

Lethal Lewis Acidity: Lead Poisoning and Toxicities of Antiquity

Story 1: Lead Poisoning in Ancient Rome



In ancient Rome a young and talented bard (professional storyteller and performer) named Saturninus was nervously preparing for the biggest show of his career, a rendition of the “Tale of Atalanta” to be performed in front of Emperor Caligula. Being a bard was an ancient form of show business and most performers would kill for the chance to entertain an Emperor.....as long as that Emperor wasn’t Caligula. Saturninus was terrified because Caligula was completely insane. The last few Roman Emperors had been lunatics but Caligula was in a league of his own. One of his chief advisors was his own horse! Caligula indulged every whim to excess and was known for erratic behavior that usually involved someone or everyone getting brutally murdered for no reason at all. During the most recent gladiatorial games, Caligula became bored and ordered the first 5 rows of spectators to enter the arena and fight each other to the death for his pleasure. Spectators that refused were killed by his guards. The “invitation” that Saturninus received earlier in the evening amounted to being kidnapped from his home at sword point by royal guards and thrown in the palace’s dungeon to “practice”

before his show began. Saturninus knew that if the show didn’t go well it would be his last. Many performers had received similar “invitations” to court in recent months and most of them were never seen again. Caligula desperately needed entertainment, despite having four wives he could not produce an heir. Caligula’s depression made him more murderous than usual.

When the guards escorted Saturninus to Caligula’s court for the show he was horrified by the decadence he saw. The lower classes were fighting over bread but the palace court was packed with revelers who were drinking the finest wines and eating syrup covered sweetened foods. Caligula sat on a marble couch with a wine goblet in one hand and a miserable expression fixed on his face. He looked like he had a horrible stomach ache and was hunched over slightly clutching his abdomen with his other arm. Caligula’s skin was ghostly pale and with great effort he extended a shaking arm and finger toward Saturninus as an order to begin the show. Saturninus felt sweat on his brow and his palms, he took a deep breath and began the story of Atalanta.....

Framing Analogy for Heavy Metal Toxicity: Fatal Attraction

Atalanta was among the deadliest of warriors. She was the fastest person alive and arguably the most beautiful woman of her era. Her father was a king who never wanted a daughter so he abandoned

her in the wild as a baby hoping she would die. Fortunately she was raised by animals and learned to survive in the wild. She spent her childhood defending herself from murderous mythological creatures,



living off the land, and developing deadly aim with both bow and spear. Atalanta's harsh upbringing made her faster and tougher than anyone alive. She never wanted a husband or children and wished only to hunt in the forest for the rest of her life. Atalanta was a worshipper of Artemis (Greek goddess of Hunting) and swore to the goddess that she would never marry in return for enhanced tracking and fighting skills.

Unfortunately Atalanta's beauty attracted many male admirers who wanted her as a wife but she refused to have anything to do with them. Tragically, this desire did little to keep her admirers away. The distracting nature of her good looks became an annoyance to her and posed a

danger to everyone who came near her. It seemed like no matter where she went men were drawn to her like a magnet. One prime example was seen in the hunt for the Calydonian Boar. The boar was a pig as large as a dinosaur created by Artemis to punish humans who failed to worship her. The boar ravaged the countryside and killed hundreds of people. Atalanta was part of an elite group of warriors tasked with killing it. The hunt went extremely well and the Boar was slain. However, after the hunt was over the other warriors engaged in a battle with each other for Atalanta's affections that proved more deadly than the one they fought with the beast. All of the male hunters killed one another.

Atalanta's beauty was a public nuisance as well, when she would walk into busy markets all of the men would come to court her leaving whatever jobs that they were doing in the process. This was a huge problem to the financial productivity of Ancient Greek cities. While men were trying to talk to her they weren't doing their work. Atlanta was sick and tired of this ridiculous attention and hoped to diminish the interest in her by implementing a deadly dating policy: she would marry the first man who could beat her in a foot race but the penalty for losing was death at the end of her spear. Because she was the fastest person alive these contests never turned out well for the men but it did not stop them from trying. Thousands of races were followed by thousands of burials.

