

**Release Notes xxxx-xx-xx :** : 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. It seems that 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. It may be worth noting there seems to be a trend to get away from copper plumbing lol. Actually looking at the old, unpublished work, "casesum", that includes Little Man, most of the text is still useful today and has been copied and pasted without attribution ( since it was a never-published work I authored ).

**ToDo :** Known problems: no refs yet, diettables have unit problems for recent noun additions

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## Utility of Copper Supplementation in Dogs

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(Dated: May 11, 2024)

Two contemporary diet related dog health issues, , hepatitic copper accumulation and dilated cardiomyopathy, may be symptoms of the same set of nutrient deficiencies with the latter reflecting cardiac copper deficiency. The inability to attack each is probably due to unexamined assumptions about cause and effect leading from diet to clinican outcomes. In particular, homeostatic mechanisms and roles may need more attention. Role may come up in cause and effect but also in action such as sequestering or depleting versus activating. This type of role confusion comes up in the copper literature. Local nutrient related feedback signals may cause more copper uptake but be unable to deliver it to the heart where it is needed. Consideration of homeostatic mechanisms, feedback loops, is often neglected and that may be the case in the present condundrum. This work describes copper supplementation to a group of dogs over several years with no robust deleitious effect established although some suspicious observations are discussed. Bnefits associated with copper supplementation, in the context of more complete supplementation, include reduced coughing likely due to infectious respiratory disease, collapsed trachea,, or dilated / hypertrophic heart. 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 mitochondrial energy production notably by the heart leading to greater volumetric efficiency and reduced size. Particular nutrients that may aid transport out of the liver would likely be those which enhance ceruloplasmin quantity or quality or otherwise modify copper handling. Tryptophan and tyrosine are two candidates for limiting copper toxicity and both were generally supplemented in this group of dogs. Both amino acids have unique functions and distribution may be modified by many factors from GI health to overall food chemistry and microbial metabolism. Some works implicating copper quantity in pathogenesis of these or other conditions is examined for hidden assumptions. Of particular note

may be that the mitochondrial copper pools are regulated by oxidized glutathione suggesting the possibility that antioxidant overdose could damage this signal leading to insufficient energy output. This work may be useful in mitigating these two unrelated issues.

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## Contents

<b>1. Introduction</b>	4
<b>2. Diseases of Interest</b>	6
2.1. Collapsed Trachea	6
2.2. DCM/HCM	6
2.3. Infection	7
2.4. Thyroid	7
2.5. AD, PD, ALS, Arthritis	7
2.6. Cancer	8
<b>3. Functions of Interest</b>	8
3.1. Cytochrome C Oxidase	9
3.2. Lysyl Oxidase	9
3.3. Ceruloplasmin	10
3.4. Macrophage et al	10
3.5. Ligandss- histidine and garlic etc	10
<b>4. Cases and Observations</b>	11
4.1. Cookie or Mixie	12
4.2. Brownie and puppies	12
4.3. Happy	13
4.4. Trixie	14
4.5. Rocky	14
4.6. Annie	15
4.7. Hershey	16
4.8. Miscellaneous Observations	18
<b>5. Discussion</b>	18
<b>6. Limitations</b>	18
<b>7. Conclusions</b>	19
<b>8. Supplemental Information</b>	19
8.1. Computer Code	19
<b>9. Bibliography</b>	19
<b>References</b>	19
<b>Acknowledgments</b>	27
<b>A. Statement of Conflicts</b>	28
<b>B. About the Authors and Facility</b>	28

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<b>C. Some Common Logical Fallacies and Misdirections</b>	28
<b>D. Background Diet Summary</b>	29
<b>E. Notable Food Components with Copper Interactions</b>	33
<b>F. Symbols, Abbreviations and Colloquialisms</b>	33
<b>G. General caveats and disclaimer</b>	33
<b>H. Citing this as a tech report or white paper</b>	33

## 1. INTRODUCTION

Copper is currently not a popular nutrient to supplement in human or dog diets. However, known and expected functions make it an ideal candidate for supplementation in many situations. The question of dietary deficiency or excess has been a topic of controversy for many years and likely copper intake alone is not the dominant issue but rather distribution. The question of supplementation then would be if there is a net benefit reducing deficiency in one place even if more excess occurs elsewhere until the bottleneck can be found. Some noisy association between intake and hepatic copper content was shown in a small study [34] but clearly that was not the major determinant of copper content. One study provided 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 [115]. Work continues to focus on concepts of deficiency or excess even though both may be matters of degree and context. Deficiency in commercial dog foods was suspected years earlier [118] while works as early as 2000 suggest supplementation would be unhelpful [116]. Excessive intake has become a concern due to increasingly frequent observation of "copper associated hepatitis" [3] [4] [21]. Low copper status is associated with liver problems too, some related to high fructose intake [128]. Copper deficient liver patients may be notable for "steatohepatitis, iron overload, malnutrition, and recurrent infections." [138]. Copper handling genetic diseases are well known in dogs [59] and some concern about excess intake may be warranted. A recent work comparing mineral content in groups of commercial dog foods found some patterns and advised against high copper foods [61].

In cases where pathological copper content exists, a better strategy is to find the processing bottleneck than be concerned with intake alone. 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 and likely cytosolic sensors exist [44]. It is also noteworthy that CTR1 transport is reduced if some histidines are mutated in either the C or N terminal tails. Normally biliary excretion increases when pathological amounts of copper begin to accumulate [23] [40] pointing to defects in excretion as a bigger concern than intake. Senescent cells may accumulate copper in the absence of autophagy [78]. Copper elevation may commit cells to differentiation in cord-blood derived cells [95] and it may be regulated during myogenic differentiation [121] raising the possibility that accumulation is due to confused signalling. In particular, ceruloplasmin is an acute phase protein and blood levels may be associated with pathological conditions [38] but a protective role is generally recognized. As a major transporter of copper out of the liver, that suggests distribution out of the liver is enhanced with certain stresses. 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. This will lead to hydrogen peroxide formation and potentially free copper both conditions likely to control infection. Copper signalling is such that remote signals may exist from the heart to liver and intestines to make more available [57] [87]. In this scenario, local shortage could induce blood stream or liver excess due to added inputs with struggling cardiac specific uptake as has been suggested for other nutrients such as tryptophan [70] and biotin [72] [69]. Note this work also suggests copper deficiency as an issue for cardiac hypertrophy in animals.

Other dietary components can impact uptake, signalling, and distribution in many ways. The dietary and genetic factors that influence copper distribution and health outcomes are complex and probably not fully known. While genetics are highly variable in dogs, some other factors include many dietary components, GI health, and signalling stimuli.

At least one source of confusion may be the interaction of copper nutrition with many other nutrients with some listed in Appendix E. Competition between Cu, Fe, and Zn was observed in Caco-2 cells [5]. Iron intake in feed has also been observed to decrease copper uptake in ruminants [26] and rats [62]. One work suggested iron disrupts copper homeostasis independent of uptake [39]. Dietary cholesterol appears to disturb copper homeostasis with atherosclerosis thought to involve copper dysregulation [63] and high fat diets in other species [47] are an issue. Fructose also inhibits relative copper absorption [88]. Zinc is a known inhibitor of copper uptake and cases of zinc induced copper deficiency in humans are known [125]. While concerns exist about copper content in dog foods, a recent survey of some zinc content shows many foods contain amount above recommended maxima and few are low or deficient [96]. Age related absorption problems in people are known [98] and other apparent deficiencies could be a consequence of insufficient B-6 alone [22]. Interestingly, B-6 is added to penicillamine treatment of Wilson's disease to avoid neurological effects [29].

