

Release Notes 2025-07-01 : I finally got this to into a state that highlights some important points about this topic but don't think I'll have a lot of time to clean it up and organize it and in any case I'd like to wait for more data but that could take a while. Copper was an early part of my interest in optimization of supplements for dogs and humans. Recent literature has expressed concern about copper so I thought I would get out generally supportive results to date although omitting much of my own personal experiences (I'm a human not a dog) that seem similarly beneficial. Often the popular press led by science catches onto incomplete or "close but not quite" ideas and reversals in recommendations are common. Curious to see how attitudes towards copper evolve. Curious for example about rhetoric related to PEX replacing copper plumbing lol. I took some of the text from a much older manuscript, probably going back to 20018 or so and it still seems apropos.

It may look like introduction and discussion have been mixed up. A lot of introductory material may be more commonly put into a discussion of later section but its important to motivate the rather simple work of designing a set of supplements for a group of dogs. One issue is "weighing" evidence about copper from different types of sources. "Ancient civilizations" are introduced almost at the end as a thought provoking topic for better context on possible health effects of widespread copper exposure.

ToDo : Most issues common with early large manuscript.

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Note that any item given to a non-human must be checked for safety alone and in combination with other ingredients or medicines for that animal. Animals including dogs and cats have decreased tolerance for many common ingredients in things meant for human consumption.

I am not a veterinarian or a doctor or health care professional and this is not particular advice for any given situation. Read the disclaimers in the appendices or text, take them seriously and take prudent steps to evaluate this information.

This work addresses a controversial topic and likely advances one or more viewpoints that are not well accepted in an attempt to resolve confusion. The reader is assumed familiar with the related literature and controversial issues and in any case should seek additional input from sources the reader trusts likely with differing opinions. For information and thought only not intended for any particular purpose. **Caveat Emptor**

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Copper Supplementation in Dogs: Listen to Her Heart Everybody's got a Hungry Heart

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Copper is important for diverse biological processes such as energy production and maintenance of cartilage quality as well as control of pathological conditions such as infection and probably cancer. However, it is not currently a trendy supplement for dogs or humans (usually omitted from lists such as most popular supplements [263]). Part of the concern with dogs is the variable genetics and observations of copper accumulation in the liver becoming more common. However, with most genetics lacking a recognized copper storage disease, copper distribution is regulated by a complex system that appears to consider organ specific demand as part of the distribution control algorithm. Such a system may malfunction to produce bottlenecks leading to uncommonly large accumulation in an organ such as the liver while another organ such as the heart is starved. Such a situation could occur due to some other nutrient limitation that fools or cripples the feedback mechanisms. Without knowing the specific bottleneck, the decision to supplement would be based on the overall benefits to the starving location versus any harms to the accumulating organ(and this dichotomy assumed monotonic increasing totals with intake which need not be the case). A better solution is to find the pathways needed to match copper supply and demand and insure they are not limited by easily fixed deficiencies. This work describes copper supplementation to a group of dogs including the larger context of more careful supplementation. No obvious significant harms were observed while in some cases coinciding benefits such as increased energy or reduced coughing. Supplementation

in the range of .3-1 mg/kgBW/day was most commonly explored with .1 thought to be too low and 3 being an old literature NOAEL. Results are considered in view of the human and dog medical literature but also from diverse sources including ruminant and mining copper literature for a more complete understanding. Important considerations for copper supplementation may include its reactivity, simultaneous meal components such as sulfur containing molecules including taurine, overall average diet composition, and GI tract details. Copper has been observed to destroy both vitamins and anti-vitamins suggesting a need to minimize contact with vitamins or at least control the interaction. This is important as "anti-vitamins" may be potent antagonists rather than just lost vitamins. Strategies considered include separate feedings, time release formulations, and use of specific forms such as copper citrate or glycinate. The absence of an early low pH step in digestion may allow idiosyncratic formation of insoluble copper compounds preventing uptake of copper and other vitamins pointing to a possible benefit of acid or chloride supplemented diets especially in the elderly. Specific less obvious dietary components may be suspects in conditions such as canine DCM as they may limit copper delivery to the heart. Some common patterns of confusion seem to turn paradigms into paradoxes making it difficult to formulate interventions in medical conditions. With copper like in other cases many of these relate to incorrect interpretation of associations that result from complex feedback systems adapting to various perturbations. Some of the more common fallacies are categorized. In particular, identification of "larger than normal" accumulation of copper points to a common problem of trying to fix a quantity regardless of what is causing that. This work will try to highlight the supremacy of cause and effect over treating numbers.

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1. INTRODUCTION

This work is organized differently from many papers due to copper's biology and the relationship between existing literature and the new results presented herein. A long redundant introduction motivates an interest in the topic in self contained pieces without requiring the entire section be read. The novel results are relatively simple dog feeding chronologies with observations and outcomes. The "case report" section that describes the results for each dog also includes some analysis and interpretation related to the introductory material that would be too distant in the discussion section. The actual discussion of the results is short comparing and contrasting the results from these dogs with expectations and tentative explanations for the entire data set followed by some likely relevant chemistry and implications for supplementation. As one theme of this work is reconciling results from different categories of evidence, a new category of exposure in other civilizations is introduced at the end for additional context.

1.1. Copper distribution is confusing and deficiency often ignored by doctors

Copper is not currently a trendy supplement for humans or dogs. This may be partially due to deficiency being a neglected diagnosis by physicians [104] [99] [367] [358] [116] [1]. In one case of simple copper deficiency with no obvious causes first presented in May 2002 was not diagnosed until December 2003 with authors concluding response to copper can be rapid avoiding inappropriate work up if recognized early [173]. An overview by Brewer [48] in 2012 was quite emphatic about copper and iron supplements in older people, suggesting few people need them and they can be dangerous particularly for cognition and recommended avoiding meat. However, a 2018 work suggested widespread copper deficiency as a cause of many diseases currently common in North America such as "obesity, ischemic heart disease, and metabolic syndrome" [254]. A 2024 work recognizes copper distribution as a contributor to atherosclerosis and deficiency as a possible issue but does fall back to chelators and ionophores as possible solutions [395] not considering the possibility of global deficiency leading to bad allocation. Isolated authors do sometimes point to copper deficiency as a major cause of diseases such as heart disease [78] [203] and copper containing or eluting stents have been investigated since 2017 [159].

Thinking out loud

Probably a lot of indirect observations also suggest a role in heart disease. For example, MnSOD polymorphisms that correlate with "deficient cardiovascular function" [19] suggest the importance of mito ROS which may be generated with copper deficiency.

In dogs, both dietary and genetic issues are a known concern. Heritable issues with copper accumulation do not appear to be well understood in terms of mutations and clinical outcome with inbreeding thought to be one contributor [96]. A specific issue with liver copper accumulation has been noted coincident with the use of a copper pre-mix that an expert consensus statement on hepatitis in dogs suggested as a cause [381] pointing to increased intake. However, known and expected functions make it a good match to several disease states motivating an interest in careful supplementation even if contrary indicators also exist. One topic of this work is concern the possible destruction of other vitamins, indeed the creation of active anti-vitamins, by a copper pre-mix. Copper nutrition does appear to be of recognized importance in dogs and the question of dietary deficiency or excess has been a topic of controversy for many years. It is likely that copper intake alone is not the dominant issue but rather distribution in the body determined by signalling, other dietary components, and genetics. The question of supplementation has to be answered within the context of a specific overall diet as well as recognized factors including genetics. If an unusually high copper concentration is measured in one location, the question remains if there would be a net benefit reducing deficiency in some other place even if more local excess occurs. And that "excess" may itself be adaptive it can't be assumed to be pathological just because it is not commonly observed in healthy hosts. This has to be answered in terms of clinical outcomes, things relevant to the host, rather than lab values absent cause and effect relations. Even in the case of known genetic diseases, copper removal to improve liver values may create clinical copper deficiency. Treatment emergent copper deficiency was observed in a Bedlington Terrier with an excretion defect that clinically resolved with cessation of chelation [319]. Perhaps as more is known about ALS, it will be an excellent example of copper distribution problems that are not really excess of global deficiency [246].

1.2. Hepatic copper excess needs context

One increasingly common concern with dogs is copper associated hepatitis [10] [11] [52]. Copper handling genetic diseases are well known in dogs [178] and some concern about excess intake may be warranted for specific animals. Some noisy association between intake and hepatic copper content was shown in a small study [95] but copper intake

may not be the major determinant of copper content . The causal role of copper "excess" in any clinical disease remains unclear. One study produced a histogram of liver Cu content (ppm dry weight) for a few hundred dogs but did not conclude there was a particular cutoff level for health vs disease [349]. Work continues to focus on concepts of deficiency or excess even though both may be matters of degree, location, and context. Deficiency in commercial dog foods was suspected years earlier [352] while works as early as 2000 suggested supplementation would be unhelpful[350]. A recent work comparing mineral content in groups of commercial dog foods found some patterns and advised against high copper foods [181]. However, other nutrients have been observed to modify copper distribution. One reason for liver copper accumulation known since at least 2011 is iron deficiency [291]. A 1997 study found riboflavin deficiency reduced heart and liver iron while increasing copper content [57] and so other nutrients could still be responsible. A high calcium diet increased liver Cu in pigs [287]. Further, copper reactions in stored food could damage some of these nutrients hypothetically at least allow creation of an association between pre-mix and accumulation but mediated more by vitamin destruction than total copper consumption. Interestingly, although riboflavin is thought to be stable under many conditions it may degrade with metal sulfates but not chelates [66]. It is possible to form anti-vitamins which may be potent inhibitors of original vitamins but with passive non-saturating uptake.

Thinking outloud

citation needed as they say on wikipedia ...

At least one report indicated that hepatic export of ceruloplasmin was stimulated by thyroid hormone [248] suggesting that hypothyroidism could allow for hepatic copper accumulation. As may be expected, copper sufficiency modifies metabolism of other entities such as amino acids and in particular tryptophan. Copper deficient rats appeared to metabolise tryptophan loads differently and excrete amino acids but only taurine was found in the urine of copper sufficient animals [121]. As amino acid status in old age may be a concern these effects of copper may be of larger importance.

Ideally observation of a pathological copper buildup in one location with symptoms of deficiency in other systems would lead to a search for the bottleneck prohibiting a better allocation. With copper this is quite complicated as a number of regulatory systems are known to control copper levels in different compartments in healthy mammals. Uptake regulation is not completely known but response to dietary or ambient levels is only part of the control loop in vivo. It is likely cytosolic sensors exist [129] to monitor cell contents but more global mechanisms appear to operate too. It turns out that copper related signalling is such that remote signals may exist from the heart to liver and intestines to make more available [168] [268]. In this scenario, local shortage in the heart could induce blood stream or liver excess due to added uptake with attempted but failed cardiac specific delivery. A similarly confusing feedback scheme has been suggested for other nutrients such as tryptophan [219] and biotin [224] [218] . Feedback regulatory systems, as with genes more generally, are likely selected by evolution but that need not make them simple or completely robust to defects in the control loop. One recurring source of defects to consider is high-infidelity translation or a specific pattern of translational defects that could be a consequence of the charge state of tRNA for particularly problematic amino acids. One recent work associated alterations in tyrosine and phenylalanine with age [157] although a lot more work is needed to understand importance of this issue. For example, copper transporter CTR1 , important for intestinal uptake [267] and distribution [187] [26] [180] has reduced function if some histidines are mutated in either the C or N terminal tails. Intestinal loss of CTR1 causes cardiac hypertrophy among other issues that are partially correctable with copper supplementation [267] This suggests cardiac copper deficiency, possibly due to histidine deficiency, can contribute to cardiac hypertrophy in animals. However, if uptake and accumulation occurs while the heart is deficient this effect, combined with other mechanisms, does not exclude simultaneous excess in the liver. Its also quite likely that a lot of early results will show to be misleading. For example, it was only recently that the zinc transporters such as ZIP5(SLC39A5) are also high affinity copper transporters [284] although a contemporary paper attributed health effects purely to zinc [64] its unclear if the hepatic metals tell the whole story.

Even with excessive intake, in most genetics biliary excretion increases when "pathological" amounts of copper begin to accumulate [59] [125] pointing to defects in excretion as another possible problem. However, many cause and effect relationships or control paths exist allowing other factors to control local copper concentrations. Senescent cells may accumulate copper in the absence of autophagy [236]. Copper elevation may commit cord-blood derived cells to differentiation [279] and it may be regulated during myogenic differentiation [362] raising the possibility that accumulation is due to confused signalling. Copper is also very important in the brain [105] where it modulates adult neurogenesis in the subventricular zone [201] and sleep-wake cycles in the locus coeruleus [206]. The major copper transporting protein ceruloplasmin is an acute phase protein and blood levels may be associated with pathological conditions [115] but a protective role is generally recognized. As a major transporter of copper out of the liver, stresses then could reduce hepatic copper. In fact, as substantiated later, it would make sense for copper to be redeployed from some mitochondria to the blood in response to pathogens or trauma or "beating plowshares into swords". Indeed, cytosolic copper accumulation has been observed in response to infection contributing to intra and extracellular defense as it regulates overall innate response [210]. If the cytosolic accumulation is at the expense of mitochondria, this can lead to hydrogen peroxide formation at complex IV which is likely to help control infection.

Emerging topics such as extracellular vesicles [29] suggest that uncharacterized mechanisms of metal homeostasis exist making definitive statements difficult.

This work will tend to support the idea of "listening to the heart" or assuming copper retention is due to need by the heart even if some accumulates in the liver. Its likely the brain needs have significant influence too.

Thinking outloud

An interesting recent work suggests that iron accumulation in aortic valve calcification is a compensatory response to global iron deficiency [199]. It remains to be seen if this is "compensatory hoarding" favoring the heart but that does have to be considered as a possibility. If you only found the hoard, you may be tempted to chelate.

1.3. Copper status is ambiguous in biochemistry and clinical outcomes

Thinking outloud

now Cp comes up twice maybe condense and lead from chem to clinic. Cu to cough a bit of leap

Location specific quantities can be the result of many contributions and don't mean much without the "cause and effect" leading to the result. Blood or serum levels are easy to obtain as part of normal practice but copper's functions often execute in less accessible locations. As details are often unknown, a colloquial analogy may be trying to infer adequacy of military hardware from measuring the amount on civilian roads. Blood vessels may be used for transport in times of stress raising levels independent of global or niche amounts. There is a recurring problem using blood levels of some thing to indicate excess or deficiency. Some blood components such as electrolytes may need to be closely regulated but this is not the case when materials are just "passing through." These blood components are regulated or influenced by specific factors having nothing to do with overall sufficiency. In the case of copper, ceruloplasmin usually dominates blood copper and it is regarded as an acute phase protein causing blood levels to elevate in response to various stresses. Association studies may then find a correlation between high blood copper and some bad state as has been noted for cardiovascular [100] and Alzheimer's [328] disease although a protective role now tends to be recognized [204]. This work describes some important well known locations that copper could exist although surprises are still likely. Recently some body of work has suggested that macrophage lysosomes may also regulate overall metal distribution [285] a location that would be expected to respond to many stimuli. Overall it appears that mitochondria and energy intensive organs like the heart may be the most important influencers.

One meta analysis of bone loss and copper suggested only supplementation studies in the 2.5-3mg/day range showed a clear benefit as blood levels and food intake did not correlate with bone improvements [300]. Its worth noting that this dose range is above common daily guidelines which are around 1mg/day. One patient with pure copper deficiency and no predisposing conditions was treated with 8mg/day [173]. Treatment of copper deficient myelopathy typically is performed with about 2mg Cu /day although up to 8 mg/day was indicated [152]. 5mg was used to demonstrate an increase in human growth hormone in 6 of 12 tested subjects [45]. This work describes supplementation to dogs with similar dose ranges although much higher doses normalized to body weight.

This work will try to evaluate the goodness of copper supplementation based on things relevant to the host's "quality of life" or clinical outcomes. One simple thing that is influenced by copper, at least in dogs, is coughing. This is certainly relevant to the host and would have to be considered an easily observable clinical outcome. However, the underlying diseases that provokes the cough may not monotonically correspond to coughing features. Coughing may be more common during excitement which does not occur with a feeling of lethargy common in disease. Careful consideration of the diseases and locations in the following section suggests that disease and this symptom could decouple with copper supplementation. That is, coughing may increase with arousal state and it is thought that initially copper may increase overall energy levels and therefore coughing frequency if another problem like heart disease or collapsed trachea also exists. However, at least one pathological state may be improved with anticipation that another pathology will recover but more slowly leading to later coughing reduction as more pathological states resolve.

1.4. This kind of confusion is common for recurring reasons

Thinking outloud

this probably is a work of its own like the manuscript I started years ago although the application to copper is relevant. Maybe a bit grandiose and verbose too but this is important. Sentences longer than one paragraph? LOL.

This work describes inclusion of copper into a set of supplements for dogs with different conditions and unknown genetics showing generally beneficial results or at least no obvious harm. This result is in contrast to some of

the popular expectations cited above. A discrepancy between expectations and outcome of this type seems to be common in medicine even as late as clinical trials so understanding the causes of that in this particular case may help optimize supplements and avoid delays in understanding the limitations of data, theory, and even anecdotes, to design therapeutic interventions. In many cases, where different types of information seem contradictory, it may turn out that resulting paradoxes are really regulatory paradigms.

Some types of problems are listed in Appendix C as a general guide. Due to the nature of the issue and time constraints, they are not well organized in any sense but may elicit an interest in further consideration of existing data.

Thinking outloud

this is rambling and vague maybe save the point for coagulation, alzheimer's etc where it is more to the point. Adding logic and organization to reasons for illogic may not be worth it ... also consider "too stupid" or "no one is that stupid" to highlight arrogance lol.

While it may help to make these things explicit by listing them or naming them, one unifying theme is missing cause and effect or system organization. Typical responses may try to disable a 'system' instead of fixing it leading to limited outcome quality. One common problem that may turn out to be relevant here is a belief in opposites and concluding that if decreasing some quantity helps then there is no benefit in increasing under different conditions or states. In fact, many control loops appear to "try harder" in response to initial deficiency with goal related feedback creating inconsistent associations between various quantities. This is most likely if something (else) doesn't work which may be due to "quality" and feedback based on a goal or result. Instead of disabling the system, fixing it with more of what it needs is likely a better approach . In the case of copper, local deficiencies simultaneous with other excesses may indicate a lack of some other nutrient that is believed to be bad. Trying to treat quantities, or make a concentration similar to healthy people, may defeat an adaptive mechanism making things worse.

Interpretation of the copper literature may be limited by some of these such as unquestioned assumptions and common logical fallacies. A 2010 work suggested that high copper and iron intake were particularly dangerous in older people observing that one study concluded high intake of both was associated with increased cognitive decline [47]. The above cites the work of Sparks finding that trace amounts of copper in water added to a high cholesterol diet produced Alzheimer's like disease in rabbits [336] which may relate to cytochrome C oxidase in the brain [249] as is a central theme here. By 2012, Brewer suggested AD was largely due to similar problems in people due to plumbing, supplements and fat [48]. The actual result appears more complicated [316] [315] with contemporary thinking similar to that suggested here that copper distribution is unclear in real disease [85].

Part of the reluctance to supplement "high" copper doses is the accumulation in the livers of some dogs but relation to any clinical disease is not clear. This may be similar to amyloid beta in Alzheimer's Disease and pointing to the need to understand cause and effect before an all out attack on one molecular entity.

Thinking outloud

keep AD section as fact collection for now

The role of copper in Alzheimer's disease may be interesting both for its likely role, discussed later, but larger fallacies inflicted upon the disease effecting interpretation of copper related data. The amyloid beta hypothesis has remained central to AD even with hints at it unravelling[92] such as a 2002 work suggesting that "tauists" and "baptists" could 'shake hands' and look for other causes [255]. Even after all the antibody work trying to identify the right physical conformation and peptide, confusion exists about the role of amyloids. A recent example may be the identification of amyloid beta as a nominally protective substance [400] [297] instead of the cause of Alzheimer's pathology and target for intervention. Recently amyloid beta was even found to promote osteogenesis [60] to counter osteoporosis. It was also found that PRSEN1 mutations do not appear to generate neurodegeneration through amyloid beta [392]. Its toxicity may even result from gamma secretase inhibition [411] which had been considered a therapeutic intervention.

Given all these revisions to cause and effect in mainstream AD literature, it may be interesting to reinterpret a 2016 Sparks work showing creased ABC1 and amyloid beta adding copper to high cholesterol [317] if there is clinical benefit due to a beneficial form of amyloid beta.

Interestingly, related to copper, is the emerging role of lysyl oxidase in Alzheimer's as a possible target where it associates with cerebral amyloid angiopathy and is thought to be a drug target [165] [361]. However, upregulation would have to be suspected as a part of regeneration attempting to fix degeneration. Indeed, LOXL2 is known to be regenerative [348].

Other counter-intuitive approaches are easy to find. In the case of coagulation, isolation of the trigger from coagulation system should stop the clotting but a low enough quality clot may never achieve that goal creating larger less functional clots. In essence similar to perhaps hypertrophy in response to cues for more. Previously, heartworm positive dogs had been given significant amounts of vitamin K [232] [229] although severe case may be conventionally treated with anticoagulants. In this case, it may not be clear that vitamin K effects clot quality and consequently may limit pathological quantities allowing for beneficial clots to form.

1.5. Copper related outcomes depend on everything starting with food preparation

One problem making reproducible statements about copper supplementation may be the interaction of copper compounds with almost everything else. Literature exists on some interactions but the versatility of copper probably makes a complete list intractable. A starting point for a 'usual suspect' reaction participants list is in Appendix E merely to indicate a lot of what is left out of the current analysis. Interactions with sulfur will be discussed in more detail later as these appear to be most important but others likely matter too.

Some of the issues include,

1. **pH dependent solubility** An early low pH step such as in the stomach may be important for later absorption.
2. **reduction** Copper is normally divalent but can be reduced leading to both more reaction products and precipitates.
3. **insoluble precipitates** Copper reacts with many things to form solids that may not be extractable from GI tract.
4. **destruction of vitamins** A big concern is creation of anti-vitamins which can be more potent than the vitamin being antagonized making it difficult to fix with more vitamins. These vitamins may be important to copper distribution and utilization leading indirectly to things like excess copper accumulation.
5. **other reactions such as Fenton chemistry** There is an ability to do a lot of oxidative damage.
6. **competition with other metals** This is most commonly considered in uptake and enzyme metallization. The copper transporter Ctr1 is thought to be selective against most divalent metals as it transports Cu(I) but is inhibited by Ag [235]. Enzymes may be subject to mis-metallization although there may be evolutionary pressure to use a variety to metals [329].

Many of these may be a concern at each step of copper handling.

1.5.1. Food Preparation

Its important to remember that all food components are chemicals and have interactions beyond their role such as a vitamin. As soon as they mix they can react during preparation, storage, or consumption. The importance of total meal chemistry for copper availability was recently made for poultry [389]. However, a couple of papers from 1964 illustrate the problem of reactivity quite clearly as "copper" toxicity varied significantly with meal formulation. Initially turkeys were fed either a natural or a purified diet with varying copper levels demonstrating toxicity in the purified diet but only minor issues combined with the natural diet [369]. A follow up work suggested the purified diet could be safe with copper as it considered vitamin A, D, and zinc additions and noted an off odor in high copper feed [341] suggestive of undesirable reaction products. Its curious no one considers these results today. The possibility of vitamin depletion and formation of toxics, notably anti-vitamins, needs to be considered in copper mixtures. This is of course in addition to copper absorption efficiency. Simple things can matter a lot for many reasons.

Ideally the optimal fate of all consumed nutrients could be identified and manipulated with both meal and diet composition. This work includes consideration of a background feeding context including real foods and controlled supplements that has been described previously [221]. This diet was further refined by consideration of the interactions described herein. The copper supplementations described here, about .3mg/kgBW/day, is likely well in excess of background levels in most known natural diets although its also worth noting that other sources may be accidentally significant as with water and air exposure [110].

1.5.2. Intestine

The initial important GI step is probably the stomach but the function of the stomach has to be considered in terms of achieving absorption in the intestines. Past the stomach into the intestines, the pH increases and mucin layers are thought to actively participate in metal or "trace element" absorption [84]. Mucin quality may also depend on nutrition such as available threonine [183]. However, they may not deal effectively with precipitates grown in the stomach.

1.5.3. Stomach or similar

The high acidity of the stomach may be important for allowing broad nutrient absorption over a large range of meal types. ZZ GI health and in particular stomach acidity may be important factors in copper uptake but also copper distribution due to other nutrient deficiencies caused by stomach defects. Interestingly, many conditions related to copper appear to be age dependent and stomach acid and chloride levels may decrease in older age. Naively, you may expect low acid to reduce solubility of metals and decrease enzymatic activity for digestion of proteins. Copper solubility is pH dependent [73] similar to the competing element zinc for which absorption has been shown to depend on salt type as well as gastric pH [135]. Interaction with food components such as polyphenols is significant and pH dependent [283] motivating a larger interest in food interactions and in particular rings such as in tyrosine. Speciation gradients may be large in the range of possible stomach acid levels. A 2021 study explored copper speciation in simulated gastric juices with food components such as tyrosine and citric acid among others [388]. Impact of GI pH on broiler chicks has been studied due to impact on nutrition and microbial populations with Cu-Zn antagonism also observed in the digestive system [277].

Some information about stomach pH variations and health outcomes may exist from the study of human PPI users. PPI's can raise stomach pH from 2 to 6 and produce "profound hypochlorhydria" [102]. The latter point may be important as Cl as much or more than H may have impact on microbiome and gastric chemistry. The literature around PPI's tends to support reduced acid as healthy but it may be important to address these issues here although not explicitly copper related.

Thinking outloud

move to cancer section

There is a conjectured tumor protective effect from PPI usage and usage for suppression of colorectal cancer has been suggested [172]. There is also some indication that pH 6 encourages cancer progression versus pH 8 [195] yet alkaline stomach pH is commonly observed in gastric carcinoma [397]. Empirically gastric cancer rates do correlate positively although arguably with PPI usage [370] [318] [71].

Thinking outloud

cancer section? nutrient interactions here

Probably the dominant effect on tumors is unrelated to ambient pH although increased pH may reduce nutrient accumulation by many cells. An absolute apoptosis rate at near neutral pH is probably not indicative of the overall fitness in the stomach. The effects going from pH 6 to 8 say nothing about the effects of going from pH 6 to pH 2 as one extreme says nothing about the other. It's important to note that they do seem to aid eradication of H pylori and therefore should reduce gastric cancer rates if bacteria are involved. The PPI's appear to attack H. Pylori directly [310] [16]. Its claimed that H pylori can survive down to pH 4 but only grow between 6 and 8 [233] affirming a role for acid in control of these pathogens. It's been observed as early as 1994 that Omeprazole inhibits survival of several organisms at low pH while H pylori only has a benefit in the presence of urea but the PPI effect is urease independent [240]. Clinical effect of PPI's probably does not relate to increased stomach pH and would not be decreased with concurrent intake of acids or chloride which may further improve microbiome.

Omeprazole was also shown to inhibit ATP7A, a copper transporter, preventing melanogenesis [237] and in fact a number of side effects are known along with vitamin deficiencies [214] with the latter likely contributors to the former many of which are common in old age motivating the idea of exaggerated medical "aging."

Other metals may also compete with copper directly or by regulatory loops. Iron intake in feed has also been observed to decrease copper uptake in ruminants [68] and rats [188]. One work suggested iron disrupts copper homeostasis independent of uptake [124]. Zinc is a known inhibitor of copper uptake and cases of zinc induced copper deficiency in humans are known [368]. In chicks, and humans as discussed later, silver may induce copper deficiency through unknown means but mercury may improve apparent copper status only being toxic in copper sufficient animals [138]. Competition between Cu, Fe, and Zn was observed in Caco-2 cells [13].

While concerns exist about copper content in dog foods, a recent survey of some zinc content shows many foods contain amounts above recommended maxima and few are low or deficient [281]. Age related absorption problems in people are known [286] and other apparent deficiencies could be a consequence of insufficient B-6 alone [55]. Interestingly, B-6 is added to penicillamine treatment of Wilson's disease to avoid neurological effects [80].

Thinking outloud

Since paradoxes are a concern here, it's worth noting that pyridoxine is an inhibitor of PLP and high doses result in functional B-6 deficiency [365].

1.5.4. The overall diet may be important for copper distribution

The complete diet probably makes contributions to the overall distribution of copper in the body and impacts ability to use copper beneficially. This includes components consumed with or separately from copper. As sulfur is one of the better studied and most important issues it is discussed in its own section.

Dietary cholesterol appears to distract copper homeostasis with atherosclerosis thought to involve copper dysregulation [194] and high fat diets in other species [132] are an issue. Fructose also inhibits relative copper absorption [269] [378]. Once in the body, the ability to distribute and use copper depends on other nutrients maybe more than is the case with other vitamins or minerals.

Body stores of copper increase with excess tyrosine in the diet of rats [393]. Some reports show specific issues when combined with vitamin C. A small trial with copper sulfate and vitamin C indicated kidney problems result [158] although alternatives with copper gluconate suggested use as food preservative [118]. Dose probably matter among other factors.

1.6. Copper interacts with dietary sulfur in other animals

The most well known issues with copper and dietary sulfur involve cows due to its common and profound economic impact but related studies have been conducted in non-ruminant lab animals. The latter may be more directly relevant to dogs and humans but the severity of the problem in cows may indicate some effects important but more subtle in the target population. In the other end of the spectrum may be poultry, mostly turkey and chickens, which may be notable for contrast to both mammals and ruminants due to the low pH proventrulus [296] as well as the gizzard with low but maybe variable pH [190]. Experiments on non-ruminants cover some of the supplements used in this work that could impact copper sufficiency and toxicity.

Thinking outloud

repeated text / citations in discussion

Taurine has been observed to reduce copper toxicity in rats with increased fecal copper amounts [149] suggesting decreased absorption. Another work demonstrated taurine reduced ceruloplasmin only in rats fed a control diet but not a high-fat diet [177]. As taurine is being explored for various indications, including DCM [241], supplementation could relate to induced copper deficiency which would likely cause some symptoms expected of copper deficiency.

Ascorbic acid in rats initially reduced absorption of copper but may eventually limit excretion [359]. In pigs, 60 percent fed a copper deficient diet died from coronary disease while supplementation as high as 250mg/kg diet, well in excess of the 10mg/kg diet requirement, can be growth promoting on a typical pig diet [86]. Pig tolerance of sulfur appears to be significant as higher sulfur diets did not seem to impact measures of copper such as liver content [167] although another work showed more complicated results with reduction in ceruloplasmin being one result [74]. The latter work noted decreased liver copper with the addition of potassium carbonate.

Exploration of optimal copper supplementation in poultry suggested copper is less available from cereals than vegetable proteins with amounts "greatly in excess of requirements" further improving results [191]. Very high dosing is common in chicks to avoid antibiotics and copper hydrochloride is often chosen for acid specific solubility [264]. An investigation of copper and sulfur containing amino acids in chicks showed marked interactions while suggesting copper toxicity was due to "chemical nature of the diet rather than to any specific copper induced nutritional deficiency" [299]. Methionine fed to chicks on a high copper diet could reduce some growth depression but it did not affect hepatic copper amounts [186] suggesting a number of possibilities that may not relate to copper uptake. Chicks apparently suffer reduced absorption of copper from sulfate in the presence of L-ascorbate and L-cysteine but some of that may be improved in some conditions using methionine or lysine chelates [12]. Interactions between methionine and copper were also investigated in turkey [163].

Ruminant sensitivity to dietary sulfur may be an interesting example of how a mild pH step can produce insoluble copper products creating profound deficiency. It's unclear on the extent to which this can occur in dogs or humans but it is illustrative. Sulfur and also molybdenum are common causes of cattle copper deficiency. They have been studied for impact on cow copper status with different background diets and shown to be significant modulators [325]. Decisions about copper supplementation are difficult though in economically important ruminants [209] and particularly in cows as concerns about toxicity [207] apparently can not be mitigated with other nutrient changes. A study of a problem with Przewalski gazelles found no difference in forage copper with clinical status but did find important difference in sulfur in forage and soil [409]. That work also identified biomarkers such as hair copper content although in this case the copper deficiency related to sulfur excess was so bad liver and blood levels were low too.

Ruminants differ substantially from non-ruminants and notably rumen pH is only around 6 reducing solubility of relevant minerals while allowing formation of insolubles [337]. This may motivate interest in issues with age related

reduced stomach acid in humans. The low pH GI stage may reduce sensitivity to dietary idiosyncrasies. The presence of a stage able to nucleate insoluble nutrient blobs may prohibit later absorption. Other factors such as microbiology however need to be examined too. In pigs, response to high copper diet varied between "germ free" and conventional groups [324].

Sulfate reducing bacteria may also contribute to confusing metabolism of taurine and methionine [375] .

1.7. Copper interactions with WHY and Cu related clinical impact

While sulfur containing amino acids have the most obvious interactions with copper, this work tends to focus on the ringed amino acids - Tryptophan (W) Histidine(H) Tyrosine(Y). W and Y are thought to vary significantly with age and histidine is important for copper binding to proteins. Notably tyrosine protexes ceruloplasmin and 6 histidines, one for each copper, are required for a functional enzyme. Mistranslation due to insufficiency will be exaggerated by the higher power if all need to be right. There is some indication that "diseases of old age" are at least partially mediated by sarcopenia, most recently atrial fibrillation [346] consistent with earlier ideas linking age to amino acid starvation [219] .

There are several works exploring the interactions in various places. In growing rate, "Excessive tyrosine and phenylalanine caused a marked increase in serum copper and ceruloplasmin activity, whereas excessive cystine, methionine, and histidine caused a decrease in the ceruloplasmin activity. " [164] Copper chelated to amino acids may be more robust against Cysteine (and ascorbate) inhibition [12].

Thinking outloud

cited elsewhere too

Interest in the interaction of tryptophan with copper go back to at least 1930 exploring the relation between tyrosine and tryptophan, among other nutrients, on total copper in hen eggs and subsequent hatchability [239]. Interest in the interaction of tryptophan with copper go back at least to 1973 when urinary metabolites were measured with different copper intakes (repeated ref) [121]. Trp was found to reduce toxicity of copper to the Caspase rach [90] and teleosts [144]. while improving response of grass copper to environmental copper [383].

One study found histidine decreased while tryptophan increased copper absorption [379].

While not directly concerning copper some related observations suggest what may occur. Drosophila shows a non-monotonic but generally increasing relationship between tryptophan intake and zinc stores and the authors point to microorganisms living or killed to be able to modulate Fe,Cu, and Zn to varying degrees [109].

Interestingly, Scavenger Receptor BI contains 8 highly conserved tryptophans [141] which appear important for cholesterol transport suggesting trp deficiency will slow down its translation , lead to early termination, or create many imperfect receptors. So, deficiency of these amino acids may produce broad non-specific problems that appear to be common in intractable diseases often associated with old age.

1.8. Recent Similar Work

At least one recent work [62] has summarized many of the same issues relating to copper and cardiovascular disease but with better editing and depth. However, it does not point to some of the cues outlined herein. For example, the issue of "other" limiting nutrients determining when copper is beneficial or not.

1.9. Copper rich diets for dogs and people are worth consideration

The known biological roles for copper suggest it may be an important limitation in functions that relate to common diseases yet understanding of the body's copper distribution is limited. This work addresses the topic by following a group of dogs with varied conditions and outcomes as supplementation changed. It is probably unique in reporting variations in many dietary components although lacking some common metrics like daily calorie consumption.

Interest in the dog feeding work is first motivated by introduction of the diseases likely to be modified by copper intake and then the specific sites of the most important copper activity. The first section makes the work relevant to achieving clinical benefits but the second part helps determine things like time scales over which changes may be observable. This is particularly important here as copper may have different effects on different time scales making symptom changes difficult to interpret.

While the diets were guided by many hypotheses, the results are hypothesis generating or refining rather than attempts at proving any specific tractable ideas. Taken together this work supports the idea that supplementation in the .5mg/kg range added to the "background diet" produces no obvious harm and may solve some of the conditions

discussed. Given the complexity of diets in general and the recurring problems with ostensibly better approaches, this may present unique data and results with atypical limitations and artifacts. The reported results should be thought provoking on their own but hopefully the overall complexity of this simple "feeding dogs at home" effort is amenable to analysis with emerging AI or related methods.

2. DISEASES OF INTEREST

Dogs here have suffered from conditions that may be modified by copper intake including cancer, heart failure, respiratory infection, collapsed trachea, and hypothyroidism. This work will focus on these conditions as well as a few others for context as listed in Table I. The dogs described in this work were suspected of having at least one of these conditions at some point with various levels of confirmation. These conditions are not mutually exclusive and in fact may relate to each other when they occur together. All of the above conditions may involve cough as one symptom and disease trajectory or symptoms may be modulated by copper status. Most of these are well associated with cough but a couple may be less obvious. Cancer may directly effect the lung but nearby tumors may also irritate the respiratory tract. Hypothyroidism is not commonly associated with cough in dogs although thyroid enlargement can occur irritating the trachea.

Copper deficient liver patients may be notable for "steatohepatitis, iron overload, malnutrition, and recurrent infections" [401].

The other diseases in Table I do not fit into this category entirely but the role of copper and the state of literature help put these diseases into context.

Besides cough, the present work relies on thyroid related symptoms (coat quality, weight distribution, energy level etc). Cough has many possible origins as discussed previously [230]. "Energy level" in most cases described here is thought to relate to shorter term fluctuations in mitochondrial copper rather than thyroid although its important to consider all possibilities. One point of this work is to interpret outcomes recognizing that symptoms and disease trajectory can decouple and notably coughing may increase as part of a disease complex resolves.

It's also important to note that a "state of health" requires a lot of things to go "right." Not everything need be "good" as many compensatory mechanisms exist to allow clinical health with different parameters. But, while a range of copper intakes may be required to allow for disease free state, failure to produce that state with more copper does not prove copper is irrelevant. And indeed even short term symptoms may not track disease trajectory. For the sake of writing tractable overviews, these considerations may be omitted in the following sections.

Disease	Host	Effect	time scale
DCM/HCM heart failure	dog		4 weeks [62]
Collapsed Trachea airway defects	dog rats		months, 60 days [270]
Hypothyroid	dog		
Infection	dog		
covid-19	human	serum levels irrelevant [302]	
Parkinson's	human	assoc benefit [404]	
Alzheimer's	human	brain depletion with excess Cp [69]	
Infection	human		
Arthritis	human	anecdotes, no trial verification	
Cancer		need to understand cause and effect	

TABLE I: Some diseases and conditions with copper involvement that may be illustrative of less obvious issues.

2.1. Collapsed Trachea

The importance of copper to quantity and composition of structural proteins, in this case elastin, has been known since at least 1954 [338].

Collapsed trachea and related airway defects have been well described in humans, dogs, poultry, and other animals such as horses. The differences in the literature are significant suggesting either important differences in diseases or literature fragmentation. The dog literature does not appear to consider copper as a factor directly but interest for this paper is motivated by consideration of the larger body of information. Copper may be involved either in cartilage quality or in infection control. Copper deficiency has been associated with lung development defects in rats [270] and airway and arteriole elastin were at least partially restored after 60 days of additional copper. Interestingly, copper

"eluting" stents are being explored to prevent blood vessel "collapse" or restenosis in humans due to [374] due to some of the properties considered here and its unclear why dietary copper would work less well. In 2025, one group has improved bioprosthetic heart valves by adding copper doped carbon dots[323].

A variety of causes are known in humans [326]. "Excessive dynamic airway collapse" notably is a rare side effect from anti-viral treatments for hepatitis [7]. In humans, it is a rare disease regardless of cause and CT observation of a "collapsed trachea" may result in debate over actual names for the condition [107] with surgery as a common treatment.

Horses and mules suffer from collapsed trachea too. Mostly small breed or miniatures horses were thought to be most susceptible but a 1992 case report of a horse with pneumonia noted that collapsed trachea resolved with infection cure and just due to infection related inflammation [93]. Currently it appears two causes are noted with the infectious resolving on cure.

In poultry infectious causes appear to dominate the concerns .Turkey infected with *Bordetella avium* experienced trachea collapse which was attributed to copper mediated crosslinking [399] even though collagen content was reduced. This points to a role for copper but suggests it makes the trachea worse. A study of silver nanoparticle effects on broiler chicks infected with *Escherichia coli* found [18].

the T3 [highest dose] group revealed congested round heart, thickening of crop and esophagus, atrophy of BF, thymus, and spleen, enlarged gall bladder with watery content, collapsed trachea, and internal hemorrhage.

which includes possible results of copper deficiency. Interestingly, high dose silver has been documented to decrease ceruloplasmin synthesis and serum copper concentration [261] [339]. Although it is also noteworthy that gold nanoparticles have been found to have some properties consistent with improved copper distribution such as reduced body fat [320]. It is not surprising that silver could be confused with copper as analogs can be inhibitory but as discussed elsewhere ceruloplasmin synthesis can proceed without copper but the protein may not be properly metallized. The reduction in synthesis is surprising although perhaps only copper containing ceruloplasmin was assayed and details need to be considered. The authors also mention other means than mis-metallization that silver or other metals can create a copper deficiency.

There is a lot of literature on dogs with many causes and therapies discussed but little overt inclusion of copper. One author introduces the topic as [347].

Tracheal collapse occurs most commonly in middle-aged, small breed dogs. Clinical signs are usually proportional to the degree of collapse, ranging from mild airway irritation and paroxysmal coughing to respiratory distress and dyspnoea. Diagnosis is made by documenting dynamic airway collapse with radiographs, bronchoscopy or fluoroscopy. Most dogs respond well to medical management and treatment of any concurrent comorbidities. Surgical intervention may need to be considered in dogs that do not respond or have respiratory compromise. A variety of surgical techniques have been reported although extraluminal ring prostheses or intraluminal stenting are the most commonly used. Both techniques have numerous potential complications and require specialised training and experience but are associated with good short- and long-term outcomes. INTRODUCTION Canine tracheal collapse is a progressive disease occurring mainly in middle-aged small and toy breed dogs. Degeneration of the tracheal cartilage rings as a result of reduced glycosaminoglycan and cellularity leads to dorsoventral flattening of the trachea and laxity of the dorsal tracheal membrane.

Alternatively, it has also been introduced as [189]

Tracheal collapse (TC) is a congenital cartilaginous tracheal ring problem to which small-breed dogs are predisposed. It is usually diagnosed by performing radiography, fluoroscopy, and tracheobronchoscopy. Tracheobronchomalacia is a structural defect of the trachea and bronchial cartilages. It results in flattening of the trachea and bronchial lumen. Affected tracheae show hypocellularity of the cartilages, loss of hyaline cartilage, and deficiencies of chondroitin sulfate, calcium, and glycosaminoglycans [7]. Fifty-one percent of dogs with a chronic cough exhibit tracheobronchomalacia, a condition regarded as a common cause of cough. More toy-breed dogs than dogs of other breeds show tracheobronchomalacia when they have a chronic cough [13]. Upper airway obstruction, infectious tracheobronchitis, heart enlargement, parasitic disease, obesity, and oral problems can exacerbate clinical signs of TC [12]. However, studies investigating TC in patients without a history of cough are lacking.

Therapies in dogs can involve surgical interventions but also some of the following [245]

Medical management can include antitussive therapy, antibiotics, bronchodilators, and/or anti-inflammation medication, e.g., corticosteroids and NSAIDs (21, 22). Many dogs respond to this medical

therapy, but some have complications, especially with long-term use of corticosteroids which increases the risk of secondary bacterial infection, increases the respiratory rate, and induces weight loss that worsens the patient's clinical signs (3, 23).

the above work also largely endorses a specific commercial product noted for polyunsaturated fatty acid content. As described later, Happy appeared to worsen on a low fat meat diet making this an interesting report.

This work is predicated on the idea that there is often a nutritional component to cartilage quality and quantity with amino acid limitation being one factor but also physiological crosslinking which depends on copper in lysyl oxidase [197]. This should be distinguished from pathological crosslinking which may occur through other mechanisms. While much is not known about cartilage crosslinking, turnover, and remodeling some recent results do point to unexpected beneficial effects of copper mediated cross linking over week time scales [234]. A role for LOXL in aggrecan processing has been described [348].

2.2. Heart Problems : DCM/HCM

Heart problems are common in dogs. Recently, diet-associated DCM has made headlines as an increasing threat with copper deficiency mentioned as a possible although unlikely contributor as it is "routinely supplemented" in commercial foods [238]. While it is thought to be diet related, no clear recipes have been identified for causing or preventing it. Recently in humans, the risk of recurrence of specific fibrillation or heart failure types was shown to segregate according to 3 nutritional indexes with HR's in the 10-20 range [405] suggesting general measures can already have value and a common nutritional origin that may include several components.

