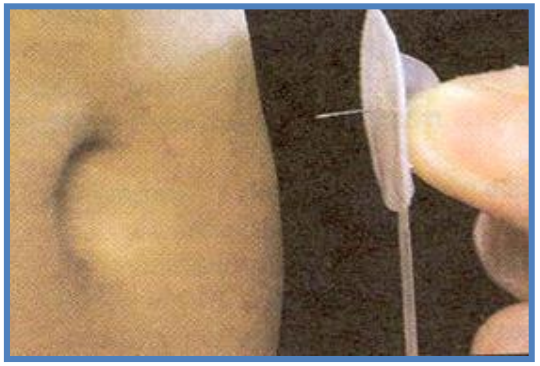
Uncontrolled iron loading of organs, such as:

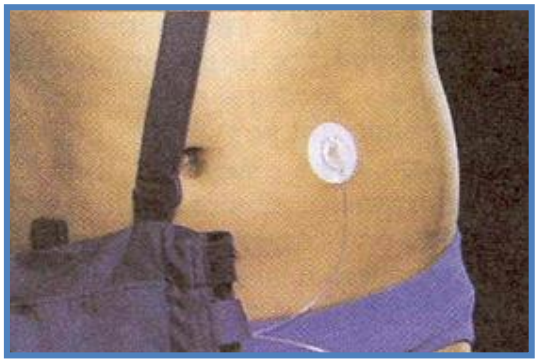


Chelation of storage iron is slow and inefficient

Desferrioxamine Therapy for Iron Overload

- Available for > 3 decades with improving survival
- Hexadentate molecule not absorbed from gut
- Short half-life (20 min), so must be given by continuous infusion
  - 8 –12 h/d, 5 – 7 d/w (40–50 mg/kg SC)
- Commenced after 15–20 transfusions or when ferritin >1000 µg/L
- Audiometric, retinopathic, and growth effects at high doses and low iron loading
- Compliance often is poor, leading to variable outcome





Porter JB, Huehns CR. *Baillieres Clin Haematol*. 1989;2:459.

Chelation
Treatment for Autism

What is Autism?

Autism, or autism spectrum disorder (ASD), refers to a broad range of conditions characterized by challenges with social skills, repetitive behaviors, speech and nonverbal communication. According to the Centers for Disease Control, autism affects an estimated 1 in 59 children in the United States today.

We know that there is not one autism but many subtypes, most influenced by a combination of genetic and environmental factors. Because autism is a spectrum disorder, each person with autism has a distinct set of strengths and challenges. The ways in which people with autism learn, think and problem-solve can range from highly skilled to severely challenged. Some people with ASD may require significant support in their daily lives, while others may need less support and, in some cases, live entirely independently.

Several factors may influence the development of autism, and it is often accompanied by sensory sensitivities and medical issues such as gastrointestinal (GI) disorders, seizures or sleep disorders, as well as mental health challenges such as anxiety, depression and attention issues.

Indicators of autism usually appear by age 2 or 3. Some associated development delays can appear even earlier, and often, it can be diagnosed as early as 18 months. Research shows that early intervention leads to positive outcomes later in life for people with autism.

** In 2013, the American Psychiatric Association merged four distinct autism diagnoses into one umbrella diagnosis of autism spectrum disorder (ASD). They included autistic disorder, childhood disintegrative disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS) and Asperger syndrome.*

Where Did I Go For Information

Search Engines:

- Psych info, Proquest Research Library, Health Reference Center, Health Wellness Resource Center, PsychArticles, Science Digest, and Google

Search Terms:

Chelation and autism
Chelation therapy
Thimerosal and autism
Mercury and autism
Alternative Therapies and autism
Autistic Spectrum Disorders (ASD)
Autism Treatments
Vaccines and autism
Developmental Disabilities

Other: Dan Doctors, CDC, FDA, American Cancer Society, American Heart Association

Relationship to Autism

The theory is that heavy metals have accumulated in the child's system and detoxification of these heavy metals (mercury) will improve symptoms.

One source of mercury is thought to be timerosol in vaccines

Therefore, if the mercury is removed from the body, the symptoms will improve

Mehl-Madrona, L., (2010). Detoxification for Heavy Metals as a Treatment for Autism. Retrieved October 10, 2010 from http://www.healing-arts.org/children/detoxification.htm

Relationship to Autism

Chelation → Approved for use with individuals that tested through blood tests to have lead arsenic, or mercury poisoning .

