

Release Notes xxxx-xx-xx : : Copper was an early part of my interest in optimization of supplements for dogs and humans. Recent literature has expressed concern about copper so I thought I would get out generally supportive results to date although omitting much of my own personal experiences (I'm a human not a dog) that seem similarly beneficial. It seems that often the popular press led by science catches onto incomplete or "close but not quite" ideas and reversals in recommendations are common. Curious to see how attitudes towards copper evolve. It may be worth noting there seems to be a trend to get away from copper plumbing lol. Actually looking at the old, unpublished work, "casesum", that includes Little Man, most of the text is still useful today and has been copied and pasted without attribution (since it was a never-published work I authored).

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

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

This is a draft and has not been peer reviewed or completely proof read but released in some state where it seems worthwhile given time or other constraints. Typographical errors are quite likely particularly in manually entered numbers. This work may include output from software which has not been fully debugged. For information only, not for use for any particular purpose see fuller disclaimers in the text. Caveat Emptor.

This document is a non-public DRAFT and contents may be speculative or undocumented or simple musings and should be read as such.

Note that any item given to a non-human must be checked for safety alone and in combination with other ingredients or medicines for that animal. Animals including dogs and cats have decreased tolerance for many common ingredients in things meant for human consumption.

I am not a veterinarian or a doctor or health care professional and this is not particular advice for any given situation. Read the disclaimers in the appendicies or text, take them seriously and take prudent steps to evaluate this information.

This work addresses a controversial topic and likely advances one or more viewpoints that are not well accepted in an attempt to resolve confusion. The reader is assumed familiar with the related literature and controversial issues and in any case should seek additional input from sources the reader trusts likely with differing opinions. For information and thought only not intended for any particular purpose. Caveat Emptor

The release may use an experimental bibliography code that is not designed to achieve a particular format but to allow multiple links to reference works with modifications to the query string to allow identification of the citing work for tracking purposes. This may be useful for a bill-of-materials and purchases later.

Copper Supplementation in Dogs: Listen to Her Heart

Mike Marchywka*
44 Crosscreek Trail Jasper GA 30143 USA
(Dated: January 12, 2025)

The known roles of copper suggest it is needed to perform functions that could mitigate several common diseases yet it is not currently a trendy supplement for dogs or humans (usually omitted from lists such as most popular supplements [190]). Part of the concern with dogs is the variable genetics and observations of copper accumulation in the liver becoming more common. However, with most genetics lacking a recognized copper storage disease, copper distribution is regulated by a complex system that appears to consider locale based demand as part of the uptake and excretion control algorithm. Such a system may produce bottlenecks leading to uncommonly large accumulation in an organ such as the liver while another organ such as the heart is starved. Such a situation could occur due to some other nutrient limitation that fools the feedback mechanisms. Without knowing the specific bottleneck, the decision to supplement would be based on the overall benefits to the starving location versus any harms to the accumulating organ. This work describes copper supplementation to a group of dogs without obvious significant harm while in some cases coinciding with benefits such as increased energy or reduced coughing. Supplementation in the range of .3-1 mg/kgBW/day was most commonly explored with .1 thought to be too low and 3 being an old literature NOAEL. The "background diet" is discussed in terms of making extra copper intake useful to the hosts. While copper interacts with just about everything, specific interactions with sulfur, amino acids, B-6, and zinc are considered in more detail. In atleast one dog, possible problems also exist with low fat diet, iron excess, and cherries (thought to be a problem with fructose) pointing to idiosyncracies that are possible. Additionally, taurine emerged as a possible interaction with copper

suggesting induced copper deficiency could limit therapeutic effect. A low pH step early in the GI tract may prevent the formation of insoluble products creating varied outcomes idiosyncratic to particular diets and hosts. Those with impaired stomach acid such as the elderly may need specific diets or additional supplements. The overall diet may help mitigate two contemporary issues, hepatic copper accumulation and diet related DCM, in dogs as well as highlight recurring issues with hidden assumptions and logical fallacies when dealing with non-obvious regulatory feedback systems. Hopefully this work leads to a starting point for a diet-related disease mitigation strategy and helps turn paradoxes into paradigms by elucidating some feedback mechanisms that may be quite common. One common issue is jumping to hypothesis testing, usually due to a "quantity" problem, rather than looking at data as a larger opportunity to generate new or refined hypotheses beyond rationalization. It may be common that "quantity" problems are a result of quality and the feedback control.