### Thinking aloud

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 [124].

Body stores of copper increase with excess tyrosine in the diet of rats [133]. Some reports show specific issues when combined with vitamin C. A small trial with copper sulfate indicated kidney problems result [55] although alternatives with copper gluconate did not (check doses too, sulfate dose -).

GI health and in particular stomach acidity may be important factors in copper uptake but also distribution if

other nutrient deficiencies are created.

Copper solubility is pH dependent [28] Zinc absorption has been shown to depend on salt type and gastric pH [50]. Interaction with food components such as polyphenols is significant and pH dependent [97] 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 did in fact explore copper speciation in simulated gastric juices with food components such as tyrosine and citric acid among others [131]. Impact of GI pH on broiler chicks has been studied due to impact on nutrition and microbial populations and Cu-Zn antagonism in the digestive system was also observed [94].

In humans, PPI usage has become common. Empirically there may be a tumor protective effect and there is a suggestion that pH 6 encourages cancer progression versus pH 8 [64] yet alkaline stomach pH is observed is commonly observed in gastric carcinoma [135]. 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.

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 with added copper. 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 and biology so understanding the causes of that in this particular case may help optimize dog supplements and avoid delays in understanding the limitations of data and theory to design therapeutic interventions. Interpretation of the copper literature is limited by unquestioned assumptions and logical fallacies that are quite common. Some types of problems are listed in Appendix C. 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 [20]. A recent example may be the identification of amyloid beta as a nominally protective substance [137] [103] instead of the cause of Alzheimer's pathology and target for intervention. That state of affairs is well documented in the works that hint at it unravelling [33] such as a 2002 work suggesting that "tauists" and "baptists" could 'shake hands' and look for other causes [83]. 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 [56] [120]. However, upregulation would have to be suspected as a part of regeneration attempting to fix degeneration. Previously, heartworm positive dogs had been given significant amounts of vitamin K [76] [73] although severe case may be 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.

This work illustrates that empirically deficiency may be more common in some groups of dogs than excess in that supplementation, in the context of the rest of the diet, improves apparent health. If that hypothesis can be shown to be more generally true, the copper literature may illustrate some common fallacies and errors common to biology related literature and likely other genres involving complicated systems. However copper intake issues are resolved, the complexity of copper handling may make it a good topic to understand larger issues in system identification.

However, the empirical data and known theory or biological pathways don't establish a causal role for excessive intake of copper as a problem in most cases. Rather, other nutrients may be lacking to properly deploy existing copper resources and likely other things. In the particular case of copper accumulation in the liver, it's important to note that import and export are controlled by different things. While import appears to be controlled by diet and remote signals from the heart and binding to albumin, export may be limited by ceruloplasmin and excretion.

Emerging mechanisms such as extracellular vesicles [10] suggest that uncharacterized mechanisms of metal homeostasis exist.

A 2016 study in mice suggested adding copper to water was worse than adding it to food and supplementation at 6, 15, and 30 ppm with increases in soluble Aβ and decreased growth rate and GSH/SOD activity [130]. With a high dose of about 100 micrograms/day (from CuSO<sub>4</sub>) and a body weight of about 30 grams, the dose was about 3.3 mg/kg.

Interestingly, 3 amino acids, the ringed "WHY" trinity (tryptophan, histidine, and tyrosine) seem to be the most important. Notably tyrosine protects ceruloplasmin and 6 histidines, one for each copper, are required for a functional enzyme. Mistranslation due to insufficiency will be amplified by the higher power if all need to be right.

Copper status may help unify other unresolved issues in dog health. More recently, diet associated dilated cardiomyopathy (DCM) has also become a concern. Hypothyroidism has been a topic in human health for a while now and has occurred in several dogs here. Interestingly, that too may be related to copper deficiency.

Given that many diseased state can be caused by low copper, and accumulation in some does does not equate to excessive intake in these dogs, possible benefits of copper were considered.

This work describes in more detail the theoretical and empirical motivation to consider copper supplementation carefully as part of a larger supplementation program. The most interesting dogs' stories are presented and discussed in terms of the effect of copper and explanation of differences between expectations and outcomes.

## 2. DISEASES OF INTEREST

The known roles of copper include pathways and functions that would seem important for many diseases that are common in dogs. The present work relies mostly on 'cough' and thyroid related symptoms (coat quality, weight distribution, energy level etc). Cough has many possible origins as discussed previously [74]. Among these are respiratory infection or irritation, collapsed trachea, heart failure, and CNS stimulation. Infection related cough is well known due to direct irritation. Collapsed trachea may cause a cough on either inhalation or exhalation with a distinct honking sound. Heart failure may initiate fluid build up in the lungs and other sources of bulk such as a tumor may cause irritation. With these sources in mind, it is not difficult to find pathways and locations that require copper for proper functioning. These have been tabulated in Table II along with time scales for the response to copper changes in copper intake. In most cases the distribution is very broad and non-specific symptoms may be expected. For example, mitochondria are everywhere although the heart may be the first to show symptoms of deficiency. It is also important to note that cough monitoring is not going to be monotonic with improvement as increased energy may occur quickly resulting in more coughing until trachea and heart can remodel.

Disease	Host	Effect	time scale
DCM/HCM	dog		
Collapsed Trachea	dog		
Hypothyroid	dog		
Infection	dog		
covid-19	human	serum levels irrelevant [105]	
Parkinson's	human	assoc benefit [140]	
Alzheimer's	human		
Infection	human		
Arthritis	human	anecdotes, no trial verification	

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

### 2.1. Collapsed Trachea

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 [77]. Copper deficiency has been associated with lung development defects in rats [89] and airway and arteriole elastin were at least partially restored after 60 days of additional copper. In poultry, infection is known to cause some tracheal symptoms [136] and relationship to copper status is considered. Copper-garlic may reduce the virulence of some of these for short periods even if not completely able to clear a pathogen [42] and in particular Cu was recently shown to be effective against the toxin of one anaerobe [19]. Collapsed trachea in dogs does not appear to be commonly associated with copper in the literature we found although copper storage disease seems to be an active area of investigation [132] and copper status does come up in other investigations of tracheal damage as highlighted above. It is possible that the original motivation is partially correct and that extra copper combined with garlic did allow for better crosslinking to stiffen tracheal cartilage and prevent dynamic collapse and "honking".

### 2.2. DCM/HCM

Dilated and hypertrophic cardiac myopathy can both be related to mitochondria and "oxidative stress" may be a signal for more copper. "Oxidative stress" has been reported to increase muscle mass while reducing performance [1]. Copper deficiency can lead to cardiac hypertrophy with increased mitochondria [79]. "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.

Copper is essential for many growth processes and can activate receptor tyrosine kinases without a ligand making it a target for cancer [46].

Copper loading of cytochrome C oxidase relies on an oxidized Cox11 to interact with Cox19 [16] 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 [45] and indeed mitochondrial related signaling [109]. 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 [18] in [109])



. However, the enhancement by GSSG suggests that the presence of oxidized antioxidants may be beneficial but not in their reduced state.

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 pointed to two genes, RNF207 and PRKAA2 as risk factors [86] but did not mention copper. However, RNF207 may mediate degradation of ATP7A [141] while PRKAA2 comes up in cuproptosis [65].