This pattern continued until one clever young man, Hippomenes, prayed to Aphrodite, goddess of love, for help. Aphrodite gave him an enchanted golden apple of irresistible beauty to throw out and distract Atalanta during the race. No one thought Hippomenes had a chance of winning and people started digging his grave before the race began. However, just before the race started, he dropped the golden apple at the starting line. Atalanta couldn't help but stare at the apple as Hippomenes ran ahead. Hippomenes crossed the finish line while Atalanta was still stuck at the starting line staring at the golden apple. As the victorious Hippomenes approached Atalanta, he taunted and insulted her about her

impending future as an obedient wife. As Hippomenes continued to praise himself in front of the amazed crowd for his cleverness he neglected to give a prayer of thanks to Aphrodite. Aphrodite was enraged at Hippomenes' ingratitude and Artemis did not want Atlanta to have to break her oath so the two goddesses transformed Atlanta into a lion that attacked Hippomenes and tore him apart. Atlanta lived out the rest of her days happily hunting in the forest as a lion no longer burdened by suitors and the grave dug for Hippomenes did not go to waste....

As Saturninus finished the story he gave a panicked look to a silent Caligula who in turn looked at his horse. The horse gave a nod of its head and Caligula broke out into raucous laughter as he clapped his hands. Saturninus had pleased the emperor and his life was spared. Taking the opportunity, Saturninus quickly bowed and headed for the exit. Moments before he left, Saturninus saw a party guest with pale skin and shaking hands spill his wine on the floor. A still laughing Caligula gave a signal to a guard who pulled out a sword and killed the man instantly.

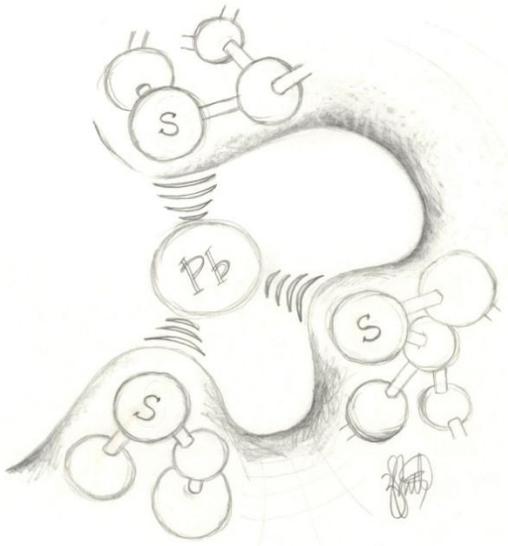
Scientific Explanation:

Caligula and the members of his court are suffering from lead poisoning. If you can understand why Atlanta's beauty was such a problem then you can definitely understand why lead and heavy metals in general are so dangerous. The story of Atlanta is all about something with the power to distract, something that could enter a room and instantly draw all attention to itself. Atlanta's beauty had this quality which essentially gave it the nature of an "attractive sphere". She was able to distract any man that was nearby, all anyone would have to do is get in range of her attractive radius and they would be drawn to her. It wouldn't matter if it was one man or a hundred; anyone who could see her from any angle was fixated on her good looks and had to approach her. The attractive sphere quality is what she has in common with lead and that is one reason why lead is so dangerous.

The real danger that Atlanta's beauty posed was that it was able to distract men from their work and destroy productivity. If a group of men were working on a tight deadline to finish a job and Atlanta came anywhere near them they would stop working and try to get her attention which might cause them to fall behind schedule and fail in their task. Atlanta fell prey to this same power when the golden apple distracted her and prevented her from winning the race. If someone is very busy then they can't afford to be distracted. Proteins are the workers of the biological world, they are always toiling within your body to finish some kind of job and many of these jobs are done on a tight time schedule with severe penalties for missing deadlines. Every organ in the body is essentially a factory that is staffed by protein workers. A lot of organs have high production demands and need their workers to be on task at all times. If something like a group of heavy metal ions come in to that factory and distracts the proteins' attention away from their duties then production falls and organs stop working correctly which leads to disease and death.

