

**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 Actually looking at the old, unpublished work, "casesum", that includes Little Man, most of the text is still useful today and has been copied and pasted without attribution ( since it was a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 ).

A lot of introductory material may be more commonly put into a discussion of later section but its important to motivate the rather simple work of desining a set of supplements for a group of dogs. The data re of course ambiguous and the discussion tries to tie the introduction to the new data without a lot of new citations.

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

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

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(Dated: April 13, 2025)

The known roles of copper suggest it is needed to perform functions that could mitigate several common diseases related to energy production, infection, cancer, or cartilage quality. However, it is not currently a trendy supplement for dogs or humans ( usually omitted from lists such as most popular supplements [255] ). Part of the concern with dogs is the variable genetics and observations of copper accumulation in the liver becoming more common. However, with most genetics lacking a recognized copper storage disease, copper distribution is regulated by a complex system that appears to consider locale based demand as part of the uptake and excretion control algorithm. Such a system may produce bottlenecks leading to uncommonly large accumulation in an organ such as the liver while another organ such as the heart is starved. Such a situation could occur due to some other nutrient limitation that fools the feedback mechanisms. Without knowing the specific bottleneck, the decision to supplement would be based on the overall benefits to the starving location versus any harms to the accumulating organ. A better solution is to find the pathways needed to match copper supply and demand and insure they are not limited by things like other vitamin deficiencies. This work describes copper supplementation to a group of dogs without obvious significant harm while in some cases coinciding with benefits such as increased energy or reduced coughing. Supplementation in the range of .3-1 mg/kgBW/day was most commonly explored with .1 thought to be too low and 3 being an old literature NOAEL. These results are discussed in the context of broad range of literature on likely copper health effects. Consideration of

observations from many sources including ruminants and mining work provides several hypotheses for reconciling conflicting ideas. Much of the confusion probably relates to digestive details and overall diet composition even with similar copper handling genetics. Copper is quite versatile and had been observed to destroy both vitamins and anti-vitamins. In general diets it may be beneficial to separate copper intake or use time release or citrate supplements. The ability of specific diets to become pathological with copper inclusion is discussed at various points. Specific issues may induce copper deficiency such as many dietary sulfur sources and notably taurine. This may be made worse by the absence of a low pH step early in digestion allowing idiosyncratic formation of insoluble copper compounds possibly taking other vitamins away too. The pH-copper relationship is not clear but its reasonable to consider acid increasing diets especially for the elderly. Some specific dietary components may be of particular interest as they are suspects in conditions such as canine DCM but they may also limit copper delivery to the heart which is discussed here as an important issue in dogs and humans. Some common patterns of confusion seem to turn paradigms into paradoxes making it difficult to formulate interventions in medical conditions. With copper like in other cases many of these relate to incorrect interpretation of associations that result from complex feedback systems adapting to various perturbations. Some of the more common fallacies are categorized. In particular, identification of "larger than normal" accumulation of copper points to a common problem of trying to fix a quantity regardless of what is causing that. This work will try to highlight the supremacy of cause and effect over trying to treat numbers.

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## 1. INTRODUCTION

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

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

Copper is not currently a trendy supplement for humans or dogs. This may be partially due to deficiency being a neglected diagnosis by physicians [100] [95] [355] [346] [113] [1]. Indeed case of simple copper deficiency with no obvious causes first presented in May 2002 was not diagnosed until December 2003 with authors concluding response to copper can be rapid avoiding inappropriate work up if recognized early [169]. An overview by Brewer [47] in 2012 was quite emphatic about copper and iron supplements in older people, suggesting few people need them and they can be dangerous particularly for cognition and recommended avoiding meat. However, a 2018 work suggested widespread copper deficiency as a cause of many diseases currently common in North America such as "obesity, ischemic heart disease, and metabolic syndrome" [247]. A 2024 work recognizes copper distribution as a contributor to atherosclerosis and deficiency as a possible issue but does fall back to chelators and ionophores as possible solutions [382] not considering the possibility of global deficiency leading to bad allocation.

In dogs however a specific issue with liver copper accumulation has been noted. An expert consensus statement on hepatitis in dogs suggested an increased incidence that coincided with a change in copper supplementation premix in commercial dog foods [369] pointing to increased intake as a cause. However, known and expected functions make it a good match to several possible problems motivating an interest in careful supplementation even if contrary indicators also exist. One topic will concern the possible destruction of other vitamins by a copper pre-mix. Isolated authors do sometimes point to copper deficiency as a major cause of diseases such as heart disease [75] [200] and copper containing or eluting stents have been investigated since 2017 [155].

#### Thinking out loud

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

Copper nutrition does appear to be of recognized importance in dogs and the question of dietary deficiency or excess has been a topic of controversy for many years. It is likely that copper intake alone is not the dominant issue but rather distribution in the body determined by signaling, other dietary components, and genetics. The question of supplementation has to be answered within the context of a specific overall diet as well as recognized factors including genetics. If an unusually high copper concentration is measured in one location, the question remains if there would be a net benefit reducing deficiency in some other place even if more local excess occurs. And that "excess" may itself be adaptive it can't be assumed to be pathological just because it is not commonly observed in healthy hosts. This has to be answered in terms of clinical outcomes, things relevant to the host, rather than lab values absent cause and effect relations. Even in the case of known genetic diseases, copper removal to improve liver values may create clinical copper deficiency. Treatment emergent copper deficiency has been observed in a Bedlington Terrier with an excretion defect that clinically resolved with cessation of chelation [308]. Perhaps as more is known about ALS, it will be an excellent example of copper distribution problems that are not really excess of global deficiency [239].

### 1.2. Hepatic copper excess needs context

One increasingly common concern with dogs is copper associated hepatitis [10] [11] [50]. Copper handling genetic diseases are well known in dogs [174] and some concern about excess intake may be warranted for specific animals. Some noisy association between intake and hepatic copper content was shown in a small study [92] but copper intake may not be the major determinant of copper content. The causal role of copper "excess" in any clinical disease remains unclear. One study produced a histogram of liver Cu content (ppm dry weight) for a few hundred dogs but did not conclude there was a particular cutoff level for health vs disease [337]. Work continues to focus on concepts of

deficiency or excess even though both may be matters of degree, location, and context. Deficiency in commercial dog foods was suspected years earlier [340] while works as early as 2000 suggested supplementation would be unhelpful[338]. A recent work comparing mineral content in groups of commercial dog foods found some patterns and advised against high copper foods [177]. However, other nutrients have been observed to modify copper distribution. One reason for liver copper accumulation known since at least 2011 is iron deficiency [283]. A 1997 study found riboflavin deficiency reduced heart and liver iron while increasing copper content [55] and so other nutrients could still be responsible. A high calcium diet increased liver Cu in pigs [279]. Further, copper reactions in stored food could damage some of these nutrients hypothetically at least allow creation of an association between pre-mix and accumulation but mediated more by vitamin destruction than total copper consumption. Interestingly, although riboflavin is thought to be stable under many conditions it may degrade with metal sulfates but not chelates [63]. It is possible to form anti-vitamins which may be potent inhibitors of original vitamins but with passive non-saturating uptake.

At least one report indicated that hepatic export of ceruloplasmin was stimulated by thyroid hormone [241] suggesting that hypothyroidism could allow for hepatic copper accumulation. Its also worth noting that cross-effects have been observed with amino acids and in particular tryptophan. Copper deficient rats appeared to metabolise tryptophan loads differently and excrete amino acids but only taurine was found in the urine of copper sufficient animals ( repeated ref ) [118]. As amino acid status in old age may be a concern these effects of copper may be of larger importance.

Ideally observation of a pathological copper buildup in one location with symptoms of deficiency in other systems would lead to a search for the bottleneck prohibiting a better allocation. With copper this is quite complicated as a number of regulatory systems are known to control copper levels in different compartments in healthy mammals. Uptake regulation is not completely known but response to dietary or ambient levels is only part of the control loop in vivo. It is likely cytosolic sensors exist [126] to monitor cell contents but more global mechanisms appear to operate too. It turns out that copper related signalling is such that remote signals may exist from the heart to liver and intestines to make more available [164] [260]. In this scenario, local shortage in the heart could induce blood stream or liver excess due to added uptake with attempted but failed cardiac specific delivery. A similarly confusing feedback scheme has been suggested for other nutrients such as tryptophan [216] and biotin [219] [215]. Feedback regulatory systems, as with genes more generally, are likely selected by evolution but that need not make them simple or completely robust to defects in the control loop. One recurring source of defects to consider is high-infidelity translation or a specific pattern of translational defects likely related to the charge state of tRNA for particularly problematic amino acids. Motivation for the current work comes from observations on conditional KO or mutational diseases relevant to copper handling. For example, copper transporter CTR1 , important for intestinal uptake [259] and distribution [183] [26] [176] has reduced function if some histidines are mutated in either the C or N terminal tails. Intestinal loss of CTR1 causes cardiac hypertrophy among other issues that are partially correctable with copper supplementation [259] This suggests cardiac copper deficiency, possibly due to histidine deficiency, can contribute to cardiac hypertrophy in animals. However, if uptake and accumulation occurs while the heart is deficient this effect, combined with other mechanisms, does not exclude simultaneous excess in the liver. Its also quite likely that a lot of early results will show to be misleading. For example, it was only recently that the zinc transporters such as ZIP5(SLC39A5) are also high affinity copper transporters [276] although a cotemporary paper attributed health effects purely to zinc [62] its unclear if the hepatic metals tell the whole story.

Even with excessive intake, in most genetics biliary excretion increases when "pathological" amounts of copper begin to accumulate [57] [122] pointing to defects in excretion as another possible problem. However, many cause and effect relationships or control paths exist allowing other factors to control local copper concentrations. Senescent cells may accumulate copper in the absence of autophagy [229]. Copper elevation may commit cord-blood derived cells to differentiation [271] and it may be regulated during myogenic differentiation [350] raising the possibility that accumulation is due to confused signalling. Copper is also very important in the brain [101] where it modulates adult neurogenesis in the subventricular zone [198] and sleep-wake cycles in the locus coeruleus [203]. The major copper transporting protein ceruloplasmin is an acute phase protein and blood levels may be associated with pathological conditions [112] but a protective role is generally recognized. As a major transporter of copper out of the liver, stresses then could reduce hepatic copper. In fact, as substantiated later, it would make sense for copper to be redeployed from some mitochondria to the blood in response to pathogens or trauma or "beating plowshares into swords". Indeed, cytosolic copper accumulation has been observed in response to infection contributing to intra and extracellular defense as it regulates overall innate response [207]. If the cytosolic accumulation is at the expense of mitochondria, this can lead to hydrogen peroxide formation at complex IV which is likely to help control infection. Emerging topics such as extracellular vesicles [29] suggest that uncharacterized mechanisms of metal homeostasis exist making definitive statements difficult.

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

**Thinking outloud**

An interesting recent work suggests that iron accumulation in aortic valve calcification is a compensatory response to global iron deficiency [196]. It remains to be seen if this is "compensatory hoarding" favoring the heart but that does have to be considered as a possibility. If you only found the hoard, you may be tempted to chelate.

**1.3. Copper status is ambiguous in biochemistry and clinical outcomes****Thinking outloud**

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

Location specific quantities can be the result of many contributions and don't mean much without the "cause and effect" leading to the result. Blood or serum levels are easy to obtain as part of normal practice but copper's functions often execute in less accessible locations. As details are often unknown, a colloquial analogy may be trying to infer adequacy of military hardware from measuring the amount on civilian roads. Blood vessels may be used for transport in times of stress raising levels independent of global or niche amounts. There is a recurring problem using blood levels of some thing to indicate excess or deficiency. Some blood components such as electrolytes may need to be closely regulated but this is not the case when materials are just "passing through." These blood components are regulated or influenced by specific factors having nothing to do with overall sufficiency. In the case of copper, ceruloplasmin usually dominates blood copper and it is regarded as an acute phase protein causing blood levels to elevate in response to various stresses. Association studies may then find a correlation between high blood copper and some bad state as has been noted for cardiovascular [96] and Alzheimer's [316] disease although a protective role now tends to be recognized [201]. This work describes some important well known locations that copper could exist although surprises are still likely. Recently some body of work has suggested that macrophage lysosome may also regulate overall metal distribution [277] a location that would be expected to respond to many stimuli. Overall it appears that mitochondria and energy intensive organs like the heart may be the most important influencers.

One meta analysis of bone loss and copper suggested only supplementation studies in the 2.5-3mg/day range showed a clear benefit as blood levels and food intake did not correlate with bone improvements [291]. Its worth noting that this dose range is above common daily guidelines which are around 1mg/day. One patient with pure copper deficiency and no predisposing conditions was treated with 8mg/day [169]. Treatment of copper deficient myopathy typically is performed with about 2mg Cu /day although up to 8 mg/day was indicated [149].

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

**1.4. Copper and blood pressure**

Blood pressure, which is not a clinical endpoint per se, has been associated with copper status. While it is not central to this work, it illustrates some of the issues introduced above and is good context for the current work on clinical diseases.

A 2021 work exploring the association between serum copper levels and hypertension in US children and adolescents stated [194]. As suggested by previous literature, serum copper appears to reflect the status of copper nutrition in both depleted and replete populations. The present work however tends to accept that ceruloplasmin and blood copper levels are a reaction to stresses such as infection and a high level simply indicates some other pathological process likely exists. While blood levels can be elevated in response to a stress, its not known how well other functions such as electron transport are able to continue.

As early as 1993, one work with Dahl salt-sensitive rats suggested that indeed copper blood levels were a response to hypertension [106].

Things that do matter to the host related to blood pressure include cardiac workload, vascular pressure handling limits and adequate nutrient delivery. Any of these are likely complicated functions of long term diet details.

### 1.5. This kind of confusion is common for recurring reasons

#### Thinking outloud

this probably is a work of its own like the manuscript I started years ago although the application to copper is relevant

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. This result is in contrast to some of the popular expectations cited above. A discrepancy between expectations and outcome of this type seems to be common in medicine even as late as clinical trials so understanding the causes of that in this particular case may help optimize dog supplements and avoid delays in understanding the limitations of data and theory to design therapeutic interventions. Interpretation of the copper literature may be limited by unquestioned assumptions and common logical fallacies. Some types of problems are listed in Appendix C as a general guide.

#### Thinking outloud

this is rambling and vague maybe save the point for coagulation, alzheimer's etc where it is more to the point

One common problem that may turn out to be relevant here is a belief in opposites and concluding that if decreasing some quantity helps then there is no benefit in increasing it at another extreme. In fact, many control loops appear to "try harder" with goal related feedback. If something doesn't work which may be due to quality and feedback measuring results. Instead of disabling the system, fix it with more of what it needs. In the case of copper, local deficiencies simultaneous with excess may indicate a lack of some other nutrient that is believed to be bad. In the case of coagulation, isolation of the trigger from coagulation system should stop the clotting but a low enough quality clot may never achieve that goal creating larger less functional clots. In essence similar to perhaps hypertrophy in response to cues for more.

