Chelation Therapy & Chelating Agents in Medicine

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Chelation Therapy

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

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**THE CHELATION KID**

"MY SON, JACK, IS AUTISTIC. WE CALL HIM THE CHELATION KID. CHELATION IS A METHOD OF REMOVING HEAVY METALS FROM THE BODY, INCLUDING MERCURY."

"-WHICH CAN CAUSE AUTISTIC SYMPTOMS"

"THE SICK THING IS WE TOOK JACK TO GET VACCINATED."

"NEVER REALIZING THAT THE VACCINES CONTAINED HIGH LEVELS OF A FORM OF MERCURY CALLED THIMEROSAL."

"YOU'LL HEAR "EXPERTS" SAYING THE VACCINES WERE SAFE AND THAT CHELATION WON'T WORK. THEY'LL DISMISS US AS KOOKS OR POOR SOULS WHO'LL BUY ANY QUACK SOLUTION."

"FOR THE RECORD - I DON'T BELIEVE IN BIGFOOT OR NESSIE OR THAT ELVIS IS ALIVE."

"BUT I DO BELIEVE WITH ALL MY HEART THAT MY SON WAS POISONED BY THE MERCURY IN HIS VACCINATIONS."

"AND, UH, I THINK THERE MIGHT BE UFOS."

* PRONOUNCED KEY-LAY-SHUN

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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 Aspergillus niger could convert sugar into citric acid. Currie also understood that Aspergillus 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

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

"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
Coordination Equilibria & Chelate effect

\[
[\text{Fe(H}_2\text{O)}_6]^{3+} + \text{NCS}^{-} \rightarrow [\text{Fe(H}_2\text{O)}_5(\text{NCS})]^{2+} + \text{H}_2\text{O}
\]

\[
K_f = [\text{Fe(H}_2\text{O)}_5(\text{NCS})]^{2+}/ [\text{Fe(H}_2\text{O)}_6]^{3+}[\text{NCS}^{-}]
\]

Equilibrium constant \( K_f \) ⇒ formation constant

\[
\text{M} + \text{L} \rightarrow \text{ML} \quad K_1 = [\text{ML}]/[\text{M}][\text{L}]
\]

\[
\text{ML} + \text{L} \rightarrow \text{ML}_2 \quad K_2 = [\text{ML}_2]/[\text{ML}][\text{L}]
\]

\[
\text{ML}_2 + \text{L} \rightarrow \text{ML}_3 \quad K_3 = [\text{ML}_3]/[\text{ML}_2][\text{L}]
\]

\[
\text{ML}_{n-1} + \text{L} \rightarrow \text{ML}_n \quad K_n = [\text{ML}_n]/[\text{ML}_{n-1}][\text{L}]
\]

- \( K_1, K_2, \ldots \) ⇒ Stepwise formation constant.
- To calculate concentration of the final product, use overall formation constant \( \beta_n \):
  
  \[
  \beta_n = [\text{ML}_n]/[\text{M}][\text{L}]^n
  \]
  
  \[
  = K_1 \times K_2 \times K_3 \times \ldots \times K_n
  \]
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 \( \rightarrow \) 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
- Alkalization 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 (CaNa₂EDTA)

**Calcium chelate of Na₂EDTA** is used clinically instead of Na₂EDTA – ethylene diamine tetracetic acid
High affinity for Pb, Zn, Cd, Mn, Cu and some radioactive metals
**MOA**: Removes the metals by exchanging with Ca²⁺
Highly ionized – not absorbed orally and that’s why acts extracellularly – rapidly excreted 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 (0.5 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 deficiency 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–transferrin-bound iron; LIP = labile iron pools.
The Challenge of Iron Chelation—
A Question of Balance

• Uncoordinated iron
• Free-radical generation
• Organ damage
• Growth failure
• Organ failure
• Cardiac death

Too much iron

• Uncoordinated chelator
• Inhibition of metalloenzymes
• Neurotoxicity
• Growth failure
• Bone marrow toxicity

Too much chelator
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)  Desferrioxamine (DFO)  Deferiprone (DFP)

Tridentate  Hexadentate  Bidentate

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.
Decreasing Cellular Toxicity with Chelators

Non-transferrin iron

Transferrin iron

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

- Normal: No NTBI produced
- 100%
- 30%
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

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

Relationship to Autism

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

<table>
<thead>
<tr>
<th>Heavy Metal</th>
<th>=</th>
<th>Mercury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury</td>
<td></td>
<td>Vaccines</td>
</tr>
<tr>
<td>Vaccines</td>
<td></td>
<td>Autism</td>
</tr>
<tr>
<td>Autism</td>
<td></td>
<td>Chelation</td>
</tr>
</tbody>
</table>
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
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
“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.”