Any charged atom or molecule is an attractive sphere. It will interact with anything of opposite charge that happens to get in range of it. This is basically a Lewis acid-base reaction. Lewis acids are electron poor which usually means that they are positively charged. Lewis acids are always after things that are electron rich like negatively charged ions, lone electron pairs, and double bonds. The attraction of something that is electron poor to something that is electron rich is the basis of Lewis acid-base chemistry. Heavy metal toxicities are cases of lethal Lewis acidity. In ionic form, heavy metals like

lead(Pb), mercury(Hg), Arsenic(As), and Cadmium(Cd) exert their fatal attractions on the electron rich sulfur molecules in proteins. Sulfur is a component of virtually every protein because it is found in the amino acids cysteine and methionine. This gives heavy metals the potential of messing with a wide



variety of proteins and causing chaos all over the body. This multi system disruption can easily be seen in Caligula and the members of his court because it is pretty obvious that something there is very, very wrong.

Lead has profound effects on the brain and can cause behavior that is both erratic and impulsive. It causes disordered thinking (i.e. believing a horse can talk), altered speech and rapid mood swings. Lead affects the nerves as well. Nerves, when working properly, allow you to move your body and sense things. Lead poisoning was interfering with nerve function in both Caligula and the unfortunate reveler who spilled his wine. This was manifested as unsteadiness in movement, weakness, and constant

shaking. Lead also messes with your blood and prevents the creation of red blood cells. Red blood cells give your skin a pink color and your cells the raw materials to make energy from. Fewer red blood cells mean that you will be weaker. Caligula and the members of his court had deathly pale skin and were very weak and tired. Lead causes harm to the digestive system as well which is why Caligula had a terrible stomach ache. Lead has a significant effect on both reproductive organs and developing organisms which can cause infertility (can't have children) or the death of a baby long before it is born. This is why Caligula had such a hard time producing an heir to his throne. Lead is extremely toxic to developing babies, infants, and children.

If you think about a developing human, on day one of life it is a single cell and nine months later it is a whole person. It is analogous to the amount of work it would take to start constructing a building with a single brick and nine days later having a fully functional skyscraper that touches the moon. In a very busy system where death is the penalty for missing deadlines if you interfere with production even a little bit disastrous consequences result.

The brain is a high demand organ at all ages. The brain always needs a lot of work to be done within it to function properly. Heavy metals like lead interfere with that work and cause visible declines in brain function. Many experts believe that lead poisoning is a cause for the insanity seen in many of the later Roman Emperors. The best part about writing a story about Caligula is that he was so crazy and bizarre that you don't have to make anything up: a horse as an advisor, forcing hundreds of spectators to kill each other, murdering people for fun, kidnapping.....all of it true and there is so much more that is even worse than that. If you take a person who is mentally unstable and give them absolute power then bad things will happen.

One important question is how did all of this lead get into their bodies in the first place? Lead was a highly abundant metal that was very easy to work with; it was used in many Roman water pipes. Some theories are that the lead exposure came through drinking water but many people think that

natural mineral deposits coated the surface of the pipes and prevented this. A more likely exposure is the wine and sweetened foods that the court members were consuming. An interesting property of lead ions is that they taste sweet. Romans liked to boil grape juice down to syrup to make it sweeter. Boiling grape juice in lead pots increased its sweetness. A lead salt (lead acetate) was used as a combination sweetener/preservative for wines as well. The Romans noticed that lead had a preservative property on foods. Food with lead added to it took a long time to go bad. This was due to the fact that the lead made the food so toxic that no bacteria or fungus could live on it. Despite it being ancient times the Romans could recognize pale skin, weakness, shaking, abdominal pain, and mental instability as signs of lead poisoning and referred to it as “Saturnine’s Curse” in reference to the planet Saturn which in Roman times was believed to be made entirely of lead.