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 [46]. The above cites the work of Sparks finding that trace amounts of copper in water added to a high cholesterol diet produced Alzheimer's like disease in rabbits [324] which may relate to cytochrome C oxidase in the brain [242] as is a central theme here. By 2012, Brewer suggested AD was largely due to similar problems in people due to plumbing, supplements and fat [47]. The actual result appears more complicated [306] [305] with contemporary thinking similar to that suggested here that copper distribution is unclear in real disease [82].

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

Even after all the antibody work trying to identify the right physical conformation and peptide, confusion exists about the role of amyloids. A recent example may be the identification of amyloid beta as a nominally protective substance [387] [288] instead of the cause of Alzheimer's pathology and target for intervention. Recently amyloid beta was even found to promote osteogenesis [58] which of course may moderate another problem common in old age osteoporosis. Recently it was found that PRSEN1 mutations do not appear to generate neurodegeneration through amyloid beta [379]. Its toxicity may even result from gamma secretase inhibition [398] which had been considered a therapeutic intervention.

It may still be possible to optimize the amount creating passing benefits that are inherently limited and difficult to control. That state of affairs is well documented in the works that hint at it unravelling [89] such as a 2002 work suggesting that "tauists" and "baptists" could 'shake hands' and look for other causes [248]. 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 [161] [349]. However, upregulation would have to be suspected as a part of regeneration attempting to fix degeneration. Indeed, LOXL2 is known to be regenerative [336].

Other counter-intuitive approaches are easy to find. Previously, heartworm positive dogs had been given significant amounts of vitamin K [225] [222] although severe cases may be conventionally treated with anticoagulants. In this case, it may not be clear that vitamin K affects clot quality and consequently may limit pathological quantities allowing for beneficial clots to form.

### 1.6. Copper related outcomes depend on everything starting with GI tract

One problem making reproducible statements about copper supplementation may be the interaction of copper compounds with almost everything else. Literature exists on some interactions but the versatility of copper probably makes a complete list intractable. Some of the 'usual suspects' are listed in Appendix E merely to indicate a lot of what is left out of the current analysis.

The confusion begins in the GI tract with chemistry ranging from the problems sorting and regulating metals to the non-enzymatic reactions copper can undergo with a variety of organics in food. The copper transporter Ctr1 is thought to be selective against most divalent metals as it transports Cu(I) but is inhibited by Ag [228]. Enzymes may be subject to mis-metallization although there may be evolutionary pressure to use a variety of metals [317].

Once in the body, the ability to distribute and use copper depends on other nutrients maybe more than is the case with other vitamins or minerals.

As many conditions linked to copper may be considered age related, quality of the GI tract as a function of age may be relevant. GI health and in particular stomach acidity may be important factors in copper uptake but also distribution if other nutrient deficiencies are created. Naively, you may expect low acid to reduce solubility of cations or metals and decrease enzymatic activity for digestion of proteins. Copper solubility is pH dependent [70] similar to the competing element zinc for which absorption has been shown to depend on salt type as well as gastric pH [132]. Interaction with food components such as polyphenols is significant and pH dependent [275] 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 [375]. Impact of GI pH on broiler chicks has been studied due to impact on nutrition and microbial populations with Cu-Zn antagonism also observed in the digestive system [269].

Past the stomach into the intestines, the pH increases and mucin layers are thought to actively participate in metal or "trace element" absorption [81]. Mucin quality may also depend on nutrition such as oral threonine [179]. However, they may not deal effectively with precipitates grown in the stomach.

Some information about stomach pH variations may come from the large number of human PPI users. PPI's can raise stomach pH from 2 to 6 and produce "profound hypochlorhydria" [98]. The latter point may be important as Cl as much or more than H may have impact on microbiome and gastric chemistry. There is a conjectured tumor protective effect from PPI usage and a suggestion that pH 6 encourages cancer progression versus pH 8 [191] yet alkaline stomach pH is observed is commonly observed in gastric carcinoma [384]. Usage for suppression of colorectal cancer has been suggested [168]. Empirically however gastric cancer rates do correlate positively although arguably with PPI usage [358] [307] [68]. Probably the dominant effect on tumors is unrelated to ambient pH although increased pH may reduce nutrient accumulation by many cells. An absolute apoptosis rate at near neutral pH is probably not indicative of the overall fitness in the stomach. The effects going from pH 6 to 8 say nothing about the effects of going from pH 6 to pH 2 as one extreme says nothing about the other. It's important to note that they do seem to aid eradication of H pylori and therefore should reduce gastric cancer rates if bacteria are involved. The PPI's appear to attack H. Pylori directly [301] [16]. It's claimed that H pylori can survive down to pH 4 but only grow between 6 and 8 [226] affirming a role for acid in control of these pathogens. It's been observed as early as 1994 that Omeprazole inhibits survival of several organisms at low pH while H pylori only has a benefit in the presence of urea but the PPI effect is urease independent [233]. Clinical effect of PPI's probably does not relate to increased stomach pH and would not be decreased with concurrent intake of acids or chloride which may further improve microbiome.

Omeprazole was also shown to inhibit ATP7A, a copper transporter, preventing melanogenesis [230] and in fact a number of side effects are known along with vitamin deficiencies [211] with the latter likely contributors to the former many of which are common in old age motivating the idea of exaggerated aging in terms of disease.

Other metals may also compete with copper directly or by regulatory loops. Iron intake in feed has also been observed to decrease copper uptake in ruminants [65] and rats [184]. One work suggested iron disrupts copper homeostasis independent of uptake [121]. Zinc is a known inhibitor of copper uptake and cases of zinc induced copper deficiency in humans are known [356]. In chicks, and humans as discussed later, silver may induce copper deficiency through unknown means but mercury may improve apparent copper status only being toxic in copper sufficient animals [135]. Competition between Cu, Fe, and Zn was observed in Caco-2 cells [13].

While concerns exist about copper content in dog foods, a recent survey of some zinc content shows many foods contain amounts above recommended maxima and few are low or deficient [273]. Age related absorption problems in people are known [278] and other apparent deficiencies could be a consequence of insufficient B-6 alone [53]. Interestingly, B-6 is added to penicillamine treatment of Wilson's disease to avoid neurological effects [77].

**Thinking outloud**

Since paradoxes are a concern here, its worth noting that pyridoxine is an inhibitor of PLP and high doses result in functional B-6 deficiency [353].

Dietary cholesterol appears to disturb copper homeostasis with atherosclerosis thought to involve copper dysregulation [190] and high fat diets in other species [129] are an issue. Fructose also inhibits relative copper absorption [261] [366].

Body stores of copper increase with excess tyrosine in the diet of rats [380]. Some reports show specific issues when combined with vitamin C. A small trial with copper sulfate and vitamin C indicated kidney problems result [154] although alternatives with copper gluconate suggested use as food preservative [115]. Dose probably matter among other factors.

### 1.7. Copper interacts with dietary sulfur in other animals

The most well known issues with copper and dietary sulfur involve cows due to its common and profound economic impact but related studies have been conducted in non-ruminant lab animals. The latter may be more directly relevant to dogs and humans but the severity of the problem in cows may indicate some effects important but more subtle in the target population. In the other end of the spectrum may be poultry, mostly turkey and chickens, which may be notable for contrast to both mammals and ruminants due to the low pH proventriculus [287] as well as the gizzard with low but maybe variable pH [186]. Experiments on non-ruminants cover some of the supplements used in this work that could impact copper sufficiency and toxicity.

**Thinking outloud**

repeated text / citations in discussion

Taurine has been observed to reduce copper toxicity in rats with increased fecal copper amounts [146] suggesting decreased absorption. Another work demonstrated taurine reduced ceruloplasmin only in rats fed a control diet but not a high-fat diet [173]. As taurine is being explored for various indications, including DCM [234], supplementation could relate to induced copper deficiency which would likely cause some symptoms expected of copper deficiency.

Ascorbic acid in rats initially reduced absorption of copper but may eventually limit excretion [347]. In pigs, 60 percent fed a copper deficient diet died from coronary disease while supplementation as high as 250mg/kg diet, well in excess of the 10mg/kg diet requirement, can be growth promoting on a typical pig diet [83]. Pig tolerance of sulfur appears to be significant as higher sulfur diets did not seem to impact measures of copper such as liver content [163] although another work showed more complicated results with reduction in ceruloplasmin being one result [71]. The latter work noted decreased liver copper with the addition of potassium carbonate.

Exploration of optimal copper supplementation in poultry suggested copper is less available from cereals than vegetable proteins with amounts "greatly in excess of requirements" further improving results [187]. Very high dosing is common in chicks to avoid antibiotics and copper hydrochloride is often chosen for acid specific solubility [256]. An investigation of copper and sulfur containing amino acids in chicks showed marked interactions while suggesting copper toxicity was due to "chemical nature of the diet rather than to any specific copper induced nutritional deficiency" [290]. Methionine fed to chicks on a high copper diet could reduce some growth depression but it did not affect hepatic copper amounts [182] suggesting a number of possibilities that may not relate to copper uptake. Chicks apparently suffer reduced absorption of copper from sulfate in the presence of L-ascorbate and L-cysteine but some of that may be improved in some conditions using methionine or lysine chelates [12]. Interactions between methionine and copper were also investigated in turkey [159].

Ruminant sensitivity to dietary sulfur may be an interesting example of how a mild pH step can produce insoluble copper products creating profound deficiency. It's unclear on the extent to which this can occur in dogs or humans but it is illustrative. Sulfur and also molybdenum are common causes of cattle copper deficiency. They have been studied for impact on cow copper status with different background diets and shown to be significant modulators [313]. Decisions about copper supplementation are difficult though in economically important ruminants [206] and particularly in cows as concerns about toxicity [204] apparently can not be mitigated with other nutrient changes. A study of a problem with Przewalski gazelles found no difference in forage copper with clinical status but did find important difference in sulfur in forage and soil [396]. That work also identified biomarkers such as hair copper content although in this case the copper deficiency related to sulfur excess was so bad liver and blood levels were low too.

Ruminants differ substantially from non-ruminants and notably rumen pH is only around 6 reducing solubility of relevant minerals while allowing formation of insolubles [325]. This may motivate interest in issues with age related reduced stomach acid in humans. The low pH GI stage may reduce sensitivity to dietary idiosyncrasies. The presence of a stage able to nucleate insoluble nutrient blobs may prohibit later absorption. Other factors such as microbiology however need to be examined too. In pigs, response to high copper diet varied between "germ free" and conventional

groups [312].

Sulfate reducing bacteria may also contribute to confusing metabolism of taurine and methionine [363] .

### 1.8. The overall diet may be important for copper distribution

A couple of papers from 1964 illustrate the problem in simple terms. Initially turkeys were fed either a natural or purified diet with varying copper levels demonstrating toxicity in the purified diet but only minor issues combined with the natural diet [357]. A follow up work suggested the purified diet could be safe with copper but considered vitamin A, D, and zinc additions and noted an off odor in high copper feed [329]. The possibility of vitamin depletion as well as formation of toxics could be factors but also as discussed later overall absorption. Simple things can matter a lot for many reasons.

The importance of overall diet chemistry for copper availability was recently made for poultry [376]. Ideally the optimal fate of all consumed nutrients could be identified and manipulated with dietary composition. This work includes consideration of a background dietary context including real foods and controlled supplements that has been described previously [217] . This diet was further refined by consideration of the interactions described herein. The copper supplementations described here, about .3mg/kgBW/day , is likely well in excess of background levels in most known natural diets although its also worth noting that other sources may be accidentally significant as with water and air exposure [107].

### 1.9. Copper interactions with WHY and Cu related clinical impact

While sulfur containing amino acids have the most obvious interactions with copper, this work tends to focus on the ringed amino acids - Tryptophan (W) Histidine(H) Tyrosine(Y). W and Y are thought to vary significantly with age and histidine is important for copper binding to proteins. Notably tyrosine protexes ceruloplasmin and 6 histidines, one for each copper, are required for a functional enzyme. Mistranslation due to insufficiency will be exaggerated by the higher power if all need to be right. There is some indication that "diseases of old age" are at least partially mediated by sarcopenia, most recently atrial fibrillation [334] consistent with earlier ideas linking age to amino acid starvation [216] .

There are several works exploring the interactions in various places. In growing rate, "Excessive tyrosine and phenylalanine caused a marked increase in serum copper and ceruloplasmin activity, whereas excessive cystine, methionine, and histidine caused a decrease in the ceruloplasmin activity. " [160] Copper chelated to amino acids may be more robust against Cysteine ( and ascorbate ) inhibition [12].

#### Thinking outloud

cited elsewhere too

Interest in the interaction of tryptophan with copper go back to at least 1930 exploring the relation between tyrosine and tryptophan, among other nutrients, on total copper in hen eggs and subsequent hatchability [232]. Interest in the interaction of tryptophan with copper go back at least to 1973 when urinary metabolites were measured with different copper intakes ( repeated ref ) [118]. Trp was found to reduce toxicity of copper to the Caspase rach [87] and teleosts [141]. while improving response of grass copper to environmental copper [371].

One study found histidine decreased while tryptophan increased copper absorption [367].

While not directly concerning copper some related observations suggest what may occur. Drosophila shows a non-monotonic but generally increasing relationship between tryptophan intake and zinc stores and the authors point to microorganisms living or killed to be able to modulate Fe,Cu, and Zn to varying degrees [105].

Interestingly, Scavenger Receptor BI contains 8 highly conserved tryptophans [138] which appear important for cholesterol transport suggesting trp deficiency will slow down its translation , lead to early termination, or create many imperfect receptors. So, deficiency of these amino acids may produce broad non-specific problems that appear to be common in intractable diseases often associated with old age.

### 1.10. Recent Similar Work

At least one recent work [60] has summarized many of the same issues relating to copper and cardiovascular disease but with better editing and depth. However, it does not point to some of the cues outlined herein. For example, the issue of "other" limiting nutrients determining when copper is beneficial or not.

### 1.11. Copper rich diets for dogs and people are worth consideration

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

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

While the diets were guided by many hypotheses, the results are hypothesis generating or refining rather than attempts at proving any specific tractable ideas. Taken together this work supports the idea that supplementation in the .5mg/kg range added to the "background diet" produces no obvious harm and may solve some of the conditions discussed. Given the complexity of diets in general and the recurring problems with ostensibly better approaches, this may present unique data and results with atypical limitations and artifacts. The reported results should be thought provoking on their own but hopefully the overall complexity of this simple "feeding dogs at home" effort is amenable to analysis with emerging AI or related methods.

## 2. DISEASES OF INTEREST

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

Copper deficient liver patients may be notable for "steatohepatitis, iron overload, malnutrition, and recurrent infections" [388].

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

Besides cough, the present work relies thyroid related symptoms (coat quality, weight distribution, energy level etc). Cough has many possible origins as discussed previously [223]. "Energy level" in most cases described here is thought to relate to shorter term fluctuations in mitochondrial copper rather than thyroid although its important to consider all possibilities. One point of this work is to interpret outcomes recognizing that symptoms and disease trajectory can decouple and notably coughing may increase as part of a disease complex resolves.

