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 Actually looking at the old, unpublished work, "casesum", that includes Little Man, most of the text is still useful today and has been copied and pasted without attribution (since it was a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

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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 observatins 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. 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. 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.

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1. INTRODUCTION

Copper is currently not a trendy nutrient to supplement in human or dog diets. 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. The question of dietary deficiency or excess has been a topic of controversy for many years and likely copper intake alone is not the dominant issue but rather distribution in the body deterined by other dietary components. The question of supplementation has to be within the context of a specific overall intake and other factors like genetics. Even if a surplus occurs in one location, the question remains if there would be a net benefit reducing deficiency in one place even if more excess occurs elsewhere. Thsis has to be answered in terms of clinical outcomes, things relevant to the host, rather than lab values. The background dietary context for this work has been described previously [74] and the copper supplementations described here is likely well in excess of background levels in most known natural foods.

Thinking outloud
its also worth noting that other sources may be significant as with water and air exposure [38]

One increasingly common concern with dogs is copper associated hepatitis [3] [4] [22]. Some noisy association between intake and hepatic copper content was shown in a small study [35] but clearly that was not the major determinant of copper content . The causal role of copper 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 [120]. Work continues to focus on concepts of deficiency or excess even though both may be matters of degree and context. Deficiency in commercial dog foods was suspected years earlier [123] while works as early as 2000 suggest supplementation would be unhelpful[121]. A recent work comparing mineral content in groups of commericial dog foods found some patterns and advised against high copper foods [64].

Low copper status is known in humans and is associated with liver problems too, some related to high fructose intake [133]. Copper deficient liver patients may be notable for "steatohepatitis, iron overload, malnutrition, and recurrent infections. " [143] . Cppper handling genetic diseases are well known in dogs [62] and some concern about excess intake may be warranted for specific animals.

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 in the copper supply. With copper this is quite complicated. A number of regulatory systems are known to control copper levels in different compartments in healthy mammals. Uptake regulation is not completely known but response to dietary or ambient levels is only part of the control loop in vivo and likely cytosolic sensors exist [47]. Its also noteworthy that CTR1 transport is reduced if some histidines are mutated in either the C or N terminal tails. One concern in thiw work relates to "high-infidelity transcription" due to limitations of specific amino acids including histidine. Normally biliary excretion increases when pathological amounts of copper begin to accumulate [24] [43] pointing to defects in excretion as a bigger concern than intake. Senescent cells may accumulate copper in the absence of autophagy [82]. Copper elevation may commit cells to differentiation i cord-blood derived cells [99] and it may be regulat4ed during myogenic differntiation [126] raisng the possibility that accumulation is due to confused signalling. In particular, ceruloplasmin is an acute phase protein and blood levels may be associated with pathological conditions [40] bit a protective role is generally recognized. As a major transporter of copper out of the liver, that sugests distrrbution out of the liver is enhanced with certain stresses. In fact, as substantiated later, it would make sense for copper to be redeployed from some mitrochondria to the blood in response to pathogens or trauma. This will lead to hydrogen peroxide formation and potentially free copper both conditions likely to control infection. Copper signalling is such that remote signals may exist from the heart to liver and intestines to make more available [60] [91]. In this scenario, local shortage could induce blood stream or liver excess due to added inputs with struggling cardiac specific uptake as has been suggested for other nutrients such as tryptophan [73] and biotin [76] [72] . Note this work also suggests copper deficiency as an issue for cardiac hypertrophy in animals.

At least one source of confusion may be the interaction of copper nutrition with many other nutrients with some listed in Appendix E. Competition between Cu, Fe, and Zn was observed in Caco-2 cells [5]. Iron intake in feed has also been observed to decrease copper uptake in ruminants [27] and rats [65] . One work suggested iron disrupts copper homeosstasis independent of uptate [42]. Dietary cholesterol appears to distrurb copper homeostasis with atherosclerosis thought to involve copper dysregulation [66] and high fat diets in other species [50] are an issue. Fructose also inhibits relative copper absorption [92]. Zinc is a known inhibitor of cuppoer uptake and cases of zinc induced copper deficiency in humans are known[130]. 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 [100]. Age related absorption problems in people are known [102] and other apparent deficiencies could be a consequence of insufficient B-6 alone [23]. Interestinly, B-6 is added to penicillamine treatment of Wilson's disease to avoid neurological effects [30].

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 [129].

Body stores of copper increase with excess tyrisone in the diet of rats [138]. Some reports show specific issues when combinted with vitamin C. A small trial with copper sulfate indicated kidney problems result [58] although alternatives with copper gluconate suggested use as food preservative [41] . Dose probably matter among other factors.

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.

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 [29] similar to the competing element zinc for which absorption has been shown to depend on salt type and gastric pH [53]. Interaction with food components such as polyphenols is significant and pH dependent [101] 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 [136]. 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 [98].

Thinking outloud
put somewhere

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 [67] yet alkaline stomach pH is observed is commonly observed in gastric carcinoma [140]. Probably the dominant effect on tumors is unrelated to ambient pH although increased pH may reduce nutrient accumulation by many cells. An absolute apoptosis rate at near neutral pH is probably not indicative of the overall fitness in the stomach.

This work describes inclusion of copper into a set of supplements for dogs with different conditions and unknown genetics showing generally beneficial results or at least no obvious harm with added copper. This result is in contrast to some of the popular expactations cited above. A descrepancy between expectations and outcome of this type seems to be common in medicine and biology so 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 is limited by unqestioned assumptions and logidcal fallacies that are quite common. Some types of problems are listed in Appendix C. A 2010 work suggested that high copper and iron intake were particularly dangerous in older people observing that one study concluded high intake of both was assoicated with increased cognitive decline [21].

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 [142] [107] instead of the cause of Alzheimer's pathology and target for intervention. That state of affairs is well documented in the works that hint at it unravelling[34] such as a 2002 work suggesting that "tauists" and "baptists" could 'shake hands" and look for other causes [87]. 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 [59] [125]. However, upregulation would have to be suspected as a part of regeneration attempting to fix degeneration. Previously, heartworm positive dogs had been given significant amounts of vitamin K [80] [77] 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.

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

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

Emerging mechanisms such as extracellular veiscles [11] suggest that uncharacterized mechanisms of metal homeostasis exist.

A 2016 study in mice suggested adding copper to water was worse than adding it to food and supplementation at 6,15, and 30 ppm with increases in soluble abeta and decreased growth rate and GSH/SOD activity [135]. With a high dose of about 100 micrgograms/day (from CuSO4) and a body weight of about 30grams, the dose was about 3.3mg/kg.

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 [119] consistent with earlier ideas linking age to amino acid staration [73] .

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.

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.

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

2. DISEASES OF INTEREST

The known roles of copper include pathways and functions that would seem important for many diseases that are common in dogs. The present works relies mostly on 'cough" and thyroid related symptoms (coat quality, weight distribution, energy level etc). Cough has many possible origins as discussed previously [78]. Among these are respiratory infection or irritation, collapsed trachea, heart failure, and CNS stimulation. Infection related cough is well known due to direct irriation. Collapsed trachea may cause a cough on either inhalation or exhalation with a distinct honking sound. Heart failure may initiate fluid build up in the lungs and other sources of bulk such as a tumor may cause irritation. With these source in mind, it is not difficult to find pathways and locations that require copper for proper functioning. These have been tabulatedin in Table II along with time scales for the response to reflect changes in copper intake. In most cases the distribution is very broad an non-specific symptoms may be expected. For example, mitochondria are eveywhere although the heart may be the first to show symptoms of deficiency. Its also important to note that cough monitoring is not going to be monotonic with improvement as increased energy may occur quickly resulting in more coughing until trachea and heart can remodel.

Disease	Host	Effect	time scale
DCM/HCM	dog		
Collapssed Trachea	dog		
Hypothyroid	dog		
Infection	dog		
covid-19	human	serum levels irrelevant [109]	
Parkinson's	human	assoc benefit [145]	
Alzheimer's	human		
Infection	human		
Arthritis	human	anecdotes, no trial verfiication	

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

2.1. Collapsed Trachea

While much is not known about cartilage crosslinking, turnover, and remodeling some recent results do point to unexpected beneficial effects of copper mediated cross linking over week time scales [81]. Copper deficiency has been associated with lung development defects in rats [93] and airway and arteriole elastin were at least partially restored after 60 days of additional copper. In poultry, infection is known to cause some tracheal symptoms [141] and relationship to copper status is considered. Copper-garlic may reduce the virulence of some of these for short periods even if not completely able to clear a pathogen[45] and in particular Cu was recently shown to be effective against the toxin of one anaerobe [20] . Collapsed trachea in dogs does not appear to be commonly associated with copper in the literature we found although copper storage disease seems to be an active area of investigation[137] and copper status does come up in other investigations of tracheal damage as highlighted above. It is possible that the original motivation is partially correct and that extra copper combined with garlic did allow for better crosslinking to stiffen tracheal cartilage and prevent dynamic collapse and "honking".

2.2. DCM/HCM

Dilated and hypertrophic cardiac myopathy can both be related to mitrochondria and "oxidative stress" may be a signal for more copper. "Oxidative stress" has been reported to increase muscle mass while reducing performance [1]. Copper deficiency can lead to cardiac hypertrophy with increased mitochondria [83]. "Oxidative stress" is often blamed in the literature as a cause of various problems but it may in fact also be a signal. ROS signalling is well known by now but specifically it may help get sufficient copper to the mitochondria.

Copper is essential for many growth processes and can activate receptor tyrosine kinases without a ligand making it a target for cancer [49].

Copper loading of cytochrome C oxidase relies on an oxidized Cox11 to interact with Cox19 [17] 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 [48] and indeed mitochondrial related signaling [113] . 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 [19] in [113]) . However, the enhancement by GSSG suggests that the presence of oxidized antioxidants may be beneficial but not in their reduced state.

Over the same time however, concerns about diet linked DCM in dogs have emerged. A genetic link is also being investgated and a recent GWAS pointed to two genes, RNF207 and PRKAA2 as risk factors [90] but did not mention copper. However, RNF207 may mediate degradation of ATP7A [146] while PRKAA2 comes up in cuproptosis [68].

Dobermans are at remarkably high risk of DCM [32]. Interestingly, "standard Dobermans" are also at high risk for hypothyroidism [97].

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

2.3. Infection

Combined copper and zinc deficiency was observed to reduce response to covid-19 mRNA vaccines with only minimal copper deficiency [25] The present work considers copper status in light of other nutrients notably amino acids such as Trp and Tyr and with zinc being a possible competitor.

In human health, zinc seems to have taken precedence over copper most recently with some headlines related to the covid-19 pandemic [6] [36] . Some studies suggest copper is not a factor in covid-19 due to measurements like serum copper levels [109] although ceruloplasmin as an acute phase protein can elevate levels during stress even with a deficiency in copper [46]. In sample of 70 patients presrribed zinc, many had symptoms consistent with copper deficiency [31]

Copper may antagonize many pathogens including H pylori [13] and clostridum

2.4. Thyroid

Inerestlingly, copper deficiency in rats can reduce thyroid hormone levels and body temeprature [71].

2.5. AD, PD, ALS, Arthritis

Deficiency seems to effect prefernetially proteins involved in neuronal projection and diabetes and iron handling [127].

Rats fed a copper deficient diet shows neurological symptoms by 7 weeks and had reduced tyrosine hydroxylase and SOD activity ZZ [86].

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 [139]. Interestingly, copper-ascorbate oxidation of tryptophan may be suppressed by Trp chelation of copper at high trp concentrations [85] 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 [56].

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 [70]. 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 [15]. In 2021, Ni was found in important amounts in a commercial abeta40 preparation [12] and was found to mediate dityrosine crosslinks [14] similar to the dityrosine crosslinks induced by copper found in 2004 [7].

A 2013 work found in vitro physiological conditions caused copper to prevent fibril formation [84].

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 [95].

One work in 2022 addressed AD as a consequence of copper deficnecy because [61]

> 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 [106] even as other controlled tests show some effects of Cu on processes related to collagen properties [44]

Remarkably, copper sulfae was shown to protect against ETC damage by MPP [110] suggesting some activity against toxic insults. Copper histidine is used to treat Menkes disease which is a defect in ATP7A [89].

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 [149]. 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 [54]/ 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 [145]

2.6. Cancer

One recent review on anti-cancer mechanisms of copper dicussed various ligands and roles for both copper depletion and overload [8].

Copper storage diseases and in essence "overdose" are well known [37] and a role in cancer is suspected [16] . 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 [112]. Lysyl oxidase activation, the goal of this therapy, is also associated with cancer spread [118][104][132] . 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 [9] or [147] and the survival curve in figure 1). Incidence of liver cancer in Wilson's Disease patients is remarkably low [88] and a discussion of possible treatment effects [131] 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 [33]. This also suggests that copper depletion per se may not kill cancer cells as much as copper complexes and that concerns about copper supplements and cancer may not be significant.

3. FUNCTIONS OF INTEREST

Location	site	Effect	time scale
Heart	mitochondria	energy production	maybe days
Heart	mitochondria	remodelling	weeks or months
Heart valves	lysyl oxidase	crosslinking [103]	weeks or months
Trachea	lysyl oxidase	proper crosslinking	months
Macrophage		infection	days
ceruloplasmin		distribution	days
foreign ligand	variable	variable	

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

3.1. Cytochrome C Oxidase

Supplemental copper has been noted to improve symptoms in one case report including symptoms such as hearing loss [55] attributed to defects in cytochrome C oxidase copper loading and restore function in mutant yeast [39] .Cytochrome C oxidase levels in rat hearts were shown to be related to copper deficiency as early as 1998 [108]. 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 [128][144] .

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 [96]) , 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 [18] and [51] . 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 [24]. However, pro-growth and angiogenesis could also be expected during regeneration which itself may require copper.

3.2. Lysyl Oxidase

Lysyl oxidase bad for vessels [10] calxification. but may be related to metallization issues [114].

Regulation at transcriptional and translation and post-translational levels is confusing. For example, it has been described in 1998 as [115],

> 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, [111]

> 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 [148] 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 [117] 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 [134]. 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[103].