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

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.
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**

<table>
<thead>
<tr>
<th></th>
<th>Group IA (s^2)</th>
<th>Group IIA (s^2)</th>
<th>Transition series (d^{1-9})</th>
<th>Group IIIB (d^{10})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position in periodic table</td>
<td>Na</td>
<td>K</td>
<td>Mg</td>
<td>Ca</td>
</tr>
<tr>
<td>Biological roles</td>
<td>Main group I</td>
<td>Main group II</td>
<td>Transition metals</td>
<td>Subgroup II</td>
</tr>
<tr>
<td>Charge-carrying and osmotic balance</td>
<td>Mobile</td>
<td>Semimobile</td>
<td>Static</td>
<td>Static</td>
</tr>
<tr>
<td>Oxidation states</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Donor atoms preferred</td>
<td>-O^-</td>
<td>-O^-</td>
<td>-O^-</td>
<td>N, -O^-</td>
</tr>
<tr>
<td>Type of complexes formed</td>
<td>Weak</td>
<td>Fairly strong</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Rate of exchange between free and complexed ions</td>
<td>Very rapid</td>
<td>Moderately fast</td>
<td>No exchange</td>
<td>No exchange</td>
</tr>
<tr>
<td>Grams per 70 Kg man</td>
<td>70</td>
<td>250</td>
<td>42</td>
<td>1700</td>
</tr>
<tr>
<td>Adult: total blood concn (μM)</td>
<td>85,200</td>
<td>44,500</td>
<td>1570</td>
<td>2420</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Acid (electron acceptor) Property</th>
<th>Hard</th>
<th>Soft</th>
<th>Base (electron donor) Property</th>
<th>Hard</th>
<th>Soft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td></td>
<td></td>
<td>Large</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td></td>
<td></td>
<td>Small</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ionic, electrostatic</td>
<td></td>
<td></td>
<td>Ionic, electrostatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Few and not easily excited</td>
<td></td>
<td></td>
<td>Low energy and inaccessible</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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**

<table>
<thead>
<tr>
<th>Hard</th>
<th>Soft</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H^+$, Li$^+$, Na$^+$, K$^+$</td>
<td>$Cu^+$, Ag$^+$, Au$^+$, Tl$^+$, Hg$^+$</td>
</tr>
<tr>
<td>Be$^{2+}$, Mg$^{2+}$, Ca$^{2+}$, Sr$^{2+}$, Mn$^{2+}$</td>
<td>Pd$^{2+}$, Cd$^{2+}$, Pt$^{2+}$, Hg$^{2+}$</td>
</tr>
<tr>
<td>Al$^{3+}$, Sc$^{3+}$, Ga$^{3+}$, In$^{3+}$, La$^{3+}$</td>
<td>CH$_3$Hg$^+$, Co(CN)$_5^{3-}$, Pt$^{4+}$, Te$^{4+}$</td>
</tr>
<tr>
<td>N$^{3+}$, Cl$^{3+}$, Gd$^{3+}$, Lu$^{3+}$</td>
<td>Tl$^{3+}$, Tl(CH$_3$)$_3$, BH$_3$, Ga(CH$_3$)$_3$</td>
</tr>
<tr>
<td>Cr$^{3+}$, Co$^{3+}$, Fe$^{3+}$, As$^{3+}$, CH$_3$Sn$^{3+}$</td>
<td>GaCl$_3$, GaI$_3$, InCl$_3$</td>
</tr>
<tr>
<td>Pu$^{4+}$, Ce$^{3+}$, Hf$^{4+}$</td>
<td>RS$^+$, RSe$^+$, RTe$^+$</td>
</tr>
<tr>
<td>UO$_2^{2+}$, (CH$_3$)$_2$Sn$^{2+}$, VO$^{2+}$, MoO$_3^{3+}$</td>
<td>I$_2$, Br$_2$, ICN, etc.</td>
</tr>
<tr>
<td>BeMe$_2$, BF$_3$, B(OR)$_3$</td>
<td>Trinitrobenzene, etc.</td>
</tr>
<tr>
<td>Al(CH$_3$)$_3$, AlCl$_3$, AlH$_5$</td>
<td>Chloranil, quinones, etc.</td>
</tr>
<tr>
<td>RPO$_2^{3+}$, ROPO$_2^{3+}$</td>
<td>Tetracyanoethylene, etc.</td>
</tr>
<tr>
<td>RSO$_2^{3+}$, ROOSO$_2^{3+}$, SO$_3^{3+}$</td>
<td>O$_2$, Cl, Br, I, N, RO$^-$, RO$_2^-$</td>
</tr>
<tr>
<td>I$^{3+}$, I$^{5+}$, Cl$^{7+}$, Cr$^{8+}$</td>
<td>M$^+$ (metal atoms)</td>
</tr>
<tr>
<td>RCO$^+$, CO$_2$, NC$^+$</td>
<td>Bulk materials</td>
</tr>
<tr>
<td>HX (hydrogen bonding molecules)</td>
<td>CH$_2$, carbenes</td>
</tr>
</tbody>
</table>