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

Disease	Host	Effect	time scale
DCM/HCM heart failure	dog		4 weeks [60]
Collapsed Trachea airway defects	dog rats		months, 60days [262]
Hypothyroid	dog		
Infection	dog		
covid-19	human	serum levels irrelevant [293]	
Parkinson's	human	assoc benefit [391]	
Alzheimer's	human	brain depletion with excess Cp [66]	
Infection	human		
Arthritis	human	anecdotes, no trial verification	
Cancer	human	need to understand cause and effect	

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

### 2.1. Collapsed Trachea

The importance of copper to quantity and composition of structural proteins, in this case elastin, has been known since at least 1954 [326].

Collapsed trachea and related airway defects have been well described in humans, dogs, poultry, and other animals such as horses. The differences in the literature are significant suggesting either important differences in diseases or literature fragmentation. The dog literature does not appear to consider copper as a factor directly but interest for this paper is motivated by consideration of the larger body of information. Copper may be involved either in cartilage quality or in infection control. Copper deficiency has been associated with lung development defects in rats [262] and airway and arteriole elastin were at least partially restored after 60 days of additional copper. Interestingly, copper "eluting" stents are being explored to prevent blood vessel "collapse" or restenosis in humans due to [362] due to some of the properties considered here and its unclear why dietary copper would work less well.

A variety of causes are known in humans [314]. "Excessive dynamic airway collapse" notably is a rare side effect from anti-viral treatments for hepatitis [7]. In humans, it is a rare disease regardless of cause and CT observation of a "collapsed trachea" may result in debate over actual names for the condition [103] with surgery as a common treatment.

Horses and mules suffer from collapsed trachea too. Mostly small breed or miniatures horses were thought to be most susceptible but a 1992 case report of a horse with pneumonia noted that collapsed trachea resolved with infection cure and just due to infection related inflammation [90]. Currently it appears two causes are noted with the infectious resolving on cure.

In poultry infectious causes appear to dominate the concerns .Turkey infected with *Bordetella avium* experienced trachea collapse which was attributed to copper mediated crosslinking [386] even though collagen content was reduced. This points to a role for copper but suggests it makes the trachea worse. A study of silver nanoparticle effects on broiler chicks infected with *Escherichia coli* found [18].

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

which includes possible results of copper deficiency. Interestingly, high dose silver has been documented to decrease ceruloplasmin synthesis and serum copper concentration [254] [327]. Although it is also noteworthy that gold nanoparticles have been found to have some properties consistent with improved copper distribution such as reduced body fat [309]. It is not surprising that silver could be confused with copper as analogs can be inhibitory but as discussed elsewhere ceruloplasmin synthesis can proceed without copper but the protein may not be properly metallized. The reduction in synthesis is surprising although perhaps only copper containing ceruloplasmin was assayed and details need to be considered. The authors also mention other means than mis-metallization that silver or other metals can create a copper deficiency.

There is a lot of literature on dogs with many causes and therapies discussed but little overt inclusion of copper. One author introduces the topic as [335].

Tracheal collapse occurs most commonly in middle-aged, small breed dogs. Clinical signs are usually proportional to the degree of collapse, ranging from mild airway irritation and paroxysmal coughing to respiratory distress and dyspnoea. Diagnosis is made by documenting dynamic airway collapse with

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

Alternatively, it has also been introduced as [185]

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

Therapies in dogs can involve surgical interventions but also some of the following [238]

Medical management can include antitussive therapy, antibiotics, bronchodilators, and/or anti-inflammation medication, e.g., corticosteroids and NSAIDs) (21, 22). Many dogs respond to this medical therapy, but some have complications, especially with long-term use of corticosteroids which increases the risk of secondary bacterial infection, increases the respiratory rate, and induces weight loss that worsens the patient's clinical signs (3, 23).

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

This work is predicated on the idea that there is often a nutritional component to cartilage quality and quantity with amino acid limitation being one factor but also physiological crosslinking which depends on copper in lysyl oxidase [193]. This should be distinguished from pathological crosslinking which may occur through other mechanisms. While much is not known about cartilage crosslinking, turnover, and remodeling some recent results do point to unexpected beneficial effects of copper mediated cross linking over week time scales [227]. A role for LOXL in aggrecan processing has been described [336].

## 2.2. Heart Problems : DCM/HCM

Heart problems are common in dogs. Recently, diet-associated DCM has made headlines as an increasing threat with copper deficiency mentioned as a possible although unlikely contributor as it is "routinely supplemented" in commercial foods [231]. While it is thought to be diet related, no clear recipes have been identified for causing or preventing it. Recently in humans, the risk of recurrence of specific fibrillation or heart failure types was shown to segregate according to 3 nutritional indexes with HR's in the 10-20 range [392] suggesting general measures can already have value and a common nutritional origin that may include several components.

The heart is particularly dependent on continuous efficient energy production and mechanical properties to insure blood flow as needed. As copper is important in both functions, distribution within the heart could be expected to be critical to overall health and therefore signalling for copper regulation. Indeed this seems to be the case. A recent review of diet related DCM mentions copper along with sulfur containing amino acids as possible issues. While expressing a concern about interactions with other metals, it does not appear to mention a possible interaction with the sulfur reducing copper usage. Copper deficiency is known to produce cardiac hypertrophy in animals along with a large number of mitochondria that may be adapted to the low copper state [236].

HCM, defined as "echocardiographically-demonstrated LV concentric hypertrophy in the absence of another known cardiac, systemic, or metabolic disease capable of producing the magnitude of LV wall thickening evident" [304]. It is considered rare although it was initially considered rare in humans while now being fairly common with a wide spectrum of symptoms [343]. Energy depletion is thought to occur due to causative mutations but as of 2019 no

disease modifying or proven therapies exist although Mavacamten apparently reduced outflow obstructions in as little as 2 weeks [343].

As early as 1993, copper restriction in rats was observed to produce cardiomyopathy [235]. While reduced cytochrome c oxidase activity was observed in 1999 particularly with simultaneously high fat diets [150]. Although confusingly copper chelation with trientine is also thought to show promise in HCM treatment [285] but its unclear exactly how it rearranges copper distribution.

The heart relies on 4 valves and a rapid contraction subsequent to depolarization to move blood through the body. Mechanical properties of the valves as well as energy efficiency may be expected to be important to maintain performance without desperate remodelling. These requirements motivate an interest in accurate protein translation, and copper dependent physiological crosslinking, removal of deposits such as mineralization, and mitochondria performance. Empirically, copper deficiency can lead to cardiac hypertrophy with increased mitochondria [237]. Dilated and hypertrophic cardiac myopathy can both be related to mitochondria with "oxidative stress" as a signal for more copper at cytochrome oxidase. "Oxidative stress" has been reported to increase muscle mass while reducing performance [5]. "Oxidative stress" is often blamed in the literature as a cause of various problems but it may in fact also be a signal. ROS signalling is well known by now but specifically it may help get sufficient copper to the mitochondria.

As early as 2008, a pressure overload mouse model of DCM regressed with copper supplementation [145]. An recent 2023 work demonstrated correlations between heart copper content and cardiac parameters in a group of identically fed mice while also pointing to the heart as a regulator of copper concentration overall [23].

Over the same time however, concerns about diet linked DCM in dogs have emerged. A genetic link is also being investigated and a recent GWAS in dobermanns pointed to two genes, RNF207 and PRKAA2 as risk factors [258] but did not mention copper. However, RNF207 may mediate degradation of ATP7A [393] while PRKAA2 comes up in cuproptosis [197].

Dobermanns are at remarkably high risk of DCM [86]. Interestingly, "standard Dobermanns" are also at high risk for hypothyroidism [266].

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

Contrary indicators also exist. A study of DCM among people exposed to metals at a mining area suggested blood copper levels increase with DCM risk and found near 100 percent DCM rates above a threshold level [212]. However, even assuming blood copper is proportional to exposure, the x-axis in the graph is more likely a sum of exposures and not just copper. That is, it is a partial derivative of DCM risk in a direction that includes copper but also other things like arsenic. This is a very common problem in association studies depending on the inputs and population. In reality blood copper is largely determined by an acute phase protein and it will be associated with stress until the total stores are too low which may be well below the deficiency amounts.

### 2.3. Infection and Microbiology

The role of copper in mammal interaction with pathogens has been well reviewed in works such as [94]. Effects of copper on infection were known since at least 2400BC with other notable observations such as benefits to copper workers against cholera in the 1800's

and today with interest in copper surfaces [298]

Combined copper and zinc deficiency was observed to reduce response to covid-19 mRNA vaccines with only minimal copper deficiency [61]. The present work considers copper status in light of other nutrients notably amino acids such as Trp and Tyr and with zinc being a possible competitor.

In human health, zinc seems to have taken precedence over copper most recently with some headlines related to the covid-19 pandemic [14] [97]. Some studies suggest copper is not a factor in covid-19 due to measurements like serum copper levels [293] although ceruloplasmin as an acute phase protein can elevate levels during stress even with a deficiency in copper [125]. In sample of 70 patients prescribed zinc, many had symptoms consistent with copper deficiency [80].

Copper was shown to reduce *Proteus mirabilis* colonization of mouse urinary tract with decreased ureas and secretion and enhanced macrophage killing although with increased biofilm formation and resistance to antibiotics [144]. This delay but ultimately grow stronger effect was also seen in cultures of *Bordetella pertussis* although the authors consider it "misleading" as the effect appears to be due to the relative Cu(i) and Cu(ii) concentrations created by ascorbate in the growth medium [289]. Another work with *Pseudomonas fluorescens* SBW25 and growth on copper surface demonstrated adaptive mutations but reduced vigor and biofilm formation in plain broth although with increased antibiotic resistance [378]. If the organisms are significantly less fit in other environments the adaptations may not matter as the organisms could die out after copper exposure.

Bacterial copper absorption is thought to passive in many cases although membranes tend to be relatively impermeable porins may exist and cytosolic copper in enterobacteria is thought to be kept under one atom per organism with zeptomolar affinity transcriptional regulators of homeostasis system [111].

Copper may antagonize many pathogens including H pylori [31] and clostridium

### Thinking outloud

Repression of toxin production by tryptophan in Clostridium botulinum type E [189].

Excess copper may also be secreted in extracellular vesicles [192], a relatively unexplored method.

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

Copper compounds may reduce the virulence of some organisms for short periods even if not completely able to clear a pathogen[124] and in particular Cu was recently shown to be effective against the toxin of one anaerobe [45].

One interesting work explored the impact of copper on virulence of some environmental communities finding decreased virulence at a higher dose with increased proeudciivity at a lower dose [180]. There are a number of limitations with this work but in general there is likely to be a beneficial zone in copper supplementation to in vivo communicities such as in GI tract.

Relevant copper microbiology begins in copper plumbing systems with studies of biofilm formation, corrosion products, and roles of nutrients such as amino acids in bacteria behaviour and molecular contents of the water [143].

Bioreactors may have to deal with copper. One experiment found that Cu(II) in the 1-10mg/L range did not destroy denitrification capabilities of the colonies but did stimulate secretion of extracellular polymers and in particular proteins which bound and reduced copper at tryptophan residues [377].

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

## 2.4. Hypothyroidism

Several works find decreased serum copper as a correlate of thyroid hormone levels [38] [15] [167] while some find no correlation [354] [9] but relevance is unclear as this may just reflect low amounts of ceruloplasmin which is an acute phase protein.

Hypothyroidism may seem out of place but it is a common problem in dogs and as it involves lethargy may be confused with unrelated energy issues such as the mitochondria considerations also discussed herein. Interesting literature on copper in poultry exists largely due to thyroid effects and anti-nutrients in common feeds. For example, canola meal contains tannins, glucosinolates, and phytic acid with broiler performance and thyroid parameters shown to improve with the addition of substantial copper sulfate to this feed [20]. This work also briefly mentions ascites and thyroid function which is interesting due to one of the heartworm dogs here getting huge fluid accumulation during recovery ( unpublished observations ). Similarly, pigs fed on 8 percent rapeseed meal benefited from both copper sulfate and iodine addition and anti-nutrients isothiocyanate and oxazolidinethione were not longer detectable in the feed with copper sulfate [208] indicating copper could destroy some anti-vitamins as well as vitamins. Similar nutrients compared to HCl treatment for mustard meal demonstrated similar benefits could be obtained in calves [342].

Copper was shown to correlate negatively with TSH in one human study and may increase T4 levels [385]. Copper supplements may compensate for marginal deficiencies of related enzymes such as in mice heterozygous for functioning peptidylglycine alpha-amidating monooxygenase [44]. In another section the existence of functional copper relevant enzyme deficiency due to amino acid deficiency is discussed.

Hypothyroidism is a common problem in dogs and has effected several here [221] including some unpublished results where it was thought to contribute to peritoneal effusion after heartworm treatment. It can be defined by elevated TSH for a subclinical condition or low free T4 or T3 [257] although even the latter remains as a biochemical definition rather than something relevant to the patient. Ingestion related ( diet low in iodine or containing goitrogen or relevant drugs ) has been described as a "Rare etiology" with "acquired primary hypothyroidism" being considered most common although iodine deficiency in dogs appears to be poorly defined [390]. In this work, there is some evidence that added components such as iodine, benzoate, tyrosine, and copper may help and could fit under the category "acquired."

Issues relevant to the patient, those truly clinical, include lethargy and weight gain [76], and heart problems [345]. With lab confirmation of hypothyroidism it is possible to correct levels with supplemental thyroid hormone intake. The relevance to this work however is the ability of copper deficiency to reduce thyroid output. In such a case T4 replacement therapy will be limited as the effects of copper deficiency may still manifest elsewhere.

Dobermanns are at remarkably high risk of DCM [86]. Interestingly, "standard Dobermanns" are also at high risk for hypothyroidism [266].

Interestingly, copper deficiency in rats can reduce thyroid hormone levels and body temperature [209].

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

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

The role of metal distribution in neurodegenerative diseases is a topic of current interest with many unresolved issues [56]. Degenerative neurological or muscular diseases may be intertwined with copper status although the relationship is again confusing. Similarly with arthritis.

Deficiency seems to effect preferentially proteins involved in neuronal projection and diabetes and iron handling [351].

Rats fed a copper deficient diet show neurological symptoms by 7 weeks and had reduced tyrosine hydroxylase and SOD activity ZZ [246].

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 [381]. Interestingly, copper-ascorbate oxidation of tryptophan may be suppressed by Trp chelation of copper at high trp concentrations [245] 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 [140].

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 [205]. By 2005 toxicity of amyloid beta and the metals zinc, iron, and copper was investigated under conditions that created more toxicity with iron and zinc but not copper while amyloid beta reduced metal toxicity in rats [35]. In 2021, Ni was found in important amounts in a commercial abeta40 preparation [30] and was found to mediate tyrosine crosslinks [32] similar to the tyrosine crosslinks induced by copper found in 2004 [17].

A 2013 work found in vitro physiological conditions caused copper to prevent fibril formation [243].

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 [264].

At least one recent 2024 work identified copper dysregulation as a contributor to microbial contributions to Alzheimer's [240]. While brain copper accumulation has been observed in mouse models of AD and appears pathological [142] any relation to real disease would be questionable but accumulation may be a defense against pathogens or due to other cues that are more disease relevant.

A 2017 work concluded with other works that whole brain copper was reduced in AD and in most areas effected by AD suggesting simultaneous observation of increased Cp point to severe depletion of intracellular functions related to energy production and SOD's [66].