3.3. Ceruloplasmin

Ceruloplasmin contains 6 coppers and histidines needed for metallization [52]. 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 [122]. 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 [105] 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. 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 [116] even as the other correlates sound pathological and its likely the inflammation being reduced would be beneficial if some other problem was corrected.

3.5. Ligandss- histidine and garlic etc

The combination of the garlic and copper, while sounding like a medieval concoction, has been described as synergistic against fungus [94] 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 [26].

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

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

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

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

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

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

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

4. CASES AND OBSERVATIONS

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

A series of rescue dogs were fed food and vitamin supplements in addition to commercial kibble products. Diet and outcomes were recorded in MUQED format [79] 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 [28]. All of the dogs currently living here received increased copper shortly after the arrival of Trixie due to apparent spread of coughing. Trixie was later treated with Clavamox leading to cure suggesting indeed an infectious cause existed. Some of the dogs, notably Happy and Rocky, had varying cough levels previously as described below.

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

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

4.1. Cookie or Mixie

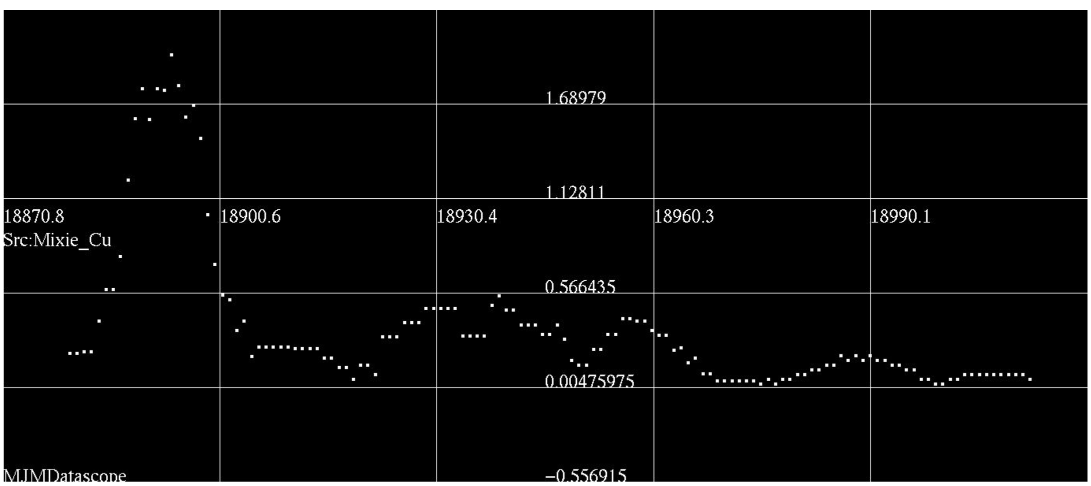

FIG. 2: Mixie daily copper (white) intake .

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

4.2. Brownie and puppies

Brownie was the subject of a prior work where ner uneventful pregnancy was notable for vitamin K consumption while heartworm posivite [80]. Subsequent to that work, her abdominal tumor was removed and diagnosed as fibroid. Briefly, Brownie was determined to be pregnant shortly after arrival . Her heartworm was treated with Diroban after weaning and fibroids removed 2021-11-15 well after the puppies were gone. She was unevntful until being doganosed with cancer and killed 2023-02-22. Prior to her diganosis, she was observed to cough occasionally for no obvious reason and appeared to have some movement issues. X-ray confirmed tumours likely responsible for both problems.

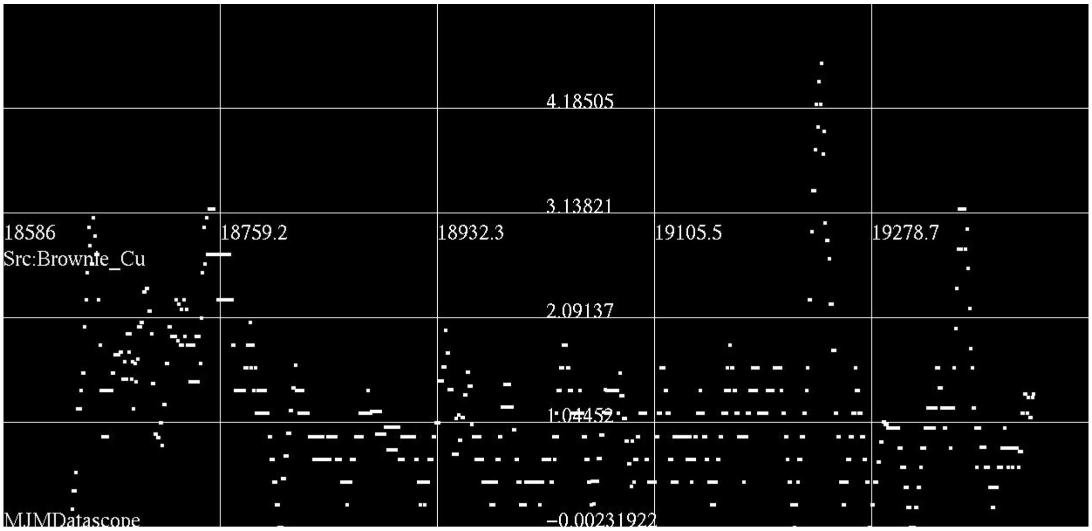

FIG. 3: Brownie 10 day trailing average copper (white) .