Heavy Metal = **Mercury**

Mercury → **Vaccines**

Vaccines → **Autism**

Autism → **Chelation**

What do the "Expert" Say?

- Blood Testing – tests present level in blood
- Hair – measures excretion
- Unprovoked urine –measures excretion (recent exposure)
- Antibody Testing – glutathione (controls excretion)
- Provocation Testing – measuring excretion

Autism Research Institute . (2005). Treatment Options for Mercury/Metal Toxicity in Autism and Related Developmental Disabilities: Consensus Position Paper . Retrieved on 17 Oct 2010. http://www.autism.com/pdf/providers/heavymetals.pdf

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“Experts” - Testing

Detoxification Testing – This proves that metals were in the system and that the detoxification agent removed the metals.

Limitations

- “One major limitation of these tests is that the reference range for the urine or stool generally involves a comparison to people who are NOT taking a detoxification agent, so that even a normal person would tend to have a high result. Thus, an experienced clinician needs to interpret the results carefully.”
- “Another limitation is that low doses of the detoxification agents may fail to increase excretion significantly. It is not fully understood, but it appears that the first part of the dose may be neutralized by the body, so higher doses may be needed for provocation testing vs. long-term treatment.”
- “One complexity of provocation tests is that the detoxification agent may preferentially bind to one metal first, so excretion of that metal may hide the presence of other metals. Mercury can be tightly bound to body tissue, and it may not be removed until significant amounts of other toxic metals have been removed.”

Autism Research Institute . **(2005). Treatment Options for Mercury/Metal Toxicity in Autism and Related Developmental Disabilities: Consensus Position Paper . Retrieved on 17 Oct 2010. http://www.autism.com/pdf/providers/heavymetals.pdf**

Is Chelation Safe?

According to the American Heart Association (2010), there are serious dangers associated with Chelation therapy. EDTA can cause the following:

- kidney failure
- bone marrow depression
- shock
- low blood pressure (hypotension)
- convulsions
- cardiac arrhythmias
- respiratory arrest
- death

American Heart Association. (2010). Questions and Answers about Chelation Therapy. http://www.americanheart.org/presenter.jhtml?identifier=3000843 Retrieved 19 September 2010

Oops!

The National Institutes of Health (NIH) through the National Center for Complementary and Alternative Medicine

- funded a five-year study of Chelation therapy
- 120 children with autism four to ten years old.
- Half were to be given Chelation pills and the other half placebos.

The study was cancelled before it started

- a study of rats with elevated lead levels that received Chelation therapy displayed improved learning, attention and arousal
- they also had lasting cognitive impairment.
- The cognitive impairment was even present in rats with normal lead levels that received the Chelation therapy.

Pediatrics for Parents. Jan 2009 v25 i1 p5 (1).

Metals, Ligands and Cancer

Metals in Vivo

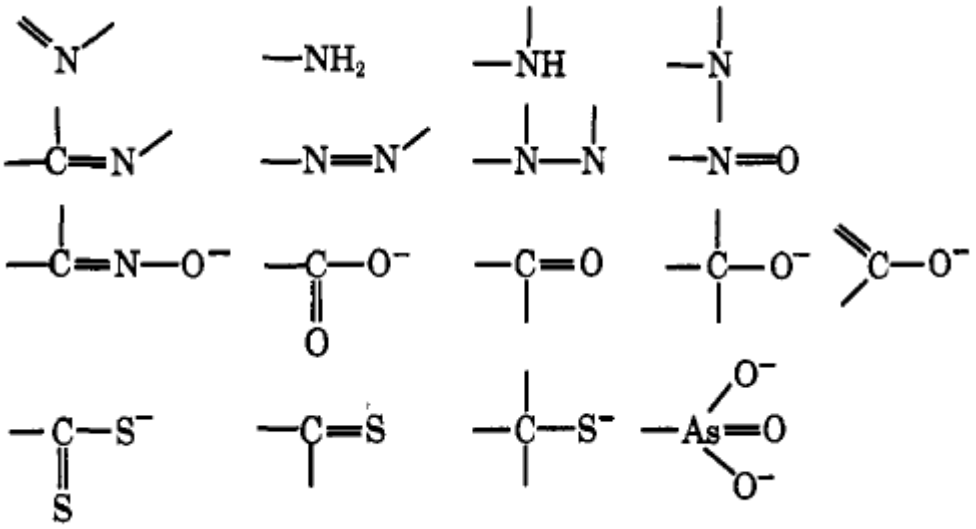
Table I

Occurrence, *in Vivo* Roles, and Complexing Characteristics of the Metals That Are Essential to Human Life[3]