Copper distribution in the brain can modulate many functions from olfaction to adult neurogenesis [3]. One work in 2022 addressed AD as a consequence of copper deficiency because [171]

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

Interestingly, iron chelation has failed in AD even as iron overload is observed with ROS generation [214]. This set of conditions could easily reflect age related copper loss as mitochondria and iron transport systems are limited. Another possibility is raised by a recent work suggesting that iron accumulation in aortic valve calcification is a compensatory response to global iron deficiency [196]. In this case then iron chelation may have to be replaced with supplementation if this "compensatory hoarding" occurs in the brain which often has priority along with the heart during nutrient limitation .

Folklore regarding copper persists and yet clinical trials for Cu in arthritis continue to show lack of any benefit [286] even as other controlled tests show some effects of Cu on processes related to collagen properties [123]

Remarkably, copper sulfide was shown to protect against ETC damage by MPP [294] suggesting some activity against toxic insults. Copper histidine is used to treat Menkes disease which is a defect in ATP7A [250].

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

#### Thinking outloud

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 [136]/ pointing to a possible more general mechanism. The work goes onto suggest possible role in Parkinson's Disease but does not address AD. At least one observational study found a negative correlation between odds ratio for Parkinson's and copper intake [391]

## 2.6. Cancer

The relationship to cancer is probably the most confusing aspects of copper interactions. However, Copper deficiency does not effect proliferation of erythropoietic cells but it does reduce differentiation and alters metabolism from mitochondria to glycolysis [48] so it can produce two central features of cancerous growth. Copper accumulation has been observed in neoplastic cells and it stimulates angiogenesis [296]. While this suggests a role supporting tumor growth, "acute phase copper" and improved blood supply can be part of a healing response. Copper seems to be important to stem cell maintenance [268].

Copper has been studied in relation to cancer being considered both as a limiting nutrient and a source of cuproptosis in the overload state [333]. Copper is essential for many growth processes and can activate receptor tyrosine kinases without a ligand making it a target for cancer [128]. However, these processes are also essential for maintenance and healing in the organism and any net benefit would have to consider host fitness as well as cancer cells again using a clinical endpoint to decide on approach. In some studies, copper depletion was considered to be motivated by the observation that copper chelators reduced cancer growth and equating chelation with depletion. However, role confusion may have applied as the chelated copper could generate ROS's with obvious cytotoxic activity.

Copper storage diseases and in essence "overdose" are well known [99] and a role in cancer is suspected [39]. However, see the comments below about complexed copper actually being an active compound similar to other drugs, perhaps Pt based for example, which may kill cancer. Copper toxicity has been noted to differ between host cell types and may be reducible, at least in Long Evans Cinnamon rats, with thiamine or lipoic acid [310]. Lysyl oxidase activation, the goal of this therapy, is also associated with cancer spread [332][281][364]. Although it is likely to remodel possible tumor locations, its role in growth or metastases in a clinically relevant situation is currently unresolved ( see for example [22] or [394] and the survival curve in figure 1). Incidence of liver cancer in Wilson's Disease patients is remarkably low [249] and a discussion of possible treatment effects [359] 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 [88]. This also suggests that copper depletion per se may not kill cancer cells as much as copper complexes and that concerns about copper supplements and cancer may not be significant.

## 3. SITES OF INTEREST

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

Copper in these 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.

Location	site	Effect	time scale
Heart	mitochondria	energy production	maybe days
Heart	mitochondria	remodelling	weeks or months
Heart valves	lysyl oxidase	crosslinking [280]	weeks or months
Trachea	lysyl oxidase	proper crosslinking	months
Macrophage		phagosome	days
Macrophage		lysosome	days
ceruloplasmin		distribution	days
foreign ligand	variable	variable	

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

### 3.1. Mito Complex IV ( was Cytochrome C Oxidase )

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

Supplemental copper has been noted to improve symptoms in one case report including symptoms such as hearing loss [139] attributed to defects in cytochrome C oxidase copper loading and restore function in mutant yeast [109]. Cytochrome C oxidase levels in rat hearts were shown to be related to copper deficiency as early as 1998 [292]. 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 [352][389].

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 [265] ), it is clear that antioxidant excess should be considered as a problem with some diets. The antioxidant paradox now seems to be gaining acceptance , for example see [42] and [130] . 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 [57]. However, pro-growth and angiogenesis could also be expected during regeneration which itself may require copper.

#### Thinking outloud

Copper loading of cytochrome C oxidase relies on an oxidized Cox11 to interact with Cox19 [41] and this may be inhibited by GSH but is enhanced by GSSG. Redox regulation in the IMS seems to be integral to proper copper disposition [127] and indeed mitochondrial related signaling [315] . The latter reference also points to tissue specific mitochondrial isoform expression suggesting that maybe some related diseases are states rather than traits and hence correctable with signaling. Certainly excess antioxidants would be suspicious ( for example reference 24 [43] in [315] ) . However, the enhancement by GSSG suggests that the presence of oxidized antioxidants may be beneficial but not in their reduced state.

#### Thinking outloud

engineering ahead of medical, protein quality

In some other context, engineering efforts to produce biological products such as bone in a reactor vessel can offer insights into factors in vivo. A 2021 work focused on similar systems by modelling the effect of amino acids and copper on antibody quality in a production setting [210],

Specifically, copper has a significant, positive effect on titer and a significant, negative effect on lactate phenomenon consistently observed in other CHO cell culture processes.[12, 13, 23, 24] A plausible expla-

nation is that the increased copper level is known to drive lactate consumption. Copper deficiency reduces cytochrome c oxidase activity, limiting the ability of cells to produce ATP via oxidative phosphorylation. As a result, cells switch to aerobic glycolysis to generate ATP, causing increased lactate production, which affects other metabolic processes.[12, 23]

### 3.1.1. Amino Acids and Confusion in Copper Regulation

Copper distribution could be disturbed due to improper transporter function but it is also possible that feedback mechanisms cause an accumulation of copper when there is some other defect in complex IV or associates such as cytochrome C due to insufficient function incorrectly attributed to copper limitation. Indeed, in AD whole brain Cu appears to be depleted even with increased Cp suggesting severe reductions in things like CoX [66].

#### Thinking outloud

3 cites for this work lol

Defects in copper containing enzymes or related transporters could occur due to high-infidelity translation due to amino acid depletion as has been observed in some cancer cells [52] and was earlier suggested as common in older covid patients [220]. Remarkably at least some W to F errors do not reduce activity significantly [267] although it may not be obvious how much change is enough to trigger some response as these seem to be highly conserved W's. Aromatics may have several functions including active site participation [40], folding [36], radical [188] or hole [117] dissipation, and membrane interface [162]

. Improper functioning of any of the complex may not provide the right feedback instead just trying to get more copper and in that case supplementation may not be useful. A W to F translation error in a detoxification chain would likely shorten enzyme lifetime even if initial performance is ok.

Tryptophan given to piglets seemed to improve mitochondrial performance after a lipopolysaccharide exposure [195] suggestive of better response to a real infection. There are many possible reasons for this but if copper is diverted to respond to infection, "beating plowshares into swords," the remaining complex IV needs to work better. Conserved cysteines or a tryptophan in coa6 can mutate leading to cardiac defects including hypertrophic cardiomyopathy that can be rescued with extra copper [108].

### 3.1.2. Fats and energy regulation

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

Mice fed a copper deficient diet had enlarged heart and liver with reduced brain weight and very low ceruloplasmin (suggestive of severe deficiency) and notably lower dihomo-gamma-linolenic acid content [69]. Copper deficient rats doubled their triacylglycerol synthesis per body weight rate from labelled acetate injection[8].

One important component of energy reserves appears to be brown adipose tissue. Notably, copper and iron content of brown adipose appear to be upregulated during cold exposure [361].

SLC25A3, a copper and phosphate transporter, may have an informative role in the relevance of these elements to some nonalcoholic fatty liver diseases. Deficiency did not have much impact on mito function until cells were exposed to eleic acid with simultaneous decrease in cytoplasmic and mitochondrial copper [252]. Its interesting to note however that phosphate has a number of uses related to modification of oil-water mixtures. Ortho and polyphosphates have shown some benefits for improving oil recovery and reducing scale for enhanced oil recovery fluids [110].

As early as 1950, it was noted that polyphosphates could inhibit the rancidity of a water-fat mixture in the presence of copper and iron [368]. More recently polyphosphates were shown to chelate iron and prevent fenton reactions in vivo [28] i maybe a special case of results from 2015 which included observation metal-polyphosphate complexes can lower levels of ROS [119] and in particular copper tolerance in *Sulfolobus solfataricus* was shown to depend on polyphosphate [323]. In 2009, Kim Schnee and Park described some of the physical chemical properties of phosphates and mentioned various uses in food processing [165]. The snacks described here typically included sunflower lecithin containing some phosphate containing compounds although for humans diet cols may be another source. Polyphosphates can form coacervates in the presence of divalent cations including calcium [244] and unusual phases may be of interest in understanding copper storage in the matrix which to date appears quite mysterious.

### 3.2. Lysyl Oxidase

Lysyl oxidase family of copper dependent enzymes contributes to controlled crosslinking of structural proteins such as in injury recover [49]. They have a central role in organ development and some activity in disease [370] with the latter association contributing to the idea that inhibition would be beneficial in many cases. However, the details again point to "fixing rather than inhibiting" as with apparently pathological coagulation. In this case, one problem may be incorrect or incomplete metallization which would be fixed with more copper. Other deficiencies may similarly alter the overall function of the LOX enzymes and it may be a better solution to fix these problems than inhibit LOX. Notable functions for tryptophan and tyrosine exist and these have been identified as potential concerns before [220] .

Several works point to the LOX family as a good target due to persumed causal role in pathological results. Lysyl oxidase was considered to be bad for vessels [24] and calcification but this may be related to metallization issues [318]. Lysyl oxidase expression has been associated with degenerative mitral valve disease in humans[280]. It has been observed to upregulate in the injured newborn lung [395] sugesting increased levels may be a response to an insult rather than a cause of damage. In 2001, it was observed that bovine lyxyl oxidase had enzymatic activity without copper but was less stable [331] although details on reactions catalyzed could not have been fully explored.

Regulation at transcriptional and translation and post-translational levels is confusing. For example, it has been described in 1998 as [319],

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, [295]

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

However, metallization may not be complete and feedback systems may increase expression to achieve an activity level. Note too that "crosslinking" is a variable modification and physiological as well as pathological crosslinking can occur. While "quantity versus quality" will be the subject of another work, its important to remember that increased expression of lysyl oxidase genes and more patholoical crosslinking could occur in the absence of sufficient copper. Mature functional lysyl oxidase contains an unusual lysine tyrosylquinone (LTQ) which itself is formed in a copper dependent process [374]. Depence on multiple tyrosines or tryptophans can increase the odss of generating dysfunctional enzymes which may be inactive or perform unintended functions when these amino acids are limited. This theme of amino acid starvation also appears in concerns about ceruloplasmin and more generally with aging.

LoX deficiency has been identified as a component of pulmonary emphysema [33] [151].

### 3.3. Ceruloplasmin

Ceruloplasmin is an acute phase protein [148] which serves as the dominant copper carrier in the blood delivering copper as Cu(I) for uptake by CTRP1 by reverting to apoenzyme at cell surfaces [72]. As an acute phase protein its concentration may correlate well with early disease stages but it generally has a productive role. Besides stress modulation, activity may depend on factors such as copper availability, estrogen and progesterone [202] and , in wilson's disease, retinoids such as ATRA may improve ceruloplasmin secretion [322]. Ceruloplasmin ( regardless of how assayed) and blod copper levels and their fluctuations do not have to reflect overall copper sufficiency.

It is also a promiscuous enzyme [360]. While best known for ferroxidase activity, it can also has oxidize activity against cyclic hydroxylamines ( used as ROS probes ) [104] as well as various amino acid derivatives such as " catechol and its analogs, such as dopamine, epinephrine, norepinephrine, 5-hydroxytryptamine, and tryptophan" [202].

#### Thinking outloud

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

Ceruloplasmin contains 6 coppers and histidines needed for metallization [131]. 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 [339]. As iron accumulation is related to AD, there is a question about the quality of the circulating ceruloplasmin. If there is high-infidelity translation due to W and Y depletion, there is also the question of how feedback mechanisms control the overall amount. First it has to metallize right which requires 6 coppers and 6 histidines and then survive with the 2 tyrosines. If any components are deficient quantity or quality may suffer. Ceruloplasmin KO mice gained weight and showed increased scatter in weight with lipid dysregulation only partially corrected wth exogenous replacement [282] sugesting tight control may matter.

### 3.4. Macrophage et al

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

While well known for a role in infection control, macrophages also have a complicated role in cardiovascular disease [59] although the impact of copper may be less apparent. Recently some work has suggested that lysosomal copper may be an important storage location [277].

The importance of copper for host-pathogen relations is well known as is a prticular usage by macrophages [178] [34]. Note that nutritional immunity may involve either an excess or limitation of copper to the patogen hinting at a common source of myths about which direction to move a quantity to achieve a given result ( see a list in Appendix C ). Much is known about interaactions of copper in macrophages with particular organisms such as Mycobacterium tuberculosis and Salmonella typhimurium [137] as well as Streptococcus pneumoniae [157] . 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 [321]. As with attempts to control amyloid beta in AD, there may be some passing benefits but taking all the information together this is likely of limited value if the simpler approach of enabling the copper based response in a well regulated way is feasible.

### 3.5. Associated Entities - histidine and garlic etc

Copper can of course form associations, with many chemical groups and diverse roles. Role confusion however seems to be a recurring issue as specific componunds may not sequester or activate copper as may be expected. One recent review on anti-cancer mechanisms of copper discussed various ligands and roles for both copper depletion and overload [21]. The combination of the garlic and copper, while sounding like a medieval concoction ( suggested as a result from Bald's Leechbook [124] ), has been described as synergistic against fungus [263] and seems plausible for generating perhaps more volatile and diffusible copper that could find otherwise inaccessible lysyl oxidase and other targets.

Dogs fed a histidine deficiencnt diet eventually developed feeding resistance and lower whole blood copper and zinc [64].

## 4. CASES AND OBSERVATIONS

This section describes the new results of adding copper to diets of a variety of dogs. Context and individual case interpretation is also included here instead of the discussion section which mostly contains general observations about the cases and more complete comparison to prior work discussed in the introductory text.



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

Copper was one of many nutrients thought to be important early on but had ceased to be a focus until the arrival of Trixie. Initial work with Little Man showed apparent benefits in coughing while with Hershy activity levels increased but so did coughing. Happy seemed to benefit around that same time but her coughing can not be eliminated today. Brownie and puppies copper exposure was significant but not high and thought to have contributed to resolution of a coughing episode among the puppies. Similarly, Cookie with an antibiotic treated respiratory infection recovered but any role of copper is unknown it did not seem to harm her. With the arrival of Trixie and apparent spread of coughing copper regained focus.