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

4.3. Happy

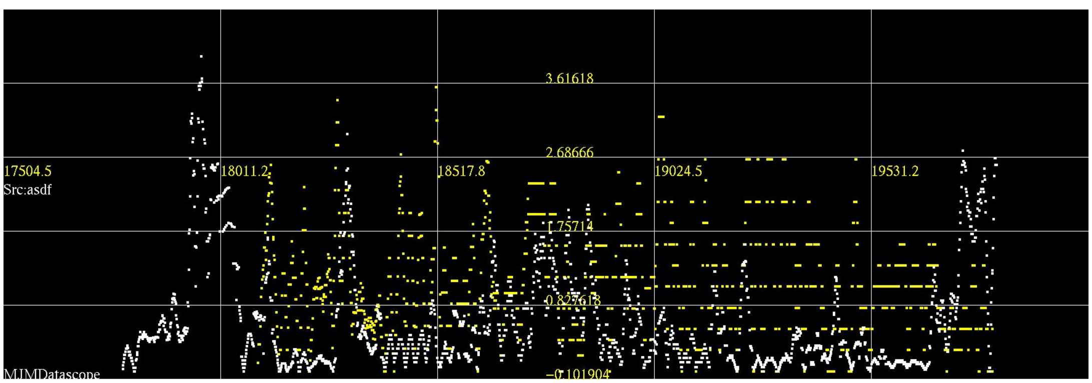

FIG. 4: Copper(white) and Zinc(yellow) dosing per day averaged over prior 10 day period as dosing was highly variable due to rotations of various nutrients. 18046 is 2019-05-30 when the cough was first noted to be gone for a few weeks. 19823 is 2024-04-10 the last date for which data was obtained. The 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 was also the subject of two prior works. Initially her heartworm recovery was described with vitamin K and other supplements [77] followed by an unusual episode which resulted in some investigation of possible role of vitamins B-2 and B-3 in her health [75] . To summarize, Happy arrived heartworm positive coughing to varying degrees. She was treaed with a slow kill approach including ivermectin and doxycycline as previously described. She later was acting sick but appeared to recover well with B vitamin supplements. Her coughing never returned to the very low levels seen after heartworm recovery until copper doses were increased with elimination of any zinc and care with tryptophan. As copper was increased due to widespread coughing after Trixie's arrival, her cough was noted to decrease. Often her excited cough appeared to be a honk on exhale suggestive of trachea collapse. She also would cough early in the morning when curled up. As outlined in the 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. Also since starting the increased copper she does not appear to have disruptive itching around her tail area. Currently she is coughing when excited but that is with significant aromatic supplementation which appears to be making her more excitable.

4.4. Trixie

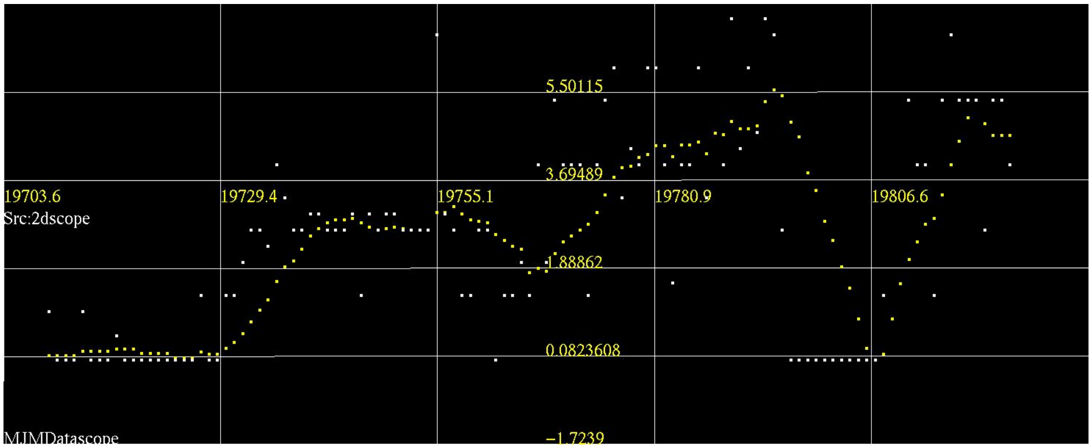

FIG. 5: Trixie copper consumption since arrival. Daily amounts (white)) and trailing 10 day average(yellow). Copper started to be significant around day 19730 in response to coughing. Day 19807 marked the end of the copper fast as well as the end of Clavamox which was prescribed due to worsening when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

Trixie began coughing shortly after arrival and was very low energy. Many other dogs began to cough or hack suggesting that she brought a communicable infectious disease. Nutrient mix was modified to add more copper and most dogs coughing returned to normal 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) .