**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$^{3+}$, Os$^{3+}$, R$_3$C$^+$, C$_6$H$_5^+$, GaH$_3$

*a Essential in vivo metal ions are italicized.*
Table 2. HSAB Classification of Bases

<table>
<thead>
<tr>
<th>Hard</th>
<th>Soft</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O, OH⁻, F⁻</td>
<td>R₂S, RSH, RS⁻</td>
</tr>
<tr>
<td>CH₃CO₂⁻, PO₄³⁻, SO₄²⁻</td>
<td>I⁻, SCN⁻, S₂O₃²⁻</td>
</tr>
<tr>
<td>Cl⁻, CO₃²⁻, ClO₄⁻, NO₃⁻</td>
<td>R₃P, R₃As, (RO)₃P</td>
</tr>
<tr>
<td>ROH, RO⁻, R₂O</td>
<td>CN⁻, RNC, CO</td>
</tr>
<tr>
<td>NH₃, RNH₂, N₂H₄</td>
<td>C₂H₄, C₆H₅</td>
</tr>
</tbody>
</table>

Borderline
C₆H₅NH₂, C₆H₅N, N₃⁻, Br⁻, NO₂⁻, SO₃²⁻, N₂

* 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**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Physical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatic hydrocarbons and amines</td>
<td>Ionizing radiation</td>
</tr>
<tr>
<td>Aromatic heterocyclic ring com-</td>
<td>Ultraviolet radiation</td>
</tr>
<tr>
<td>pounds</td>
<td>Burns</td>
</tr>
<tr>
<td>4-Nitroquinoline oxide</td>
<td></td>
</tr>
<tr>
<td>Nitrosamines</td>
<td></td>
</tr>
<tr>
<td>Azo compounds</td>
<td>Other</td>
</tr>
<tr>
<td>Alkylation agents</td>
<td>Chromosomal abnormalities</td>
</tr>
<tr>
<td>Urethanes</td>
<td>Viruses</td>
</tr>
<tr>
<td>Polymers</td>
<td></td>
</tr>
</tbody>
</table>
Carcinogens as Ligands

- 2-amino-1-naphthol
- Phosphate of 2-amino-1-naphthol
- Metabolites 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 transport into cells occurs by the binding of diferric transferrin to the TfR1 followed by receptor-mediated endocytosis.

Iron and Copper Metabolism

Iron Storage in ferritin

Copper efflux

ATP7A

Cu(I) HAH1

Incorporation of copper into apoceruloplasmin

Iron Storage in ferritin

Incorporation of copper into metallothionein, Cu/Zn-SOD, hemocyanin and other copper containing proteins.

Transmembrane reductase (Steap?)

hCTR1

Cu(I) GSH

ATP7B

Cu(II)

Cu(I)
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 4.6 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 tachpyridine 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 tetrathiomolybdate-treated 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-κB signaling cascade.
References: