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 Actually looking at the old, unpublished work, "casesum", that includes Little Man, most of the text is still useful today and has been copied and pasted without attribution (since it was a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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(Dated: April 26, 2024)

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

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1. INTRODUCTION

Copper has become a concern in dog food over the past few years due to the more common observation of "copper associated hepatitis" [3] [4] [19]. This work describes inclusion of copper into a set of supplements for dogs with diverse genetics and conditions showing generally beneficial results with added copper. 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. A recent example may be the identification of amyloid beta as a nominally protective substance instead of the cause of Alzheimer's pathology and target for intervention. Interestingly, related to copper, is the emerging role of lysyl oxidase in Alzheimer's as a possible target Lysyl oxidase is also found as topic in Alzherimer's disease where it associates with cerebral amyloid angiopathy and is thought to be a drug target [90] although upregulation would have to be suspected as a part of regeneration attempting to fix degeneration. 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. **regulatory landscape :** As life is generally robust control systems have evolved but may have non-obvious failure modes.
3. **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.
4. **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.

This work illustrates that empirically deficiency may be more common in some groups of dogs than excess in that supplementation 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.

Factors other than intake may effect local copper concentrations in nominally normal genetics. However, senescent cells may accumulate copper in the absence of autophagy [56]. Copper elevation may commit cells to differentiation i cord-blood derived cells [70] and it may be regulat4ed during myogenic differntiation [91] rasiing the ossibility that accumulation is due to confused signalling.

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. Ceruloplasmin contains 6 coppers and histidines needed for metallization [38]. as well as 2 tyrosines. Independent errors in metallization will multiple and reduce likelyhood of functional enzyme.

Dogs fed a histidine deficienct diet eventually developed feeding resistance and lower whole blood copper and zinc [22].

More recently, diet associated dilated cardiomyopathy (DCM) has also become a concern.

2. MOTIVATION

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 [54]. 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 I 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.

Location	site	Effect	time scale
Heart	mitochondria	energy production	maybe days
Heart	mitochondria	remodelling	weeks or months
Heart valves	lysyl oxidase	crosslinking [73]	weeks or months
Trachea	lysyl oxidase	proper crosslinking	months
Macrophage		infection	days
ceruloplasmin		distribution	days
foreign ligand	variable	variable	

TABLE I: 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.

Inerestlingly, copper deficiency in rats can reduce thyroid hormone levels and body temeprature [53].

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.

Emerging mechanisms such as extracellular veiscles [9] suggest that uncharacterized mechanisms of metal homeostasis exist.

Combined copper and zinc deficiency was observed to reduce response to covid-19 mRNA vaccines with only minimal copper deficiency [21] 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 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.

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 [57].

Regulation at transcriptional and translation and post-translational levels is confusing. For example, it has been described in 1998 as [83],

> 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, [79]

> 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 [109] 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 [85] 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 [97]. 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[73].

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 [62] but did not mention copper. However, RNF207 may mediate degradation of ATP7A [107] while PRKAA2 comes up in cuproptosis [50].

Dobermans are at remarkably high risk of DCM [26]. Interestingly, "standard Dobermans" are also at high risk for hypothyroidism [68].

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

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.

3. CASES AND OBSERVATIONS

A series of rescue dogs were fed food and vitamin supplements in addition to commercial kibble products. Diet and outcomes were recorded after supplemented meals in MUQED format. Most dogs receieved 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 this includes copper.

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 putiative confounding factor.

We tried to set a hard upper limit of 3mg/kg body weight of supplemental copper per day based on some quoted NOAEL's but the original source from 1972 discussed in [24].

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	50	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

TABLE II: 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

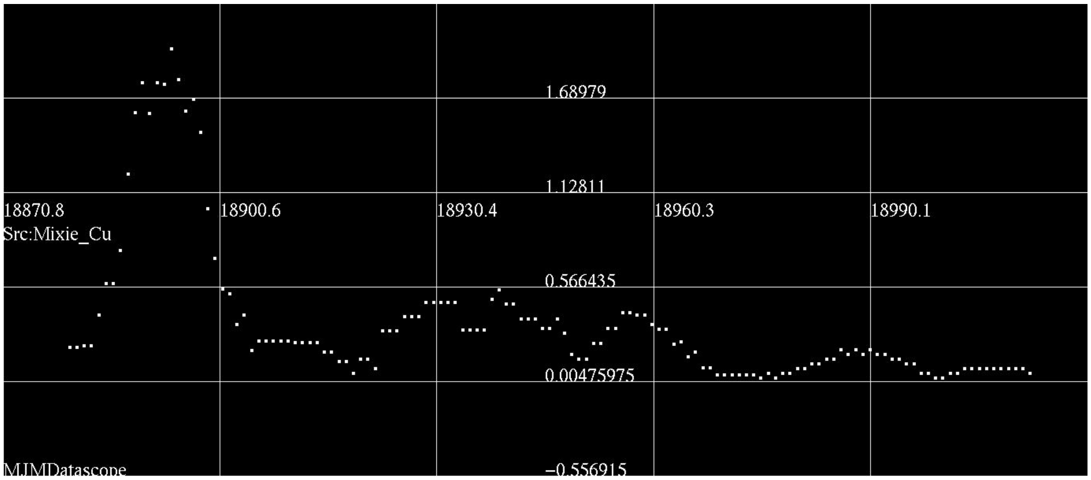

FIG. 1: Mixie daily copper (white) intake .

3.1. Cookie or Mixie

Arrived with diagnosed respiratory infection and azirhtromycin. Copper and other nutirents were added and eventually infection resolved well.

3.2. Brownie and puppies

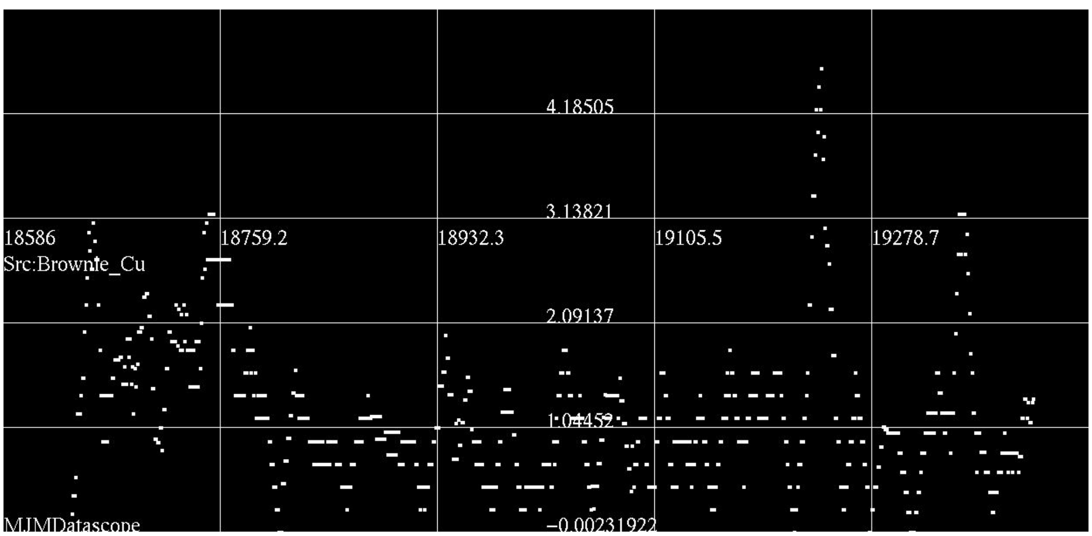

FIG. 2: Brownie 10 day trailing average copper (white) .

Brownie was determined to be pregnant shortly after arrival and her diet may be notable for includsion of both copper and vitamin K. Other conidtions indluce heartworm positive, treated after weaning with Diroban, and fibroids removed 2021-11-15 well after puppies were gone. She was unevntful until being doganosed with cancer and killed 2023-02-22.

3.3. Happy

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

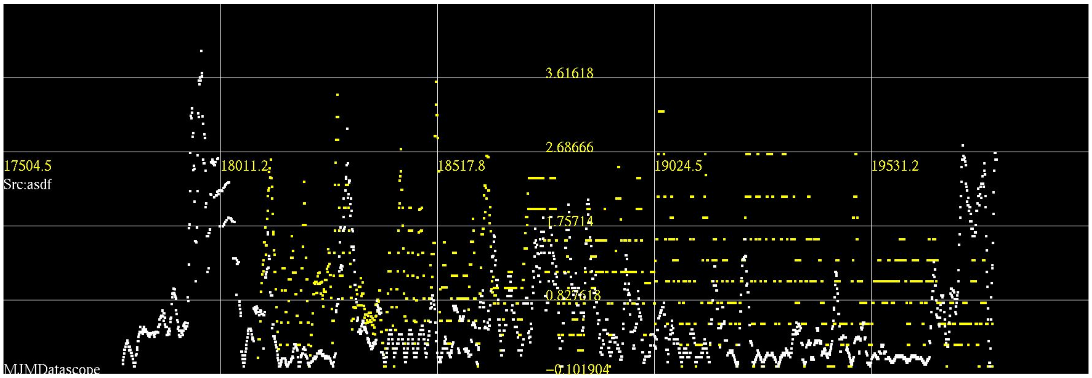

FIG. 3: Copper(white) and Zinc(yellow) dosing per day averaged over prior 10 day period as dosing was highly variable due to rotations of various nutrients. 18046 is 2019-05-30 when the cough was first noted to be gone for a few weeks. 19823 is 2024-04-10 the last date for which data was obtained. The 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.

vitamin supplements. But her coughing never returned to the very low levels seen after heart worm 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.

3.4. Trixie

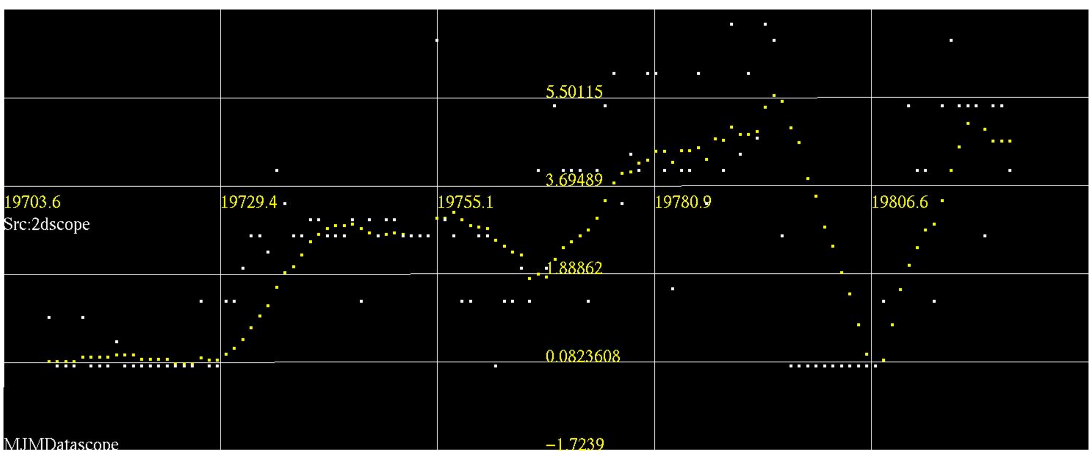

FIG. 4: Trixie copper consumption since arrival. Daily amounts (white)) and trailing 10 day average(yellow). Copper started to be significant around day 19730 in response to coughing. Day 19807 marked the end of the copper fast as well as the end of Clavamox which was prescribed due to worsening when 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 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 still does not run.

3.5. 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

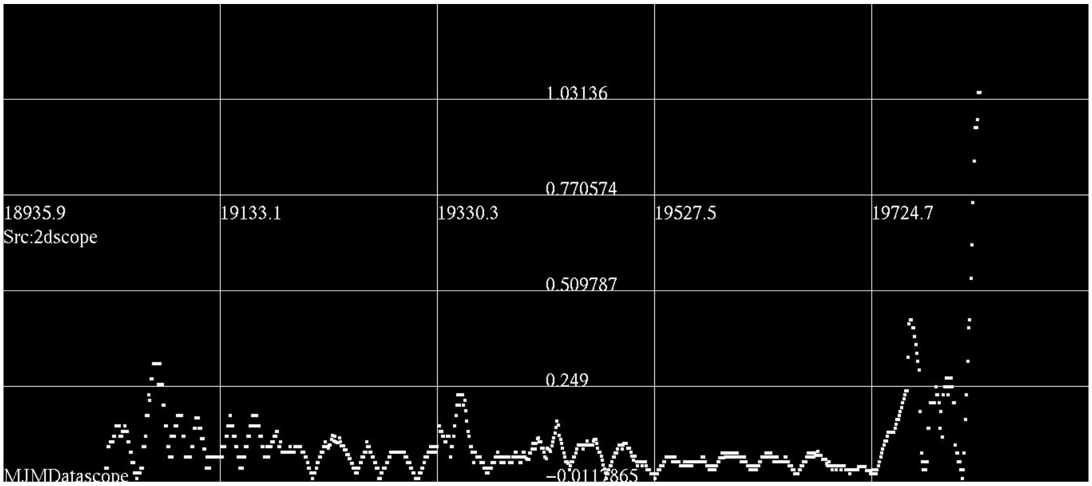

FIG. 5: Rocky 10 day trailing average copper (white) .

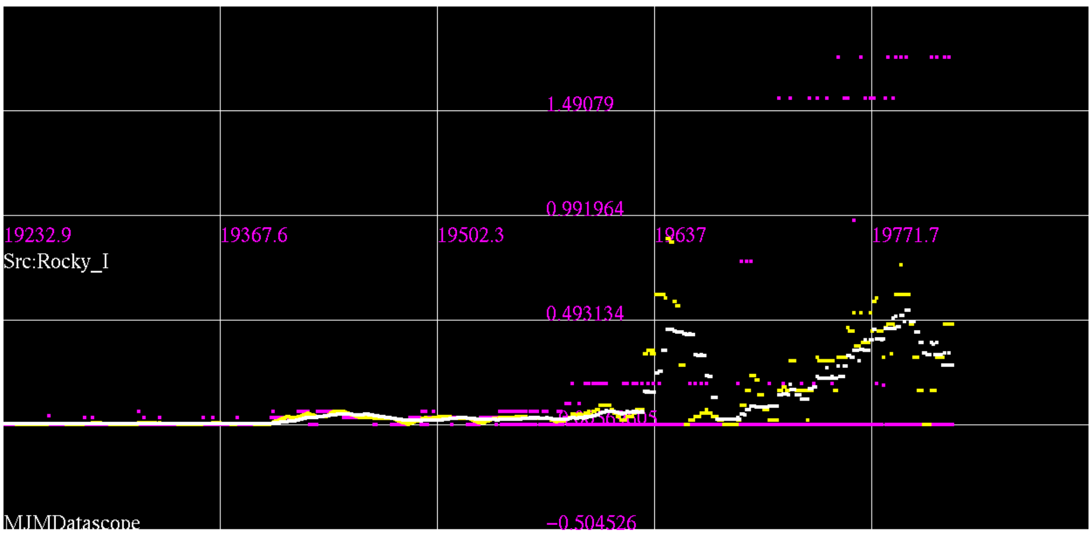

FIG. 6: Rocky iodine intake daily and with 10 and 30 day trailing averages. Patterns are difficult to discern with the pulsed dosing.

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.

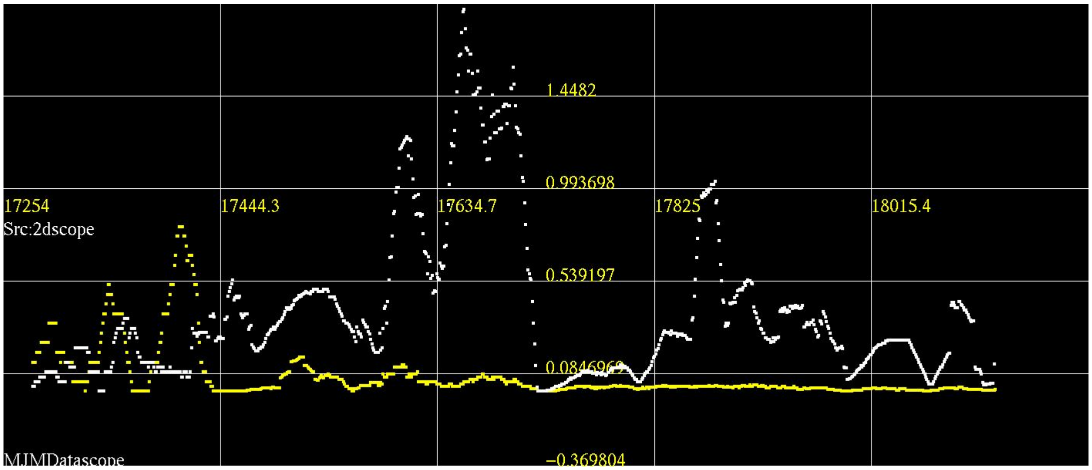

FIG. 7: Herhsey 10 day trailing average copper (white) and iodine (yellow).

3.6. 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 III: 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 features could be rationalized as related to thyroid output, his iodine intake was elevated.

3.7. Miscellaneous Observations

Rocky seemed to do better but was also 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.

Chloride tended to be low and bicarbonate high.

4. DISCUSSION

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.

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

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 [55]. Copper deficiency has been associated with lung development defects in rats [64] 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 [104] 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[33] and in particular Cu was recently shown to be effective against the toxin of one anaerobe [18] . 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[100] 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".

B-6 deficiency has been linked to excess copper excretion [20] possibly making copper a secondary excretion issue rather than a primary absorption problem.

Supplemental copper has been noted to improve symptoms in one case report including symptoms such as hearing loss [42] attributed to defects in cytochrome C oxidase copper loading and restore function in mutant yeast [29] .Cytochrome C oxidase levels in rat hearts were shown to be related to copper deficiency as early as 1998 [77]. 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 [93][106] . Remarkably, copper sulfae was shown to protect against ETC damage by MPP [78] suggesting some activity against toxic insults.

Age related absorption problems in people are known [72] and other apparent deficiencies could be a consequence of insufficient B-6 alone [20][8][30].

Deficiencies are not always correctable by simply eating more of something- for example, calcium intake alone may not fix osteoporosis. Distribution may be a concern as it is possible to have both too much and too little in differing locations due to defects not with absorption but rather handling proteins that would transport or chaperone copper compounds. The combination of the garlic and copper, while sounding like a medieval concoction, has been described as synergistic against fungus [65] and seems plausible for generating perhaps more volatile and diffusable copper that could find otherwise inaccessible lysyl oxidase and other targets. Folklore regarding copper persists and yet clinical trials for Cu in arthritis continue to show lack of any benefit [76] even as other controlled tests show some effects of

Cu on processes related to collagen properties [32] Copper dosing with dogs of unknown background may raise some very real cause for concern and deficiency has not been considered a problem [87] although suspected years earlier in commercial foods [89] and low copper is associated with liver problems related to high fructose(including increased heaptic iron) [96] and fat diets in other species [36] . Copper storage diseases and in essence "overdose" are well known [28] and a role in cancer is suspected [14] . 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 [80]. Lysyl oxidase activation, the goal of this therapy, is also associated with cancer spread [86][74][95] . 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 [6] or [108] and the survival curve in figure 1). Incidence of liver cancer in Wilson's Disease patients is remarkably low [61] and a discussion of possible treatment effects [94] 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.

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 [67]) , 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 [16] and [37] . Copper loading of cytochrome C oxidase relies on an oxidized Cox11 to interact with Cox19 [15] 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 [34] and indeed mitochondrial related signaling [81] . 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 [17] in [81]) . However, the enhancement by GSSG suggests that the presence of oxidized antioxidants may be beneficial but not in their reduced state. 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 [27]. 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.

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 tyrosine and tryptophan.

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 [84] even as the other correlates sound pathological and its likely the inflammation being reduced would be beneficial if some other problem was corrected.

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 [52]. 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 [13].

Copper signalling is such that remote signals may exist from the heart to liver and intestines to make more available [46] [63]. In this scenario, local shortage could induce blood stream excess due to added inputs with struggling cardiac specific uptake as has been suggested for other nutrients such as tryptophan and biotin. Note this work also suggests copper deficiency as an issue for cardiac hypertrophy in animals. Copper uptake may depend on anions such as chloride at least in some animals [31] ,suggesting GI chloride per se rather than pH may be an issue. A series of copper deficient liver patients were notable for "steatohepatitis, iron overload, malnutrition, and recurrent infections. " [105] . Its interesting that iron overload occurs along with general malnutrition and sepcific copper deficiency.

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 [40]/ pointing to a possible more general mechnism. The work goes onto suggest possible role in Parkinson's Disease but does not address AD.

In 2021, Ni was found in important amounts in a commercial abeta40 preparation [10] and was found to mediate dityrosine crosslinks [12] similar to the dityrosine crosslinks induced by copper found in 2004 [5].

A 2013 work found in vitro physiological conditions caused copper to prevent fibril formation [58].

Copper is essential for many growth processes and can activate receptor tyrosine kinases without a ligand making it a target for cancer [35].

Rats fed a copper deficient diet shows neurological symptoms by 7 weeks and had reduced tyrosine hydroxylase and SOD activity ZZ [60].

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 [102]. Interestingly, copper-ascorbate oxidation of tryptophan may be suppressed by Trp chelation of copper at high trp concentrations [59] 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 [43].

Body stores of copper increases with excess tyrisone in the diet of rats [101].

By 2022, work focusing on moving copper into the cell considered many aspects of copper misallocation and devised a copper specific shuttle peptide [66]. Recognition that the cells need copper is important .

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 [98]. 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.

One work in 2022 addressed AD as a consequence of copper deficnecy because [47]

> 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.

Lysyl oxidase bad for vessels [7] calxification. but may be related to metallization issues [82].

Ceruloplasmin contains a chain of W and Y that are thought important for enzyme preservation [88]. 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. Ceruloplasmin KO mice gained weight and showed increased scatter in weight with lipid dysregulation only partially corrected wth exogenous replacement [75].

Deficiency seems to effect prefernetially proteins involved in neuronal projection and diabetes and iron handling [92].

Copper may antagonize many pathogens including H pylori [11] and clostridum

Combined with vitamin C literature is confusing. It may be bad [45] although alternatives with copper gluconate instead of sulfate

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

Copper solubility is pH dependent [25]

Content in drinking water is variable and may be perceived by humans depending on factors like pH [41] sugesting it may be perceived by dogs too. Interaction with food components such as polyphenols is significant and pH dependent [71] motivating a larger interest in food interactions and in particular rings such as in tyorinse. 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 [99].

Zinc absorption has been shown to depend on salt type and gastric pH [39].

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 [69]. Iron intake in ruminant feed has also been observed to decrease copper uptake [23]. 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 [49] yet alkaline stomach pH is observed is commonly observed in gastric carcinoma [103]. 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.

5. 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.

6. 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.

7. 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.

7.1. 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"
```

8. BIBLIOGRAPHY

[1] Bumsoo Ahn, Rojina Ranjit, Pavithra Premkumar, Gavin Pharaoh, Katarzyna M. Piekarz, Satoshi Matsuzaki, Dennis R. Claflin, Kaitlyn Riddle, Jennifer Judge, Shylesh Bhaskaran, Kavithalakshmi Satara Natarajan, Erika Barboza, Benjamin Wronowski, Michael Kinter, Kenneth M. Humphries, Timothy M. Griffin, Willard M. Freeman, Arlan Richardson, Susan V. Brooks, and Holly Van Remmen. Mitochondrial oxidative stress impairs contractile function but paradoxically increases muscle mass via fibre branching. *Journal of Cachexia, Sarcopenia and Muscle*, 10, 2019. Available from: http://dx.doi.org/10.1002/jcsm.12375, doi:10.1002/jcsm.12375.

[2] Robert J Aiello, Patricia-Ann Bourassa, Qing Zhang, Jeffrey Dubins, Daniel R Goldberg, Stephane De Lombaert, Marc Humbert, Christophe Guignabert, Maria A Cavasin, Timothy A McKinsey, and Vishwas Paralkar. Tryptophan hydroxylase 1 inhibition impacts pulmonary vascular remodeling in two rat models of pulmonary hypertension. *The Journal of pharmacology and experimental therapeutics*, pages 267–279, 12 2016. Available from: https://pubmed.ncbi.nlm.nih.gov/27927914/, doi:10.1124/jpet.116.237933.

[3] Laura Amundson, Brent Kirn, Erik Swensson, Allison Millican, and George Fahey. Copper metabolism and its implications for canine nutrition. *Translational Animal Science*, 8:txad147, 01 2024. Available from: https://doi.org/10.1093/tas/txad147, arXiv:https://academic.oup.com/tas/article-pdf/doi/10.1093/tas/txad147/55674607/txad147.pdf, doi:10.1093/tas/txad147.

[4] LauraA Amundson, BrentN Kirn, ErikJ Swensson, AllisonA Millican, and GeorgeC Fahey. Copper metabolism and its implications for canine nutrition. *Translational Animal Science*, 01 2024. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10787350/, doi:10.1093/tas/txad147.

[5] Craig S. Atwood, George Perry, Hong Zeng, Yoji Kato, Walton D. Jones, Ke-Qing Ling, Xudong Huang, Robert D. Moir, Dandan Wang, Lawrence M. Sayre, Mark A. Smith, Shu G. Chen, and Ashley I. Bush. Copper mediates dityrosine cross-linking of alzheimer's amyloid-upbeta. *Biochemistry*, 43, 01 2004. Available from: http://dx.doi.org/10.1021/bi0358824, doi:10.1021/bi0358824.

[6] MV Bais, MA Nugent, DN Stephens, SS Sume, KH Kirsch, GE Sonenshein, and PC Trackman. Recombinant lysyl oxidase propeptide protein inhibits growth and promotes apoptosis of pre-existing murine breast cancer xenografts. *PLoS ONE*, 7(2), 2012. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3280126/.

[7] Carme Ballester-Servera, Judith Alonso, Manel Tauron, Noemi Rotllan, Cristina Rodriguez, and Jose Martinez-Gonzalez. Lysyl oxidase expression in smooth muscle cells determines the level of intima calcification in hypercholesterolemia-induced atherosclerosis. *Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis*, 02 2024. Available from: https://pubmed.ncbi.nlm.nih.gov/38402026/, doi:10.1016/j.arteri.2024.01.003.

[8] F Baumgart and I Rodriguez-Crespo. D-amino acids in the brain: the biochemistry of brain serine racemase. *The FEBS journal*, 275(14):3538–45, 2008. Available from: http://www.ncbi.nlm.nih.gov/pubmed/articles/18564178/.

[9] Shayne A. Bellingham, Belinda Guo, and Andrew F. Hill. The secret life of extracellular vesicles in metal homeostasis and neurodegeneration. *Biology of the Cell*, 107, 2015. Available from: http://dx.doi.org/10.1111/boc.201500030, doi:10.1111/boc.201500030.

[10] Stéphane L. Benoit and Robert J. Maier. The nickel-chelator dimethylglyoxime inhibits human amyloid beta peptide in vitro aggregation. *Scientific Reports*, 11, 03 2021. Available from: https://www.nature.com/articles/s41598-021-86060-1?fromPaywallRec=false, doi:10.1038/s41598-021-86060-1.

[11] Sabine Bernegger, Cyrill Brunner, Matej VizoviUx0161[bad char vv=353]ek, Marko Fonovic, Gaetano Cuciniello, Flavia Giordano, Vesna Stanojlovic, Miroslaw Jarzab, Philip Simister, Stephan M. Feller, Gerhard Obermeyer, Gernot Posselt, Boris Turk, Chiara Cabrele, Gisbert Schneider, and Silja Wessler. A novel fret peptide assay reveals efficient helicobacter pylori htra inhibition through zinc and copper binding. *Scientific Reports*, 10, 06 2020. Available from: https://www.nature.com/articles/s41598-020-67578-2, doi:10.1038/s41598-020-67578-2.

[12] Elina Berntsson, Faraz Vosough, Teodor Svantesson, Jonathan Pansieri, Igor A. Iashchishyn, Lucija OstojiUx0107[bad char vv=263], Xiaolin Dong, Suman Paul, Jüri Jarvet, Per M. Roos, Andreas Barth, Ludmilla A. Morozova-Roche, Astrid Gräslund, and Sebastian S. Wärmländer. Residue-specific binding of ni(ii) ions influences the structure and aggregation of amyloid beta (aupbeta) peptides. *Scientific Reports*, 13, 02 2023. Available from: https://www.nature.com/articles/s41598-023-29901-5?fromPaywallRec=false, doi:10.1038/s41598-023-29901-5.

[13] Glenda M. Bishop and Stephen R. Robinson. The amyloid paradox: Amyloidupbetametal complexes can be neurotoxic and neuroprotective. *Brain Pathology*, 14, 2004. Available from: http://dx.doi.org/10.1111/j.1750-3639.2004.tb00089.x, doi:10.1111/j.1750-3639.2004.tb00089.x.

[14] S Blockhuys and P Wittung-Stafshede. Roles of copper-binding proteins in breast cancer. *International Journal of Molecular Sciences*, 18(4), 2017. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5412452/.

[15] Manuela Bode, Michael W. Woellhaf, Maria Bohnert, Martin van der Laan, Frederik Sommer, Martin Jung, Richard Zimmermann, Michael Schroda, and Johannes M. Herrmann. Redox-regulated dynamic interplay between cox19 and the copper-binding protein cox11 in the intermembrane space of mitochondria facilitates biogenesis of cytochrome c oxidase. *Molecular Biology of the Cell*, 26(13):2385–2401, 2015. Available from: http://www.molbiolcell.org/content/26/13/2385.abstract, arXiv:http://www.molbiolcell.org/content/26/13/2385.full.pdf+html, doi:10.1091/mbc.

E14-11-1526.

[16] MY Bonner and JL Arbiser. The antioxidant paradox: what are antioxidants and how should they be used in a therapeutic context for cancer. *Future medicinal chemistry*, 6(12):1413–22, 2014. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4412352/.

[17] M Bourens, F Fontanesi, IC Soto, J Liu, and A Barrientos. Redox and reactive oxygen species regulation of mitochondrial cytochrome c oxidase biogenesis. *Antioxidants & Redox Signaling*, 19(16):1940–52, 2013. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3852343/.

[18] Paul T. Bremer, Sabine Pellett, James P. Carolan, William H. Tepp, Lisa M. Eubanks, Karen N. Allen, Eric A. Johnson, and Kim D. Janda. Metal ions effectively ablate the action of botulinum neurotoxin a. *Journal of the American Chemical Society*, 139(21):7264–7272, 2017. PMID: 28475321. Available from: http://dx.doi.org/10.1021/jacs.7b01084, arXiv:http://dx.doi.org/10.1021/jacs.7b01084, doi:10.1021/jacs.7b01084.

[19] Sharon A. Center, Keith P. Richter, David C. Twedt, Joseph J. Wakshlag, Penny J. Watson, and Cynthia R. L. Webster. Is it time to reconsider current guidelines for copper content in commercial dog foods? *Journal of the American Veterinary Medical Association*, 258, 02 2021. Available from: http://dx.doi.org/10.2460/javma.258.4.357, doi:10.2460/javma.258.4.357.

[20] ML Channa, FJ Burger, JB Ubbink, and SG Reinach. Zinc, copper and iron balance in the vitamin b-6-deficient rat. *vitaminologie et de nutrition*, 64(3):204–11, 1994. Available from: http://www.ncbi.nlm.nih.gov/pubmed/articles/7814236/.

[21] Thilo Samson Chillon, Kamil Demircan, Julian Hackler, Raban A. Heller, Peyman Kaghazian, Arash Moghaddam, and Lutz Schomburg. Combined copper and zinc deficiency is associated with reduced sars-cov-2 immunization response to bnt162b2 vaccination. *Heliyon*, 9, 2023. Available from: http://dx.doi.org/10.1016/j.heliyon.2023.e20919, doi:10.1016/j.heliyon.2023.e20919.

[22] Bruno Cianciaruso, Michael R. Jones, and Joel D. Kopple. Histidine, an essential amino acid for adult dogs. *The Journal of Nutrition*, 111, 1981. Available from: http://dx.doi.org/10.1093/jn/111.6.1074, doi:10.1093/jn/111.6.1074.