Contents

1. Introduction	4
1.1. Copper distribution is confusing and deficiency often ignored by doctors	4
1.2. Hepatic copper excess observed in some dogs may be misleading	4
1.3. Copper status is ambiguous in biochemistry and clinical outcomes	5
1.4. Copper and blood pressure	6
1.5. This kind of confusion is common for recurring reasons	6
1.6. Copper related outcomes depend on everything starting with GI tract	7
1.7. Copper interacts with dietary sulfur in other animals	8
1.8. The overall diet may be important for copper distribution	9
1.9. Copper interactions with WHY and Cu related clinical impact	9
1.10. Recent Similar Work	9
1.11. Copper rich diets for dogs and people are worth consideration	9
2. Diseases of Interest	10
2.1. Collapsed Trachea	11
2.2. Heart Problems : DCM/HCM	12
2.3. Infection	13
2.4. Hypothyroidism	13
2.5. Degenerative diseases AD, PD, ALS, Arthritis	14
2.6. Cancer	15
3. Sites of Interest	15
3.1. Cytochrome C Oxidase	16
3.2. Lysyl Oxidase	17
3.3. Ceruloplasmin	17
3.4. Macrophage et al	18
3.5. Associated Entities - histidine and garlic etc	18
4. Cases and Observations	18
4.1. Dexter	20
4.2. Cookie or Mixie	21
4.3. Brownie and puppies	21
4.4. Happy	22
4.5. Trixie	24
4.6. Rocky	25
4.7. Annie	26
4.8. Hershey	27

*Electronic address: marchywka@hotmail.com; to cite or credit this work, see bibtex in H

5. Discussion	30
5.1. Aspects of Copper Chemistry	31
5.2. Aspects of Copper Garlic Chemistry	33
5.3. Supplement Selection and Dosing Considerations	34
6. Limitations	34
7. Conclusions	35
8. Supplemental Information	35
8.1. Computer Code	35
9. Bibliography	35
References	35
Acknowledgments	52
A. Statement of Conflicts	53
B. About the Authors and Facility	53
C. Some Common Logical Fallacies and Misdirections	53
D. Background Diet Summary	55
E. Notable Food Components with Copper Interactions	59
F. Symbols, Abbreviations and Colloquialisms	59
G. General caveats and disclaimer	59
H. Citing this as a tech report or white paper	59

Citing information should also be available in machine readable form in the pdf extended information,

```
@techreport{marchywka-MJM-2024-010,
filename ={copper} ,
run-date ={January 12, 2025} ,
title ={Copper Supplementation in Dogs: Listen to Her Heart } ,
author ={Mike J Marchywka } ,
type ={techreport} ,
name ={marchywka-MJM-2024-010} ,
number ={MJM-2024-010} ,
version ={0.00} ,
institution ={not institutionalized, independent } ,
address ={ 44 Crosscreek Trail Jasper GA 30143 USA} ,
date ={January 12, 2025} ,
startdate ={2024-04-12} ,
day ={12} ,
month ={1} ,
year ={2025} ,
author1email ={marchywka@hotmail.com} ,
contact ={marchywka@hotmail.com} ,
author1id ={orcid.org/0000-0001-9237-455X} ,
pages ={ 62}
}
```

1. INTRODUCTION

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

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

Copper is not currently a trendy supplement for humans or dogs. This may be partially due to deficiency being a neglected diagnosis by physicians [70] [66] [274] [266] [78] [1]. In dogs however a specific issue with liver copper accumulation has been noted. An expert consensus statement on hepatitis in dogs suggested an increased incidence that coincided with a change in copper supplementation premix in commercial dog foods [286] pointing to increased intake as a cause. However, known and expected functions make it a good match to several possible problems motivating an interest in supplementation even if contrary indicators also exist. In fact, isolated authors do sometimes point to it as a major cause of diseases such as heart disease [52] [146] and copper containing or eluting stents have been investigated since 2017 [111]. Copper appears to be of recognized importance in dogs and the question of dietary deficiency or excess has been a topic of controversy for many years. It is likely that copper intake alone is not the dominant issue but rather distribution in the body determined by signalling, other dietary components, and genetics. The question of supplementation has to be answered within the context of a specific overall diet as well as recognized factors including genetics. If an unusually high concentration is measured in one location, the question remains if there would be a net benefit reducing deficiency in some other place even if more local excess occurs. This has to be answered in terms of clinical outcomes, things relevant to the host, rather than lab values. Even in the case of known genetic diseases, copper removal to improve liver values may create clinical copper deficiency. Treatment emergent copper deficiency has been observed in a Bedlington Terrier with an excretion defect that clinically resolved with cessation of chelation [235].

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

One increasingly common concern with dogs is copper associated hepatitis [7] [8] [34]. Copper handling genetic diseases are well known in dogs [126] and some concern about excess intake may be warranted for specific animals. Some noisy association between intake and hepatic copper content was shown in a small study [65] but copper intake may not be the major determinant of copper content. The causal role of copper "excess" in any clinical disease remains unclear. One study produced a histogram of liver Cu content (ppm dry weight) for a few hundred dogs but did not conclude there was a particular cutoff level for health vs disease [259]. Work continues to focus on concepts of deficiency or excess even though both may be matters of degree, location, and context. Deficiency in commercial dog foods was suspected years earlier [262] while works as early as 2000 suggested supplementation would be unhelpful [260]. A recent work comparing mineral content in groups of commercial dog foods found some patterns and advised against high copper foods [129]. One reason for liver copper accumulation known since at least 2011 is iron deficiency [214]. A 1997 study found riboflavin deficiency reduced heart and liver iron while increasing copper content [38] and so other nutrients could still be responsible.

Ideally observation of a pathological copper buildup in one location with symptoms of deficiency in other systems would lead to a search for the bottleneck prohibiting a better allocation. With copper this is quite complicated as a number of regulatory systems are known to control copper levels in different compartments in healthy mammals. Uptake regulation is not completely known but response to dietary or ambient levels is only part of the control loop in vivo. It is likely cytosolic sensors exist [87] to monitor cell contents but more global mechanisms appear to operate too.

It turns out that copper related signalling is such that remote signals may exist from the heart to liver and intestines to make more available [119] [195]. In this scenario, local shortage in the heart could induce blood stream or liver excess due to added uptake with attempted but failed cardiac specific delivery. A similarly confusing feedback scheme has been suggested for other nutrients such as tryptophan [158] and biotin [161] [157]. Feedback regulatory systems, as with genes more generally, are likely selected by evolution but that need not make them simple or completely robust to defects in the control loop. One recurring source of defects to consider is high-infidelity translation or a

specific pattern of translational defects likely related to the charge state of tRNA for particularly problematic amino acids. Motivation for the current work comes from observations on conditional KO or mutational diseases relevant to copper handling. For example, copper transporter CTR1 , important for intestinal uptake [194] and distribution [133] [19] [28] has reduced function if some histidines are mutated in either the C or N terminal tails. Intestinal loss of CTR1 causes cardiac hypertrophy among other issues that are partially correctable with copper supplementation [194] This suggests cardiac copper deficiency, possibly due to histidine deficiency, can contribute to cardiac hypertrophy in animals. However, if uptake and accumulation occurs while the heart is deficient this effect, combined with other mechanisms, does not exclude simultaneous excess in the liver.