	Group IA (s^1)		*Group IIA (s^2)*		*Transition series (d^{1-9})*					*Group IIB (d^{10})*
	Na	*K*	*Mg*	*Ca*	*Mn*	*Fe*	*Co*	*Cu*	*Mo*	*Zn*
Position in periodic table	Main group I		Main group II		Transition metals					Subgroup II
Biological roles	Charge-carriers and osmotic balance		Structure formation and trigger reactions		Redox catalysis and enzyme structures					Super-acid catalysts
Location	Mobile		Semimobile		Static					Static
Oxidation states	I	I	II	II	II/III	II/III	II/III	I/II	V/VI	II
Donor atoms preferred	$-O^-$	$-O^-$	$-O^-$	$-O^-$	$-O^-$	N, $-O^-$	N, $-O^-$	N, $-S^-$	$-S^-$	N, $-S^-$
Type of complexes formed	Weak		Fairly strong		Strong					Strong
Rate of exchange between free and complexed ions	Very rapid		Moderately fast		No exchange					No exchange
Grams per 70 Kg man	70	250	42	1700	<1	7	<1	<1	<1	<1
Adult: total blood concn (μM)	85,200	44,500	1570	2420	2.18	8590	0.71	14.8		138.4

Ligand Donor Groups in Vivo

A. Donor Atoms



Donor groups commonly used in modern pharmaceuticals

B. Ligand-Metal Bonding Considered Through the HSAB Approach

- The strengths of metal-ligand bonds are conveniently systematized using the theory of hard and soft acids and bases (HSAB).
- This approach assumes that all bonds between heteroatoms may be considered as having an acid and a base portion.
- Properties employed in classifying a species as hard or soft, acid or base, are summarized **below table**

Table : Classification of Hard and Soft Acids and Bases

Acid (electron acceptor)			*Base (electron donor)*		
Hard	*Property*[a]	*Soft*	*Hard*	*Property*[a]	*Soft*
Low	Polarizability	High	Low	Polarizability	High
High	Electropositivity	Low	High	Electronegativity	Low
Large	Positive charge or oxidation state	Small	Large	Negative charge	Small
Small	Size	Large	Small	Size	Large
Ionic, electrostatic	Types of bond usually associated with the acid	Covalent, π	Ionic, electrostatic	Types of bond usually associated with the base	Covalent, π
Few and not easily excited	Outer electrons on donor atoms	Several, easily excited	High energy and inaccessible	Available empty orbitals on donor atom	Low-lying and accessible

[a] These properties may be used as guide lines for classifying species. The whole column need not be satisfied for a species to be called hard or soft but the more properties that are true, the greater the degree of hardness or softness.

- The main principle behind HSAB theory is that strong bonds are only formed between hard acids and hard bases or between soft acids and soft bases.
- Hard-soft bonds are either very weak or do not exist. Using these concepts, the commoner species encountered *in vivo are included in Tables 1 and 2*