The heart is particularly dependent on continuous efficient energy production and mechanical properties to insure blood flow as needed. As copper is important in both functions, distribution within the heart could be expected to be critical to overall health and therefore signalling for copper regulation. Indeed this seems to be the case. A recent review of diet related DCM mentions copper along with sulfur containing amino acids as possible issues. While expressing a concern about interactions with other metals, it does not appear to mention a possible interaction with the sulfur reducing copper usage. Copper deficiency is known to produce cardiac hypertrophy in animals along with a large number of mitochondria that may be adapted to the low copper state [243].

HCM, defined as "echocardiographically-demonstrated LV concentric hypertrophy in the absence of another known cardiac, systemic, or metabolic disease capable of producing the magnitude of LV wall thickening evident" [314]. It is considered rare although it was initially considered rare in humans while now being fairly common with a wide spectrum of symptoms [355]. Energy depletion is thought to occur due to causative mutations but as of 2019 no disease modifying or proven therapies exist although Mavacamten apparently reduced outflow obstructions in as little as 2 weeks [355].

As early as 1993, copper restriction in rats was observed to produce cardiomyopathy [242]. While reduced cytochrome c oxidase activity was observed in 1999 particularly with simultaneously high fat diets [153]. Although confusingly copper chelation with trientine is also thought to show promise in HCM treatment [293] but its unclear exactly how it rearranges copper distribution.

The heart relies on 4 valves and a rapid contraction subsequent to depolarization to move blood through the body. Mechanical properties of the valves as well as energy efficiency may be expected to be important to maintain performance without desperate remodelling. These requirements motivate an interest in accurate protein translation, and copper dependent physiological crosslinking, removal of deposits such as mineralization, and mitochondria performance. Empirically, copper deficiency can lead to cardiac hypertrophy with increased mitochondria [244]. Dilated and hypertrophic cardiac myopathy can both be related to mitochondria with "oxidative stress" as a signal for more copper at cytochrome oxidase. "Oxidative stress" has been reported to increase muscle mass while reducing performance [5]. "Oxidative stress" is often blamed in the literature as a cause of various problems but it may in fact also be a signal. ROS signalling is well known by now but specifically it may help get sufficient copper to the mitochondria.

As early as 2008, a pressure overload mouse model of DCM regressed with copper supplementation [148]. An recent 2023 work demonstrated correlations between heart copper content and cardiac parameters in a group of identically fed mice while also pointing to the heart as a regulator of copper concentration overall [23].

Over the same time however, concerns about diet linked DCM in dogs have emerged. A genetic link is also being investigated and a recent GWAS in dobermanns pointed to two genes, RNF207 and PRKAA2 as risk factors [266] but did not mention copper. However, RNF207 may mediate degradation of ATP7A [406] while PRKAA2 comes up in cuproptosis [200].

Dobermanns are at remarkably high risk of DCM [89]. Interestingly, "standard Dobermanns" are also at high risk for hypothyroidism [274].

It's possible the two concerns are related in more copper is being absorbed as less is transported to target organs such as the heart. This connection between dysregulated copper metabolism and heart disease has been considered recently in humans [203] in a work that reviews many important aspects of copper metabolism. .

Contrary indicators also exist. A study of DCM among people exposed to metals at a mining area suggested blood copper levels increase with DCM risk and found near 100 percent DCM rates above a threshold level [215]. However, even assuming blood copper is proportional to exposure, the x-axis in the graph is more likely a sum of exposures and not just copper. That it, is a partial derivative of DCM risk in a direction that includes copper but also other things like arsenic. This is a very common problem in association studies depending on the inputs and population. In reality blood copper is largely determined by an acute phase protein and it will be associated with stress until the total stores are too low which may be well below the deficiency amounts.

2.3. Infection and Microbiology

The role of copper in mammal interaction with pathogens has been well reviewed in works such as [98]. Effects of copper on infection were known since at least 2400BC with other notable observations such as benefits to copper workers against cholera in the 1800's

and today with interest in copper surfaces [307]

Combined copper and zinc deficiency was observed to reduce response to covid-19 mRNA vaccines with only minimal copper deficiency [63] The present work considers copper status in light of other nutrients notably amino acids such as Trp and Tyr and with zinc being a possible competitor.

In human health, zinc seems to have taken precedence over copper most recently with some headlines related to the covid-19 pandemic [14] [101] . Some studies suggest copper is not a factor in covid-19 due to measurements like serum copper levels [302] although ceruloplasmin as an acute phase protein can elevate levels during stress even with a deficiency in copper [128]. In sample of 70 patients prescribed zinc, many had symptoms consistent with copper deficiency [83]

Copper was shown to reduce *Proteus mirabilis* colonization of mouse urinary tract with decreased ureas and secretion and enhanced macrophage killing although with increased biofilm formation and resistance to antibiotics [147]. This delay but ultimately grow stronger effect was also seen in cultures of *Bordetella pertussis* although the authors consider it "misleading" as the effect appears to be due to the relative Cu(i) and Cu(ii) concentrations created by ascorbate in the growth medium [298]. Another work with *Pseudomonas fluorescens* SBW25 and growth on copper surface demonstrated adaptive mutations but reduced vigor and biofilm formation in plain broth although with increased antibiotic resistance [391]. If the organisms are significantly less fit in other environments the adaptations may not matter as the organisms could die out after copper exposure.

Bacterial copper absorption is thought to passive in many cases although membranes tend to be relatively impermeable porins may exist and cytosolic copper in enterobacteria is thought to be kept under one atom per organism with zeptomolar affinity transcriptional regulators of homeostasis system [114].

Copper may antagonize many pathogens including *H. pylori* [31] and *Clostridium*

Thinking out loud

Repression of toxin production by tryptophan in *Clostridium botulinum* type E [193].

Excess copper may also be secreted in extracellular vesicles [196], a relatively unexplored method.

Various *Pseudomonas* also synthesize a copper containing antibiotic, Fluopsin C, with activity against plant pathogenic gram negative bacteria and some fungi [4].

Copper compounds may reduce the virulence of some organisms for short periods even if not completely able to clear a pathogen[127] and in particular Cu was recently shown to be effective against the toxin of one anaerobe [46] .

One interesting work explored the impact of copper on virulence of some environmental communities finding decreased virulence at a higher dose with increased proeudiability at a lower dose [184]. There are a number of limitations with this work but in general there is likely to be a beneficial zone in copper supplementation to in vivo communities such as in GI tract.

Relevant copper microbiology begins in copper plumbing systems with studies of biofilm formation, corrosion products, and roles of nutrients such as amino acids in bacteria behaviour and molecular contents of the water [146].

Bioreactors may have to deal with copper. One experiment found that Cu(II) in the 1-10mg/L range did not destroy denitrification capabilities of the colonies but did stimulate secretion of extracellular polymers and in particular proteins which bound and reduced copper at tryptophan residues [390].

Copper, in combination with tryptophan, can reduce damage caused by colibactin from various Enterobacteriaceae [27].

It may also be worth noting that some efficacy has been observed against GI parasites in other animals [294] [262] .

2.4. Hypothyroidism

Several works find decreased serum copper as a correlate of thyroid hormone levels [38] [15] [171] while some find no correlation [366] [9] but relevance is unclear as this may just reflect low amounts of ceruloplasmin which is an acute phase protein.

Hypothyroidism may seem out of place but it is a common problem in dogs and as it involves lethargy may be confused with unrelated energy issues such as the mitochondria considerations also discussed herein. Interesting literature on copper in poultry exists largely due to thyroid effects and anti-nutrients in common feeds. For example, canola meal contains tannins, glucosinolates, and phytic acid with broiler performance and thyroid parameters shown to improve with the addition of substantial copper sulfate to this feed [20]. This work also briefly mentions ascites and thyroid function which is interesting due to one of the heartworm dogs here getting huge fluid accumulation during recovery (unpublished observations). Similarly, pigs fed on 8 percent rapeseed meal benefited from both copper sulfate and iodine addition and anti-nutrients isothiocyanate and oxazolidinethione were not longer detectable in the feed with copper sulfate [211] indicating copper could destroy some anti-vitamins as well as vitamins. Similar nutrients compared to HCl treatment for mustard meal demonstrated similar benefits could be obtained in calves [354].

Copper was shown to correlate negatively with TSH in one human study and may increase T4 levels [398]. Copper supplements may compensate for marginal deficiencies of related enzymes such as in mice heterozygous for peptidylglycine alpha-amidating monooxygenase [44]. In another section the existence of functional copper relevant enzyme deficiency due to amino acid deficiency is discussed.

Hypothyroidism is a common problem in dogs and has effected several here [228] including some unpublished results where it was thought to contribute to peritoneal effusion after heartworm treatment. It can be defined by elevated TSH for a subclinical condition or low free T4 or T3 [265] although even the latter remains as a biochemical definition rather than something relevant to the patient. Ingestion related (diet low in iodine or containing goitrogen or relevant drugs) has been described as a "Rare etiology" with "acquired primary hypothyroidism" being considered most common although iodine deficiency in dogs appears to be poorly defined [403]. In this work, there is some evidence that added components such as iodine, benzoate, tyrosine, and copper may help and could fit under the category "acquired."

Issues relevant to the patient, those truly clinical, include lethargy and weight gain [79], and heart problems [357]. With lab confirmation of hypothyroidism it is possible to correct levels with supplemental thyroid hormone intake. The relevance to this work however is the ability of copper deficiency to reduce thyroid output. In such a case T4 replacement therapy will be limited as the effects of copper deficiency may still manifest elsewhere.

Dobermanns are at remarkably high risk of DCM [89]. Interestingly, "standard Dobermanns" are also at high risk for hypothyroidism [274].

Interestingly, copper deficiency in rats can reduce thyroid hormone levels and body temperature [212].

Of the dogs discussed here, only Rocky was a concern for hypothyroidism although Happy came back with very low normal thyroid hormone result prompting further consideration. Besides iodine, other contributors may include tyrosine and sodium benzoate.

2.5. Degenerative diseases AD, PD, ALS, Arthritis

Thinking out loud

fact collection, keep analysis in "confusion" section I guess

The role of metal distribution in neurodegenerative diseases is a topic of current interest with many unresolved issues [58]. Degenerative neurological or muscular diseases may be intertwined with copper status although the relationship is again confusing. Similarly with arthritis.

Deficiency seems to effect preferentially proteins involved in neuronal projection and diabetes and iron handling [363].

Rats fed a copper deficient diet shows neurological symptoms by 7 weeks and had reduced tyrosine hydroxylase and SOD activity ZZ [253].

A 2017 study explored the effects of copper and vitamin C as well as other molecules such as clioquinol on abeta and in vitro neurons suggesting abeta could be cleaved by copper in the presence of oxygen as well as an anti-oxidant such as vitamin C although restoration of neuronal functioning was only partial [394]. Interestingly, copper-ascorbate oxidation of tryptophan may be suppressed by Trp chelation of copper at high trp concentrations [252] suggesting reduced amounts may give copper more ability to damage an already low supply. This is interesting in terms of a nutrient interaction hypothesis on copper toxicity. And in fact as early as 2012 it was determined that tryptophan intake could reduce copper toxicity at least in carp [143].

Some precedence for metal modulated toxicity existed back to 1999 when work with cultured neurons showed a dose dependent reduction in abeta toxicity with Zn [208]. By 2005 toxicity of amyloid beta and the metals zinc, iron, and copper was investigated under conditions that created more toxicity with iron and zinc but not copper while amyloid beta reduced metal toxicity in rats [35]. In 2021, Ni was found in important amounts in a commercial abeta40 preparation [30] and was found to mediate tyrosine crosslinks [32] similar to the tyrosine crosslinks induced by copper found in 2004 [17].

A 2013 work found in vitro physiological conditions caused copper to prevent fibril formation [250].

By 2022, work focusing on moving copper into the cell considered many aspects of copper misallocation and devised a copper specific shuttle peptide to deliver Cu from abeta [272].

At least one recent 2024 work identified copper dysregulation as a contributor to microbial contributions to Alzheimer's [247]. While brain copper accumulation has been observed in mouse models of AD and appears pathological [145] any relation to real disease would be questionable but accumulation may be a defense against pathogens or due to other cues that are more disease relevant.

A 2017 work concluded with other works that whole brain copper was reduced in AD and in most areas effected by AD suggesting simultaneous observation of increased Cp point to severe depletion of intracellular functions related to energy production and SOD's [69].

Copper distribution in the brain can modulate many functions from olfaction to adult neurogenesis [3]. One work in 2022 addressed AD as a consequence of copper deficiency because [175]

It is hypothesised that copper deficiency is a plausible cause of Alzheimer's disease(Reference Klevay84). Patients are thinner than normal; weight loss precedes dementia and is associated with greater dementia and neurobehavioural symptoms. Nutritional compromise contributes to morbidity. Cytochrome oxidase depends on copper for activity; at least fourteen publications reveal decreased activity in brain of Alzheimer's patients. Brain copper and caeruloplasmin also are decreased. This hypothesis is the only one that explains why Alzheimer's disease occurs earlier and is more common in Down's syndrome. Superoxide dismutase (SOD1) depends on copper for activity; its gene is on chromosome 21. This enzyme is elevated in Down's syndrome (trisomy 21) and is decreased in people with monosomy. It seems likely that people with Down's syndrome have a higher than average requirement for dietary copper because copper is incorporated into superoxide dismutase and is unavailable for other uses. Thus, Alzheimer's disease fulfills the first two of Golden's criteria (above) for deficiency.

Interestingly, iron chelation has failed in AD even as iron overload is observed with ROS generation [217]. This set of conditions could easily reflect age related copper loss as mitochondria and iron transport systems are limited. Another possibility is raised by a recent work suggesting that iron accumulation in aortic valve calcification is a compensatory response to global iron deficiency [199]. In this case then iron chelation may have to be replaced with supplementation if this "compensatory hoarding" occurs in the brain which often has priority along with the heart during nutrient limitation .

Folklore regarding copper persists and yet clinical trials for Cu in arthritis continue to show lack of any benefit [295] even as other controlled tests show some effects of Cu on processes related to collagen properties [126]

Remarkably, copper sulfide was shown to protect against ETC damage by MPP [303] suggesting some activity against toxic insults. Copper histidine is used to treat Menkes disease which is a defect in ATP7A [257].

At least one report found a potentially meaningful association between copper intake and kidney stone odds ratio with a non-linear but monotonic inverse relationship [410]. This is interesting in the case of Hershey who was found to have bladder stones.

Thinking out loud

this may not belong here but relevant to other Cu stuff, A recently published work suggests copper delivery is the important part of a new ALS drug but the work also suggests a "hyperreductive state" around hypoxic mito that promote release of Cu from the drug complex [139]/ pointing to a possible more general mechanism. The work goes onto suggest possible role in Parkinson's Disease but does not address AD. At least one observational study found a negative correlation between odds ratio for Parkinson's and copper intake [404]

2.6. Cancer

The relationship to cancer is probably the most confusing aspects of copper interactions. However, Copper deficiency does not effect proliferation of erythropoietic cells but it does reduce differentiation and alters metabolism from mitochondria to glycolysis [49] so it can produce two central features of cancerous growth. Copper accumulation has been observed in neoplastic cells and it stimulates angiogenesis [305]. While this suggests a role supporting tumor

growth, "acute phase copper" and improved blood supply can be part of a healing response. Copper seems to be important to stem cell maintenance [276].

Copper has been studied in relation to cancer being considered both as a limiting nutrient and a source of cuproptosis in the overload state [345]. Copper is essential for many growth processes and can activate receptor tyrosine kinases without a ligand making it a target for cancer [131]. However, these processes are also essential for maintenance and healing in the organism and any net benefit would have to consider host fitness as well as cancer cells again using a clinical endpoint to decide on approach. In some studies, copper depletion was considered to be motivated by the observation that copper chelators reduced cancer growth and equating chelation with depletion. However, role confusion may have applied as the chelated copper could generate ROS's with obvious cytotoxic activity.

Copper storage diseases and in essence "overdose" are well known [103] and a role in cancer is suspected [39]. However, see the comments below about complexed copper actually being an active compound similar to other drugs, perhaps Pt based for example, which may kill cancer. Copper toxicity has been noted to differ between host cell types and may be reducible, at least in Long Evans Cinnamon rats, with thiamine or lipoic acid [321]. Lysyl oxidase activation, the goal of this therapy, is also associated with cancer spread [344][289][376]. Although it is likely to remodel possible tumor locations, its role in growth or metastases in a clinically relevant situation is currently unresolved (see for example [22] or [407] and the survival curve in figure 1). Incidence of liver cancer in Wilson's Disease patients is remarkably low [256] and a discussion of possible treatment effects [371] points out that the copper per se rather than removal is likely to help while also mentioning differences with iron overload. Indeed, extra copper that prevents iron overload may be therapeutic as originally intended.

We should note that complexed copper is not equivalent to copper deficiency as the complex may not be inert. However, when an ROS generating complex has been observed its effects were diminished by antioxidants [91]. This also suggests that copper depletion per se may not kill cancer cells as much as copper complexes and that concerns about copper supplements and cancer may not be significant.

3. SITES OF INTEREST

There are specific locations or interactions that can make extra dietary copper beneficial in the above conditions and others. These are tabulated in Table II. In addition to specific locations, novel copper compounds may go to many locations. A few examples are given but this is not exhaustive.

Copper in these organs may be beneficial through accumulation in macrophages and other locations, use by lysyl oxidase to stiffen trachea and other structural organs, and for energy production notably by the heart leading to greater volumetric efficiency.

Location	site	Effect	time scale
Heart	mitochondria	energy production	maybe days
Heart	mitochondria	remodelling	weeks or months
Heart valves	lysyl oxidase	crosslinking [288]	weeks or months
Trachea	lysyl oxidase	proper crosslinking	months
Macrophage		phagosome	days
Macrophage		lysosome	days
ceruloplasmin		distribution	days
foreign ligand	variable	variable	

TABLE II: Some expected benefits of copper that guided the original interest and observations although sometimes the goals were lost in the details of the diet and outcomes.

3.1. Mito Complex IV (was Cytochrome C Oxidase)

High energy consumers such as the brain and heart appear to be significant in regulating copper distribution presumably largely due to a need to ensure adequate mitochondrial ATP production. Within the mitochondria, copper is used in cytochrome C oxidase but more generally complex IV status may be what is sensed to signal copper status. While this must remain as speculation for now, this section considers some features of complex IV that could modulate the overall effectiveness of cytochrome C oxidase. While perhaps strictly synonymous, the complex term will be used to include consideration of cytochrome c and the overall environment. Besides copper, one possible problem in old age is high-infidelity translation that could affect cytochrome C and the oxidase. If these become dysfunctional that could confuse copper signalling.

Supplemental copper has been noted to improve symptoms in one case report including symptoms such as hearing loss [142] attributed to defects in cytochrome C oxidase copper loading and restore function in mutant yeast [112]. Cytochrome C oxidase levels in rat hearts were shown to be related to copper deficiency as early as 1998 [301]. It would be interesting to determine if more problems in dogs are related to specific mutations in mitochondrial copper handling. We note again that vitamin K could contribute in similar places and may be synergistic with copper for connective tissue quality as well as in eukaryotic mitochondria [364][402].

Two types of excess have been identified as potentially important to pathogenesis- mineral and antioxidant. Iron overload copper deficiency was identified early on as a concern with animals getting high iron diets and generally free of parasites in stark contrast to the likely situation over evolutionary time scales. A second type emerged on consideration of the copper response and cytochrome C oxidase copper loading - that of antioxidant overload. ROS have generally gained more acceptance as having physiological roles at low concentrations rather than simply being a source of damage. Literature related to these experiments suggests a very specific role in mitochondrial function. The original concern about antioxidant overload was mostly confined to vitamin E-K antagonism and it is not clear how or if these concerns relate. Coupled with empirical deleterious effects of some antioxidant combinations in clinical trials (one high profile example [273]) , it is clear that antioxidant excess should be considered as a problem with some diets. The antioxidant paradox now seems to be gaining acceptance , for example see [42] and [133] . Copper is decidedly pro-angiogenic and several studies have shown effects of copper consumption increasing tumor growth in animals while both chelators and ionophores are being investigated for treatments [59]. However, pro-growth and angiogenesis could also be expected during regeneration which itself may require copper.

Thinking outloud

Copper loading of cytochrome C oxidase relies on an oxidized Cox11 to interact with Cox19 [41] and this may be inhibited by GSH but is enhanced by GSSG. Redox regulation in the IMS seems to be integral to proper copper disposition [130] and indeed mitochondrial related signaling [327] . The latter reference also points to tissue specific mitochondrial isoform expression suggesting that maybe some related diseases are states rather than traits and hence correctable with signaling. Certainly excess antioxidants would be suspicious (for example reference 24 [43] in [327]) . However, the enhancement by GSSG suggests that the presence of oxidized antioxidants may be beneficial but not in their reduced state.

Thinking outloud

engineering ahead of medical, protein quality

In some other context, engineering efforts to produce biological products such as bone in a reacor vessel can offer insights into factors in vivo. A 2021 work focused on similar systems by modelling the effect of amino acids and copper on antobody quality in a production setting [213],

Specifically, copper has a significant, positive effect on titer and a significant, negative effect on lactatea phenomenon consistently observed in other CHO cell culture processes.[12, 13, 23, 24] A plausible explanation is that the increased copper level is known to drive lactate consumption. Copper deficiency reduces cytochrome c oxidase activity, limiting the ability of cells to produce ATP via oxidative phosphorylation. As a result, cells switch to aerobic glycolysis to generate ATP, causing increased lactate production, which affects other metabolic processes.[12, 23]

3.1.1. Amino Acids and Confusion in Copper Regulation

Copper distribution could be disturbed due to improper transporter function but it is also possible that feedback mechanisms cause an accumulation of copper when there is some other defect in complex IV or associates such as cytochrome C due to insufficient function incorrectly attributed to copper limitation. Indeed, in AD whole brain Cu appears to be depleted even with increased Cp suggesting severe reductions in things like CoX [69].

Thinking outloud

3 cites for this work lol

Defects in copper containing enzymes or related transporters could occur due to high-infidelity translation due to amino acid depletion as has been observed in some cancer cells [54] and was earlier suggested as common in older covid patients [227]. Remarkably at least some W to F errors do not reduce activity significantly [275] although it may not be obvious how much change is enough to trigger some response as these seem to be highly conserved W's. Aromatics may have several functions including active site participation [40] , folding [36] , radical [192] or hole [120] dissipation , and membrane interface [166]

. Improper functioning of any of the complex may not provide the right feedback instead just trying to get more copper and in that case supplementation may not be useful. A W to F translation error in a detoxification chain

would likely shorten enzyme lifetime even if initial performance is ok.

Tryptophan given to piglets seemed to improve mitochondrial performance after a lipopolysaccharide exposure [198] suggestive of better response to a real infection. There are many possible reasons for this but if copper is diverted to respond to infection, "beating plowshares into swords," the remaining complex IV needs to work better. Conserved cysteines or a tryptophan in coa6 can mutate leading to cardiac defects including hypertrophic cardiomyopathy that can be rescued with extra copper [111].

3.1.2. Fats and energy regulation

One aspect of copper regulation and response has to do with fats and lipids. As iodine seemed important to some of these dogs, consideration of thyroid role in energy usage and accumulation of "stuff" is also relevant. Hypothyroidism may be associated with the accumulation of fat, fate of brown adipose tissue, and myxedema or the cutaneous deposition of proteins and mucopolysaccharides leading to the accumulation of fluid.

Mice fed a copper deficient diet had enlarged heart and liver with reduced brain weight and very low ceruloplasmin (suggestive of severe deficiency) and notably lower dihomoo-gamma-linolenic acid content [72], Copper deficient rats doubled their triacylglycerol synthesis per body weight rate from labelled acetate injection[8].

One important component of energy reserves appears to be brown adipose tissue. Notably, copper and iron content of brown adipose appear to be upregulated during cold exposure [373].

SLC25A3, a copper and phosphate transporter, may have an informative role in the relevance of these elements to some nonalcoholic fatty liver diseases. Deficiency did not have much impact on mito function until cells were exposed to eleic acid with simultaneous decrease in cytoplasmic and mitochondrial copper [259]. Its interesting to note however that phosphate has a number of uses related to modification of oil-water mixtures. Ortho and polyphosphates have shown some benefits for improving oil recovery and reducing scale for enhanced oil recovery fluids [113].

As early as 1950, it was noted that polyphosphates could inhibit the rancidity of a water-fat mixture in the presence of copper and iron [380]. More recently polyphosphates were shown to chelate iron and prevent fenton reactions in vivo [28] i maybe a special case of results from 2015 which included observation metal-polyphosphate complexes can lower levels of ROS [122] and in particular copper tolerance in Sulfolobus solfataricus was shown to depend on polyphosphate [335]. In 2009, Kim Schnee and Park described some of the physical chemical properties of phosphates and mentioned various uses in food processing [169]. The snacks described here typically included sunflower lecithin containing some phosphate containing compounds although for humans diet cols may be another source. Polyphosphates can form coacervates in the presence of divalent cations including calcium [251] and unusual phases may be of interest in understanding copper storage in the matrix which to date appears quite mysterious.

3.2. Lysyl Oxidase

Lysyl oxidase family of copper dependent enzymes contributes to controlled crosslinking of structural proteins such as in injury recover [51]. They have a central role in organ development and some activity in disease [382] with the latter association contributing to the idea that inhibition would be beneficial in many cases. However, the details again point to "fixing rather than inhibiting" as with apparently pathological coagulation. In this case, one problem may be incorrect or incomplete metallization which would be fixed with more copper. Other deficiencies may similarly alter the overall function of the LOX enzymes and it may be a better solution to fix these problems than inhibit LOX. Notable functions for tryptophan and tyrosine exist and these have been identified as potential concerns before [227].

Several works point to the LOX family as a good target due to presumed causal role in pathological results. Lysyl oxidase was considered to be bad for vessels [24] and calcification but this may be related to metallization issues [330]. Lysyl oxidase expression has been associated with degenerative mitral valve disease in humans[288]. It has been observed to upregulate in the injured newborn lung [408] suggesting increased levels may be a response to an insult rather than a cause of damage. In 2001, it was observed that bovine lysyl oxidase had enzymatic activity without copper but was less stable [343] although details on reactions catalyzed could not have been fully explored.

Regulation at transcriptional and translation and post-translational levels is confusing. For example, it has been described in 1998 as [331],

While enzyme activity levels were decreased in the skin of weanling rats fed a copper deficient diet, the basal, steady-state levels of LO specific mRNA or immunodetectable LO protein were not significantly reduced (Rucker et al., 1996). These results suggest both that the biosynthesis of the enzyme is not markedly affected by copper deficient diets and that the increasing percentage of copper-deficient, catalytically compromised enzyme molecules presumed to accumulate during this dietary treatment remain

relatively stable. Notably, copper-deficient diets significantly reduced cardiac LO activity and induced cardiac pathology in male but not in female rats (Werman et al., 1995).

or more to the point from the same year, [304]

Although nutritional copper status does not influence the accumulation of lysyl oxidase as protein or lysyl oxidase steady state messenger RNA concentrations, the direct influence of dietary copper on the functional activity of lysyl oxidase is clear. The hypothesis is based on the possibility that copper efflux and lysyl oxidase secretion from cells may share a common pathway. The change in functional activity is most likely the result of posttranslational processing of lysyl oxidase.

However, metallization may not be complete and feedback systems may increase expression to achieve an activity level. Note too that "crosslinking" is a variable modification and physiological as well as pathological crosslinking can occur. While "quantity versus quality" will be the subject of another work, its important to remember that increased expression of lysyl oxidase genes and more patholoical crosslinking could occur in the absence of sufficient copper. Mature functional lysyl oxidase contains an unusual lysine tyrosylquinone (LTQ) which itself is formed in a copper dependent process [387]. Dependence on multiple tyrosines or tryptophans can increase the odds of generating dysfunctional enzymes which may be inactive or perform unintended functions when these amino acids are limited. This theme of amino acid starvation also appears in concerns about ceruloplasmin and more generally with aging.

LoX deficiency has been identified as a component of pulmonary emphysema [33] [154].

3.3. Ceruloplasmin

Ceruloplasmin is an acute phase protein [151] which serves as the dominant copper carrier in the blood delivering copper as Cu(I) for uptake by CTRP1 by reverting to apoenzyme at cell surfaces [75]. As an acute phase protein its concentration may correlate well with early disease stages but it generally has a productive role. Besides stress modulation, activity may depend on factors such as copper availability, estrogen and progesterone [205] and, in Wilson's disease, retinoids such as ATRA may improve ceruloplasmin secretion [334]. Ceruloplasmin (regardless of how assayed) and blood copper levels and their fluctuations do not have to reflect overall copper sufficiency.

It is also a promiscuous enzyme [372]. While best known for ferroxidase activity, it can also has oxidize activity against cyclic hydroxylamines (used as ROS probes) [108] as well as various amino acid derivatives such as "catechol and its analogs, such as dopamine, epinephrine, norepinephrine, 5-hydroxytryptamine, and tryptophan" [205].

Thinking out loud

may be promiscuous towards neurotransmitter and amino acid analogs which may make it a good means to get rid of spurious analogs with build up of these if it is deficiency. Suspected roles in dementia include iron and copper control although not sure if amine oxidase is considered as a way to remove brain "poisons."

Ceruloplasmin contains 6 coppers and histidines needed for metallization [134], as well as 2 tyrosines. Independent errors in metallization will multiply and reduce likelihood of functional enzyme.

The blood levels of ceruloplasmin may correlate well with copper blood levels but it can vary in quality too. A chain of W and Y are thought important for enzyme preservation with ceruloplasmin containing a chain of two tyrosines [351]. As iron accumulation is related to AD, there is a question about the quality of the circulating ceruloplasmin. If there is high-infidelity translation due to W and Y depletion, there is also the question of how feedback mechanisms control the overall amount. First it has to metallize right which requires 6 coppers and 6 histidines and then survive with the 2 tyrosines. If any components are deficient quantity or quality may suffer. Ceruloplasmin KO mice gained weight and showed increased scatter in weight with lipid dysregulation only partially corrected with exogenous replacement [290] suggesting tight control may matter.

3.4. Macrophage et al

Copper in these dogs may be beneficial through accumulation in macrophages and other locations, use by lysyl oxidase to stiffen trachea and other structural organs, and for energy production notably by the heart leading to greater volumetric efficiency.

While well known for a role in infection control, macrophages also have a complicated role in cardiovascular disease [61] although the impact of copper may be less apparent. Recently some work has suggested that lysosomal copper may be an important storage location [285].

The importance of copper for host-pathogen relations is well known as is a particular usage by macrophages [182] [34]. Note that nutritional immunity may involve either an excess or limitation of copper to the pathogen hinting at a

common source of myths about which direction to move a quantity to achieve a given result (see a list in Appendix C) . Much is known about interaactions of copper in macrophages with particular organisms such as Mycobacterium tuberculosis and Salmonella typhimurium [140] as well as Streptococcus pneumoniae [161] . As with most other sites, copper in macrophages can be considered pathological and attempts may be made to limit rather than enhance it. For example, targeting mitochondrial copper with "rationally" designed metformin dimers [333]. As with attempts to control amyloid beta in AD, there may be some passing benefits but taking all the information together this is likely of limited value if the simpler approach of enabling the copper based response in a well regulated way is feasible.

3.5. Associated Entities - histidine and garlic etc

Copper can of course form associations, with many chemical groups and diverse roles. Role confusion however seems to be a recurring issue as specific componunds may not sequester or activate copper as may be expected. One recent review on anti-cancer mechanisms of copper dicussed various ligands and roles for both copper depletion and overload [21]. The combination of the garlic and copper, while sounding like a medieval concoction (suggested as a result from Bald's Leechbook [127]), has been described as synergistic against fungus [271] and seems plausible for generating perhaps more volatile and diffusible copper that could find otherwise inaccessible lysyl oxidase and other targets.

Dogs fed a histidine deficienct diet eventually developed feeding resistance and lower whole blood copper and zinc [67].

4. CASES AND OBSERVATIONS

This section describes the novel data collected for this work documenting response to copper and other supplements in a variety of dogs as larger attempts were made to optimize their health through diet. Context and individual case interpretation is also included in this section instead of the discussion section which mostly compares and contrasts cases with more complete comparison to the prior work discussed in the introductory text. As essentially case reports, and as should be clear from the introductory and concluding remarks, this work is meant to be hypothesis generating and not a particularly well controlled test of any well defined idea. The general objective is to explore and refine ideas about a role for copper in a more complete context by documenting the results from these dogs. Although not often considered with copper, iodine comes up as an important confounding variable as hypothyroisidm possibly related to food is a continuing issue. Goitrogens may be a common issue with dog food and the iodine related chemistry and dosing schedule may matter. As weith copper, any relationship between thyroid hormones and iodine intake is not always clear. Vague notions like "energy level" may be impacted by net effect on thyroid Iodine dosing will be shown for some dogs along with copper but the complete data set is available as described in the Supplemenal Information section and should be examined by interested readers. Other suspects that came up during the work are considered in the discussion afterwards.



FIG. 1: Some of the dogs described from left to right then top to bottom: Happy, Rocky, Annie, Mixie, Trixie, Brownie. At the bottom is Dexter in 2020. As breed may be important but unknown visual inspection may be helpful for guessing about genetic background.

The overall process and setting have been described previously in the case of Happy [222] [229] and Brownie [232]. More context may also be obtained from the cases of Spicey [228] and Sarah [223]. Briefly, rescue dogs living in a residential setting are given supplemental vitamins that are recorded along with outcome and other observations in MUQED format [231]. MUQED was still being developed as initial feeding work was being performed leading to some issues with earlier data. Typically dogs would get commercial dog food meals (kibble and canned foods) that may only be partially recorded along with two "snacks" (AM and PM) containing consistent human quality food components along with variable vitamins [221]. Snacks containing vitamins were generally consumed within minutes of preparation although in some cases snacks would be refrigerated and eaten 12 or so hours later sometimes with AM and PM snacks together. As stability is a concern with copper, this point may be important. Generally intake was recorded right after feeding with immediate syntax checking. Obvious errors or questionable data found later were corrected when found, usually during data analysis, and usually indicated with a "DMEL" entry in the MUQED file.

While all supplement data were recorded and many ingredients varied significantly over time, only a few are discussed here. Generally the overall supplement mixture was designed to be the "best shot" at either improving dog health or evaluating some alternatives. Usually this is a complicated mixture as deficiencies would be expected in combinations (such as multiple SMVT substrates, amino acids or metals). Many of the dogs in this setting have had either symptoms that could be due to hypothyroidism or overt lab confirmed low thyronid hormone levels. As

iodine intake fluctuated wildly as the copper was adjusted, it is included in some of the graphs as a possible factor confounding inferences about copper. The premise of this work is that the meal and diet are a "confounding factors" and readers are encouraged to check the MUQED data for other patterns. Besides iodine, some attention should be given to sulfur sources such as amino acids including taurine.

While most supplements and medicines were recorded in good detail, many caveats exist, see Table III.

1. Meal sizes and food ingredient quantities are missing or arbitrary.
2. Not all meals are routinely recorded due to initial logistic issues with multiple people feeding the dogs and later a desire to maintain consistency.
3. Some preparation habits may not have been described completely. Metals were generally added last as mentioned in the text but other things like keeping the supplements dry and nominally unexposed to light could be important.
4. Some items combined with isolated supplements for palitability and acceptance were not included.
5. Initially MUQED unit conversions were not used and weights were entered even as in almost all cases bulk supplements were measured by volume. Some were eventually converted to actual volume or numbers available to the "chef" while others continued to use a measured density.
6. The "MgCitrate" entries reflect actual amount of the supplement not elemental magnesium as opposed to most other metal supplements. . This was retained but an issue early on making decisions about MUQED conventions.

TABLE III: Known caveats with the MUQED diet data. Most of these limitations should not effect interpretations given here but due to interactions and complexity of copper all details may matter. Many of these issues can be fixed with better planning and the use of a more complete MUQED system.

Several common diet parameters like total calorie intake cannot be inferred from these data. In paricular, normalization of the "dinner" amounts is variable between dogs. Besides the meal or snack , most dogs received additional meals of commercial dog food and uncontrolled scraps or treats while others routinely ate toys or yard debris or drank from streams. However, some results appear to relate to the vitamin mix and notably inclusion of copper. Copper dosing, like with other supplements, was sometimes rotated with specific nutrients such as other metals leading to high doses some days with none on intervening days. This schedule may require more care in analysis than fixed amounts. A hard upper limit of 3mg/kg body weight of supplemental copper per day was maintained based on quoted NOAEL's from an original source dated 1972 [70] although higher doses may be acceptable in a pathological low absorption state. Some of the discussion will also reference unpublised notes on "Little Man" who was given copper and other nutrients before the MUQED system was operating.

The subset of data considered here focuses on variations in copper intake after the arrival of a new dog, Trixie, with various health conditions. Most of the dogs currently living here received increased copper shortly after her arrival due to apparent spread of coughing. Some of the dogs, notably Happy and Rocky, had varying cough levels previously as described below.

While influenced by Trixie, these cases are to some extent unrelated. Supplements were chosen based on the condition(s) of the dog and thinking at the time. Copper was one of many nutrients thought to be important early on but had ceased to be a focus. Initial work with Little Man in 2016 showed apparent benefits in coughing while with Hershy activity levels increased but so did coughing. Happy seemed to benefit around that same time but her coughing can not be eliminated today. Brownie and puppies copper exposure was significant but not high and thought to have contributed to resolution of a coughing episode among the puppies. Similarly, Cookie with an antibiotic treated respiratory infection recovered but any role of copper is unknown it did not seem to harm her.

Three dogs, Daisy, Claire, and Frankie (aka Autumn), were here prior to Trixie and have been essentially event free while taking nominal amounts of copper along with iodine and other entities as described in the Supplemtal Information data.

Dog	Dates	Condition	weight(lbs)	Cu(mg/day)	Cu(mg/kg)	Outcomes
LittleMan	2016	multiple			.8	honking stopped
Hershey	17-04-22 19-08-27	multiple	8.2 - 9	2	.52	transient improvements
Hershey	17-04-22 19-08-27	multiple	8.2 - 9	.2-.6	.1	fatal heart failure
Happy	18-09-07 24-04-10	several	13.4 - 17.7			
Happy	18-09-07 19-05-30	heartworm/doxycycline	13.4	2	.29	cough gone briefly
Brownie	21-01-12 21-02-14	pregnant, fibroids, heartworm	≈ 60	1.5-2.5		uneventful
Brownie	21-01-12 23-02-22		49 - 64	1 variable		pts due to cancer
puppies	21-03-23 21-06-09	cough	104	4.5	.095	cleared
Cookie	21-09-10 22-01-21	Resp infection/azithromycin	13.5	2	.33	cleared
Trixie	23-12-16 24-04-10	resp infection/Clavamox	37.6 - 44.6	5	.276	cleared
Happy	24-03-26	coughs	15.2 - 15.5	2	.29	rare coughing
Trixie	24-05-15 24-06-01	deep cough returned	44.2	6.7	.3	greatly reduced
Rocky	22-02-05 24-04-10		4.4 - 8.3	1	.37	subjectively better
Annie	2022-09-21	excessive sleep, apathy	7.74- 9.9	2	.5	briefly active again
Dexter	2017-04-25	picky eating	5 - 6.8	variable low	"low"	see text
dogs given Cu but not detailed						
Claire	2018-07-08	none		see data		none
Frankie	2019-10-12	none		see data		none, aka "Autumn"
Daisy	2023-03-28	UTI early on		see data		none

TABLE IV: List of dogs considered in this work. Only Dexter showed possible negative response related to copper supplementation. Dexter was just given whatever was in the shared snacks but he had an adverse event that may be associated with copper intake. Cu amount given is largest thought to be therapeutic and in case of Hershey amount near death in (). Claire and Frankie were essentially uneventful while Daisy had some issues upon arrival she has remained healthy since. The puppies were born on 2021-02-14 but only recorded as weaning began. Puppy weight reflects total and their food shares are unknown.

Unless otherwise noted, most plots show day number on the X-axis and milligrams on the Y-axis. Day number zero is from an arbitrary "epoch" origin.

4.1. Hershey

In retrospect, Hershey should have been an important clue as he reacted quickly to the copper but there was undue concern for increased coughing suggesting no real benefit for him. Only later was it realized the coughing is consistent with more excitement and energy.

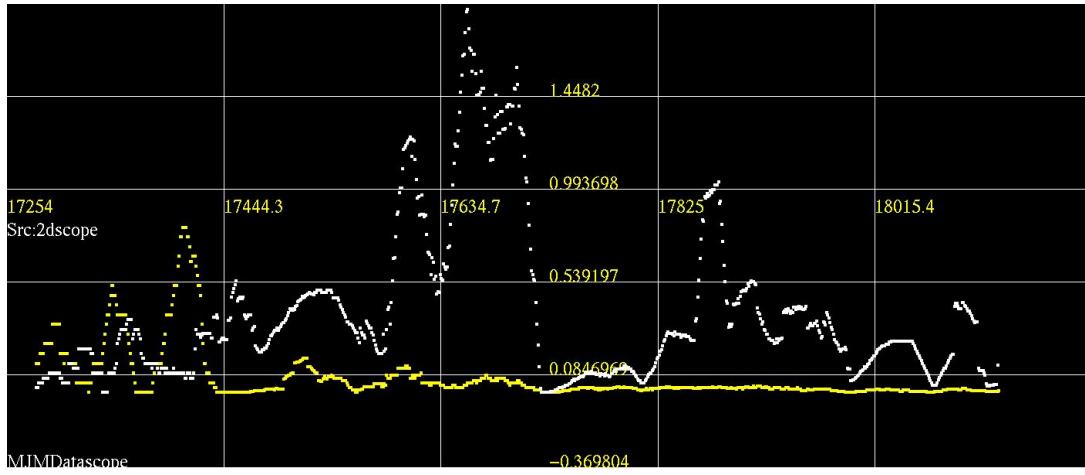


FIG. 2: Herhsey 10 day trailing average copper (white) and iodine (yellow).

Date	Day number	Comment
2017-09-25		developed skin problem, vet prescribed clavamox and miconazole chlorhexidine shampoo Malaseb
2017-10-13		blotches mostly gone yesterday Barb still notes some
2017-11-01		stumbled down steps did not come up until after PMSNACK restart lipoicacid
2017-11-13		struggles up deck steps but finally made it
2017-12-12	17512	seems to be coughing a lot
2018-03-06	17596	seems to cough less, continue copper
2018-04-19	17640	came up steps on own again cadence sounded good
2018-04-20		fur seems thicker except for small area on back behind neck. Still coughing though
2018-04-28	17649	appears alert more flexible and good up steps while still planning although he did stumble the other day
2018-04-29	17650	seems ok on steps, hair filling in.
2018-05-29	17680	not coughing much and energetic but refused to eat and diarrhea. Ate small amount indicated around 830AM. He seems ok at noon not coughing much but subdued.
2018-07-02	17714	lighter and not coughing except when really agitated. Made it up steps good. Could be just weight although not that much lost, something in yard wiped out with spraying, or something like potassium chloride or the lysine making him worse
2018-07-15	17727	had rear leg problem, Barb gave rimadyl
2018-09-04	17778	seems to be stumbling more on steps last day or 2 but yesterday later came up good with fish at top ...
2018-09-19	17793	left rear leg bad had to help up steps still limping in kitchen 5 mintues of so. Gave some b7ngnnnc rested ok. Made it up steps after PMSNACK ok although aborted on attempt but it is 95F out.
2018-10-12	17816	planning and cirling on bottom step then doing good up steps
2018-11-02	17837	walked up first few steps in the rain and then faster up last few no slipping. Rear left leg may be more useful now.
2018-11-26	17861	better again on steps walking up but coughing still
2018-12-04	17869	coughing a lot again try stopping Cu for day or two
2018-12-17	17882	probably made it up steps on own, saw he was gone then heard barking and clumsy step noise. Seems good still coughing on and off, went around shed today.
2018-12-27	17892	coughing less and went out to pee, maybe the extra copper yesterday helped quickly
2019-01-08	17904	seems generally more active maybe coughing less for all the barking with the other 2 BCAA's
2019-03-12	17967	pretty good up steps almost back to recent bests. Coughing like always but darted out the door to deck quite well went around shed etc.
2019-03-14	17969	leapt up some steps then stumbled near top, went around near side of shed ok and wandered yard for a while
2019-04-02	17988	good on steps leaping not slipping
2019-04-26	18012	came up steps without crying on his own.
2019-05-13	18029	Hershey slower than yesterday more normal
2019-06-03	18050	Vet found heart failure on X-ray and bladder stones.

TABLE V: An abbreviated set of note on Herhsey. Increased coughing may have occurred due to increased excitability and energy prior to heart remodelling and may have been mistaken as a sign of pathology rather than recovery leading to some confusion.

