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 Actually looking at the old, unpublished work, "casesum", that includes Little Man, most of the text is still useful today and has been copied and pasted without attribution (since it was a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

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(Dated: July 17, 2024)

The known roles of copper suggest it is needed to perform functions that could mitigate several common diseases yet it is not currently a trendy supplement for dogs or humans. 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. Surch 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. 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. The "background diet" is discussed in terms of making extra copper intake useful to the hosts. While copper interacts with just about everything, specific interactions with amino acids, B-6, and zinc are considered in more detail. In atleast one dog, possible problems also exist with low fat diet, iron excess, and cherries (thought to be a problem with fructose) pointing to idiosyncracies that are possible. Additionally, taurine emerged as a possible interaction with copper suggesting induced copper deficiency could limit therapeutric

effect. This may also be another case where an early low pH step prvents the formation of insoluble products creating varied outcomes idiosyncartic to particular diets suggesting those with impaired stomach acid such as the elderly may need specific diets or additional supplements. The overall diet may help mitigate two contemporary issues, hepatic copper accumulation and diet related DCM, in dogs as well as highlight rrecurring issues with hidden assumptions and logical fallacies when dealing with non-obvious regulatory feedback systems. Hopefully this workd leads to a starting point for a diet-related disease mitigation strategy and helps turn paradoxes into paradigms be elucidating some feedback mechanisms that may be quite common. One common issue is jumping to hypothesis testing rather than looking at data as a larger opportunity to generate new or refined hypotheses beyond rationalization.

Contents

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1. INTRODUCTION

This work is organized differently from many papers due to copper's biology and the relationshup between existing literature and the new results presented herein. A long redundant introduction motivates an interest in the topic without reading the whole thing completely. The novel results are relatively simple dog feeding chronologies and observations of outcomes. The "case report" section that descirbes the results for each dog also includes some analysis and interpretation given the introductory material that would be too distant in the discussion section. The discussion is short comparing and contracting the results from these dogs with existing literature.

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 [49] [46] [185] [179] [55] [1] . 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 conincided with a change in copper supplementation premix in commercial dog foods [191] pointing to increased intake as a cause. However, known and expected functions make it a good match to several possible problems motivating an interestt in supplementation even if contrary indicators also exist. In fact, isolated authors do sometimes point to it as a major cause of diseases such as heart disease [38] [100] . Copper appears to be of recognized importance in dogs and the question of dietary deficiency or excess has been a topic of controversy for many years. Its is likely that copper intake alone is not the dominant issue but rather distribution in the body deterined by singalling, 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 concentration if 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. Thsis has to be answered in terms of clinical outcomes, things relevant to the host, rather than lab values. 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 [158].

1.2. Hepatic copper excess observed in some dogs may be misleading

One increasingly common concern with dogs is copper associated hepatitis [4] [5] [28]. Cppper handling genetic diseases are well known in dogs [85] 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 [45] 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 conlucde there was a particular cutoff level for health vs disease [173]. 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 [176] while works as early as 2000 suggested supplementation would be unhelpful[174]. A recent work comparing mineral content in groups of commericial dog foods found some patterns and advised against high copper foods [88].

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 [62] 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 [82] [133]. 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 [107] and biotin [110] [106] . 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 paricularly 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 [132] and distribution [91] [14] [87] 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 [132] 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.

Even with excessive intake, in most genetics biliary excretion increases when "pathological" amounts of copper begin to accumulate [30] [58] pointing to defects in excretion as another possible problem. However, many cuase 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 [117]. Copper elevation may commit cord-blood derived cells to differentitaion [141] and it may be regulat4ed during myogenic differntiation [181] raisng the possibility that accumulation is due to confused signalling. The major copper transporting protein ceruloplasmin is an acute phase protein and blood levels may be associated with pathological conditions [54] but a protective role is generally recognized. As a major transporter of copper out of the liver, stresses then could export copper out of the liver. In fact, as substantiated later, it would make sense for copper to be redeployed from some mitrochondria to the blood in response to pathogens or trauma. This will lead to hydrogen peroxide formation and potentially anti-pathogen copper both conditions likely to control infection. Emerging mechanisms such as extracellular veiscles [15] suggest that uncharacterized mechanisms of metal homeostasis exist.

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.

1.3. Copper status is ambiguous in biochemisty and clinical outcomes

Copper is used in several important location and a reasonably complete snapshot of copper sufficiency would in general be a vector. Easily accesible values such as blood levels are more responsive to acute pathological situations than overall body total copper. As details are unknown, a colloquial analogy may be trying to infer adequacy of military hardware from measuring the amount on civilian roads.

There is a recurring problem using blood levels of some thing to indicate excess or deficiency even though most blood components are regulated or influenced by specific factor 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 resposne to various stresses. Recently some body of work has suggested that macrophage lysosome may also regulate overll metal distribution [144] a location that would be expected to respond to many stimuli.

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 is coughing. This is certainly relevant to the host and would hvae to be considered an easily observable a clinical outcome. However, the underlying diseases that provokes the cough may not monotonically correspond to coughins 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 therfore 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. Coppr and blood pressure

Blood peressure, which is not a clinical endpoint per se , has been associated with coppers 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 [98] " 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 erly as 1993, one work with Dahl salt-sensitive rats suggested that indeed copper blood levels were a response to hypertension [51].

Things that do matter to the host related to blood pressure include cardiac workload, vascular pressure hhandling 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

This work describes inclusion of copper into a set of supplements for dogs with different conditions and unknown genetics showing generally beneficial results or at least no obvious harm with added copper. This result is in contrast to some of the popular expactations cited above. A descrepancy between expectations and outcome of this type seems to be common in medicine even as late as clinical trials o understanding the causes of that in this partciular 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 unqestioned assumptions and logidcal fallacies that are quite common. Some types of problems are listed in Appendix C as a general giuide. 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 assoicated with increased cognitive decline [26].

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.

A recent example may be the identification of amyloid beta as a nominally protective substance [198] [151] instead of the cause of Alzheimer's pathology and target for 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[43] such as a 2002 work suggesting that "tauists" and "baptists" could 'shake hands" and look for other causes [126]. 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 [81] [180]. However, upregulation would have to be suspected as a part of regeneration attempting to fix degeneration. Indeed, LOXL2 is known to be regenerative [172].

Previously, heartworm positive dogs had been given significant amounts of vitamin K [115] [112] although severe case may be treated with anitcoagulants. In thise case, it may not be clear that vitamin K effects clot quality and consequently may limite 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 intreractions but the versaility of copper probably makes a copmlete 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.

Thie confusion begins in the GI tract with chemisty ranging from the problems sorting and regulating metals to the non-enzymatic reactions copper can undergo with a variety of organics in food. 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 facotrs in copper uptake but also distribution if other nutrient deficiencies are created. Copper solubility is pH dependent [37] similar to the competing element zinc for which absorption has been shown to depend on salt type and gastric pH [68]. Interaction with food components such as polyphenols is significant and pH dependent [143] 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 gastic juices with food components such as tyrosine and citric acid among others [193]. Impact of GI pH on broiler chicks has been studied due to impact on nutrition and micrbial populations and Cu-Zn antagonism in the digestive system was also observed [140].