Table 1. HSAB Classification of Acids

Hard	*Soft*
H^+, Li^+, Na^+, K^+	Cu^+, Ag^+, Au^+, Tl^+, Hg^+
Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Mn^{2+}	Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+}
	CH_3Hg^+, $Co(CN)_5^{2-}$,
	Pt^{4+}, Te^{4+}
Al^{3+}, Sc^{3+}, Ga^{3+}, In^{3+}, La^{3+}	Tl^{3+}, $Tl(CH_3)_3$, BH_3, $Ga(CH_3)_3$
N^{3+}, Cl^{3+}, Gd^{3+}, Lu^{3+}	$GaCl_3$, GaI_3, $InCl_3$
Cr^{3+}, Co^{3+}, Fe^{3+}, As^{3+}, CH_3Sn^{3+}	RS^+, RSe^+, RTe^+
Pu^{4+}, Ce^{3+}, Hf^{4+}	
UO_2^{2+}, $(CH_3)_2Sn^{2+}$, VO^{2+}, MoO^{3+}	I_2, Br_2, ICN, etc.
$BeMe_2$, BF_3, $B(OR)_3$	Trinitrobenzene, etc.
$Al(CH_3)_3$, $AlCl_3$, AlH_3	Chloranil, quinones, etc.
RPO_2^+, $ROPO_2^+$	Tetracyanoethylene, etc.
RSO_2^+, $ROSO_2^+$, SO_3	O, Cl, Br, I, N, $RO\cdot$, $RO_2\cdot$
I^{7+}, I^{5+}, Cl^{7+}, Cr^{6+}	M^0 (metal atoms)
RCO^+, CO_2, NC^+	Bulk materials
HX (hydrogen bonding molecules)	CH_2, carbenes
Borderline	
Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Sn^{2+}, Sb^{3+}, Bi^{3+}, Rh^{3+}, Ir^{3+}, $B(CH_3)_3$, SO_2, NO^+, Ru^{2+}, Os^{2+}, R_3C^+, $C_6H_5^+$, GaH_3	

[a] Essential *in vivo* metal ions are italicized.

Table 2. HSAB Classification of Bases

Hard	*Soft*
H_2O, OH^-, F^-	R_2S, RSH, RS^-
$CH_3CO_2^-$, PO_4^{3-}, SO_4^{2-}	I^-, SCN^-, $S_2O_3^{2-}$
Cl^-, CO_3^{2-}, ClO_4^-, NO_3^-	R_3P, R_3As, $(RO)_3P$
ROH, RO^-, R_2O	CN^-, RNC, CO
NH_3, RNH_2, N_2H_4	C_2H_4, C_6H_6
	H^-, R^-

Borderline

$C_6H_5NH_2$, C_6H_5N, N_3^-, Br^-, NO_2^-, SO_3^{2-}, N_2

[a] The symbol R stands for an alkyl or aryl group.

Cancer

- Roe has defined cancer as “a disease of multicellular organisms which is characterized by the seemingly uncontrolled multiplication and spread within the organism of apparently abnormal forms of the organism’s own cells.

- This term “cancer” actually embodies hundreds of different types of neoplastic diseases ranging from localized skin cancers to whole body leukemias with representative cure rates as high as 95 % or as low as 0 %

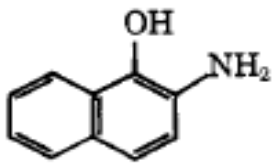
Description of Cancer

- Cancer is caused by carcinogens which may be defined as substances that are capable of producing tumors in any test species by any route and at any dose level.
- This term includes quite inert materials such as gold, silver, sodium chloride, or plastics which can cause cancer by localized irritation, but, in general, it refers to the more widely recognized carcinogens summarized in **below table**

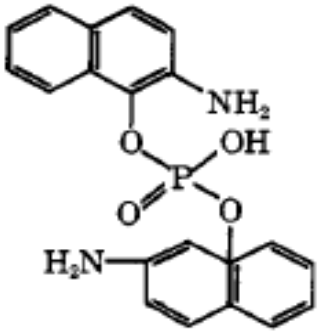
Table : Classification of Agents Known to Cause Cancer

Chemical	*Physical*
Aromatic hydrocarbons and amines	Ionizing radiation
Aromatic heterocyclic ring compounds	Ultraviolet radiation
4-Nitroquinoline oxide	Burns
Nitrosamines	
Azo compounds	*Other*
Alkylating agents	Chromosomal abnormalities
Urethanes	
Polymers	Viruses