[23] Andrea H. Clarkson, Stuart W. Paine, and Nigel R. Kendall. Evaluation of the solubility of a range of copper sources and the effects of iron & sulphur on copper solubility under rumen simulated conditions. *Journal of Trace Elements in Medicine and Biology*, 68, 2021. Available from: http://dx.doi.org/10.1016/j.jtemb.2021.126815, doi:10.1016/j.jtemb.2021.126815.

[24] National Research Council. *Copper in Drinking Water*. The National Academies Press, Washington, DC, 2000. Available from: https://www.nap.edu/catalog/9782/copper-in-drinking-water, doi:10.17226/9782.

[25] Jonathan D. Cuppett, Susan E. Duncan, and Andrea M. Dietrich. Evaluation of Copper Speciation and Water Quality Factors That Affect Aqueous Copper Tasting Response. *Chemical Senses*, 31(7):689–697, 07 2006. Available from: https://doi.org/10.1093/chemse/bjl010, arXiv:https://academic.oup.com/chemse/article-pdf/31/7/689/779389/bjl010.pdf, doi:10.1093/chemse/bjl010.

[26] Sini Ezer, Auli Saarinen, Shintaro Katayama, Masahito Yoshihara, Abdul Kadir Mukarram, Rasha Fahad Aljelaify, Fiona Ross, Amitha Raman, Irene Stevens, Oleg Gusev, Danika Bannasch, Jeffrey J. Schoenebeck, Juha Kere, W. Glen Pyle, Jonas Donner, Alex V. Postma, Tosso Leeb, Göran Andersson, Marjo K. Hytönen, Jens Häggström, Maria Wiberg, Jana Friederich, Jenny Eberhard, Magdalena Harakalova, Frank G. van Steenbeek, Gerhard Wess, Hannes Lohi, Julia E. Niskanen, AAsa Ohlsson, Ingrid Ljungvall, Michaela Drögemüller, Robert F. Ernst, Dennis Dooijes, Hanneke W. M. van Deutekom, J. Peter van Tintelen, Christian J. B. Snijders Blok, Marion van Vugt, Jessica van Setten, Folkert W. Asselbergs, Aleksandra Domanjko PetriUx010d[bad char vv=269], Milla Salonen, Sruthi Hundi, Matthias Hörtenhuber, Carsten Daub, César L. Araujo, Ileana B. Quintero, Kaisa Kyöstilä, Maria Kaukonen, Meharji Arumilli, Riika Sarviaho, Jenni Puurunen, Sini Sulkama, Sini Karjalainen, Antti Sukura, Pernilla Syrjä, Niina Airas, Henna Pekkarinen, Ilona Kareinen, Hanna-Maaria Javela, Anna Knuuttila, Heli Nordgren, Karoliina Hagner, Tarja Pääkkönen, Antti Iivanainen, and Kaarel Krjutskov. Identification of novel genetic risk factors of dilated cardiomyopathy: from canine to human. *Genome Medicine*, 15, 2023. Available from: http://dx.doi.org/10.1186/s13073-023-01221-3, doi:10.1186/s13073-023-01221-3.

[27] M Fatfat, RA Merhi, O Rahal, DA Stoyanovsky, A Zaki, H Haidar, VE Kagan, H Gali-Muhtasib, and K Machaca. Copper chelation selectively kills colon cancer cells through redox cycling and generation of reactive oxygen species. *BMC Cancer*, 14:527, 2014. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4223620/.

[28] I. Carmen Fuentealba and Enrique M. Aburto. Animal models of copper-associated liver disease. *Comparative Hepatology*, 2(1):5, 2003. Available from: http://dx.doi.org/10.1186/1476-5926-2-5, doi:10.1186/1476-5926-2-5.

[29] Alok Ghosh, Prachi P. Trivedi, Shrishiv A. Timbalia, Aaron T. Griffin, Jennifer J. Rahn, Sherine S. L. Chan, and Vishal M. Gohil. Copper supplementation restores cytochrome c oxidase assembly defect in a mitochondrial disease model of coa6 deficiency. *Human Molecular Genetics*, 23(13):3596, 2014. Available from: http://dx.doi.org/10.1093/hmg/ddu069, arXiv:/oup/backfile/content_public/journal/hmg/23/13/10.1093/hmg/ddu069/2/ddu069.pdf, doi:10.1093/hmg/ddu069.

[30] Tomas R. Guilarte. Regional changes in the concentrations of glutamate, glycine, taurine, and gaba in the vitamin b-6 deficient developing rat brain: Association with neonatal seizures. *Neurochemical Research*, 14(9):889–897, 1989. Available from: http://dx.doi.org/10.1007/BF00964820, doi:10.1007/BF00964820.

[31] R. D. Handy, M. M. Musonda, C. Phillips, and S. J. Falla. Mechanisms of gastrointestinal copper absorption in the african walking catfish: Copper dose-effects and a novel anion-dependent pathway in the intestine. *Journal of Experimental Biology*, 203, 08 2000. Available from: http://dx.doi.org/10.1242/jeb.203.15.2365, doi:10.1242/jeb.203.15.2365.

[32] ED Harris, JK Rayton, JE Balthrop, RA DiSilvestro, and M Garcia-de Quevedo. Copper and the synthesis of elastin and collagen. *Ciba Foundation symposium*, 79:163–82, 1980. Available from: http://www.ncbi.nlm.nih.gov/pubmed/

articles/6110524/.

[33] F Harrison, AEL Roberts, R Gabrilska, KP Rumbaugh, C Lee, and SP Diggle. A 1,000-year-old antimicrobial remedy with antistaphylococcal activity. *mBio*, 6(4), 2015. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4542191/.

[34] Yuta Hatori, Sachiye Inouye, and Reiko Akagi. Thiol-based copper handling by the copper chaperone atox1. *IUBMB Life*, 69(4):246–254, 2017. Available from: http://dx.doi.org/10.1002/iub.1620, doi:10.1002/iub.1620.

[35] Fang He, Cong Chang, Bowen Liu, Zhu Li, Hao Li, Na Cai, and Hong-Hui Wang. Copper (ii) ions activate ligand-independent receptor tyrosine kinase (rtk) signaling pathway. *BioMed Research International*, 05 2019. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6537018/, doi:10.1155/2019/4158415.

[36] MC Heffern, HM Park, HY Au-Yeung, de Bittner GC Van, CM Ackerman, A Stahl, and CJ Chang. In vivo bioluminescence imaging reveals copper deficiency in a murine model of nonalcoholic fatty liver disease. *Proceedings of the National Academy of Sciences of the United States of America*, 113(50):14219–24, 2016. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167165/.

[37] S Hekimi, Y Wang, and A Noë. Mitochondrial ros and the effectors of the intrinsic apoptotic pathway in aging cells: The discerning killers! *Frontiers in Genetics*, 7, 2016. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5021979/.

[38] Nathan E. Hellman, Satoshi Kono, Grazia M. Mancini, A.J. Hoogeboom, G.J. de Jong, and Jonathan D. Gitlin. Mechanisms of copper incorporation into human ceruloplasmin. *Journal of Biological Chemistry*, 277, 2002. Available from: http://dx.doi.org/10.1074/jbc.m206246200, doi:10.1074/jbc.m206246200.

[39] L M Henderson, G J Brewer, J B Dressman, S Z Swidan, D J DuRoss, C H Adair, J L Barnett, and R R Berardi. Effect of intragastric ph on the absorption of oral zinc acetate and zinc oxide in young healthy volunteers. *JPEN. Journal of parenteral and enteral nutrition*, pages 393–7, Sep-Oct 1995. Available from: https://pubmed.ncbi.nlm.nih.gov/8577018/, doi:10.1177/0148607195019005393.

[40] James W. Hilton, Kai Kysenius, Jeffrey R. Liddell, Stephen W. Mercer, Bence Paul, Joseph S. Beckman, Catriona A. McLean, Anthony R. White, Paul S. Donnelly, Ashley I. Bush, Dominic J. Hare, Blaine R. Roberts, and Peter J. Crouch. Evidence for disrupted copper availability in human spinal cord supports cuii(atsm) as a treatment option for sporadic cases of als. *Scientific Reports*, 14, 03 2024. Available from: https://www.nature.com/articles/s41598-024-55832-w, doi:10.1038/s41598-024-55832-w.

[41] Jae Hee Hong, Susan E. Duncan, and Andrea M. Dietrich. Effect of copper speciation at different ph on temporal sensory attributes of copper. *Food Quality and Preference*, 21, 2010. Available from: http://dx.doi.org/10.1016/j.foodqual.2009.08.010, doi:10.1016/j.foodqual.2009.08.010.

[42] R Horvath, P Freisinger, R Rubio, T Merl, R Bax, JA Mayr, Shawan, J Muller-Hocker, D Pongratz, LB Moller, N Horn, and M Jaksch. Congenital cataract, muscular hypotonia, developmental delay and sensorineural hearing loss associated with a defect in copper metabolism. *Journal of inherited metabolic disease*, 28(4):479–92, 2005. Available from: http://www.ncbi.nlm.nih.gov/pubmed/articles/15902551/.

[43] Seyyed Morteza Hoseini, Seyed Abbas Hosseini, and Mohammad Soudagar. Dietary tryptophan changes serum stress markers, enzyme activity, and ions concentration of wild common carp cyprinus carpio exposed to ambient copper. *Fish Physiology and Biochemistry*, 38, 2012. doi:10.1007/s10695-012-9629-x.

[44] Leo S. Jensen and Denzil V. Maurice. Influence of sulfur amino acids on copper toxicity in chicks. *The Journal of Nutrition*, 109, 1979. Available from: http://dx.doi.org/10.1093/jn/109.1.91, doi:10.1093/jn/109.1.91.

[45] Rui Jiang, Yang Sui, Jingru Hong, Manabu Niimi, Qiaojing Yan, Zhuheng Shi, and Jian Yao. The combined administration of vitamin c and copper induces a systemic oxidative stress and kidney injury. *Biomolecules*, 13, 2023. Available from: http://dx.doi.org/10.3390/biom13010143, doi:10.3390/biom13010143.