Dobermans are at remarkably high risk of DCM [31]. Interestingly, "standard Dobermans" are also at high risk for hypothyroidism [93].

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 [66] in a work that reviews many important aspects of copper metabolism. .

### 2.3. Infection

Combined copper and zinc deficiency was observed to reduce response to covid-19 mRNA vaccines with only minimal copper deficiency [24] 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 [6] [35] . Some studies suggest copper is not a factor in covid-19 due to measurements like serum copper levels [105] although ceruloplasmin as an acute phase protein can elevate levels during stress even with a deficiency in copper [43]. In sample of 70 patients prescribed zinc, many had symptoms consistent with copper deficiency [30]

Copper may antagonize many pathogens including H pylori [12] and clostridium

### 2.4. Thyroid

Interestingly, copper deficiency in rats can reduce thyroid hormone levels and body temperature [68].

### 2.5. AD, PD, ALS, Arthritis

Deficiency seems to effect preferentially proteins involved in neuronal projection and diabetes and iron handling [122].

Rats fed a copper deficient diet shows neurological symptoms by 7 weeks and had reduced tyrosine hydroxylase and SOD activity [82].

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 [134]. Interestingly, copper-ascorbate oxidation of tryptophan may be suppressed by Trp chelation of copper at high trp concentrations [81] 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 [53].

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 [67]. 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 [14]. In 2021, Ni was found in important amounts in a commercial abeta40 preparation [11] and was found to mediate dityrosine crosslinks [13] similar to the dityrosine crosslinks induced by copper found in 2004 [7].

A 2013 work found in vitro physiological conditions caused copper to prevent fibril formation [80].

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 [91].

One work in 2022 addressed AD as a consequence of copper deficiency because [58]

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.

Folklore regarding copper persists and yet clinical trials for Cu in arthritis continue to show lack of any benefit [102] even as other controlled tests show some effects of Cu on processes related to collagen properties [41]

Remarkably, copper sulfide was shown to protect against ETC damage by MPP [106] suggesting some activity against toxic insults. Copper histidine is used to treat Menkes disease which is a defect in ATP7A [85].

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 [144]. This is interesting in the case of Hershey who was found to have bladder stones.

#### Thinking aloud

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 [51]/ pointing to a possible more general mechanism. The work goes on to 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 [140]

## 2.6. Cancer

Copper storage diseases and in essence "overdose" are well known [36] and a role in cancer is suspected [15]. 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 [108]. Lysyl oxidase activation, the goal of this therapy, is also associated with cancer spread [114][100][127]. 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 [8] or [142] and the survival curve in figure 1). Incidence of liver cancer in Wilson’s Disease patients is remarkably low [84] and a discussion of possible treatment effects [126] 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 [32]. 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. FUNCTIONS OF INTEREST

Location	site	Effect	time scale
Heart	mitochondria	energy production	maybe days
Heart	mitochondria	remodelling	weeks or months
Heart valves	lysyl oxidase	crosslinking [99]	weeks or months
Trachea	lysyl oxidase	proper crosslinking	months
Macrophage		infection	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. Cytochrome C Oxidase

Supplemental copper has been noted to improve symptoms in one case report including symptoms such as hearing loss [52] attributed to defects in cytochrome C oxidase copper loading and restore function in mutant yeast [37]. Cytochrome C oxidase levels in rat hearts were shown to be related to copper deficiency as early as 1998 [104]. 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 [123][139].

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 [92] ), 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 [17] and [48] . 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 [23]. However, pro-growth and angiogenesis could also be expected during regeneration which itself may require copper.

### 3.2. Lysyl Oxidase

Lysyl oxidase bad for vessels [9] calcification. but may be related to metallization issues [110].

Regulation at transcriptional and translation and post-translational levels is confusing. For example, it has been described in 1998 as [111],

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, [107]

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.

It has been observed to upregulate in the injured newborn lung [143] 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 [113] although details on reactions catalyzed could not have been fully explored.

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 pathological 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 [129]. 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.

Lysyl oxidase expression has been associated with degenerative mitral valve disease in humans[99].

### 3.3. Ceruloplasmin

Ceruloplasmin contains 6 coppers and histidines needed for metallization [49]. as well as 2 tyrosines. Independent errors in metallization will multiple 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 [117]. 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 is has to metalize 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 [101] 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. 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 [112] even as the other correlates sound pathological and its likely the inflammation being reduced would be beneficial if some other problem was corrected.

### 3.5. Ligandss- histidine and garlic etc

The combination of the garlic and copper, while sounding like a medieval concoction, has been described as synergistic against fungus [90] and seems plausible for generating perhaps more volatile and diffusable copper that could find otherwise inaccessible lysyl oxidase and other targets.

Dogs fed a histidine deficient diet eventually developed feeding resistance and lower whole blood copper and zinc [25].

Copper homeostasis is a much larger issue including in human health with regard to such unresolved diseases as Alzheimer's where the decades of work on amyloid beta is becoming more clearly futile.

In humans lysyl oxidase is sometimes discussed as a drug target as its quantity seems to increase in pathological situations. This may suggest that additional copper would not likely help.

To help with this apparent conundrum, this work describes variable copper supplementation to a group of dogs over several years including one pregnant pit bull with uterine fibroids. Generally beneficial results were associated with copper supplementation in the context of broader rationally designed supplements. Apparent benefits to a group of puppies included infection control. Additional respiratory infections were thought to be modulated in older dogs described here as Cookie( AKA Mixie ) and Trixie. It may have reduced transmission to the larger group in the latter case. Also an association with likely non-infectious coughing was seen in the case of Happy.

Given the varied canine genetics and known copper related diseases, vigilance for adverse reactions was maintained but to date only questionable events, such as reduced appetite, remain.

Copper and vitamin K have both seen literature suggesting a role for liver health under some conditions. Vitamin K is note worthy because of many efforts to antagonize its effects similar to the present concerns with copper.

These cases are described in more detail with the hope of sorting out cause and effect between diet and clinical outcomes as fixation on one nutrient at a time may not be productive.

The original motivation for copper was based on notions similar to the table below which reflects current thinking based on results presented here.

#### 4. CASES AND OBSERVATIONS



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

A series of rescue dogs were fed food and vitamin supplements in addition to commercial kibble products. Diet and outcomes were recorded in MUQED format [75] immediately after feeding. While most supplements and medicines were recorded in sufficient detail to reproduce, the meal or snack most dogs received additional meals of commercial dog food and unfortunately uncontrolled scraps or treats while others routinely ate toys or yard debris. However, some results appear to relate to the vitamin mix and notably inclusion of copper. Total calorie intake is not reflected in the data although some details of the products are indicated in the MUQED data ( see Supplementary Information ). In particular normalization of the "dinner" amounts is variable between dogs.

Some of the discussion will also reference unpublished notes on "Little Man" who was given copper and other nutrients before the MUQED system was operating.

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 flucuated wildly, it is included in some of the graphs as a putative factor confounding inferences about copper. The premise of this work is that the total diet is a "confounding factor" and readers are encouraged to check the MUQED data for other patterns.

Generally copper dosing was rotated leading to high doses some days with none on intervening days. 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 [27]. All of the dogs currently living here received increased copper shortly after the arrival of Trixie due to apparent spread of coughing. Trixie was later treated with Clavamox leading to cure suggesting indeed an infectious cause existed. Some of the dogs, notably Happy and Rocky, had varying cough levels previously as described below.