Hershey quickly demonstrated several problems not long after arrival. He had problems with his fur, digestion, and coughing while ultimately being diagnosed with heart failure and bladder stones. As many initial features could be rationalized as related to thyroid output, his iodine intake was elevated. During his time here, his diet was varied and he was observed for overall eating and behavior with specific interest in coughing and ability to make it up a short flight of steps from the backyard to the deck. As has often been the case, the notes were not sufficient to fully capture the dynamics of his condition but some representative ones have been edited into the above list. Some correspondence with copper intake is noted. In the last few days of his life, he would pass out and quickly regain consciousness until one day he did not recover presumably due to heart failure. In retrospect, his initial response to increased copper may have been to be more energetic but that increased his coughing leading to a dosage reduction. The time scale analysis for various conditions that may relate to copper deficiency is consistent with this idea making the prognosis

for coughing reduction and increased energy good with continued copper and maybe other nutrients. Clearly the data are incomplete but suggestive now of some benefits.

4.2. Happy

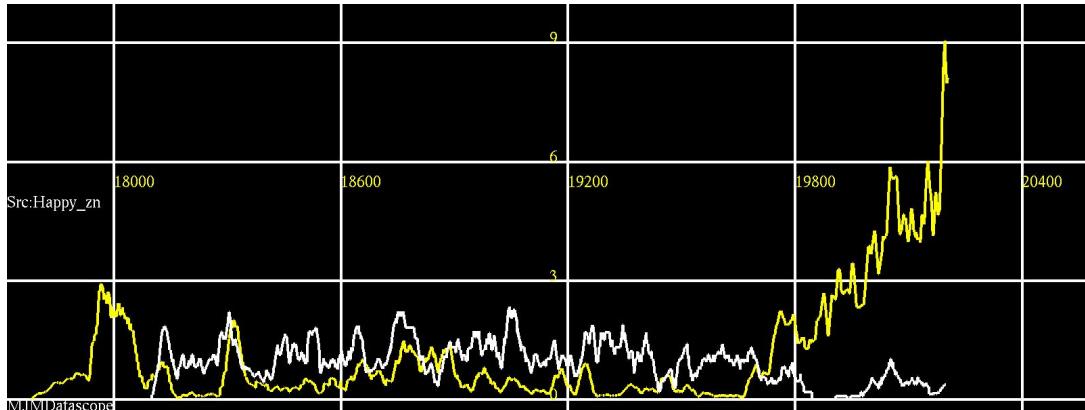


FIG. 3: Copper(yellow) and Zinc(white) 30 day trailing average for Happy.

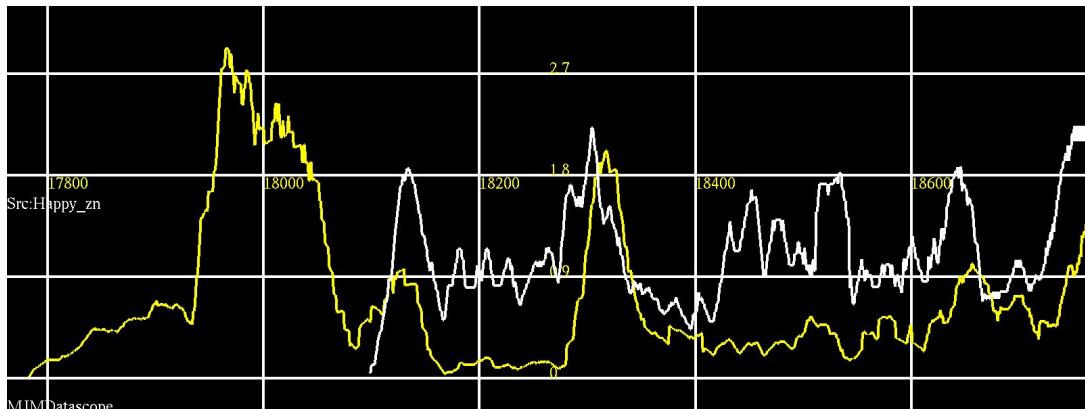


FIG. 4: 30 day trailing average for Happy copper(yellow) and zinc(white). 2019-05-30 (18046) when the cough was first noted to be gone for a few weeks. In retrospect decreasing copper and the start of zinc should have been significant concerns.

Happy arrived here in September 2018 heartworm positive. Her coughing was eliminated for a few weeks in 2019 and since then it has been coming and going to varying degrees. Over the years, she has experienced brief periods of sickness but generally been active and apparently healthy except for the cough. She has shown radiographic evidence of enlarged heart and possibly narrow trachea. Her heartworm recovery was described as she received doxycycline and ivermectin with vitamin K and other supplements [229]. Later she had an unusual episode which resulted in some investigation of possible role of vitamins B-2 and B-3 in her health [222] . She had two episodes resulting in emergency vet visits and blood work. On 2022-02-02, after apparently choking on a carrot, lab results were notable for elevated creatine kinase(609U/L, 10-200) slightly high glucose (123mg/dL, 63-114) , low normal Ca (8.5 mg/dl, 8.4-11.8) and Cl (108mmol/L, 108-119) with high normal bicarbonate(26mmol/L, 13-27). ALP(35 U/L, 5-160) was normal and total T4 low normal (1.2mug/dL , 1.0-4.0). On 2024-10-04, after having difficulty jumping, at a different clinic glucose was normal (111mg/dL, 70-143) and ALP was low normal (31U/L, 23-212) with no measures of creatine kinase or blood chemistry. The change in ALP appears to be largely due to reference ranges as numbers are similar between visits.

Thinking outloud

not enough context to be useful here. Add or remove?

For comparison, Little Man on 2016-12-29 while on steroids IIRC had elevated ALP (231 U/L, 0-140) and high glucose (126ml/dL, 75-124) and low BUN (8.6 mg/dl, 9-29). ALP may have been elevated due to steroids rather than copper toxicity.

Happy also had episodes of "flopping" as if trying to scratch back on furniture or floor. When first noted circa 2019-08-27(18135) it was treated successfully with Apoquel. Subsequently it would come and go but was generally not bad enough to treat.

As copper was increased due to widespread coughing after Trixie's arrival, her cough was noted to decrease to lower than prior levels. Review of the copper dosing suggested it had fallen prior to Trixie's arrival. Often her excited cough appeared to be a honk on exhale suggestive of trachea collapse. She also would cough early in the morning when curled up. As outlined in the introductory material, it was later realized that earlier concerns about aromatic amino acids could be due to simple excitability rather than any disease worsening. This most recent effort considered some coughing increase normal and in Winter of 2024-2025 she may have reduced coughing, good energy level, and maybe some aromatic amino acid sensitivity.

During the increased copper interval it was noted that her frantic "rubbing", where she tries to rub her lower back on furniture or rolled over on the floor, had stopped. This was most severe years ago when it was treated successfully with Apoquel between 2019-08-27 and 2019-11-03. After that, it had come and gone but never appeared distressing enough to treat again. A review of the copper and zinc dosing during the Apoquel treated spell suggests very low copper (maybe less than 1mg per day) and substantial zinc (3mg on some days). The resolution with either copper or Apoquel points to the possibility of a pathogen involvement as will be discussed with Trixie and Annie's coat problems.

She was coughing a lot while on the presumed optimal copper and fat diet for several weeks into August 2024 although with no evidence of cardiovascular limitations to her activity. Generally good in the park it may be a household respiratory irritant as she may stop coughing when barking for a while such as before dinner although then coughing after dinner while quieter but anticipating left overs.

In the fall of 2024, she was coughing when excited, now several days after significant aromatic supplementation, but her exercise capacity from jumping during dinner to trotting in the park is very good. It remains to be seen if continued copper supplementation can eliminate the cough presumed due to defects or limitations in trachea properties.

For Happy copper may be necessary but not sufficient. Concern at that time was around restriction of aromatic amino acids, notably tryptophan, iodine, and iron, along with adequate meat fats from beef, turkey, and chicken. By the Spring of 2025, lipoic acid was also considered.

On 2024-12-20 (200077) Happy and the others started to get a new bulk copper citrate supplement. As of early 2025 she and Trixie may be coughing less now on a more consistent schedule of copper citrate late in the evening with garlic in meat or canned food without other supplements. In April 2025 lipoic acid was begun more regularly replacing one of the copper doses but that seems to have coincided roughly with increased coughing. Although currently the belief is increased coughing is due to histidine making her more alert.

4.3. Brownie and puppies

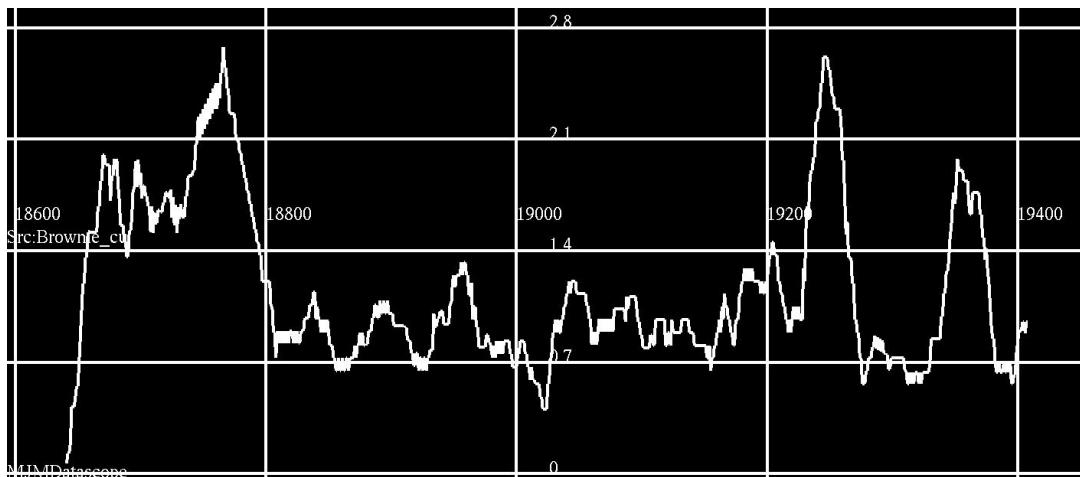


FIG. 5: Brownie 30 day trailing average copper.

Brownie was the subject of a prior work where her uneventful pregnancy was notable for vitamin K consumption while heartworm positive [232]. She was notable for one bad eye and abdominal lump. Briefly, Brownie was determined to be pregnant shortly after arrival . She gave birth on 2021-02-14 (day 18672) to 10 live puppies and 2 dead or died

shortly after delivery. One died later after apparently being sat on. Her heartworm was treated after weaning with Diroban on 2021-07-13 and 14 (days 18821 and 18822) . She was then spayed on 2021-09-13 (18883) but suffered complications requiring emergency intervention to drain fluid. Subsequent to that work, her abdominal lump was removed and diagnosed by vet as fibroids on 2021-11-15 (18946) . She was uneventful until she was observed to cough occasionally for no obvious reason and appeared to have some movement issues. X-ray confirmed tumors were likely responsible for both problems. The vet suggested steroids which may have caused a variety of problems and made it impossible to encourage immune stimulation in any meaningful way and probably not much could be done with added copper. She became agitated and appeared to have a hard time navigating as if her bad eye had been giving her some information earlier. She was put to sleep on 2023-02-22 (19410). She never received high copper dosages but given her overall state of health and pregnancy she may be an interesting case for context.

4.4. Cookie or Mixie

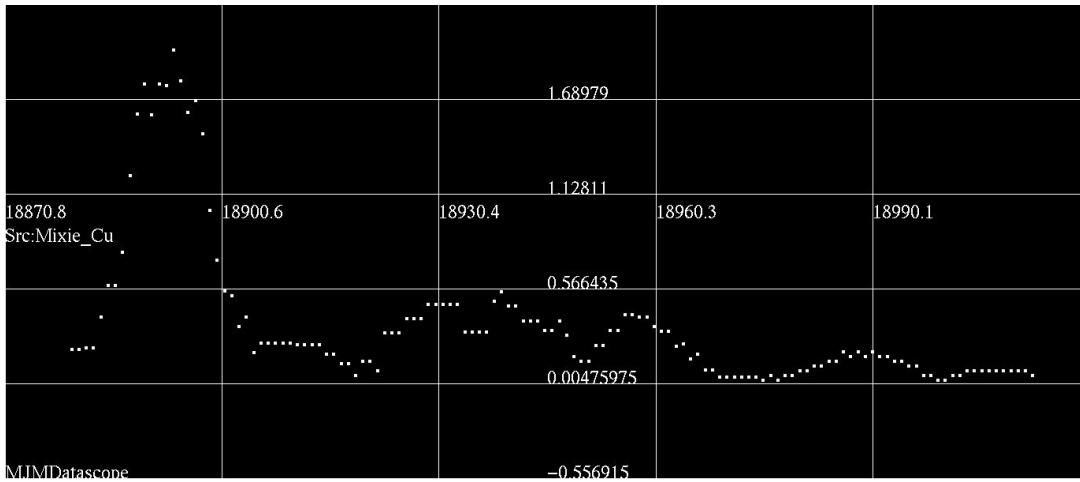


FIG. 6: Mixie daily copper (white) intake .

Arrived with diagnosed respiratory infection and prescribed azithromycin. Copper and other nutrients were added and eventually infection resolved well. Contribution of any nutrient is unknown but recovery seemed uneventful.

4.5. Trixie

Trixie began coughing shortly after arrival and was very low energy. Her coat was notable for a sticky feeling that seemed to recur after one bath with special shampoo (don't remember if it was prescription check notes) . Many other dogs began to cough or hack suggesting that she brought a communicable infectious disease which was the motivation for increasing copper again. Nutrient mix was modified to add more copper and most dogs' coughing returned to normal quantity and quality although her's did not entirely resolve. Copper stopped for a couple days (I was gone) and owner took her to the vet as she began coughing more. Clavamox was prescribed and her coughing stopped within a few days. Her energy level has improved but she did not run until 2024-05-02 (19845) . She had a renewed cough around 2024-05-22 (19865) subsequent to copper withdrawal on 2024-05-15 (19858). Cough seems deep on excitement not honk/wheeze like Happy. Copper resumed 2024-05-27 and is greatly reduced by 2024-06-01 . She appeared more energetic than when I left and walked well although maybe still tired at end of walk. Her coat continues to feel clean although difficult to determine if bathing alone would have achieved same result.

More recently she has been getting more complete supplementation including tryptophan and tyrosine with iron and lipoic acid and continues to gain energy. Coughing is very rare and her mobility seems ok not hesitating as much to run or jump a little. Around December 2024 her cough seemed to return unless she had copper/garlic. By early January, her cough was greatly decreased but still common although her attention level continues to increase and right now the cough is thought to be tolerable.

After another round of antibiotics in response to coughing and low energy , she continues with increased copper, lipoic acid, and histidine along with intermittent iodine. The histidine may increase her alertness but also possibly

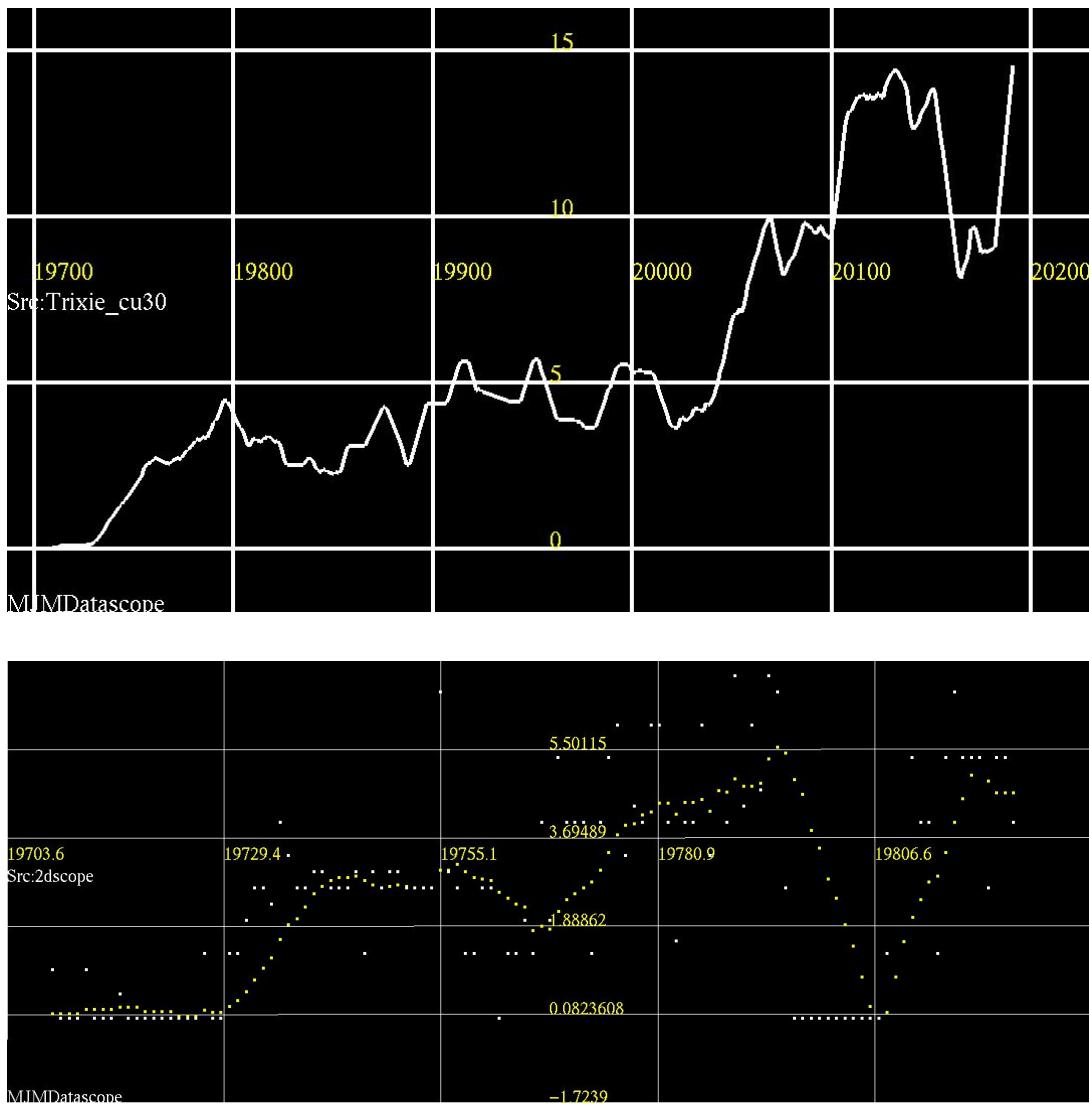


FIG. 7: Trixie copper consumption since arrival. Top plot 30 day trailing average per day. Daily amounts (white)) and trailing 10 day average(yellow).n bottom Copper started to be significant around day 19730 in response to coughing. Day 19807 marked the end of the copper fast as well as the end of Clavamox which was prescribed due to worsening when copper stopped days earlier.

aggressivness. Engagement with surroundings on walk improves although cough still comes and goes. Daisy tries to play with her but she has limited interst.

4.6. Rocky

Rocky arrived here on 2022-02-05 in generally good condition although notable for a "rubber block" or "plastic" body type or feel. Notes on his condition including cough were sparse although he tended to stay covered up on the couch a lot as other small dogs tend to do. Rocky will hopefully be the subject of another work as he responded significantly to iodine and sodium benzoate which was attributed to, but never lab confirmed, low thyroid output. His "plastic" body type changed into a more normal "flexible" type and he began to feel like the other dogs when picked up rather than being stiff. The addition of copper may have reduced his morning cough but he continued to have apparent congestion after eating sometimes breathing through his mouth and sneezing. That too has cleared up by 2024-06-01. Most recently he had notable muscle tone which had been lacking. His overall activity increased but that may be due to social factors such as feeding ritual. Some coughing now coincides with exposure to cigarette smoke.

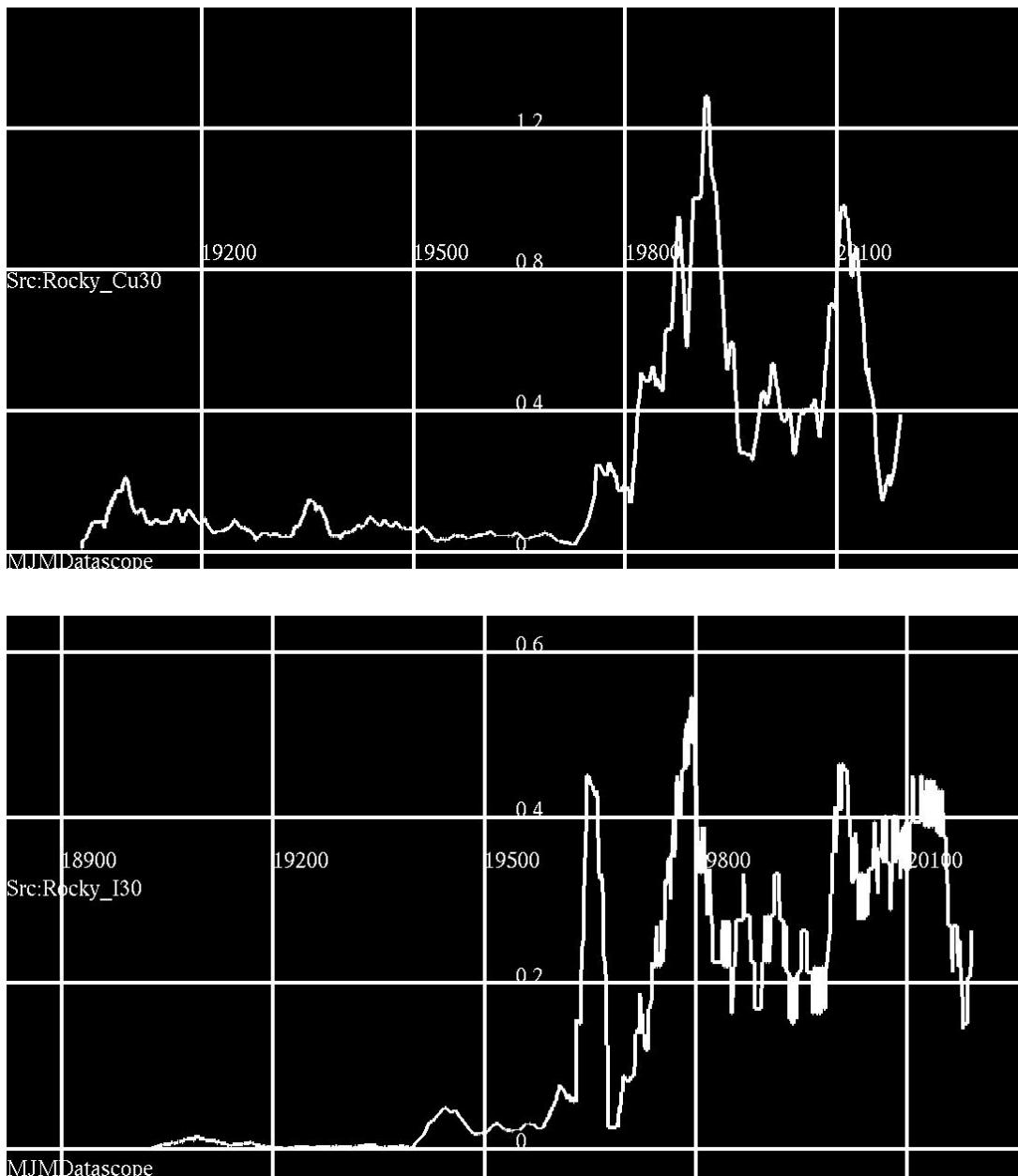


FIG. 8: Rocky 30 day trailing average copper (above) and iodine (below). It's probably important to note that iodine was only given every few days and this much continuous iodine may have different net effects. This average is just included to illustrate correlations with a likely confounding factor.

Copper was shown to correlate negatively with TSH in one human study and may increase T4 levels [398]. As benzoate may be an important confounding factor, a brief digression here may be helpful. Benzoate was included in snacks before and notably in the case of Beauty [220] for a variety of possible benefits. A recent study on rats fed benzoate demonstrated some insignificant indication of increased T4 and decreased TSH which the authors summarize as, [356],

Minor variations in T4 and TSH levels were not considered treatment-related because they were not noted in a dose responsive manner, were not generally statistically significant, or were observed in a direction that would be generally not be considered toxicologically relevant. These minor variations also fell within the range of levels noted for historical controls.”

If there is a beneficial effect, it likely depends on many factors such as overall diet and may vary across species. He eats a lot more vigorously and consistently than in the past although he also may have benefited from added

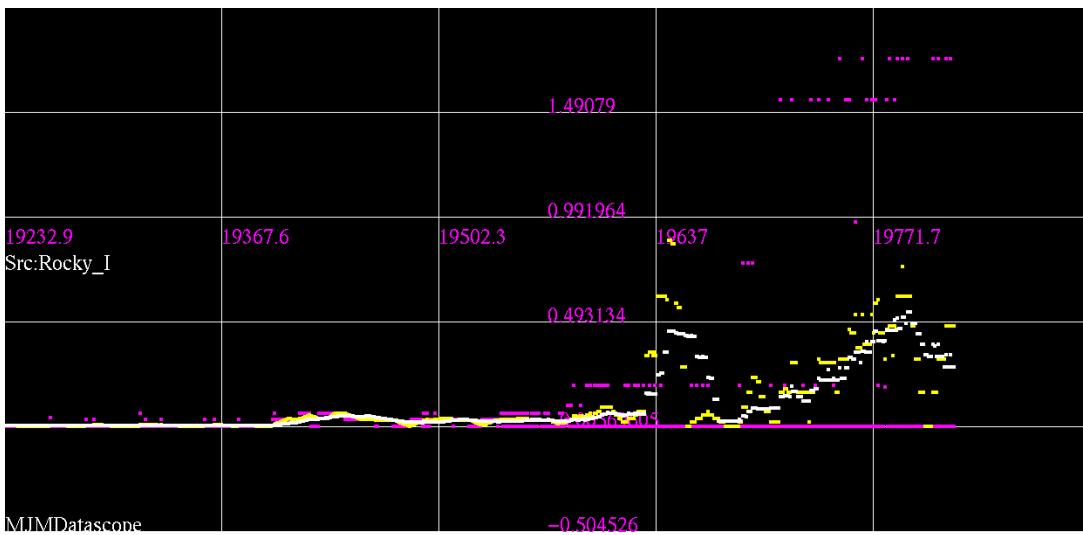


FIG. 9: Rocky iodine intake daily and with 10 and 30 day trailing averages. Patterns are difficult to discern with the pulsed dosing.

iron.

4.7. Annie

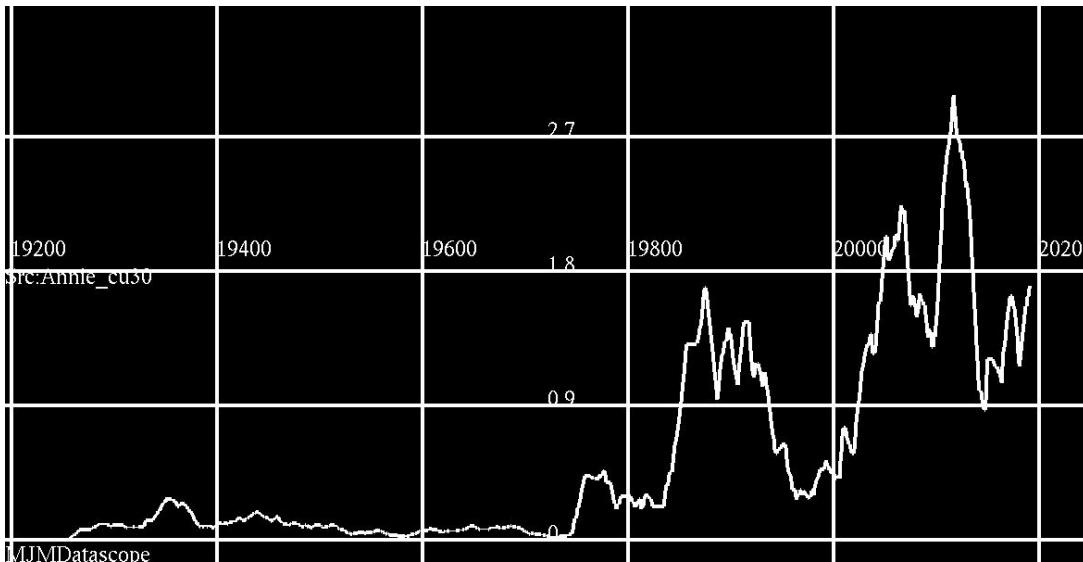


FIG. 10: Annie overall 30 day lagging average daily Cu (mg).

Annie probably showed the clearest improvement coincident with increased copper (and a few other components described below) on two occasions. Annie arrived thin but in generally good condition although seemed old for stated age of 6 years . She ate well but had some limitations in sight and hearing. She seemed to get skin or paw irritations easily. Coughing was variable and not well documented. She feels a little "frail." She began to sleep excessively in early 2024 and a special copper snack was started on 2024-05-01 (19844). This consisted of 2mg of copper along with sodium benzoate, KCl, and B-6 in chicken broth which was more readily accepted than the full snacks for everyone else. As these other components had been quite common they were not considered significant although the sodium benzoate had also been stopped earlier. Lost vigor suddenly regained in a few days and seemed restored to her more typical self by 2024-05-05 (19848) with continuing improvements in energy and appetite. Her exercise interest improved and she walked and cried out with good energy.

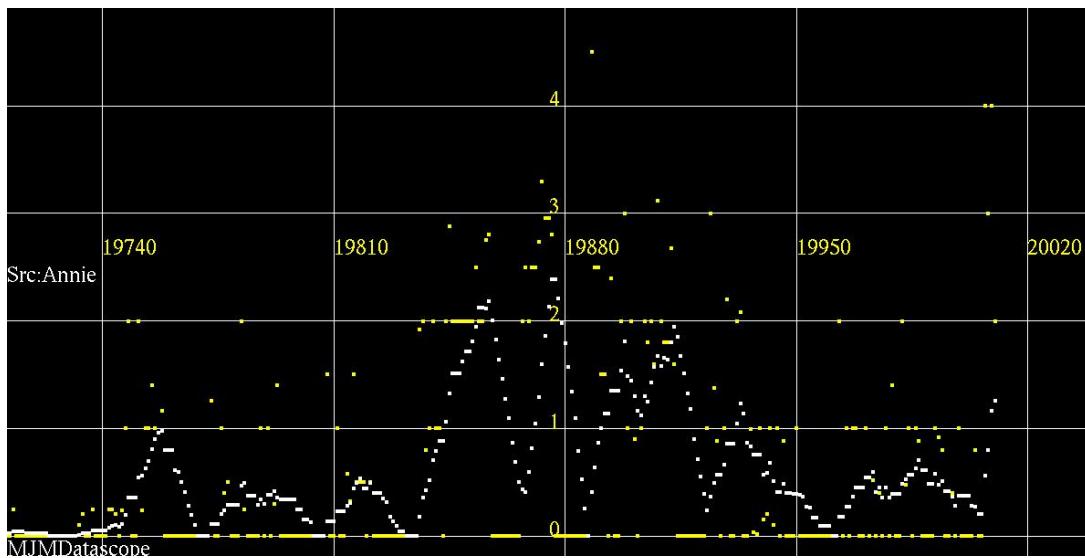


FIG. 11: Annie zoom in on recent days as copper was increased around 19848.

Around 2024-10-11 (2007) Annie was noted to have swelling under her left eye. As she had not been eating the PMSNACK regularly her copper intake had again been reduced so I added it alone to canned dog food which she ate well. By her vet visit 3 days later on Monday, the swelling was gone. She was prescribed Clavamox and an "artificial tear" solution.

She generally have a preference for marrow, some amino acids (tryptophan, tyrosine, methionine), and iron and some for benzoate.

As of January 2025, she was slowly deteriorating with apparent decreases in eyesight and awareness. Up until a week or so ago she had been eating reliably but may have had too much zinc.

In mid April 2025, she is fairly stable eating well most of the time with some episodes of not eating. She wanders around bumping into things and sleeps a lot sometimes barking when everyone else is barking.

4.8. Dexter

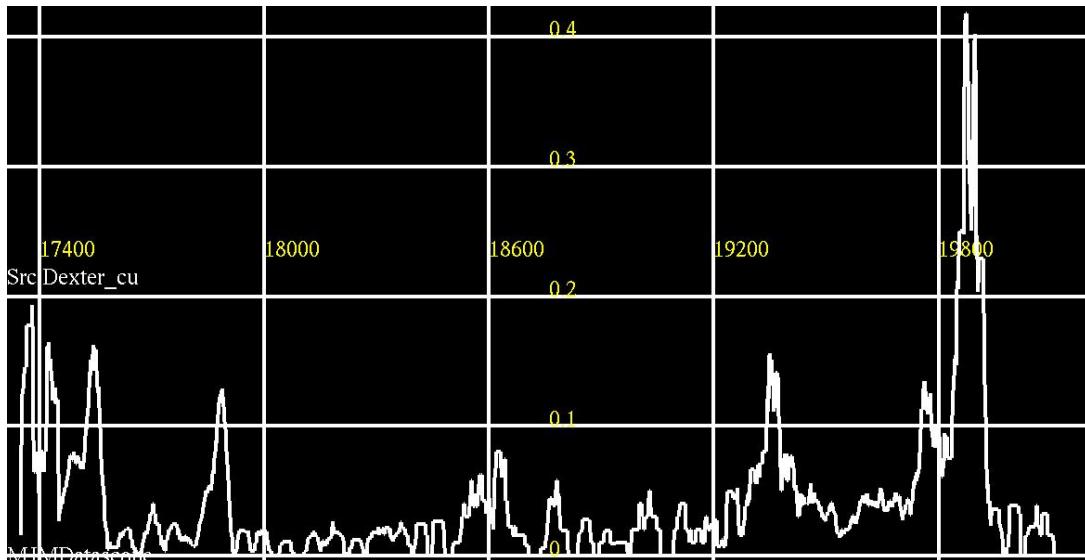


FIG. 12: Dexter daily copper intake since arrival 30 day trailing average.

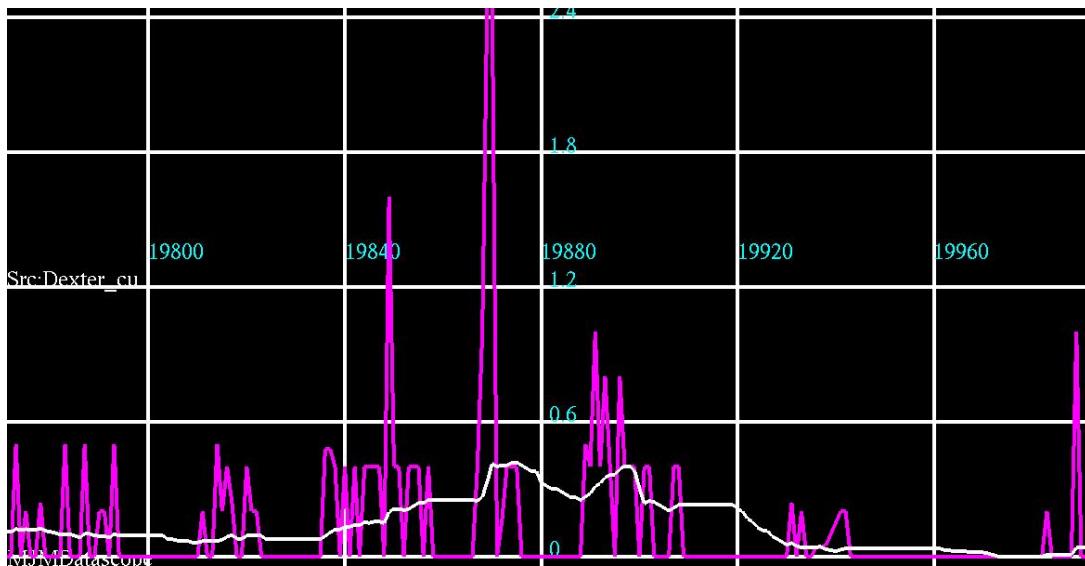


FIG. 13: Dexter daily copper intake around blood test on day 19926 . Daily amount in red 10 day trailing 30 day average in white. While his consumption had recently been higher than normal he had not had any for about 18 days prior to blood test.

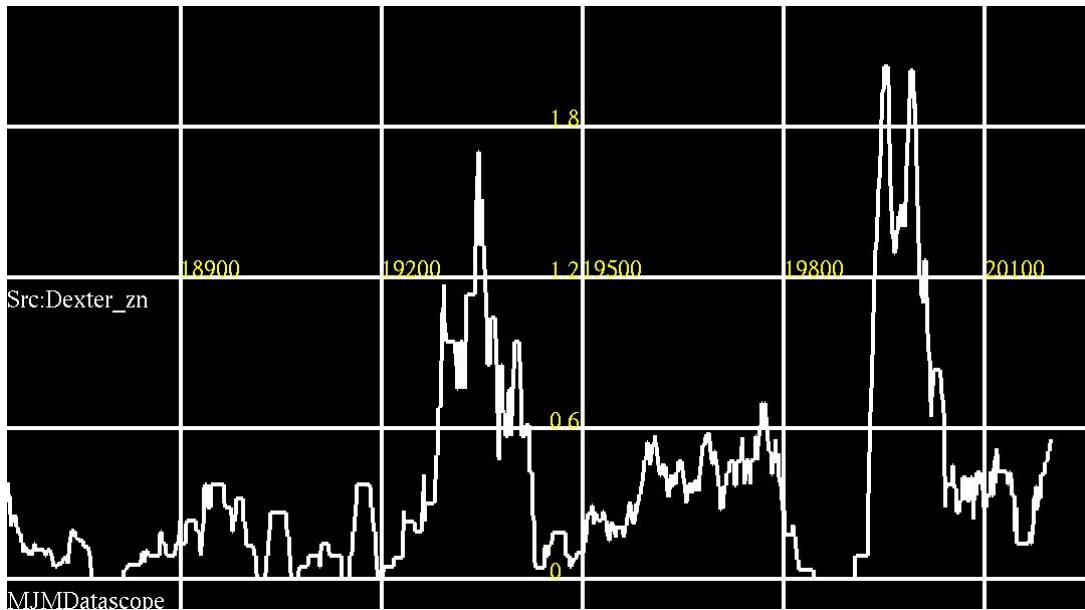


FIG. 14: 30 day trailing moving average zinc intake for Dexter. Interestingly he seems to have gained weight after the peaks and the null was prior to his vet visit. It is likely he is sensitive to zinc and does seem to be responding well to the occasional "DEXSNACK" containing several non-copper metals.

Dexter was not originally part of the copper study but was included after showing signs of distress and elevated bilirubin. He had always been a picky eater but otherwise in good health with plenty of energy. While I was gone he went to the vet for vomiting. His recent copper intake over the last few months had been much higher than normal but he had not eaten any copper since 2024-07-04(19908), 18 days prior, and was not exhibiting any signs inconsistent with his normal pickiness. Blood work on 24-07-22(19926) was notable for elevated ALT of 140 (10-125 U/l) , total bilirubin of 1.8(0-.9 ng/dl) and ALP < 10 (23-212 U/l). Low ALP with signs of liver failure may be diagnostic of Wilson's Disease but the copper intake pattern did not seem consistent with that. In Wilson's Disease, ceruloplasmin is low [396] and it may be a case of insufficiency coexisting with surplus leading to a supplementation dilemma introduced earlier. Low ALP activity may be due to zinc and magnesium deficiency [292]. Zinc and manganese did raise ALP levels in chicks although copper did not appear important under the conditions tested [312]. His zinc history, see Fig. 13 does show lack of supplementation prior to this event and weight gains occur after more prolonged higher supplementation . Rats have been observed to have similarly reduced food intake with zinc deficiency as well

as bone abnormalities [65]. Based largely on the low ALP he was given a metal mixture along with KCl and various others components (see "DEXSNACK" in MUQED data) such as amino acids. The mixture added to kibble was well accepted by Dexter and others including Annie and Rocky. Metals included iron, magnesium, zinc, and rarely copper and manganese. He subjectively improved and he may be even eating better than before.

Other instances of spitting up were recorded inconsistently. He was noted for spitting up yellow on 2024-08-09 after having .2mg on 2024-08-07 and -06. He had also been noted to spit up on 2023-08-08 after having no known copper since 2023-08-02. Its not real likely but he may be sensitive to copper and it was not a priority to give him more so follow on doses remain sporadic. Eventually he seemed to respond well to added vitamin D which was thought important due to bumps on his ribs and possible bone problems. Currently he seems to be gaining weight and eating more consistently with possible improvement after the switch to cooked beef adding cinc acid and KCl to his diet. Chloride may be important as well as the non-copper metals.

4.9. Others

Daisy, Claire, and Frankie (Autumn) were pretty much event free during this time although Daisy had a UTI early after arrival. Complete daily copper exposure (mg/day) is shown averaged over trailing 30 days.

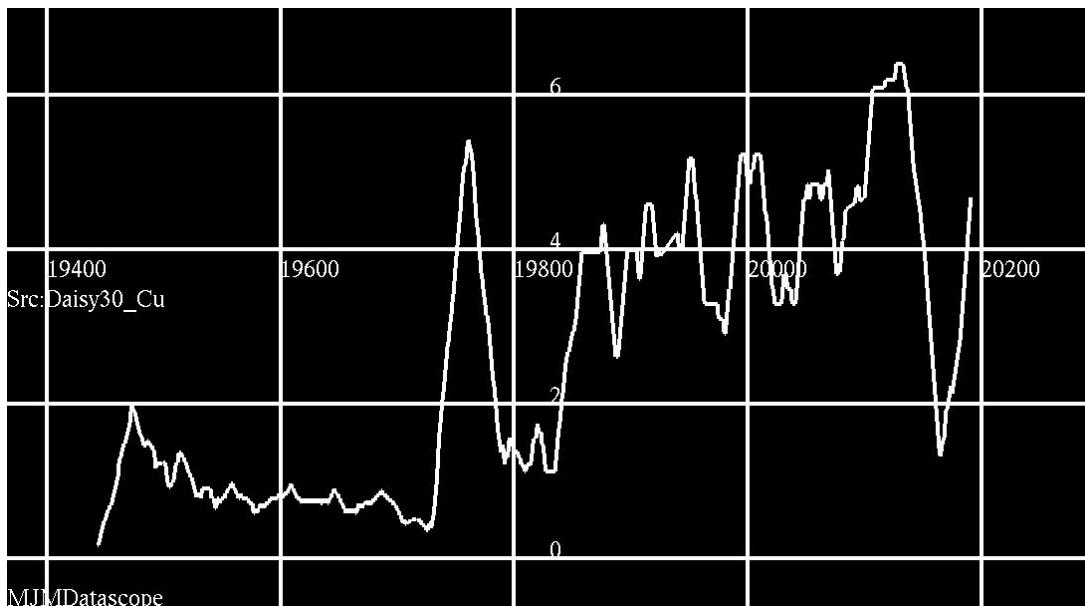


FIG. 15: Daisy monthly copper/day averages

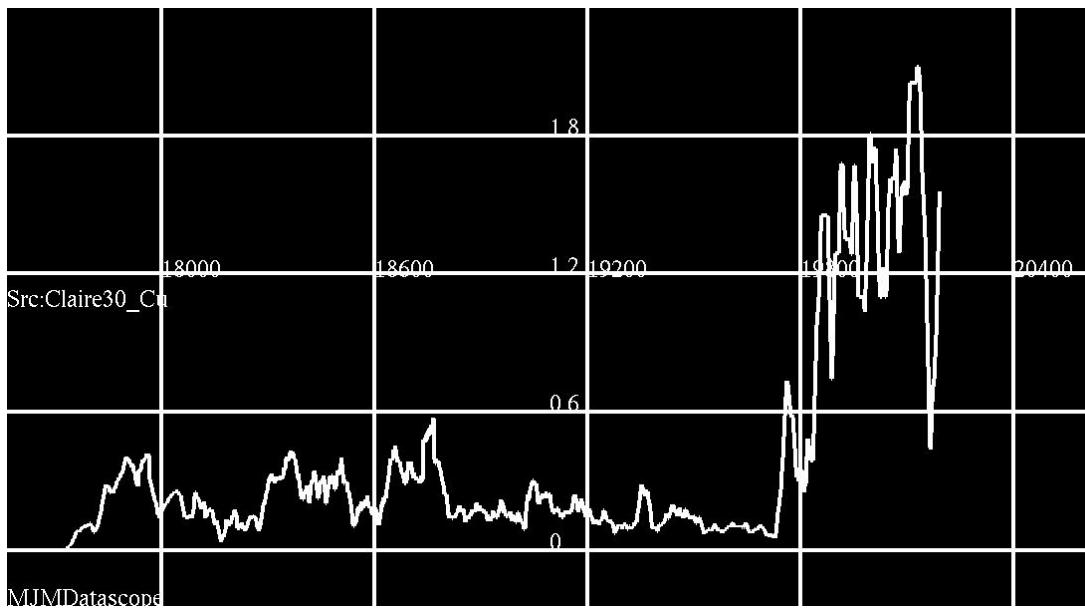


FIG. 16: Claire monthly copper/day averages

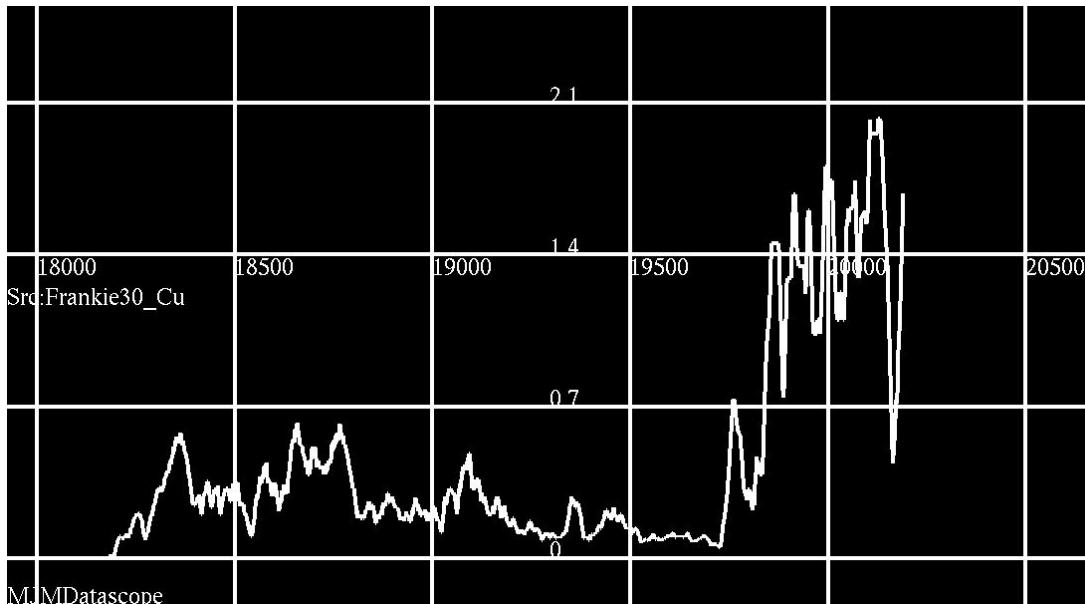


FIG. 17: Frankie monthly copper/day averages

5. DISCUSSION

5.1. General observations on these cases

Copper supplementation averaging around .2 to as high as .8 mg/kgBW/day appeared beneficial in this group of dogs as symptom improvement often followed days or weeks of dosing. This is contrary to some expectations from popular concerns about excessive copper in commercial dog foods but as described later this may be due keeping the copper away from other nutrients. Several problems can be attributed to copper deficiency and they may recover on different time scales leading to confusing symptoms during copper repletion. Some dogs such as Annie and Hershey appeared to become more active within days although with Hershey increased coughing was an inaccurate concern. Copper does not appear to be a complete solution for Annie as she has gone blind and continues to become less active although as described below other nutrients may be moderating that problem now.