Even with excessive intake, in most genetics biliary excretion increases when "pathological" amounts of copper begin to accumulate [39] [83] pointing to defects in excretion as another possible problem. However, many cause and effect relationships or control paths exist allowing other factors to control local copper concentrations. Senescent cells may accumulate copper in the absence of autophagy [171]. Copper elevation may commit cord-blood derived cells to differentitaion [204] and it may be regulat4ed during myogenic differntiation [270] raisng the possibility that accumulation is due to confused signalling. Copper signalling is also very important in the brain. The major copper transporting protein ceruloplasmin is an acute phase protein and blood levels may be associated with pathological conditions [77] but a protective role is generally recognized. As a major transporter of copper out of the liver, stresses then could reduce hepatic copper. In fact, as substantiated later, it would make sense for copper to be redeployed from some mitochondria to the blood in response to pathogens or trauma or "beating plowshares into swords". This will lead to hydrogen peroxide formation at the mitochondria and potentially anti-pathogen copper deployment, both conditions likely to control infection. Emerging topics such as extracellular vesicles [20] suggest that uncharacterized mechanisms of metal homeostasis exist making definitive statements difficult.

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

Thinking outloud

An interesting recent work suggests that iron accumulation in aortic valve calcification is a compensatory response to global iron deficiency [143]. It remains to be seen if this is "compensatory hoarding" favoring the heart but that does have to be considered as a possibility. If you only found the hoard, you may be tempted to chelate.

1.3. Copper status is ambiguous in biochemistry and clinical outcomes

Copper is used in several important locations and a reasonably complete snapshot of copper sufficiency would be a vector. Easily accessible values such as blood levels are more responsive to acute pathological situations than overall body total copper. As details are unknown, a colloquial analogy may be trying to infer adequacy of military hardware from measuring the amount on civilian roads. Blood vessels may be used for transport in times of stress raising levels independent of global amounts.

There is a recurring problem using blood levels of some thing to indicate excess or deficiency. Some blood components such as electrolytes may need to be closely regulated but this is not the case when materials are just "passing through." These blood components are regulated or influenced by specific factors having nothing to do with overall sufficiency. In the case of copper, ceruloplasmin usually dominates blood copper and it is regarded as an acute phase protein causing blood levels to elevate in resposne to various stresses. Recently some body of work has suggested that macrophage lysosome may also regulate overll metal distribution [209] a location that would be expected to respond to many stimuli. One meta analysis of bone loss and copper suggested only supplementation studies in the 2.5-3mg/day range showed a clear benefit as blood levels and food intake did not correlate with bone improvements [221]. Its worth noting that this dose range is above common daily guidelines which are around 1mg/day.

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

1.4. Copper and blood pressure

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

A 2021 work exploring the association between serum copper levels and hypertension in US children and adolescents stated [142] "As suggested by previous literature, serum copper appears to reflect the status of copper nutrition in both depleted and replete populations." The present work however tends to accept that ceruloplasmin and blood copper levels are a reaction to stresses such as infection and a high level simply indicates some other pathological process likely exists. While blood levels can be elevated in response to a stress, its not known how well other functions such as electron transport are able to continue.

As early as 1993, one work with Dahl salt-sensitive rats suggested that indeed copper blood levels were a response to hypertension [74].

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

1.5. This kind of confusion is common for recurring reasons

This work describes inclusion of copper into a set of supplements for dogs with different conditions and unknown genetics showing generally beneficial results or at least no obvious harm with added copper. This result is in contrast to some of the popular expectations cited above. A discrepancy between expectations and outcome of this type seems to be common in medicine even as late as clinical trials so understanding the causes of that in this particular case may help optimize dog supplements and avoid delays in understanding the limitations of data and theory to design therapeutic interventions. Interpretation of the copper literature may be limited by unquestioned assumptions and common logical fallacies. Some types of problems are listed in Appendix C as a general guide.

Thinking out loud

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

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

A 2010 work suggested that high copper and iron intake were particularly dangerous in older people observing that one study concluded high intake of both was associated with increased cognitive decline [31]. Part of the reluctance to supplement "high" copper doses is the accumulation in the livers of some dogs but relation to any clinical disease is not clear. This may be similar to amyloid beta in Alzheimer's Disease and pointing to the need to understand cause and effect before an all out attack on one molecular entity.

Even after all the antibody work trying to identify the right physical conformation and peptide, confusion exists about the role of amyloids. A recent example may be the identification of amyloid beta as a nominally protective substance [301] [219] instead of the cause of Alzheimer's pathology and target for intervention. Recently amyloid beta was even found to promote osteogenesis [40] which of course may moderate another problem common in old age osteoporosis. Recently it was found that PRSEN1 mutations do not appear to generate neurodegeneration through amyloid beta [294]. Its toxicity may even result from gamma secretase inhibition [311] which had been considered a therapeutic intervention.

It may still be possible to optimize the amount creating passing benefits that are inherently limited and difficult to control. That state of affairs is well documented in the works that hint at it unravelling [62] such as a 2002 work suggesting that "tauists" and "baptists" could 'shake hands' and look for other causes [184]. Interestingly, related to copper, is the emerging role of lysyl oxidase in Alzheimer's as a possible target where it associates with cerebral amyloid angiopathy and is thought to be a drug target [117] [269]. However, upregulation would have to be suspected as a part of regeneration attempting to fix degeneration. Indeed, LOXL2 is known to be regenerative [258].

Other counter-intuitive approaches are easy to find. Previously, heartworm positive dogs had been given significant amounts of vitamin K [167] [164] although severe cases may be conventionally treated with anticoagulants. In this case, it may not be clear that vitamin K affects clot quality and consequently may limit pathological quantities

allowing for beneficial clots to form.

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

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

The confusion begins in the GI tract with chemistry ranging from the problems sorting and regulating metals to the non-enzymatic reactions copper can undergo with a variety of organics in food. The copper transporter Ctrl1 is thought to be selective against most divalent metals as it transports Cu(I) but is inhibited by Ag [170]. Enzymes may be subject to mis-metallization although there may be evolutionary pressure to use a variety of metals [242].

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

As many conditions linked to copper may be considered age related, quality of the GI tract as a function of age may be relevant. GI health and in particular stomach acidity may be important factors in copper uptake but also distribution if other nutrient deficiencies are created. Naively, you may expect low acid to reduce solubility of cations or metals and decrease enzymatic activity for digestion of proteins. Copper solubility is pH dependent [48] similar to the competing element zinc for which absorption has been shown to depend on salt type as well as gastric pH [93]. Interaction with food components such as polyphenols is significant and pH dependent [208] motivating a larger interest in food interactions and in particular rings such as in tyrosine. Speciation gradients may be large in the range of possible stomach acid levels. A 2021 study did in fact explore copper speciation in simulated gastric juices with food components such as tyrosine and citric acid among others [292]. Impact of GI pH on broiler chicks has been studied due to impact on nutrition and microbial populations with Cu-Zn antagonism also observed in the digestive system [202].

Some information about stomach pH variations may come from the large number of human PPI users. PPI's can raise stomach pH from 2 to 6 and produce "profound hypochlorhydria" [68]. The latter point may be important as Cl as much or more than H may have impact on microbiome and gastric chemistry. There is a conjectured tumor protective effect from PPI usage and a suggestion that pH 6 encourages cancer progression versus pH 8 [140] yet alkaline stomach pH is observed is commonly observed in gastric carcinoma [298]. Usage for suppression of colorectal cancer has been suggested [121]. Empirically however gastric cancer rates do correlate positively although arguably with PPI usage [277] [234] [47]. Probably the dominant effect on tumors is unrelated to ambient pH although increased pH may reduce nutrient accumulation by many cells. An absolute apoptosis rate at near neutral pH is probably not indicative of the overall fitness in the stomach. The effects going from pH 6 to 8 say nothing about the effects of going from pH 6 to pH 2 as one extreme says nothing about the other. It's important to note that they do seem to aid eradication of H pylori and therefore should reduce gastric cancer rates if bacteria are involved. The PPI's appear to attack H. Pylori directly [230] [12]. It's claimed that H pylori can survive down to pH 4 but only grow between 6 and 8 [168] affirming a role for acid in control of these pathogens. It's been observed as early as 1994 that Omeprazole inhibits survival of several organisms at low pH while H pylori only has a benefit in the presence of urea but the PPI effect is urease independent [175]. Clinical effect of PPI's probably does not relate to increased stomach pH and would not be decreased with concurrent intake of acids or chloride which may further improve microbiome.

Omeprazole was also shown to inhibit ATP7A, a copper transporter, preventing melanogenesis [172] and in fact a number of side effects are known along with vitamin deficiencies [153] with the latter likely contributors to the former many of which are common in old age motivating the idea of exaggerated aging in terms of disease.

Other metals may also compete with copper directly or by regulatory loops. Iron intake in feed has also been observed to decrease copper uptake in ruminants [45] and rats [134]. One work suggested iron disrupts copper homeostasis independent of uptake [82]. Zinc is a known inhibitor of copper uptake and cases of zinc induced copper deficiency in humans are known [275]. In chicks, and humans as discussed later, silver may induce copper deficiency through unknown means but mercury may improve apparent copper status only being toxic in copper sufficient animals [95]. Competition between Cu, Fe, and Zn was observed in Caco-2 cells [10].

While concerns exist about copper content in dog foods, a recent survey of some zinc content shows many foods contain amounts above recommended maxima and few are low or deficient [206]. Age related absorption problems in people are known [210] and other apparent deficiencies could be a consequence of insufficient B-6 alone [36]. Interestingly, B-6 is added to penicillamine treatment of Wilson's disease to avoid neurological effects [53].

Thinking out loud

Since paradoxes are a concern here, it's worth noting that pyridoxine is an inhibitor of PLP and high doses result in functional B-6 deficiency [273].

Dietary cholesterol appears to distract copper homeostasis with atherosclerosis thought to involve copper dysregulation [139] and high fat diets in other species [90] are an issue. Fructose also inhibits relative copper absorption [196] [284].

Body stores of copper increase with excess tyrosine in the diet of rats [295]. Some reports show specific issues when combined with vitamin C. A small trial with copper sulfate and vitamin C indicated kidney problems result [110] although alternatives with copper gluconate suggested use as food preservative [80]. Dose probably matter among other factors.

1.7. Copper interacts with dietary sulfur in other animals

The most well known issues with copper and dietary sulfur involve cows due to its common and profound economic impact but related studies have been conducted in non-ruminant lab animals. The latter may be more directly relevant to dogs and humans but the severity of the problem in cows may indicate some effects important but more subtle in the target population. In the "middle" is poultry, mostly turkey and chickens, which may be notable for contrast to both mammals and ruminants due to the low pH proventriculus [218] as well as the gizzard with low but maybe variable pH [136]. Experiments on non-ruminants cover some of the supplements used in this work that could impact copper sufficiency and toxicity.

Thinking out loud

repeated text / citations in discussion

Taurine has been observed to reduce copper toxicity in rats with increased fecal copper amounts [104] suggesting decreased absorption. Another work demonstrated taurine reduced ceruloplasmin only in rats fed a control diet but not a high-fat diet [125]. As taurine is being explored for various indications, including DCM [176], supplementation could relate to induced copper deficiency which would likely cause some symptoms expected of copper deficiency.

Ascorbic acid in rats initially reduced absorption of copper but may eventually limit excretion [267]. ZZm

In pigs, 60 percent fed a copper deficient diet died from coronary disease while supplementation as high as 250mg/kg diet, well in excess of the 10mg/kg diet requirement, can be growth promoting on a typical pig diet [56]. Pig tolerance of sulfur appears to be significant as higher sulfur diets did not seem to impact measures of copper such as liver content [118] although another work showed more complicated results with reduction in ceruloplasmin being one result [49]. The latter work noted decreased liver copper with the addition of potassium carbonate.