Dog	Dates	Condition	weight(lbs)	Cu(mg/day)	Cu(mg/kg)	Outcomes
Cookie	21-09-10 22-01-21	Resp infection/azithromycin	13.5	2	.33	cleared
Happy	18-09-07 24-04-10	several	13.4 - 17.7			
Happy	18-09-07 19-05-30	heartworm/doxycycline	13.4 - 17.2	2	.29	cough gone
Happy	24-03-26	coughs	15.2 - 15.5	2	.29	rare coughing
Brownie	21-01-12 23-02-22		49 - 64	1 variable		pts due to cancer
Brownie	21-01-12 21-02-14	pregnant, fibroids, heartworm	$\approx 60$	1.5-2.5		uneventful
puppies	21-03-23 21-06-09	cough	104	4.5	.095	cleared
Trixie	23-12-16 24-04-10	resp infection/Clavamox	37.6 - 44.6	5	.276	cleared
Rocky	22-02-05 24-04-10		4.4 - 8.3	1	.37	subjective better
Hershey	17-04-22 19-08-27	multiple	8.2 - 9	.2-.6	.1	heart failure
Hershey	17-04-22 19-08-27	multiple	8.2 - 9	2	.52	transient improvements
LittleMan	2016	multiple			.8	honking stopped
Annie	2022-09-21	excessive sleep, apathy	7.74- 9.9	2	.5	active again

TABLE III: List of dogs most effected by copper supplementation. Cu amount given is largest thought to be therapeutic and in case of Herhsy amount near death in (). The puppies were born on 2021-02-14 but only recorded as weaning began. Puppie weight reflects total as they were placed elsewhere and food shares are unknown

#### 4.1. Cookie or Mixie

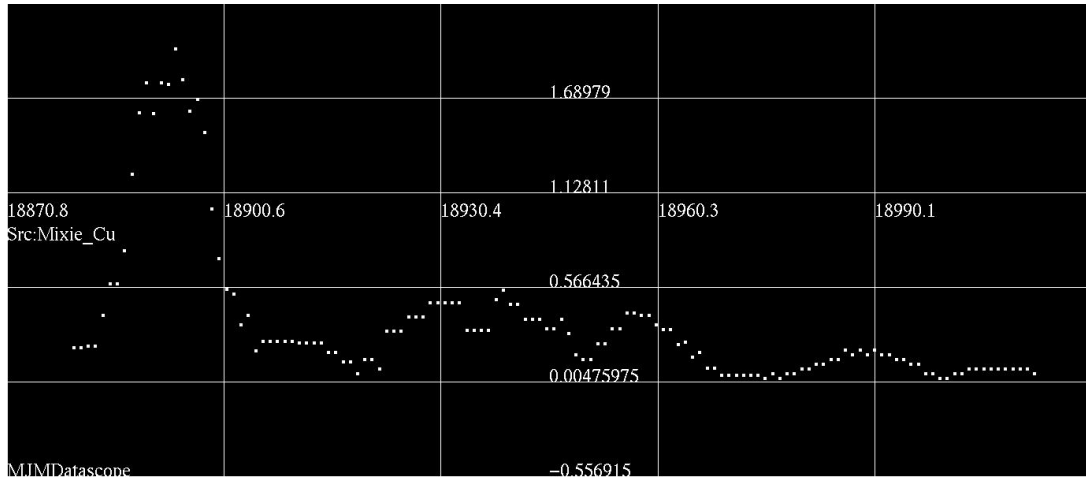


FIG. 2: Mixie daily copper (white ) intake .

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

#### 4.2. Brownie and puppies

Brownie was the subject of a prior work where ner uneventful pregnancy was notable for vitamin K consumption while heartworm posivite [76]. Subsequent to that work, her abdominal tumor was removed and diagnosed as fibroid. Briefly, Brownie was determined to be pregnant shortly after arrival . Her heartworm was treated with Diroban after weaning and fibroids removed 2021-11-15 well after the puppies were gone. She was unevntful until being doganosed with cancer and killed 2023-02-22. Prior to her diganosis, she was observed to cough occasionally for no obvious reason and appeared to have some movement issues. X-ray confirmed tumours likely responsible for both problems.

Her copper supplementation was fairly minimal but given her overall state of health and pregnancy she may be an interesting case for context.



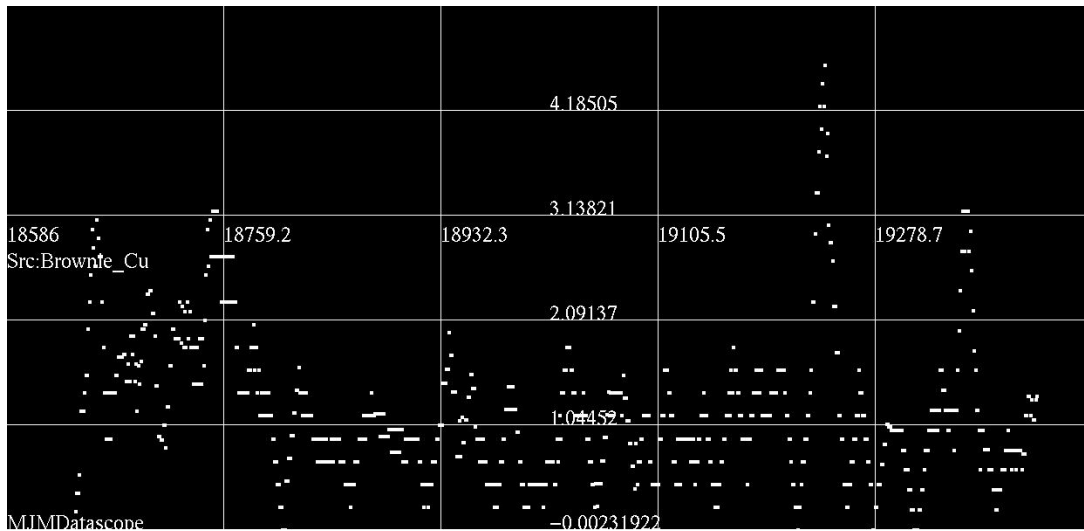


FIG. 3: Brownie 10 day trailing average copper (white) .

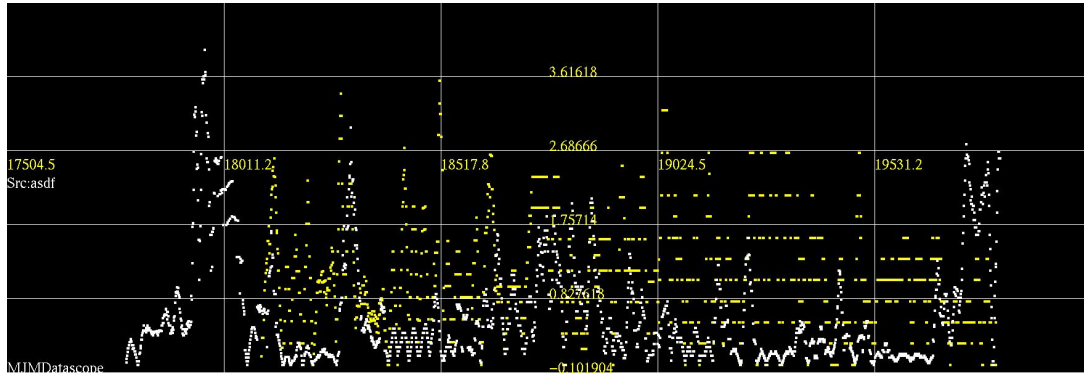


FIG. 4: Copper(white) and Zinc(yellow) dosing per day averaged over prior 10 day period as dosing was highly variable due to rotations of various nutrients. 18046 is 2019-05-30 when the cough was first noted to be gone for a few weeks. 19823 is 2024-04-10 the last date for which data was obtained. The cough stopped prior to the start of the Zinc and gradually increased to a notable background level over most of this interval although notes were incomplete. 19531 2023-06-23 notes the start of Cu depletion and chronic cough was noted by late Fall. During this time Zinc greatly exceeded copper dosing.