[46] Byung-Eun Kim, Michelle L. Turski, Yasuhiro Nose, Michelle Casad, Howard A. Rockman, and Dennis J. Thiele. Cardiac copper deficiency activates a systemic signaling mechanism that communicates with the copper acquisition and storage organs. *Cell Metabolism*, 11, 2010. Available from: http://dx.doi.org/10.1016/j.cmet.2010.04.003, doi:10.1016/j.cmet.2010.04.003.

[47] Leslie M. Klevay. The contemporaneous epidemic of chronic, copper deficiency. *Journal of Nutritional Science*, 11, 2022. Available from: http://dx.doi.org/10.1017/jns.2022.83, doi:10.1017/jns.2022.83.

[48] Meena Kumari and Kalpana Platel. Effect of sulfur-containing spices on the bioaccessibility of trace minerals from selected cereals and pulses. *Journal of the Science of Food and Agriculture*, pages n/a–n/a, 2016. JSFA-16-2048.R1. Available from: http://dx.doi.org/10.1002/jsfa.8113, doi:10.1002/jsfa.8113.

[49] Wenjie Li, Ying Zhou, Chunyu Shang, Hui Sang, and Hong Zhu. Effects of environmental ph on the growth of gastric cancer cells. *Gastroenterology Research and Practice*, 03 2020. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7085403/, doi:10.1155/2020/3245359.

[50] Jiao Liu, Yang Liu, Yuan Wang, Rui Kang, and Daolin Tang. Hmgb1 is a mediator of cuproptosis-related sterile inflammation. *Frontiers in Cell and Developmental Biology*, 10, 2022. Available from: https://www.frontiersin.org/articles/10.3389/fcell.2022.996307, doi:10.3389/fcell.2022.996307.

[51] Yun Liu and Ji Miao. An emerging role of defective copper metabolism in heart disease. *Nutrients*, 02 2022. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8838622/, doi:10.3390/nu14030700.

[52] Mark A. Lovell, Chengsong Xie, and William R. Markesbery. Protection against amyloid beta peptide toxicity by zinc. *Brain Research*, 823, 1999. Available from: http://dx.doi.org/10.1016/s0006-8993(99)01114-2, doi:10.1016/s0006-8993(99)01114-2.

[53] Henry C. Lukaski, Clinton B. Hall, and Martin J. Marchello. Body temperature and thyroid hormone metabolism of

copper-deficient rats. *The Journal of Nutritional Biochemistry*, 6, 1995. Available from: http://dx.doi.org/10.1016/0955-2863(95)00062-5, doi:10.1016/0955-2863(95)00062-5.

[54] M.J. Marchywka. Canine heartworm treated with doxycycline, ivermectin and various supplements. Technical Report MJM-2019-001, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, March 2021. May be recycled in appropriate media. Available from: https://www.researchgate.net/publication/350442384_Canine_Heartworm_Treated_with_Doxycycline_Ivermectin_and_Various_Supplements.

[55] B Marelli, Nihouannen D Le, SA Hacking, S Tran, J Li, M Murshed, CJ Doillon, CE Ghezzi, YL Zhang, SN Nazhat, and JE Barralet. Newly identified interfibrillar collagen crosslinking suppresses cell proliferation and remodelling. *Biomaterials*, 54:126–35, 2015. Available from: http://www.ncbi.nlm.nih.gov/pubmed/articles/25907046/.

[56] Shashank Masaldan, Sharnel A.S. Clatworthy, Cristina Gamell, Zoe M. Smith, Paul S. Francis, Delphine Denoyer, Peter M. Meggyesy, Sharon La Fontaine, and Michael A. Cater. Copper accumulation in senescent cells: Interplay between copper transporters and impaired autophagy. *Redox Biology*, 16, 2018. Available from: http://dx.doi.org/10.1016/j.redox.2018.03.007, doi:10.1016/j.redox.2018.03.007.

[57] Denis M Medeiros and Dianne Jennings. Role of copper in mitochondrial biogenesis via interaction with atp synthase and cytochrome c oxidase. *Journal of bioenergetics and biomembranes*, pages 389–95, Oct 2002. Available from: https://pubmed.ncbi.nlm.nih.gov/12539966/, doi:10.1023/a:1021206220851.

[58] Matthew Mold, Larissa Ouro-Gnao, Beata M Wieckowski, and Christopher Exley. Copper prevents amyloid-upbeta1-42 from forming amyloid fibrils under near-physiological conditions in vitro. *Scientific Reports*, 3, 02 2013. Available from: https://www.nature.com/articles/srep01256, doi:10.1038/srep01256.

[59] V Moreaux, I Birlouez-Aragon, and C Ducauze. Copper chelation by tryptophan inhibits the copper-ascorbate oxidation of tryptophan. *Redox report : communications in free radical research*, pages 191–7, Jun 1996. Available from: https://pubmed.ncbi.nlm.nih.gov/27406076/, doi:10.1080/13510002.1996.11747048.

[60] R. F. Morgan and B. L. O'Dell. Effect of copper deficiency on the concentrations of catecholamines and related enzyme activities in the rat BRAIN[1]. *Journal of Neurochemistry*, 28, 1977. Available from: http://dx.doi.org/10.1111/j.1471-4159.1977.tb07728.x, doi:10.1111/j.1471-4159.1977.tb07728.x.

[61] Y Mukai, H Wada, H Eguchi, D Yamada, T Asaoka, T Noda, K Kawamoto, K Gotoh, Y Takeda, M Tanemura, K Umeshita, Y Hori, E Morii, Y Doki, and M Mori. Intrahepatic cholangiocarcinoma in a patient with wilson's disease: a case report. *Surgical Case Reports*, 2, 2016. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4803712/.

[62] Julia E. Niskanen, sa Ohlsson, Ingrid Ljungvall, Michaela Drgemller, Robert F. Ernst, Dennis Dooijes, Hanneke M. van Deutekom, J. Peter van Tintelen, Christian B. Snijders Blok, Marion van Vugt, Jessica van Setten, Folkert W. Asselbergs, Aleksandra Domanjko Petri, Milla Salonen, Sruthi Hundi, Matthias Hrtenhuber, Juha Kere, W. Glen Pyle, Jonas Donner, Alex V. Postma, Tosso Leeb, Gran Andersson, Marjo K. Hytnen, Jens Hggstrm, Maria Wiberg, Jana Friederich, Jenny Eberhard, Magdalena Harakalova, Frank G. van Steenbeek, Gerhard Wess, and Hannes Lohi. Identification of novel genetic risk factors of dilated cardiomyopathy: from canine to human. *Genome Medicine*, 09 2023. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10506233/, doi:10.1186/s13073-023-01221-3.

[63] Yasuhiro Nose and Dennis J Thiele. Mechanism and regulation of intestinal copper absorption. *Genes & Nutrition*, 5, 2010. Available from: http://dx.doi.org/10.1007/s12263-010-0202-x, doi:10.1007/s12263-010-0202-x.

[64] BL O'Dell, KH Kilburn, WN McKenzie, and RJ Thurston. The lung of the copper-deficient rat. a model for developmental pulmonary emphysema. *The American Journal of Pathology*, 91(3):413–32, 1978. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2018314/.

[65] A Ogita, K Hirooka, Y Yamamoto, N Tsutsui, K Fujita, M Taniguchi, and T Tanaka. Synergistic fungicidal activity of cu(2+) and allicin, an allyl sulfur compound from garlic, and its relation to the role of alkyl hydroperoxide reductase 1 as a cell surface defense in saccharomyces cerevisiae. *Toxicology*, 215(3):205–13, 2005. Available from: http://www.ncbi.nlm.nih.gov/pubmed/articles/16102883/.

[66] Michael Okafor, Paulina Gonzalez, Pascale Ronot, Islah El Masoudi, Anne Boos, Stéphane Ory, Sylvette Chasserot-Golaz, Stéphane Gasman, Laurent Raibaut, Christelle Hureau, Nicolas Vitale, and Peter Faller. Development of cu(ii)-specific peptide shuttles capable of preventing cu-amyloid beta toxicity and importing bioavailable cu into cells. *Chem. Sci.*, 13:11829–11840, 2022. Available from: http://dx.doi.org/10.1039/D2SC02593K, doi:10.1039/D2SC02593K.

[67] Gilbert S. Omenn, Gary E. Goodman, Mark D. Thornquist, John Balmes, Mark R. Cullen, Andrew Glass, James P. Keogh, Frank L. Jr. Meyskens, Barbara Valanis, James H. Jr. Williams, Scott Barnhart, and Samuel Hammar. Effects of a combination of beta carotene and vitamin a on lung cancer and cardiovascular disease. *New England Journal of Medicine*, 334(18):1150–1155, 1996. PMID: 8602180. Available from: http://dx.doi.org/10.1056/NEJM199605023341802, arXiv:http://dx.doi.org/10.1056/NEJM199605023341802, doi:10.1056/NEJM199605023341802.

[68] Dan G. ONeill, Janine Pheng Khoo, Dave C. Brodbelt, David B. Church, Camilla Pegram, and Rebecca F. Geddes. Frequency, breed predispositions and other demographic risk factors for diagnosis of hypothyroidism in dogs under primary veterinary care in the uk. *Canine Medicine and Genetics*, 10 2022. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9552398/, doi:10.1186/s40575-022-00123-8.