The larger effort is designed to understand their diet and supplement needs with the hope of optimized feeding for each dog. The subset of data considered here focuses on variations in copper intake after the arrival of a new dog, Trixie, with various health conditions. All dogs were fed suitable human quality food and vitamin supplements in addition to commercial kibble and canned dog food products. Relevant part of the diet and outcomes were recorded in MUQED format [224] immediately after feeding and as events occurred. MUQED was still being developed as initial feeding work was being performed leading to some issues with earlier data.

While most supplements and medicines were recorded in good detail, several common diet parameters can not be inferred from this data. Snacks containing vitamins were generally consumed within minutes of preparation although in some cases snacks would be refrigerated and eaten 12 or so hours later sometimes with AM and PM snacks together.

As stability is a concern with copper, this point may be important. Besides 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. See Table III.

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 [67]. 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.

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

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

While all supplement data were recorded and many varied significantly over time, only a few are discussed here. Many of the dogs in this setting have had either symptoms that could be due to hypothyroidism or overt lab confirmed low thyronid hormone levels. As iodine intake fluctuated wildly, 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. As copper chemistry in the GI tract may be impacted by sulfur, some attention should be given to sulfur sources such as amino acids including taurine.

Dog	Dates	Condition	weight(lbs)	Cu(mg/day)	Cu(mg/kg)	Outcomes
LittleMan	2016	multiple			.8	honking stopped
Hershey	17-04-22 19-08-27	multiple	8.2 - 9	.2-.6	.1	heart failure
Hershey	17-04-22 19-08-27	multiple	8.2 - 9	2	.52	transient improvements
Happy	18-09-07 24-04-10	several	13.4 - 17.7			
Happy	18-09-07 19-05-30	heartworm/doxycycline	13.4	2	.29	cough gone
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	≈ 60	1.5-2.5		uneventful
puppies	21-03-23 21-06-09	cough	104	4.5	.095	cleared
Cookie	21-09-10 22-01-21	Resp infection/azithromycin	13.5	2	.33	cleared
Trixie	23-12-16 24-04-10	resp infection/Clavamox	37.6 - 44.6	5	.276	cleared
Happy	24-03-26	coughs	15.2 - 15.5	2	.29	rare coughing
Trixie	24-05-15 24-06-01	deep cough returned	44.2	6.7	.3	greatly reduced
Rocky	22-02-05 24-04-10		4.4 - 8.3	1	.37	subjectively better
Annie	2022-09-21	excessive sleep, apathy	7.74- 9.9	2	.5	active again
Dexter	2017-04-25	picky eating	5 - 6.8	variable low	"low"	see text

TABLE IV: List of dogs considered in this work. All of them except Dexter showed the most response after copper supplementation. Dexter was just given whatever was in the shared snacks but he had an adverse event that may be associated with copper intake. Cu amount given is largest thought to be therapeutic and in case of Hershy amount near death in (). The puppies were born on 2021-02-14 but only recorded as weaning began. Puppy weight reflects total as they were placed elsewhere and food shares are unknown

#### 4.1. Dexter



FIG. 2: Dexter daily copper intake around blood test on day 19926 . Daily amount in red 10 day trailing average in white.

Dexter was not originally part of the copper study but was included after showing signs of distress and elevated bilirubin. He had always been a picky eater but otherwise in good health with plenty of energy. Blood work on 24-07-22 was notable for elevated ALT of 140 ( 10-125 U/l ) , total bilirubin of 1.8( 0.9 ng/dl ) and ALP < 10 ( 23-212 U/l ). Low ALP with signs of liver failure may be diagnostic of Wilson's Disease but the copper intake pattern did not seem consistent with that. In Wilson's Disease, ceruloplasmin is low [383] and it may be a case of insufficiency coexisting with surplus leading to a supplementation dilemma introduced earlier. Low ALP activity may be due to zinc and magnesium deficiency [284]. Zinc and manganese did raise ALP levels in chicks although copper did not appear important under the conditions tested [302]. Based largely on the low ALP he was given a metal mixture along with KCl and various others components ( see "DEXSNACK" in MUQED data ) such as amino acids. The mixture added to kibble was well accepted by Dexter and others including Annie and Rocky. Metals included iron, magnesium, zinc, and rarely copper and manganese. He subjectively improved and he may be even eating better than before. The copper intake history did not suggest it was higher prior to the event during relevant time periods than it had been during prior times thought too distant to be relevant. His vet visit was on 2024-07-29 with last recorded copper intake of .4mg on 2024-07-04 and on 2024-07-03. He noted for spitting up yellow on 2024-08-09 after having .2mg on 2024-08-07 and -06. He had also been noted to spit up on 2023-08-08 after having no known copper since 2023-08-02. Its not real likely but he may be sensitive to copper and it was not a priority to give him more so follow on doses remain sporadic. Eventually he seemed to respond well to added vitamin D which was thought important due to bumps on his ribs and possible bone problems. Currently he seems to be gaining weight and eating more consistently with possible improvement after the switch to cooked beef adding citric acid and KCl to his diet. Chloride may be important as well as the non-copper metals.

#### 4.2. Cookie or Mixie

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

#### 4.3. Brownie and puppies

Brownie was the subject of a prior work where her uneventful pregnancy was notable for vitamin K consumption while heartworm positive [225]. Subsequent to that work, her abdominal tumor was removed and diagnosed by vet as fibroids. 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 uneventful until being diagnosed with cancer and killed 2023-02-22. Prior to her diagnosis, she was observed to cough occasionally for no obvious reason and appeared to have some movement issues. X-ray confirmed tumors likely responsible for both problems.

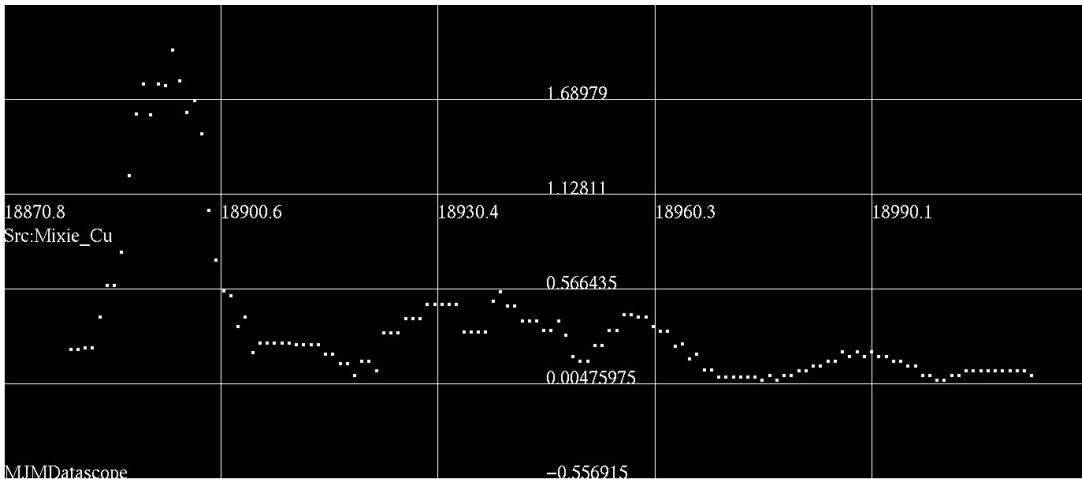


FIG. 3: Mixie daily copper (white ) intake .

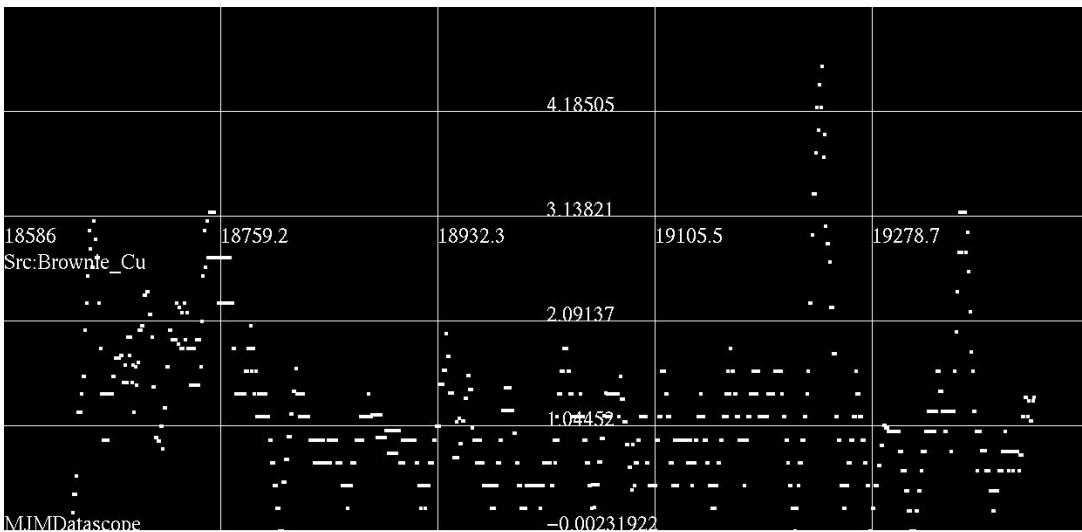


FIG. 4: Brownie 10 day trailing average copper (white ) .

Her copper supplementation was fairly minimal but given her overall state of health and pregnancy she may be an interesting case for context. As the role of copper in cancer progression is not clear, her tumors may also be a concern.

#### 4.4. Happy

Happy arrived here in September 2018 heartworm positive. Her coughing was eliminated for a few weeks in 2019 and since then it has been coming and going to varying degrees. Over the years, she has experienced brief periods of sickness but generally been active and apparently healthy except for the cough. She has shown radiographic evidence of enlarged heart and possibly narrow trachea. Her heartworm recovery was described with vitamin K and other supplements [222] followed by an unusual episode which resulted in some investigation of possible role of vitamins B-2 and B-3 in her health [218]. She had two episodes resulting in emergency vet visits and blood work. On 2022-02-02 lab results were notable for elevated creatine kinase( 609U/L, 10-200) slightly high glucose ( 123mg/dL, 63-114) , low normal Ca ( 8.5 mg/dl, 8.4-11.8) and Cl ( 108mmol/L, 108-119) with high normal bicarbonate( 26mmol/L, 13-27). ALP( 35 U/L, 5-160 ) was normal and total T4 low normal ( 1.2mug/dL , 1.0-4.0 ). On 2024-10-04 at a different clinic glucose was normal ( 111mg/dL, 70-143) and ALP was low normal ( 31U/L, 23-212) with no measures of creatine kinase or blood chemistry. The change in ALP appears to be largely due to reference ranges as numbers are similar between visits. For comparison, Little Man on 2016-12-29 while on steroids IIRC had elevated ALP ( 231

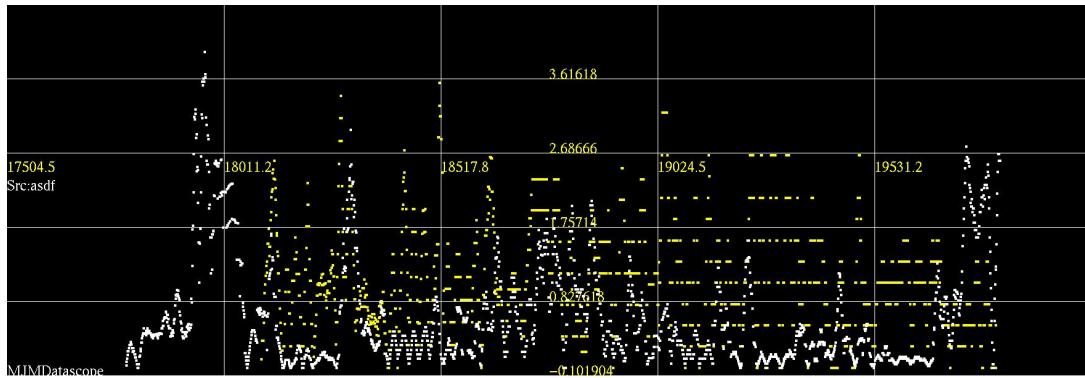


FIG. 5: Copper(white) and Zinc(yellow) dosing per day averaged over prior 10 day period as dosing was highly variable due to rotations of various nutrients. 18046 is 2019-05-30 when the cough was first noted to be gone for a few weeks. 19823 is 2024-04-10 the last date for which data was obtained. The 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.

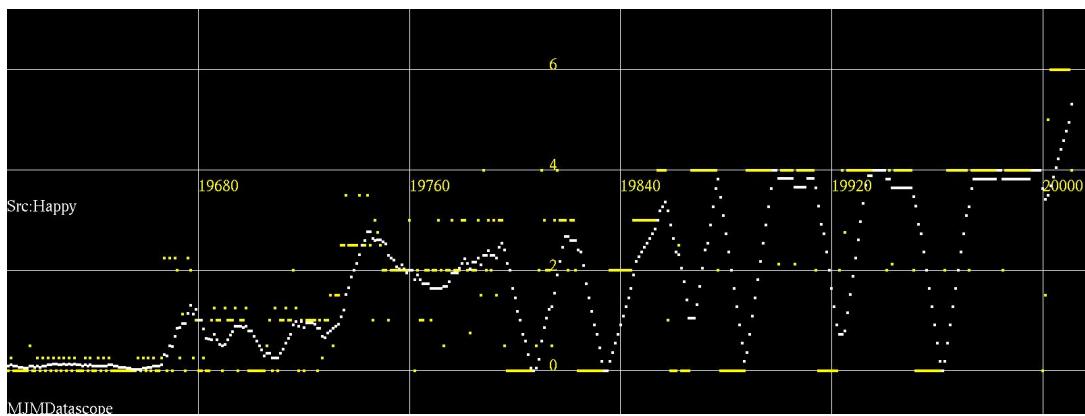


FIG. 6: Most recent with some passing progress

U/L, 0-140 )i and high glucose (126ml/dL, 75-124) and low BUN ( 8.6 mg/dl, 9-29). ALP may have been elevated due to steroids as well as copper toxicity.