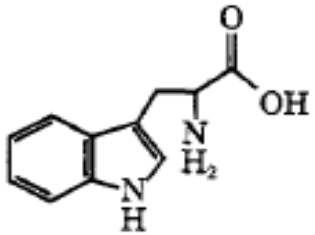
Carcinogens as Ligands



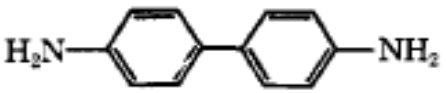
2-amino-1-naphthol



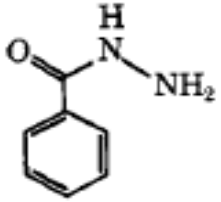
phosphate of
2-amino-1-naphthol



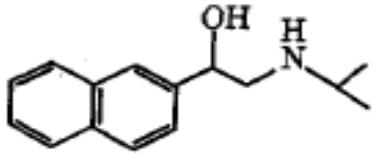
metabolities of tryptophan



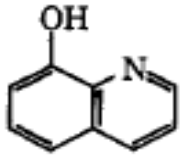
benzidine



isoniazid

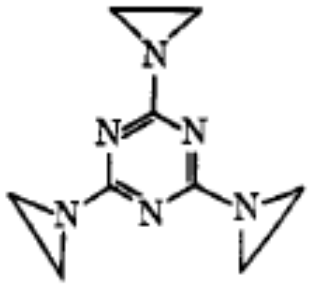


pronethanol

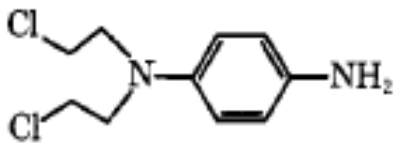


8-hydroxyquinoline

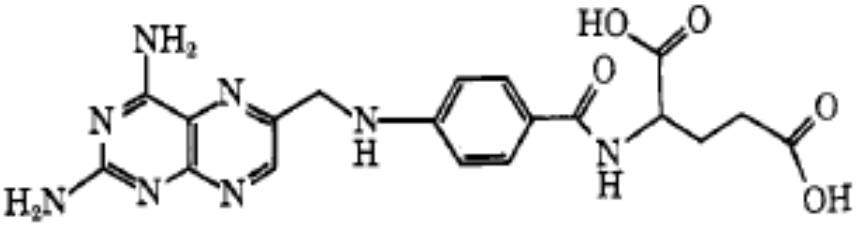
Anticancer Drugs As Ligands



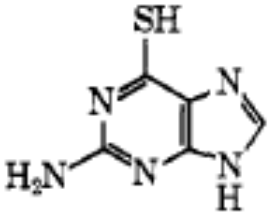
triethylenemelamine



p-phenylenediamine nitrogen mustard

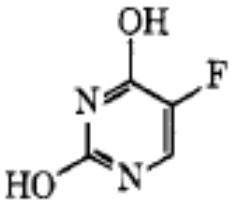


aminopterin



6-mercaptopurine

EDTA derivatives (see Figure 3)