Exploration of optimal copper supplementation in poultry suggested copper is less available from cereals than vegetable proteins with amounts "greatly in excess of requirements" further improving results [137]. Very high dosing is common in chicks to avoid antibiotics and copper hydrochloride is often chosen for acid specific solubility [191]. An investigation of copper and sulfur containing amino acids in chicks showed marked interactions while suggesting copper toxicity was due to "chemical nature of the diet rather than to any specific copper induced nutritional deficiency" [220]. Methionine fed to chicks on a high copper diet could reduce some growth depression but it did not affect hepatic copper amounts [132] suggesting a number of possibilities that may not relate to copper uptake. Interactions between methionine and copper were also investigated in turkey [115].

Ruminant sensitivity to dietary sulfur may be an interesting example of how a mild pH step can produce insoluble copper products creating profound deficiency. It's unclear on the extent to which this can occur in dogs or humans but it is illustrative. Sulfur and also molybdenum are common causes of cattle copper deficiency. They have been studied for impact on cow copper status with different background diets and shown to be significant modulators [239]. Decisions about copper supplementation are difficult though in economically important ruminants [150] and particularly in cows as concerns about toxicity [148] apparently can not be mitigated with other nutrient changes. A study of a problem with Przewalski gazelles found no difference in forage copper with clinical status but did find important difference in sulfur in forage and soil [309]. That work also identified biomarkers such as hair copper content although in this case the copper deficiency related to sulfur excess was so bad liver and blood levels were low too.

Ruminants differ substantially from non-ruminants and notably rumen pH is only around 6 reducing solubility of relevant minerals while allowing formation of insolubles [248]. This may motivate interest in issues with age related reduced stomach acid in humans. The low pH GI stage may reduce sensitivity to dietary idiosyncrasies. The presence of a stage able to nucleate insoluble nutrient blobs may prohibit later absorption. Other factors such as microbiology however need to be examined too. In pigs, response to high copper diet varied between "germ free" and conventional groups [238].

Sulfate reducing bacteria may also contribute to confusing metabolism of taurine and methionine [281].

1.8. The overall diet may be important for copper distribution

A couple of papers from 1964 illustrate the problem in simple terms. Initially turkeys were fed either a natural or purified diet with varying copper levels demonstrating toxicity in the purified diet but only minor issues combined with the natural diet [276]. A follow up work suggested the purified diet could be safe with copper but considered vitamin A, D, and zinc additions and noted an off odor in high copper feed [251]. The possibility of vitamin depletion as well as formation of toxics could be factors but also as discussed later overall absorption. Simple things can matter a lot for many reasons.

The importance of overall diet chemistry for copper availability was recently made for poultry [293]. Ideally the optimal fate of all consumed nutrients could be identified and manipulated with dietary composition. This work includes consideration of a background dietary context including real foods and controlled supplements that has been described previously [159]. This diet was further refined by consideration of the interactions described herein. The copper supplementations described here, about .3mg/kgBW/day, is likely well in excess of background levels in most known natural diets although its also worth noting that other sources may be accidentally significant as with water and air exposure [75].

1.9. Copper interactions with WHY and Cu related clinical impact

While sulfur containing amino acids have the most obvious interactions with copper, this work tends to focus on the ringed amino acids - Tryptophan (W) Histidine(H) Tyrosine(Y). W and Y are thought to vary significantly with age and histidine is important for copper binding to proteins. Notably tyrosine protexes ceruloplasmin and 6 histidines, one for each copper, are required for a functional enzyme. Mistranslation due to insufficiency will be exaggerated by the higher power if all need to be right. There is some indication that "diseases of old age" are at least partially mediated by sarcopenia, most recently atrial fibrillation [256] consistent with earlier ideas linking age to amino acid starvation [158].

There are several works exploring the interactions in various places. In growing rate, "Excessive tyrosine and phenylalanine caused a marked increase in serum copper and ceruloplasmin activity, whereas excessive cystine, methionine, and histidine caused a decrease in the ceruloplasmin activity." [116] Copper chelated to amino acids may be more robust against Cysteine (and ascorbate) inhibition [9].