In humans, PPI usage has become common. Empirically thate may be a tumor protective effect and there is a suggestion that pH 6 encourages cancer progression versus pH 8 [96] yet alkaline stomach pH is observed is commonly observed in gastric carcinoma [196]. 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.

within and beyond the GI tract, a variety of other factors likely matter. Competition between Cu, Fe, and Zn was observed in Caco-2 cells [6]. Iron intake in feed has also been observed to decrease copper uptake in ruminants [35] and rats [92] . One work suggested iron disrupts copper homeosstasis independent of uptate [57]. Dietary cholesterol appears to distrurb copper homeostasis with atherosclerosis thought to involve copper dysregulation [95] and high

fat diets in other species [65] are an issue. Fructose also inhibits relative copper absorption [134]. Zinc is a known inhibitor of cuppoer uptake and cases of zinc induced copper deficiency in humans are known[186]. 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 [69].

While concerns exist about copper content in dog foods, a recent survey of some zinc content shous many foods contain amount above recommended maxima and few are low or deficient [142]. Age related absorption problems in people are known [145] and other apparent deficiencies could be a consequence of insufficient B-6 alone [29]. Interestinly, B-6 is added to penicillamine treatment of Wilson's disease to avoid neurological effects [39].

Thinking outloud
Since paradoxes are a concern here, its worth noting that pyridoxine is an inhibitor of PLP and high dosese result in functional B-6 deficiency [184].

Body stores of copper increase with excess tyrisone in the diet of rats [194]. Some reports show specific issues when combinted with vitamin C. A small trial with copper sulfate indicated kidney problems result [79] although alternatives with copper gluconate suggested use as food preservative [56] . Dose probably matter among other factors.

1.7. The overall diet may be important for copper distribution

Ideally the optimal fate of all consumed nutrients could be identified and manipulated somewhat with overall dietary composition. This work includes consideration of a background dietary context including real foods and controlled supplements that has been described previously [108] . This diet was further refined by consideration of the itneractions 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 [52].

1.8. Copper interacts with dietary sulfur in other animals

While not a primary focus of this work, the issues with forage quality in grazing animals may be instructive and even suggest issues with low stomach acid.

Decisions about copper supplementation are also difficult in economically important ruminants [102].

Ruminants differ substantially from non-ruminants and notably rumen pH is only around 6 reducing solubility of relevant minerals while allowing formation of insolubles [165]. This may motivate interest in issues with age related reduced stomach acid in humans. The low pH GI stage may reduce sensitivity to dietary idiosyncracies. The presence of a stage able to nucleate insoluble nutrient blobs may prohbit later abosprtion.

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 soi [206]. 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.

Sulfate reducing bacteria may contribute to confusing metabolism of taurine and methionine [188] .

Recognized low copper status is known in humans and may be related to dietary issues such as high fructose intake [190] although sulfur containing amino acids do not appear to be generally recognized as an issue.

1.9. Copper interactions with WHY and Cu related clinical impact

The present work gives details of most of the dietary components but analysis is largely confined to a select few such as tryptophan, tyroine, histidine, and vitamin B-6. Its worth noting that copper is quite reactive and can form coompounds with many aromatic rings, nitrogens, sulgurs, or other common chemical groups.

Interestingly, 3 amino acids, the ringed "WHY" trinity (tryptophan, histidine, and tyrosine) seem to be the most important. Notably tyrosine protexts ceruloplasmin and 6 histidines, one for each copper, are required for a functional enzyme. Mistranslation due to insufficiency will be amplified byt the higher power if all need to be right. There is some indication that "diseases of old age" are at least partially medicated by sarcopenia, most reecently atrial fibrillation [170] consistent with earlier ideas linking age to amino acid staration [107] . Interestingly, Scavenger Rceptor BI contains 8 highly conserved tryptophans [72] which appear important for cholesterol transport suggesting trp deficiency will slow down its translation or create many imperefect 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.

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

Thinking outloud
engineering ahead of medical

In some other context, engineering efforts to produce biological products such as bone in a reacor vessel can offer insights into factors in vivo. A 2021 work focused on similar systems by modelling the effect of amino acids and copper on antobody quality in a production setting [104],

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

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

1.10. Recent Similar Work

At least one recent work [32] has summarized many of the same issues relating to copper and cardiovasular 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 biolgoical roles for copper suggest it may be an important limitation in functions that relate to common diseases yet understadning of the body's copper distribution is limited. This work addresses the topic by folloing 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 amernable 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 decribed 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 irriate

the respiratory tract. Hypothyroidism is not commonly associated with cough in dogs although thyroid enlargement can occur irritating the trachea.

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

Besides cough, the present works relies thyroid related symptoms (coat quality, weight distribution, energy level etc). Cough has many possible origins as discussed previously [113]. "Enegy level" in most cases described here is thought to relate to shorter term fluctuations in mitrochondrial copper rather than thyroid although its important to consider all possiblitites. 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 diseas complex resolves.

Its also important to note that a "state of health" requires a lot of things to go "right." Not everything need be "good" as many compensatory mechanisms exist to allow clinical health with differnet 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 disase trajectory. For the sake of writing tractable overviews, these considerations may be omitted in the following sections.

Disease	Host	Effect	time scale
DCM/HCM	dog		
heart failure			4 weeks [32]
Collapssed Trachea	dog		
airway defects	rats		months, 60days [135]
Hypothyroid	dog		
Infection	dog		
covid-19	human	serum levels irrelevant [153]	
Parkinson's	human	assoc benefit [202]	
Alzheimer's	human		
Infection	human		
Arthritis	human	anecdotes, no trial verfiication	
Cancer		need to understand cause and effect	

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

2.1. Collapsed Trachea

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 consdieration 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 [135] and airway and arteriole elastin were at least partially restored after 60 days of additional copper.

A variety of causes are know in humans [160]. 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 [50] with surgery as a common treatment.

Horses and mules suffer from collapsed trachea too. Mostly small breed or miniatures horeses 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 [44] . 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 expereienced trachea collapse which was attributed to copper mediated crosslinking [197] 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 [9].

> 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 [129] [166]. It is not surprising that silver could be confused with copper as analogs can be inhibitory but as discussed elsewhere cerulomplasmin synthesis can proceed without copper but the protein may not be properly metallized. The reduction in synthesis is surpising although perhaps

only copper containing ceruloplasmin was assayed and details need to be considered. The authors aldo mention other means than mis-metallization that silver or othermetals 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 [171].

> 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 consideredin 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 thetracheal 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 [93]

> 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 [122]

> 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 polyunsatured 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 lysuyl oxidase [97]. 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 [116]. A role for LOXL in aggrecan processing has been described [172].

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 [118] . While it is thourght to be diet related, no clear recipies have been identified for causing or preventing it. 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.

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" [157]. It is considered rare although it was initially considered rare in humans whie now being fairly common with a wide spectrum of symptoms [177]. . Energy depletoin is thought to occur due to causative mutations but as of 2019 no disease modifying or proven therapies exist although Mavacamten apaprently reduced outflow obstructions in as little as 2 weeks [177].

As early as 1993, copper restriction in rats was observed to produce cardiomuuoptahy [120]. while reduced cytochrome c oxidase activity was observed in 1999 paricularly with simultaneously high fat diets [77]. Altohough confusingly copper chelation with trientine is also thought to show promise in HCM treatment [149] but its unclear exactly how 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 physsiological crosslinking, removal of deposits such as mineralization, and mitochondria performance. Empirically, copper deficiency can lead to cardiac hypertrophy with increased mitochondria [121]. Dilated and hypertrophic cardiac myopathy can both be related to mitrochondria with "oxidative stress" as a signal for more copper at cytochrome oxidase. "Oxidative stress" has been reported to increase muscle mass while reducing performance [2]. "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 DEM regressed with copper supplementation [75]. 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 [12].