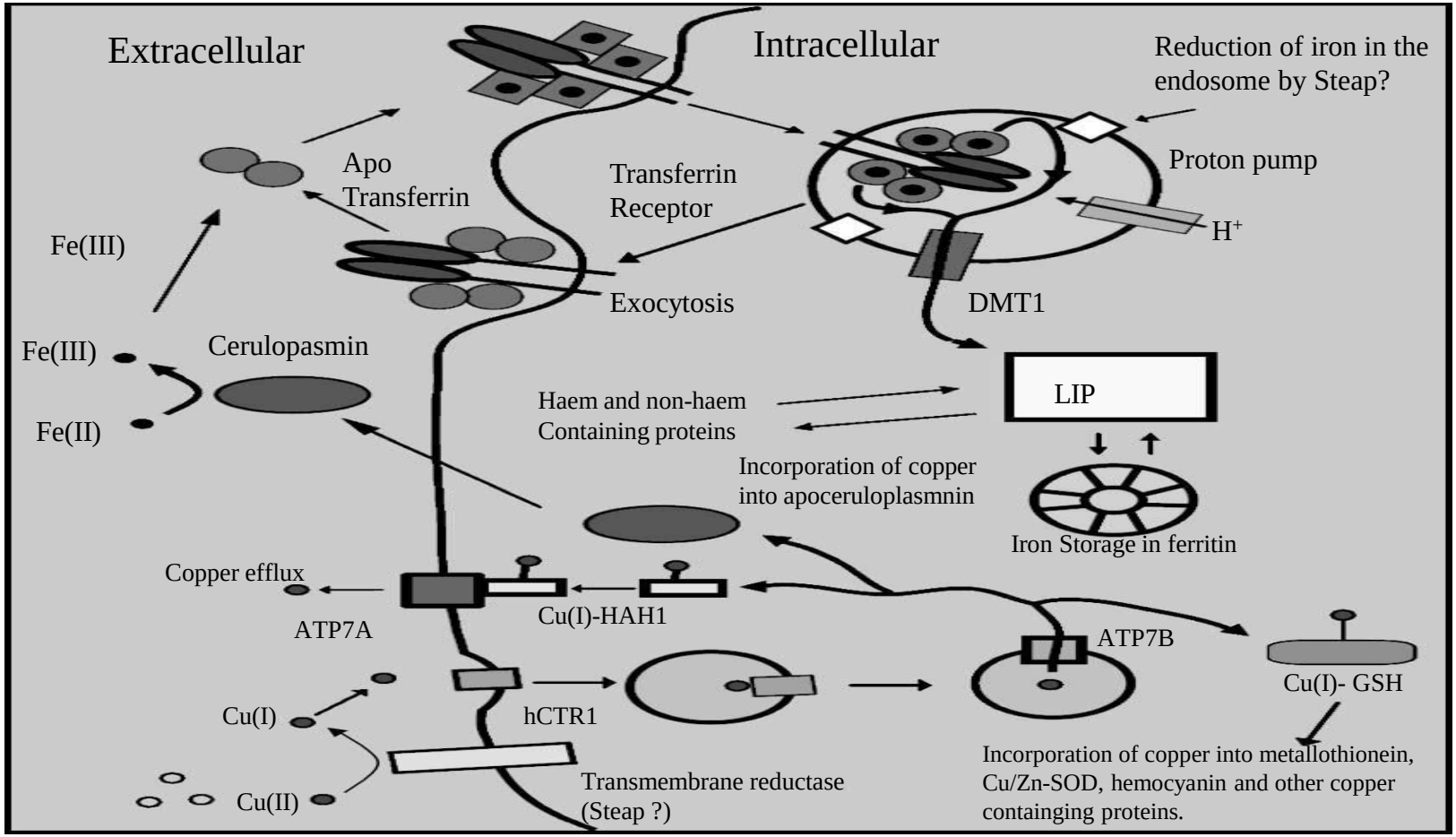


5-fluorouracil

Chelators at the cancer coalface

Iron and CopperMetabolism

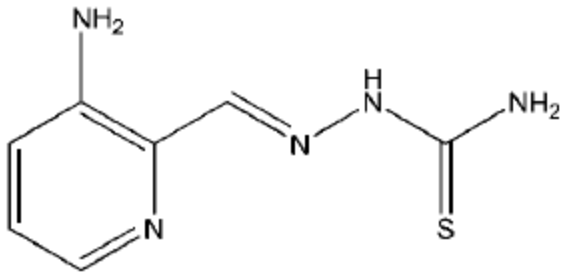
Iron transport into cells occurs by the binding of diferric transferrin to the TfR1 followed by receptor-mediated endocytosis



New-Generation Lipophilic Fe Chelators

A. Triapine.

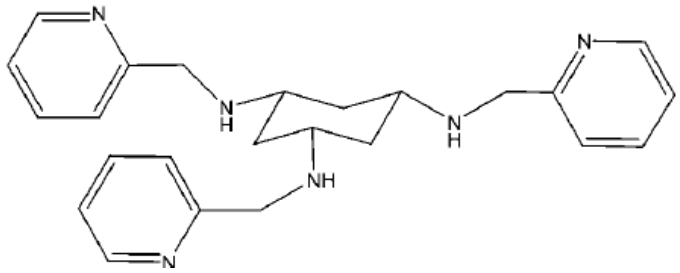
- Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone is a tridentate chelator that ligates Fe via a sulfur and two nitrogen donor atoms.
- Triapine has been suggested to be one of the most potent inhibitors of ribonucleotide reductase yet identified.



- Triapine can equally inhibit both R2 and p53R2, whereas the clinically used ribonucleotide reductase inhibitor, hydroxyurea, was relatively ineffective at inhibiting ribonucleotide reductase activity of the p53R2 subunit.
- Triapine-Fe(II) complex was significantly more active at inhibiting ribonucleotide reductase than free Triapine.
- Triapine did not remove Fe from the active site of R2 or p53R2.
- This chelator formed a complex with Fe(III), which was reduced to Fe(II) that generated reactive oxygen species and quenched the ribonucleotide
- reductase tyrosyl radical.