Coughing and other subjective signs were often used to monitor progress and notes were not always sufficient.

Coughing as described before can be produced by many causes. Here, we were concerned mostly with infection, trachea collapse, and heart enlargement. Honking related to trachea collapse may be more common when the dog is excited. In this case, improving "energy" may produce more coughing even though the dog is largely healthier but the heart is still large or trachea still soft. This is further complicated with additions of vitamins that tend to promote alertness as was observed with histidine (indeed there was some concern about aggression when initiating it). This may not have been fully appreciated early on.

In some cases, the copper supplementation appeared to reduce coughing within days and without side effects such as reduced activity. In these cases it was thought to control but not cure infection as subsequent antibiotics appeared to stop the coughing. Withdrawl of copper supplements may coincide with increased coughing for no obvious reason such as increased activity but it would resolve with antibiotics. In thoses cases the copper was thought to control but not eliminate pathogens.

Its unclear how many if any infections were avoided with added copper as some dogs benefited from antibiotics even with the copper at the recorded doses. Its possible it slows the growth or reduced virulence but does not clear some infections. This may allow it to become larger before clearing with antibiotics. One work in mice did show increased antibiotic tolerance to *P. mirabilis* that survived copper exposure [147].

Coat or skin issues occurred with Annie, Trixie, and Happy. All three of them seem to have improved but the role of copper or pathogens is not known. Currently Annie still bites her paws sometimes although Happy no longer shows signs of skin irritation and Tricie's coat feels clean. Happy's prior rubbing episodes, initially treated with Apoquel but subsequently just "waited out", did not appear after increasing copper even though she had been doing that on and off recently. She sometimes took to "rolling over" later but mostly for attention. This "allergy" could be pathogenic via immune response to either allergen or actual patogen that becomes resolving with more copper although symptoms could be treated with Apoquel known and likely side effects make this a cleaner solution.

The only case suspicious for counterproductive copper effects was Dexter. Although he had not had copper for 18 days prior to his blood work he had high doses in the prior few months. However, he has spit up sporadically since arrival and may still do it on occaison now. However, when he is not eating robustly the mixture of zinc, magnesium, iron, calcium, and potassium chloride seems to help. It is not given consistently due to hassle and concerns with excess zinc but only when it appears to be needed. His weight, unlike the other dogs appears to be directly related to how well he is eating as fluid and tumor or other issues are probably not important. His weight seems to increase after sustained zinc supplementation and maybe more frequency weighting, better acceptance notes, and more attention to zinc and magnesium can sort out his quirks.

In order to get best resolution in similar cases it is likely that other vitamins will be needed too. In the following sections some copper quirks are discussed in terms of interactions with other variables but here competing supplements are discussed. Right now for these guys a short list would include iodine, lipoic acid, and histidine. Iodine was antiticipated for reasons previously discussed and at least with Rocky may be a dominant factor in his overall improvements. While Annie continues to become less active, histidine may be helping. Histidine any lipoic acid may be helping Trxie while Happy may also benefit from the lipoic acid. In dogs lipoic acid is an insulin mimetic which may encourage the consumption of glucose if that is an energy limiting issue. Histidine would presumably be metabolized into the neurotransmitter histamine.

Reconciliation with various concerns and failures relies on the complex interaction with other dietary components which may be important over a large range of genetics. Copper was just one of many nutrients explored and it requires some of these for proper handling. Any optimization strategy would need to continually be finding the performance limiting nutrient in turn as each is tweaked. Copper was considered to be important early but despite some successes was lost in the shuffle. While the conditions for beneficial usage remain unknown, several suspects can be identified. Histidine addition was the most obviously correlated with increased alertness, animation, and aggression although there may have been some expectation bias considering increased histamine contributint to these states. These responses could increase coughing leading to the erroneous conclusions it was making something worse.

"Geeral energy level" is a bit subjective and confounding vitamins may include iodine, lipoicacid, and histidine although many others such as iron could contribute too. Iodine was a major concern due to prior dogs with lab confirmed hypothyroidism and the existence of "goitrogens" in dog foods.

Hypothyroidism is common but may be due to a nutrient deficiency suzh as iodine or less obviously copper. Some of the symptoms associated with hypothyroidism could be explained by copper deficiency alone. The role of sodium benzoate may be important but difficult to characterize but may be a topic of a later work on Rocky.

At least in one dog, Happy, copper was required to conol coughing but it did not work in the context of a low fat diet and may also be limited by zinc, iron, or cherries that contain fructose. The search for suspected diet link to DCM in dogs may want to consider copper availability as an issue and ingredients such as these as possible problems.

The overall concern with Happy and aromatic amino acids ist still not clear. Increased energy may lead to more coughing but pulmonary hypertension may be controlled by serotonin [6] and therefore tryptophan intake. Pulmonary hypertension is itself pathological and should be avoided while increased arousal state would be important for quality

of life so investigation may be useful.

Thinking outloud
repeated in intro

Besides the molecules already mentioned, it is worth noting that taurine was a consistent dietary component. Sulfates are observed to create copper deficiency in ruminants and the possibility exists that taurine exhibits related chemistry in the GI tract. Indeed, it has been observed to reduce copper toxicity in rats with increased fecal copper amounts [149] suggesting decreased absorption. Another work demonstrated taurine reduced ceruloplasmin only in rats fed a control diet but not a high-fat diet [177]. As taurine is being explored for various indications, including DCM [241], apparent limitations in supplementation could relate to induced copper deficiency which would likely cause some symptoms expected of copper deficiency.

B-6 deficiency has been linked to excess copper excretion [55] possibly making copper a secondary excretion issue rather than a primary absorption problem. However, the concern with excess B-6 intake creating effective deficiency is a reminder to look more carefully at all data.

Over a broad range of genetics, it's likely that copper intake can be raised as long as other nutrients are also given to handle the copper beneficially. Candidate nutrients include tyrosine and tryptophan.

Several issues came up during the execution of this effort. The pulsed dosing made for confusing results sometimes. Shared snacks caused recipe modifications for one dog to impact others and target doses to drift as they were lost in the shuffle. Another difficulty is due to pulsed dosing. This was chosen to allow rotation of various nutrients and make it easier to see short term effects of comparatively high doses. However, it did require that time series be averaged for analysis. Happy's copper intake dropped much lower than normal preceding a period of excessive coughing. It was only after copper was started due to Trixie's respiratory infection that the data were examined more carefully and the pattern noted. Ideally the filtering would be a lagging average weighted to some suspected biological parameters but even uniform moving average was useful.

Attempts to standardize the vitamins and split one snack for everyone often resulted in reduced copper supplementation for some of the dogs who needed it. The afternoon snack was used for the daily copper but it was not as well accepted as the morning snack. Special snacks with copper or other isolated nutrients in canned food worked for individual dogs.

Thinking outloud

maybe add Daisy as she had earlier infection

5.2. Aspects of Copper Chemistry

Thinking outloud

collection of facts thoughts and citations coming together well but needs more time for organization

This work discussed concerns about copper availability and degradation of other nutrients with consideration of an entire meal and digestive system. A range of environments are encountered from formulation or growth to absorption. Initially the relevant chemistry relates to copper in food and supplements while it is mixed, stored, or cooked. Later, the chemistry of the GI tract notably the stomach is important for interactions with the total intake. Surprisingly the literature from remediation and leaching may be relevant here.

A central topic is copper speciation or oxidation state. Perhaps four copper oxidation states have been considered in the biological context. Solid Cu(0), Cu(I), Cu(II), and rarely Cu(III). Cu(I) and Cu(II) are probably the most relevant to food effects. Solid copper or Cu(0) has been claimed to have environmental remediation capabilities [76]. Cu(III) is thought to be an intermediary in the copper Fenton reaction at near neutral pH with bicarbonate and sodium chloride present [282]. Cu(III) production for degradation was also enhanced with histidine [278].

The first concern, the formation of insolubles that have decreased availability of the copper, is most clearly seen with sulfides but many other stable copper compounds are known. Copper minerals represent some compounds that exhibit low solubility in their native settings. Wikipedia lists several copper ore minerals [386] containing sulfur, iron, antimony, zinc, carbonate, hydroxide, aluminum, silicon, hydrogen, arsenic, and water. Of course an infinite number of organics could be formed with variable stability. Early XPS work suggested many copper minerals contain copper in the +1 state [258] although work continues to clarify specific issues [117]. Generally the minerals can be leached in acid to recover the copper and that chemistry may be useful here.

It has been noted that Cu(II) is converted to Cu(I) prior to transport and therefore some benefit may be obtained by making the conversion from Cu(II) earlier. However, as with some other nutrients, this may be counterproductive when normal mechanisms are operational. CTR1 for example will convert prior to transport [162]. This is likely similar to the situation with iron [309].

The two drawbacks of iron chemical characteristics, that is, Fe³⁺ insolubility and toxic radical production by free iron, must be jointly addressed in some biological processes, such as the process of iron absorption by enterocytes at the duodenum. Iron is oxidized by stomach gastric juices, and most iron reaches the duodenum in the Fe³⁺ form (32). As the stomach has a pH < 3, Fe³⁺ remains soluble until it passes to the duodenum where the pH is significantly higher. Thus, to enter into the enterocyte Fe³⁺ must be reduced to Fe²⁺. The absorption of the as-formed Fe²⁺ must be done quickly to avoid the formation of hydroxyl radicals. To overcome this inconvenience, humans have developed a very efficient mechanism based on a protein pair. Iron transfer through the enterocyte membrane occurs due to the combined activities of two proteins: the DMT1 Fe²⁺ transporter and the conjugated DcytB, which can reduce Fe³⁺ to Fe²⁺ (33). The DcytB/DMT1 pair is required for iron absorption since iron enters the small intestine lumen mainly as Fe³⁺. DcytB, an ironregulated ferrireductase protein is highly expressed at duodenal enterocytes and reduces the Fe³⁺. Upon reduction, Fe²⁺ is transferred across the apical membrane of enterocytes by divalent metal transporters, mainly DMT1 (Fig. 6).

The same work [309] may be a good background for understanding copper more generally as a lot of issues with iron may be similar.

Reactions of Cu(I) may reduce net uptake due to precipitate formation that requires re-dissolution to absorb.

Copper "Fenton" reactions have been extensively explored for pollution remediation by destruction of toxic chemicals. Many of these reactions occur under mild nearly physiological conditions suggesting they may be able to degrade nutrients. In particular, bicarbonate in the 4mM range improves the degradation rates for a Fenton like Cu system [280]. In fact, carbonate species are thought to be the active products not hydroxyl in neutral or alkali media [150]. Bicarbonate is being investigated for pollutant degradation optimization [377] as it apparently is quite active.

Thinking outloud

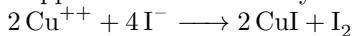
The photograph in Fig. 18 shows the side of a baking pan on the right which was representative of the surface to the left prior to heating for a while in baking soda water. The carbonate derived species may easily react with or make soluble the oxidized food grease which I thought was just a "like dissolves like" issue but may be as stated here. An ammonium bicarbonate electrochemical etch apparently optimized the mechanical properties of carbon fibers [170].



FIG. 18: A previously brown baking pan with baked on carbonized food largely grease. Heating in oven cleaned the metal submerged in baking soda water while leaving the metal above the water line dark. See if bicarbonate has any relevance here or save for another work lol.

Cu(II) is the more common species but it can be reduced under relevant conditions by ascorbate, riboflavin leading to DNA damage [260](although maybe assisted with light [155]) or reducing sugar at elevated temperatures which may occur during food processing. While sometimes associated with alkaline pH it can occur with pH of 3[136]. It can be reduced and complexed with niacin [56]. It may be worth noting however even the interaction with ascorbate is controversial with redox competing with a catalytic mechanism leaving the Cu unchanged [322]. Generally copper absorption has been reported to decrease with higher dietary ascorbate with a confusing interaction with iron [160] which may be easy to rationalize a increased copper reduction prior to uptake.

Copper can be reduced by several things.



Once Cu(I) is formed, it can undergo undesirable reactions.

[308]



disproportionation,



Its also worth mentioning that several "electroless copper" formulations exist and there may be similar mixtures that occur in food or in vivo. ZZ

Thinking outloud

Personally applying Cu saturated ammonia to the skin can leave a light blue residue or wash off but topical peroxide may produce a nice "copper tone" lol.

It is quite reasonable to consider the possibility that uptake is limited by stomach acid and chloride assuming that once soluble the copper can be stabilized on something available. Stomach pH has been noted as a concern particularly among the elderly in past work on covid [227] and Alzheimer's [225].

First its interesting to note that many high-school level chemistry examples are probably relevant. Copper is used to detect reducing sugars. This is one reaction that may damage other components such as sugars. Interactions with iodine are textbook illustrations.

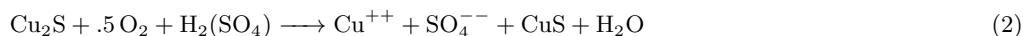
Once a copper sulfide is formed, the copper may be recovered in processes such as commercial leaching that can go at 30C. In an acid environment both chloride and iron are important to getting optimal copper extraction from sulfide ore [306].

And some have observed chloride may be generally better for extractions of metals from sulfides, [137]

Generally, the leaching of the sulfides occurs more easily in solutions of chloride rather than sulfate (Lu et al., 2000a, Lu et al., 2000b, Fisher, 1994, Fisher et al., 1992, Chu and Lawson, 1991a, Chu and Lawson, 1991b).

In a completely unrelated study of the electocatalytic behavior of cobalt sulfides, the authors found a surprising role for chloride in converting sulfides to hydroxides against prior predictions [123].

Some leaching reactions include [313]



(3)

FIG. 19: Some leaching reactions [313] at ambient or elevated temperatures

Ultimately food and stomach contents form a complicated variable mixture of chemicals with varying ability to interact with copper and a survey of such properties such as [216] may be useful .

Reactions with "Reducing sugars" and iodine are examples where nutrients are transformed or made insoluble by interaction with copper. although assay solutions typically are used at elevated temperatures slower reactions may be observed at room temperature.

Details may be important for minimizing these unintended or spoiling reactions but elucidation is currently incomplete and may be quite context specific.

A brief theoretical digression may also seem out of place but it will help to invoke literature often ignored in this context. Copper's outer shell is $4s^13d^{10}$ (compared to iron $4s^23d^6$ and off hand you may expect filled or emptied s or d orbitals to be more stable.

A discussion of the phase diagram and related materials issues of the copper-sulfur system may be a bit tangential but it also picks up issues with metastability and cooking. Relatively high concentrations of copper ions may occur during mixing or segregation. It may be possible to stop formation of the worst phases, those that sequester copper in organisms or make it mobile in integrated circuits, even if sulfur can not be well eliminated.

Copper sulfides can form varying large unit cell crystals with correspondingly high integer stoichiometry. They apparently are not molecular crystals. Unit cells may contain 24 or 62 distinct copper atoms and some phases contain a sulphur HCP structure with interstitial Cu that become fluid above 100C [88].

This may appear unrelated to anything biologically relevant but a number of unknowns exist around the interaction of copper with mitochondrial ligand CuL. For example [97],

Mobilization of Cu into the mitochondrial matrix was also shown to occur bound to a non-proteinaceous fluorescent ligand, termed CuL [110, 113, 114]. CuL levels were found to correlate with cellular Cu levels and COX assembly [110, 115]. CuL, suggested to be coordinated by citrate and oxaloacetate, migrates with a mass of 13 000 Da, hinting at larger ligands. Fluorescence anisotropy experiments showed that the CuL complex is transported by SLC25A3 and MRS3 transporters [115117]. Although the molecular identity of CuL and the mechanism for exiting the matrix and delivering Cu to apo-COX17 in the inter-membrane space remain unclear, its biophysical properties suggest it contributes to buffering cytosolic Cu and facilitating Cu uptake into mitochondria [110, 113]

If these are not resolved in simple well known structures they could involve unusual interactions with things like citrate or phosphate.

A phase diagram around Cu₂S was published in 1981 showing phase transformations above 72C [87] which is too high to be biologically relevant except for cooking but may be important in IC failure modes. A more complete phase diagram from CMU 1983 is also available [53]. Metastability may be common due to need to rearrange hcp.

Most well studied crystals have simple unit cells containing only a few atoms. To make these crystals, rather than amorphous materials, state information must be propagated through many bonds. This could be due to various electron configuration issue or long range forces.

Dexter, who may be copper sensitive, has a varying preference for turkey and this was eliminated from Happy's diet for a while on the concern it reduces copper uptake.

5.3. Aspects of Copper Garlic Chemistry

With the preceding discussion of copper chemistry in general, discussion of specific garlic chemistry is put into context. It's important to distinguish "garlic sulfur" from the sulfur sources consumed by cattle leading to disease given their rumen properties and other sources of sulfur common in human or dog diets. Cattle may ingest weeds that accumulate sulfur from high sulfur soil but may also get sulfates from feed formulations and the local water sources. Rumen bacteria tend to reduce these to sulfides. Cruciferous vegetables tend to contain sugar modified amino acids called glucosinolates. Legumes largely contain cysteine.

Often, copper supplement was combined with crushed garlic prior to mixing into the larger snack. While best known for containing unstable and volatile sulfur compounds, other components of garlic may be important for overall effects on copper fate and health effects.

The literature on garlic-metal interactions includes bioavailability and corrosion inhibition with modern techniques applied to results analysis.

The most well known sulfur compounds in garlic tend to be organic sulfurs with 1 or 2 sulfurs attached to an alkane or alkene a few carbons long. As these have an odor they likely have a high vapor pressure and may diffuse easily in some settings. A copper or other metal attached to the sulfurs would not likely be held in an insoluble solid but rather allowed to move more freely. The question would then remain about getting to a suitable location and liberating the copper from the sulfur carrier.

Some works have cataloged and generalized the types of sulfur compounds prevalent in various food categories [81].

Empirically, organic polysulfides common in garlic, onions, shallots and related products are thought to have some cardioprotective effect but are difficult to analyze due to instability [353]. One small study suggested that garlic added to a diet could reduce some signs of copper deficiency in a fructose rich diet [94]. Interestingly, both copper and garlic demonstrated some favorable effects on cholesterol with copper reducing levels of fatty acid synthetase and garlic thought to slow the rate limiting step in cholesterol synthesis [176] although the interaction between copper and cholesterol (and fructose) relating to glucose intolerance has been known for decades has also been neglected [174].

Thinking out loud

this belongs in something on age related conditions too

Some attempts have been made to identify and characterize volatile components of garlic in various states [2] but the situation is quite complicated. A large number of sulfides exist as well as volatile organic solvents.

5.4. Supplement Selection and Dosing Considerations

It's expected after all of this that benefit or harm from copper can depend on details of the diet, preparation, storage, and supplement. Side reactions have to be considered at first contact between copper and anything else and

in general minimizing time and temperature may be beneficial. Time-release or limited solubility forms may be useful for pre-mixing or copper could be given in isolation from any other food intake.

Common supplement forms include copper sulfate, copper gluconate, copper glycinate, and copper citrate. Glycinate appears to be popular due to solubility and reputed bioavailability. Sulfate appears to be common due to cost [389]. Gluconate was used in a lot of the latter part of this work as it was the only bulk form available in reasonable price and quantity. A priori and currently there is some reason to consider citrate as desirable. This was eventually purchased in kilogram quantities from China and had been used early on as it is a common form in small supplement capsules.

Sulfate, glycinate, and proteinate effects were compared in pigs and sulfate was found to be less absorbed and associated with reduced microbial diversity [384].

Citrate salts have been well studied in a variety of contexts. Calcium citrate in particular has been explored as it may have benefits for calcium handling in biological settings [202]. It appears to become more soluble with excess citrate although the Ca activity is reduced [360]. As most of the snacks formulated here included significant citric acid, the 'citrate dissolves citrate' notion may be applicable although the effects of complexing are not known. Reduced reactivity may be a benefit however.

Citric acid appeared to improve biological activity of copper as an algeacide in the presence of bicarbonate even when derived from copper sulfate [342].

Studies have also shown that mixing copper citrate with amino acids improves solubility [332] which may be relevant here as most snacks contained many amino acid supplements.

The rabbit, notable for a functional significant cecum, demonstrated differential changes in cecal microbiome due to copper citrate, sulfate, and chloride additions with citrate reducing diarrhea [82].

Generally copper citrate is probably a good choice but in any case avoiding high temperatures and storage times may be a good idea. Humans would often turn to supplements which of course spend little time with food and even that can be minimized by taking on an empty stomach. Companion animals however tend to eat supplemented commercial food which requires all the nutrients be packaged together. In the present work most supplementation involved mixing the copper with food but consumption tended to be immediate or within hours.

As of May 2025, Happy may be heading towards zero coughing and gasping along with "good energy." While she was already doing well, the supplement was switched to a Carlson product containing copper glycinate and cellulose and stearate components suggesting some finite solubility times. This was also combined with lipoic acid supplementation obscuring the role of supplement selection but maybe improving outcome.

5.5. Life is Robust- Numerically Pathological States may be Adaptive

Life has worked pretty reliably long before "you" found the most recent pathway to cure all of life's diseases. Uncommon quantities of some thing in a diseased state could be the result of many processes that adapt as best as possible to changing or limiting conditions. The adapted response may not appear beneficial in a clinical setting but may make evolutionary sense. The paradigm case may be clotting and vitamin K. The proposed curve relating coagulation tendencies to vitamin K cycling rate [226] suggests a "quantity quality tradeoff" as may occur when feedback is based on some stimulus that needs to be removed by the product. Without as much vitamin K clot quality may suffer requiring more clots but these low quality clots may easily become pathological. In most cases full control pathways are not known certainly not quantitatively across all genetics. The partial pathways have to be assumed to contain additional features that make the system work most of the time in real life. Those other features have to be guessed but that is more likely to help than assuming some state is pathological merely because it is not common in healthy people. With copper this suggests several issues. The initial statements in this work described a "bottleneck" leading to copper accumulation in places like the liver. This itself may become pathological but may not be the biggest problem to fix. One reason would be signals preventing further distribution or acquired defects in the distribution system which may occur from high-infidelity translation or perhaps small molecule toxins. Eliminating the store by force, chelators are a common knee jerk reaction, may reduce some local problems but not fix the major ones one overall make things worse. Copper quantity (in some location) probably does not relate directly to the "quality" of the copper as it may for some proteins but to the overall handling system. Elementals may be worth hoarding for example hoping for other vitamins to arrive later.

6. LIMITATIONS

This is a hypothesis generating work designed to collect "real world" evidence and as puts many limits on data interpretation and particular the risks and benefits of copper added to an uncontrolled diet in haphazard ways. While the other components were mentioned as important, it needs to be reiterated that the other snack components

could have effected copper handling significantly and supplementation with another diet lacking these components may not be beneficial but copper restriction may not be either. Most food ingredient interact with metals to varying degrees and this notably contained citric acid and spinach along with amino acids.

The residential setting made it difficult to control or monitor all of the factors which could effect health. Besides the main kibble meals not being recorded for some dogs, intake of food and foreign objects was common and unpredictable. Supplement quantities were often measured by volume using kitchen utensils known to be poorly calibrated. Completely unknown experiences or factors may be involved in their subjective behaviors. Cigarette smoke exposure was common but variable. As is always the case, despite MUQED's ability to keep structured outcome notes on things like cough, the resulting outcome data was very sparse and relies on memory in some cases. The lesson remains that notes and data always need to be more complete.

7. PERSPECTIVE : COPPER IN PAST CIVILIZATIONS

Thinking outloud

always introduce new topic at the end lol

Given copper's lustre and malleability it may not be surprising that there is a long history of special treatment for copper in past civilizations. The point of raising this experience towards the end of this work is to put the apparent risks and benefits into perspective. That is, it sounds like only a very sophisticated Western audience could encounter copper and actually benefit but that may not be the case either due to luck, hidden knowledge, or a more favorable risk benefit profile from copper exposure. These "macro" observations may help put the "micro" observations into a better range of implications. "Micro" results may seem more precise and scientific but are by design isolated and miss a lot of important context.

It sounds as if copper may require substantial care to supplement but as a final thought its worth remembering that many older civilizations appeared to recognize copper as particularly "good" in some ways from cookware [25], ritual uses, to medicinal[340]. Many appeared to persist for quite some time but it would be interesting to see if they had signs of copper toxicity or generally better health than those ignoring copper.

Copper is mentioned in some of the earliest known papyrus, we used by many historical "great" civilizations such as Egyptians, Greeks, Romans, and Aztecs with rediscovery in the 19th century to be replaced in medicine by antibiotics in 1932 [119]. Even today, copper sulfate is burned in Buddhist and Hindu buildings for good luck or religious reasons [106]. If exposure contributed to the downfall of any of these societies it is generally not explicit. There is some interest in revival of ancient antibiotics such as described in the Leechbook [77] previously mentioned but we don't know how effective these are in real world conditions. Copper combinations also arise in the study of ancient medicinal plants [37] . A review of scholarly literature may be biased with contemporary expectations. Health effects are difficult to infer but would have to be compared to competing exposures and impurities such as arsenic that may have been common in a given community. Apparently arsenic was present in the area of Peruvian Andes [185]. Given the adoption of modern antibiotics, they likely had clear superiority to known copper formulations.

Its also worth noting the intake of various acid foods in other cultures and how this may relate to copper and other nutrient uptake. Many health fads such as the Mediterranean diet contain acidic components such as vinegar but these are rarely highlighted probably because of confirmation bias issues, see the recurring fallacy appendix. Fermented foods are also common. Fermented foods are defined by the FDA as achieving a pH of less than 4.6 [50] clearly the acid content is considered important. Currently however there is the popular notion of a "dietary acid load" of unknown significance tends to make people think they should avoid acid intake although the actual issue is thought to be renal acid load making intake of organic acids just fine [385]. Despite vinegar having likely benefits for glucose metabolism [311] it is almost never mentioned in the context of the Mediterranean diet.

8. CONCLUSIONS

Thinking outloud

replace the madlib conclusions, repeat the intro lol, with more alapoint darlings. Contrast engineering approach of "trying to do something better" with academic study.

This work documents responses from a group of dogs to a designed set of supplements with particular attention to effects of incremental changes in copper intake. The real world data from this engineering approach fall between micro focused well controlled lab or clinical tests and macro observational studies that look for associations. While the former may be considered simple and precise, the failure to optimize or even consider context makes extrapolation to intervention design difficult. The latter association studies are well known for

being misleading. This work creates more complicated data that is difficult to analyze but "we have computers"

Thinking outloud

Life During Wartime lol

. As the best "proof" of an analysis is synthesis, testing was continually built in as outcome optimization was always considered based on all available information. Clearly this is not hypothesis testing but rather hypothesis generating with the outcome based results as motivating evidence. However, the process itself is also being tested by its ability to gather useful intervention design information.

Its difficult to evaluate one nutrient in isolation while ignoring the entire background diet, state, and genetics. This real world example dealt with copper which is more intertwined than many nutrients but may show a way to create more complicated but ultimately more useful hypothesis generating data. Jumping to hypothesis testing without even knowing what to control doesn't always produce useful results by hiding behind randomization. Its probably easier to analyze accidents than plan successes with so many unknowns.

This work may contribute important real world evidence about the roles of copper that is missed in either well controlled copper dosing studies or macro association studies. In the former case optimization or relevance of the controlled or randomized factors is often ignored but clearly they are important. In the latter case causality is ignored as well as these other factors. This work attempted to evaluate copper in the context of a "best shot" at creating good outcomes but with an ability to react to possible responses. By sampling relevant parameter space its likely better hypotheses can be generated and data more directly relevant to intervention design is collected.

Another set of evidence that includes many effects relevant to people is the effects of "everyday" copper exposure and usage on other societies. This "very macro view" may need further investigation but its worth noting that many societies thrived with copper interaction which may be contrary to some modern scientific expectations.

Copper is probably one of the interventions most in need of such an effort due to the versatility described earlier. Supplementation circa .3-1mg/kgBW for this group of dogs did not appear to generate any adverse events with the possible exception of Dexter who appears to require supplemental zinc. Responses observed in some dogs included increased energy level and reduced infection symptoms. One main goal to eliminate Happy's cough was not achieved with the final diet (May 2025) although her ALP remains normal suggesting she may tolerate even more copper due to either worsening absorption or some quirks of the current diet. The initial idea that copper is under-appreciated has been refined and it is likely most important in cases of "low energy" and heart or cartilage problems. Several other "usual suspects" including lipoic acid, iodine, and histidine, could be combined to observe any incremental improvements. Alternatively, cases of "poicky eating" as exemplified by Dexter and Annie may benefit more from zinc especially with lab indications such as low ALP.

Copper availability may depend on stomach pH, intestinal health, and other dietary components such as sulfur or zinc. As the pH is reduced the effect of some other components may be reduced. Overall distribution in the body may also depend on a variety of other nutrients. These remain as open issues that could be explored with modifications of this background diet.

While the above quirks may create an isolated copper specific deficiency, in general with GI impairments common in old age other nutrients are likely needed too to see significant benefit.

Copper is widely distributed according to many signals and a good status indicator would have to be a large vector. Adaptations to copper imbalance may obscure the underlying problem motivating an interest in treating symptoms. With concerns about safety and no easy way to verify deficiency as a cause there may be hesitancy to add copper to a diet for such unrelated conditions as heart or thyroid diseases. This decision tree may require further exploration.

Concerns about excess copper accumulation may be due to other dietary defects and not copper content per se except with specific genetics. There may be thoughts along the lines of "balance" but that is probably a garbage word leading to deadend tautologies. More to the point may be "limiting nutrients" or factors that allow a given intake of other things like copper to be assets rather than liabilities. While some were discussed here, there are many and even this is likely a simplification of the "response surface." Its quite possible that copper is limiting in the ability to handle calories generally and it would be interesting to see if copper supplements can equal calorie limitations (with the appropriate background diet components).

Note too that this work was largely empirical but guided by ideas of theoretical or abstract cause and effect. This is related to but different from the idea of finding a "root cause" as this is difficult to define since cause and effect can be chased indefinitely. The point here is to just go far enough to make sure interventions fix an actual problem in a reasonably safe and robust way. In this case, copper shortage in some location may be a problem per se but that is caused by something else that is not being corrected with supplements. Often, interventions may fix symptoms of little consequence.

So, the approach here is largely to pursue causes rather than mere associations which are often misleading for intervention ideas. While cause and effect tend to be theoretical or abstract notions, they can be empirically tested. In this case, correlations of say cough with diet would have been purely noise as cough may respond to short term improvements in a misleading way. Prophecy, predicting a result, may be the closest thing to understanding ever

achieved. In the end, the importance of the investigation design seems to be to help luck dominate over stupidity.

Thinking outloud

oh my darlings, integrate the zingers better lol

9. SUPPLEMENTAL INFORMATION

Dog diet data files are available online at <https://github.com/mmarchywka/dogdata> or other locations as may be required. The author may also be contacted if onlines sources are not avialble. Raw MUQED format as well as parsed text formats are available although MUQED software availability is in the works.

9.1. Computer Code

note anything using "snacks_Collated.ssv" is obsolete as it messed up adjectives etc. use "linc_graph -dt-mo" NB : the "datealias" entries need to be updated not just datemin and datemax and the latter may not even do anything lol. A note also "reporting units" for many new nouns are not right as tsp has replaced mg etc.

```
diet tables,
2766 ./run_linc_graph -dt-mo txt/happy2cu.txt
2767 texfrag -include xxxtable
2768 mv xxxtable /home/documents/latex/proj/copper/keep/monthly.tex

datascope output,
./run_linc_graph -2dscope Iodine "Happy" "filter=lag20"
```

10. BIBLIOGRAPHY

- [1] Alireza Abdolmohammadi and Vivek R. Sharma. Copper deficiency: A forgotten disorder? *Blood*, 118, 11 2011. Available from: <http://dx.doi.org/10.1182/blood.v118.21.5275.5275>, doi:10.1182/blood.v118.21.5275.5275.
- [2] Kazuki Abe, Yoji Hori, and Takao Myoda. Volatile compounds of fresh and processed garlic (review). *Experimental and Therapeutic Medicine*, 12 2019. Available from: <https://doi.org/10.3892/etm.2019.8394>, doi:10.3892/etm.2019.8394.
- [3] Sherleen Xue-Fu Adamson, Wei Zheng, Zeynep Sena Agim, Sarah Du, Sheila Fleming, Jonathan Shannahan, and Jason Cannon. Systemic copper disorders influence the olfactory function in adult rats: Roles of altered adult neurogenesis and neurochemical imbalance. *Biomolecules*, 09 2021. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8471899/>, doi:10.3390/biom11091315.
- [4] Leandro Afonso, Matheus Felipe de Lima Andreata, Andreas Lazaros Chryssafidis, Stefani Fabiola Alarcon, Ana Paula das Neves, João Vittor Frossard Rodrigues da Silva, Gilmar da Silva Gonçalves, Leonardo Dib de Sousa Abussafi, Ane Stefano Simionato, Martha Viviana Torres Cely, and Galdino Andrade. Fluopsin c: A review of the antimicrobial activity against phytopathogens. *Agronomy*, 12, 12 2022. Available from: <https://doi.org/10.3390/agronomy12122997>, doi:10.3390/agronomy12122997.
- [5] Bumsoo Ahn, Rojina Ranjit, Pavithra Premkumar, Gavin Pharaoh, Katarzyna M. Piekarz, Satoshi Matsuzaki, Dennis R. Clafflin, Kaitlyn Riddle, Jennifer Judge, Shylesh Bhaskaran, Kavithalakshmi Satara Natarajan, Erika Barboza, Benjamin Wronowski, Michael Kinter, Kenneth M. Humphries, Timothy M. Griffin, Willard M. Freeman, Arlan Richardson, Susan V. Brooks, and Holly Van Remmen. Mitochondrial oxidative stress impairs contractile function but paradoxically increases muscle mass via fibre branching. *Journal of Cachexia, Sarcopenia and Muscle*, 10, 2019. Available from: <http://dx.doi.org/10.1002/jcsm.12375>, doi:10.1002/jcsm.12375.
- [6] Robert J Aiello, Patricia-Ann Bourassa, Qing Zhang, Jeffrey Dubins, Daniel R Goldberg, Stephane De Lombaert, Marc Humbert, Christophe Guignabert, Maria A Cavasin, Timothy A McKinsey, and Vishwas Paralkar. Tryptophan hydroxylase 1 inhibition impacts pulmonary vascular remodeling in two rat models of pulmonary hypertension. *The Journal of pharmacology and experimental therapeutics*, pages 267–279, 12 2016. Available from: <https://pubmed.ncbi.nlm.nih.gov/27927914/>, doi:10.1124/jpet.116.237933.

- [7] Muhammad Zain Akhtar, Ghias Nabi Tayab, Muhammad Imran Nawaz, and Iqra Seher. Excessive dynamic airway collapse after entecavir use in a patient with pegylated interferon-induced undifferentiated connective tissue disease and entecavir use to prevent hepatitis b virus reactivation upon giving rituximab. *Cureus*. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11260405/>, doi:10.7759/cureus.62835.
- [8] A. A. Al-Othman, F. Rosenstein, and K. Y. Lei. Copper deficiency increases in vivo hepatic synthesis of fatty acids, triacylglycerols, and phospholipids in rats. *Experimental Biology and Medicine*, 204, 10 1993. Available from: <https://doi.org/10.3181/00379727-204-43640>, doi:10.3181/00379727-204-43640.
- [9] Eham Amir Ali, Hussein Kadhem Abdul Hussein, and Yildiz Hassan Tahssen. Estimation of serum copper, manganese, selenium, and zinc in hypothyroid patients. *Journal of the Faculty of Medicine Bagdad*, 50, 06 2019. Available from: <https://doi.org/10.32007/jfacmedbagdad.5021291>, doi:10.32007/jfacmedbagdad.5021291.
- [10] Laura Amundson, Brent Kirn, Erik Swensson, Allison Millican, and George Fahey. Copper metabolism and its implications for canine nutrition. *Translational Animal Science*, 8:txad147, 01 2024. Available from: <https://doi.org/10.1093/tas/txad147>, arXiv:<https://academic.oup.com/tas/article-pdf/doi/10.1093/tas/txad147/55674607/txad147.pdf>, doi:10.1093/tas/txad147.
- [11] LauraA Amundson, BrentN Kirn, ErikJ Swensson, AllisonA Millican, and GeorgeC Fahey. Copper metabolism and its implications for canine nutrition. *Translational Animal Science*, 01 2024. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10787350/>, doi:10.1093/tas/txad147.
- [12] Seiji Aoyagi and David H Baker. Copper-amino acid complexes are partially protected against inhibitory effects of l-cysteine and l-ascorbic acid on copper absorption in chicks. *The Journal of Nutrition*, 124, 03 1994. Available from: <http://dx.doi.org/10.1093/jn/124.3.388>, doi:10.1093/jn/124.3.388.
- [13] MIGUEL ARREDONDO, RONNY MARTÍNEZ, MARCO T NÚÑEZ, MANUEL RUZ, and MANUEL OLIVARES. Inhibition of iron and copper uptake by iron, copper and zinc. *Biological Research*, 39, 2006. Available from: <http://dx.doi.org/10.4067/s0716-97602006000100011>, doi:10.4067/s0716-97602006000100011.
- [14] Anooshah Ata and Anthony Bradshaw. Zinc supplementation-induced copper deficiency myeloneuropathy: Another relic of the covid-19 pandemic (p8-11.014). *Neurology*, 102, 04 2024. Available from: <http://dx.doi.org/10.1212/wnl.0000000000208190>, doi:10.1212/wnl.0000000000208190.
- [15] Diana Athokpham, Shrabani Mohanty, and Venkata BharatKumar Pinnelli. Status of serum calcium, phosphorus, magnesium and copper in hypothyroid patients- a case control study. *JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH*, 2020. Available from: <https://doi.org/10.7860/jcdr/2020/44711.14094>, doi:10.7860/jcdr/2020/44711.14094.
- [16] Allah Nazar Atif, Atousa Hatefi, Asadullah Arven, Alireza Foroumadi, Sara Kadkhodaei, Alireza Sadjadi, and Farideh Siavoshi. Consumption of non-antibacterial drugs may have negative impact on helicobacter pylori colonization in the stomach. *Heliyon*, 10, 03 2024. Available from: <http://dx.doi.org/10.1016/j.heliyon.2024.e27327>, doi:10.1016/j.heliyon.2024.e27327.
- [17] Craig S. Atwood, George Perry, Hong Zeng, Yoji Kato, Walton D. Jones, Ke-Qing Ling, Xudong Huang, Robert D. Moir, Dandan Wang, Lawrence M. Sayre, Mark A. Smith, Shu G. Chen, and Ashley I. Bush. Copper mediates dityrosine cross-linking of alzheimer's amyloid-upbeta. *Biochemistry*, 43, 01 2004. Available from: <http://dx.doi.org/10.1021/bi0358824>, doi:10.1021/bi0358824.
- [18] M.H.H. Awaad, K. M.El. Moustafa, S.A. Zoulfakar, M.S. Elhalawany, F.F. Mohammed, R.M. El-Refay, and E.A. Morsy. The role of silver nanoparticles in the reluctance of colisepticemia in broiler chickens. *Journal of Applied Poultry Research*, 30, 2021. Available from: <http://dx.doi.org/10.1016/j.japr.2021.100155>, doi:10.1016/j.japr.2021.100155.
- [19] Jahaun Azadmanesh, Katelyn Slobodnik, Lucas R. Struble, William E. Lutz, Leighton Coates, Kevin L. Weiss, Dean A. Myles, Thomas Kroll, and Gloria O. Borgstahl. Revealing the atomic and electronic mechanism of human manganese superoxide dismutase product inhibition. *Nature Communications*, 15, 07 2024. Available from: <https://www.nature.com/articles/s41467-024-50260-w>, doi:10.1038/s41467-024-50260-w.
- [20] Saba Azimi-Youvalari, Parviz Farhoomand, Payam Baghban-Kanani, Sina Payvastegan, Alireza Seidavi, and Carlos Augusto Fernandes de Oliveira. Copper sulfate and arginine supplements on performance, thyroid hormones and blood biochemistry of broilers fed with canola meal-based diets. *Ciencia Rural*, 52, 2022. Available from: <https://doi.org/10.1590/0103-8478cr20201069>, doi:10.1590/0103-8478cr20201069.
- [21] Maria V. Babak and Dohyun Ahn. Modulation of intracellular copper levels as the mechanism of action of anti-cancer copper complexes: Clinical relevance. *Biomedicines*, 9, 2021. Available from: <http://dx.doi.org/10.3390/biomedicines9080852>, doi:10.3390/biomedicines9080852.
- [22] MV Bais, MA Nugent, DN Stephens, SS Sume, KH Kirsch, GE Sonenshein, and PC Trackman. Recombinant lysyl oxidase propeptide protein inhibits growth and promotes apoptosis of pre-existing murine breast cancer xenografts. *PLoS ONE*, 7(2), 2012. Available from: [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3280126/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3280126/).
- [23] Akhilesh Kumar Bajpai, Qingqing Gu, Buyan-Ochir Orgil, Fuyi Xu, Carolina Torres-Rojas, Wenyuan Zhao, Chen Chen, Athena Starlard-Davenport, Byron Jones, Djamel Lebeche, Jeffrey A. Towbin, Enkhsaikhan Purejav, Lu Lu, and Wenjing Zhang. Cardiac copper content and its relationship with heart physiology: Insights based on quantitative genetic and functional analyses using bxd family mice. *Frontiers in Cardiovascular Medicine*, 10, 2023. Available from: <https://www.frontiersin.org/articles/10.3389/fcvm.2023.1089963>, doi:10.3389/fcvm.2023.1089963.
- [24] Carme Ballester-Servera, Judith Alonso, Manel Tauron, Noemí Rotllan, Cristina Rodriguez, and Jose Martinez-Gonzalez. Lysyl oxidase expression in smooth muscle cells determines the level of intima calcification in hypercholesterolemia-induced atherosclerosis. *Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis*, 02 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/38402026/>, doi:10.1016/j.arteri.2024.01.003.