Over the same time however, concerns about diet linked DCM in dogs have emerged. A genetic link is also being investgated and a recent GWAS in dobermans pointed to two genes, RNF207 and PRKAA2 as risk factors [131] but did not mention copper. However, RNF207 may mediate degradation of ATP7A [203] while PRKAA2 comes up in cuproptosis [99].

Dobermans are at remarkably high risk of DCM [41]. Interestingly, "standard Dobermans" are also at high risk for hypothyroidism [139].

Its 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 [100] 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 [105]. However, even assuming blood copper is proptional to exposure, the x-axis in the graph is more likely a sum of exposures and not just copper. That it, is a partial derivative of DCM risk in a direction that includes copper but also other things like arsenic. This is a very common problem in association studies depending on the inputs and population. In reality blood copper is largely deteremined by an acuate 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

Combined copper and zinc deficiency was observed to reduce response to covid-19 mRNA vaccines with only minimal copper deficiency [33] 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 [7] [47] . Some studies suggest copper is not a factor in covid-19 due to measurements like serum copper levels [153] although ceruloplasmin as an acute phase protein can elevate levels during stress even with a deficiency in copper [61]. In sample of 70 patients presrribed zinc, many had symptoms consistent with copper deficiency [40]

Copper may antagonize many pathogens including H pylori [17] and clostridum

Thinking outloud
Repression of toxin production by tryptophan in Clostridium botulinum type E [94].

Copper compounds may reduce the virulence of some organisms for short periods even if not completely able to clear a pathogen[60] and in particular Cu was recently shown to be effective against the toxin of one anaerobe [25] .

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 [90]. There are a number of limitations

with this work but in general there is likely to be a beneificial zone in cupper supplementation to in vivo communicities such as in GI tract.

2.4. Hypothyroidism

Copper deficient liver patients may be notable for "steatohepatitis, iron overload, malnutrition, and recurrent infections " [199].

Hypothyroidism is a common problem in dogs and has effected several here [111] including some unbpuslihed results where it was thought to contribute to peritoneal effusion after hearworm treatment. It can be defined by elevated TSH for a subclinical condition or low free T4 or T3 [130] although even the latter remains as a biochemical defintion 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 "aqcuired primary hypothyroidism " being considered most common although iodine deficiency in dogs appears to be poorly defined [201]. In this work, theer is some evidence that added components such as iodine, benzoate, tyrosine, and copper may help and could fit under the catagory " aqauired."

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

Dobermans are at remarkably high risk of DCM [41]. Interestingly, "standard Dobermans" are also at high risk for hypothyroidism [139].

Inerestlingly, copper deficiency in rats can reduce thyroid hormone levels and body temeprature [103].

Of the dofs discussed here, only Rocky was a concern for hypothyroiism although Happy came back with very low normal thyrroid hormone result prompting further consideration. Besides iodinne, other contributros may include tyrisone and sodium benzoate.

2.5. Degenerative diseases AD, PD, ALS, Arthritis

Degenerative neurological or muscular diseases may be intertwined with copper status although the relationship is again confusing. Similarly with arthritis.

Deficiency seems to effect prefernetially proteins involved in neuronal projection and diabetes and iron handling [182].

Rats fed a copper deficient diet shows neurological symptoms by 7 weeks and had reduced tyrosine hydroxylase and SOD activity ZZ [125].

A 2017 study explored the effects of copper and vitamin C as well as other molecules such as clioquninol 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 [195]. Interestingly, copper-ascorbate oxidation of tryptophan may be suppressed by Trp chelation of copper at high trp concentrations [124] suggesting reduced amounts may give copper more ability to damage an already low supply. This is interesting in terms of a utrient 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 [74].

Some precednce for metal modulated toxicity existed back to 1999 when work with cultured neurons showed a dose dependent reduction in abeta toxicity with Zn [101]. 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 [20]. In 2021, Ni was found in important amounts in a commercial abeta40 preparation [16] and was found to mediate dityrosine crosslinks [18] similar to the dityrosine crosslinks induced by copper found in 2004 [8].

A 2013 work found in vitro physiological conditions caused copper to prevent fibril formation [123].

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 [137].

One work in 2022 addressed AD as a consequence of copper deficnecy because [83]

> It is hypothesised that copper deficiency is a plausible cause of Alzheimer's disease(Reference Klevay84). Patients are thinner than normal; weight loss precedes dementia and is associated with greater dementia and neurobehavioural symptoms. Nutritional compromise contributes to morbidity. Cytochrome oxidase depends on copper for activity; at least fourteen publications reveal decreased activity in brain of Alzheimer's patients. Brain copper and caeruloplasmin also are decreased. This hypothesis is the only

one that explains why Alzheimer's disease occurs earlier and is more common in Down's syndrome. Superoxide dismutase (SOD1) depends on copper for activity; its gene is on chromosome 21. This enzyme is elevated in Down's syndrome (trisomy 21) and is decreased in people with monosomy. It seems likely that people with Down's syndrome have a higher than average requirement for dietary copper because copper is incorporated into superoxide dismutase and is unavailable for other uses. Thus, Alzheimer's disease fulfills the first two of Golden's criteria (above) for deficiency.

Folklore regarding copper persists and yet clinical trials for Cu in arthritis continue to show lack of any benefit [150] even as other controlled tests show some effects of Cu on processes related to collagen properties [59]

Remarkably, copper sulfae was shown to protect against ETC damage by MPP [154] suggesting some activity against toxic insults. Copper histidine is used to treat Menkes disease which is a defect in ATP7A [128].

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 [207]. 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 relase of Cu from the drug complex [70]/ pointing to a possible more general mechnism. 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 [202]

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 mitrochondria to glycolysis [27] so it can produce two central fetures of cancerous growth. Copper accumulation has been observed in neoplastic cells and it stimulates angiogenesis [156]. While this suggests a role supporting turmor growth, "acute phase copper" and improved bllod supply can be part of a healing response.

Copper has been studied in relation to cancer being considreed both as a limiting nutrient and a source of cuproptosis in the overload state [169]. Copper is essential for many growth processes and can activate receptor tyrosine kinases without a ligand making it a target for cancer [64]. However, these processes are also esential 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 deciee on approach. In some studies, copper depletion was considered to be motivated by the observation that copper chelatiors 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 acitivity.

Copper storage diseases and in essence "overdose" are well known [48] and a role in cancer is suspected [21] . 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 [159]. Lysyl oxidase activation, the goal of this therapy, is also associated with cancer spread [168][147][189] . 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 [11] or [204] and the survival curve in figure 1). Incidence of liver cancer in Wilson's Disease patients is remarkably low [127] and a discussion of possible treatment effects [187] 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 it effects were diminished by antioxidants [42]. 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 tabulatedin 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.

Location	site	Effect	time scale
Heart	mitochondria	energy production	maybe days
Heart	mitochondria	remodelling	weeks or months
Heart valves	lysyl oxidase	crosslinking [146]	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. Cytochrome C Oxidase

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.

Supplemental copper has been noted to improve symptoms in one case report including symptoms such as hearing loss [73] attributed to defects in cytochrome C oxidase copper loading and restore function in mutant yeast [53] .Cytochrome C oxidase levels in rat hearts were shown to be related to copper deficiency as early as 1998 [152]. 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 [183][200] .

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 [138]) , 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 [23] and [66] . 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 [30]. 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 [22] 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 [63] and indeed mitochondrial related signaling [161] . 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 [24] in [161]) . However, the enhancement by GSSG suggests that the presence of oxidized antioxidants may be beneficial but not in their reduced state.

3.2. Lysyl Oxidase

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.

Lysyl oxidase bad for vessels [13] calxification. but may be related to metallization issues [162].

Regulation at transcriptional and translation and post-translational levels is confusing. For example, it has been described in 1998 as [163],

> 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, [155]

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

It has been observed to upregulate in the injured newborn lung [205] 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 [167] although details on reactions catalyzed could not have been fully explored.

However, metallization may not be complete and feedback systems may increase expression to achieve an activity level. Note too that "crosslinking" is a variable modification and physiological as well as pathological crosslinking can occur. While "quantity versus quality" will be the subject of another work, its important to remember that increased expression of lysyl oxidase genes and more 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 [192]. 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.

Lysyl oxidase expression has been associated with degenerative mitral valve disease in humans[146].

3.3. Ceruloplasmin

Ceruloplasmin contains 6 coppers and histidines needed for metallization [67]. as well as 2 tyrosines. Independent errors in metallization will multiple and reduce likelyhood of functional enzyme.

The blood leveels 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 [175]. As iron accumulation is related to AD, there is a question about the quality of the circulating ceruloplasmin. If there is high-infidelity translation due to W and Y depletion, there is also the question of how feedback mechanisms control the overall amount. First is has to metalize right which requires 6 coppers and 6 histidines and then survive with the 2 tyrosines. If any components are deficient quantity or quality may suffer. Ceruloplasmin KO mice gained weight and showed increased scatter in weight with lipid dysregulation only partially corrected wth exogenous replacement [148] 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 [31] although the impact of copper may be less apparent. Recently some work has suggested that lysomal copper may be an important storage location [144].

The importance of copper for host-pathogen relations is well known as is a prticular usage by macrophages [89] [19]. Note that nutritional immunity may involve either an excess or limittation 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 [71] as well as Streptococcus pneumoniae [80] . 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 [164]. As with attempts to control amyloid beta in AD, there may be some passing benefits but taking all the information together this is likely of limited value if the simpler approach of enabling the copper based response in a well regulated way is feasible.

3.5. Associated Entities - histidine and garlic etc

Copper can of course form associations, with many chemical groups and diverse roles. Role confusion however seems to be a recurring issue as specific componunds may not sequester or activate copper as may be expected. One recent review on anti-cancer mechanisms of copper dicussed various ligands and roles for both copper depletion and overload [10]. The combination of the garlic and copper, while sounding like a medieval concoction (suggested as a result from Bald's Leechbook [60]) , has been described as synergistic against fungus [136] and seems plausible for generating perhaps more volatile and diffusable copper that could find otherwise inaccessible lysyl oxidase and other targets.

Dogs fed a histidine deficienct diet eventually developed feeding resistance and lower whole blood copper and zinc [34].

4. CASES AND OBSERVATIONS

This section describes the results of adding copper to diets for a variety of dogs. Context and interpretation is also included here, instead of the discussion section.

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

A series of rescue dogs were fed food and vitamin supplements in addition to commercial kibble products. Diet and outcomes were recorded in MUQED format [114] immediately after feeding. While most supplements and medicines were recorded in sufficient detail to reproduce, the meal or snack most dogs received additional meals of commercial dog food and unfortuntately 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 paricular normalization of the "dinner" amounts is variable between dogs.

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

Many of the dogs in this setting have had either symptoms that could be due to hypothyroidism or overt lab confirmed low thyronid hormone levels. As iodine intake flucuated wildly, it is included in some of the graphs as a

putative factor confounding inferences about copper. The premise of this work is that the total diet is a "confounding factor" and readers are encouraged to check the MUQED data for other patterns.

Generally copper dosing was rotated leading to high doses some days with none on intervening days. A hard upper limit of 3mg/kg body weight of supplemental copper per day was maintained based on quoted NOAEL's from an original source dated 1972 [36]. All of the dogs currently living here received increased copper shortly after the arrival of Trixie due to apparent spread of coughing. Trixie was later treated with Clavamox leading to cure suggesting indeed an infectious cause existed. Some of the dogs, notably Happy and Rocky, had varying cough levels previously as described below.

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

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

4.1. Cookie or Mixie

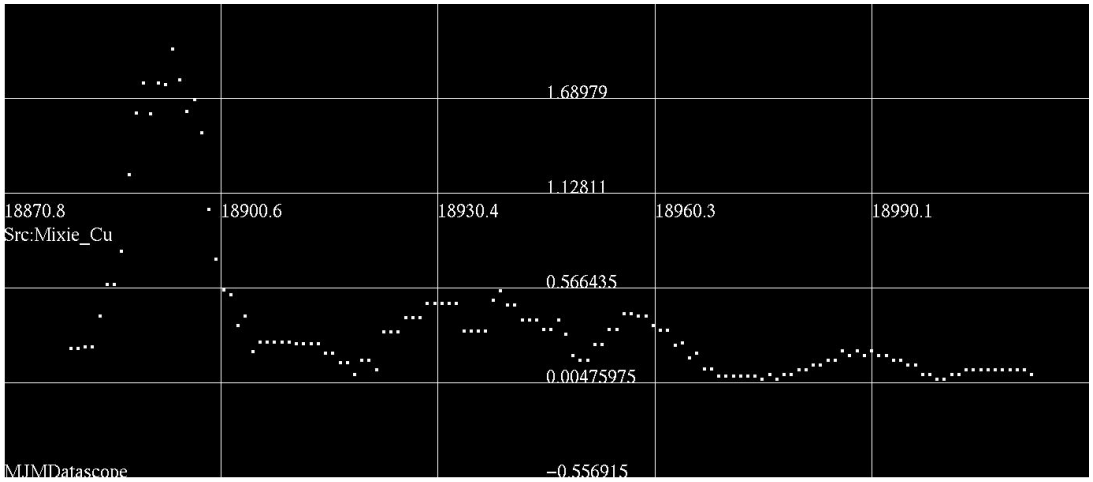

FIG. 2: Mixie daily copper (white) intake .

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

4.2. Brownie and puppies

Brownie was the subject of a prior work where her uneventful pregnancy was notable for vitamin K consumption while heartworm posivite [115]. Subsequent to that work, her abdominal tumor was removed and diagnosed as fibroid.

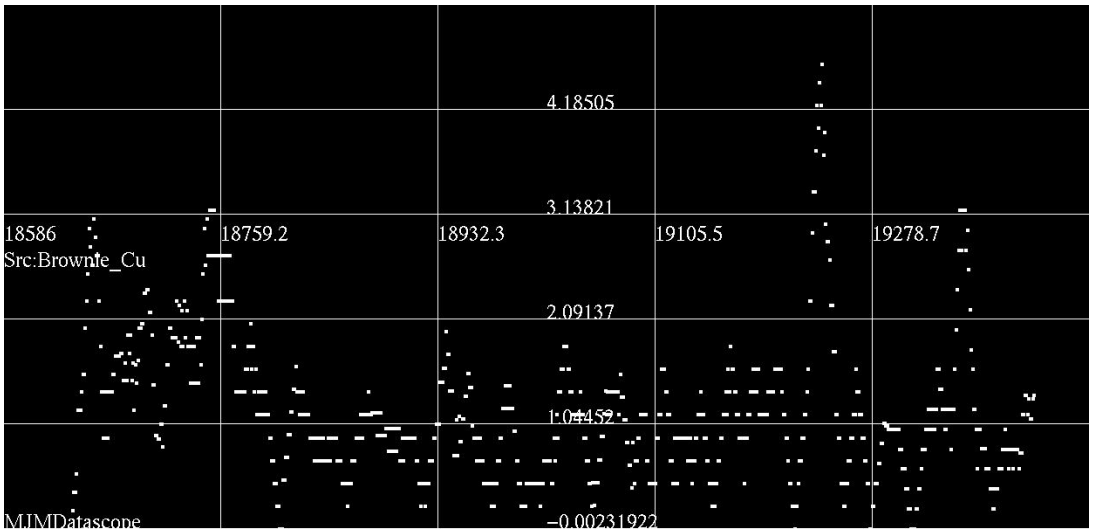

FIG. 3: Brownie 10 day trailing average copper (white) .

Briefly, Brownie was determined to be pregnant shortly after arrival . Her heartworm was treated with Diroban after weaning and fibroids removed 2021-11-15 well after the puppies were gone. She was unevntful until being doganosed with cancer and killed 2023-02-22. Prior to her diganosis, she was observed to cough occasionally for no obvious reason and appeared to have some movement issues. X-ray confirmed tumours likely responsible for both problems.

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

4.3. Happy

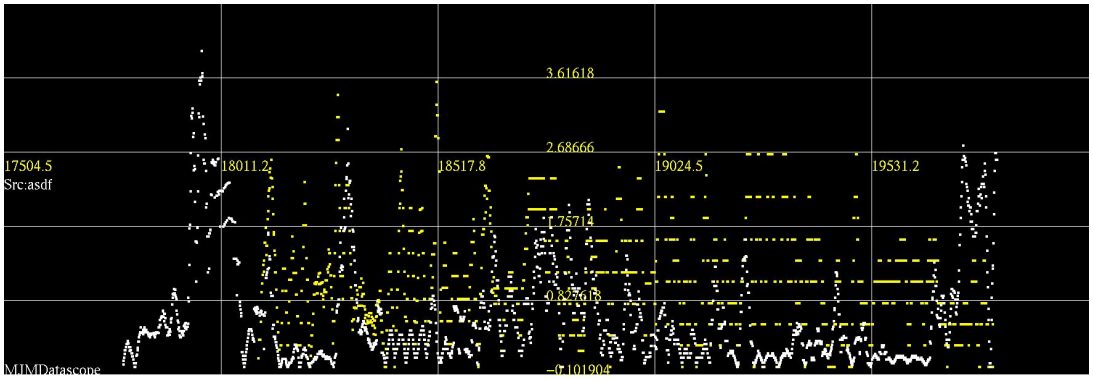

FIG. 4: Copper(white) and Zinc(yellow) dosing per day averaged over prior 10 day period as dosing was highly variable due to rotations of various nutrients. 18046 is 2019-05-30 when the cough was first noted to be gone for a few weeks. 19823 is 2024-04-10 the last date for which data was obtained. The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

Happy, like Brownie, was also the subject of two prior works. Initially her heartworm recovery was described with vitamin K and other supplements [112] followed by an unusual episode which resulted in some investigation of possible role of vitamins B-2 and B-3 in her health [109] . To summarize, Happy arrived heartworm positive coughing to varying degrees. She was treated with a slow kill approach including ivermectin and doxycycline as previously described. She later was acting sick but appeared to recover well with B vitamin supplements. Her coughing never returned to the very low levels seen after heartworm recovery until copper doses were increased with elimination of any zinc and care with tryptophan. As copper was increased due to widespread coughing after Trixie's arrival, her

cough was noted to decrease to lower than prior levels. Review of the copper dosing suggested it had fallen prior to Tricie'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 introductiory material, it was later realized that earlier conserns 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 fucniture 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 of 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 exercize capacity from jumping during dinner to trotting in the bark 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, turykey, and chicken.

4.4. Trixie

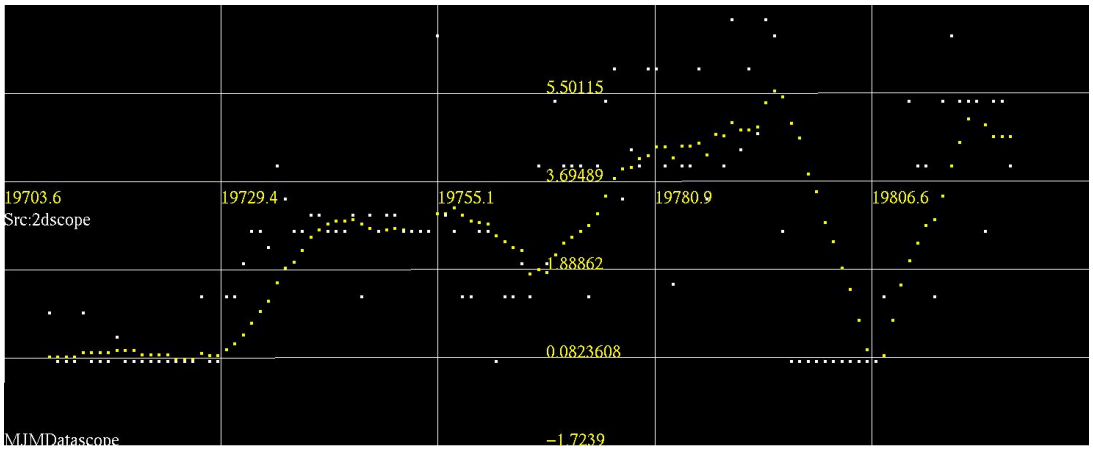

FIG. 5: Trixie copper consumption since arrival. Daily amounts (white)) and trailing 10 day average(yellow). Copper started to be significant around day 19730 in response to coughing. Day 19807 marked the end of the copper fast as well as the end of Clavamox which was prescribed due to worsening when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

Trixie began coughing shortly after arrival and was very low energy. Her coat was notable for a sticky feeling that seemeed to recur after a bath. Many other dogs began to cough or hack suggesting that she brought a communicable infectious disease. Nutrient mix was modified to add more copper and most dogs' coughing returned to normal quanity and qualitiy although her's did not entirely resolve. Copper stopped for a couple day (I was gone) and owner took he to the vet as she began coughing more. Clavamox was prescribed and her coughing stopped within a few days. Her energy level has improved but she did not run until 2024-05-02 (19845) . She had a renwed cough around 2024-05-22 (19865) subsequent to copper withdrawl 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.

4.5. Rocky

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

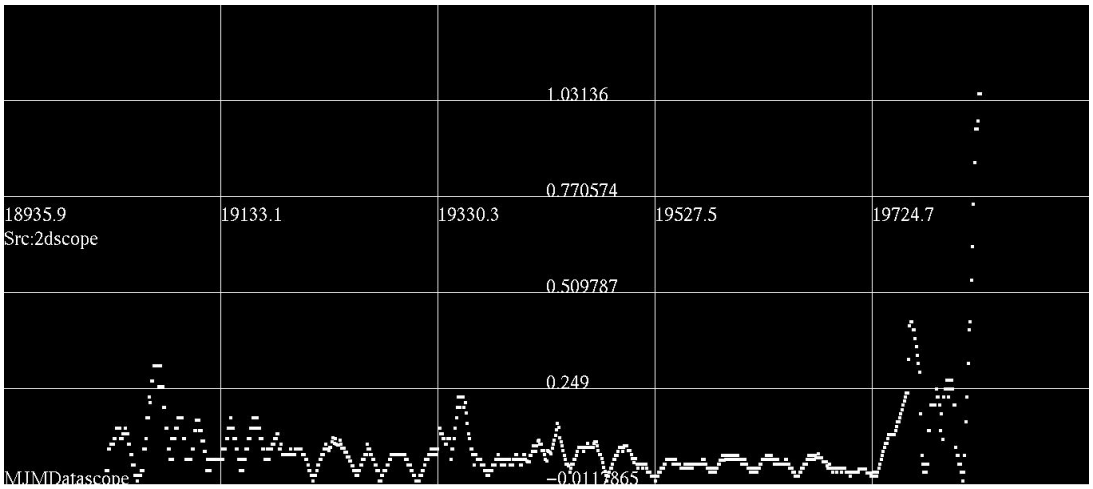

FIG. 6: Rocky 10 day trailing average copper (white) .

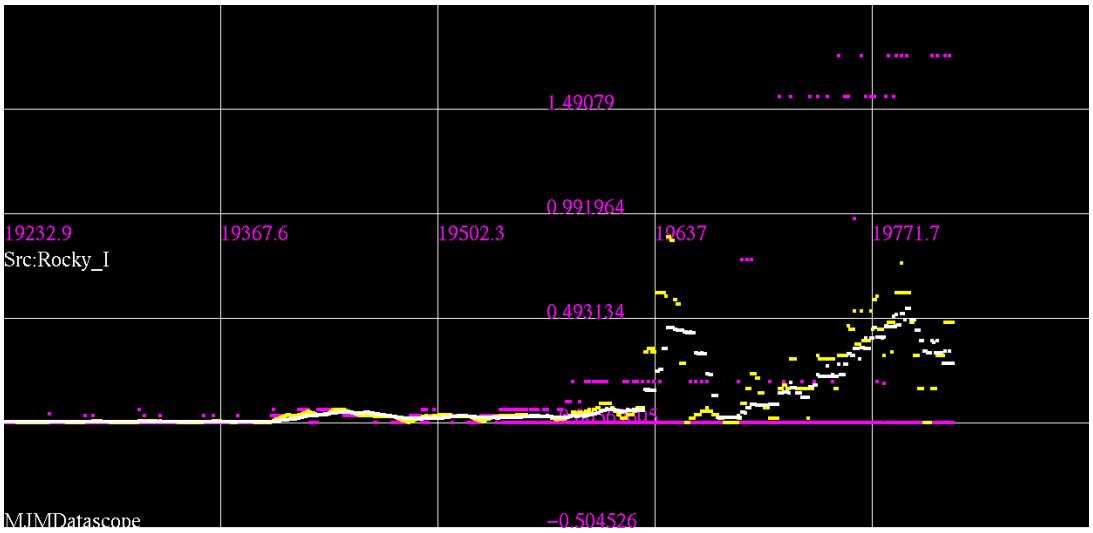

FIG. 7: Rocky iodine intake daily and with 10 and 30 day trailing averages. Patterns are difficult to discern with the pulsed dosing.

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. Probably most coughing now coincides with exposure to cigarette smoke.

As benzoate may be an important coundounding 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, [178] ,

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

If there is a beneficial effect, it likely depends on many factors such as overall diet and may vary across species.

4.6. Annie

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

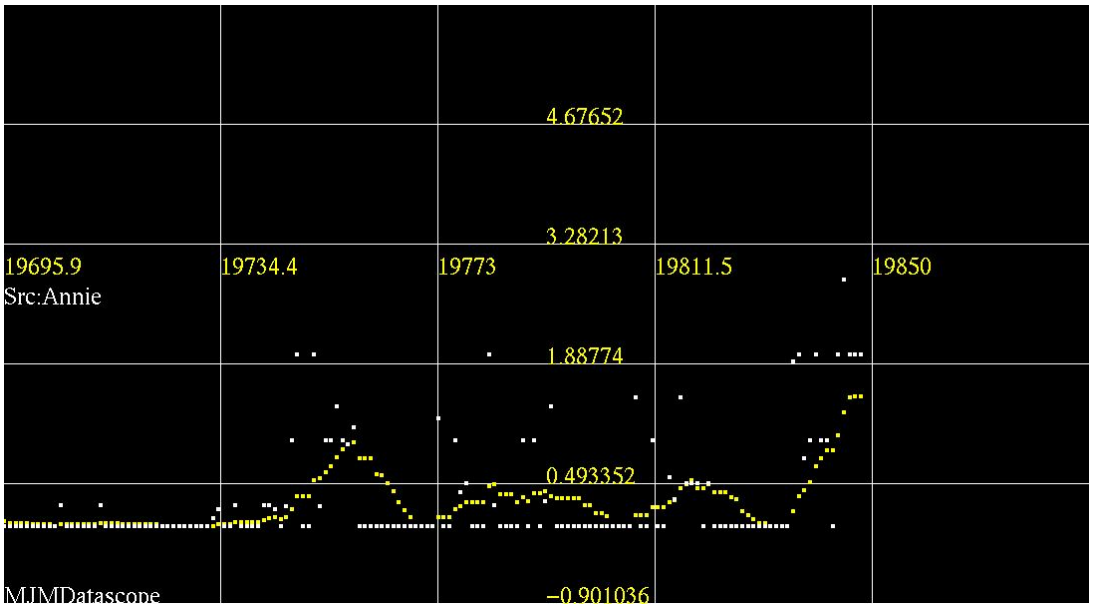

FIG. 8: Annie

generally ate well but had some limitations in sight and hearing. She seemed to get skin or paw irritations easily. 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.

4.7. 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.

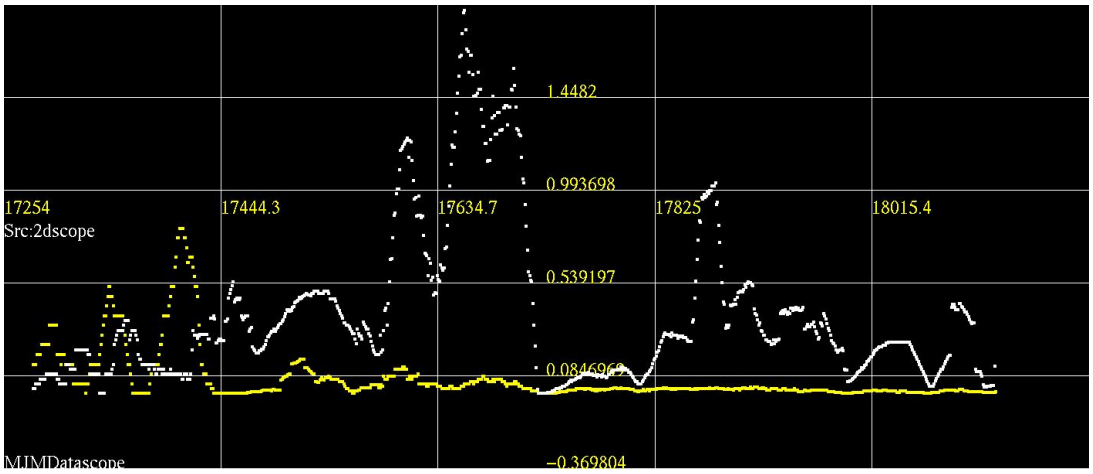

FIG. 9: Herhsey 10 day trailing average copper (white) and iodine (yellow).

Date	Day number	Comment
2017-09-25		developed skin problem, vet prescribed clavamox and miconazole chlorhexidine shampoo Malaseb
2017-10-13		blotches mostly gone yesterday Barb still notes some
2017-11-01		stumbled down steps did not come up until after PMSNACK restart lipoicacid
2017-11-13		struggles up deck steps but finally made it
2017-12-12	17512	seems to be coughing a lot
2018-03-06	17596	seems to cough less, continue copper
2018-04-19	17640	came up steps on own again cadence sounded good
2018-04-20		fur seems thicker except for small area on back behind neck. Still coughing though
2018-04-28	17649	appears alert more flexible and good up steps while still planning although he did stumble the other day
2018-04-29	17650	seems ok on steps, hair filling in.
2018-05-29	17680	not coughing much and energetic but refused to eat and diarrhea. Ate small amount indicated around 830AM. He seems ok at noon not coughing much but subdued.
2018-07-02	17714	lighter and not coughing except when really agitated. Made it up steps good. Could be just weight although not that much lost, something in yard wiped out with spraying, or something like potassium chlorde or the lysine making him worse
2018-07-15	17727	had rear leg problem, Barb gave rimadyl
2018-09-04	17778	seems to be stumbling more on steps last day or 2 but yesterday later came up good with fish at top ...
2018-09-19	17793	left rear leg bad had to help up steps still limping in kitchen 5 mintues of so. Gave some b7ngnnc rested ok. Made it up steps after PMSNACK ok although aborted on attempt but it is 95F out.
2018-10-12	17816	planning and 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 IV: An abbreviated set of note on Herhsey. Increased coughing may have occured 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 bahvior 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 captures 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 tretropsect, 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

Copper supplementation averaging around .2 to as high as .8 mg/kgBW/day appeared beneficial in this group of dogs as symptom improvement often followed weeks of dosing. Several suspicious observations were noted but nothing robustly correlated with copper intake. As some symptoms such as coughing are the product of many factors, interpretation is difficult during the initial response 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 persumably 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 preceeding 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.

The overall concern with Happy and aromatic amino acids ist still not clear. Increased energy may lead to more coughing but pulmonary hypertension may be controlled by serotonin [3] 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. This "allergy" could be pathogenic via immune response to either allergen or actual patogen that becomes resolving with more copper although symptoms could be treated with Apoquel known and likely side effects make this a cleaner solution.

Reconciliation with various concerns and failures relies on the complex interaction with other dietary componets 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 conintually be finding the performance limiting nutrient in turn as each is tweaked.

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

Copper was considered to be important early but despite some successes was lost in the shuffle. While the conditions for benehficial usage remain unknown, several suspects can be identified. Histidine addition was the most obviously correlated with increased alertness, animation, and aggression although there may have been some expectation bias considering increased histamine contributint to these states. These responses could increase coughing leading to the erroneous conclusions it was making something worse.

Besides the mulecules althready 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 chemisty in the GI tract. Indeed, it has been observed to reduce copper toxicity in rats with increased feacal copper amounts [76] suggesting decreased absorption. Another work demonstrated taurine reduced ceruloplasmin only in rats fed a control diet but not a high-fat diet [84]. As taurine is being explored for various indications, including DCM [119], apaprent limitations in supplementation could related to induced copper defieincy which would likely cause some symptoms expectedd of taurine defieincy.

Several likely benefits of copper suypplementation were observed but no clear robust clinical symptoms got worse. This is contrary to some indications from populat 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 [29] 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 nutirents are also given to handle the copper beneficially. Candidate nutrients include tryrosine and tryptophan.

6. LIMITATIONS

While the other components were mentioned as important, it needs to be reiterated that the the other snack components could have effected copper handling significantly and supplementation with another diet lacking these components may not be beneficiail but copper restriction may not be either. Most food ingredient interact with matals 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 foriegn 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 strcutured outcome notes on things like cough, the resulting outcome data was very sparse and relies on memory in some cases. The lesson remains that notes and data always need to be more complete.