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

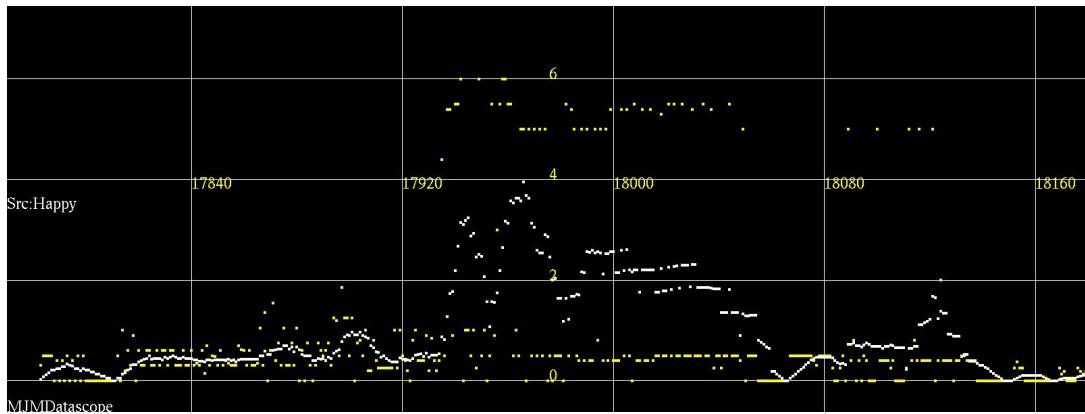


FIG. 7: Earlier when she was cough free for a whlie

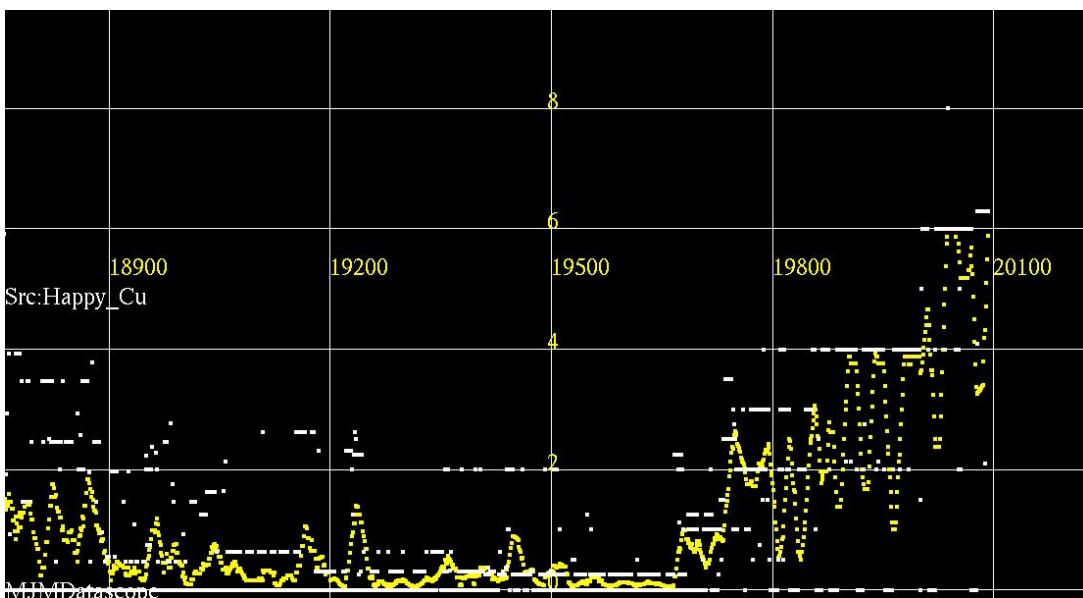


FIG. 8: Post script switch to Chinese citrate and increase dosing to no obvious benefit

### Thinking outloud

Happy, like Brownie, was also the subject of two prior works. Initially her heartworm recovery was described with vitamin K and other supplements [222] followed by an unusual episode which resulted in some investigation of possible role of vitamins B-2 and B-3 in her health [218]. 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. Years later she 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 to lower than prior levels. Review of the copper dosing suggested it had fallen prior to Trixie's arrival. Often her excited cough appeared to be a honk on exhale suggestive of trachea collapse. She also would cough early in the morning when curled up. As outlined in the introductory material, it was later realized that earlier concerns about aromatic amino acids could be due to simple excitability rather than any disease worsening. This most recent effort considered some coughing increase normal and now she seems to have reduced coughing, good energy level, and maybe some aromatic amino acid sensitivity.

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

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

For Happy copper may be necessary but not sufficient. Current concern is around restriction of aromatic amino acids, notably tryptophan, iodine, and iron, along with adequate meat fats from beef, turkey, and chicken.

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

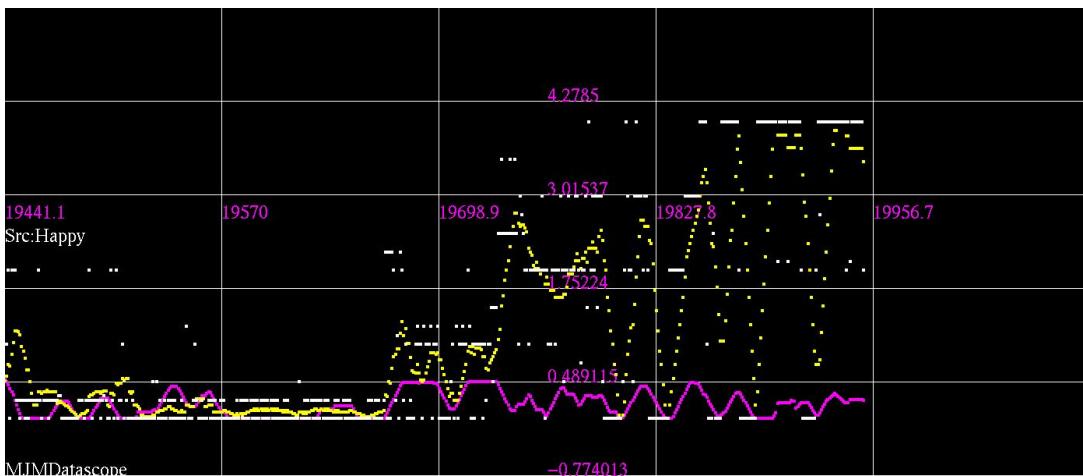


FIG. 9: Copper shown for daily and 10 day trailing average along with chicken thighs ( magenta) as a measure of fat intake. Recovery from low fat diet appears to take longer than recovery from only copper deficiency.

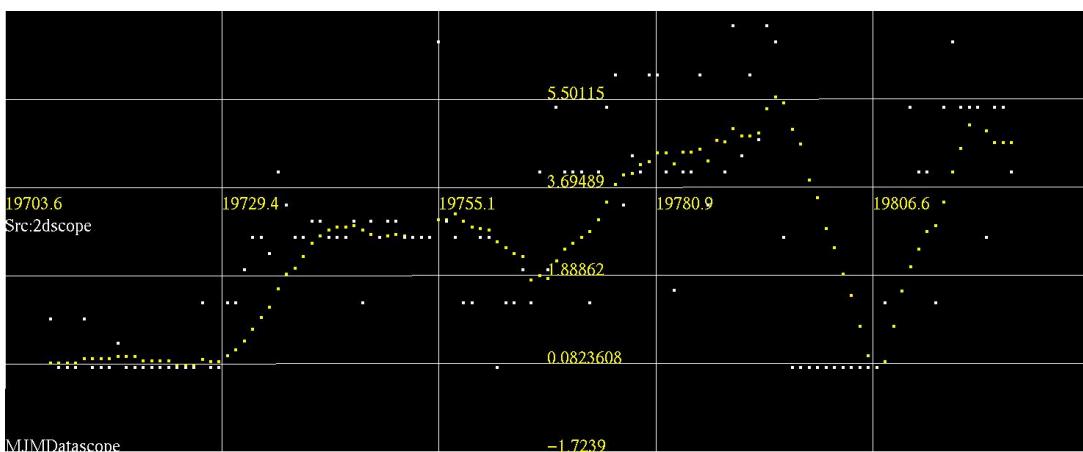


FIG. 10: Trixie copper consumption since arrival. Daily amounts ( white)) and trailing 10 day average( yellow). Copper started to be significant around day 19730 in response to coughing. Day 19807 marked the end of the copper fast as well as the end of Clavamox which was prescribed due to worsening when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

#### 4.5. Trixie

Trixie began coughing shortly after arrival and was very low energy. Her coat was notable for a sticky feeling that seemed to recur after a bath. Many other dogs began to cough or hack suggesting that she brought a communicable infectious disease which was the motivation for increasing copper again. Nutrient mix was modified to add more copper and most dogs' coughing returned to normal quantity and quality although her's did not entirely resolve. Copper stopped for a couple days ( I was gone ) and owner took her to the vet as she began coughing more. Clavamox was prescribed and her coughing stopped within a few days. Her energy level has improved but she did not run until 2024-05-02 ( 19845 ) . She had a renewed cough around 2024-05-22 (19865) subsequent to copper withdrawal on 2024-05-15 (19858). Cough seems deep on excitement not honk/wheeze like Happy. Copper resumed 2024-05-27 and is greatly reduced by 2025-06-01 . She appeared more energetic than when I left and walked well although maybe still tired at end of walk. Her coat now feels clean.

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

#### 4.6. Rocky

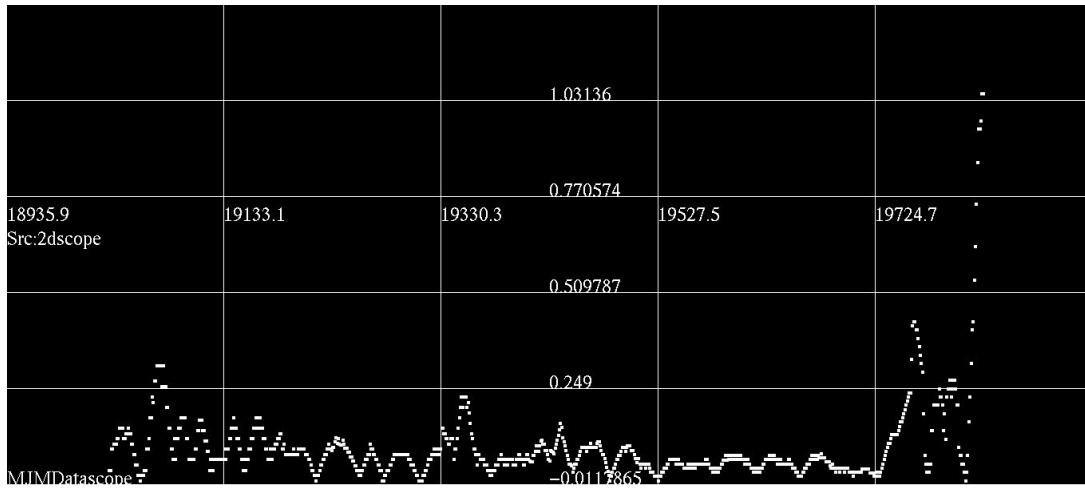


FIG. 11: Rocky 10 day trailing average copper (white) .

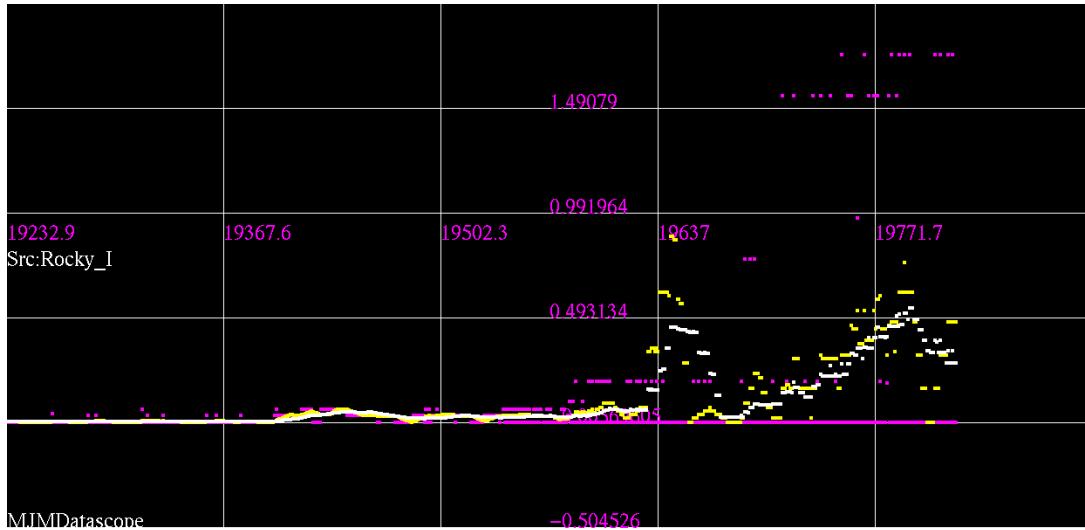


FIG. 12: Rocky iodine intake daily and with 10 and 30 day trailing averages. Patterns are difficult to discern with the pulsed dosing.

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

Copper was shown to correlate negatively with TSH in one human study and may increase T4 levels [385].

As benzoate may be an important confounding factor, a brief digression here may be helpful. A recent study on rats fed benzoate demonstrated some insignificant indication of increased T4 and decreased TSH which the authors summarize as, [344] ,

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.

#### 4.7. Annie

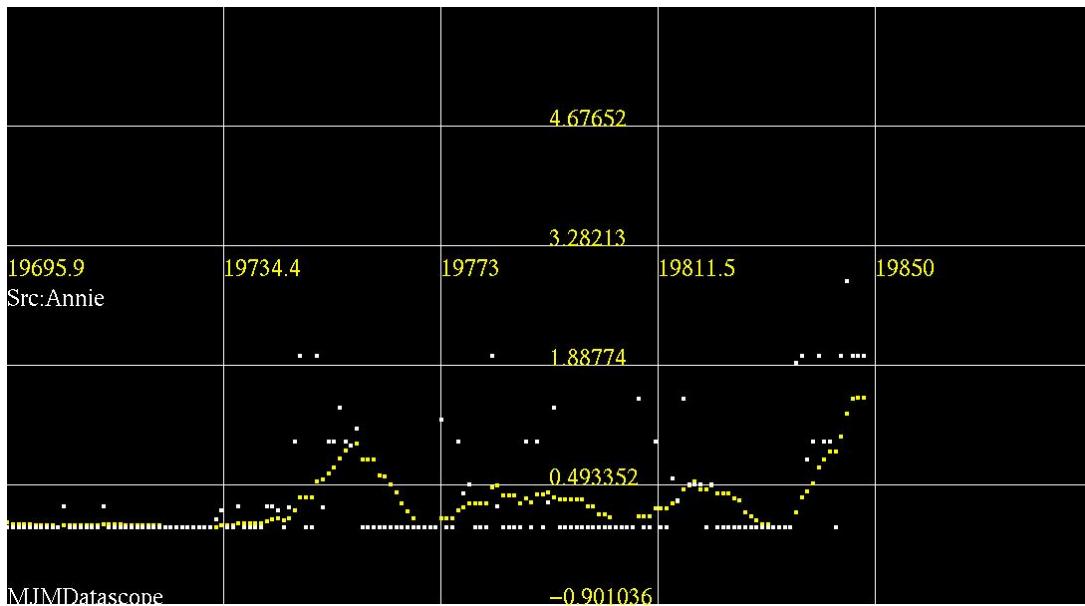


FIG. 13: Annie

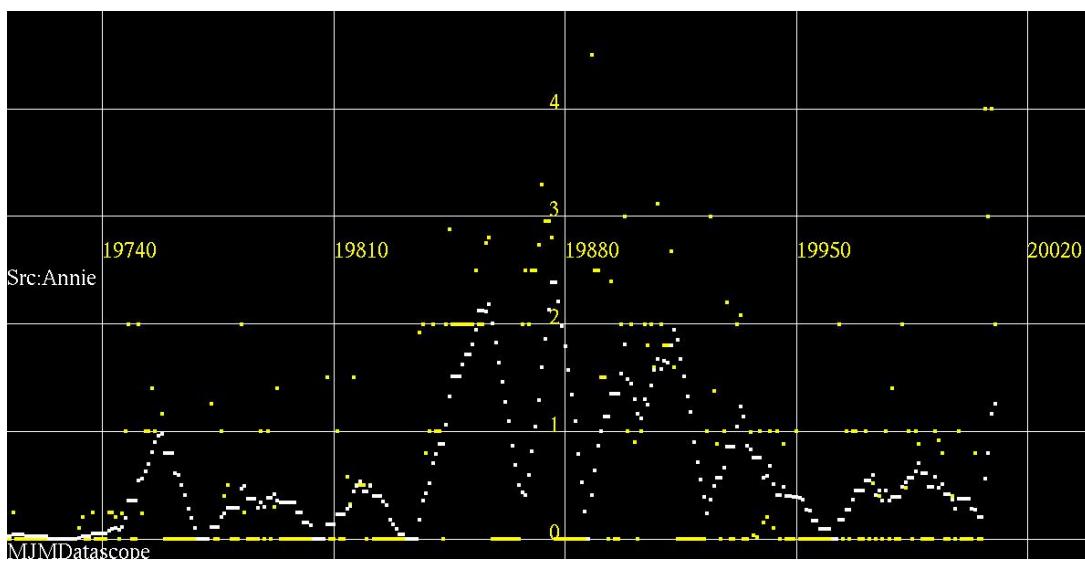


FIG. 14: Annie zoom in on recent days as copper was increased due to swelling under eye.