- [25] Charu Bansal, Saleha Zaina, and Vinod Parihar. Review on health impact of hazardous and safest traditional cookware with ayurvedic approach. *AYUSHDHARA*, 03 2020. Available from: <https://doi.org/10.47070/ayushdhara.v7i1.519>, doi:10.47070/ayushdhara.v7i1.519.
- [26] Spyros Batzios, Galit Tal, Andrew T DiStasio, Yanyan Peng, Christiana Charalambous, Paola Nicolaides, Erik-Jan Kamsteeg, Stanley H Korman, Hanna Mandel, Peter J Steinbach, Ling Yi, Summer R Fair, Mark E Hester, Anthi Drousiotou, and Stephen G Kaler. Newly identified disorder of copper metabolism caused by variants in *ctr1*, a high-affinity copper transporter. *Human molecular genetics*, pages 4121–4130, Dec 2022. Available from: <https://pubmed.ncbi.nlm.nih.gov/35913762/>, doi:10.1093/hmg/ddac156.
- [27] Charlie Bayne, Magali Boutard, Tom Zaplana, and Andrew C. Tolonen. L-tryptophan and copper interactions linked to reduced colibactin genotoxicity in *pks+ escherichia coli*. *mSystems*, 9, 10 2024. Available from: <https://doi.org/10.1128/msystems.00992-24>, doi:10.1128/msystems.00992-24.
- [28] François Beaufay, Ellen Quarles, Allison Franz, Olivia Katamanin, Wei-Yun Wholey, and Ursula Jakob. Polyphosphate functions *in vivo* as an iron chelator and fenton reaction inhibitor. *mBio*, 11, 08 2020. Available from: <https://doi.org/10.1128/mbio.01017-20>, doi:10.1128/mbio.01017-20.
- [29] Shayne A. Bellingham, Belinda Guo, and Andrew F. Hill. The secret life of extracellular vesicles in metal homeostasis and neurodegeneration. *Biology of the Cell*, 107, 2015. Available from: <http://dx.doi.org/10.1111/boc.201500030>, doi:10.1111/boc.201500030.
- [30] Stéphane L. Benoit and Robert J. Maier. The nickel-chelator dimethylglyoxime inhibits human amyloid beta peptide *in vitro* aggregation. *Scientific Reports*, 11, 03 2021. Available from: [https://www.nature.com/articles/s41598-021-86060-1](https://www.nature.com/articles/s41598-021-86060-1?fromPaywallRec=false), doi:10.1038/s41598-021-86060-1.
- [31] Sabine Bernegger, Cyrill Brunner, Matej VizoviUx0161[bad char vv=353]ek, Marko Fonovic, Gaetano Cuciniello, Flavia Giordano, Vesna Stanojlovic, Miroslaw Jarzab, Philip Simister, Stephan M. Feller, Gerhard Obermeyer, Gernot Posselt, Boris Turk, Chiara Cabrele, Gisbert Schneider, and Silja Wessler. A novel fret peptide assay reveals efficient helicobacter pylori htrA inhibition through zinc and copper binding. *Scientific Reports*, 10, 06 2020. Available from: <https://www.nature.com/articles/s41598-020-67578-2>, doi:10.1038/s41598-020-67578-2.
- [32] Elina Berntsson, Faraz Vosough, Teodor Svantesson, Jonathan Pansieri, Igor A. Iashchishyn, Lucija OstojiUx0107[bad char vv=263], Xiaolin Dong, Suman Paul, Jüri Jarvet, Per M. Roos, Andreas Barth, Ludmilla A. Morozova-Roche, Astrid Gräslund, and Sebastian S. Wärmländer. Residue-specific binding of ni(ii) ions influences the structure and aggregation of amyloid beta (aupbeta) peptides. *Scientific Reports*, 13, 02 2023. Available from: [https://www.nature.com/articles/s41598-023-29901-5](https://www.nature.com/articles/s41598-023-29901-5?fromPaywallRec=false), doi:10.1038/s41598-023-29901-5.
- [33] Neziha Besiktepe, Ozgecan Kayalar, Ezel Ersen, and Fusun Oztay. The copper dependent-lysyl oxidases contribute to the pathogenesis of pulmonary emphysema in chronic obstructive pulmonary disease patients. *Journal of Trace Elements in Medicine and Biology*, 44, 12 2017. Available from: <https://doi.org/10.1016/j.jtemb.2017.08.011>, doi:10.1016/j.jtemb.2017.08.011.
- [34] Angelique N. Besold, Edward M. Culbertson, and Valeria C. Culotta. The yin and yang of copper during infection. *Journal of biological inorganic chemistry : JBIC : a publication of the Society of Biological Inorganic Chemistry*, pages 137–44, 01 2016. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5535265/>, doi:10.1007/s00775-016-1335-1.
- [35] Glenda M. Bishop and Stephen R. Robinson. The amyloid paradox: Amyloidupbeta metal complexes can be neurotoxic and neuroprotective. *Brain Pathology*, 14, 2004. Available from: <http://dx.doi.org/10.1111/j.1750-3639.2004.tb00089.x>, doi:10.1111/j.1750-3639.2004.tb00089.x.
- [36] K M Black, I Clark-Lewis, and C J Wallace. Conserved tryptophan in cytochrome c: importance of the unique side-chain features of the indole moiety. *Biochemical Journal*, pages 715–20, Nov 2001. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC1222194/>.
- [37] Rebecca Blakeney, Irene Teixidor-Toneu, Karoline Kjesrud, and Anneleen Kool. Finding medieval medicine through archaeobotany: An ontological approach. *Environmental Archaeology*, 30, 01 2025. Available from: <https://doi.org/10.1080/14614103.2023.2202933>, doi:10.1080/14614103.2023.2202933.
- [38] Sarah Blasig, Peter Kühnen, Andrea Schuette, Oliver Blaenkenstein, Jens Mittag, and Lutz Schomburg. Positive correlation of thyroid hormones and serum copper in children with congenital hypothyroidism. *Journal of Trace Elements in Medicine and Biology*, 37, 09 2016. Available from: <https://doi.org/10.1016/j.jtemb.2016.05.007>, doi:10.1016/j.jtemb.2016.05.007.
- [39] S Blockhuys and P Wittung-Stafshede. Roles of copper-binding proteins in breast cancer. *International Journal of Molecular Sciences*, 18(4), 2017. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5412452/>.
- [40] Margareta R. A. Blomberg. Mechanism of oxygen reduction in cytochrome c oxidase and the role of the active site tyrosine. *Biochemistry*, 55, 01 2016. Available from: <https://doi.org/10.1021/acs.biochem.5b01205>, doi:10.1021/acs.biochem.5b01205.
- [41] Manuela Bode, Michael W. Woellhaf, Maria Bohnert, Martin van der Laan, Frederik Sommer, Martin Jung, Richard Zimmermann, Michael Schroda, and Johannes M. Herrmann. Redox-regulated dynamic interplay between cox19 and the copper-binding protein cox11 in the intermembrane space of mitochondria facilitates biogenesis of cytochrome c oxidase. *Molecular Biology of the Cell*, 26(13):2385–2401, 2015. Available from: <http://www.molbiolcell.org/content/26/13/2385.abstract>, arXiv:<http://www.molbiolcell.org/content/26/13/2385.full.pdf+html>, doi:10.1091/mbc.E14-11-1526.
- [42] MY Bonner and JL Arbiser. The antioxidant paradox: what are antioxidants and how should they be used in a therapeutic context for cancer. *Future medicinal chemistry*, 6(12):1413–22, 2014. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4412352/>.

- [43] M Bourens, F Fontanesi, IC Soto, J Liu, and A Barrientos. Redox and reactive oxygen species regulation of mitochondrial cytochrome c oxidase biogenesis. *Antioxidants & Redox Signaling*, 19(16):1940–52, 2013. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3852343/>.
- [44] D. Bousquet-Moore, X. M. Ma, E. A. Nillni, T. A. Czyzyk, J. E. Pintar, B. A. Eipper, and R. E. Mains. Reversal of physiological deficits caused by diminished levels of peptidylglycine upalpha-amidating monooxygenase by dietary copper. *Endocrinology*, 150, 04 2009. Available from: <https://doi.org/10.1210/en.2008-1202>, doi:10.1210/en.2008-1202.
- [45] J Brandao-Neto, J G Vieira, K O Nonaka, J S Marchini, T Shuhama, L C Gomes, and J Antunes-Rodrigues. Effect of copper on the secretion of human growth hormone. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas*, pages 259–61, 1988. Available from: <https://pubmed.ncbi.nlm.nih.gov/3203160/>.
- [46] Paul T. Bremer, Sabine Pellett, James P. Carolan, William H. Tepp, Lisa M. Eubanks, Karen N. Allen, Eric A. Johnson, and Kim D. Janda. Metal ions effectively ablate the action of botulinum neurotoxin a. *Journal of the American Chemical Society*, 139(21):7264–7272, 2017. PMID: 28475321. Available from: <http://dx.doi.org/10.1021/jacs.7b01084>, arXiv: <http://dx.doi.org/10.1021/jacs.7b01084>, doi:10.1021/jacs.7b01084.
- [47] George J. Brewer. Risks of copper and iron toxicity during aging in humans. *Chemical Research in Toxicology*, 23, 02 2010. Available from: https://www.researchgate.net/profile/George-Brewer-2/publication/40455171_Risks_of_Copper_and_Iron_Toxicity_during_Aging_in_Humans/links/5ce2ce1da6fdccc9ddbf8bc/Risks-of-Copper-and-Iron-Toxicity-during-Aging-in-Humans.pdf, doi:10.1021/tx900338d.
- [48] George J. Brewer. Copper toxicity in alzheimer's disease: Cognitive loss from ingestion of inorganic copper. *Journal of Trace Elements in Medicine and Biology*, 26, 06 2012. Available from: <https://doi.org/10.1016/j.jtemb.2012.04.019>, doi:10.1016/j.jtemb.2012.04.019.
- [49] Rodrigo I. Bustos, Erik L. Jensen, Lina M. Ruiz, Salvador Rivera, Sebastián Ruiz, Felipe Simon, Claudia Riedel, David Ferrick, and Alvaro A. Elorza. Copper deficiency alters cell bioenergetics and induces mitochondrial fusion through up-regulation of mfn2 and opa1 in erythropoietic cells. *Biochemical and Biophysical Research Communications*, 437, 2013. Available from: <http://dx.doi.org/10.1016/j.bbrc.2013.06.095>, doi:10.1016/j.bbrc.2013.06.095.
- [50] Elisa B Caffrey, Dalia Perelman, Catherine P Ward, Erica D Sonnenburg, Christopher D Gardner, and Justin L Sonnenburg. Unpacking food fermentation: Clinically relevant tools for fermented food identification and consumption. *Advances in Nutrition*, 03 2025. Available from: <https://doi.org/10.1016/j.advnut.2025.100412>, doi:10.1016/j.advnut.2025.100412.
- [51] Linyi Cai, Xin Xiong, Xiangli Kong, and Jing Xie. The role of the lysyl oxidases in tissue repair and remodeling: A concise review. *Tissue Engineering and Regenerative Medicine*, pages 15–30, 01 2017. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6171574/>, doi:10.1007/s13770-016-0007-0.
- [52] Sharon A. Center, Keith P. Richter, David C. Twedt, Joseph J. Wakshlag, Penny J. Watson, and Cynthia R. L. Webster. Is it time to reconsider current guidelines for copper content in commercial dog foods? *Journal of the American Veterinary Medical Association*, 258, 02 2021. Available from: <http://dx.doi.org/10.2460/javma.258.4.357>, doi:10.2460/javma.258.4.357.
- [53] D. J. Chakrabarti and D. E. Laughlin. The cu-s (copper-sulfur) system. *Bulletin of Alloy Phase Diagrams*, 4, 11 1983. Available from: <https://www.contrib.andrew.cmu.edu/~dl0p/laughlin/pdf/037.pdf>, doi:10.1007/bf02868665.
- [54] Julien Champagne, Morten M Nielsen, Xiaodong Feng, Jasmine Montenegro Navarro, Abhijeet Pataskar, Rhianne Voogd, Lisanne Giebel, Remco Nagel, Nadine Berenst, Amos Fumagalli, Adva Kochavi, Domenica Lovecchio, Lorenzo Valcanover, Yuval Malka, Weiwen Yang, Maarja Laos, Yingqian Li, Natalie Proost, Marieke van de Ven, Olaf van Tellingen, Onno B Bleijerveld, John G Haanen, Johanna Olweus, and Reuven Agami. Adoptive t cell therapy targeting an inducible and broadly shared product of aberrant mrna translation. *Immunity*, pages 247–262.e9, 01 2025. Available from: <https://pubmed.ncbi.nlm.nih.gov/39755122/>, doi:10.1016/j.immuni.2024.12.004.
- [55] ML Channa, FJ Burger, JB Ubbink, and SG Reinach. Zinc, copper and iron balance in the vitamin b-6-deficient rat. *vitaminologie et de nutrition*, 64(3):204–11, 1994. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/articles/7814236/>.
- [56] Jadwiga UrbaUx0144[bad char vv=324]ska and Halina PodsiadUx0142[bad char vv=322]y. Interaction of niacin with copper ions. *Polyhedron*, 60, 08 2013. Available from: <http://dx.doi.org/10.1016/j.poly.2013.05.023>, doi:10.1016/j.poly.2013.05.023.
- [57] HuiJun Chen, Mieko Kimura, and Yoshinori Itokawa. Changes in iron, calcium, magnesium, copper, and zinc levels in different tissues of riboflavin-deficient rats. *Biological Trace Element Research*, 56(3):311–319, Mar 1997. Available from: <https://doi.org/10.1007/BF02785302>, doi:10.1007/BF02785302.
- [58] Leilei Chen, Qingqing Shen, Yingjuan Liu, Yunqi Zhang, Liping Sun, Xizhen Ma, Ning Song, and Junxia Xie. Homeostasis and metabolism of iron and other metal ions in neurodegenerative diseases. *Signal Transduction and Targeted Therapy*, 02 2025. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11788444/>, doi:10.1038/s41392-024-02071-0.
- [59] Liyun Chen, Junxia Min, and Fudi Wang. Copper homeostasis and cuproptosis in health and disease. *Signal Transduction and Targeted Therapy*, 7, 11 2022. Available from: <https://www.nature.com/articles/s41392-022-01229-y>, doi:10.1038/s41392-022-01229-y.
- [60] Qiang Chen, Shaoqin Tu, Dongxiao Tang, Jiaming Wei, Nan Wei, Hong Ai, Bu Yang, and Zheng Chen. Amyloid- peptide treatment reverses bone loss in the mandibular condyle via wnt signalling pathway. *Bone Reports*, 07 2024. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11301219/>, doi:10.1016/j.bonr.2024.101788.
- [61] Runkai Chen, Hongrui Zhang, Botao Tang, Yukun Luo, Yufei Yang, Xin Zhong, Sifei Chen, Xinjie Xu, Shengkang Huang, and Canzhao Liu. Macrophages in cardiovascular diseases: molecular mechanisms and therapeutic targets. *Signal Transduction and Targeted Therapy*, 9, 05 2024. Available from: <https://www.nature.com/articles/s41392-024-01840-1>,

- doi:10.1038/s41392-024-01840-1.
- [62] Xinyue Chen, Qi Cai, Ruikai Liang, Deju Zhang, Xiao Liu, Meiyi Zhang, Yan Xiong, Minxuan Xu, Qi Liu, Pengyang Li, Peng Yu, and Ao Shi. Copper homeostasis and copper-induced cell death in the pathogenesis of cardiovascular disease and therapeutic strategies. *Cell Death & Disease*, 14, 02 2023. Available from: <https://www.nature.com/articles/s41419-023-05639-w>, doi:10.1038/s41419-023-05639-w.
- [63] Thilo Samson Chillon, Kamil Demircan, Julian Hackler, Raban A. Heller, Peyman Kaghazian, Arash Moghaddam, and Lutz Schomburg. Combined copper and zinc deficiency is associated with reduced sars-cov-2 immunization response to bnt162b2 vaccination. *Heliyon*, 9, 2023. Available from: <http://dx.doi.org/10.1016/j.heliyon.2023.e20919>, doi:10.1016/j.heliyon.2023.e20919.
- [64] Shek Man Chim, Kristen Howell, John Dronzek, Weizhen Wu, Christopher Van Hout, Manuel Revez Ferreira, Bin Ye, Alexander Li, Susannah Brydges, Vinayagam Arunachalam, Anthony Marcketta, Adam E Locke, Jonas Bovijn, Niek Verweij, Tania De, Luca Lotta, Lyndon Mitnaul, Michelle G. LeBlanc, David Carey, Olle Melander, Alan Shuldiner, Katia Karalis, Aris N. Economides, and Harikiran Nistala. Genetic inactivation of zinc transporter slc39a5 improves liver function and hyperglycemia in obesogenic settings. *eLife Sciences Publications, Ltd*, sep 2023. Available from: <http://dx.doi.org/10.7554/eLife.90419.1>, doi:10.7554/elife.90419.1.
- [65] Young-Eun Cho, Ria-Ann R. Lomeda, Sang-Hoon Ryu, Ho-Yong Sohn, Hong-In Shin, John H. Beattie, and In-Sook Kwun. Zinc deficiency negatively affects alkaline phosphatase and the concentration of ca, mg and p in rats. *Nutrition Research and Practice*, pages 113–9, 06 2007. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC2882585/>, doi:10.4162/nrp.2007.1.2.113.
- [66] Eunok Choe, Rongmin Huang, and David B. Min. Chemical reactions and stability of riboflavin in foods. *Journal of Food Science*, 70, 01 2005. Available from: <http://lib3.dss.go.th/fulltext/Journal/Journal%20of%20food%20science/2005%20v.70/no.1/23464jfsv70n1pR0028-0036ms20040361%5B1%5D.pdf>, doi:10.1111/j.1365-2621.2005.tb09055.x.
- [67] Bruno Cianciaruso, Michael R. Jones, and Joel D. Kopple. Histidine, an essential amino acid for adult dogs. *The Journal of Nutrition*, 111, 1981. Available from: <http://dx.doi.org/10.1093/jn/111.6.1074>, doi:10.1093/jn/111.6.1074.
- [68] Andrea H. Clarkson, Stuart W. Paine, and Nigel R. Kendall. Evaluation of the solubility of a range of copper sources and the effects of iron & sulphur on copper solubility under rumen simulated conditions. *Journal of Trace Elements in Medicine and Biology*, 68, 2021. Available from: <http://dx.doi.org/10.1016/j.jtemb.2021.126815>, doi:10.1016/j.jtemb.2021.126815.
- [69] Garth J. S. Cooper, Jingshu Xu, Stephanie J. Church, Stefano Patassini, Paul Begley, Henry J. Waldvogel, Maurice A. Curtis, Richard L. M. Faull, and Richard D. Unwin. Evidence for widespread, severe brain copper deficiency in alzheimer's dementia. *Metalomics*, 9, 2017. Available from: <https://doi.org/10.1039/c7mt00074j>, doi:10.1039/c7mt00074j.
- [70] National Research Council. *Copper in Drinking Water*. The National Academies Press, Washington, DC, 2000. Available from: <https://www.nap.edu/catalog/9782/copper-in-drinking-water>, doi:10.17226/9782.
- [71] Pellegrino Crafa, Marilisa Franceschi, Kryssia Isabel Rodriguez-Castro, Lorella Franzoni, Michele Russo, Giovanni Brandimarte, Antonio Tursi, Massimo Rugge, and Francesco Di Mario. Ppis and gastric cancer: any causal relationship? *Acta Bio Medica : Atenei Parmensis*, 06 2023. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10308480/>, doi:10.23750/abm.v94i3.14105.
- [72] S.C. Cunnane, K.R. McAdoo, and J.R. Prohaska. Lipid and fatty acid composition of organs from copper-deficient mice. *The Journal of Nutrition*, 116, 07 1986. Available from: <https://doi.org/10.1093/jn/116.7.1248>, doi:10.1093/jn/116.7.1248.
- [73] Jonathan D. Cuppett, Susan E. Duncan, and Andrea M. Dietrich. Evaluation of Copper Speciation and Water Quality Factors That Affect Aqueous Copper Tasting Response. *Chemical Senses*, 31(7):689–697, 07 2006. Available from: <https://doi.org/10.1093/chemse/bjl010>, arXiv:<https://academic.oup.com/chemse/article-pdf/31/7/689/779389/bjl010.pdf>, doi:10.1093/chemse/bjl010.
- [74] S. E. Dale, R. C. Ewan, V. C. Speer, and Dean R. Zimmerman. Copper, molybdenum and sulfate interaction in young swine. *Journal of Animal Science*, 37, 10 1973. Available from: <https://doi.org/10.2527/jas1973.374913x>, doi:10.2527/jas1973.374913x.
- [75] Ramos Danny, Mar David, Ishida Michael, Vargas Rebecca, Gaite Michaella, Montgomery Aaron, and Maria C. Linder. Mechanism of copper uptake from blood plasma ceruloplasmin by mammalian cells. *PLOS ONE*, 11(3):1–23, 03 2016. Available from: <https://doi.org/10.1371/journal.pone.0149516>, doi:10.1371/journal.pone.0149516.
- [76] Paloma Ferreira de Sousa, André Fernando de Oliveira, Antônio Alberto da Silva, and Renata Pereira Lopes. Environmental remediation processes by zero valence copper: reaction mechanisms. *Environmental Science and Pollution Research*, 26(15):14883–14903, May 2019. Available from: <https://doi.org/10.1007/s11356-019-04989-3>, doi:10.1007/s11356-019-04989-3.
- [77] Miguel Angel Díaz-Guerrero, Israel Castillo-Juárez, Rimma Zurabian, Alejandra Valdez, Kokila Kota, Yuki Hoshiko, Ekaprana Ramesh, Mariano Martínez Vazquez, Corina Diana CeapUx0103[bad char vv=259], Mariel Hernandez-Garnica, Frederic Cadet, and Rodolfo García Contreras. Reviving the past for a healthier future: Ancient molecules and remedies as a solution to the antibiotic crisis. *MDPI AG*, 05 2024. Available from: <https://doi.org/10.20944/preprints202405.0208.v1>, doi:10.20944/preprints202405.0208.v1.
- [78] James J DiNicolantonio, Dennis Mangan, and James H O'Keefe. Copper deficiency may be a leading cause of ischaemic heart disease. *Open Heart*, 5(2), 2018. Available from: <https://openheart.bmj.com/content/5/2/e000784>, arXiv:<https://openheart.bmj.com/content/5/2/e000784.full.pdf>, doi:10.1136/openhrt-2018-000784.
- [79] M. Dixon, S. W. J. Reid, and C. T. Mooney. Epidemiological, clinical, haematological and biochemical characteristics of canine hypothyroidism. *Veterinary Record*, 145, 10 1999. Available from: <https://doi.org/10.1136/vr.145.17.481>,

doi:10.1136/vr.145.17.481.

- [80] Qin-Yun Dong and Zhi-Ying Wu. Advance in the pathogenesis and treatment of wilson disease. *Translational Neurodegeneration*, page 23, 11 2012. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3526418/>, doi:10.1186/2047-9158-1-23.
- [81] Dani Dordevic, Jana Capikova, Simona Dordevic, Bohuslava Tremlov, Mri Gajdcs, and Ivan Kushkevych. Sulfur content in foods and beverages and its role in human and animal metabolism: A scoping review of recent studies. *Helijon*, 04 2023. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10130226/>, doi:10.1016/j.heliyon.2023.e15452.
- [82] Yanan Du, Yun Tu, Zeyang Zhou, Rui Hong, Jiayou Yan, and Gong-Wei Zhang. Effects of organic and inorganic copper on cecal microbiota and short-chain fatty acids in growing rabbits. *Frontiers in Veterinary Science*, 10, 2023. Available from: <https://www.frontiersin.org/journals/veterinary-science/articles/10.3389/fvets.2023.1179374>, doi:10.3389/fvets.2023.1179374.
- [83] Andrew Duncan, Calum Yacoubian, Neil Watson, and Ian Morrison. The risk of copper deficiency in patients prescribed zinc supplements. *Journal of clinical pathology*, pages 723–5, 06 2015. Available from: <https://pubmed.ncbi.nlm.nih.gov/26085547/>, doi:10.1136/jclinpath-2014-202837.
- [84] Vincent Einhorn, Hajo Haase, and Maria Maares. Interaction and competition for intestinal absorption by zinc, iron, copper, and manganese at the intestinal mucus layer. *Journal of Trace Elements in Medicine and Biology*, 84, 07 2024. Available from: <https://doi.org/10.1016/j.jtemb.2024.127459>, doi:10.1016/j.jtemb.2024.127459.
- [85] Hafza Wajeeha Ejaz, Wei Wang, and Minglin Lang. Copper toxicity links to pathogenesis of alzheimer's disease and therapeutics approaches. *International Journal of Molecular Sciences*, 21, 10 2020. Available from: <https://doi.org/10.3390/ijms21207660>, doi:10.3390/ijms21207660.
- [86] Charmaine D. Espinosa and Hans H. Stein. Digestibility and metabolism of copper in diets for pigs and influence of dietary copper on growth performance, intestinal health, and overall immune status: a review. *Journal of Animal Science and Biotechnology*, 12, 12 2021. Available from: <http://dx.doi.org/10.1186/s40104-020-00533-3>, doi:10.1186/s40104-020-00533-3.
- [87] H. T. Jun. Evans. Copper coordination in low chalcocite and djurleite and other copper-rich sulfides. *American Mineralogist*, 66:807–818, 1981. Available from: http://www.minsocam.org/ammin/AM66/AM66_807.pdf.
- [88] Howard T. Evans. The crystal structures of low chalcocite and djurleite. *Zeitschrift für Kristallographie - Crystalline Materials*, 150, 1979. Available from: https://rruff.geo.arizona.edu/doclib/zk/vol150/ZK150_299.pdf, doi:10.1524/zkri.1979.150.14.299.
- [89] Sini Ezer, Auli Saarinen, Shintaro Katayama, Masahito Yoshihara, Abdul Kadir Mukarram, Rasha Fahad Aljelaify, Fiona Ross, Amitha Raman, Irene Stevens, Oleg Gusev, Danika Bannasch, Jeffrey J. Schoenebeck, Juha Kere, W. Glen Pyle, Jonas Donner, Alex V. Postma, Tosso Leeb, Göran Andersson, Marjo K. Hytönen, Jens Häggström, Maria Wiberg, Jana Friederich, Jenny Eberhard, Magdalena Harakalova, Frank G. van Steenbeek, Gerhard Wess, Hannes Lohi, Julia E. Niskanen, AAasa Ohlsson, Ingrid Ljungvall, Michaela Drögemüller, Robert F. Ernst, Dennis Dooijes, Hanneke W. M. van Deutekom, J. Peter van Tintelen, Christian J. B. Snijders Blok, Marion van Vugt, Jessica van Setten, Folkert W. Asselbergs, Aleksandra Domanjko PetriUx010d[bad char vv=269], Milla Salonen, Sruthi Hundt, Matthias Hörtenhuber, Carsten Daub, César L. Araujo, Ileana B. Quintero, Kaisa Kyöstilä, Maria Kaukonen, Meharji Arumilli, Riika Sarviah, Jenni Puurunen, Sini Sulkama, Sini Karjalainen, Antti Sukura, Pernilla Syrjä, Niina Airas, Henna Pekkarinen, Ilona Kareinen, Hanna-Maaria Javela, Anna Knuutila, Heli Nordgren, Karoliina Hagner, Tarja Pääkkönen, Antti Iivanainen, and Kaarel Krjutskov. Identification of novel genetic risk factors of dilated cardiomyopathy: from canine to human. *Genome Medicine*, 15, 2023. Available from: <http://dx.doi.org/10.1186/s13073-023-01221-3>, doi:10.1186/s13073-023-01221-3.
- [90] Sajjad Fatahi and Seyyed Morteza Hoseini. Effect of dietary tryptophan and betaine on tolerance of caspian roach (*rutilus rutilus caspicus*) to copper toxicity. *International Journal of Aquatic Biology*, 1(2):76–81, May 2013. Available from: <https://ij-aquaticbiology.com/index.php/ijab/article/view/29>, doi:10.22034/ijab.v1i2.29.
- [91] M Fatfat, RA Merhi, O Rahal, DA Stoyanovsky, A Zaki, H Haidar, VE Kagan, H Gali-Muhtasib, and K Machaca. Copper chelation selectively kills colon cancer cells through redox cycling and generation of reactive oxygen species. *BMC Cancer*, 14:527, 2014. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4223620/>.
- [92] E Fedele. Anti-amyloid therapies for alzheimer's disease and the amyloid cascade hypothesis. *International journal of molecular sciences*, 24(19), 2023. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC10578107/>.
- [93] C K Fenger and C W Kohn. Tracheal obstruction from tracheal collapse associated with pneumonia in a horse. *Journal of the American Veterinary Medical Association*, pages 1698–700, Jun 1992. Available from: <https://pubmed.ncbi.nlm.nih.gov/1624350/>.
- [94] M Fields, C G Lewis, and M D Lure. Garlic oil extract ameliorates the severity of copper deficiency. *Journal of the American College of Nutrition*, 11, 06 1992. Available from: <https://doi.org/10.1080/07315724.1992.10718235>, doi:10.1080/07315724.1992.10718235.
- [95] H. Fieten, B.D. HooijerNouwens, V.C. Biourge, P.A.J. Leegwater, A.L. Watson, T.S.G.A.M. van den Ingh, and J. Rothuizen. Association of dietary copper and zinc levels with hepatic copper and zinc concentration in labrador retrievers. *Journal of Veterinary Internal Medicine*, 26, 2012. Available from: <http://dx.doi.org/10.1111/j.1939-1676.2012.01001.x>, doi:10.1111/j.1939-1676.2012.01001.x.
- [96] Hille Fieten, Peter J Leegwater, Adrian L Watson, and Jan Rothuizen. Canine models of copper toxicosis for understanding mammalian copper metabolism. *Mammalian genome : official journal of the International Mammalian Genome Society*, pages 62–75, 12 2011. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3275736/>, doi:10.1007/s00335-011-9378-7.
- [97] Fa'alataitaua M Fitisemanu and Teresita Padilla-Benavides. Emerging perspectives of copper-mediated transcriptional

- regulation in mammalian cell development. *Metalloomics*, 16, 10 2024. Available from: <https://doi.org/10.1093/mtomcs/mfae046>, doi:10.1093/mtomcs/mfae046.
- [98] Francesca Focarelli, Andrea Giachino, and Kevin John Waldron. Copper microenvironments in the human body define patterns of copper adaptation in pathogenic bacteria. *PLoS Pathogens*, 07 2022. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9302775/>, doi:10.1371/journal.ppat.1010617.
- [99] T. Fong, R. Vij, A. Vijayan, J. DiPersio, and M. Blinder. Copper deficiency: an important consideration in the differential diagnosis of myelodysplastic syndrome. *Haematologica*, 92, 10 2007. Available from: <http://dx.doi.org/10.3324/haematol.11314>, doi:10.3324/haematol.11314.
- [100] Paul L Fox, Barsanit Mazumder, Eduardo Ehrenwald, and Chinmay K Mukhopadhyay. Ceruloplasmin and cardiovascular disease. *Free Radical Biology and Medicine*, 28, 06 2000. Available from: [https://doi.org/10.1016/s0891-5849\(00\)00231-8](https://doi.org/10.1016/s0891-5849(00)00231-8), doi:10.1016/s0891-5849(00)00231-8.
- [101] Zola Francis, George Book, Cara Litvin, and Benjamin Kalivas. The covid-19 pandemic and zinc-induced copper deficiency: An important link. *The American Journal of Medicine*, pages e290–1, 04 2022. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8970610/>, doi:10.1016/j.amjmed.2022.03.008.
- [102] Daniel E. Freedberg, Benjamin Lebwohl, and Julian A. Abrams. The impact of proton pump inhibitors on the human gastrointestinal microbiome. *Clinics in laboratory medicine*, pages 771–85, 09 2014. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4254461/>, doi:10.1016/j.cll.2014.08.008.
- [103] I. Carmen Fuentealba and Enrique M. Aburto. Animal models of copper-associated liver disease. *Comparative Hepatology*, 2(1):5, 2003. Available from: <http://dx.doi.org/10.1186/1476-5926-2-5>, doi:10.1186/1476-5926-2-5.
- [104] Hirohisa Fujikawa and Junji Haruta. Copper deficiency: An overlooked diagnosis. *Cureus*. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10733163/>, doi:10.7759/cureus.49139.
- [105] Jenna Gale and Elias Aizenman. The physiological and pathophysiological roles of copper in the nervous system. *European Journal of Neuroscience*, 60, 07 2024. Available from: <https://doi.org/10.1111/ejn.16370>, doi:10.1111/ejn.16370.
- [106] Champika SSK Gamakaranage, Chaturaka Rodrigo, Sajitha Weerasinghe, Ariaranee Gnanathasan, Visvalingam Puwanaraj, and Harshani Fernando. Complications and management of acute copper sulphate poisoning; a case discussion. *Journal of Occupational Medicine and Toxicology*, 6, 12 2011. Available from: <https://doi.org/10.1186/1745-6673-6-34>, doi:10.1186/1745-6673-6-34.
- [107] Mohammed D Gani, Vanessa C Rogers, Khalid H Sachak, and Joseph K Marzouk. Flat trachea syndrome: a rare condition with symptoms similar to obstructive airway disease. *BMJ Case Reports*, 02 2015. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4342702/>, doi:10.1136/bcr-2014-207063.
- [108] Douglas Ganini, Donatella Canistro, JinJie Jang, Krisztian Stadler, Ronald P. Mason, and Maria B. Kadiiska. Ceruloplasmin (ferroxidase) oxidizes hydroxylamine probes: deceptive implications for free radical detection. *Free radical biology & medicine*, pages 1514–21, 07 2012. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3448871/>, doi:10.1016/j.freeradbiomed.2012.07.013.
- [109] Erika Garay, Nils Schuth, Alessandra Barbanente, Carlos Tejeda-Guzmán, Daniele Vitone, Beatriz Osorio, Adam H. Clark, Maarten Nachtegaal, Michael Haumann, Holger Dau, Alberto Vela, Fabio Arnesano, Liliana Quintanar, and Fanis Missirlis. Tryptophan regulates *drosophilazinc* stores. *Proceedings of the National Academy of Sciences*, 119, 04 2022. Available from: <http://dx.doi.org/10.1073/pnas.2117807119>, doi:10.1073/pnas.2117807119.
- [110] Panos G Georgopoulos, Sheng Wei Wang, Ioannis G Georgopoulos, Mary Jean Yonone-Lioy, and Paul J Lioy. Assessment of human exposure to copper: A case study using the nhexas database. *Journal of Exposure Science & Environmental Epidemiology*, 16, 2006. Available from: <https://www.nature.com/articles/7500462>, doi:10.1038/sj.jea.7500462.
- [111] Alok Ghosh, Prachi P. Trivedi, Shrishiv A. Timbalia, Aaron T. Griffin, Jennifer J. Rahn, Sherine L. Chan, and Vishal M. Gohil. Copper supplementation restores cytochrome c oxidase assembly defect in a mitochondrial disease model of coa⁶ deficiency. *Human Molecular Genetics*, pages 3596–606, 02 2014. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC4049311/>, doi:10.1093/hmg/ddu069.
- [112] Alok Ghosh, Prachi P. Trivedi, Shrishiv A. Timbalia, Aaron T. Griffin, Jennifer J. Rahn, Sherine S. L. Chan, and Vishal M. Gohil. Copper supplementation restores cytochrome c oxidase assembly defect in a mitochondrial disease model of coa⁶ deficiency. *Human Molecular Genetics*, 23(13):3596, 2014. Available from: http://dx.doi.org/10.1093/hmg/ddu069, arXiv:/oup/backfile/content_public/journal/hmg/23/13/10.1093/hmg/ddu069/2/ddu069.pdf, doi:10.1093/hmg/ddu069.
- [113] Bisweswar Ghosh, Liying Sun, and Nithin Chacko Thomas. Compatibility evaluation of modified seawater for eor in carbonate reservoirs through the introduction of polyphosphate compound. *Petroleum Science*, 17(2):393–408, Apr 2020. Available from: <https://doi.org/10.1007/s12182-019-00380-6>, doi:10.1007/s12182-019-00380-6.
- [114] Andrea Giachino and Kevin J. Waldron. Copper tolerance in bacteria requires the activation of multiple accessory pathways. *Molecular Microbiology*, 114, 09 2020. Available from: <https://doi.org/10.1111/mmi.14522>, doi:10.1111/mmi.14522.
- [115] Natalia Giurgea, Mihaela Ioana Constantinescu, Ramona Stanciu, Soimita Suciu, and Adriana Muresan. Ceruloplasmin - acute-phase reactant or endogenous antioxidant? the case of cardiovascular disease. *Medical science monitor : international medical journal of experimental and clinical research*, pages RA48–51, Feb 2005. Available from: <https://pubmed.ncbi.nlm.nih.gov/15668644/>.
- [116] Helly R. Goez, Francois D. Jacob, Robert D. Fealey, Marc C. Patterson, Vijay Ramaswamy, Rabin Persad, Edward S. Johnson, and Jerome Y. Yager. An unusual presentation of copper metabolism disorder and a possible connection with niemann-pick type c. *Journal of Child Neurology*, 26, 2011. Available from: <http://dx.doi.org/10.1177/0883073810383983>, doi:10.1177/0883073810383983.

- [117] Siew Wei Goh, Alan N. Buckley, Robert N. Lamb, Richard A. Rosenberg, and Damian Moran. The oxidation states of copper and iron in mineral sulfides, and the oxides formed on initial exposure of chalcopyrite and bornite to air. *Geochimica et Cosmochimica Acta*, 70, 05 2006. Available from: <http://dx.doi.org/10.1016/j.gca.2006.02.007>, doi:10.1016/j.gca.2006.02.007.
- [118] Ernst Graf. Copper(ii) ascorbate: A novel food preservation system. *Journal of Agricultural and Food Chemistry*, 42, 1994. Available from: <http://dx.doi.org/10.1021/jf00044a006>, doi:10.1021/jf00044a006.
- [119] Gregor Grass, Christopher Rensing, and Marc Solioz. Metallic copper as an antimicrobial surface. *Applied and Environmental Microbiology*, 77, 03 2011. Available from: <https://doi.org/10.1128/aem.02766-10>, doi:10.1128/aem.02766-10.
- [120] Harry B. Gray and Jay R. Winkler. Hole hopping through tyrosine/tryptophan chains protects proteins from oxidative damage. *Proceedings of the National Academy of Sciences*, 112, 09 2015. Available from: <https://doi.org/10.1073/pnas.1512704112>, doi:10.1073/pnas.1512704112.
- [121] Louise F. Gray and Louise J. Daniel. Effect of copper status on the urinary excretion of tryptophan metabolites and amino acids by the rat. *The Journal of Nutrition*, 103, 12 1973. Available from: <http://dx.doi.org/10.1093/jn/103.12.1764>, doi:10.1093/jn/103.12.1764.
- [122] Michael J Gray and Ursula Jakob. Oxidative stress protection by polyphosphatene new roles for an old player. *Current Opinion in Microbiology*, 24, 04 2015. Available from: <https://doi.org/10.1016/j.mib.2014.12.004>, doi:10.1016/j.mib.2014.12.004.
- [123] Jiexin Guan, Lihong Ge, Qing Yu, Bo Ouyang, Yilin Deng, and Huaming Li. Unraveling the structural evolution of cobalt sulfides in electrocatalytic no(3)rr: the inescapable influence of cl(). *Inorganic chemistry*, 02 2025. Available from: <https://pubmed.ncbi.nlm.nih.gov/39915902/>, doi:10.1021/acs.inorgchem.4c04780.
- [124] Jung-Heun Ha, Caglar Doguer, and James F. Collins. Consumption of a high-iron diet disrupts homeostatic regulation of intestinal copper absorption in adolescent mice. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, 313, 10 2017. Available from: <http://dx.doi.org/10.1152/ajpgi.00169.2017>, doi:10.1152/ajpgi.00169.2017.
- [125] Iqbal Hamza and Jonathan D Gitlin. Hepatic copper transport. *Landes Bioscience*, 2013. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK6381/>.
- [126] ED Harris, JK Rayton, JE Balthrop, RA DiSilvestro, and M Garcia-de Quevedo. Copper and the synthesis of elastin and collagen. *Ciba Foundation symposium*, 79:163–82, 1980. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/articles/6110524/>.
- [127] F Harrison, AEL Roberts, R Gabrilksa, KP Rumbaugh, C Lee, and SP Diggle. A 1,000-year-old antimicrobial remedy with antistaphylococcal activity. *mBio*, 6(4), 2015. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4542191/>.
- [128] Linda J. Harvey and Harry J. McArdle. Biomarkers of copper status: a brief update. *British Journal of Nutrition*, 99, 2008. Available from: <http://dx.doi.org/10.1017/s0007114508006806>, doi:10.1017/s0007114508006806.
- [129] Nesrin M. Hasan and Svetlana Lutsenko. Regulation of copper transporters in human cells. *Current topics in membranes*, pages 137–61, 2012. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6365104/>, doi:10.1016/B978-0-12-394390-3.00006-9.
- [130] Yuta Hatori, Sachie Inouye, and Reiko Akagi. Thiol-based copper handling by the copper chaperone atox1. *IUBMB Life*, 69(4):246–254, 2017. Available from: <http://dx.doi.org/10.1002/iub.1620>, doi:10.1002/iub.1620.
- [131] Fang He, Cong Chang, Bowen Liu, Zhu Li, Hao Li, Na Cai, and Hong-Hui Wang. Copper (ii) ions activate ligand-independent receptor tyrosine kinase (rtk) signaling pathway. *BioMed Research International*, 05 2019. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6537018/>, doi:10.1155/2019/4158415.
- [132] MC Heffern, HM Park, HY Au-Yeung, de Bittner GC Van, CM Ackerman, A Stahl, and CJ Chang. In vivo bioluminescence imaging reveals copper deficiency in a murine model of nonalcoholic fatty liver disease. *Proceedings of the National Academy of Sciences of the United States of America*, 113(50):14219–24, 2016. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167165/>.
- [133] S Hekimi, Y Wang, and A Noë. Mitochondrial ros and the effectors of the intrinsic apoptotic pathway in aging cells: The discerning killers! *Frontiers in Genetics*, 7, 2016. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5021979/>.
- [134] Nathan E. Hellman, Satoshi Kono, Grazia M. Mancini, A.J. Hoogeboom, G.J. de Jong, and Jonathan D. Gitlin. Mechanisms of copper incorporation into human ceruloplasmin. *Journal of Biological Chemistry*, 277, 2002. Available from: <http://dx.doi.org/10.1074/jbc.m206246200>, doi:10.1074/jbc.m206246200.
- [135] L M Henderson, G J Brewer, J B Dressman, S Z Swidan, D J DuRoss, C H Adair, J L Barnett, and R R Berardi. Effect of intragastric ph on the absorption of oral zinc acetate and zinc oxide in young healthy volunteers. *JPEN. Journal of parenteral and enteral nutrition*, pages 393–7, Sep-Oct 1995. Available from: <https://pubmed.ncbi.nlm.nih.gov/8577018/>, doi:10.1177/0148607195019005393.
- [136] Alejandro Hernández-López, Daniel A. Sánchez Félix, Zenaida Zuñiga Sierra, Itzel García Bravo, Tzvetanka D. Dinkova, and Alma X. Avila-Alejandre. Quantification of reducing sugars based on the qualitative technique of benedict. *ACS Omega*, 5, 12 2020. Available from: <https://doi.org/10.1021/acsomega.0c04467>, doi:10.1021/acsomega.0c04467.
- [137] O. Herreros and J. Viñals. Leaching of sulfide copper ore in a nacl-h₂so₄-o₂ media with acid pre-treatment. *Hydrometallurgy*, 89, 12 2007. Available from: <http://dx.doi.org/10.1016/j.hydromet.2007.07.011>, doi:10.1016/j.hydromet.2007.07.011.
- [138] C.H. Hill, B. Starcher, and G. Matrone. Mercury and silver interrelationships with copper. *The Journal of Nutrition*, 83, 1964. Available from: <http://dx.doi.org/10.1093/jn/83.2.107>, doi:10.1093/jn/83.2.107.

- [139] James W. Hilton, Kai Kysenius, Jeffrey R. Liddell, Stephen W. Mercer, Bence Paul, Joseph S. Beckman, Catriona A. McLean, Anthony R. White, Paul S. Donnelly, Ashley I. Bush, Dominic J. Hare, Blaine R. Roberts, and Peter J. Crouch. Evidence for disrupted copper availability in human spinal cord supports cuii(atsm) as a treatment option for sporadic cases of als. *Scientific Reports*, 14, 03 2024. Available from: <https://www.nature.com/articles/s41598-024-55832-w>, doi:10.1038/s41598-024-55832-w.
- [140] Victoria Hodgkinson and Michael J. Petris. Copper homeostasis at the host-pathogen interface*. *The Journal of Biological Chemistry*, pages 13549–55, 03 2012. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3340201/>, doi:10.1074/jbc.R111.316406.
- [141] Rebecca L. Holme, James J. Miller, Kay Nicholson, and Daisy Sahoo. Tryptophan 415 is critical for the cholesterol transport functions of scavenger receptor bi. *Biochemistry*, 55, 01 2016. Available from: <http://dx.doi.org/10.1021/acs.biochem.5b00804>, doi:10.1021/acs.biochem.5b00804.
- [142] R Horvath, P Freisinger, R Rubio, T Merl, R Bax, JA Mayr, Shawan, J Muller-Hocker, D Pongratz, LB Moller, N Horn, and M Jakob. Congenital cataract, muscular hypotonia, developmental delay and sensorineural hearing loss associated with a defect in copper metabolism. *Journal of inherited metabolic disease*, 28(4):479–92, 2005. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/articles/15902551/>.
- [143] Seyyed Morteza Hoseini, Seyed Abbas Hosseini, and Mohammad Soudagar. Dietary tryptophan changes serum stress markers, enzyme activity, and ions concentration of wild common carp cyprinus carpio exposed to ambient copper. *Fish Physiology and Biochemistry*, 38, 2012. doi:10.1007/s10695-012-9629-x.
- [144] Seyyed Morteza Hoseini, Amalia Pérez Jiménez, Benjamin Costas, Rita Azereedo, and Manuel Gesto. Physiological roles of tryptophan in teleosts: current knowledge and perspectives for future studies. *Reviews in Aquaculture*, 11, 02 2019. Available from: <http://dx.doi.org/10.1111/raq.12223>, doi:10.1111/raq.12223.
- [145] Md Selim Hossain, Archita Das, Ashiq M Rafiq, Ferenc Deak, Zsolt Bagi, Rashelle Outlaw, Varadarajan Sudhahar, Mai Yamamoto, Jack H Kaplan, Masuko Ushio-Fukai, and Tohru Fukai. Altered copper transport in oxidative stress-dependent brain endothelial barrier dysfunction associated with alzheimer's disease. *Vascular pharmacology*, page 107433, 09 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39317307/>, doi:10.1016/j.vph.2024.107433.
- [146] Jun Hu, Chen Wang, Bijuan Shao, Lingxiao Fu, Jianming Yu, Zhimin Qiang, and Jianmeng Chen. Enhanced formation of carbonaceous and nitrogenous disinfection byproducts from biofilm extracellular polymeric substances undercatalysis of copper corrosion products. *Science of The Total Environment*, 723, 06 2020. Available from: <https://doi.org/10.1016/j.scitotenv.2020.138160>, doi:10.1016/j.scitotenv.2020.138160.
- [147] Wei-Syuan Huang, Yuan-Ju Lee, Lu Wang, Hsuan-Hsuan Chen, Yueh-Jung Chao, Vivien Cheng, and Shwu-Jen Liaw. Copper affects virulence and diverse phenotypes of uropathogenic proteus mirabilis. *Journal of Microbiology, Immunology and Infection*, 57, 06 2024. Available from: <https://doi.org/10.1016/j.jmii.2024.02.007>, doi:10.1016/j.jmii.2024.02.007.
- [148] William Jr Hughes, Walter E Rodriguez, Dorothea Rosenberger, Jing Chen, Utpal Sen, Neetu Tyagi, Karni S Moshal, Thomas Vacek, Y James Kang, and Suresh C Tyagi. Role of copper and homocysteine in pressure overload heart failure. *Cardiovascular toxicology*, pages 137–44, Fall 2008. Available from: <https://pubmed.ncbi.nlm.nih.gov/18679830/>, doi:10.1007/s12012-008-9021-3.
- [149] D F Hwang, L C Wang, and H M Cheng. Effect of taurine on toxicity of copper in rats. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association*, pages 239–44, Mar 1998. Available from: <https://pubmed.ncbi.nlm.nih.gov/9609396/>, doi:10.1016/s0278-6915(97)00146-4.
- [150] Erzsebet Illes, Amir Mizrahi, Vered Marks, and Dan Meyerstein. Carbonate-radical-anions, and not hydroxyl radicals, are the products of the fenton reaction in neutral solutions containing bicarbonate. *Free radical biology & medicine*, pages 1–6, 11 2018. Available from: <https://pubmed.ncbi.nlm.nih.gov/30458276/>, doi:10.1016/j.freeradbiomed.2018.11.015.
- [151] Sachin Jain, Vidhi Gautam, and Sania Naseem. Acute-phase proteins: As diagnostic tool. *Journal of Pharmacy and Bioallied Sciences*, pages 118–27, Jan-Mar 2011. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3053509/>, doi:10.4103/0975-7406.76489.
- [152] Stephan R. Jaiser and Gavin P. Winston. Copper deficiency myelopathy. *Journal of Neurology*, pages 869–81, 03 2010. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3691478/>, doi:10.1007/s00415-010-5511-x.
- [153] Thunder Jalili, Denis M. Medeiros, and Robert E.C. Wildman. Aspects of cardiomyopathy are exacerbated by elevated dietary fat in copper-restricted rats. *The Journal of Nutrition*, 126, 1996. Available from: <http://dx.doi.org/10.1093/jn/126.4.807>, doi:10.1093/jn/126.4.807.
- [154] Rob Janssen, Bart de Brouwer, Jan H. von der Thüsen, and Emiel F.M. Wouters. Copper as the most likely pathogenic divergence factor between lung fibrosis and emphysema. *Medical Hypotheses*, 120, 11 2018. Available from: <https://doi.org/10.1016/j.mehy.2018.08.003>, doi:10.1016/j.mehy.2018.08.003.
- [155] M M Jazzaar and I Naseem. Genotoxicity of photoilluminated riboflavin in the presence of cu(ii). *Free radical biology & medicine*, pages 7–14, 1996. Available from: <https://pubmed.ncbi.nlm.nih.gov/8791088/>, doi:10.1016/0891-5849(95)02156-6.
- [156] Leo S. Jensen and Denzil V. Maurice. Influence of sulfur amino acids on copper toxicity in chicks. *The Journal of Nutrition*, 109, 1979. Available from: <http://dx.doi.org/10.1093/jn/109.1.91>, doi:10.1093/jn/109.1.91.
- [157] Megha Jhanji, Ashita Bhan, Colin Arrowood, Dina W Yakout, Ankit Shroff, Danielle McManus, Henrietta Gifford, Janay Vacharasin, Sofia B Lizarraga, Taras Y Nazarko, Angela M Mabb, and Mathew Sajish. Tyrosine and phenylalanine activate neuronal dna repair but exhibit opposing effects on global transcription and adult female mice are resilient to tyrrs/yars1 depletion. *IUBMB life*, page e70030, Jun 2025. Available from: <https://pubmed.ncbi.nlm.nih.gov/40476370/>, doi:10.1002/iub.70030.

- [158] Rui Jiang, Yang Sui, Jingru Hong, Manabu Niimi, Qiaojing Yan, Zhuheng Shi, and Jian Yao. The combined administration of vitamin c and copper induces a systemic oxidative stress and kidney injury. *Biomolecules*, 13, 2023. Available from: <http://dx.doi.org/10.3390/biom13010143>, doi:10.3390/biom13010143.
- [159] Shujing Jin, Xun Qi, Bin Zhang, Ziqing Sun, Bingchun Zhang, Hui Yang, Tongmin Wang, Bo Zheng, Xingang Wang, Qiuping Shi, Ming Chen, Ling Ren, Ke Yang, and Hongshan Zhong. Evaluation of promoting effect of a novel cu-bearing metal stent on endothelialization process from in vitro and in vivo studies. *Scientific Reports*, 7, 12 2017. Available from: <https://www.nature.com/articles/s41598-017-17737-9>, doi:10.1038/s41598-017-17737-9.
- [160] Mary Ann Johnson and Cynthia Lee Murphy. *Effect of High Dietary Iron and Ascorbic Acid on Copper and Iron Utilization during Copper Deficiency*, pages 545–546. Springer US, Boston, MA, 1988. Available from: https://doi.org/10.1007/978-1-4613-0723-5_194, doi:10.1007/978-1-4613-0723-5_194.
- [161] Michael D. L. Johnson, Thomas E. Kehl-Fie, Roger Klein, Jacqueline Kelly, Corinna Burnham, Beth Mann, and Jason W. Rosch. Role of copper efflux in pneumococcal pathogenesis and resistance to macrophage-mediated immune clearance. *Infection and Immunity*, 83, 2015. Available from: <http://dx.doi.org/10.1128/iai.03015-14>, doi:10.1128/iai.03015-14.
- [162] Sumanta Kar, Samarpita Sen, Saptarshi Maji, Deepashri Saraf, Ruturaj, Rupam Paul, Sohini Dutt, Basudeb Mondal, Enrique Rodriguez-Boulan, Ryan Schreiner, Durba Sengupta, and Arnab Gupta. Copper(ii) import and reduction are dependent on his-met clusters in the extracellular amino terminus of human copper transporter-1. *Journal of Biological Chemistry*, 298, 03 2022. Available from: <http://dx.doi.org/10.1016/j.jbc.2022.101631>, doi:10.1016/j.jbc.2022.101631.
- [163] A.B. KASHANI, H. SAMIE, R.J. EMERICK, and C.W. CARLSON. Effect of copper with three levels of sulfur containing amino acids in diets for turkeys. *Poultry Science*, 65, 09 1986. Available from: <http://dx.doi.org/10.3382/ps.0651754>, doi:10.3382/ps.0651754.
- [164] Tetsuyuki KATAYAMA, Junko HAYASHI, Masato KISHIDA, and Norihisa KATO. Effects of dietary excess amino acids on the concentrations of cholesterol, α-tocopherol, ascorbic acid, and copper in serum and tissues of rats. *Journal of Nutritional Science and Vitaminology*, 36(5):485–495, 1990. Available from: https://www.jstage.jst.go.jp/article/jnsv1973/36/5/36_5_485/_article/-char/ja/, doi:10.3177/jnsv.36.485.
- [165] Louise Kelly, Matthew Macgregor Sharp, Isabelle Thomas, Christopher Brown, Matthew Schrag, Lissa Ventura Antunes, Elena Solopova, José Martinez-Gonzalez, Cristina Rodríguez, and Roxana Octavia Carare. Targeting lysyl-oxidase (lox) may facilitate intramural periarterial drainage for the treatment of alzheimer's disease. *Cerebral Circulation - Cognition and Behavior*, 5, 2023. Available from: <http://dx.doi.org/10.1016/j.cccb.2023.100171>, doi:10.1016/j.cccb.2023.100171.
- [166] Sonia Khemaissa, Astrid Walrant, and Sandrine Sagan. Tryptophan, more than just an interfacial amino acid in the membrane activity of cationic cell-penetrating and antimicrobial peptides. *Quarterly Reviews of Biophysics*, 55, 2022. Available from: <https://doi.org/10.1017/s0033583522000105>, doi:10.1017/s0033583522000105.
- [167] B. G. Kim, D. Y. Kil, D. C. Mahan, G. M. Hill, and H. H. Stein. Effects of dietary sulfur and distillers dried grains with solubles on carcass characteristics, loin quality, and tissue concentrations of sulfur, selenium, and copper in growing-finishing pigs1. *Journal of Animal Science*, 92, 10 2014. Available from: <https://doi.org/10.2527/jas.2013-6323>, doi:10.2527/jas.2013-6323.
- [168] Byung-Eun Kim, Michelle L. Turski, Yasuhiro Nose, Michelle Casad, Howard A. Rockman, and Dennis J. Thiele. Cardiac copper deficiency activates a systemic signaling mechanism that communicates with the copper acquisition and storage organs. *Cell Metabolism*, 11, 2010. Available from: <http://dx.doi.org/10.1016/j.cmet.2010.04.003>, doi:10.1016/j.cmet.2010.04.003.
- [169] JINSOO KIM, RAINER SCHNEE, and JAE W. PARK. Chemical and functional properties of various blends of phosphates. *Journal of Food Quality*, 32, 08 2009. Available from: <https://doi.org/10.1111/j.1745-4557.2009.00265.x>, doi:10.1111/j.1745-4557.2009.00265.x.
- [170] Kwan-Woo Kim, Jin-Soo Jeong, Kay-Hyeok An, and Byung-Joo Kim. A study on the microstructural changes and mechanical behaviors of carbon fibers induced by optimized electrochemical etching. *Composites Part B: Engineering*, 165, 05 2019. Available from: <http://dx.doi.org/10.1016/j.compositesb.2019.02.055>, doi:10.1016/j.compositesb.2019.02.055.
- [171] Min Joo Kim, Soo Chin Kim, Soie Chung, Serim Kim, Ji Won Yoon, and Young Joo Park. Exploring the role of copper and selenium in the maintenance of normal thyroid function among healthy koreans. *Journal of Trace Elements in Medicine and Biology*, 61, 09 2020. Available from: <https://doi.org/10.1016/j.jtemb.2020.126558>, doi:10.1016/j.jtemb.2020.126558.
- [172] Yoon Jae Kim, Jeong Sang Lee, Kyung Sook Hong, Jun Won Chung, Ju Hyun Kim, and Ki Baik Hahm. Novel application of proton pump inhibitor for the prevention of colitis-induced colorectal carcinogenesis beyond acid suppression. *Cancer Prevention Research*, 3. Available from: <http://dx.doi.org/10.1158/1940-6207.capr-10-0033>, doi:10.1158/1940-6207.capr-10-0033.
- [173] Leslie M. Klevay. Myelodysplasia, myeloneuropathy, and copper deficiency. *Mayo Clinic Proceedings*, 81, 01 2006. Available from: <https://doi.org/10.4065/81.1.132>, doi:10.4065/81.1.132.
- [174] Leslie M. Klevay. Metabolic interactions among dietary cholesterol, copper, and fructose. *American Journal of Physiology-Endocrinology and Metabolism*, 298, 01 2010. Available from: <https://doi.org/10.1152/ajpendo.00591.2009>, doi:10.1152/ajpendo.00591.2009.
- [175] Leslie M. Klevay. The contemporaneous epidemic of chronic, copper deficiency. *Journal of Nutritional Science*, 11, 2022. Available from: <http://dx.doi.org/10.1017/jns.2022.83>, doi:10.1017/jns.2022.83.

- [176] VH Konjufca, GM Pesti, and RI Bakalli. Modulation of cholesterol levels in broiler meat by dietary garlic and copper. *Poultry Science*, 76, 09 1997. Available from: <https://doi.org/10.1093/ps/76.9.1264>, doi:10.1093/ps/76.9.1264.
- [177] Ewelina Król, Monika Okulicz, and Justyna Kupsz. The influence of taurine supplementation on serum and tissular fe, zn and cu levels in normal and diet-induced insulin-resistant rats. *Biological Trace Element Research*, 198(2):592–601, Dec 2020. Available from: <https://doi.org/10.1007/s12011-020-02100-3>, doi:10.1007/s12011-020-02100-3.
- [178] Hedwig S. Kruitwagen and Louis C. Penning. Preclinical models of wilsons disease, why dogs are catchy alternatives. *Annals of Translational Medicine*, Apr 2019. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6531654/>, doi:10.21037/atm.2019.02.06.
- [179] Meena Kumari and Kalpana Patel. Effect of sulfur-containing spices on the bioaccessibility of trace minerals from selected cereals and pulses. *Journal of the Science of Food and Agriculture*, pages n/a–n/a, 2016. JSFA-16-2048.R1. Available from: <http://dx.doi.org/10.1002/jsfa.8113>, doi:10.1002/jsfa.8113.
- [180] Yien-Ming Kuo, Bing Zhou, Dominique Cosco, and Jane Gitschier. The copper transporter ctrl provides an essential function in mammalian embryonic development. *Proceedings of the National Academy of Sciences of the United States of America*, pages 6836–41, Jun 2001. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC34439/>, doi:10.1073/pnas.111057298.
- [181] Jagoda KUx0119[bad char vv=281]piUx0144[bad char vv=324]ska Pacelik, Wioletta Biel, Robert Witkowicz, and Cezary PodsiadUx0142[bad char vv=322]o. Mineral and heavy metal content in dry dog foods with different main animal components. *Scientific Reports*, 13, 04 2023. Available from: <https://www.nature.com/articles/s41598-023-33224-w>, doi:10.1038/s41598-023-33224-w.
- [182] Erik Ladomersky and Michael J Petris. Copper tolerance and virulence in bacteria. *Metallooms*, 7(6):957–964, 01 2015. Available from: <https://doi.org/10.1039/c4mt00327f>, arXiv:<https://academic.oup.com/metallooms/article-pdf/7/6/957/34785053/c4mt00327f.pdf>, doi:10.1039/c4mt00327f.
- [183] Garson K. Law, Robert F. Bertolo, Alfred Adjiri-Awere, Paul B. Pencharz, and Ronald O. Ball. Adequate oral threonine is critical for mucin production and gut function in neonatal piglets. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, 292, 05 2007. Available from: <https://doi.org/10.1152/ajpgi.00221.2006>, doi:10.1152/ajpgi.00221.2006.
- [184] Luke Lear, Dan Padfield, Elze Hesse, Suzanne Kay, Angus Buckling, and Michiel Vos. Copper reduces the virulence of bacterial communities at environmentally relevant concentrations. *Environment International*, 182, 2023. Available from: <http://dx.doi.org/10.1016/j.envint.2023.108295>, doi:10.1016/j.envint.2023.108295.
- [185] Heather Lechtman and Sabine Klein. The production of copper-arsenic alloys (arsenic bronze) by cosmelting: Modern experiment, ancient practice. *Journal of Archaeological Science*, 26, 05 1999. Available from: <https://doi.org/10.1006/jasc.1998.0324>, doi:10.1006/jasc.1998.0324.
- [186] D.R. LEDOUX, R.D. MILES, C.B. AMMERMAN, and R.H. HARMS. Interaction of dietary nutrient concentration and supplemental copper on chick performance and tissue copper concentrations. *Poultry Science*, 66, 08 1987. Available from: <https://doi.org/10.3382/ps.0661379>, doi:10.3382/ps.0661379.
- [187] Jaekwon Lee, Joseph R. Prohaska, and Dennis J. Thiele. Essential role for mammalian copper transporter ctrl in copper homeostasis and embryonic development. *Proceedings of the National Academy of Sciences*, 98, 06 2001. Available from: <http://dx.doi.org/10.1073/pnas.111058698>, doi:10.1073/pnas.111058698.
- [188] Jennifer K. Lee, Jung-Heun Ha, and James F. Collins. Dietary iron intake in excess of requirements impairs intestinal copper absorption in sprague dawley rat dams, causing copper deficiency in suckling pups. *Biomedicines*, 9, 2021. Available from: <http://dx.doi.org/10.3390/biomedicines9040338>, doi:10.3390/biomedicines9040338.
- [189] Jeosoon Lee, Sookyoung Yun, Inhyung Lee, Mincheol Choi, and Junghee Yoon. Fluoroscopic characteristics of tracheal collapse and cervical lung herniation in dogs: 222 cases (20122015). *Journal of Veterinary Science*, pages 499–505, 12 2017. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5746443/>, doi:10.4142/jvs.2017.18.4.499.
- [190] S. A. Lee, J. Dunne, T. Mottram, and M. R. Bedford. Effect of diet phase change, dietary ca and p level and phytase on bird performance and real-time gizzard ph measurements. *British Poultry Science*, 58, 05 2017. Available from: <https://doi.org/10.1080/00071668.2017.1293799>, doi:10.1080/00071668.2017.1293799.
- [191] S. Leeson. Copper metabolism and dietary needs. *World's Poultry Science Journal*, 65, 09 2009. Available from: <https://doi.org/10.1017/s0043933909000269>, doi:10.1017/s0043933909000269.
- [192] Patrizia Lemma-Gray, Susan T. Weintraub, Christopher A. Carroll, Andrej Musatov, and Neal C. Robinson. Tryptophan 334 oxidation in bovine cytochrome c oxidase subunit i involves free radical migration. *FEBS Letters*, 581, 02 2007. Available from: <https://doi.org/10.1016/j.febslet.2006.12.054>, doi:10.1016/j.febslet.2006.12.054.
- [193] G J Leyer and E A Johnson. Repression of toxin production by tryptophan in clostridium botulinum type e. *Archives of microbiology*, pages 443–7, 1990. Available from: <https://pubmed.ncbi.nlm.nih.gov/2256780/>, doi:10.1007/BF00245225.
- [194] Hualin Li, Lijun Zhao, Tao Wang, and Y James Kang. Dietary cholesterol supplements disturb copper homeostasis in multiple organs in rabbits: Aorta copper concentrations negatively correlate with the severity of atherosclerotic lesions. *Biological trace element research*, pages 164–171, 03 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/33661473/>, doi:10.1007/s12011-021-02618-0.
- [195] Wenjie Li, Ying Zhou, Chunyu Shang, Hui Sang, and Hong Zhu. Effects of environmental ph on the growth of gastric cancer cells. *Gastroenterology Research and Practice*, 03 2020. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7085403/>, doi:10.1155/2020/3245359.
- [196] Steeve Lima, Jorge Matinha-Cardoso, Joaquín Giner-Lamia, Narciso Couto, Catarina C. Pacheco, Francisco J. Florencio, Phillip C. Wright, Paula Tamagnini, and Paulo Oliveira. Extracellular vesicles as an alternative copper-secretion mechanism in bacteria. *Journal of Hazardous Materials*, 431, 06 2022. Available from: <https://doi.org/10.1016/j.jhazmat>.

- 2022.128594, doi:10.1016/j.jhazmat.2022.128594.
- [197] Weiping Lin, Liangliang Xu, and Gang Li. Molecular insights into lysyl oxidases in cartilage regeneration and rejuvenation. *Frontiers in Bioengineering and Biotechnology*, 04 2020. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7204390/>, doi:10.3389/fbioe.2020.00359.
- [198] Guangmang Liu, Weixiao Sun, Fang Wang, Gang Jia, Hua Zhao, Xiaoling Chen, Gang Tian, Jingyi Cai, and Jing Wang. Dietary tryptophan supplementation enhances mitochondrial function and reduces pyroptosis in the spleen and thymus of piglets after lipopolysaccharide challenge. *animal*, 17, 03 2023. Available from: <https://doi.org/10.1016/j.animal.2023.100714>, doi:10.1016/j.animal.2023.100714.
- [199] Huiruo Liu, Zeyu Yang, Hourong Sun, Zerui Wang, Feng Xu, Yuguo Chen, and Chuanbao Li. Iron deficiency promotes intra-leaflet haemorrhage-induced aortic valve calcification: an experimental study. *International journal of surgery (London, England)*, 12 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39728514/>, doi:10.1097/JJS.0000000000002208.
- [200] Jiao Liu, Yang Liu, Yuan Wang, Rui Kang, and Daolin Tang. Hmgb1 is a mediator of cuproptosis-related sterile inflammation. *Frontiers in Cell and Developmental Biology*, 10, 2022. Available from: <https://www.frontiersin.org/articles/10.3389/fcell.2022.996307>, doi:10.3389/fcell.2022.996307.
- [201] Luke L. Liu, Richard M. van Rijn, and Wei Zheng. Copper modulates adult neurogenesis in brain subventricular zone. *International Journal of Molecular Sciences*, 08 2022. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9456150/>, doi:10.3390/ijms23179888.
- [202] Xiao-Chen Liu and Leif H. Skibsted. Citrate in calcium transport and biominerallisation. *International Dairy Journal*, 139, 04 2023. Available from: <https://doi.org/10.1016/j.idairyj.2022.105561>, doi:10.1016/j.idairyj.2022.105561.
- [203] Yun Liu and Ji Miao. An emerging role of defective copper metabolism in heart disease. *Nutrients*, 02 2022. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8838622/>, doi:10.3390/nu14030700.
- [204] Zhidong Liu, Miao Wang, Chunbo Zhang, Shigao Zhou, and Guang Ji. Molecular functions of ceruloplasmin in metabolic disease pathology. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, Volume 15, 03 2022. Available from: <https://doi.org/10.2147/dmso.s346648>, doi:10.2147/dmso.s346648.
- [205] Zhidong Liu, Miao Wang, Chunbo Zhang, Shigao Zhou, and Guang Ji. Molecular functions of ceruloplasmin in metabolic disease pathology. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, pages 695–711, 03 2022. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8901420/>, doi:10.2147/DMSO.S346648.
- [206] Maria N Lo, Leah J Damon, Jian Wei Tay, Shang Jia, Amy E Palmer, Tong Xiao, Cheri M Ackerman, Elizabeth C Carroll, Shang Jia, Adam Hoagland, Jefferson Chan, Bao Thai, Christine S Liu, Ehud Y Isacoff, and Christopher J Chang. Single cell analysis reveals multiple requirements for zinc in the mammalian cell cycle.copper regulates rest-activity cycles through the locus coeruleus-norepinephrine system. *eLifeNature chemical biology*, pages 655–63, 06 2018. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6008210/>, doi:10.1038/s41589-018-0062-z.
- [207] Marta López-Alonso and Marta Miranda. Copper supplementation, a challenge in cattle. *Animals*, 10, 10 2020. Available from: <https://doi.org/10.3390/ani10101890>, doi:10.3390/ani10101890.
- [208] Mark A. Lovell, Chengsong Xie, and William R. Markesberry. Protection against amyloid beta peptide toxicity by zinc. *Brain Research*, 823, 1999. Available from: [http://dx.doi.org/10.1016/s0006-8993\(99\)01114-2](http://dx.doi.org/10.1016/s0006-8993(99)01114-2), doi:10.1016/s0006-8993(99)01114-2.
- [209] Marta Lpez-Alonso and Marta Miranda. Copper supplementation, a challenge in cattle. *Animals : an Open Access Journal from MDPI*, 10 2020. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7602799/>, doi:10.3390/ani10101890.
- [210] Jing Lu, Xue Liu, Xinghua Li, Hongyan Li, Liwa Shi, Xin Xia, Bai-liang He, Thomas F. Meyer, Xiaofeng Li, Hongzhe Sun, and Ximeng Yang. Copper regulates the host innate immune response against bacterial infection via activation of alpk1 kinase. *Proceedings of the National Academy of Sciences*, 121, 01 2024. Available from: <https://doi.org/10.1073/pnas.2311630121>, doi:10.1073/pnas.2311630121.
- [211] H. Lüdke and F. Schöne. Copper and iodine in pig diets with high glucosinolate rapeseed meal. i. performance and thyroid hormone status of growing pigs fed on a diet with rapeseed meal treated with copper sulphate solution or untreated and supplements of iodine, copper or a quinoxaline derivative. *Animal Feed Science and Technology*, 22, 11 1988. Available from: [https://doi.org/10.1016/0377-8401\(88\)90072-7](https://doi.org/10.1016/0377-8401(88)90072-7), doi:10.1016/0377-8401(88)90072-7.
- [212] Henry C. Lukaski, Clinton B. Hall, and Martin J. Marchello. Body temperature and thyroid hormone metabolism of copper-deficient rats. *The Journal of Nutritional Biochemistry*, 6, 1995. Available from: [http://dx.doi.org/10.1016/0955-2863\(95\)00062-5](http://dx.doi.org/10.1016/0955-2863(95)00062-5), doi:10.1016/0955-2863(95)00062-5.
- [213] Yu Luo, Robert J Lovelett, J Vincent Price, Devesh Radhakrishnan, Kristopher Barnthouse, Ping Hu, Eugene Schaefer, John Cunningham, Kelvin H Lee, Raghunath B Shivappa, and Babatunde A Ogunnaike. Modeling the effect of amino acids and copper on monoclonal antibody productivity and glycosylation: A modular approach. *Biotechnology journal*, page e2000261, 09 2020. Available from: <https://pubmed.ncbi.nlm.nih.gov/32875683/>, doi:10.1002/biot.202000261.
- [214] Naina Pakkhir Maideen. Adverse effects associated with long-term use of proton pump inhibitors. *Chonnam Medical Journal*, pages 115–27, 05 2023. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10248387/>, doi:10.4068/cmj.2023.59.2.115.
- [215] Didier Malamba-Lez, Désiré Tshala-Katumbay, Virginie Bito, Jean-Michel Rigo, Richie Kipenge Kyandabike, Eric Ngoy Yolola, Philippe Katchunga, Béatrice Koba-Bora, and Dophra Ngoy-Nkulu. Concurrent heavy metal exposures and idiopathic dilated cardiomyopathy: A case-control study from the katanga mining area of the democratic republic of congo. *International Journal of Environmental Research and Public Health*, 18, 2021. Available from: <http://dx.doi.org/10.3390/ijerph18094956>, doi:10.3390/ijerph18094956.

- [216] Alain Manceau and Anthony Matynia. The nature of cu bonding to natural organic matter. *Geochimica et Cosmochimica Acta*, 74, 05 2010. Available from: <https://doi.org/10.1016/j.gca.2010.01.027>, doi:10.1016/j.gca.2010.01.027.
- [217] Pravat K Mandal, Joseph C Maroon, Avantika Samkaria, Yashika Arora, Shallu Sharma, and Ashutosh Pandey. Iron chelators and alzheimer's disease clinical trials. *Journal of Alzheimer's disease : JAD*, 07 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39031369/>, doi:10.3233/JAD-240605.
- [218] Mike J Marchywka. The paradox paradigm: When could amino acid supplements be beneficial? techreport MJM-2021-015, not institutionalized, independent, 306 Charles Cox , Canton GA 30115, 12 2021. Available from: https://www.researchgate.net/publication/357250784_The_Paradox_Paradigm_When_Could_Amino_Acid_Supplements_Be_Beneficial.
- [219] Mike J Marchywka. Update to covid-19 age distribution notes. Technical Report MJM-2021-007, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, 8 2021. Version .1, may change significantly if less than 1.00. Available from: https://www.researchgate.net/publication/353946686_Draft_table_comparing_expectations_to_recent_results_with_covid-19.
- [220] Mike J Marchywka. Clinical and microbiological improvement in dog after metal and benzoate containing supplement mix. techreport MJM-2022-013, not institutionalized, independent, 44 Crosscreek Trail, Jasper GA 30143, 11 2022. Available from: <https://zenodo.org/record/7293723#.Y2WaP3XMLCI>, doi:10.5281/zenodo.7293723.
- [221] Mike J Marchywka. Experiences with a family of science based kitchen snacks for dogs. techreport MJM-2021-018, not institutionalized, independent, 306 Charles Cox , Canton GA 30115, 1 2022. Available from: https://www.researchgate.net/publication/357517852_Experiences_with_a_Family_of_Science_Based_Kitchen_Snacks_for_Dogs.
- [222] Mike J Marchywka. Happy again : Possible canine riboflavin deficiency. techreport MJM-2022-009, not institutionalized, independent, 306 Charles Cox , Canton GA 30115, 3 2022. Available from: https://www.researchgate.net/publication/359504498_Happy_Again_Possible_Canine_Riboflavin_Deficiency.
- [223] Mike J Marchywka. No improvement in cataracts with diet. techreport MJM-2022-002, not institutionalized, independent, 306 Charles Cox , Canton GA 30115, 1 2022. Available from: https://www.researchgate.net/publication/357606003_No_improvement_in_a_dog_with_cataracts.
- [224] Mike J Marchywka. Vitamin d: Towards a conflict resolving hypothesis. techreport MJM-2022-010, not institutionalized, independent, 306 Charles Cox , Canton GA 30115, 7 2022. Available from: https://www.researchgate.net/publication/362303875_Vitamin_D_Towards_A_Conflict_Resolving_Hypothesis, doi:10.5281/zenodo.6922402.
- [225] Mike J Marchywka. Brain microbiome : Make your garden grow? feed your head. techreport MJM-2023-008, not institutionalized, independent, 44 Crosscreek Trail, Jasper GA 30143, 10 2023. Available from: https://www.researchgate.net/publication/374946157_potuse-2023-10-24-v3, doi:10.5281/zenodo.10038912.
- [226] Mike J Marchywka. Recent vitamin k literature in the conext of a non-monotonic response curve : Local vs global optima and other speculation. techreport MJM-2022-015, not institutionalized, independent, 44 Crosscreek Trail Jasper GA 30143, 1 2023. Available from: https://www.researchgate.net/publication/366642398_Recent_Vitamin_K_Literature_in_the_Conext_of_a_non-Monotonic_Response_Curve_Local_vs_Global_Optima_and_other_Speculation, doi:10.13140/RG.2.2.34218.29124.
- [227] M.J. Marchywka. On the age distribution of sars-cov-2 patients. Technical Report MJM-2020-002-0.10, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, 7 2020. Version 0.10 , may change significantly if less than 1.00. Available from: <https://www.linkedin.com/posts/marchywka-notes-on-aging-as-it-relates-to-covid19-activity-6684083706170265601-JMnN>.
- [228] M.J. Marchywka. Supplement history for a senior hypothyroid chihuahua. Technical Report MJM-2020-007, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, 12 2020. Version 0.50 , may change significantly if less than 1.00. Available from: https://www.researchgate.net/publication/355493547_Supplement_History_for_a_Senior_Hypothyroid_Chihuahua.
- [229] M.J. Marchywka. Canine heartworm treated with doxycycline, ivermectin and various supplements. Technical Report MJM-2019-001, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, March 2021. May be recycled in appropriate media. Available from: <https://www.linkedin.com/posts/marchywka-happyheart-activity-6781666969885167616--HfQ>.
- [230] M.J. Marchywka. Canine heartworm treated with doxycycline, ivermectin and various supplements. Technical Report MJM-2019-001, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, March 2021. May be recycled in appropriate media. Available from: https://www.researchgate.net/publication/350442384_Canine_Heartworm_Treated_with_Doxycycline_Ivermectin_and_Various_Supplements.
- [231] M.J. Marchywka. Muqed: a multi-use quantitative event diary for dog diet analysis. Technical Report MJM-2020-004, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, April 2021. May be recycled in appropriate media. Available from: https://www.researchgate.net/publication/350636753_MUQED_a_Multi-Use_Quantitative_Event_Diary_For_Dog_Diet_Analysis.
- [232] M.J. Marchywka. Supplement usage including vitamin k by a heartworm positive pregnant pit bull and her puppies. Technical Report MJM-2021-003, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, 05 2021. Version 0.50 , may change significantly if less than 1.00. Available from: https://www.researchgate.net/publication/354924460_Supplement_Usage_Including_Vitamin_K_by_a_Heartworm_Positive_Pregnant_Pit_Bull_and_Her_Puppies.
- [233] Elizabeth A. Marcus and David R. Scott. *Gastric Colonization by H. pylori*, pages 25–37. Springer Nature Singapore, Singapore, 2023. Available from: https://doi.org/10.1007/978-981-97-0013-4_2.

- [234] B Marelli, Nihouannen D Le, SA Hacking, S Tran, J Li, M Murshed, CJ Doillon, CE Ghezzi, YL Zhang, SN Nazhat, and JE Barralet. Newly identified interfibrillar collagen crosslinking suppresses cell proliferation and remodelling. *Biomaterials*, 54:126–35, 2015. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/articles/25907046/>.
- [235] Edward B. Maryon, Shannon A. Molloy, Kristin Ivy, Huijun Yu, and Jack H. Kaplan. Rate and regulation of copper transport by human copper transporter 1 (hctr1)*. *The Journal of Biological Chemistry*, pages 18035–46, 05 2013. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3689948/>, doi:10.1074/jbc.M112.442426.
- [236] Shashank Masaldan, Sharnel A.S. Clatworthy, Cristina Gamell, Zoe M. Smith, Paul S. Francis, Delphine Denoyer, Peter M. Meggyesy, Sharon La Fontaine, and Michael A. Cater. Copper accumulation in senescent cells: Interplay between copper transporters and impaired autophagy. *Redox Biology*, 16, 2018. Available from: <http://dx.doi.org/10.1016/j.redox.2018.03.007>, doi:10.1016/j.redox.2018.03.007.
- [237] Mary S. Matsui, Michael J. Petris, Yoko Niki, Nevena Karaman-Jurukovska, Neelam Muizzuddin, Masamitsu Ichihashi, and Daniel B. Yarosh. Omeprazole, a gastric proton pump inhibitor, inhibits melanogenesis by blocking atp7a trafficking. *Journal of Investigative Dermatology*, 135, 03 2015. Available from: <http://dx.doi.org/10.1038/jid.2014.461>, doi:10.1038/jid.2014.461.
- [238] Sydney R McCauley, Stephanie D Clark, Bradley W Quest, Renee M Streeter, and Eva M Oxford. Review of canine dilated cardiomyopathy in the wake of diet-associated concerns. *Journal of Animal Science*, 98(6):skaa155, 06 2020. Available from: <https://doi.org/10.1093/jas/skaa155>, arXiv:<https://academic.oup.com/jas/article-pdf/98/6/skaa155/33683311/skaa155.pdf>, doi:10.1093/jas/skaa155.
- [239] William Douglas McFarlane, Hugh Lehman Fulmer, and Thomas Hughes Jukes. Studies in embryonic mortality in the chick: The effect of diet upon the nitrogen, amino-nitrogen, tyrosine, tryptophan, cystine and iron content of the proteins and on the total copper of the hen's egg. *Biochemical Journal*, pages 1611–31, 1930. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1254774/pdf/biochemj01123-0023.pdf>.
- [240] Catherine C. McGowan, Timothy L. Cover, and Martin J. Blaser. The proton pump inhibitor omeprazole inhibits acid survival of helicobacter pylori by a urease-independent mechanism. *Gastroenterology*, 107, 11 1994. Available from: [https://dx.doi.org/10.1016/0016-5085\(94\)90582-7](https://dx.doi.org/10.1016/0016-5085(94)90582-7), doi:10.1016/0016-5085(94)90582-7.
- [241] Kathryn A. McGurk, Melpomeni Kasapi, and James S. Ware. Effect of taurine administration on symptoms, severity, or clinical outcome of dilated cardiomyopathy and heart failure in humans: a systematic review. *Wellcome Open Research*, 07 2022. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9257265/>, doi:10.12688/wellcomeopenres.17505.3.
- [242] D. M. Medeiros, J. Davidson, and J. E. Jenkins. A unified perspective on copper deficiency and cardiomyopathy. *Experimental Biology and Medicine*, 203, 07 1993. Available from: <http://dx.doi.org/10.3181/00379727-203-43599>, doi:10.3181/00379727-203-43599.
- [243] Denis M. Medeiros and Dianne Jennings. Role of copper in mitochondrial biogenesis via interaction with atp synthase and cytochrome c oxidase. *Journal of Bioenergetics and Biomembranes*, 34(5):389–395, Oct 2002. Available from: <https://doi.org/10.1023/A:1021206220851>, doi:10.1023/A:1021206220851.
- [244] Denis M Medeiros and Dianne Jennings. Role of copper in mitochondrial biogenesis via interaction with atp synthase and cytochrome c oxidase. *Journal of bioenergetics and biomembranes*, pages 389–95, Oct 2002. Available from: <https://pubmed.ncbi.nlm.nih.gov/12539966/>, doi:10.1023/a:1021206220851.
- [245] Raktham Mektrirat, Thareerat Rueangsri, Waraporn Keeratichandacha, Sasiwimon Soonsawat, Chavalit Boonyapakorn, and Wanpitak Pongkan. Polyunsaturated fatty acid eab-277 supplementation improved heart rate variability and clinical signs in tracheal collapse dogs. *Frontiers in Veterinary Science*, 07 2022. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9330478/>, doi:10.3389/fvets.2022.880952.
- [246] Jin-Hong Min, Heela Sarlus, and Robert A. Harris. Copper toxicity and deficiency: the vicious cycle at the core of protein aggregation in als. *Frontiers in Molecular Neuroscience*, 17, 2024. Available from: <https://www.frontiersin.org/journals/molecular-neuroscience/articles/10.3389/fnmol.2024.1408159>, doi:10.3389/fnmol.2024.1408159.
- [247] Jin-Hong Min, Heela Sarlus, and Robert A Harris. Mad-microbial (origin of) alzheimer's disease hypothesis: from infection and the antimicrobial response to disruption of key copper-based systems. *Frontiers in neuroscience*, page 1467333, 10 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39416952/>, doi:10.3389/fnins.2024.1467333.
- [248] Jens Mittag, Thomas Behrends, Kristina Nordström, Joao Anselmo, Björn Vennström, and Lutz Schomburg. Serum copper as a novel biomarker for resistance to thyroid hormone. *Biochemical Journal*, 443, 04 2012. Available from: <https://doi.org/10.1042/bj20111817>, doi:10.1042/bj20111817.
- [249] Neetu Mohan, Trevor Alleyne, Jerome Joseph, and Andrew Adogwa. Low activity and poor membrane tethering for rabbit brain cytochrome c oxidase in cholesterol-copper alzheimer's model. *Journal of Molecular Neuroscience*, 38(3):273–279, Jul 2009. Available from: <https://doi.org/10.1007/s12031-009-9209-4>, doi:10.1007/s12031-009-9209-4.
- [250] Matthew Mold, Larissa Ouro-Gnao, Beata M Wieckowski, and Christopher Exley. Copper prevents amyloid-upbeta1-42 from forming amyloid fibrils under near-physiological conditions in vitro. *Scientific Reports*, 3, 02 2013. Available from: <https://www.nature.com/articles/srep01256>, doi:10.1038/srep01256.
- [251] Arash Momeni and Mark Joseph Filiaggi. Rheology of polyphosphate coacervates. *Journal of Rheology*, 60, 01 2016. Available from: <https://doi.org/10.1122/1.4935127>, doi:10.1122/1.4935127.
- [252] V Moreaux, I Birlouez-Aragon, and C Ducauze. Copper chelation by tryptophan inhibits the copper-ascorbate oxidation of tryptophan. *Redox report : communications in free radical research*, pages 191–7, Jun 1996. Available from: <https://pubmed.ncbi.nlm.nih.gov/27406076/>, doi:10.1080/13510002.1996.11747048.
- [253] R. F. Morgan and B. L. O'Dell. Effect of copper deficiency on the concentrations of catecholamines and related enzyme activities in the rat BRAIN¹. *Journal of Neurochemistry*, 28, 1977. Available from: <http://dx.doi.org/10.1111/j.1471-4158.1977.tb04111.x>

- 1471-4159.1977.tb07728.x, doi:10.1111/j.1471-4159.1977.tb07728.x.
- [254] Austin Morrell, Savannah Tallino, Lei Yu, and Jason L. Burkhead. The role of insufficient copper in lipid synthesis and fatty-liver disease. *IUBMB life*, pages 263–70, 03 2017. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5619695/>, doi:10.1002/iub.1613.
- [255] A Mudher and S Lovestone. Alzheimer's disease-do tauists and baptists finally shake hands? *Trends in neurosciences*, 25(1):22–6, 2002. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/articles/11801334/>.
- [256] Y Mukai, H Wada, H Eguchi, D Yamada, T Asaoka, T Noda, K Kawamoto, K Gotoh, Y Takeda, M Tanemura, K Umeshita, Y Hori, E Morii, Y Doki, and M Mori. Intrahepatic cholangiocarcinoma in a patient with wilson's disease: a case report. *Surgical Case Reports*, 2, 2016. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4803712/>.
- [257] Mitsutoshi Munakata, Osamu Sakamoto, Taro Kitamura, Mamiko Ishitobi, Hiroyuki Yokoyama, Kazuhiro Hagiwara, Noriko Togashi, Hajime Tamura, Shuichi Higano, Shoki Takahashi, Toshihiro Ohura, Yasuko Kobayashi, Akira Onuma, and Kazuie Iinuma. The effects of copper-histidine therapy on brain metabolism in a patient with menkes disease: a proton magnetic resonance spectroscopic study. *Brain and Development*, 27, 2005. Available from: <http://dx.doi.org/10.1016/j.braindev.2004.08.002>.
- [258] Izumi NAKAI, Mihoko IZAWA, Yoshinori SUGITANI, Yoshio NIWA, and Kozo NAGASHIMA. X-ray photoelectron spectroscopic study of copper minerals. *Mineralogical Journal*, 8(2):135–138, 1976. Available from: https://www.jstage.jst.go.jp/article/minerj/8/2/8_2_135/_pdf, doi:10.2465/minerj.8.135.
- [259] Takeo Nakanishi, Yuki Kawasaki, Yoshinobu Nakamura, Yuuki Kimura, Kotone Kawamura, Melody N. Shumba, and Noriaki Shimokawa. An implication of the mitochondrial carrier slc25a3 as an oxidative stress modulator in nafld. *Experimental Cell Research*, 431, 10 2023. Available from: <https://doi.org/10.1016/j.yexcr.2023.113740>, doi:10.1016/j.yexcr.2023.113740.
- [260] I Naseem, M S Ahmed, R Bhat, and S M Hadi. Cu(ii)-dependent degradation of dna by riboflavin. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association*, pages 589–97, Aug 1993. Available from: <https://pubmed.ncbi.nlm.nih.gov/8349205/>, doi:10.1016/0278-6915(93)90209-h.
- [261] Ethan A. Natelson, Kelty R. Baker, and David W. Pyatt. Anemia and leukopenia following intravenous colloidal silver infusionsclinical and hematological features, unique peripheral blood film appearance and effective therapy with supplemental oral copper and apheresis. *Clinical Case Reports*, 7, 2019. Available from: <http://dx.doi.org/10.1002/ccr3.2316>, doi:10.1002/ccr3.2316.
- [262] Abigail L. Needleman, Megan C. Wright, John J. Schaefer, Ricardo Videla, and Andrea S. Lear. Copper oxide wire particles effective against gastrointestinal nematodes in adult alpacas during a randomized clinical trial. *American Journal of Veterinary Research*, 83, 11 2022. Available from: <https://doi.org/10.2460/ajvr.22.07.0115>, doi:10.2460/ajvr.22.07.0115.
- [263] New Hope Network. Top 100 supplements by 2023 u.s. sales. *Top 100 Supplements by 2023 U.S. Sales*. Available from: <https://store.newhope.comandhttps://store.newhope.comandhttps://store.newhope.com/products/chart-top-100-supplements-by-us-sales>.
- [264] Hoai Thanh Nguyen, Sarbast K. Kheravii, Shu-biao Wu, Julie R. Roberts, Robert A. Swick, and Mehdi Toghyani. Sources and levels of copper affect liver copper profile, intestinal morphology and cecal microbiota population of broiler chickens fed wheat-soybean meal diets. *Scientific Reports*, 12, 02 2022. Available from: <https://www.nature.com/articles/s41598-022-06204-9>, doi:10.1038/s41598-022-06204-9.
- [265] Ning Ning, Dengfeng Gao, Vincenzo Triggiani, Massimo Iacoviello, Judith E. Mitchell, Rui Ma, Yan Zhang, and Huijuan Kou. Prognostic role of hypothyroidism in heart failure: A meta-analysis. *Medicine*, 07 2015. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4554113/>, doi:10.1097/MD.0000000000001159.
- [266] Julia E. Niskanen, sa Ohlsson, Ingrid Ljungvall, Michaela Drgemller, Robert F. Ernst, Dennis Dooijes, Hanneke M. van Deutekom, J. Peter van Tintelen, Christian B. Snijders Blok, Marion van Vugt, Jessica van Setten, Folkert W. Asselbergs, Aleksandra Domanjko Petri, Milla Salonen, Sruthi Hundt, Matthias Hrtenhuber, Juha Kere, W. Glen Pyle, Jonas Donner, Alex V. Postma, Tosso Leeb, Gran Andersson, Marjo K. Hytnen, Jens Hggstrm, Maria Wiberg, Jana Friederich, Jenny Eberhard, Magdalena Harakalova, Frank G. van Steenbeek, Gerhard Wess, and Hannes Lohi. Identification of novel genetic risk factors of dilated cardiomyopathy: from canine to human. *Genome Medicine*, 09 2023. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10506233/>, doi:10.1186/s13073-023-01221-3.
- [267] Yasuhiro Nose, Byung-Eun Kim, and Dennis J. Thiele. Ctr1 drives intestinal copper absorption and is essential for growth, iron metabolism, and neonatal cardiac function. *Cell Metabolism*, 4, 2006. Available from: <http://dx.doi.org/10.1016/j.cmet.2006.08.009>, doi:10.1016/j.cmet.2006.08.009.
- [268] Yasuhiro Nose and Dennis J Thiele. Mechanism and regulation of intestinal copper absorption. *Genes & Nutrition*, 5, 2010. Available from: <http://dx.doi.org/10.1007/s12263-010-0202-x>, doi:10.1007/s12263-010-0202-x.
- [269] BL O'Dell. Fructose and mineral metabolism. *The American Journal of Clinical Nutrition*, 58, 1993. Available from: <http://dx.doi.org/10.1093/ajcn/58.5.771s>, doi:10.1093/ajcn/58.5.771s.
- [270] BL O'Dell, KH Kilburn, WN McKenzie, and RJ Thurston. The lung of the copper-deficient rat. a model for developmental pulmonary emphysema. *The American Journal of Pathology*, 91(3):413–32, 1978. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2018314/>.
- [271] A Ogita, K Hirooka, Y Yamamoto, N Tsutsui, K Fujita, M Taniguchi, and T Tanaka. Synergistic fungicidal activity of cu(2+) and allicin, an allyl sulfur compound from garlic, and its relation to the role of alkyl hydroperoxide reductase 1 as a cell surface defense in saccharomyces cerevisiae. *Toxicology*, 215(3):205–13, 2005. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/articles/16102883/>.
- [272] Michael Okafor, Paulina Gonzalez, Pascale Ronot, Islah El Masoudi, Anne Boos, Stéphane Ory, Sylvette Chasserot-Golaz,

- Stéphane Gasman, Laurent Raibaut, Christelle Hureau, Nicolas Vitale, and Peter Fallar. Development of cu(ii)-specific peptide shuttles capable of preventing cu-amylloid beta toxicity and importing bioavailable cu into cells. *Chem. Sci.*, 13:11829–11840, 2022. Available from: <http://dx.doi.org/10.1039/D2SC02593K>, doi:10.1039/D2SC02593K.
- [273] Gilbert S. Omenn, Gary E. Goodman, Mark D. Thornquist, John Balmes, Mark R. Cullen, Andrew Glass, James P. Keogh, Frank L. Jr. Meyskens, Barbara Valanis, James H. Jr. Williams, Scott Barnhart, and Samuel Hammar. Effects of a combination of beta carotene and vitamin a on lung cancer and cardiovascular disease. *New England Journal of Medicine*, 334(18):1150–1155, 1996. PMID: 8602180. Available from: <http://dx.doi.org/10.1056/NEJM199605023341802>, arXiv: <http://dx.doi.org/10.1056/NEJM199605023341802>, doi:10.1056/NEJM199605023341802.
- [274] Dan G. O'Neill, Janine Pheng Khoo, Dave C. Brodbelt, David B. Church, Camilla Pegram, and Rebecca F. Geddes. Frequency, breed predispositions and other demographic risk factors for diagnosis of hypothyroidism in dogs under primary veterinary care in the uk. *Canine Medicine and Genetics*, 10 2022. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9552398/>, doi:10.1186/s40575-022-00123-8.
- [275] Michael H. Overholtzer, Peter S. Yakowec, and Vicki Cameron. The effect of amino acid substitutions in the conserved aromatic region of subunit ii of cytochrome c oxidase in *saccharomyces cerevisiae*. *Journal of Biological Chemistry*, 271, 03 1996. Available from: <https://doi.org/10.1074/jbc.271.13.7719>, doi:10.1074/jbc.271.13.7719.
- [276] Ruixin Pang, Kajjing Liu, Biou Liu, and Jing Yang. Enhancement of adipose stem cell quality via cumon: Transcriptome and bioinformatics analysis of normal and diabetic stem cells. *FASEB BioAdvances*, 01 2025. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11886605/>, doi:10.1096/fba.2024-00153.
- [277] Y. Pang and T.J. Applegate. Effects of dietary copper supplementation and copper source on digesta ph, calcium, zinc, and copper complex size in the gastrointestinal tract of the broiler chicken. *Poultry Science*, 86, 2007. Available from: <http://dx.doi.org/10.1093/ps/86.3.531>, doi:10.1093/ps/86.3.531.
- [278] Erwin Jongwoo Park, Ki-Myeong Lee, Taewan Kim, Donghyun Lee, Min Sik Kim, and Changha Lee. Trivalent copper ion-mediated dual oxidation in the copper-catalyzed fenton-like system in the presence of histidine. *Environmental Science & Technology*, 58, 06 2024. Available from: <http://dx.doi.org/10.1021/acs.est.4c03689>, doi:10.1021/acs.est.4c03689.
- [279] Tony Peled, Efrat Landau, Eugenia Prus, Abraham J Treves, Arnon Nagler, and Eitan Fibach. Cellular copper content modulates differentiation and self-renewal in cultures of cord blood-derived cd34+ cells. *British journal of haematology*, pages 655–61, Mar 2002. Available from: <https://pubmed.ncbi.nlm.nih.gov/11849228/>, doi:10.1046/j.0007-1048.2001.03316.x.
- [280] Jianbiao Peng, Chaonan Zhang, Ya Zhang, Dong Miao, Yaozong Zhang, Haijin Liu, Jinghua Li, Lei Xu, Jialu Shi, Guoguang Liu, and Shixiang Gao. Enhanced cu(ii)-mediated fenton-like oxidation of antimicrobials in bicarbonate aqueous solution: Kinetics, mechanism and toxicity evaluation. *Environmental Pollution*, 252, 09 2019. Available from: <http://dx.doi.org/10.1016/j.envpol.2019.05.148>, doi:10.1016/j.envpol.2019.05.148.
- [281] Ana Margarida Pereira, Margarida G. Maia, Antnio Mira Fonseca, and Ana Jordo Cabrita. Zinc in dog nutrition, health and disease: A review. *Animals : an Open Access Journal from MDPI*, 04 2021. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8066201/>, doi:10.3390/ani11040978.
- [282] A. Ninh Pham, Guowei Xing, Christopher J. Miller, and T. David Waite. Fenton-like copper redox chemistry revisited: Hydrogen peroxide and superoxide mediation of copper-catalyzed oxidant production. *Journal of Catalysis*, 301, 05 2013. Available from: <http://dx.doi.org/10.1016/j.jcat.2013.01.025>, doi:10.1016/j.jcat.2013.01.025.
- [283] Katharina F. Pirker, Maria Camilla Baratto, Riccardo Basosi, and Bernard A. Goodman. Influence of ph on the speciation of copper(ii) in reactions with the green tea polyphenols, epigallocatechin gallate and gallic acid. *Journal of Inorganic Biochemistry*, pages 10–6, Jul 2012. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3401972/>, doi:10.1016/j.jinorgbio.2011.12.010.
- [284] Marcello Polesel, Alvaro Ingles-Prieto, Eirini Christodoulaki, Evandro Ferrada, Cédric Doucerain, Patrick Alternatt, Michelle Knecht, Michael Kuhn, Anna-Lena Steck, Maria Wilhelm, and Vania Manolova. Functional characterization of slc39 family members zip5 and zip10 in overexpressing hek293 cells reveals selective copper transport activity. *BioMetals*, 36(1):227–237, Feb 2023. Available from: <https://doi.org/10.1007/s10534-022-00474-6>, doi:10.1007/s10534-022-00474-6.
- [285] Elena V Polishchuk and Roman S Polishchuk. The emerging role of lysosomes in copper homeostasis. *Metalomics*, 8(9):853–862, 06 2016. Available from: <https://doi.org/10.1039/c6mt00058d>, arXiv:<https://academic.oup.com/metalomics/article-pdf/8/9/853/34735754/c6mt00058d.pdf>, doi:10.1039/c6mt00058d.
- [286] K Porter, L Hoey, CF Hughes, M Ward, and H McNulty. Causes, consequences and public health implications of low b-vitamin status in ageing. *Nutrients*, 8(11), 2016. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5133110/>.
- [287] T. J. Prince, V. W. Hays, and G. L. Cromwell. Interactive effects of dietary calcium, phosphorus and copper on performance and liver stores of pigs. *Journal of Animal Science*, 58, 02 1984. Available from: <https://doi.org/10.2527/jas1984.582356x>, doi:10.2527/jas1984.582356x.
- [288] K-Raman Purushothaman, Meeranari Purushothaman, Irene C. Turnbull, David H. Adams, Anelechi Anyanwu, Prakash Krishnan, Annapoorna Kini, Samin K. Sharma, William N OConnor, and Pedro R. Moreno. Association of altered collagen content and lysyl oxidase expression in degenerative mitral valve disease. *Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology*, pages 11–8, 04 2017. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541772/>, doi:10.1016/j.carpath.2017.04.001.
- [289] C Rachman-Tzemah, S Zaffryar-Eilot, M Grossman, D Ribero, M Timaner, JM Mäki, J Myllyharju, F Bertolini, D Herskovitz, I Sagi, P Hasson, and Y Shaked. Blocking surgically induced lysyl oxidase activity reduces the risk of lung metas-

- tases. *Cell Reports*, 19(4):774–84, 2017. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5413586/>.
- [290] Sara Raia, Antonio Conti, Alan Zanardi, Barbara Ferrini, Giulia Maria Scotti, Enrica Gilberti, Giuseppe De Palma, Samuel David, and Massimo Alessio. Ceruloplasmin-deficient mice show dysregulation of lipid metabolism in liver and adipose tissue reduced by a protein replacement. *International Journal of Molecular Sciences*, 24, 2023. Available from: <http://dx.doi.org/10.3390/ijms24021150>, doi:10.3390/ijms24021150.
- [291] Perungavur N. Ranganathan, Yan Lu, Lingli Jiang, Changae Kim, and James F. Collins. Serum ceruloplasmin protein expression and activity increases in iron-deficient rats and is further enhanced by higher dietary copper intake. *Blood*, 118, 09 2011. Available from: <http://dx.doi.org/10.1182/blood-2011-05-352112>, doi:10.1182/blood-2011-05-352112.
- [292] Chinmaya Sundar Ray, Bratati Singh, Itishri Jena, Sudeshna Behera, and Subhashree Ray. Low alkaline phosphatase (alp) in adult population an indicator of zinc (zn) and magnesium (mg) deficiency. *Current Research in Nutrition and Food Science Journal*, 5. Available from: <http://dx.doi.org/10.12944/crnfsj.5.3.20>, doi:10.12944/crnfsj.5.3.20.
- [293] Anna Reid, Christopher Miller, John Peter Farrant, Rahul Polturi, David Clark, Simon Ray, Garth Cooper, and Matthias Schmitt. Copper chelation in patients with hypertrophic cardiomyopathy. *Open Heart*, 9(1), 2022. Available from: <https://openheart.bmj.com/content/9/1/e001803>, arXiv:<https://openheart.bmj.com/content/9/1/e001803.full.pdf>, doi:10.1136/openhrt-2021-001803.
- [294] Carla Juliana Ribeiro Dolenga, Alan dos Anjos, Eduardo José Arruda, and Marcelo Beltrão Molento. Copper chloride and copper sulphate in combination with nitroxynil against gastrointestinal nematodes of ruminants: A possible hitchhiking synergic effect at low concentrations. *International Journal for Parasitology*, 53, 03 2023. Available from: <https://doi.org/10.1016/j.ijpara.2022.12.003>, doi:10.1016/j.ijpara.2022.12.003.
- [295] Stewart J. Richmond, Shalmini Gunadasa, Martin Bland, and Hugh MacPherson. Copper bracelets and magnetic wrist straps for rheumatoid arthritis – analgesic and anti-inflammatory effects: A randomised double-blind placebo controlled crossover trial. *PLOS ONE*, 8(9):1–9, 09 2013. Available from: <https://doi.org/10.1371/journal.pone.0071529>, doi:10.1371/journal.pone.0071529.
- [296] WILLIAM W. RILEY and RICHARD E. AUSTIC. Influence of dietary electrolytes on digestive tract ph and acid-base status of chicks. *Poultry Science*, 63, 11 1984. Available from: <https://doi.org/10.3382/ps.0632247>, doi:10.3382/ps.0632247.
- [297] Elise Brochner Rischel, Michael Gejl, Birgitte Brock, Jorgen Rungby, and Albert Gjedde. In alzheimer's disease, amyloid beta accumulation is a protective mechanism that ultimately fails. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, 06 2022. Available from: <https://pubmed.ncbi.nlm.nih.gov/35673950/>, doi:10.1002/alz.12701.
- [298] Alex Rivera-Millot, Stéphanie Slupek, Jonathan Chatagnon, Gauthier Roy, Jean-Michel Saliou, Gabriel Billon, Véronique Alaimo, David Hot, Sophie Salomé-Desnoulez, Camille Locht, Rudy Antoine, and Françoise Jacob-Dubuisson. Streamlined copper defenses make bordetella pertussis reliant on custom-made operon. *Communications Biology*, 4, 01 2021. Available from: <https://www.nature.com/articles/s42003-020-01580-2>, doi:10.1038/s42003-020-01580-2.
- [299] KELLY R. ROBBINS and DAVID H. BAKER. Effect of high-level copper feeding on the sulfur amino acid need of chicks fed corn-soybean meal and purified crystalline amino acid diets. *Poultry Science*, 59, 05 1980. Available from: <http://dx.doi.org/10.3382/ps.0591099>, doi:10.3382/ps.0591099.
- [300] Mariangela Rondanelli, Milena Anna Faliva, Vittoria Infantino, Clara Gasparri, Giancarlo Iannello, Simone Perna, Antonella Riva, Giovanna Petrangolini, Alice Tartara, and Gabriella Peroni. Copper as dietary supplement for bone metabolism: A review. *Nutrients*, 06 2021. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8308383/>, doi:10.3390/nu13072246.
- [301] Luisa Rossi, Giovanna Lippe, Eliana Marchese, Angelo De Martino, Irene Mavelli, Giuseppe Rotilio, and Maria R. Ciriolo. Decrease of cytochrome c oxidase protein in heart mitochondria of copper-deficient rats. *Biometals*, 11(3):207–212, 1998. Available from: <http://dx.doi.org/10.1023/A:1009274131473>, doi:10.1023/A:1009274131473.
- [302] Sander Rozemeijer, Henrike M. Hamer, Annemieke C. Heijboer, Robert de Jonge, Connie R. Jimenez, Nicole P. Juffermans, Romein W. G. Dujardin, Armand R. J. Girbes, and Angélique M. E. de Man. Micronutrient status of critically ill patients with covid-19 pneumonia. *Nutrients*, 16, 2024. Available from: <http://dx.doi.org/10.3390/nu16030385>, doi:10.3390/nu16030385.
- [303] Moisés Rubio-Osornio, Marisol Orozco-Ibarra, Araceli Díaz-Ruiz, Eduardo Brambila, Marie-Catherine Boll, Antonio Monroy-Noyola, Jorge Guevara, Sergio Montes, and Camilo Ríos. Copper sulfate pretreatment prevents mitochondrial electron transport chain damage and apoptosis against mpp+-induced neurotoxicity. *Chemico-Biological Interactions*, 271:1 – 8, 2017. Available from: <http://www.sciencedirect.com/science/article/pii/S0009279717301527>, doi:<http://dx.doi.org/10.1016/j.cbi.2017.04.016>.
- [304] RB Rucker, T Kosonen, MS Clegg, AE Mitchell, BR Rucker, JY Uriu-Hare, and CL Keen. Copper, lysyl oxidase, and extracellular matrix protein cross-linking. *The American Journal of Clinical Nutrition*, 67, 1998. Available from: <http://dx.doi.org/10.1093/ajcn/67.5.996s>, doi:10.1093/ajcn/67.5.996s.
- [305] Lina M. Ruiz, Allan Libedinsky, and Alvaro A. Elorza. Role of copper on mitochondrial function and metabolism. *Frontiers in Molecular Biosciences*, 08 2021. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8421569/>, doi:10.3389/fmolb.2021.711227.
- [306] Karina E. Salinas, Osvaldo Herreros, and Cynthia M. Torres. Leaching of primary copper sulfide ore in chloride-ferrous media. *Minerals*, 8, 08 2018. Available from: <http://dx.doi.org/10.3390/min8080312>, doi:10.3390/min8080312.
- [307] Marie I. Samanovic, Chen Ding, Dennis J. Thiele, and K.Heran Darwin. Copper in microbial pathogenesis: Meddling with the metal. *Cell Host & Microbe*, 11, 02 2012. Available from: <https://doi.org/10.1016/j.chom.2012.01.009>, doi:10.1016/j.chom.2012.01.009.
- [308] Amram SAMUNI, Jacob ARONOVITCH, Dina GODINGER, Mordechai CHEVION, and Gidon CZAPSKI. On the

- cytotoxicity of vitamin c and metal ions. *European Journal of Biochemistry*, 137, 12 1983. Available from: <http://dx.doi.org/10.1111/j.1432-1033.1983.tb07804.x>, doi:10.1111/j.1432-1033.1983.tb07804.x.
- [309] Manu Sánchez, Laura Sabio, Natividad Gálvez, Mercè Capdevila, and Jose M. DominguezVera. Iron chemistry at the service of life. *IUBMB Life*, 69, 06 2017. Available from: <http://dx.doi.org/10.1002/iub.1602>, doi:10.1002/iub.1602.
- [310] Parastoo Saniee, Somayeh Shahreza, and Farideh Siavoshi. Negative effect of protonpump inhibitors (<scp>ppi</scp>s) on *helicobacter pylori* growth, morphology, and urease test and recovery after <scp>ppi</scp> removal - an in vitro study. *Helicobacter*, 21, 04 2016. Available from: <http://dx.doi.org/10.1111/hel.12246>, doi:10.1111/hel.12246.
- [311] Heitor O. Santos, Wilson M.A.M. de Moraes, Guilherme A.R. da Silva, Jonato Prestes, and Brad J. Schoenfeld. Vinegar (acetic acid) intake on glucose metabolism: A narrative review. *Clinical Nutrition ESPEN*, 32, 08 2019. Available from: <https://doi.org/10.1016/j.clnesp.2019.05.008>, doi:10.1016/j.clnesp.2019.05.008.
- [312] LFJ Santos, AM Gonçalves, LM Neira, VS Nakagi, M Macari, AC Laurentiz, and JM Pizauro. Effects of supplementation of zinc, manganese, or copper and different phytase levels in serum and bone acid and alkaline phosphatases of broiler chicks. *Brazilian Journal of Poultry Science*, 25, 2023. Available from: <http://dx.doi.org/10.1590/1806-9061-2022-1722>, doi:10.1590/1806-9061-2022-1722.
- [313] Mark E. Schlesinger, Matthew J. King, Kathryn C. Sole, and William G. Davenport. Hydrometallurgical copper extraction, 2011. Available from: <https://doi.org/10.1016/b978-0-08-096789-9.10015-0>, doi:10.1016/b978-0-08-096789-9.10015-0.
- [314] Karsten E. Schober, Phillip R. Fox, Jonathan Abbott, Etienne Côté, Virginia LuisFuentes, Jose Novo Matos, Joshua A. Stern, Lance Visser, Katherine F. Scollan, Valerie Chetboul, Donald Schrophe, Tony Glaus, Roberto Santilli, Romain Pariaut, Rebecca Stepien, Vanessa ArquedSoubeyran, Marco Baron Toaldo, Amara Estrada, Kristin MacDonald, Emily T. Karlin, and John Rush. Retrospective evaluation of hypertrophic cardiomyopathy in 68 dogs. *Journal of Veterinary Internal Medicine*, 36, 2022. Available from: <http://dx.doi.org/10.1111/jvim.16402>, doi:10.1111/jvim.16402.
- [315] Bernard G. Schreurs. Cholesterol and copper affect learning and memory in the rabbit. *International Journal of Alzheimer's Disease*, 08 2013. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3773440/>, doi:10.1155/2013/518780.
- [316] Bernard G. Schreurs, Carrie A. Smith-Bell, Deya S. Darwish, Desheng Wang, Lauren B. Burhans, Jimena Gonzales-Joekes, Stephen Deci, Goran Stankovic, and D. Larry Sparks. Cholesterol enhances classical conditioning of the rabbit heart rate response. *Behavioural Brain Research*, 181, 07 2007. Available from: <https://doi.org/10.1016/j.bbr.2007.03.024>, doi:10.1016/j.bbr.2007.03.024.
- [317] Bernard G Schreurs and D Larry Sparks. Dietary high cholesterol and trace metals in the drinking water increase levels of abca1 in the rabbit hippocampus and temporal cortex. *Journal of Alzheimer's disease : JAD*, pages 201–9, 2016. Available from: <https://pubmed.ncbi.nlm.nih.gov/26444796/>, doi:10.3233/JAD-150601.
- [318] Daniel Segna, Nele Brusselaers, Damian Glaus, Niklas Krupka, and Benjamin Misselwitz. Association between proton-pump inhibitors and the risk of gastric cancer: a systematic review with meta-analysis. *Therapeutic Advances in Gastroenterology*, 14, 01 2021. Available from: <http://dx.doi.org/10.1177/17562848211051463>, doi:10.1177/17562848211051463.
- [319] M. Alexis Seguin and Susan E. Bunch. Iatrogenic copper deficiency associated with long-term copper chelation for treatment of copper storage disease in a bedlington terrier. *Journal of the American Veterinary Medical Association*, 218, 05 2001. Available from: <http://dx.doi.org/10.2460/javma.2001.218.1593>, doi:10.2460/javma.2001.218.1593.
- [320] Rana M. Selima, Israa A. Saleem, Mamdouh M. Shawki, Amira A. Darwish, Mona A. Yehia, and Ehab I. Mohamed. Effect of gold nanoparticles treatment on rats-induced obesity by evaluating body-composition directly and indirectly via bioelectric impedance analysis. *Scientific Reports*, 15, 02 2025. Available from: <https://www.nature.com/articles/s41598-025-87971-z>, doi:10.1038/s41598-025-87971-z.
- [321] Christian T. Sheline, Eric H. Choi, Jeong-Sook Kim-Han, Laura L. Dugan, and Dennis W. Choi. Cofactors of mitochondrial enzymes attenuate copper-induced death in vitro and in vivo. *Annals of Neurology*, 52(2):195–204, 2002. Available from: <http://dx.doi.org/10.1002/ana.10276>, doi:10.1002/ana.10276.
- [322] Jiaqi Shen, Paul T. Griffiths, Steven J. Campbell, Battist Uttinger, Markus Kalberer, and Suzanne E. Paulson. Ascorbate oxidation by iron, copper and reactive oxygen species: review, model development, and derivation of key rate constants. *Scientific Reports*, 11, 04 2021. Available from: <https://www.nature.com/articles/s41598-021-86477-8>, doi:10.1038/s41598-021-86477-8.
- [323] Shubin Shi, Xu Wei, Xu Peng, Xinyun Pu, Shaoxiong Feng, Xi Gao, and Xixun Yu. An oxidized chondroitin sulfate-crosslinked and cucds-loaded decellularized bovine pericardium with improved anti-coagulation, pro-endothelialization and anti-calcification properties for bhvs. *Journal of materials chemistry. B*, 05 2025. Available from: <https://pubmed.ncbi.nlm.nih.gov/40424007/>, doi:10.1039/d5tb00827a.
- [324] G. C. Shurson, P. K. Ku, G. L. Waxler, M. T. Yokoyama, and E. R. Miller. Physiological relationships between microbiological status and dietary copper levels in the pig. *Journal of Animal Science*, 68, 04 1990. Available from: <https://doi.org/10.2527/1990.6841061x>, doi:10.2527/1990.6841061x.
- [325] L.A. Sinclair, D. Johnson, S. Wilson, and A.M. Mackenzie. Added dietary sulfur and molybdenum has a greater influence on hepatic copper concentration, intake, and performance in holstein-friesian dairy cows offered a grass silage- rather than corn silage-based diet. *Journal of Dairy Science*, 100, 06 2017. Available from: <https://doi.org/10.3168/jds.2016-12217>, doi:10.3168/jds.2016-12217.
- [326] Girish Sindhwani, Rakhee Sodhi, Manju Saini, Varuna Jethani, Sushant Khanduri, and Baltej Singh. Tracheobronchomalacia/excessive dynamic airway collapse in patients with chronic obstructive pulmonary disease with persistent expiratory wheeze: A pilot study. *Lung India : Official Organ of Indian Chest Society*, pages 381–4, Jul-Aug 2016. Available from:

- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4948224/>, doi:10.4103/0970-2113.184870.
- [327] CA Sinkler, H Kalpage, J Shay, I Lee, MH Malek, LI Grossman, and M Hüttemann. Tissue- and condition-specific isoforms of mammalian cytochrome c oxidase subunits: From function to human disease. *Oxidative Medicine and Cellular Longevity*, 2017, 2017. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5448071/>.
- [328] Mariacristina Siotto, Ilaria Simonelli, Patrizio Pasqualetti, Stefania Mariani, Deborah Caprara, Serena Bucossi, Mariacarla Ventriglia, Rossana Molinario, Mirca Antenucci, Mauro Rongioletti, Paolo Maria Rossini, and Rosanna Squitti. Association between serum ceruloplasmin specific activity and risk of alzheimer's disease. *Journal of Alzheimer's Disease*, 50, 02 2016. Available from: <https://doi.org/10.3233/jad-150611>, doi:10.3233/jad-150611.
- [329] Daniel G.J. Smethurst and Natalia Shcherbik. Interchangeable utilization of metals: New perspectives on the impacts of metal ions employed in ancient and extant biomolecules. *The Journal of Biological Chemistry*, 10 2021. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8633580/>, doi:10.1016/j.jbc.2021.101374.
- [330] L I Smith-Mungo and H M Kagan. Lysyl oxidase: properties, regulation and multiple functions in biology. *Matrix biology : journal of the International Society for Matrix Biology*, pages 387–98, Feb 1998. Available from: <https://pubmed.ncbi.nlm.nih.gov/9524359/>, doi:10.1016/s0945-053x(98)90012-9.
- [331] Lynda I. Smith-Mungo and Herbert M. Kagan. Lysyl oxidase: Properties, regulation and multiple functions in biology. *Matrix Biology*, 16, 1998. Available from: [http://dx.doi.org/10.1016/s0945-053x\(98\)90012-9](http://dx.doi.org/10.1016/s0945-053x(98)90012-9), doi:10.1016/s0945-053x(98)90012-9.
- [332] Sabrina Sobel, Allison Haigney, Michael Kim, Daniel Kim, Gregory Theophall, James Nuñez, Dionna Williams, Billy Hickling, and Joseph Sinacori. The complexation of aqueous metal ions relevant to biological applications. 2. reactions of copper(ii) citrate and copper(ii) succinate with selected amino acids. *Chemical Speciation & Bioavailability*, 22. Available from: <https://doi.org/10.3184/095422910x12692705325385>, doi:10.3184/095422910x12692705325385.
- [333] Stéphanie Solier, Sebastian Müller, Tatiana Cañequé, Antoine Versini, Arnaud Mansart, Fabien Sindikubwabo, Leeroy Baron, Laila Emam, Pierre Gestraud, G. Dan PantoUx0219[bad char vv=537], Vincent Gandon, Christine Gaillet, Ting-Di Wu, Florent Dingli, Damarys Loew, Sylvain Baulande, Sylvère Durand, Valentin Sencio, Cyril Robil, François Trottein, David Péricat, Emmanuel Näsér, Céline Cougoule, Etienne Meunier, Anne-Laure Bègue, Hélène Salmon, Nicolas Manel, Alain Puisieux, Sarah Watson, Mark A. Dawson, Nicolas Servant, Guido Kroemer, Djillali Annane, and Raphaël Rodriguez. A druggable copper-signalling pathway that drives inflammation. *Nature*, 617, 2023. Available from: [https://www.nature.com/articles/s41586-023-06017-4](https://www.nature.com/articles/s41586-023-06017-4#Sec1), doi:10.1038/s41586-023-06017-4.
- [334] Dan Song, Gou Takahashi, Yun-Wen Zheng, Mami Matsuo-Takasaki, Jingyue Li, Miho Takami, Yuri An, Yasuko Hemmi, Natsumi Miharada, Tsuyoshi Fujioka, Michiya Noguchi, Takashi Nakajima, Megumu K. Saito, Yukio Nakamura, Tatsuya Oda, Yuichiro Miyaoka, and Yohei Hayashi. Retinoids rescue ceruloplasmin secretion and alleviate oxidative stress in wilson's disease-specific hepatocytes. *bioRxiv*, 2021. Available from: <https://www.biorxiv.org/content/early/2021/08/10/2021.08.10.455792>, arXiv:<https://www.biorxiv.org/content/early/2021/08/10/2021.08.10.455792.full.pdf>, doi:10.1101/2021.08.10.455792.
- [335] Daniela F. Soto, Alejandra Recalde, Alvaro Orell, Sonja-Verena Albers, Alberto Paradela, Claudio A. Navarro, and Carlos A. Jerez. Global effect of the lack of inorganic polyphosphate in the extremophilic archaeon sulfobolbus solfataricus: A proteomic approach. *Journal of Proteomics*, 191, 01 2019. Available from: <https://doi.org/10.1016/j.jprot.2018.02.024>, doi:10.1016/j.jprot.2018.02.024.
- [336] D. Larry Sparks and Bernard G. Schreurs. Trace amounts of copper in water induce upbeta-amyloid plaques and learning deficits in a rabbit model of alzheimer's disease. *Proceedings of the National Academy of Sciences*, 100, 09 2003. Available from: <https://doi.org/10.1073/pnas.1832769100>, doi:10.1073/pnas.1832769100.
- [337] Jerry W. Spears. Trace mineral bioavailability in ruminants. *The Journal of Nutrition*, 133, 2003. Available from: <http://dx.doi.org/10.1093/jn/133.5.1506s>, doi:10.1093/jn/133.5.1506s.
- [338] Barry Starcher, Charles H. Hill, and Gennard Matrone. Importance of dietary copper in the formation of aortic elastin. *The Journal of Nutrition*, 82, 03 1964. Available from: <http://dx.doi.org/10.1093/jn/82.3.318>, doi:10.1093/jn/82.3.318.
- [339] Karolina M Stepien and Andrew Taylor. Colloidal silver ingestion with copper and caeruloplasmin deficiency. *Annals of Clinical Biochemistry: International Journal of Laboratory Medicine*, 49, 2012. Available from: <http://dx.doi.org/10.1258/acb.2011.011199>, doi:10.1258/acb.2011.011199.
- [340] Subramanian Sugunthan, Rajathurai Shailaja, and Kannabiran Parthasarathy. A review on usage of copper and its extractives satthu in siddha system of medicine. *Journal of Research in Siddha Medicine*, 5, 2022. Available from: https://doi.org/10.4103/jrsm.jrsm_1_23, doi:10.4103/jrsm.jrsm_1_23.
- [341] W.C. Supplee. Observations on the effect of copper additions to purified turkey diets. *Poultry Science*, 43, 11 1964. Available from: <http://dx.doi.org/10.3382/ps.0431599>, doi:10.3382/ps.0431599.
- [342] J.A. Swader and Wing-Yee Chan. Citric acid enhancement of copper solubility and toxicity in bicarbonate solutions. *Pesticide Biochemistry and Physiology*, 5, 10 1975. Available from: [https://doi.org/10.1016/0048-3575\(75\)90013-9](https://doi.org/10.1016/0048-3575(75)90013-9), doi:10.1016/0048-3575(75)90013-9.
- [343] Chunlin Tang and Judith P. Klinman. The catalytic function of bovine lysyl oxidase in the absence of copper. *Journal of Biological Chemistry*, 276, 2001. Available from: <http://dx.doi.org/10.1074/jbc.c100138200>, doi:10.1074/jbc.c100138200.
- [344] H Tang, L Leung, G Saturno, A Viros, D Smith, Leva G Di, E Morrison, D Niculescu-Duvaz, F Lopes, L Johnson, N Dhomen, C Springer, and R Marais. Lysyl oxidase drives tumour progression by trapping egf receptors at the cell surface. *Nature Communications*, 8, 2017. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5399287/>.
- [345] Xiaolong Tang, Zaihua Yan, Yandong Miao, Wuhua Ha, Zheng Li, Lixia Yang, and Denghai Mi. Copper in cancer: from

- limiting nutrient to therapeutic target. *Frontiers in Oncology*, 06 2023. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10327296/>, doi:10.3389/fonc.2023.1209156.
- [346] Yiyang Tang, Zhenghui Liu, Qin Chen, Mukamengjiang Juaiti, Zaixin Yu, Benhui Liang, and Lihuang Zha. Association of sarcopenia with the long-term risk of atrial fibrillation: A prospective cohort study. *Aging cell*, page e14198, 05 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/38739369/>, doi:10.1111/acel.14198.
- [347] S. W. Tappin. Canine tracheal collapse. *Journal of Small Animal Practice*, 57, 2016. Available from: <http://dx.doi.org/10.1111/jsap.12436>, doi:10.1111/jsap.12436.
- [348] Mustafa M. Tashkandi, Saeer F. Alsaqer, Thabet Alhousami, Faiza Ali, Yu-Chiao Wu, Jennifer Shin, Pushkar Mehra, Larry M. Wolford, Louis C. Gerstenfeld, Mary B. Goldring, and Manish V. Bais. Loxl2 promotes aggrecan and gender-specific anabolic differences to tmj cartilage. *Scientific Reports*, 10, 11 2020. Available from: <https://www.nature.com/articles/s41598-020-77178-9>, doi:10.1038/s41598-020-77178-9.
- [349] L. P. Thornburg, G. Rottinghaus, M. McGowan, K. Kupka, S. Crawford, and S. Forbes. Hepatic copper concentrations in purebred and mixed-breed dogs. *Veterinary Pathology*, 27, 1990. Available from: <http://dx.doi.org/10.1177/030098589002700202>, doi:10.1177/030098589002700202.
- [350] Larry P. Thornburg. A perspective on copper and liver disease in the dog. *Journal of Veterinary Diagnostic Investigation*, 12(2):101–110, 2000. PMID: 10730937. Available from: <http://dx.doi.org/10.1177/104063870001200201>, arXiv:<http://dx.doi.org/10.1177/104063870001200201>, doi:10.1177/104063870001200201.
- [351] Shiliang Tian, Stephen M. Jones, and Edward I. Solomon. Role of a tyrosine radical in human ceruloplasmin catalysis. *ACS Central Science*, 6, 10 2020. Available from: <http://dx.doi.org/10.1021/acscentsci.0c00953>, doi:10.1021/acscentsci.0c00953.
- [352] Huber TL, Laflamme DP, Medleau L, Comer KM, and Rakich PM. Comparison of procedures for assessing adequacy of dog foods. *Journal of the American Veterinary Medical Association*, 199. Available from: <http://europepmc.org/abstract/med/1659568>.
- [353] Restituto Tocmo, Dong Liang, Yi Lin, and Dejian Huang. Chemical and biochemical mechanisms underlying the cardio-protective roles of dietary organopolysulfides. *Frontiers in Nutrition*, 02 2015. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC4428374/>, doi:10.3389/fnut.2015.00001.
- [354] M.K Tripathi, I.S Agrawal, S.D Sharma, and D.P Mishra. Effect of untreated, hcl treated or copper and iodine supplemented high glucosinolate mustard (*Brassica juncea*) meal on nutrient utilization, liver enzymes, thyroid hormones and growth of calves. *Animal Feed Science and Technology*, 92, 07 2001. Available from: [https://doi.org/10.1016/s0377-8401\(01\)00243-7](https://doi.org/10.1016/s0377-8401(01)00243-7), doi:10.1016/s0377-8401(01)00243-7.
- [355] C. Vaughan Tuohy, Sanjiv Kaul, Howard K. Song, Babak Nazer, and Stephen B. Heitner. Hypertrophic cardiomyopathy: the future of treatment. *European Journal of Heart Failure*, 22, 2020. Available from: <http://dx.doi.org/10.1002/ejhf.1715>, doi:10.1002/ejhf.1715.
- [356] Duncan Turnbull, Maia M. Jack, Pragati S. Coder, Catherine A. Picut, and Joseph V. Rodricks. Extended one-generation reproductive toxicity (eogrt) study of benzoic acid in sprague dawley rats. *Regulatory Toxicology and Pharmacology*, 122:104897, 2021. Available from: <https://www.sciencedirect.com/science/article/pii/S0273230021000374>, doi: <https://doi.org/10.1016/j.yrph.2021.104897>.
- [357] Maja Uдовичиц, Raul Herrera Pena, Bhargavi Patham, Laila Tabatabai, and Abhishek Kansara. Hypothyroidism and the heart. *Methodist DeBakey Cardiovascular Journal*, pages 55–9, Apr-Jun 2017. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5512679/>, doi:10.14797/mdcj-13-2-55.
- [358] S. Urtiaga, R. Terrero, M. Malumbres, and A. Pinel. Myelopathy secondary to copper deficiency: The great imitator. *Neurología (English Edition)*, 33, 2018. Available from: <http://dx.doi.org/10.1016/j.nrleng.2017.02.002>, doi:10.1016/j.nrleng.2017.02.002.
- [359] Gerrit J. Van den Berg, Shiguang Yu, Arnoldina G. Lemmens, and Anton C. Beynen. Ascorbic acid feeding of rats reduces copper absorption, causing impaired copper status and depressed biliary copper excretion. *Biological Trace Element Research*, 41(1):47–58, Apr 1994. Available from: <https://doi.org/10.1007/BF02917216>, doi:10.1007/BF02917216.
- [360] Martina Vavrusova and Leif H. Skibsted. Aqueous solubility of calcium citrate and interconversion between the tetrahydrate and the hexahydrate as a balance between endothermic dissolution and exothermic complex formation. *International Dairy Journal*, 57, 06 2016. Available from: <https://doi.org/10.1016/j.idairyj.2016.02.033>, doi:10.1016/j.idairyj.2016.02.033.
- [361] Lissa Ventura-Antunes, Alex Nackenoff, Wilber Romero-Fernandez, Allison M Bosworth, Alex Prusky, Emmeline Wang, Cristian Carvajal-Tapia, Alena Shostak, Hannah Harmsen, Bret Mobley, Jose Maldonado, Elena Solopova, J Caleb Snider, W David Merryman, Ethan S Lippmann, and Matthew Schrag. Arteriolar degeneration and stiffness in cerebral amyloid angiopathy are linked to beta-amyloid deposition and lysyl oxidase., 04 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/38659767/>, doi:10.1101/2024.03.08.583563.
- [362] Katherine E Vest, Amanda L Paskavitz, Joseph B Lee, and Teresita Padilla-Benavides. Dynamic changes in copper homeostasis and post-transcriptional regulation of atp7a during myogenic differentiation. *Metalomics : integrated biometal science*, pages 309–322, Feb 2018. Available from: <https://pubmed.ncbi.nlm.nih.gov/29333545/>, doi:10.1039/c7mt00324b.
- [363] Birgitte Villadsen, Camilla Thygesen, Manuela Grebing, Stefan J Kempf, Marie B Sandberg, Pia Jensen, Stefanie H Kolstrup, Helle H Nielsen, Martin R Larsen, and Bente Finsen. Ceruloplasmin-deficient mice show changes in ptm profiles of proteins involved in messenger rna processing and neuronal projections and synaptic processes. *Journal of neurochemistry*, pages 76–94, 01 2023. Available from: <https://pubmed.ncbi.nlm.nih.gov/36583241/>, doi:10.1111/jnc.15754.

- [364] Melissa Vos, Giovanni Esposito, Janaka N. Edirisinghe, Sven Vilain, Dominik M. Haddad, Jan R. Slabbaert, Stefanie Van Meensel, Onno Schaap, Bart De Strooper, R. Meganathan, Vanessa A. Morais, and Patrik Verstreken. Vitamin k2 is a mitochondrial electron carrier that rescues pink1 deficiency. *Science*, 336(6086):1306–1310, 2012. Available from: <http://science.sciencemag.org/content/336/6086/1306>, arXiv:<http://science.sciencemag.org/content/336/6086/1306.full.pdf>, doi:10.1126/science.1218632.
- [365] Misha F. Vrolijk, Antoon Opperhuizen, Eugène H.J.M. Jansen, Geja J. Hageman, Aalt Bast, and Guido R.M.M. Haenen. The vitamin b6 paradox: Supplementation with high concentrations of pyridoxine leads to decreased vitamin b6 function. *Toxicology in Vitro*, 44, 2017. Available from: <http://dx.doi.org/10.1016/j.tiv.2017.07.009>, doi:10.1016/j.tiv.2017.07.009.
- [366] Ux0130[bad char vv=304]ham Al-juboori, Rafi Al-rawi, and Hussein A-hakeim. Estimation of serum copper, manganese, selenium, and zinc in hypothyroidism patients. *European Journal of Biology*, 68, 11 2010. Available from: <https://dergipark.org.tr/en/pub/iufsjb/issue/9050/112893>.
- [367] Ahsan Wahab, Kamran Mushtaq, Samuel G. Borak, and Naresh Bellam. Zincinduced copper deficiency, sideroblastic anemia, and neutropenia: A perplexing facet of zinc excess. *Clinical Case Reports*, 8, 2020. Available from: <http://dx.doi.org/10.1002/CCR3.2987>, doi:10.1002/CCR3.2987.
- [368] Ahsan Wahab, Kamran Mushtaq, Samuel G. Borak, and Naresh Bellam. Zincinduced copper deficiency, sideroblastic anemia, and neutropenia: A perplexing facet of zinc excess. *Clinical Case Reports*, pages 1666–71, 05 2020. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7495772/>, doi:10.1002/CCR3.2987.
- [369] P.E. Waibel, D.C. Snetsinger, R.A. Ball, and J.H. Sautter. Variation in tolerance of turkeys to dietary copper. *Poultry Science*, 43, 03 1964. Available from: <http://dx.doi.org/10.3382/ps.0430504>, doi:10.3382/ps.0430504.
- [370] Helge L. Waldum, Øystein Sordal, and Reidar Fossmark. Proton pump inhibitors (ppis) may cause gastric cancer - clinical consequences. *Scandinavian Journal of Gastroenterology*, 53, 06 2018. Available from: <http://dx.doi.org/10.1080/00365521.2018.1450442>, doi:10.1080/00365521.2018.1450442.
- [371] J.M. Walshe, E. Waldenström, V. Sams, H. Nordlinder, and K. Westermark. Abdominal malignancies in patients with wilson's disease. *QJM: An International Journal of Medicine*, 96(9):657, 2003. Available from: +<http://dx.doi.org/10.1093/qjmed/hcg114>, arXiv:[/oup/backfile/content_public/journal/qjmed/96/9/10.1093/qjmed/hcg114/2/hcg114.pdf](http://oup/backfile/content_public/journal/qjmed/96/9/10.1093/qjmed/hcg114/2/hcg114.pdf), doi:10.1093/qjmed/hcg114.
- [372] Bo Wang and Xiao-Ping Wang. Does ceruloplasmin defend against neurodegenerative diseases? *Current Neuropharmacology*, pages 539–49, 2019. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6712297/>.
- [373] Chao Wang, Xiaojuan Liang, Cong Tao, Xiaolei Yao, Yajun Wang, Yanfang Wang, and Kui Li. Induction of copper and iron in acute cold-stimulated brown adipose tissues. *Biochemical and Biophysical Research Communications*, 488, 07 2017. Available from: <https://doi.org/10.1016/j.bbrc.2017.05.073>, doi:10.1016/j.bbrc.2017.05.073.
- [374] Peng Wang, Xiaohe Xu, Guisong Gu, Qianwen Guo, Yanzhi Rao, Ke Yang, Tong Xi, Yonghui Yuan, Shanshan Chen, and Xun Qi. Inhibition effect of copper-bearing metals on arterial neointimal hyperplasia via the akt/nrf2/are pathway in vitro and in vivo. *Regenerative Biomaterials*, 04 2024. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11256920/>, doi:10.1093/rb/rbae042.
- [375] Rui Wang. Hydrogen sulfide, microbiota, and sulfur amino acid restriction diet. *Frigid Zone Medicine*, 1. Available from: <http://dx.doi.org/10.2478/fzm-2021-0003>, doi:10.2478/fzm-2021-0003.
- [376] TH Wang, SM Hsia, and TM Shieh. Lysyl oxidase and the tumor microenvironment. *International Journal of Molecular Sciences*, 18(1), 2017. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5297697/>.
- [377] Yuqiong Wang, Zonghui Zhang, Lele Zhao, Chong Ma, Qi Hu, and Xiaohong Hou. Bicarbonate ions promote rapid degradation of pollutants in co(ii)fe(ii)/peroxyacetic acid systems. *Journal of hazardous materials*, page 136918, 12 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39708608/>, doi:10.1016/j.jhazmat.2024.136918.
- [378] RA Wapnir and G Devas. Copper deficiency: interaction with high-fructose and high-fat diets in rats. *The American journal of clinical nutrition*, 61(1):105–10, 1995. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/articles/7825519/>.
- [379] Raul A. Wapnir and Cheryl Balkman. Intestinal absorption of copper: Effect of amino acids. *Nutrition Research*, 10, 05 1990. Available from: [http://dx.doi.org/10.1016/s0271-5317\(05\)80068-5](http://dx.doi.org/10.1016/s0271-5317(05)80068-5), doi:10.1016/s0271-5317(05)80068-5.
- [380] Betty M. Watts. Polyphosphates as synergistic antioxidants. *Journal of the American Oil Chemists' Society*, 27, 02 1950. Available from: <https://doi.org/10.1007/bf02634877>, doi:10.1007/bf02634877.
- [381] Cynthia L. Webster, Sharon A. Center, John M. Cullen, Dominique G. Penninck, Keith P. Richter, David C. Twedt, and Penny J. Watson. Acvim consensus statement on the diagnosis and treatment of chronic hepatitis in dogs. *Journal of Veterinary Internal Medicine*, pages 1173–200, 03 2019. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6524396/>, doi:10.1111/jvim.15467.
- [382] Shanzun Wei, Liang Gao, Changjing Wu, Feng Qin, and JiuHong Yuan. Role of the lysyl oxidase family in organ development (review). *Experimental and Therapeutic Medicine*, pages 163–72, 05 2020. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7282176/>, doi:10.3892/etm.2020.8731.
- [383] Hailang Wen, Lin Feng, Weidan Jiang, Yang Liu, Jun Jiang, Shuhong Li, Ling Tang, Yongan Zhang, Shengyao Kuang, and Xiaoqiu Zhou. Dietary tryptophan modulates intestinal immune response, barrier function, antioxidant status and gene expression of tor and nrf2 in young grass carp (ctenopharyngodon idella). *Fish & Shellfish Immunology*, 40, 09 2014. Available from: <http://dx.doi.org/10.1016/j.fsi.2014.07.004>, doi:10.1016/j.fsi.2014.07.004.
- [384] Yang Wen, Runxian Li, Xiangshu Piao, Gang Lin, and Pingli He. Different copper sources and levels affect growth performance, copper content, carcass characteristics, intestinal microorganism and metabolism of finishing pigs. *Animal Nutrition*, pages 321–30, 11 2021. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8718720/>, doi:10.

- 1016/j.aninu.2021.10.007.
- [385] Michiel J. Wiers, Beverley Beynon-Cobb, Wesley J. Visser, and Ilias Attaye. Dietary acid load in health and disease. *Pflugers Archiv*, pages 427–43, 01 2024. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11006742/>, doi: 10.1007/s00424-024-02910-7.
- [386] Contributors to Wikimedia projects. List of copper ores. *Wikipedia*, 05 2024. Available from: https://en.wikipedia.org/wiki/List_of_copper_ores.
- [387] Carrie M. Wilmot and Victor L. Davidson. Uncovering novel biochemistry in the mechanism of tryptophan tryptophylquinone cofactor biosynthesis. *Current opinion in chemical biology*, pages 462–7, 08 2009. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2749888/>, doi:10.1016/j.cbpa.2009.06.026.
- [388] Min Wu, Leqin Ke, Mingyu Zhi, Yumei Qin, and Jianzhong Han. The influence of gastrointestinal ph on speciation of copper in simulated digestive juice. *Food Science & Nutrition*, pages 5174–82, 07 2021. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8441336/>, doi:10.1002/fsn3.2490.
- [389] Min Wu, Guofeng Tan, Ruirui Shi, Dewen Chen, Yumei Qin, and Jianzhong Han. In vitro bioaccessibility of inorganic and organic copper in different diets. *Poultry Science*, 08 2024. Available from: <http://dx.doi.org/10.1016/j.psj.2024.104206>, doi:10.1016/j.psj.2024.104206.
- [390] Tanghuan Xie, Yanni Xi, Yanfen Liu, Huinian Liu, Zhu Su, Yicai Huang, Weihua Xu, Dongbo Wang, Chang Zhang, and Xin Li. Long-term effects of cu(ii) on denitrification in hydrogen-based membrane biofilm reactor: Performance, extracellular polymeric substances and microbial communities. *The Science of the total environment*, page 154526, 03 2022. Available from: <https://pubmed.ncbi.nlm.nih.gov/35288132/>, doi:10.1016/j.scitotenv.2022.154526.
- [391] Feng Xu, Sha Liu, Naran Naren, Lily Li, Luyan Z. Ma, and XueXian Zhang. Experimental evolution of bacterial survival on metallic copper. *Ecology and Evolution*, 12, 08 2022. Available from: <https://doi.org/10.1002/ece3.9225>, doi:10.1002/ece3.9225.
- [392] Kuo Yan, Chen Zhang, Jongkyun Kang, Paola Montenegro, and Jie Shen. Cortical neurodegeneration caused by psen1 mutations is independent of abeta. *Proceedings of the National Academy of Sciences of the United States of America*, page e2409343121, 08 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39136994/>, doi:10.1073/pnas.2409343121.
- [393] Ben-Shan Yang, Hideki Noda, and Norihisa Kato. Elevated intestinal absorption of copper in rats fed on a excessive tyrosine diet. *Bioscience, Biotechnology, and Biochemistry*, 57. Available from: <http://dx.doi.org/10.1271/bbb.57.2179>, doi:10.1271/bbb.57.2179.
- [394] Jing Yang, Xueli Zhang, Yiyi Zhu, Emily Lenczowski, Yanli Tian, Jian Yang, Can Zhang, Markus Hardt, Chunhua Qiao, Rudolph E. Tanzi, Anna Moore, Hui Ye, and Chongzhao Ran. The double-edged role of copper in the fate of amyloid beta in the presence of anti-oxidants. *Chem. Sci.*, 8:6155–6164, 2017. Available from: <http://dx.doi.org/10.1039/C7SC01787A>, doi:10.1039/C7SC01787A.
- [395] Shengjie Yang, Yujuan Li, Lijun Zhou, Xinyue Wang, Longtao Liu, and Min Wu. Copper homeostasis and cuproptosis in atherosclerosis: metabolism, mechanisms and potential therapeutic strategies. *Cell Death Discovery*, 10, 01 2024. Available from: <https://www.nature.com/articles/s41420-023-01796-1>, doi:10.1038/s41420-023-01796-1.
- [396] Yue Yang, Wenjie Hao, Taohua Wei, LuLu Tang, Nannan Qian, Yulong Yang, Hu Xi, Shijie Zhang, and Wenming Yang. Role of serum ceruloplasmin in the diagnosis of wilson's disease: A large chinese study. *Frontiers in Neurology*, 12 2022. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9768184/>, doi:10.3389/fneur.2022.1058642.
- [397] Akihiro Yasui, Sebastian F. Hoeft, Hubert J. Stein, Tom R. DeMeester, Ross M. Bremner, and Yuji Nimura. An alkaline stomach is common to barrett's esophagus and gastric carcinoma. In Kin-ichi Nabeya, Tateo Hanaoka, and Hiroshi Nogami, editors, *Recent Advances in Diseases of the Esophagus*, pages 169–172, Tokyo, 1993. Springer Japan. Available from: https://link.springer.com/chapter/10.1007/978-4-431-68246-2_26.
- [398] Yanshi Ye, Ye Li, Qintao Ma, Ying Li, Huxian Zeng, Yaosheng Luo, Yongqian Liang, Lan Liu, Lingling Liu, Xu Lin, Genfeng Yu, Cheng Song, Heng Wan, and Jie Shen. Association of multiple blood metals with thyroid function in general adults: A crossminussectional study. *Frontiers in Endocrinology*, 14, 2023. Available from: <https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2023.1134208>, doi:10.3389/fendo.2023.1134208.
- [399] A.G. Yersin, F.W. Edens, and D.F. Simmons. The effects of bordetella avium infection on elastin and collagen content of turkey trachea and aorta. *Poultry Science*, 77, 1998. Available from: <http://dx.doi.org/10.1093/ps/77.11.1654>, doi:10.1093/ps/77.11.1654.
- [400] Hao Yu and Jie Wu. Amyloid-upbeta: A double agent in alzheimer's disease? *Biomedicine & Pharmacotherapy*, 139, 2021. Available from: <http://dx.doi.org/10.1016/j.biopha.2021.111575>, doi:10.1016/j.biopha.2021.111575.
- [401] Lei Yu, Iris W. Liou, Scott W. Biggins, Matthew Yeh, Florencia Jalikis, LingtakNeander Chan, and Jason Burkhead. Copper deficiency in liver diseases: A case series and pathophysiological considerations. *Hepatology Communications*, 3, 2019. Available from: <http://dx.doi.org/10.1002/hep4.1393>, doi:10.1002/hep4.1393.
- [402] Yx Yu, Yp Li, F Gao, Qs Hu, Y Zhang, D Chen, and Gh Wang. Vitamin k2 suppresses rotenone-induced microglial activation in vitro. *Acta Pharmacologica Sinica*, 37(9):1178–89, 2016. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5022102/>.
- [403] Taesik Yun, Yejin Na, Dohee Lee, Yoonhoi Koo, Yeon Chae, Hyeyeon Nam, Byeong-Teck Kang, Mhan-Pyo Yang, and Hakhyun Kim. Case report: Technetium-99m pertechnetate scintigraphy findings in a dog with iodine deficiency-induced goitrous hypothyroidism. *Frontiers in Veterinary Science*, 9, 06 2022. Available from: <http://dx.doi.org/10.3389/fvets.2022.922456>, doi:10.3389/fvets.2022.922456.
- [404] Zhaohao Zeng, Yanmei Cen, Lijiao Xiong, Guo Hong, Yu Luo, and Xiaoguang Luo. Dietary copper intake and risk of parkinson's disease: a cross-sectional study. *Biological Trace Element Research*, 202(3):955–964, Mar 2024. Available from: <https://doi.org/10.1007/s12011-023-03750-9>, doi:10.1007/s12011-023-03750-9.

- [405] Zixi Zhang, Cancan Wang, Qiming Liu, Yichao Xiao, Jiabao Zhou, Keke Wu, Yunying Huang, Zeying Zhang, Shiping Liu, and Qiuzhen Lin. The risk of malnutrition as a predictor of arrhythmia recurrence after catheter ablation in patients with paroxysmal non-valvular atrial fibrillation and heart failure with preserved ejection fraction. *PLOS ONE*, 01 2025. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11785320/>, doi:10.1371/journal.pone.0317721.
- [406] J. Zhao, Y. Zeng, A. Wang, W. Zhang, J. Li, J. Zhu, Z. Liu, and J.-a. Huang. P1.02-04 targeting atp7a by elesclomol-copper derived endoplasmic reticulum stress to mediate cuproptosis in kras-g12 mutant luad. *Journal of Thoracic Oncology*, 18, 2023. Available from: <http://dx.doi.org/10.1016/j.jtho.2023.09.295>, doi:10.1016/j.jtho.2023.09.295.
- [407] W Zheng, X Wang, Q Chen, K Fang, L Wang, F Chen, X Li, Z Li, J Wang, Y Liu, D Yang, and X Song. Low extracellular lysyl oxidase expression is associated with poor prognosis in patients with prostate cancer. *Oncology Letters*, 12(5):3161–6, 2016. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5103911/>.
- [408] Ying Zhong, Rose C. Mahoney, Zehedina Khatun, Howard H. Chen, Christopher T. Nguyen, Peter Caravan, and Jesse D. Roberts. Lysyl oxidase regulation and protein aldehydes in the injured newborn lung. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 322, 02 2022. Available from: <http://dx.doi.org/10.1152/ajplung.00158.2021>, doi:10.1152/ajplung.00158.2021.
- [409] LiYe Zhou, RiJun Long, XiuYing Pu, Juan Qi, and WeiWei Zhang. Studies of a naturally occurring sulfur-induced copper deficiency in przewalskis gazelles. *The Canadian Veterinary Journal*, pages 1269–72, Dec 2009. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2777290/>.
- [410] Weidong Zhu, Chunying Wang, Jianping Wu, Shuqiu Chen, Weipu Mao, Yu Chen, and Ming Chen. Dietary copper intake and the prevalence of kidney stones among adult in the united states: A propensity score matching study. *Frontiers in Public Health*, 08 2022. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9469499/>, doi:10.3389/fpubh.2022.973887.
- [411] Katarzyna Marta Zoltowska, Utpal Das, Sam Lismont, Thomas Enzlein, Masato Maesako, Mei Q Houser, Maria Luisa Franco, Burcu Ozcan, Diana Gomes Moreira, Dmitry Karachentsev, Ann Becker, Carsten Hopf, Marcal Vilar, Oksana Berezovska, William Mobley, and Lucia Chavez-Gutierrez. Alzheimer's disease linked abeta42 exerts product feedback inhibition on gamma-secretase impairing downstream cell signaling. *eLife*, 07 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39027984/>, doi:10.7554/eLife.90690.

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Appendix A: Statement of Conflicts

No specific funding was used in this effort and there are no relationships with others that could create a conflict of interest. I would like to develop these ideas further and have obvious bias towards making them appear successful. Barbara Cade, the dog owner, has worked in the pet food industry but this does not likely create a conflict. We have no interest in the makers of any of the products named in this work.

Appendix B: About the Authors and Facility

This work was performed at a dog rescue run by Barbara Cade and housed in rural Georgia. The author of this report ,Mike Marchywka, has a background in electrical engineering and has done extensive research using free online literature sources. I hope to find additional people interested in critically examining the results and verify that they can be reproduced effectively to treat other dogs.

Appendix C: Some Common Logical Fallacies and Misdirections

The analysis errors that confuse the problem with the solution may be catagorized in a number of way but consider the following possibilities. No attempt is made to organize, catagorize, or make entries "orthogonal" as its unclear how or why to do that right now. It seems the other sciences such as materials science are ahead of medicine in a number of ways. There is a lot to be learned from trying to synthesize a system similar to the one you want to fix. Much of the problem appears to be attacking quantities associated with a pathological state without understanding the cause and effect that mediates from treatable problem to distracting symptoms.

1. **first impressions last :** You see this even in physics. Once a mystery has been (partially) solved it becomes entrenched dogma. In some compression technologies its safe to assume the first thing you see is most common but that doesn't seem to work in science lol.
2. **people over data :** Thjis comes up in essays on long lived metdical myths. Opinions, votes, don't determine natural laws
3. **X is a Y so it must do Z :** There is no small molecule with only one function and even antibodies are proteins and may have off target targets and can be immunogenic. With copper this comes up with chelators but may also apply to anti-oxidants or even water.
4. **X is a Y so it does Z :** Role confusion leads to more untested assumptions. A Rose by any other name would have a different billing code and label
5. **local optimum :** Moving some quantity in one direction perturbs the system in a sort of beneficial way preventing anyone from looking the other way for a better result.
6. **supply v demand :** An excess quantity is not inherently due to either supply or demand
7. **fraud and conspiracies :** If following the data doesn't make sense follow the money (no citation but something I saw on the internet).
8. **quantity may be due to a quality problem. :** The feedback that produces inducible effectors may not go away until the job is done. If the effectors dont' work you will get more of them. Getting rid of them will not fix the original problem that may be important if this control system evolved well lol.
9. **false dichotomy :** good and evil
10. **non-monotonic curves :** *show me a monotonic dose response curve and I'll show you a fool*
11. **fix or remove :** Often there are 2 approaches to getting the same result with a partially broken system.
12. **a ratio is not a derivative :** Associaion or fit parameters relating X to Y are averaged over an entire data set but the derivative at current state is what would be relevant to an intervention.
13. **one extreme says nothing about the other :** Both invcreasing or decreasing some quantity may produce the same (beneficial or evil) effect.

14. **presumed antagonists may work together** : One example cited osteoclast activation as not be the opposite osteogenesis and in fact vigorous remodelling may be important for healthy bones.
15. **hidden interaction** : The observed result requires some interaction partners
16. **local optimum** : prohibits consideration of global optimum over rugged parameter space with bad figure of merit.
17. **rabbit trail** : Successive approximations, even as advocated in this series of works, can lead a strategy down the wrong path.
18. **platitudes** : better to be safe than sorry lol
19. **philosophy over dynamics** : feedback can be complicated and commonly observed associations misleading
20. **equations** : consider spherical horse linear approx
21. **proxies** : Almost only counts in horseshoes and handgrenades
22. **models** : This usually means cause and effect is tossed out and the premise of the work has nothing to do with the premise of the real disease and that is often not even known well.
23. **only relies on empirical observations** : no cause and effect established
24. **ignoring empirical observations** : "sanity check " Theory based on incomplete system topology needs to be consistent with empirical observations
25. **ignoring empirical observations** : Theory based on incomplete system topology needs to be consistent with empirical observations
26. **other state variables** : Hidden variables include a limiting nutrient that is needed to beneficially use the entity under test.
27. **regulatory landscape** : As life is generally robust control systems have evolved but may have non-obvious failure modes.
28. **trying harder** : If a preferred response is frustrated in attaining a survival relevant goal, there may be signals to try a less orderly response more vigorously. The disorganized response can be suppressed by enabling the effective one.
29. **narrow corridor** : Given host-other evolution, you could expect dose response curves with many features but more likely a tight tolerance means that the approach is missing something more robust.

Appendix D: Background Diet Summary

Name	2023-10 Oct	2023-11 Nov	2023-12 Dec	2024-01 Jan	2024-02 Feb
FOOD					
KCl(tsp kcl)	0.045 ;0.031;23/23	0.047 ;0.031;30/30	0.085 ;0.062;24/24	0.094 ;0.062;31/31	0.093 ;0.062;29/29
KibbleAmJrLaPo	0.036 ;0.037;22/23	0.065 ;0.075;30/30	0.07 ;0.075;23/24	0.075 ;0.075;31/31	0.071 ;0.098;29/29
KibbleLogic	0.024 ;0.025;22/23	0.043 ;0.05;30/30	0.047 ;0.05;23/24	0.05 ;0.05;31/31	0.047 ;0.065;29/29
b10ngnc ^(c)	0.019 ;0.25;1/23	0.11 ;0.25;9/30	0.047 ;0.25;3/24	0.11 ;1;7/31	0.067 ;0.25;5/29
b15ngnc ^(c)		0.044 ;0.25;5/30	0.021 ;0.25;1/24	0.06 ;0.25;4/31	
b20ngnc ^(c)	0.18 ;0.25;14/23	0.13 ;0.25;10/30	0.25 ;0.25;14/24	0.14 ;0.25;11/31	0.28 ;0.25;19/29
b25ngnc	0.11 ;0.25;9/23	0.067 ;0.25;6/30	0.026 ;0.25;2/24	0.02 ;0.25;2/31	0.039 ;0.25;4/29
b7ngnc ^(c)	0.1 ;0.25;8/23	0.14 ;0.25;11/30	0.14 ;0.25;9/24	0.2 ;0.25;17/31	0.11 ;0.25;7/29
blackberry		0.058 ;0.25;5/30	0.3 ;0.25;20/24		
blueberry	2.4 ;3.8;23/23	2.4 ;2.2;30/30	1.9 ;2;20/24	0.71 ;1.5;13/31	1.2 ;1.5;29/29
carrot	0.35 ;0.25;23/23	0.36 ;0.25;30/30	0.36 ;0.25;24/24	0.38 ;0.25;31/31	0.38 ;0.25;29/29
cbbrothbs					0.022 ;0.25;3/29
cbbroth	0.16 ;0.25;10/23	0.071 ;0.25;6/30		0.21 ;0.25;15/31	0.25 ;0.25;16/29
citrate(tsp citrate)	0.045 ;0.031;23/23	0.047 ;0.031;30/30	0.048 ;0.062;24/24	0.058 ;0.062;31/31	0.092 ;0.062;29/29
ctbrothbs	0.082 ;0.25;5/23	0.4 ;0.25;25/30	0.48 ;0.25;24/24	0.29 ;0.25;19/31	0.22 ;0.25;14/29
ctbroth	0.17 ;0.25;11/23			0.032 ;1;1/31	
egg03	0.065 ;0.12;23/23	0.062 ;0.062;30/30	0.055 ;0.12;20/24	0.062 ;0.062;31/31	0.062 ;0.062;29/29
eggo			0.01 ;0.062;4/24		
eggshell	0.13 ;0.25;23/23	0.12 ;0.12;30/30	0.11 ;0.25;21/24		
garlic	0.022 ;0.25;2/23	0.22 ;0.25;26/30	0.083 ;0.25;8/24	1.2 ;1;27/31	0.99 ;1;22/29
marrow	0.19 ;0.25;12/23	0.37 ;0.25;30/30	0.083 ;0.25;6/24		0.078 ;0.25;7/29
oliveoil(tsp)	0.035 ;0.12;8/23	0.014 ;0.12;4/30			0.039 ;0.12;9/29
pepper	0.36 ;0.25;23/23	0.38 ;0.25;30/30	0.35 ;0.25;24/24	0.36 ;0.25;31/31	0.38 ;0.25;29/29
pineapple			0.021 ;0.25;2/24		
raspberry	0.32 ;0.25;23/23	0.28 ;0.25;24/30			
salmon		0.043 ;0.25;8/30		0.025 ;0.25;3/31	
shrimp(grams)		3 ;38;5/30	4.9 ;16;9/24	2.8 ;16;8/31	1.8 ;13;4/29
spinach		0.15 ;0.25;12/30	0.36 ;0.25;24/24	0.38 ;0.25;31/31	0.36 ;0.25;28/29
sunflowerseed	0.23 ;0.25;21/23	0.25 ;0.25;30/30	0.21 ;0.25;20/24		0.034 ;0.25;4/29
tomato	0.36 ;0.25;23/23	0.23 ;0.25;19/30	0.18 ;0.25;12/24	0.17 ;0.25;15/31	0.19 ;0.25;29/29
tuna(oz)					
turkey	0.34 ;0.25;23/23	0.37 ;0.25;30/30	0.35 ;0.25;24/24	0.36 ;0.25;31/31	0.36 ;0.25;29/29
vinegar(tsp)	0.09 ;0.062;23/23	0.094 ;0.062;30/30	0.09 ;0.062;24/24	0.068 ;0.062;24/31	2.16e-03 ;0.062;1/29
VITAMIN					
B-1(mg)	4.09e-03 ;0.012;15/23	5.87e-03 ;0.0059;30/30	6.12e-03 ;0.012;24/24	5.69e-03 ;0.0059;30/31	5.87e-03 ;0.0059;29/29
B-12(mg)	0.033 ;0.25;5/23	0.029 ;0.25;5/30	0.047 ;0.25;6/24	0.024 ;0.25;5/31	0.034 ;0.12;8/29
B-2(mg)	5.7 ;16;15/23	7.9 ;8.1;29/30	8.1 ;16;24/24	21 ;32;30/31	43 ;65;29/29
B-3(mg)	8.3 ;24;15/23	12 ;12;30/30	12 ;24;23/24	31 ;48;30/31	60 ;48;29/29
B-6(mg)	6 ;12;11/23	12 ;12;28/30	11 ;12;21/24	8.9 ;12;29/31	5.8 ;12;26/29
B-multi(count)	0.022 ;0.062;8/23			2.02e-03 ;0.062;1/31	
Cu(mg)	0.11 ;0.25;10/23	0.76 ;2;19/30	0.86 ;2;19/24	1.9 ;2;30/31	1.9 ;2;28/29
D-3(iu)	91 ;300;7/23	60 ;300;6/30	62 ;300;5/24	58 ;300;6/31	52 ;300;5/29
Iodine(mg) ^(a)	2.3 ;12;8/23	0.1 ;0.78;4/30	0.065 ;0.78;2/24	0.1 ;0.78;4/31	0.13 ;0.78;5/29
K1(mg)	0.38 ;1.2;7/23	0.92 ;1.2;22/30	1.1 ;1.2;22/24	1.1 ;1.2;27/31	1.2 ;1.2;28/29
K2(mg)	1 ;1.6;15/23	0.3 ;1.9;7/30	0.47 ;3.8;3/24	0.91 ;3.8;8/31	0.81 ;3.8;8/29
K2MK7(mg)	1.63e-03 ;0.025;2/23	5.83e-03 ;0.025;7/30	2.08e-03 ;0.025;2/24		
MgCitrate(mg)	96 ;200;21/23	100 ;100;30/30	92 ;100;22/24	31 ;100;10/31	76 ;100;22/29
Mn(mg)			0.042 ;1;1/24	0.21 ;0.62;12/31	0.12 ;1;6/29
Se(mcg)		0.42 ;12;1/30			0.43 ;12;1/29

TABLE VI: Part 1 of 2. Events Summary for Happy from 2023-10-01 to 2024-04-10A summary of most dietary components and events for selected months between 2023-10-01and 2024-04-10. Format is average daily amount ;maximum; days given/ days in interval . Units are arbitrary except where noted. Any superscripts are defined as follows: **a)** SMVT substrate. Biotin, Pantothenate, Lipoic Acid, and Iodine known to compete..**c)** hamburger with varying fat percentages- 7,10,15,20, etc. ..

Name	2023-10 Oct	2023-11 Nov	2023-12 Dec	2024-01 Jan	2024-02 Feb
Zn(mg zn)	1.3 ;5.9;9/23	1.1 ;5.9;10/30	0.73 ;2.9;6/24	0.47 ;2.9;5/31	0.61 ;5.9;5/29
arginine(mg)	68 ;175;9/23	82 ;350;10/30	51 ;175;7/24	79 ;350;12/31	275 ;350;15/29
biotin(mg) ^(a)	2.4 ;5;11/23	4.3 ;5;26/30	4 ;5;19/24	3.5 ;5;22/31	3.6 ;5;21/29
folate(mg)	0.022 ;0.12;5/23	0.019 ;0.12;6/30	0.018 ;0.12;4/24	0.016 ;0.12;5/31	0.011 ;0.12;3/29
histidine(tsp)					2.42e-03 ;0.016;7/29
histidinehcl(mg)	3.7 ;85;1/23	1.4 ;42;1/30	1.6 ;38;1/24		
iron(mg)		1 ;4;8/30	1.8 ;4;11/24	1.3 ;4;10/31	2.2 ;4;18/29
isoleucine(mg)	30 ;200;5/23	47 ;200;8/30	17 ;200;2/24	48 ;200;9/31	45 ;200;8/29
lecithin(mg)	215 ;225;22/23	225 ;225;30/30	281 ;225;22/24	330 ;225;31/31	338 ;225;29/29
lecithin(tsp)	0.046 ;0.062;22/23	0.036 ;0.042;30/30	0.012 ;0.062;8/24		
leucine(mg)	74 ;162;20/23	76 ;81;28/30	85 ;162;24/24	66 ;81;25/31	67 ;81;24/29
leucine					
lipoicacid(mg) ^(a)	3.1 ;25;5/23	7.6 ;25;16/30	24 ;25;21/24	18 ;25;22/31	31 ;25;28/29
lysinehcl(mg)	170 ;162;23/23	203 ;162;30/30	186 ;162;24/24	218 ;325;30/31	235 ;325;14/29
methionine(mg)	57 ;62;21/23	46 ;62;22/30	38 ;125;20/24	4 ;62;3/31	9.7 ;62;7/29
pantothenate(mg) ^(a)	22 ;78;12/23	20 ;39;15/30	21 ;39;13/24	32 ;39;25/31	30 ;39;22/29
phenylalanine(mg)	38 ;125;7/23	23 ;125;6/30	18 ;125;4/24	8.1 ;125;2/31	15 ;125;4/29
proline(mg)	143 ;100;23/23	35 ;100;7/30			
taurine(mg)	323 ;225;23/23	338 ;225;30/30	323 ;225;24/24	345 ;225;31/31	338 ;225;29/29
threonine(mg)	95 ;162;23/23	374 ;325;30/30	467 ;325;24/24	488 ;325;31/31	487 ;325;29/29
tryptophan(mg)	52 ;150;14/23	40 ;150;14/30	25 ;150;6/24	17 ;150;6/31	24 ;75;10/29
tyrosine(mg)	17 ;100;4/23	6.7 ;100;2/30	12 ;100;3/24	19 ;100;6/31	19 ;100;6/29
valine(mg)	165 ;200;19/23	160 ;200;24/30	133 ;200;16/24	135 ;200;21/31	159 ;200;23/29
vitamina(iu)	489 ;2250;5/23	600 ;2250;8/30	656 ;4500;6/24	435 ;2250;6/31	466 ;2250;6/29
vitaminc(tsp)	3.23e-03 ;0.0078;11/23	3.39e-03 ;0.0078;13/30	8.14e-04 ;0.0039;5/24	5.04e-04 ;0.0039;4/31	5.39e-04 ;0.0078;2/29
vitamine(iu)	8.2 ;38;5/23	8.8 ;38;7/30	9.4 ;38;6/24	7.3 ;38;6/31	6.5 ;38;5/29
MEDICINE					
SnAg				1.1 ;1;13/31	0.66 ;1;12/29
sodiumbenzoate(tsp)	0.011 ;0.016;12/23	8.85e-03 ;0.016;12/30	0.012 ;0.031;15/24	0.018 ;0.016;25/31	0.018 ;0.016;24/29
RESULT					
weight(lbs)			0.63 ;15;1/24		1.1 ;16;2/29
sorbitol(tsp)	0.045 ;0.031;23/23	0.047 ;0.031;30/30	0.045 ;0.031;24/24	0.046 ;0.062;31/31	0.047 ;0.031;29/29

TABLE VII: Part 2 of 2. Events Summary for Happy from 2023-10-01 to 2024-04-10A summary of most dietary components and events for selected months between 2023-10-01and 2024-04-10. Format is average daily amount ;maximum; days given/ days in interval . Units are arbitrary except where noted. Any superscripts are defined as follows: **a)** SMVT substrate. Biotin, Pantothenate, Lipoic Acid, and Iodine known to compete..**c)** hamburger with varying fat percentages- 7,10,15,20, etc. ..

Name	2024-03 Mar	2024-04 Apr
FOOD		
KCl(tsp kcl)	0.084 ;0.062;20/20	0.087 ;0.062;10/10
KibbleAmJrLaPo	0.034 ;0.037;18/20	0.034 ;0.037;9/10
KibbleLogic	0.023 ;0.025;18/20	0.022 ;0.025;9/10
b10ngnc ^(c)	0.069 ;0.25;4/20	0.056 ;0.25;2/10
b15ngnc ^(c)	0.022 ;0.25;2/20	
b20ngnc ^(c)	0.33 ;0.25;17/20	0.19 ;0.25;6/10
b25ngnc		
b7ngnc ^(c)		0.16 ;0.25;4/10
blackberry		
blueberry	0.75 ;0.75;20/20	0.9 ;1;10/10
carrot	0.35 ;0.25;20/20	0.35 ;0.25;10/10
cbbrothbs		
cbbroth	0.1 ;0.25;5/20	
citrate(tsp citrate)	0.081 ;0.062;20/20	0.086 ;0.062;10/10
ctbrothbs	0.33 ;0.25;17/20	0.41 ;0.25;10/10
ctbroth		
eggo3	0.025 ;0.062;8/20	0.062 ;0.062;10/10
eggo	0.037 ;0.062;12/20	
eggshell		
garlic	1.4 ;1;18/20	1.1 ;1;10/10
marrow		
oliveoil(tsp)	0.042 ;0.12;6/20	
pepper	0.36 ;0.25;20/20	0.35 ;0.25;10/10
pineapple		
raspberry		
salmon		
shrimp(grams)		
spinach	0.35 ;0.25;20/20	0.35 ;0.25;10/10
sunflowerseed	0.037 ;0.25;3/20	0.2 ;0.25;8/10
tomato	0.12 ;0.12;20/20	0.12 ;0.12;10/10
tuna(oz)	0.062 ;0.25;5/20	0.075 ;0.25;3/10
turkey	0.33 ;0.25;20/20	0.35 ;0.25;10/10
vinegar(tsp)	6.25e-03 ;0.062;3/20	3.13e-03 ;0.031;1/10
VITAMIN		
B-1(mg)	5.58e-03 ;0.012;18/20	5.87e-03 ;0.0059;10/10
B-12(mg)	0.05 ;0.25;6/20	0.025 ;0.12;2/10
B-2(mg)	47 ;16;20/20	37 ;16;10/10
B-3(mg)	69 ;24;20/20	55 ;24;10/10
B-6(mg)	4.7 ;6.2;15/20	3.8 ;6.2;6/10
B-multi(count)	3.13e-03 ;0.062;1/20	
Cu(mg)	2.2 ;2;20/20	2.6 ;2;10/10
D-3(iu)	62 ;350;4/20	60 ;300;2/10
Iodine(mg) ^(a)	0.19 ;0.78;5/20	0.16 ;0.78;2/10
K1(mg)	1.1 ;1.2;17/20	1.2 ;1.2;10/10
K2(mg)	0.75 ;3.1;6/20	
K2MK7(mg)		
MgCitrate(mg)	88 ;100;18/20	90 ;100;9/10
Mn(mg)	0.14 ;1.2;3/20	
Se(mcg)		

TABLE VIII: Part 1 of 2. Events Summary for Happy from 2023-10-01 to 2024-04-10A summary of most dietary components and events for selected months between 2023-10-01and 2024-04-10. Format is average daily amount ;maximum; days given/ days in interval . Units are arbitrary except where noted. Any superscripts are defined as follows: **a)** SMVT substrate. Biotin, Pantothenate, Lipoic Acid, and Iodine known to compete..**c)** hamburger with varying fat percentages- 7,10,15,20, etc. ..

Name	2024-03 Mar	2024-04 Apr
Zn(mg zn)	0.73 ;5.9;3/20	0.59 ;5.9;1/10
arginine(mg)	245 ;350;10/20	228 ;350;5/10
biotin(mg) ^(a)	3.4 ;5;14/20	3.5 ;5;7/10
folate(mg)	0.013 ;0.12;3/20	
histidine(tsp)	0.021 ;0.016;19/20	0.02 ;0.031;8/10
histidinehcl(mg)		
iron(mg)	2.4 ;5.3;17/20	5.3 ;5.3;8/10
isoleucine(mg)	25 ;200;3/20	20 ;200;1/10
lecithin(mg)	315 ;225;20/20	315 ;225;10/10
lecithin(tsp)		
leucine(mg)	73 ;81;18/20	81 ;81;10/10
leucine		
lipoicacid(mg) ^(a)	16 ;25;12/20	20 ;25;8/10
lysinehcl(mg)	228 ;325;10/20	244 ;325;5/10
methionine(mg)	12 ;62;8/20	25 ;62;4/10
pantothenate(mg) ^(a)	33 ;39;17/20	35 ;39;9/10
phenylalanine(mg)	28 ;125;5/20	12 ;125;1/10
proline(mg)		
taurine(mg)	315 ;225;20/20	315 ;225;10/10
threonine(mg)	455 ;325;20/20	422 ;325;10/10
tryptophan(mg)	26 ;75;7/20	22 ;75;4/10
tyrosine(mg)	22 ;100;6/20	30 ;100;3/10
valine(mg)	160 ;200;16/20	160 ;200;8/10
vitamina(iu)	506 ;2250;5/20	675 ;2250;3/10
vitaminc(tsp)	8.79e-04 ;0.0039;5/20	1.95e-03 ;0.0039;5/10
vitamine(iu)	7.5 ;38;4/20	7.5 ;38;2/10
MEDICINE		
SnAg		
sodiumbenzoate(tsp)	0.016 ;0.016;14/20	7.81e-04 ;0.0078;1/10
wormer	0.075 ;1.5;1/20	
RESULT		
weight(lbs)		
sorbitol(tsp)	0.044 ;0.031;20/20	0.041 ;0.031;10/10

TABLE IX: Part 2 of 2. Events Summary for Happy from 2023-10-01 to 2024-04-10A summary of most dietary components and events for selected months between 2023-10-01and 2024-04-10. Format is average daily amount ;maximum; days given/ days in interval . Units are arbitrary except where noted. Any superscripts are defined as follows: **a)** SMVT substrate. Biotin, Pantothenate, Lipoic Acid, and Iodine known to compete..**c)** hamburger with varying fat percentages- 7,10,15,20, etc. ..

Appendix E: Notable Food Components with Copper Interactions

Entity	Comments
Cu	
Zn	
Fe	
Mo	
H/ OH	
S and amino acids	reduce toxicity [156]
PO4	
Fructose	
Tyr	
Trp	
His	
Pi-complex	
Fenton	
Ammonia, Amides, N	
Citrate	
Ascorbate	
garlic	enhance uptake [179]
Microbial products	
phytate	

TABLE X: Some entities that may interact with copper. Copper chemistry is complex and bioavailability or indeed ability to use copper effectively may depend on a lot of other things. Most notably is the ability to form insoluble precipitate sequestering almost all copper from the host.

Appendix F: Symbols, Abbreviations and Colloquialisms

TERM definition and meaning

Appendix G: General caveats and disclaimer

This document was created in the hope it will be interesting to someone including me by providing information about some topic that may include personal experience or a literature review or description of a speculative theory or idea. There is no assurance that the content of this work will be useful for any particular purpose.

All statements in this document were true to the best of my knowledge at the time they were made and every attempt is made to assure they are not misleading or confusing. However, information provided by others and observations that can be manipulated by unknown causes ("gaslighting") may be misleading. Any use of this information should be preceded by validation including replication where feasible. Errors may enter into the final work at every step from conception and research to final editing.

Documents labelled "NOTES" or "not public" contain substantial informal or speculative content that may be terse and poorly edited or even sarcastic or profane. Documents labelled as "public" have generally been edited to be more coherent but probably have not been reviewed or proof read.

Generally non-public documents are labelled as such to avoid confusion and embarrassment and should be read with that understanding.

Appendix H: Citing this as a tech report or white paper

Note: This is mostly manually entered and not assured to be error free.
This is tech report MJM-2024-010.

Version	Date	Comments
0.01	2024-04-12	Create from empty.tex template
-	July 1, 2025	version 0.01 MJM-2024-010
1.0	20xx-xx-xx	First revision for distribution

Released versions,
build script needs to include empty releases.tex

Version	Date	URL
.01	2025-07-01	https://zenodo.org/records/15785347
.01	2025-07-01	https://www.academia.edu/130280509/Copper_2025_07_01_v
.01	2025-07-01	https://www.researchgate.net/publication/393240388_Copper_Supplementation_in_Dogs

```
@techreport{marchywka-MJM-2024-010-0.01 ,
filename ={copper} ,
run-date ={July 1, 2025} ,
title ={Copper Supplementation in Dogs: Listen to Her Heart Everybody's got a Hungry Heart } ,
author ={Mike J Marchywka } ,
type ={techreport} ,
name ={marchywka-MJM-2024-010-0.01 } ,
number ={MJM-2024-010} ,
version ={0.01} ,
institution ={not institutionalized, independent } ,
address ={ 157 Zachary Drive Talking Rock GA 30175 GA } ,
date ={July 1, 2025} ,
startdate ={2024-04-12} ,
day ={1} ,
month ={7} ,
year ={2025} ,
doi ={10.5281/zenodo.15785347} ,
author1email ={marchywka@hotmail.com} ,
contact ={marchywka@hotmail.com} ,
author1id ={orcid.org/0000-0001-9237-455X} ,
pages ={ 77}
}
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Supporting files. Note that some dates,sizes, and md5's will change as this is rebuilt.

This really needs to include the data analysis code but right now it is auto generated picking up things from prior build in many cases

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3801 Apr 15 19:06 ancient_copper.tex bf786ae4120d8f54b7745327ce11cf6
322861 May 23 2020 ../casesum/casesum.bib e3f31502ec3535aa4116c6682917678b
7994 Jul 1 13:42 comment.cut 5d9276d0082c053aad50870abafe0d91
66652 Jul 1 13:42 copper.aux e90b6574247031442a452c602b7ddb3a
198232 Jul 1 13:42 copper.bbl 0aff1fb4e57a13e3348a3979c874473d
1660461 Jul 1 13:42 copper.bib fdeffd16dd664c6a5034cb6f78de6b68
7034 Jul 1 13:42 copper.blg 1a7ab3f7e6790cae897b57af8bbbf740
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3450 May 14 17:43 copper_doit_best.tex 010d321e6fd46274f9b9d8213fdb699
34934 Jul 1 13:42 copper.flx aee03a19b63f39f5b165f39f09f46233
14270 Apr 28 16:19 copper_food_chem.tex 47e49d6e7be7959afdc267efc0672209
2928 Feb 11 12:34 copper_gralic_chem.tex 1cf451e5b2e8b0258ad189caa28986f7
3 Jul 1 13:42 copper.last_page 2b44a59db15a3ee2f1605ac82b028b20
70033 Jul 1 13:42 copper.log 1a34db6c14173271c08f884c99573e4e
12986 Jul 1 13:42 copper.out 8f29c731281daf5ba236e9e2d0fa7cea
5243897 Jul 1 13:42 copper.pdf 2b55a90add2c2c0c23a17edc01606d78
217387 Jul 1 13:42 copper.tex 1b631acaf5ce7e65909d7d1a77fd995d
5704 Jul 1 13:42 copper.toc 46829ab10aae885a2fc6a47e1f6e6c66
48207 Jun 23 14:50 /home/documents/latex/bib/mjm_tr.bib c1e418073aff2480bc78f63905450638
48577 Jul 1 13:22 /home/documents/latex/bib/releases.bib ce81ca81e02983d06819760344cc0b10
7331 Jan 24 2019 /home/documents/latex/pkg/fltpage.sty 73b3a2493ca297ef0d59d6c1b921684b
7434 Oct 21 1999 /home/documents/latex/pkg/lgrind.sty ea74beead1aa2b711ec2669ba60562c3
1069 Oct 15 2021 /home/documents/latex/share/includes/disclaimer-gaslight.tex 94142
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425 Oct 11 2020 /home/documents/latex/share/includes/disclaimer-status.tex b276f09e06a3a9114f927e4199f379f7
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4867 Jun 23 15:03 /home/documents/latex/share/includes/mycommands.tex d78deef4710745e9b4b29511fd3b610d
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