### 4.3. Happy

Happy was also the subject of two prior works. Initially her heartworm recovery was described with vitamin K and other supplements [73] followed by an unusual episode which resulted in some investigation of possible role of vitamins B-2 and B-3 in her health [71] . To summarize, Happy arrived heartworm positive coughing to varying degrees. She was treated with a slow kill approach including ivermectin and doxycycline as previously described. She later was acting sick but appeared to recover well with B vitamin supplements. Her coughing never returned to the very low levels seen after heartworm recovery until copper doses were increased with elimination of any zinc and care with tryptophan. As copper was increased due to widespread coughing after Trixie's arrival, her cough was noted to decrease. 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 now she seems to have reduced coughing, good energy level, and maybe some aromatic amino acid sensitivity. Also since starting the increased copper she does not appear to have disruptive itching around her tail area. Currently she is coughing when excited but that is with significant aromatic supplementation which appears to be making her more excitable.

4.4. Trixie

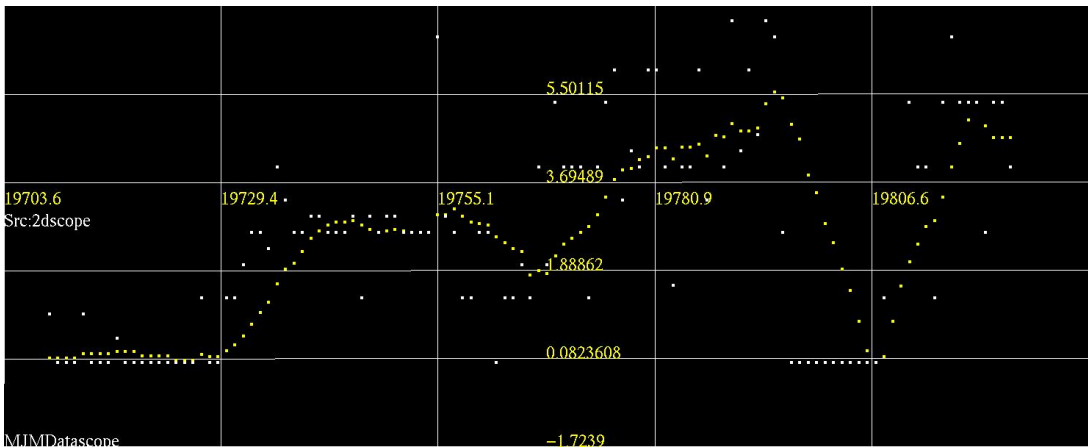


FIG. 5: Trixie copper consumption since arrival. Daily amounts ( white)) and trailing 10 day average( yellow). Copper started to be significant around day 19730 in response to coughing. Day 19807 marked the end of the copper fast as well as the end of Clavamox which was prescribed due to worsening when copper stopped days earlier.

Trixie began coughing shortly after arrival and was very low energy. Many other dogs began to cough or hack suggesting that she brought a communicable infectious disease. 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 day ( I was gone ) and owner took he 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 ) .

4.5. Rocky

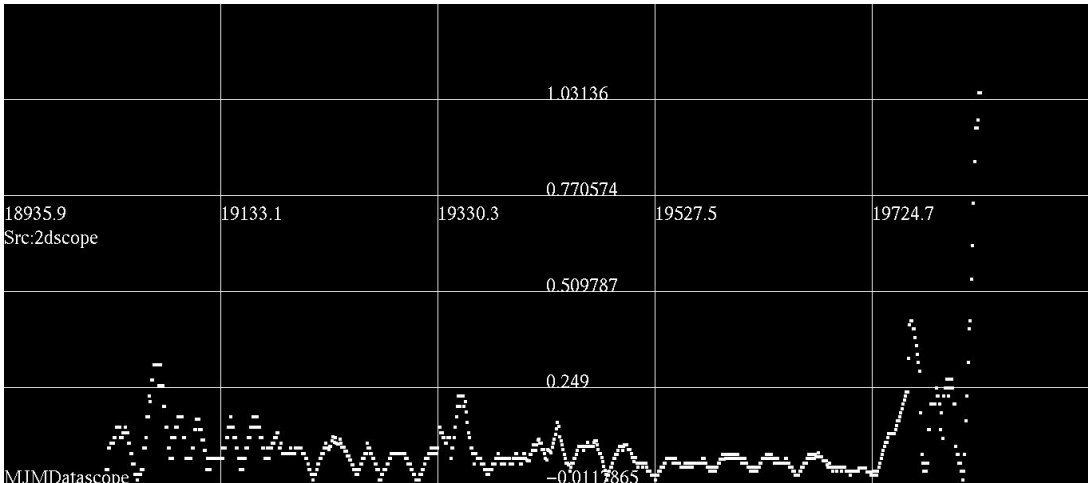


FIG. 6: Rocky 10 day trailing average copper (white ) .

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 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. 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.



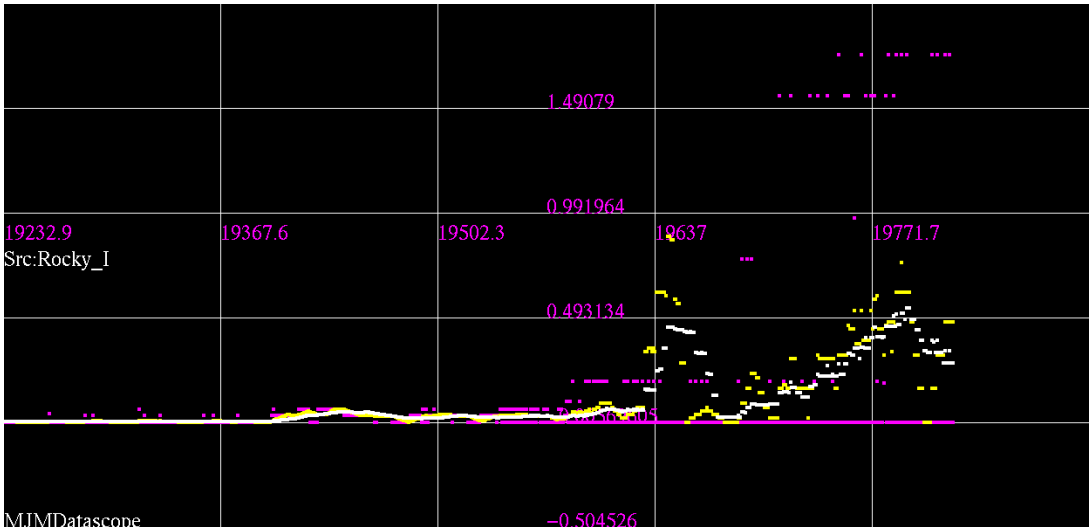


FIG. 7: Rocky iodine intake daily and with 10 and 30 day trailing averages. Patterns are difficult to discern with the pulsed dosing.