4.5. Rocky

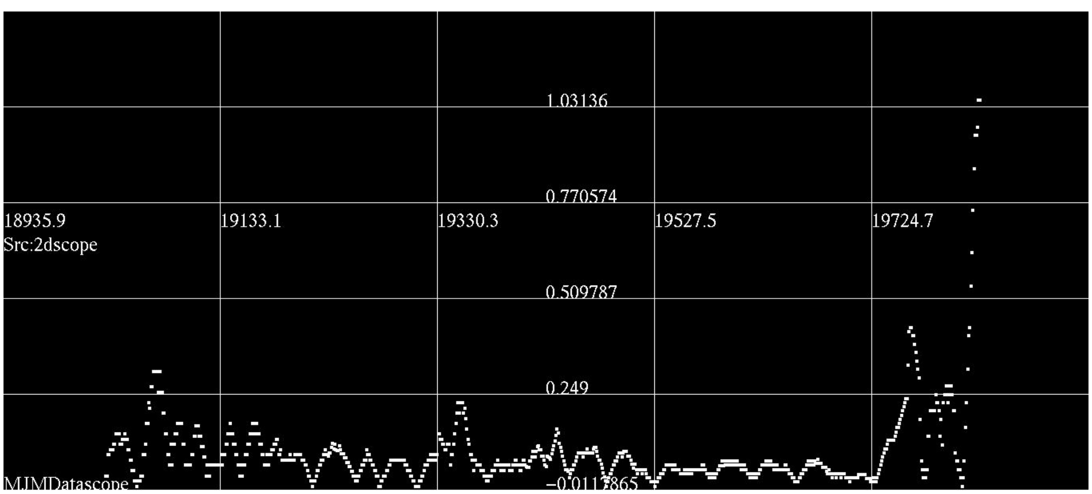

FIG. 6: Rocky 10 day trailing average copper (white) .

Rocky will hopefully be the subject of another work as he responded significantly to iodine and sodium benzoate which was attributed to, but never lab confirmed, low thyroid output. His "plastic" body type changed into a more normal "flexible" type and he began to feel like the other dogs when picked up rather than stiff. The addition of

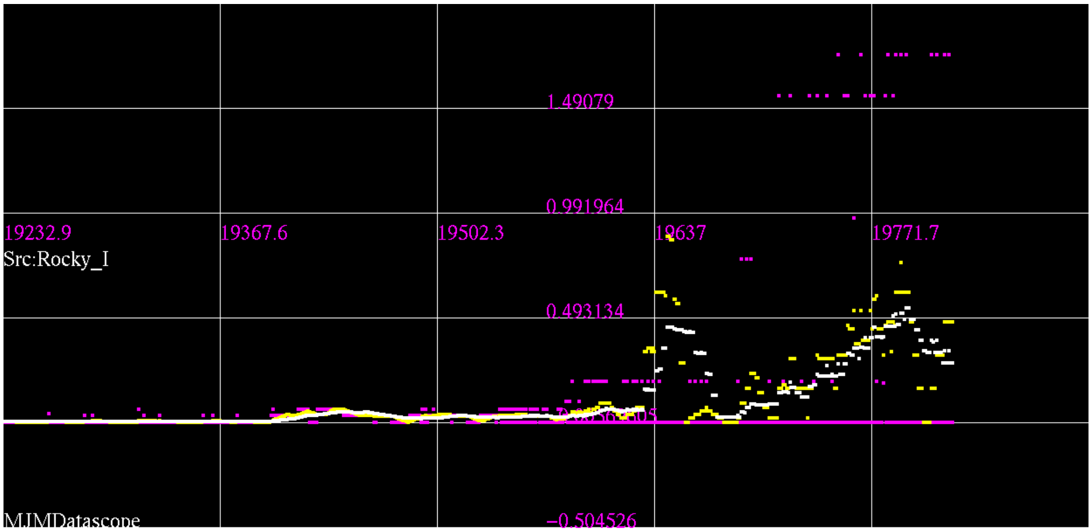

FIG. 7: Rocky iodine intake daily and with 10 and 30 day trailing averages. Patterns are difficult to discern with the pulsed dosing.

copper may have reduced his morning cough but he continued to have apparent congestion after eating sometimes breathing through his mouth and sneezing. 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.

A recent study on rats fed benzoate demonstrated some insignificant indication of increased T4 and decreased TSH which the authors summarize as, [124] ,

> 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 generally ate well but had some limitations in sight and hearing. She seemed to get skin or paw infections easily. She began to sleep excessively and a special copper snack was started on 2024-05-01 (19844). This consited 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 suddently regained in a few days and seemed restored to her more typical self by 2024-05-05 (10948). Her exercise interest improved and she walked and cried with good energy.