7. CONCLUSIONS

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

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

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

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

8. SUPPLEMENTAL INFORMATION

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

8.1. Computer Code

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

```
diet tables,

2766 ./run_linc_graph -dt-mo txt/happy2cu.txt
 2767 texfrag -include 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 catagorized in a number of way but consider the following possibilities. No attempt is made to organize, catagorize, or make entries "orthogonal" as its unclear how or why to do that right now.

1. **people over data :** Thjis comes up in essays on long lived metdical myths. Opinions, votes, don't determine natural laws
2. **supply v demand :** An excess quantity is not inherently due to either supply or demand
3. **false dichotomy :** good and evil
4. **non-monotonic curves :** *show me a monotonic dose response curve and I'll show you a fool*
5. **fix or remove :** Often there are 2 approaches to getting the same result with a partially broken system.
6. **one extreme says nothing about theother :** Both invcreasing or decreasing some quantity may produce the same (beneficial or evil) effect.
7. **hidden interaction :** The observed result requires some interaction partners
8. **X is a Y :** Role confusion leads to more untested assumptions.
9. **local optimum :** prohibits consideration of global optimum over rugged parameter space with bad figure of merit.
10. **rabbit trail :** Successive approcimations, even as advocated in this seris of works, can lead a strategy down the wrong path.
11. **platitudes :** better to be safe than sorry lol
12. **equations :** consider spherical horse linear approx
13. **proxies :** Almost only counts in horseshoes and handgrenades
14. **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.
15. **only relies on empirical obervations :** no cuase and effect stablished
16. **irnores empirical obervations :** "sanity check " Theory based on incomplete system topology needs to be consistent with empirical observations
17. **irnores empirical obervations :** Theory based on incomplete system topology needs to be consistent with empirical observations

18. **other state variables :** Hidden variables include a limting nutrient that is needed to beneficially use the entity under test.

19. **regulatory landscape :** As life is generally robust control systems have evolved but may have non-obvious failure modes.

20. **trying harder :** If a prefered response is frustrated in attaining a survival relevant goal, there may be signals to try a less orderly response more vigorously. The disorganized response can be suppressed by enabling the effective one.

21. **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 Sumnary

Name	2023-10 Oct	2023-11 Nov	2023-12 Dec	2024-01 Jan	2024-02 Feb
FOOD					
KCl(tsp kcl)	0.045 ;0.031;23/23	0.047 ;0.031;30/30	0.085 ;0.062;24/24	0.094 ;0.062;31/31	0.093 ;0.062;29/29
KibbleAmJrLaPo	0.036 ;0.037;22/23	0.065 ;0.075;30/30	0.07 ;0.075;23/24	0.075 ;0.075;31/31	0.071 ;0.098;29/29
KibbleLogic	0.024 ;0.025;22/23	0.043 ;0.05;30/30	0.047 ;0.05;23/24	0.05 ;0.05;31/31	0.047 ;0.065;29/29
b10ngnc[(c)]	0.019 ;0.25;1/23	0.11 ;0.25;9/30	0.047 ;0.25;3/24	0.11 ;1;7/31	0.067 ;0.25;5/29
b15ngnc[(c)]		0.044 ;0.25;5/30	0.021 ;0.25;1/24	0.06 ;0.25;4/31	
b20ngnc[(c)]	0.18 ;0.25;14/23	0.13 ;0.25;10/30	0.25 ;0.25;14/24	0.14 ;0.25;11/31	0.28 ;0.25;19/29
b25ngnc	0.11 ;0.25;9/23	0.067 ;0.25;6/30	0.026 ;0.25;2/24	0.02 ;0.25;2/31	0.039 ;0.25;4/29
b7ngnc[(c)]	0.1 ;0.25;8/23	0.14 ;0.25;11/30	0.14 ;0.25;9/24	0.2 ;0.25;17/31	0.11 ;0.25;7/29
blackberry		0.058 ;0.25;5/30	0.3 ;0.25;20/24		
blueberry	2.4 ;3.8;23/23	2.4 ;2.2;30/30	1.9 ;2;20/24	0.71 ;1.5;13/31	1.2 ;1.5;29/29
carrot	0.35 ;0.25;23/23	0.36 ;0.25;30/30	0.36 ;0.25;24/24	0.38 ;0.25;31/31	0.38 ;0.25;29/29
cbbrothbs					0.022 ;0.25;3/29
cbbroth	0.16 ;0.25;10/23	0.071 ;0.25;6/30		0.21 ;0.25;15/31	0.25 ;0.25;16/29
citrate(tsp citrate)	0.045 ;0.031;23/23	0.047 ;0.031;30/30	0.048 ;0.062;24/24	0.058 ;0.062;31/31	0.092 ;0.062;29/29
ctbrothbs	0.082 ;0.25;5/23	0.4 ;0.25;25/30	0.48 ;0.25;24/24	0.29 ;0.25;19/31	0.22 ;0.25;14/29
ctbroth	0.17 ;0.25;11/23			0.032 ;1;1/31	
eggo3	0.065 ;0.12;23/23	0.062 ;0.062;30/30	0.055 ;0.12;20/24	0.062 ;0.062;31/31	0.062 ;0.062;29/29
eggo			0.01 ;0.062;4/24		
eggshell	0.13 ;0.25;23/23	0.12 ;0.12;30/30	0.11 ;0.25;21/24		
garlic	0.022 ;0.25;2/23	0.22 ;0.25;26/30	0.083 ;0.25;8/24	1.2 ;1;27/31	0.99 ;1;22/29
marrow	0.19 ;0.25;12/23	0.37 ;0.25;30/30	0.083 ;0.25;6/24		0.078 ;0.25;7/29
oliveoil(tsp)	0.035 ;0.12;8/23	0.014 ;0.12;4/30			0.039 ;0.12;9/29
pepper	0.36 ;0.25;23/23	0.38 ;0.25;30/30	0.35 ;0.25;24/24	0.36 ;0.25;31/31	0.38 ;0.25;29/29
pineapple			0.021 ;0.25;2/24		
raspberry	0.32 ;0.25;23/23	0.28 ;0.25;24/30			
salmon		0.043 ;0.25;8/30		0.025 ;0.25;3/31	
shrimp(grams)		3 ;38;5/30	4.9 ;16;9/24	2.8 ;16;8/31	1.8 ;13;4/29
spinach		0.15 ;0.25;12/30	0.36 ;0.25;24/24	0.38 ;0.25;31/31	0.36 ;0.25;28/29
sunflowerseed	0.23 ;0.25;21/23	0.25 ;0.25;30/30	0.21 ;0.25;20/24		0.034 ;0.25;4/29
tomato	0.36 ;0.25;23/23	0.23 ;0.25;19/30	0.18 ;0.25;12/24	0.17 ;0.25;15/31	0.19 ;0.25;29/29
tuna(oz)					
turkey	0.34 ;0.25;23/23	0.37 ;0.25;30/30	0.35 ;0.25;24/24	0.36 ;0.25;31/31	0.36 ;0.25;29/29
vinegar(tsp)	0.09 ;0.062;23/23	0.094 ;0.062;30/30	0.09 ;0.062;24/24	0.068 ;0.062;24/31	2.16e-03 ;0.062;1/29
VITAMIN					
B-1(mg)	4.09e-03 ;0.012;15/23	5.87e-03 ;0.0059;30/30	6.12e-03 ;0.012;24/24	5.69e-03 ;0.0059;30/31	5.87e-03 ;0.0059;29/29
B-12(mg)	0.033 ;0.25;5/23	0.029 ;0.25;5/30	0.047 ;0.25;6/24	0.024 ;0.25;5/31	0.034 ;0.12;8/29
B-2(mg)	5.7 ;16;15/23	7.9 ;8.1;29/30	8.1 ;16;24/24	21 ;32;30/31	43 ;65;29/29
B-3(mg)	8.3 ;24;15/23	12 ;12;30/30	12 ;24;23/24	31 ;48;30/31	60 ;48;29/29
B-6(mg)	6 ;12;11/23	12 ;12;28/30	11 ;12;21/24	8.9 ;12;29/31	5.8 ;12;26/29
B-multi(count)	0.022 ;0.062;8/23			2.02e-03 ;0.062;1/31	
Cu(mg)	0.11 ;0.25;10/23	0.76 ;2;19/30	0.86 ;2;19/24	1.9 ;2;30/31	1.9 ;2;28/29
D-3(iu)	91 ;300;7/23	60 ;300;6/30	62 ;300;5/24	58 ;300;6/31	52 ;300;5/29
Iodine(mg)[(a)]	2.3 ;12;8/23	0.1 ;0.78;4/30	0.065 ;0.78;2/24	0.1 ;0.78;4/31	0.13 ;0.78;5/29
K1(mg)	0.38 ;1.2;7/23	0.92 ;1.2;22/30	1.1 ;1.2;22/24	1.1 ;1.2;27/31	1.2 ;1.2;28/29
K2(mg)	1 ;1.6;15/23	0.3 ;1.9;7/30	0.47 ;3.8;3/24	0.91 ;3.8;8/31	0.81 ;3.8;8/29
K2MK7(mg)	1.63e-03 ;0.025;2/23	5.83e-03 ;0.025;7/30	2.08e-03 ;0.025;2/24		
MgCitrate(mg)	96 ;200;21/23	100 ;100;30/30	92 ;100;22/24	31 ;100;10/31	76 ;100;22/29
Mn(mg)			0.042 ;1;1/24	0.21 ;0.62;12/31	0.12 ;1;6/29
Se(mcg)		0.42 ;12;1/30			0.43 ;12;1/29

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

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

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

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

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

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

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

Appendix E: Notable Food Components with Copper Interactions

Title	
Cu	
Zn	
Fe	
Mo	
H/ OH	
S and amino acids	reduce toxicity [78]
PO4	
Fructose	
Tyr	
Trp	
Pi-complex	
Fenton	
Ammonia, Amides, N	
Citrate	
Ascorbate	
garlic	enhancing bioavailability Cu etc [86]
Microbial products	
phytate	

TABLE IX: Some entities that may interact with copper

Appendix F: Symbols, Abbreviations and Colloquialisms

TERM definition and meaning

Appendix G: General caveats and disclaimer

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

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

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

Version	Date	Comments
0.01	2024-04-12	Create from empty.tex template
-	July 17, 2024	version 0.00 MJM-2024-010
1.0	20xx-xx-xx	First revision for distribution

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

Version	Date	URL

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run-date ={July 17, 2024} ,
title ={Copper Supplementation in Dogs: Listen to Her Heart } ,
author ={Mike J Marchywka } ,
type ={techreport} ,
name ={marchywka-MJM-2024-010} ,
number ={MJM-2024-010} ,
version ={0.00} ,
institution ={not institutionalized, independent } ,
address ={ 44 Crosscreek Trail Jasper GA 30143 USA} ,
date ={July 17, 2024} ,
startdate ={2024-04-12} ,
day ={17} ,
month ={7} ,
year ={2024} ,
author1email ={marchywka@hotmail.com} ,
contact ={marchywka@hotmail.com} ,
author1id ={orcid.org/0000-0001-9237-455X} ,
pages ={ 45}
}

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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