A recent study on rats fed benzoate demonstrated some insignificant indication of increased T4 and decreased TSH which the authors summarize as, [119] ,

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.

4.6. Annie

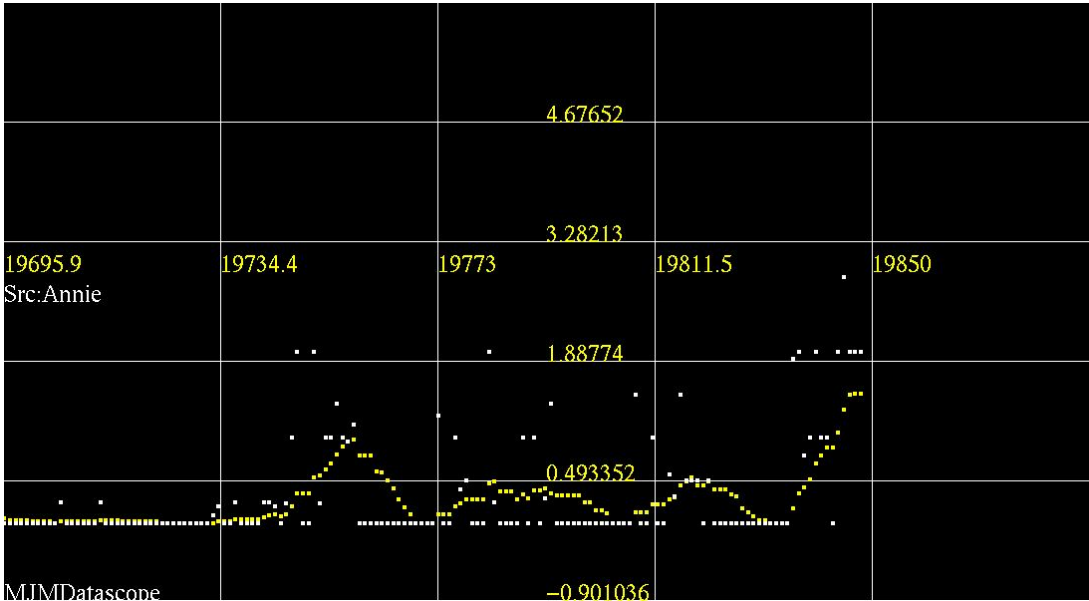


FIG. 8: Annie

Annie probably showed the clearest improvement coincident with increased copper ( and a few other components described below). Annie arrived in generally good condition although seemed old for stated age of 6 years. She

generally ate well but had some limitations in sight and hearing. She seemed to get skin or paw infections easily. She began to sleep excessively 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 ( 10948 ). Her exercise interest improved and she walked and cried with good energy.

#### 4.7. Hershey

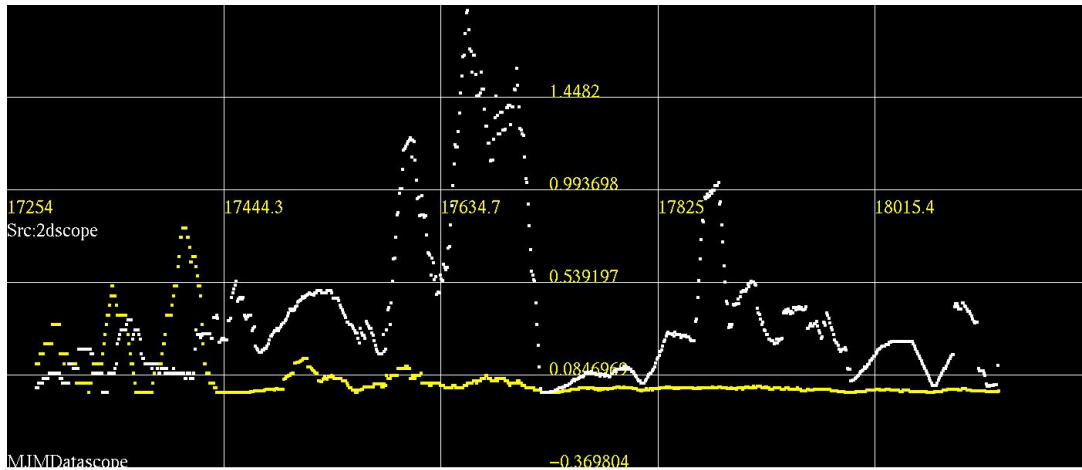


FIG. 9: Herhsey 10 day trailing average copper (white ) and iodine (yellow).

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 b7ngnnc rested ok. Made it up steps after PMSNACK ok although aborted on attempt but it is 95F out.
2018-10-12	17816	planning and circling 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 IV: 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. 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. Again, 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. As many initial features could be rationalized as related to thyroid output, his iodine intake was elevated.

#### 4.8. Miscellaneous Observations

Rocky seemed to do better but had also been responding to benzoate and iodine.

In initial attempts to formulate a vitamin mix, copper was added but no zinc. There was some possible feeding hesitation that went away when zinc was added. However a causal link was not established although copper was moderated afterwards. Annie may lose some appetite with excessive copper. However, a causal link was not established.

In a quick review of blood tests, chloride tended to be low and bicarbonate high.

### 5. DISCUSSION

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 weeks of dosing. Several suspicious observations were noted but nothing robustly correlated with copper intake. As some symptoms such as coughing are the product of many factors, interpretation is difficult during the initial response phases. Most notably, increased general energy may increase coughing in the presence of a weak or collapsed trachea or with some heart conditions which may take longer to mitigate and achieve more complete resolution. 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 a 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.

Pulmonary hypertension may be controlled by serotonin [2] and therefore tryptophan intake.

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 contribution to these states. These responses could increase coughing leading to the erroneous conclusions it was making something worse.

Several likely benefits of copper supplementation were observed but no clear robust clinical symptoms got worse. This is contrary to some indications from population concerns about excessive copper in commercial dog foods. Copper use requires uptake and transportation to various targets. Transport out of the liver can be hindered for reasons such as ceruloplasmin defects.

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.

B-6 deficiency has been linked to excess copper excretion [22] possibly making copper a secondary excretion issue rather than a primary absorption problem.

Over a broad range of genetics, it is 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.

### 6. LIMITATIONS

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 ingredients 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. CONCLUSIONS

Copper has to be suspected of being important in dogs for functions that likely include strengthening of structural elements such as the trachea, volumetric energy efficiency of the heart, and infection control. In the GI tract, it may moderate pathogenic phenotypes and change community structure of microbiome. Accumulation in the liver may reflect export problems rather than too much intake as signalling exists to regulate uptake and disposal. Defects may be due to other nutrients and particularly anything that interferes with ceruloplasmin synthesis or quality.

Internal transport and uptake however may both rely on GI defects which limit nutrient availability. Low stomach acid may be one common problem.

Zinc excess may also interfere with copper deployment. Dog genetics are varied and specifics likely vary too. Similar considerations may apply to humans.

Liver pathology that includes atypical amounts of copper may not reflect excess dietary intake but some other problem that needs to be fixed.

## 8. 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 online sources are not available. Raw MUQED format as well as parsed text formats are available although MUQED software availability is in the works.