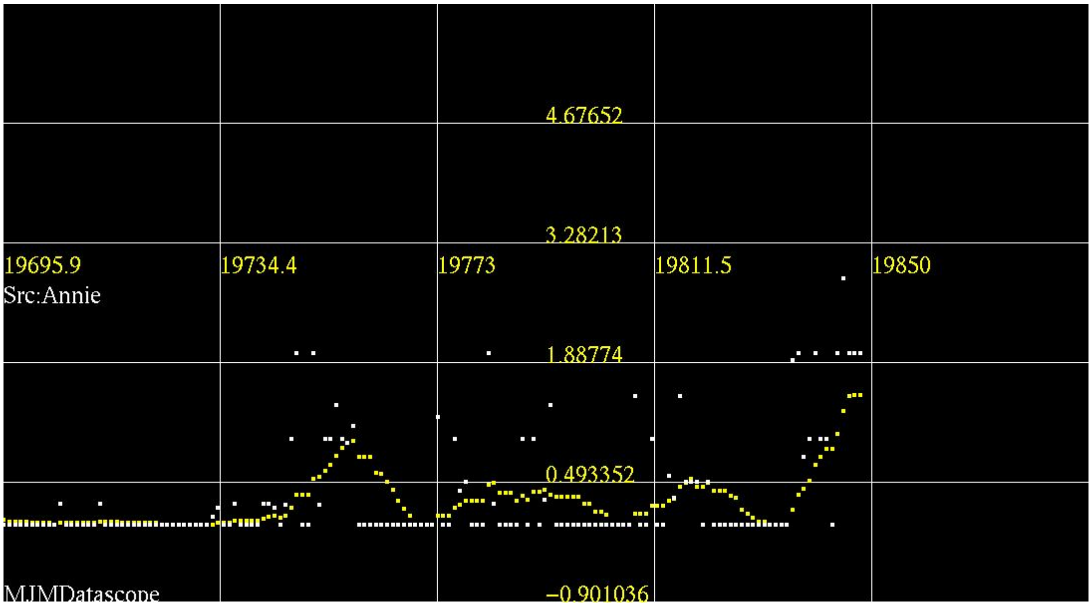

FIG. 8: Annie

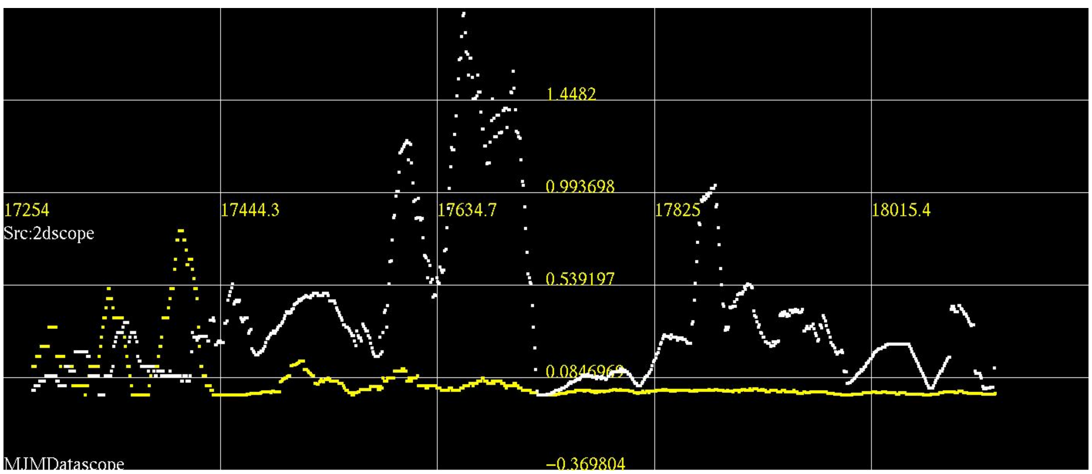

FIG. 9: Herhsey 10 day trailing average copper (white) and iodine (yellow).

4.7. Hershey

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.

4.8. Miscellaneous Observations

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

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

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

5. DISCUSSION

Copper supplementation averaging around .2 to as high as .8 mg/kgBW/day appeared beneficial in this group of dogs as symptom improvement often followed weeks of dosing. Several suspicious observations were noted but nothing robustly correlated with copper intake. As some symptoms such as coughing are the product of many factors, interpretation is difficult during the initial response phases. Most notably, increased general energy may increase coughing in the presence of a weak of collapsed trachea or with some heart conditions which may take longer to mitigate and achieve more complete resolution. Another difficulty is due to pulxed dosing. This was chosen to allow rotoation 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 a respiratory infection that the data were examined more carefully and the pattern noted. Ideally the filtering would be a lagging average weighted to some suspected biological parameters but even uniform moving average was useful.

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

Reconciliation with various concerns and failures felies on the complex interaction with other dietary componets which may be important over a large range of genetis. 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.

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.

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 [23] possibly making copper a secondary excretion issue rather than a primary absorption problem.

ver 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,

1. **supply v demand :** An excess quantity is not inherently due to either supply or demand
2. **false dichotomy :** good and evil
3. **non-monotonic curves :** *show me a monotonic dose response curve and I'll show you a fool*
4. **hidden interaction :** The observed result requires some interaction partners
5. **X is a Y :** Role confusion leads to more untested assumptions.
6. **only relies on empirical obervations :** no cuase and effect stablished
7. **irnores empirical obervations :** "sanity check " Theory based on incomplete system topology needs to be consistent with empirical observations
8. **irnores empirical obervations :** Theory based on incomplete system topology needs to be consistent with empirical observations
9. **other state variables :** Hidden variables include a limting nutrient that is needed to beneficially use the entity under test.
10. **regulatory landscape :** As life is generally robust control systems have evolved but may have non-obvious failure modes.
11. **trying harder :** If a prefered response is frustrated in attaining a survival relevant goal, there may be signals to try a less orderly response more vigorously. The disorganized response can be suppressed by enabling the effective one.
12. **narrow corridor :** Given host-other evolution, you could expect dose response curves with many features but more likely a tight tolerance means that the approach is missing something more robust.

Appendix D: Background Diet 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 [57]
PO4			
Fructose			
Tyr			
Trp			
Pi-complex			
Fenton			
Ammonia, Amides, N			
Citrate			
Ascorbate			
garlic			enhancing bioavailability Cu etc [63]
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
-	May 14, 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

@techreport{marchywka-MJM-2024-010,
filename ={copper} ,
run-date ={May 14, 2024} ,
title ={Utility of Copper Supplementation in Dogs} ,
author ={Mike J Marchywka } ,
type ={techreport} ,
name ={marchywka-MJM-2024-010} ,
number ={MJM-2024-010} ,
version ={0.00} ,
institution ={not institutionalized, independent } ,
address ={ 44 Crosscreek Trail Jasper GA 30143 USA} ,
date ={May 14, 2024} ,
startdate ={2024-04-12} ,
day ={14} ,
month ={5} ,
year ={2024} ,
author1email ={marchywka@hotmail.com} ,
contact ={marchywka@hotmail.com} ,
author1id ={orcid.org/0000-0001-9237-455X} ,
pages ={ 36}
}

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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4583 May 11 19:31 comment.cut def36423cf24137ea6031881bf6b32bc
27672 May 11 19:31 copper.aux 0a57da860ef0aab72dd269080c68f304
69262 May 11 19:31 copper.bbl cdb3e89133eec445138267563cba7e7f
557312 May 11 19:31 copper.bib 87159d0e773ba1b82c38773be5cb4825
5836 May 11 19:31 copper.blg 048f3a92b6cf98ab7a5b0738dd1a94c4
0 May 12 18:41 copper.bundle_checksums d41d8cd98f00b204e9800998ecf8427e
32968 May 11 19:31 copper.fls 5dcb631dcde23708ca941dc8892f77f6
3 May 11 19:31 copper.last_page 649ee93d50739c656e94ec88a32c7ffe
56272 May 11 19:31 copper.log a1cf96cfef9bd587444a5fda3a13255f
6083 May 11 19:31 copper.out 8fff88fc6d06f6a720c8a02240d416a0
3613463 May 11 19:31 copper.pdf 9c0a4e3364f166e4f8e81f79fce1cbe8
82427 May 11 17:36 copper.tex 026273e7ae494bfebeb1ec1319c18bc6
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45970 Apr 18 12:01 /home/documents/latex/bib/mjm_tr.bib e455440cebe55000e46177de11c09ce0
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7434 Oct 21 1999 /home/documents/latex/pkg/lgrind.sty ea74beead1aa2b711ec2669ba60562c3
1069 Oct 15 2021 /home/documents/latex/share/includes/disclaimer-gaslight.tex 94142
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425 Oct 11 2020 /home/documents/latex/share/includes/disclaimer-status.tex b276f09e06a3a9114f927e4199f379f7
3927 May 2 13:06 /home/documents/latex/share/includes/mjmaddbib.tex d58183f98615737b38f9d6e03fc064de
117 Oct 16 2023 /home/documents/latex/share/includes/mjmlistings.tex c1c3bd564b7fb321b4d8f223c7d3cde3
4351 Mar 26 16:38 /home/documents/latex/share/includes/mycommands.tex 8970c9fcbd1d3961c6b774d03462ccea
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1538 Aug 14 2021 /home/documents/latex/share/includes/recent_template.tex 49763d2c29f74e4b54fa53b25c2cc439
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