B. Tachypyridine.

- N,N’,N’’-tris(2-pyridylmethyl)-cis,cis-1,3,5 triaminocyclohexane is a hexadentate chelator.
- Tachpyridine is cytotoxic to bladder cancer cells with an IC_{50} of µ4.6 Amol/L compared with 70 µmol/L for desferrioxamine



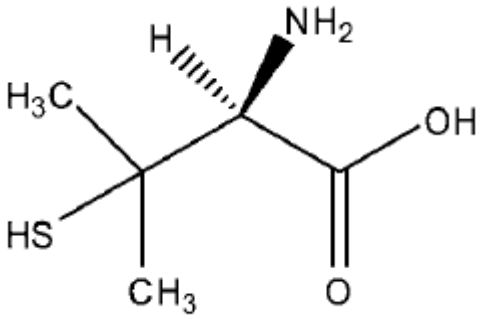
- Although tachpyridine binds Ca(II), Mg(II), Mn(II), Cu(II), and Zn(II), toxicity studies with tachypyridine complexes suggest that Fe depletion mediates its cytotoxic effects.
- Similar to Triapine and Dp44mT, tachpyridine induces apoptotic death independent of functional p53

Copper and Cancer Therapy

- The dependence of tumor growth on angiogenesis was first hypothesized by Folkman.
- This theory suggested that angiogenesis inhibitors might be useful cancer chemotherapeutics.
- In fact, angiogenesis was found to be important for metastasis
- It has long been known that Cu plays an essential role in angiogenesis.
- Pioneering studies showed that Cu became concentrated in the rabbit cornea during neo vascularization

Penicillamine

- The copper chelators penicillamine and trientine are used in the treatment of the copper-loading disease, Wilson's disease.

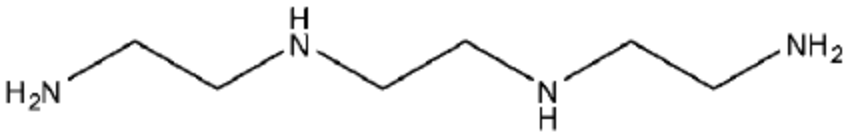


- The success of these chelators in treating copper toxicity has led to their examination as angiogenesis inhibitors against cancer

- A landmark study compared the invasiveness of the VX2 rabbit brain carcinoma in normocupremic animals relative to rabbits copper-depleted by diet and penicillamine .

- Normocupremic rabbits developed large vascularized VX2 carcinomas, whereas small and relatively avascular tumors were found in copper-depleted rabbits

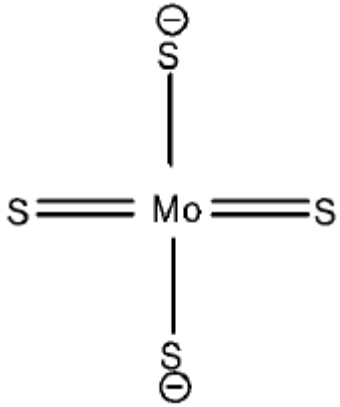
Trientine



- Studies with the Cu chelator, trientine, also showed suppressed tumor development and angiogenesis in vivo .
- In comparison with penicillamine, trientine was more effective at inhibiting growth of a murine hepatocellular carcinoma xenograft model and resulted in marked suppression of neovascularization.
- More recently, trientine, in combination with methotrexate, exerted a tumoricidal effect in a human colorectal carcinoma xenograft in mice and led to ‘‘tumor dormancy’’ .

Tetrathiomolybdate

- The Cu chelator tetrathiomolybdate is another example of a ligand originally developed for Wilson's disease that inhibits angiogenesis and reduces tumor growth .



- This promising antiangiogenesis agent induced Cu deficiency and suppressed tumor growth in the SUM 149 murine breast cancer xenograft model to 31% of untreated Controls.
- Reduction in vascular density and tumor metastases had also been reported in tetrathiomolybdatetreated mice bearing SUM149 breast cancer xenografts.
- The activity of tetrathiomolybdate has been attributed to its ability to form a high-affinity tripartite complex with copper and albumin, to chelate copper from the bloodstream, and to suppress the nuclear factor-*k*B signaling cascade

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