Why Heavy Metals are so Dangerous: Theory of Hard and Soft Acids and Bases

Here is a question; there are lots of positively charged ions in the body like Na^+ and K^+ but why aren’t they as dangerous as Pb^{2+} or any of the other heavy metal ions? The answer lies in the theory of Hard and Soft Acids and Bases. Pay special attention to this because you won’t find anything like it outside of an advanced inorganic chemistry text. It is one of the most useful and applicable chemical principles and is also very easy to understand. The “hardness” or “softness” of an ion has to do with the mass to charge ratio of the atom in question. Essentially atoms with a high mass to charge ratio are considered soft and atoms with a low mass to charge ratio are considered hard. **Hard Lewis acids are strongly attracted to hard Lewis bases and soft Lewis acids are strongly attracted to soft Lewis bases.** You might notice this in the classic chemistry experiment where you get some soft Lewis acid (like silver) to precipitate from solution with Iodine (soft) rather than chloride (hard). Some examples of hard Lewis acids are: Na^+ , K^+ , Ca^{2+} , Fe^{3+} and Mg^{2+} . The most common hard bases in the body are the amines in proteins ($-\text{NH}_2$), H_2O , and OH^- . Good examples of soft acids are all heavy metals: (mercury) Hg^+ , (lead) Pb^{2+} , (gold) Au^+ , (silver) Ag^+ , (arsenic) As^{3+} and (cadmium) Cd^{2+} . The most common soft base in the body is sulfur. In general, the softer the acid the more sulfur binding ability it has and the more toxic it will be. Fe^{3+} is harder than Fe^{2+} because Fe^{3+} has a lower mass to charge ratio than Fe^{2+} . This is reflected in nature where Fe^{3+} forms oxides and Fe^{2+} forms sulfides. Pb^{2+} is actually borderline hard and can form oxides as well as sulfides. This relationship is seen in geology where galena (PbS), a lead sulfide, was the ore that the Romans used as their natural source of lead. Galena was heated with Litharge (PbO), a lead oxide, to isolate elemental lead through this reaction: $2 \text{PbO} + \text{PbS} \rightarrow 3 \text{Pb} + \text{SO}_2$. The lead isolated from this reaction was used to make all of the pipes of the aqueducts as well as those delightful cooking pots that possibly ended up destroying the whole empire.

The answer to the question posed at the beginning of the paragraph is that Na^+ and K^+ are hard Lewis acids and do not form strong bonds to sulfur, a soft Lewis base, so they don’t interfere with proteins. In general soft acids are toxic but so are very hard bases like fluoride. A Table of hard and soft Lewis acids is included as supplemental material at the end of this lesson. Lead poisoning is very common and is associated with old things like old paint, old houses, old canned foods, and old types of gasoline. Lets see if you can spot lead poisoning in modern times.

Story 2: Lead Poisoning in 2012



Ms. Delgado is a 20 year old single mother who lives with her 4 year old son Philip. They moved into an old house in the city of Providence 2 years ago. The house was in horrible condition, there was old flaking paint on the walls in every room but the rent was very affordable. Ms. Delgado has noticed a disturbing change in Philip's behavior in the last year, he has become increasingly impulsive and angry. One week ago he lost his temper and threw a plate at dinner, he has a harder time sitting still than usual, and he is constantly disruptive in his kindergarten class and frequently fights with his classmates. Philip also seems to do more poorly on tests than his classmates. He

complains of stomach aches a few times a week. Though Philip is more easily distracted than usual he is not energetic and actually seems to tire out faster than his friends when they play outside. Philip is also a little bit shorter than other children his age. Ms. Delgado wonders if Philip has trouble hearing because she has to shout at him to get his attention. Sometimes when she speaks softly he doesn't seem to notice her. The most disturbing thing she has seen him do is eat flaking chips of paint off of the walls of their home. No matter how many times she keeps telling him to stop, she always catches him eating paint chips. Ms. Delgado takes her son to a new pediatrician because of all of these concerns. She does not take him to see a pediatrician regularly because he is never sick, the last time he saw his pediatrician was when he was 2 years old. In the office his blood is taken for tests and it turns out his blood lead level is 58 $\mu\text{g}/\text{dL}$ (normal is less than 10 $\mu\text{g}/\text{dL}$). Ms. Delgado is given some education on lead exposure, advised to find another place to live, and her son is given a drug called succimer to help eliminate the lead from his body. Ms. Delgado moves to a newer apartment building and takes Philip to the pediatrician more regularly and the amount of lead in his blood decreases. His behavior problems improve and he starts to perform better in school.

Scientific Explanation:

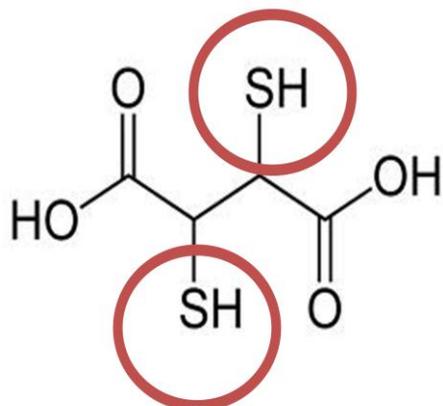
You might have recognized some of the signs of lead poisoning in Philip. Signs of lead's effects on his brain and nervous system included his new impulsive and aggressive behaviors, poor school performance, and hearing loss. IQ is thought to decrease by $\frac{1}{2}$ point for every 1 $\mu\text{g}/\text{dL}$ increase in lead level. Fortunately some studies indicate it is reversible and IQ will improve as lead is eliminated from the body. His decreased energy level is a sign that lead was lowering his number of red blood cells. The

stomach aches were a sign that lead was affecting his digestive system. Lead exposure is also associated with decreased height.

How did poor Philip get all of this lead into his body? He was eating paint chips. In the past, paint had higher levels of lead than it does now. Because of the high lead level paint chips actually taste sweet and that is one reason why children eat them. Older houses have walls painted with older paint. Housing is a principal risk factor for lead exposure especially if the homes are older than the 1950's. A child is at risk even if he/she does not live in an older home but instead visits an older home regularly to play with a friend or visit a grandparent. If paint is flaking off of the walls it also means that it is getting on the floors and the counters as well. Very fine paint chips can get into food or on a person's hands and get into their body when they eat something. Frequent hand washing and not your sticking hands in your mouth are two ways to reduce lead exposure in an old house. A lead inspection of a home should be taken very seriously especially if children are going to be living there. Old homes that are loaded with lead are a major problem in urban areas. Risk factors for lead exposure are visiting homes built before 1950, visiting homes currently being remodeled that were built before 1980, or a close friend or sibling that has elevated lead levels. If you have a best friend who you hang out with all the time and he/she got exposed to lead then chances are so did you.

Since the 1980's there is a serious campaign to eliminate lead from as many sources as possible. It was estimated that between 1976 and 1980 more than 85% of American preschool aged children had a blood lead level that was 10µg/dL or higher. Since then lead has been reduced or eliminated in several things: paint, gasoline (it is why you use unleaded in your car), and solder used to seal canned foods. Gasoline actually works better when it has lead in it so leaded gasoline is still used in airplanes and foreign countries. Lead acid batteries are another source of lead exposure. The vigilance towards lead exposure paid off and by the year 2000 less than 3% of American children had blood lead levels higher than 10µg/dL. Unfortunately lead is a global problem and some sources estimate as many as 20% of the world's children have a blood lead level higher than 10µg/dL. In high risk areas children are tested for lead poisoning routinely. Typically children get tested once on their first birthday and again when they turn 2 years old. This is one of the reasons not to miss a doctor's appointment because the surveillance of health requires regular visits to establish and track changes in your body; you also receive routine vaccinations to protect you from dangerous diseases. If Philip's mom had taken him to appointments more frequently physicians might have been able to intervene before his lead level was 58µg/dL. How high a lead level has to be in order to become concerning is point of debate. Some doctors say 10µg/dL is the threshold while others don't get concerned until it gets closer to 20µg/dL. The lead level does not correlate well to the symptoms that people display. A child could have a level of 40µg/dL and not show any visible symptoms or be symptomatic and have a level around 10µg/dL. The higher the levels are the more danger you are in. The value of the lead level is used to determine what therapy to give. Generally if the level is below 45µg/dL then no drugs are used to reduce the lead level. Avoidance of the lead contaminated environment is recommended and education on sources of lead exposure is given. Repeat checkups are necessary to make sure that the lead level is going down. In our story Philip had a lead level of 58µg/dL so he was given a drug called succimer to eliminate the lead from his body. The solution is no different than the golden apples used by Hippomenes to distract Atalanta and take her out of the race.