[69] Y. Pang and T.J. Applegate. Effects of dietary copper supplementation and copper source on digesta ph, calcium, zinc, and copper complex size in the gastrointestinal tract of the broiler chicken. *Poultry Science*, 86, 2007. Available from: http://dx.doi.org/10.1093/ps/86.3.531, doi:10.1093/ps/86.3.531.

[70] Tony Peled, Efrat Landau, Eugenia Prus, Abraham J Treves, Arnon Nagler, and Eitan Fibach. Cellular copper content modulates differentiation and self-renewal in cultures of cord blood-derived cd34+ cells. *British journal of haematology*, pages 655–61, Mar 2002. Available from: https://pubmed.ncbi.nlm.nih.gov/11849228/, doi:10.1046/j.0007-1048.2001.03316.x.

[71] Katharina F. Pirker, Maria Camilla Baratto, Riccardo Basosi, and Bernard A. Goodman. Influence of ph on the speciation of copper(ii) in reactions with the green tea polyphenols, epigallocatechin gallate and gallic acid. *Journal of Inorganic Biochemistry*, pages 10–6, Jul 2012. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3401972/, doi:10.1016/j.jinorgbio.2011.12.010.

[72] K Porter, L Hoey, CF Hughes, M Ward, and H McNulty. Causes, consequences and public health implications of low b-vitamin status in ageing. *Nutrients*, 8(11), 2016. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5133110/.

[73] K-Raman Purushothaman, Meerarani Purushothaman, Irene C. Turnbull, David H. Adams, Anelechi Anyanwu, Prakash Krishnan, Annapoorna Kini, Samin K. Sharma, William N OConnor, and Pedro R. Moreno. Association of altered collagen content and lysyl oxidase expression in degenerative mitral valve disease. *Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology*, pages 11–8, 04 2017. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541772/, doi:10.1016/j.carpath.2017.04.001.

[74] C Rachman-Tzemah, S Zaffryar-Eilot, M Grossman, D Ribero, M Timaner, JM Mäki, J Myllyharju, F Bertolini, D Hershkovitz, I Sagi, P Hasson, and Y Shaked. Blocking surgically induced lysyl oxidase activity reduces the risk of lung metastases. *Cell Reports*, 19(4):774–84, 2017. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5413586/.

[75] Sara Raia, Antonio Conti, Alan Zanardi, Barbara Ferrini, Giulia Maria Scotti, Enrica Gilberti, Giuseppe De Palma, Samuel David, and Massimo Alessio. Ceruloplasmin-deficient mice show dysregulation of lipid metabolism in liver and adipose tissue reduced by a protein replacement. *International Journal of Molecular Sciences*, 24, 2023. Available from: http://dx.doi.org/10.3390/ijms24021150, doi:10.3390/ijms24021150.

[76] Stewart J. Richmond, Shalmini Gunadasa, Martin Bland, and Hugh MacPherson. Copper bracelets and magnetic wrist straps for rheumatoid arthritis – analgesic and anti-inflammatory effects: A randomised double-blind placebo controlled crossover trial. *PLOS ONE*, 8(9):1–9, 09 2013. Available from: https://doi.org/10.1371/journal.pone.0071529, doi:10.1371/journal.pone.0071529.

[77] Luisa Rossi, Giovanna Lippe, Eliana Marchese, Angelo De Martino, Irene Mavelli, Giuseppe Rotilio, and Maria R. Ciriolo. Decrease of cytochrome c oxidase protein in heart mitochondria of copper-deficient rats. *Biometals*, 11(3):207–212, 1998. Available from: http://dx.doi.org/10.1023/A:1009274131473, doi:10.1023/A:1009274131473.

[78] Moisés Rubio-Osornio, Marisol Orozco-Ibarra, Araceli Díaz-Ruiz, Eduardo Brambila, Marie-Catherine Boll, Antonio Monroy-Noyola, Jorge Guevara, Sergio Montes, and Camilo Ríos. Copper sulfate pretreatment prevents mitochondrial electron transport chain damage and apoptosis against mpp+-induced neurotoxicity. *Chemico-Biological Interactions*, 271:1 – 8, 2017. Available from: http://www.sciencedirect.com/science/article/pii/S0009279717301527, doi:http://dx.doi.org/10.1016/j.cbi.2017.04.016.

[79] RB Rucker, T Kosonen, MS Clegg, AE Mitchell, BR Rucker, JY Uriu-Hare, and CL Keen. Copper, lysyl oxidase, and extracellular matrix protein cross-linking. *The American Journal of Clinical Nutrition*, 67, 1998. Available from: http://dx.doi.org/10.1093/ajcn/67.5.996s, doi:10.1093/ajcn/67.5.996s.

[80] Christian T. Sheline, Eric H. Choi, Jeong-Sook Kim-Han, Laura L. Dugan, and Dennis W. Choi. Cofactors of mitochondrial enzymes attenuate copper-induced death in vitro and in vivo. *Annals of Neurology*, 52(2):195–204, 2002. Available from: http://dx.doi.org/10.1002/ana.10276, doi:10.1002/ana.10276.

[81] CA Sinkler, H Kalpage, J Shay, I Lee, MH Malek, LI Grossman, and M Hüttemann. Tissue- and condition-specific isoforms of mammalian cytochrome c oxidase subunits: From function to human disease. *Oxidative Medicine and Cellular Longevity*, 2017, 2017. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5448071/.

[82] L I Smith-Mungo and H M Kagan. Lysyl oxidase: properties, regulation and multiple functions in biology. *Matrix biology : journal of the International Society for Matrix Biology*, pages 387–98, Feb 1998. Available from: https://pubmed.ncbi.nlm.nih.gov/9524359/, doi:10.1016/s0945-053x(98)90012-9.

[83] Lynda I. Smith-Mungo and Herbert M. Kagan. Lysyl oxidase: Properties, regulation and multiple functions in biology. *Matrix Biology*, 16, 1998. Available from: http://dx.doi.org/10.1016/s0945-053x(98)90012-9, doi:10.1016/s0945-053x(98)90012-9.

[84] Stéphanie Solier, Sebastian Müller, Tatiana Cañeque, Antoine Versini, Arnaud Mansart, Fabien Sindikubwabo, Leeroy Baron, Laila Emam, Pierre Gestraud, G. Dan PantoUx0219[bad char vv=537], Vincent Gandon, Christine Gaillet, Ting-Di Wu, Florent Dingli, Damarys Loew, Sylvain Baulande, Sylvère Durand, Valentin Sencio, Cyril Robil, François Trottein, David Péricat, Emmanuelle Näser, Céline Cougoule, Etienne Meunier, Anne-Laure Bègue, Hélène Salmon, Nicolas Manel, Alain Puisieux, Sarah Watson, Mark A. Dawson, Nicolas Servant, Guido Kroemer, Djillali Annane, and Raphaël Rodriguez. A druggable copper-signalling pathway that drives inflammation. *Nature*, 617, 2023. Available from: https://www.nature.com/articles/s41586-023-06017-4#Sec1, doi:10.1038/s41586-023-06017-4.

[85] Chunlin Tang and Judith P. Klinman. The catalytic function of bovine lysyl oxidase in the absence of copper. *Journal of Biological Chemistry*, 276, 2001. Available from: http://dx.doi.org/10.1074/jbc.c100138200, doi:10.1074/jbc.c100138200.

[86] H Tang, L Leung, G Saturno, A Viros, D Smith, Leva G Di, E Morrison, D Niculescu-Duvaz, F Lopes, L Johnson, N Dhomen, C Springer, and R Marais. Lysyl oxidase drives tumour progression by trapping egf receptors at the cell surface. *Nature Communications*, 8, 2017. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5399287/.

[87] Larry P. Thornburg. A perspective on copper and liver disease in the dog. *Journal of Veterinary Diagnostic Investigation*, 12(2):101–110, 2000. PMID: 10730937. Available from: http://dx.doi.org/10.1177/104063870001200201, arXiv:http://dx.doi.org/10.1177/104063870001200201, doi:10.1177/104063870001200201.

[88] Shiliang Tian, Stephen M. Jones, and Edward I. Solomon. Role of a tyrosine radical in human ceruloplasmin catalysis. *ACS Central Science*, 6, 10 2020. Available from: http://dx.doi.org/10.1021/acscentsci.0c00953, doi:10.1021/

acscentsci.0c00953.

[89] Huber TL, Laflamme DP, Medleau L, Comer KM, and Rakich PM. Comparison of procedures for assessing adequacy of dog foods. *Journal of the American Veterinary Medical Association*, 199. Available from: http://europepmc.org/abstract/med/1659568.

[90] Lissa Ventura-Antunes, Alex Nackenoff, Wilber Romero-Fernandez, Allison M Bosworth, Alex Prusky, Emmeline Wang, Cristian Carvajal-Tapia, Alena Shostak, Hannah Harmsen, Bret Mobley, Jose Maldonado, Elena Solopova, J Caleb Snider, W David Merryman, Ethan S Lippmann, and Matthew Schrag. Arteriolar degeneration and stiffness in cerebral amyloid angiopathy are linked to beta-amyloid deposition and lysyl oxidase., 04 2024. Available from: https://pubmed.ncbi.nlm.nih.gov/38659767/, doi:10.1101/2024.03.08.583563.

[91] Katherine E Vest, Amanda L Paskavitz, Joseph B Lee, and Teresita Padilla-Benavides. Dynamic changes in copper homeostasis and post-transcriptional regulation of atp7a during myogenic differentiation. *Metallomics : integrated biometal science*, pages 309–322, Feb 2018. Available from: https://pubmed.ncbi.nlm.nih.gov/29333545/, doi:10.1039/c7mt00324b.