### 8.1. 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 xxtable
2768 mv xxtable /home/documents/latex/proj/copper/keep/monthly.tex
```

datascope output,

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

## 9. BIBLIOGRAPHY

- 
- [1] Bumsoo Ahn, Rojina Ranjit, Pavithra Premkumar, Gavin Pharaoh, Katarzyna M. Piekarczyk, Satoshi Matsuzaki, Dennis R. Clafin, 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.

- [2] 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.
- [3] 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.
- [4] 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.
- [5] 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.
- [6] 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.000000000000208190>, doi:10.1212/wnl.000000000000208190.
- [7] 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.
- [8] 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/>.
- [9] Carne Ballester-Servera, Judith Alonso, Manel Tauron, Noemi 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.
- [10] 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.
- [11] 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?fromPaywallRec=false>, doi:10.1038/s41598-021-86060-1.
- [12] Sabine Bernegger, Cyrill Brunner, Matej Vizovič, [bad char vv=353]ek, Marko Fonovic, Gaetano Cuciniello, Flavia Giordano, Vesna Stanojlovic, Mirosław 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.
- [13] Elina Berntsson, Faraz Vosough, Teodor Svantesson, Jonathan Pansieri, Igor A. Iashchishyn, Lucija Ostojčič, [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?fromPaywallRec=false>, doi:10.1038/s41598-023-29901-5.
- [14] Glenda M. Bishop and Stephen R. Robinson. The amyloid paradox: Amyloidupbetametall 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.
- [15] 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/>.
- [16] 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.
- [17] 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/>.
- [18] 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/>.
- [19] 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](http://arxiv.org/abs/10.1021/jacs.7b01084), [doi:10.1021/jacs.7b01084](https://doi.org/10.1021/jacs.7b01084).
- [20] George J. Brewer. Risks of copper and iron toxicity during aging in humans. *Chemical Research in Toxicology*, 23, 02 2010. Available from: <http://dx.doi.org/10.1021/tx900338d>, [doi:10.1021/tx900338d](https://doi.org/10.1021/tx900338d).
  - [21] 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](https://doi.org/10.2460/javma.258.4.357).
  - [22] 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/>.
  - [23] 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](https://doi.org/10.1038/s41392-022-01229-y).
  - [24] 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](https://doi.org/10.1016/j.heliyon.2023.e20919).
  - [25] 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](https://doi.org/10.1093/jn/111.6.1074).
  - [26] 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](https://doi.org/10.1016/j.jtemb.2021.126815).
  - [27] 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](https://doi.org/10.17226/9782).
  - [28] 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](https://academic.oup.com/chemse/article-pdf/31/7/689/779389/bjl010.pdf), [doi:10.1093/chemse/bjl010](https://doi.org/10.1093/chemse/bjl010).
  - [29] 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](https://doi.org/10.1186/2047-9158-1-23).
  - [30] 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](https://doi.org/10.1136/jclinpath-2014-202837).
  - [31] 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, AAsa 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 Hundi, Matthias Hörtenhuber, Carsten Daub, César L. Araujo, Ileana B. Quintero, Kaisa Kyöstilä, Maria Kaukonen, Meharji Arumilli, Riika Sarviaho, Jenni Puurunen, Sini Sulkama, Sini Karjalainen, Antti Sukura, Pernilla Syrjä, Niina Airas, Henna Pekkarinen, Ilona Kareinen, Hanna-Maaria Javela, Anna Knuuttila, 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](https://doi.org/10.1186/s13073-023-01221-3).
  - [32] 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: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4223620/>.
  - [33] 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/>.
  - [34] 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](https://doi.org/10.1111/j.1939-1676.2012.01001.x).
  - [35] 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](https://doi.org/10.1016/j.amjmed.2022.03.008).
  - [36] 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](https://doi.org/10.1186/1476-5926-2-5).
  - [37] 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:1506.06644](https://arxiv.org/abs/1506.06644), <http://pubmed.ncbi.nlm.nih.gov/25668644/>, doi:10.1093/hmg/ddu069.
- [38] Natalia Giurgea, Mihaela Ioana Constantinescu, Ramona Stanciu, Soimita Suci, 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/>.
- [39] 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.
- [40] Iqbal Hamza and Jonathan D Gitlin. Hepatic copper transport. *Landes Bioscience*, 2013. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK6381/>.
- [41] 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/>.
- [42] F Harrison, AEL Roberts, R Gabriliska, 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/>.
- [43] 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.
- [44] 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/PMC365104/>, doi:10.1016/B978-0-12-394390-3.00006-9.
- [45] Yuta Hatori, Sachiye 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.
- [46] 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.
- [47] 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/>.
- [48] 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/>.
- [49] 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.
- [50] 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.
- [51] 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 Cu(II) 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.
- [52] R Horvath, P Freisinger, R Rubio, T Merl, R Bax, JA Mayr, Shawan, J Muller-Hocker, D Pongratz, LB Moller, N Horn, and M Jaksch. 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/>.
- [53] Seyyed Morteza Hoseini, Seyyed 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.
- [54] 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.
- [55] 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.
- [56] Louise Kelly, Matthew Macgregor Sharp, Isabelle Thomas, Christopher Brown, Matthew Schrag, Lissa Ventura Antunes, Elena Solopova, José Martínez-González, 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.

- [57] 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.
- [58] 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.
- [59] 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.
- [60] 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.
- [61] 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.
- [62] 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.
- [63] 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.
- [64] 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.
- [65] 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.
- [66] 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.
- [67] Mark A. Lovell, Chengsong Xie, and William R. Markesbery. 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.
- [68] 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.
- [69] 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](https://www.researchgate.net/publication/357250784_The_Paradox_Paradigm_When_Could_Amino_Acid_Supplements_Be_Beneficial).
- [70] 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](https://www.researchgate.net/publication/353946686_Draft_table_comparing_expectations_to_recent_results_with_covid-19).
- [71] 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](https://www.researchgate.net/publication/359504498_Happy_Again_Possible_Canine_Riboflavin_Deficiency).
- [72] 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](https://www.researchgate.net/publication/362303875_Vitamin_D_Towards_A_Conflict_Resolving_Hypothesis), doi:10.5281/zenodo.6922402.
- [73] 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](https://www.linkedin.com/posts/marchywka_happyheart-activity-6781666969885167616--HfQ).
- [74] 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](https://www.researchgate.net/publication/350442384_Canine_Heartworm_Treated_with_Doxycycline_Ivermectin_and_Various_Supplements).
- [75] 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](https://www.researchgate.net/publication/350636753_MUQED_a_Multi-Use_Quantitative_Event_Diary_For_Dog_Diet_Analysis).
- [76] 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](https://www.researchgate.net/publication/354924460_Supplement_Usage_Including_Vitamin_K_by_a_Heartworm_Positive_Pregnant_Pit_Bull_and_Her_Puppies).
- [77] 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/>.
- [78] 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.
- [79] 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.
- [80] 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.
- [81] 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.
- [82] R. F. Morgan and B. L. O'Dell. Effect of copper deficiency on the concentrations of catecholamines and related enzyme activities in the rat BRAIN<sup>1</sup>. *Journal of Neurochemistry*, 28, 1977. Available from: <http://dx.doi.org/10.1111/j.1471-4159.1977.tb07728.x>, doi:10.1111/j.1471-4159.1977.tb07728.x.
- [83] 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/>.
- [84] 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/>.
- [85] Mitsutoshi Munakata, Osamu Sakamoto, Taro Kitamura, Mamiko Ishitobi, Hiroyuki Yokoyama, Kazuhiro Haginoya, 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>, doi:10.1016/j.braindev.2004.08.002.
- [86] Julia E. Niskanen, sa Ohlsson, Ingrid Ljungvall, Michaela Drngemler, 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 Hundi, Matthias Hrtenhuber, Juha Kere, W. Glen Pyle, Jonas Donner, Alex V. Postma, Tosso Leeb, Gran Andersson, Marjo K. Hytinen, 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.
- [87] 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.