Annie probably showed the clearest improvement coincident with increased copper ( and a few other components described below) on two occasions. Annie arrived thin but in generally good condition although seemed old for stated age of 6 years . She ate well but had some limitations in sight and hearing. She seemed to get skin or paw irritations easily. Coughing was variable and not well documented. She feels a little "frail." She began to sleep excessively in early 2024 and a special copper snack was started on 2024-05-01 ( 19844). This consisted of 2mg of copper along with sodium benzoate, KCl, and B-6 in chicken broth which was more readily accepted than the full snacks for everyone

else. As these other components had been quite common they were not considered significant although the sodium benzoate had also been stopped earlier. Lost vigor suddenly regained in a few days and seemed restored to her more typical self by 2024-05-05 ( 10948 ) with continuing improvements in energy and appetite. Her exercise interest improved and she walked and cried with good energy.

Around 2024-10-11 ( 20007 ) Annie was noted to have swelling under her left eye. As she had not been eating the PMSNACK regularly her copper intake had again been reduced so I added it alone to canned dog food which she ate well. By her vet visit 3 days later on Monday, the swelling was gone. She was prescribed Clavamox and an "artificial tear" solution.

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

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

#### 4.8. Hershey

In retrospect, Hershey should have been an important clue as he reacted quickly to the copper but there was undue concern for increased coughing.

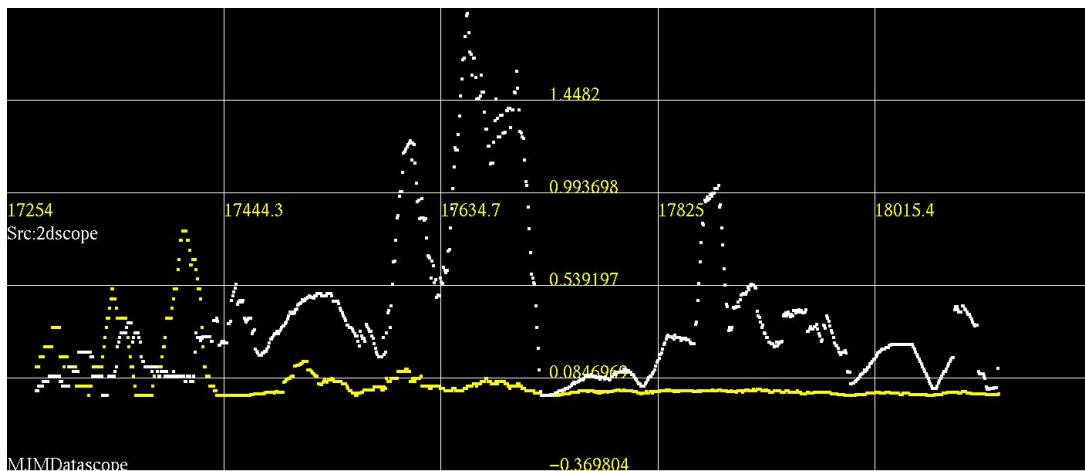


FIG. 15: Herhsey 10 day trailing average copper (white) and iodine (yellow).

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 b7ngnncc rested ok. Made it up steps after PMSNACK ok although aborted on attempt but it is 95F out.
2018-10-12	17816	planning and cirling on bottom step then doing good up steps
2018-11-02	17837	walked up first few steps in the rain and then faster up last few no slipping. Rear left leg may be more useful now.
2018-11-26	17861	better again on steps walking up but coughing still
2018-12-04	17869	coughing a lot again try stopping Cu for day or two
2018-12-17	17882	probably made it up steps on own, saw he was gone then heard barking and clumsy step noise. Seems good still coughing on and off, went around shed today.
2018-12-27	17892	coughing less and went out to pee, maybe the extra copper yesterday helped quickly
2019-01-08	17904	seems generally more active maybe coughing less for all the barking with the other 2 BCAA's
2019-03-12	17967	pretty good up steps almost back to recent bests. Coughing like always but darted out the door to deck quite well went around shed etc.
2019-03-14	17969	leapt up some steps then stumbled near top, went around near side of shed ok and wandered yard for a while
2019-04-02	17988	good on steps leaping not slipping
2019-04-26	18012	came up steps without crying on his own.
2019-05-13	18029	Hershey slower than yesterday more normal
2019-06-03	18050	Vet found heart failure on X-ray and bladder stones.

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

Hershey quickly demonstrated several problems not long after arrival. He had problems with his fur, digestion, and coughing while ultimately being diagnosed with heart failure and bladder stones. 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. In retrospect, his initial response to increased copper may have been to be more energetic but that increased his coughing leading to a dosage reduction. Clearly the data are incomplete but suggestive now of some benefits.

## 5. DISCUSSION

### 5.1. General observations on these cases

Copper supplementation averaging around .2 to as high as .8 mg/kgBW/day appeared beneficial in this group of dogs as symptom improvement often followed weeks of dosing. In the case of Annie, two results appeared just a couple days after copper intake was increased. 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 phase. Most notably, increased general energy may increase coughing in the presence of a weak or collapsed trachea or with some heart conditions. Initial response would be to increased energy production and presumably a feeling of wellbeing but remodelling and stiffening may take longer to 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 Trixie's respiratory infection that the data were examined more carefully and the pattern noted. Ideally the filtering would be a lagging average weighted to some suspected biological parameters but even uniform moving average was useful.

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

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

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

Happy's prior rubbing episodes, initially treated with Apoquel but subsequently just "waited out", did not appear after increasing copper even though she had been doing that on and off recently. She sometimes took to "rolling over" later but mostly for attention. This "allergy" could be pathogenic via immune response to either allergen or actual pathogen that becomes resolving with more copper although symptoms could be treated with Apoquel known and likely side effects make this a cleaner solution.

It's unclear how many if any infections were avoided with added copper as some dogs benefited from antibiotics even with the copper at the recorded doses. It's possible it slows the growth or reduced virulence but does not clear some infections. This may allow it to become larger before clearing with antibiotics. One work in mice did show increased antibiotic tolerance to *P. mirabilis* that survived copper exposure [144].

**Thinking outloud**

maybe add Daisy as she had earlier infection

Annie's foot irritations apparently went away although she may still have had eye infections.

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.

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

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

**Thinking outloud**

repeated in intro

Besides the molecules already mentioned, it is worth noting that taurine was a consistent dietary component. Sulfates are observed to create copper deficiency in ruminants and the possibility exists that taurine exhibits related chemistry in the GI tract. Indeed, it has been observed to reduce copper toxicity in rats with increased fecal copper

amounts [146] suggesting decreased absorption. Another work demonstrated taurine reduced ceruloplasmin only in rats fed a control diet but not a high-fat diet [173]. As taurine is being explored for various indications, including DCM [234], apparent limitations in supplementation could relate to induced copper deficiency which would likely cause some symptoms expected of copper deficiency.

Several likely benefits of copper supplementation were observed but no clear robust clinical symptoms got worse. This is contrary to some indications from popular 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 [53] possibly making copper a secondary excretion issue rather than a primary absorption problem. However, the concern with excess B-6 intake creating effective deficiency is a reminder to look more carefully at all data.

Iver a broad range of genetics, its 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.

## 5.2. Aspects of Copper Chemistry

### Thinking outloud

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

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

A central topic is copper speciation or oxidation state. Perhaps four copper oxidation states have been considered in the biological context. Solid Cu(0), Cu(I), Cu(II), and rarely Cu(III). Cu(I) and Cu(II) are probably the most relevant to food effects. Solid copper or Cu(0) has been claimed to have environmental remediation capabilities [73]. Cu(III) is thought to be an intermediary in the copper Fenton reaction at near neutral pH with bicarbonate and sodium chloride present [274]. Cu(III) production for degradation was also enhanced with histidine [270].

The first concern, the formation of insolubles that have decreased availability of the copper, is most clearly seen with sulfides but many other stable copper compounds are known. Copper minerals represent some compounds that exhibit low solubility in their native settings. Wikipedia lists several copper ore minerals [373] containing sulfur, iron, antimony, zinc, carbonate, hydroxide, aluminum, silicon, hydrogen, arsenic, and water. Of course an infinite number of organics could be formed with variable stability. Early XPS work suggested many copper minerals contain copper in the +1 state [251] although work continues to clarify specific issues [114]. Generally the minerals can be leached in acid to recover the copper and that chemistry may be useful here.

It has been noted that Cu(II) is converted to Cu(I) prior to transport and therefore some benefit may be obtained by making the conversion from Cu(II) earlier. However, as with some other nutrients, this may be counterproductive when normal mechanisms are operational. CTR1 for example will convert prior to transport [158]. This is likely similar to the situation with iron [300].

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

mainly as Fe31. DcytB, an ironregulated ferrireductase protein is highly expressed at duodenal enterocytes and reduces the Fe31. Upon reduction, Fe21 is transferred across the apical membrane of enterocytes by divalent metal transporters, mainly DMT1 (Fig. 6).

The same work [300] may be a good background for understanding copper more generally as a lot of issues with iron may be similar.

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

Copper "Fenton" reactions have been extensively explored for pollution remediation by destruction of toxic chemicals. Many of these reactions occur under mild nearly physiological conditions suggesting they may be able to degrade nutrients. In particular, bicarbonate in the 4mM range improves the degradation rates for a Fenton like Cu system [272]. In fact, carbonate species are thought to be the active products not hydroxyl in neutral or alkali media [147]. Bicarbonbte is being investigated for pollutant degradation optimization [365] as it apparently is quite active.

### Thinking outloud

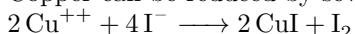
The photograph in Fig. 16 shows the side of a baking pan on the right which was representative of the surface to the left prior to heating for a while in baking soda water. The carbonate derived species may easily react with or make soluble the oxidized food grease which I thought was just a "like dissolves like" issue but may be as stated here. An ammonium bicarbonate electrochemical etch aparently optimized the mechanical properties of carbon fibers [166].



FIG. 16: A previously brown baking pan with baked on carbonized food largely grease. Heating in oven cleaned the metal submerged in baking soda water while leaving the metal above the water line dark. See if bicarbonate has any relevance here or save for another work lol.

Cu(II) is the more common species but it can be reduced under relevant conditions by ascorbate, riboflavin leading to DNA damage [253]( although maybe assisted with light [152] ) or reducing sugar at elevated temperatures which may occur during food processing. While sometimes associated with alkaline pH it can occur with pH of 3[133]. It can be reduced and complexed with niacin [54]. It may be worth noting however even the interaction with ascorbate is controversial with redox competing with a catalytic mechanism leaving the Cu unchanged [311]. Generally copper absorption has been reported to decrease with higher dietary ascorbate with a confusing interaction with iron [156] which may be easy to rationalize a increased copper reduction prior to uptake.

Copper can be reduced by several things.

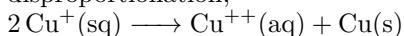


Once Cu(I) is formed, it can undergo undesirable reactions.

[299]



disproportionation,



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

**Thinking outloud**

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

It is quite reasonable to consider the possibility that uptake is limited by stomach acid and chloride assuming that once soluble the copper can be stabilized on something available.

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

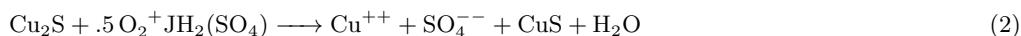
Once a copper sulfide is formed, the copper may be recovered in processes such as commercial leaching that can go at 30C. In an acid environment both chloride and iron are important to getting optimal copper extraction from sulfide ore [297].

And some have observed chloride may be generally better for extractions of metals from sulfides, [134]

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

In a completely unrelated study of the electrocatalytic behavior of cobalt sulfides, the authors found a surprising role for chloride in converting sulfides to hydroxides against prior predictions [120].

Some leaching reactions include [303]



(3)

FIG. 17: Some leaching reactions [303] at ambient or elevated temperatures

Ultimately food and stomach contents form a complicated variable mixture of chemicals with varying ability to interact with copper and a survey of such properties such as [213] may be useful.

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

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

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

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

Copper sulfides can form varying large unit cell crystals with correspondingly high integer stoichiometry. They apparently are not molecular crystals. Unit cells may contain 24 or 62 distinct copper atoms and some phases contain a sulphur HCP structure with interstitial Cu that become fluid above 100C [85].

This may appear unrelated to anything biologically relevant but a number of unknowns exist around the interaction of copper with mitochondrial ligand CuL. For example [93],

Mobilization of Cu into the mitochondrial matrix was also shown to occur bound to a non-proteinaceous fluorescent ligand, termed CuL [110, 113, 114]. CuL levels were found to correlate with cellular Cu levels and COX assembly [110, 115]. CuL, suggested to be coordinated by citrate and oxaloacetate, migrates with a mass of 13 000 Da, hinting at larger ligands. Fluorescence anisotropy experiments showed that the CuL complex is transported by SLC25A3 and MRS3 transporters [115-117]. Although the molecular identity of CuL and the mechanism for exiting the matrix and delivering Cu to apo-COX17 in the inter-membrane space remain unclear, its biophysical properties suggest it contributes to buffering cytosolic Cu and facilitating Cu uptake into mitochondria [110, 113].

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

A phase diagram around Cu<sub>2</sub>S was published in 1981 showing phase transformations above 72C [84] which is too high to be biologically relevant except for cooking but may be important in IC failure modes. A more complete phase diagram from CMU 1983 is also available [51]. Metastability may be common due to need to rearrange hcp.

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

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

### 5.3. Aspects of Copper Garlic Chemistry

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

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

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

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

Some works have cataloged and generalized the types of sulfur compounds prevalent in various food categories [78].

Empirically, organic polysulfides common in garlic, onions, shallots and related products are thought to have some cardioprotective effect but are difficult to analyze due to instability [341]. One small study suggested that garlic added to a diet could reduce some signs of copper deficiency in a fructose rich diet [91]. Interestingly, both copper and garlic demonstrated some favorable effects on cholesterol with copper reducing levels of fatty acid synthetase and garlic thought to slow the rate limiting step in cholesterol synthesis [172] although the interaction between copper and cholesterol ( and fructose ) relating to glucose intolerance has been known for decades has also been neglected [170].