[92] Birgitte Villadsen, Camilla Thygesen, Manuela Grebing, Stefan J Kempf, Marie B Sandberg, Pia Jensen, Stefanie H Kolstrup, Helle H Nielsen, Martin R Larsen, and Bente Finsen. Ceruloplasmin-deficient mice show changes in ptm profiles of proteins involved in messenger rna processing and neuronal projections and synaptic processes. *Journal of neurochemistry*, pages 76–94, 01 2023. Available from: https://pubmed.ncbi.nlm.nih.gov/36583241/, doi:10.1111/jnc.15754.

[93] Melissa Vos, Giovanni Esposito, Janaka N. Edirisinghe, Sven Vilain, Dominik M. Haddad, Jan R. Slabbaert, Stefanie Van Meensel, Onno Schaap, Bart De Strooper, R. Meganathan, Vanessa A. Morais, and Patrik Verstreken. Vitamin k2 is a mitochondrial electron carrier that rescues pink1 deficiency. *Science*, 336(6086):1306–1310, 2012. Available from: http://science.sciencemag.org/content/336/6086/1306, arXiv:http://science.sciencemag.org/content/336/6086/1306.full.pdf, doi:10.1126/science.1218632.

[94] J.M. Walshe, E. Waldenström, V. Sams, H. Nordlinder, and K. Westermark. Abdominal malignancies in patients with wilson's disease. *QJM: An International Journal of Medicine*, 96(9):657, 2003. Available from: +http://dx.doi.org/10.1093/qjmed/hcg114, arXiv:/oup/backfile/content_public/journal/qjmed/96/9/10.1093/qjmed/hcg114/2/hcg114.pdf, doi:10.1093/qjmed/hcg114.

[95] TH Wang, SM Hsia, and TM Shieh. Lysyl oxidase and the tumor microenvironment. *International Journal of Molecular Sciences*, 18(1), 2017. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5297697/.

[96] RA Wapnir and G Devas. Copper deficiency: interaction with high-fructose and high-fat diets in rats. *The American journal of clinical nutrition*, 61(1):105–10, 1995. Available from: http://www.ncbi.nlm.nih.gov/pubmed/articles/7825519/.

[97] Carrie M. Wilmot and Victor L. Davidson. Uncovering novel biochemistry in the mechanism of tryptophan tryptophylquinone cofactor biosynthesis. *Current opinion in chemical biology*, pages 462–7, 08 2009. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2749888/, doi:10.1016/j.cbpa.2009.06.026.

[98] Min Wu, Feifei Han, Weisha Gong, Lifang Feng, and Jianzhong Han. The effect of copper from water and food: changes of serum nonceruloplasmin copper and brain's amyloid-beta in mice. *Food & Function*, 7, 2016. Available from: http://dx.doi.org/10.1039/c6fo00809g, doi:10.1039/c6fo00809g.

[99] Min Wu, Leqin Ke, Mingyu Zhi, Yumei Qin, and Jianzhong Han. The influence of gastrointestinal ph on speciation of copper in simulated digestive juice. *Food Science & Nutrition*, pages 5174–82, 07 2021. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8441336/, doi:10.1002/fsn3.2490.

[100] X Wu, PAJ Leegwater, and H Fieten. Canine models for copper homeostasis disorders. *International Journal of Molecular Sciences*, 17(2), 2016. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4783930/.

[101] Ben-Shan Yang, Hideki Noda, and Norihisa Kato. Elevated intestinal absorption of copper in rats fed on a excessive tyrosine diet. *Bioscience, Biotechnology, and Biochemistry*, 57. Available from: http://dx.doi.org/10.1271/bbb.57.2179, doi:10.1271/bbb.57.2179.

[102] Jing Yang, Xueli Zhang, Yiying Zhu, Emily Lenczowski, Yanli Tian, Jian Yang, Can Zhang, Markus Hardt, Chunhua Qiao, Rudolph E. Tanzi, Anna Moore, Hui Ye, and Chongzhao Ran. The double-edged role of copper in the fate of amyloid beta in the presence of anti-oxidants. *Chem. Sci.*, 8:6155–6164, 2017. Available from: http://dx.doi.org/10.1039/C7SC01787A, doi:10.1039/C7SC01787A.

[103] Akihiro Yasui, Sebastian F. Hoeft, Hubert J. Stein, Tom R. DeMeester, Ross M. Bremner, and Yuji Nimura. An alkaline stomach is common to barrett's esophagus and gastric carcinoma. In Kin-ichi Nabeya, Tateo Hanaoka, and Hiroshi Nogami, editors, *Recent Advances in Diseases of the Esophagus*, pages 169–172, Tokyo, 1993. Springer Japan. Available from: https://link.springer.com/chapter/10.1007/978-4-431-68246-2_26.

[104] AG Yersin, FW Edens, and DF Simmons. The effects of bordetella avium infection on elastin and collagen content of turkey trachea and aorta. *Poultry science*, 77(11):1654–60, 1998. Available from: http://www.ncbi.nlm.nih.gov/pubmed/articles/9835339/.

[105] Lei Yu, Iris W. Liou, Scott W. Biggins, Matthew Yeh, Florencia Jalikis, LingtakNeander Chan, and Jason Burkhead. Copper deficiency in liver diseases: A case series and pathophysiological considerations. *Hepatology Communications*, 3, 2019. Available from: http://dx.doi.org/10.1002/hep4.1393, doi:10.1002/hep4.1393.

[106] Yx Yu, Yp Li, F Gao, Qs Hu, Y Zhang, D Chen, and Gh Wang. Vitamin k2 suppresses rotenone-induced microglial activation in vitro. *Acta Pharmacologica Sinica*, 37(9):1178–89, 2016. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5022102/.

[107] J. Zhao, Y. Zeng, A. Wang, W. Zhang, J. Li, J. Zhu, Z. Liu, and J-a. Huang. P1.02-04 targeting atp7a by elesclomol-copper

derived endoplasmic reticulum stress to mediate cuproptosis in kras-g12 mutant luad. *Journal of Thoracic Oncology*, 18, 2023. Available from: http://dx.doi.org/10.1016/j.jtho.2023.09.295, doi:10.1016/j.jtho.2023.09.295.

[108] W Zheng, X Wang, Q Chen, K Fang, L Wang, F Chen, X Li, Z Li, J Wang, Y Liu, D Yang, and X Song. Low extracellular lysyl oxidase expression is associated with poor prognosis in patients with prostate cancer. *Oncology Letters*, 12(5):3161–6, 2016. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5103911/.

[109] Ying Zhong, Rose C. Mahoney, Zehedina Khatun, Howard H. Chen, Christopher T. Nguyen, Peter Caravan, and Jesse D. Roberts. Lysyl oxidase regulation and protein aldehydes in the injured newborn lung. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 322, 02 2022. Available from: http://dx.doi.org/10.1152/ajplung.00158.2021, doi:10.1152/ajplung.00158.2021.

[110] Weidong Zhu, Chunying Wang, Jianping Wu, Shuqiu Chen, Weipu Mao, Yu Chen, and Ming Chen. Dietary copper intake and the prevalence of kidney stones among adult in the united states: A propensity score matching study. *Frontiers in Public Health*, 08 2022. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9469499/, doi:10.3389/fpubh.2022.973887.

Acknowledgments

1. Pubmed eutils facilities and the basic research it provides.
2. Free software including Linux, R, LaTex etc.
3. Thanks everyone who contributed incidental support.

Appendix A: Statement of Conflicts

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

Appendix B: About the Authors and Facility

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

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

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

Appendix D: Notable Food Components with Copper Interactions

Title		
Cu		
Zn		
Fe		
Mo		
H/ OH		
S and amino acids		reduce toxicity [44]
PO4		
Fructose		
Tyr		
Trp		
Pi-complex		
Fenton		
Ammonia, Amides, N		
Citrate		
Ascorbate		
garlic		enhancing bioavailability Cu etc [48]
Microbial products		
phytate		

TABLE VIII: Some entities that may interact with copper

Appendix E: Symbols, Abbreviations and Colloquialisms

TERM	definition and meaning

Appendix F: 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 G: Citing this as a tech report or white paper

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

Version	Date	Comments
0.01	2024-04-12	Create from empty.tex template
-	April 26, 2024	version 0.00 MJM-2024-010
1.0	20xx-xx-xx	First revision for distribution

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

Version	Date	URL

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filename ={copper} ,
run-date ={April 26, 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 ={April 26, 2024} ,
startdate ={2024-04-12} ,
day ={26} ,
month ={4} ,
year ={2024} ,
author1email ={marchywka@hotmail.com} ,
contact ={marchywka@hotmail.com} ,
author1id ={orcid.org/0000-0001-9237-455X} ,
pages ={ 29}
}

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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19453 Apr 21 08:04 copper.aux dac2c414c16b61f5302a3e839a6d4383
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