- [88] 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.
- [89] 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/>.
- [90] 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/>.
- [91] 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 Fallier. Development of cu(ii)-specific peptide shuttles capable of preventing cu-amyloid 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.
- [92] 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.
- [93] 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.

- [94] 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.
- [95] 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.
- [96] 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.
- [97] 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.
- [98] 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/>.
- [99] K-Raman Purushothaman, Meerarani 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.
- [100] 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 metastases. *Cell Reports*, 19(4):774–84, 2017. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5413586/>.
- [101] 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.
- [102] 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.
- [103] 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.
- [104] 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.
- [105] 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.
- [106] 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.
- [107] 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.
- [108] 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.
- [109] 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/>.
- [110] 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.
- [111] 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.
- [112] Stéphanie Solier, Sebastian Müller, Tatiana Cañeque, 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, Emmanuelle Näser, 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#Sec1>, doi:10.1038/s41586-023-06017-4.
- [113] 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.
- [114] 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/>.
- [115] 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.
- [116] 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>.
- [117] 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.
- [118] 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>.
- [119] 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/S02732320021000374>, doi: <https://doi.org/10.1016/j.yrtph.2021.104897>.
- [120] 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.
- [121] 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. *Metallomics : integrated biometal science*, pages 309–322, Feb 2018. Available from: <https://pubmed.ncbi.nlm.nih.gov/29333545/>, doi:10.1039/c7mt00324b.
- [122] 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.
- [123] 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.
- [124] 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.
- [125] 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.
- [126] J.M. Walshe, E. Waldenström, V. Sams, H. Nordlinder, and K. Westermarck. 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.
- [127] 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/>.
- [128] 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/>.
- [129] Carrie M. Wilmot and Victor L. Davidson. Uncovering novel biochemistry in the mechanism of tryptophan trypt-



- tophylquinone 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.
- [130] Min Wu, Feifei Han, Weisha Gong, Lifang Feng, and Jianzhong Han. The effect of copper from water and food: changes of serum nonceruloplasmin copper and brain's amyloid-beta in mice. *Food & Function*, 7, 2016. Available from: <http://dx.doi.org/10.1039/c6fo00809g>, doi:10.1039/c6fo00809g.
- [131] 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.
- [132] X Wu, PAJ Leegwater, and H Fieten. Canine models for copper homeostasis disorders. *International Journal of Molecular Sciences*, 17(2), 2016. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4783930/>.
- [133] 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.
- [134] Jing Yang, Xueli Zhang, Yiying 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.
- [135] 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](https://link.springer.com/chapter/10.1007/978-4-431-68246-2_26).
- [136] AG Yersin, FW Edens, and DF Simmons. The effects of bordetella avium infection on elastin and collagen content of turkey trachea and aorta. *Poultry science*, 77(11):1654–60, 1998. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/articles/9835339/>.
- [137] 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.
- [138] 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.
- [139] 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: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5022102/>.
- [140] 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.
- [141] 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 lud. *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.
- [142] 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/>.
- [143] 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.
- [144] 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.

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3. Thanks everyone who contributed incidental support.

### 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,

1. **supply v demand** : An excess quantity is not inherently due to either supply or demand
2. **false dichotomy** : good and evil
3. **non-monotonic curves** : *show me a monotonic dose response curve and I'll show you a fool*
4. **hidden interaction** : The observed result requires some interaction partners
5. **X is a Y** : Role confusion leads to more untested assumptions.
6. **only relies on empirical obervations** : no cuase and effect established
7. **irnores empirical obervations** : "sanity check " Theory based on incomplete system topology needs to be consistent with empirical observations
8. **irnores empirical obervations** : Theory based on incomplete system topology needs to be consistent with empirical observations
9. **other state variables** : Hidden variables include a limting nutrient that is needed to beneficially use the entity under test.
10. **regulatory landscape** : As life is generally robust control systems have evolved but may have non-obvious failure modes.
11. **trying harder** : If a prefered 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.
12. **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
<b>FOOD</b>					
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 <sup>(c)</sup>	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 <sup>(c)</sup>		0.044 ;0.25;5/30	0.021 ;0.25;1/24	0.06 ;0.25;4/31	
b20ngnc <sup>(c)</sup>	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 <sup>(c)</sup>	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	
eggo3	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
<b>VITAMIN</b>					
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) <sup>(a)</sup>	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 V: 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) <sup>(a)</sup>	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) <sup>(a)</sup>	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) <sup>(a)</sup>	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
vitamin(c)(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
<b>MEDICINE</b>					
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
wormer					
<b>RESULT</b>					
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 VI: 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
<b>FOOD</b>		
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 <sup>(c)</sup>	0.069 ;0.25;4/20	0.056 ;0.25;2/10
b15ngnc <sup>(c)</sup>	0.022 ;0.25;2/20	
b20ngnc <sup>(c)</sup>	0.33 ;0.25;17/20	0.19 ;0.25;6/10
b25ngnc		
b7ngnc <sup>(c)</sup>		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
<b>VITAMIN</b>		
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) <sup>(a)</sup>	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 VII: 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, Lipic 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) <sup>(a)</sup>	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) <sup>(a)</sup>	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) <sup>(a)</sup>	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
<b>MEDICINE</b>		
SnAg		
sodiumbenzoate(tsp)	0.016 ;0.016;14/20	7.81e-04 ;0.0078;1/10
wormer	0.075 ;1.5;1/20	
<b>RESULT</b>		
weight(lbs)		
sorbitol(tsp)	0.044 ;0.031;20/20	0.041 ;0.031;10/10

TABLE VIII: 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

Title	
Cu	reduce toxicity [54]
Zn	
Fe	
Mo	
H/ OH	
S and amino acids	
PO4	
Fructose	
Tyr	
Trp	
Pi-complex	
Fenton	
Ammonia, Amides, N	
Citrate	
Ascorbate	
garlic	enhancing bioavailability Cu etc [60]
Microbial products	
phytate	

TABLE IX: Some entities that may interact with copper

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
-	May 11, 2024	version 0.00 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

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filename = {copper} ,
run-date = {May 11, 2024} ,
title = {Utility of Copper Supplementation in Dogs} ,
author = {Mike J Marchywka } ,
type = {techreport} ,
name = {marchywka-MJM-2024-010} ,
number = {MJM-2024-010} ,
version = {0.00} ,
institution = {not institutionalized, independent } ,
address = { 44 Crosscreek Trail Jasper GA 30143 USA } ,
date = {May 11, 2024} ,
startdate = {2024-04-12} ,
day = {11} ,
month = {5} ,
year = {2024} ,
author1email = {marchywka@hotmail.com} ,
contact = {marchywka@hotmail.com} ,
author1id = {orcid.org/0000-0001-9237-455X} ,
pages = { 35}
}
```

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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322861 May 23 2020 ../casesum/casesum.bib e3f31502ec3535aa4116c6682917678b
4450 May 5 18:50 comment.cut c24d24abfb882f415374c9dacba65c95
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64692 May 5 18:50 copper.bbl e3592920252f11c2d93c44939c2146de
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