Figure 1: Structure of Succimer



If you will notice the key structural feature in succimer are its two sulfur containing thiol (-SH) groups. Pb^{2+} is dangerous because it attracts the thiol groups in your proteins. The theory behind succimer is that it binds lead and distracts it before the lead can interact with your proteins and cause disease. The lead-succimer complex is then eliminated in the urine fairly quickly which gets the lead out of your body. Succimer attracts lead and takes it out of the body just as the golden apple attracted Atalanta and took her out of the race.

Take Home Message: Ions interact as an attractive sphere, electron poor atoms (Lewis acids) are always attracted to electron rich atoms (Lewis bases). Lewis acids with high mass to charge ratios interact strongly with Lewis bases with high mass to charge ratios. Lead is a very dangerous metal and it is important to know the risk factors for lead exposure and avoid them whenever possible. Once lead gets in you it can't be completely eliminated.

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SUPPLEMENTAL MATERIALS:

Reading you might enjoy:

These two links feature more information about lead in the ancient Rome.

http://penelope.uchicago.edu/~grout/encyclopaedia_romana/wine/leadpoisoning.html,

<http://www.ncbi.nlm.nih.gov/pubmed/6750289>.

Here is some more information about Caligula and other questionable Roman Emperors (just a word of warning, Caligula is not for the faint of heart, his whole life would have received an MPAA rating of NC-17, read about him at your own risk).

<http://lilitheden.hubpages.com/hub/The-Emperor-Gaius-also-known-as-Caligula>,

<http://listverse.com/2010/05/09/top-10-worst-roman-emperors/>.

Table of Hard and Soft Lewis Acids:

Classification of Lewis Acids

Class (a)/Hard	Class (b)/Soft
H ⁺ , Li ⁺ , Na ⁺ , K ⁺	Cu ⁺ , Ag ⁺ , Au ⁺ , Tl ⁺ , Hg ⁺ , Cs ⁺
Be ²⁺ , Mg ²⁺ , Ca ²⁺ , Sr ²⁺ , Sn ²⁺	Pd ²⁺ , Cd ²⁺ , Pt ²⁺ , Hg ²⁺
Al ³⁺ , Se ³⁺ , Ga ³⁺ , In ³⁺ , La ³⁺	CH ₃ Hg ⁺
Cr ³⁺ , Co ³⁺ , Fe ³⁺ , As ³⁺ , Ir ³⁺	Tl ³⁺ , Tl(CH ₃) ₃ , RH ₃
Si ⁴⁺ , Ti ⁴⁺ , Zr ⁴⁺ , Th ⁴⁺ , Pu ⁴⁺ , VO ²⁺	RS ⁺ , RSe ⁺ , RTe ⁺
UO ₂ ²⁺ , (CH ₃) ₂ Sn ²⁺	I ⁺ , Br ⁺ , HO ⁺ , RO ⁺
BeMe ₂ , BF ₃ , BCl ₃ , B(OR) ₃	I ₂ , Br ₂ , INC, etc.
Al(CH ₃) ₃ , Ga(CH ₃) ₃ , In(CH ₃) ₃	Trinitrobenzene, etc.
RPO ₂ ⁺ , ROPO ₂ ⁺	Chloranil, quinones, etc.
RSO ₂ ⁺ , ROSO ₂ ⁺ , SO ₃	Tetracyanoethylene, etc.
I ⁷⁺ , I ⁵⁺ , Cl ⁷⁺	O, Cl, Br, I, R ₃ C
R ₃ C ⁺ , RCO ⁺ , CO ₂ , NC ⁺	M ⁰ (metal atoms)
	Bulk metals
<i>HX (hydrogen-bonding molecules)</i>	
<i>Borderline</i>	
Fe ²⁺ , Co ²⁺ , Ni ²⁺ , Cu ²⁺ , Zn ²⁺ , Pb ²⁺	
B(CH ₃) ₃ , SO ₂ , NO ⁺	