#### Thinking out loud

this belongs in something on age related conditions too

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

### 5.4. Supplement Selection and Dosing Considerations

It's expected after all of this that benefit or harm from copper can depend on details of the diet, preparation, storage, and supplement. Side reactions have to be considered at first contact between copper and anything else and in general minimizing time and temperature may be beneficial. Time-release or limited solubility forms may be useful for pre-mixing or copper could be given in isolation from any other food intake.

Common supplement forms include copper sulfate, copper gluconate, copper glycinate, and copper citrate. Glycinate appears to be popular due to solubility and reputed bioavailability. Sulfate appears to be common due to cost [376]. Gluconate was used in a lot of the latter part of this work as it was the only bulk form available in reasonable price and quantity. A priori and currently there is some reason to consider citrate as desirable. This was eventually purchased in kilogram quantities from China and had been used early on as it is a common form in small supplement capsules.

Sulfate, glycinate, and proteinate effects were compared in pigs and sulfate was found to be less absorbed and associated with reduced microbial diversity [372].

Citrate salts have been well studied in a variety of contexts. Calcium citrate in particular has been explored as it may have benefits for calcium handling in biological settings [199]. It appears to become more soluble with excess

citrate although the Ca activity is reduced [348]. As most of the snacks formulated here included significant citric acid, the 'citrate dissolves citrate' notion may be applicable although the effects of complexing are not known. Reduced reactivity may be a benefit however.

Citric acid appeared to improve biological activity of copper as an algeacide in the presence of bicarbonate even when derived from copper sulfate [330].

Studies have also shown that mixing copper citrate with amino acids improves solubility [320] which may be relevant here as most snacks contained many amino acid supplements.

The rabbit, notable for a functional significant cecum, demonstrated differential changes in cecal microbiome due to copper citrate, sulfate, and chloride additions with citrate reducing diarrhea [79].

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

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

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

## 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 ingredient interact with metals to varying degrees and this notably contained citric acid and spinach along with amino acids.

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

## 7. PERSPECTIVE : COPPER IN PAST CIVILIZATIONS

Thinking out loud

always introduce new topic at the end lol

Given copper's lustre and malleability it may not be surprising that there is a long history of special treatment for copper in past civilizations. The point of raising this experience towards the end of this work is to put the apparent

risks and benefits into perspective. That is, it sounds like only a very sophisticated Western audience could encounter copper and actually benefit but that may not be the case either due to luck, hidden knowledge, or a more favorable risk benefit profile from copper exposure. These "macro" observations may help put the "micro" observations into a better range of implications. "Micro" results may seem more precise and scientific but are by design isolated and miss a lot of important context.

It sounds as if copper may require substantial care to supplement but as a final thought its worth remembering that many older civilizations appeared to recognize copper as particularly "good" in some ways from cookware [25], ritual uses, to medicinal[328]. Many appeared to persist for quite some time but it would be interesting to see if they had signs of copper toxicity or generally better health than those ignoring copper.

Copper is mentioned in some of the earliest known papyrus, we used by many historical "great" civilizations such as Egyptians, Greeks, Romans, and Aztecs with rediscovery in the 19th century to be replaed in medicine by antioovics in 1932 [116]. Even today, copper sulfate is burned in Buddhist and Hindu buildings for good luck or religious reasons [102]. If exposure contributed to the downfall of any of these societies it is generally not explicit. There is some interest in revival of ancient antibiotics such as described in the Leechbook [74] previously mentioned but we don't know how effective these are in real world conditions. Copper combinations also arise in the study of ancient medicinal plants [37] . A review of scholarly literature may be biased with conemperary expectations. Health effects are difficult to infer but would have to be compared to competing exposures and impurities such as arsenic that may have been common in a given community. Apparently arsenic was present in the area of Peruvian Andes [181]. Given the adoption of modern antibiotics, they likely had clear superiority to known copper formulations.

## 8. CONCLUSIONS

Copper supplementation circa .3-1mg/kgBW for this group of dogs did not appear to generate any adverse events with the possible exception of Dexter who was never dosed consistently. Responses observed included increased energy level and reduced infection symptoms. The main goal of eliminating Happy's cough was not achieved with the final diet although her ALP remains low suggesting she may benefit from even more copper due to either worsening disease or some quirks of the current diet.

Copper availability may depend on stomach pH, intestinal health, and other dietary components such as sulfur or zinc. As the pH is reduced the effect of other components may be reduced. Overall distribution in the body may also depend on a variety of other nutirents.

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

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

Concerns about excess accumulation may be due to other dietary defects and not copper content per se. There may be thoughts along the lines of "balance" but that is probably a garbage word leading to tautologies. More to the point may be "limiting nutrients" or factors that aloow a given intake of other things like copper to be assets rather than liabilities. While some were discussed here, there are many and even this is likely a simplification of the "response surface."

While "root causes" are a trendy topic, it may be worth noting that you can keep chasing cause and effect indefinitely but the point is to find the most suitable intervention. Copper loss per se is causing problems and needs to be fixed but ultimately a better solution probably exists in determining the cause of insufficient copper despite higher than normal intake. So, the approach here is largely to pursue causes rather than mere associations which are often misleading for intervention ideas.

## 9. SUPPLEMENTAL INFORMATION

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

### 9.1. Computer Code

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

diet tables,

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

datascope output,

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

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### Appendix A: Statement of Conflicts

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

### Appendix B: About the Authors and Facility

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

### Appendix C: Some Common Logical Fallacies and Misdirections

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

1. **first impressions last :** You see this even in physics. Once a mystery has been ( partially ) solved it becomes entrenched dogma. In some compression technologies it's safe to assume the first thing you see is most common but that doesn't seem to work in science lol.
2. **people over data :** This comes up in essays on long lived medical myths. Opinions, votes, don't determine natural laws
3. **X is a Y so it must do Z :** There is no small molecule with only one function and even antibodies are proteins and may have off target targets and can be immunogenic. With copper this comes up with chelators but may also apply to anti-oxidants or even water.
4. **X is a Y so it does Z :** Role confusion leads to more untested assumptions. A Rose by any other name would have a different billing code and label
5. **local optimum :** Moving some quantity in one direction perturbs the system in a sort of beneficial way preventing anyone from looking the other way for a better result.
6. **supply v demand :** An excess quantity is not inherently due to either supply or demand
7. **quantity may be due to a quality problem. :** The feedback that produces inducible effectors may not go away until the job is done. If the effectors don't work you will get more of them. Getting rid of them will not fix the original problem that may be important if this control system evolved well lol.
8. **false dichotomy :** good and evil
9. **non-monotonic curves :** *show me a monotonic dose response curve and I'll show you a fool*
10. **fix or remove :** Often there are 2 approaches to getting the same result with a partially broken system.
11. **one extreme says nothing about the other :** Both increasing or decreasing some quantity may produce the same ( beneficial or evil ) effect.
12. **presumed antagonists may work together :** One example cited osteoclast activation as not be the opposite osteogenesis and in fact vigorous remodelling may be important for healthy bones.
13. **hidden interaction :** The observed result requires some interaction partners

14. **local optimum** : prohibits consideration of global optimum over rugged parameter space with bad figure of merit.
15. **rabbit trail** : Successive approximations, even as advocated in this series of works, can lead a strategy down the wrong path.
16. **platitudes** : better to be safe than sorry lol
17. **philosophy over dynamics** : feedback can be complicated and commonly observed associations misleading
18. **equations** : consider spherical horse linear approx
19. **proxies** : Almost only counts in horseshoes and handgrenades
20. **models** : This usually means cause and effect is tossed out and the premise of the work has nothing to do with the premise of the real disease and that is often not even known well.
21. **only relies on empirical observations** : no cause and effect established
22. **ignoring empirical observations** : "sanity check" Theory based on incomplete system topology needs to be consistent with empirical observations
23. **ignoring empirical observations** : Theory based on incomplete system topology needs to be consistent with empirical observations
24. **other state variables** : Hidden variables include a limiting nutrient that is needed to beneficially use the entity under test.
25. **regulatory landscape** : As life is generally robust control systems have evolved but may have non-obvious failure modes.
26. **trying harder** : If a preferred response is frustrated in attaining a survival relevant goal, there may be signals to try a less orderly response more vigorously. The disorganized response can be suppressed by enabling the effective one.
27. **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	
egg03	0.065 ;0.12;23/23	0.062 ;0.062;30/30	0.055 ;0.12;20/24	0.062 ;0.062;31/31	0.062 ;0.062;29/29
eggo			0.01 ;0.062;4/24		
eggshell	0.13 ;0.25;23/23	0.12 ;0.12;30/30	0.11 ;0.25;21/24		
garlic	0.022 ;0.25;2/23	0.22 ;0.25;26/30	0.083 ;0.25;8/24	1.2 ;1;27/31	0.99 ;1;22/29
marrow	0.19 ;0.25;12/23	0.37 ;0.25;30/30	0.083 ;0.25;6/24		0.078 ;0.25;7/29
oliveoil(tsp)	0.035 ;0.12;8/23	0.014 ;0.12;4/30			0.039 ;0.12;9/29
pepper	0.36 ;0.25;23/23	0.38 ;0.25;30/30	0.35 ;0.25;24/24	0.36 ;0.25;31/31	0.38 ;0.25;29/29
pineapple			0.021 ;0.25;2/24		
raspberry	0.32 ;0.25;23/23	0.28 ;0.25;24/30			
salmon		0.043 ;0.25;8/30		0.025 ;0.25;3/31	
shrimp(grams)		3 ;38;5/30	4.9 ;16;9/24	2.8 ;16;8/31	1.8 ;13;4/29
spinach		0.15 ;0.25;12/30	0.36 ;0.25;24/24	0.38 ;0.25;31/31	0.36 ;0.25;28/29
sunflowerseed	0.23 ;0.25;21/23	0.25 ;0.25;30/30	0.21 ;0.25;20/24		0.034 ;0.25;4/29
tomato	0.36 ;0.25;23/23	0.23 ;0.25;19/30	0.18 ;0.25;12/24	0.17 ;0.25;15/31	0.19 ;0.25;29/29
tuna(oz)					
turkey	0.34 ;0.25;23/23	0.37 ;0.25;30/30	0.35 ;0.25;24/24	0.36 ;0.25;31/31	0.36 ;0.25;29/29
vinegar(tsp)	0.09 ;0.062;23/23	0.094 ;0.062;30/30	0.09 ;0.062;24/24	0.068 ;0.062;24/31	2.16e-03 ;0.062;1/29
<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 VI: Part 1 of 2. Events Summary for Happy from 2023-10-01 to 2024-04-10A summary of most dietary components and events for selected months between 2023-10-01and 2024-04-10. Format is average daily amount ;maximum; days given/ days in interval . Units are arbitrary except where noted. Any superscripts are defined as follows: **a)** SMVT substrate. Biotin, Pantothenate, Lipoic Acid, and Iodine known to compete..**c)** hamburger with varying fat percentages- 7,10,15,20, etc. ..

Name	2023-10 Oct	2023-11 Nov	2023-12 Dec	2024-01 Jan	2024-02 Feb
Zn(mg zn)	1.3 ;5.9;9/23	1.1 ;5.9;10/30	0.73 ;2.9;6/24	0.47 ;2.9;5/31	0.61 ;5.9;5/29
arginine(mg)	68 ;175;9/23	82 ;350;10/30	51 ;175;7/24	79 ;350;12/31	275 ;350;15/29
biotin(mg) <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
vitaminc(tsp)	3.23e-03 ;0.0078;11/23	3.39e-03 ;0.0078;13/30	8.14e-04 ;0.0039;5/24	5.04e-04 ;0.0039;4/31	5.39e-04 ;0.0078;2/29
vitamine(iu)	8.2 ;38;5/23	8.8 ;38;7/30	9.4 ;38;6/24	7.3 ;38;6/31	6.5 ;38;5/29
<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 VII: Part 2 of 2. Events Summary for Happy from 2023-10-01 to 2024-04-10A summary of most dietary components and events for selected months between 2023-10-01and 2024-04-10. Format is average daily amount ;maximum; days given/ days in interval . Units are arbitrary except where noted. Any superscripts are defined as follows: **a)** SMVT substrate. Biotin, Pantothenate, Lipoic Acid, and Iodine known to compete..**c)** hamburger with varying fat percentages- 7,10,15,20, etc. ..

Name	2024-03 Mar	2024-04 Apr
<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 VIII: Part 1 of 2. Events Summary for Happy from 2023-10-01 to 2024-04-10A summary of most dietary components and events for selected months between 2023-10-01and 2024-04-10. Format is average daily amount ;maximum; days given/ days in interval . Units are arbitrary except where noted. Any superscripts are defined as follows: **a)** SMVT substrate. Biotin, Pantothenate, Lipoic Acid, and Iodine known to compete..**c)** hamburger with varying fat percentages- 7,10,15,20, etc. ..

Name	2024-03 Mar	2024-04 Apr
Zn(mg zn)	0.73 ;5.9;3/20	0.59 ;5.9;1/10
arginine(mg)	245 ;350;10/20	228 ;350;5/10
biotin(mg) <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 IX: Part 2 of 2. Events Summary for Happy from 2023-10-01 to 2024-04-10A summary of most dietary components and events for selected months between 2023-10-01and 2024-04-10. Format is average daily amount ;maximum; days given/ days in interval . Units are arbitrary except where noted. Any superscripts are defined as follows: **a)** SMVT substrate. Biotin, Pantothenate, Lipoic Acid, and Iodine known to compete..**c)** hamburger with varying fat percentages- 7,10,15,20, etc. ..

## Appendix E: Notable Food Components with Copper Interactions

Entity	Comments
Cu	
Zn	
Fe	
Mo	
H/ OH	
S and amino acids	reduce toxicity [153]
PO4	
Fructose	
Tyr	
Trp	
His	
Pi-complex	
Fenton	
Ammonia, Amides, N	
Citrate	
Ascorbate	
garlic	enhance uptake [175]
Microbial products	
phytate	

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

## Appendix F: Symbols, Abbreviations and Colloquialisms

### TERM definition and meaning

## Appendix G: General caveats and disclaimer

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

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

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

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

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

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

Version	Date	Comments
0.01	2024-04-12	Create from empty.tex template
-	April 13, 2025	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 ={April 13, 2025} ,
title ={Copper Supplementation in Dogs: Listen to Her Heart Everybody's got a Hungry Heart } ,
author ={Mike J Marchywka } ,
type ={techreport} ,
name ={marchywka-MJM-2024-010} ,
number ={MJM-2024-010} ,
version ={0.00} ,
institution ={not institutionalized, independent } ,
address ={ 157 Zachary Drive Talking Rock GA 30175 GA } ,
date ={April 13, 2025} ,
startdate ={2024-04-12} ,
day ={13} ,
month ={4} ,
year ={2025} ,
author1email ={marchywka@hotmail.com} ,
contact ={marchywka@hotmail.com} ,
author1id ={orcid.org/0000-0001-9237-455X} ,
pages ={ 72}
}
```

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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63261 Mar 24 07:47 copper.aux 7649f4953260967bfdb3a1f573fa3290
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