Interest in the interaction of tryptophan with copper go back to at least 1930 exploring the relation between tyrosine and tryptophan, among other nutrients, on total copper in hen eggs and subsequent hatchability [174]. Interest in the interaction of tryptophan with copper go back at least to 1973 when urinary metabolites were measured with different copper intakes [81]. Trp was found to reduce toxicity of copper to the Caspian rach [60] and teleosts [101], while improving response of grass copper to environmental copper [288].

One study found histidine decreased while tryptophan increased copper absorption [285].

While not directly comparing copper some related observations suggest what may occur. Drosophila shows a non-monotonic but generally increasing relationship between tryptophan intake and zinc stores and the authors point to microorganisms living or killed to be able to modulate Fe,Cu, and Zn to varying degrees [73].

Interestingly, Scavenger Receptor BI contains 8 highly conserved tryptophans [98] which appear important for cholesterol transport suggesting trp deficiency will slow down its translation, lead to early termination, or create many imperfect receptors. So, deficiency of these amino acids may produce broad non-specific problems that appear to be common in intractable diseases often associated with old age.

1.10. Recent Similar Work

At least one recent work [42] has summarized many of the same issues relating to copper and cardiovascular disease but with better editing and depth. However, it does not point to some of the cues outlined herein. For example, the issue of "other" limiting nutrients determining when copper is beneficial or not.

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

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

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

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

2. DISEASES OF INTEREST

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

Copper deficient liver patients may be notable for "steatohepatitis, iron overload, malnutrition, and recurrent infections" [302].

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

Besides cough, the present work relies thyroid related symptoms (coat quality, weight distribution, energy level etc). Cough has many possible origins as discussed previously [165]. "Energy level" in most cases described here is thought to relate to shorter term fluctuations in mitochondrial copper rather than thyroid although its important to consider all possibilities. One point of this work is to interpret outcomes recognizing that symptoms and disease trajectory can decouple and notably coughing may increase as part of a disease complex resolves.

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

Disease	Host	Effect	time scale
DCM/HCM	dog		
heart failure			4 weeks [42]
Collapsed Trachea	dog		
airway defects	rats		months, 60days [197]
Hypothyroid	dog		
Infection	dog		
covid-19	human	serum levels irrelevant [223]	
Parkinson's	human	assoc benefit [305]	
Alzheimer's	human		
Infection	human		
Arthritis	human	anecdotes, no trial verification	
Cancer		need to understand cause and effect	

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

2.1. Collapsed Trachea

The importance of copper to quantity and composition of structural proteins, in this case elastin, has been known since at least 1954 [249].

Collapsed trachea and related airway defects have been well described in humans, dogs, poultry, and other animals such as horses. The differences in the literature are significant suggesting either important differences in diseases or literature fragmentation. The dog literature does not appear to consider copper as a factor directly but interest for this paper is motivated by consideration of the larger body of information. Copper may be involved either in cartilage quality or in infection control. Copper deficiency has been associated with lung development defects in rats [197] and airway and arteriole elastin were at least partially restored after 60 days of additional copper. Interestingly, copper "eluting" stents are being explored to prevent blood vessel "collapse" or restenosis in humans due to [280] due to some of the properties considered here and its unclear why dietary copper would work less well.

A variety of causes are known in humans [240]. "Excessive dynamic airway collapse" notably is a rare side effect from anti-viral treatments for hepatitis [6]. In humans, it is a rare disease regardless of cause and CT observation of a "collapsed trachea" may result in debate over actual names for the condition [71] with surgery as a common treatment.

Horses and mules suffer from collapsed trachea too. Mostly small breed or miniatures horses were thought to be most susceptible but a 1992 case report of a horse with pneumonia noted that collapsed trachea resolved with infection cure and just due to infection related inflammation [63]. Currently it appears two causes are noted with the infectious resolving on cure.

In poultry infectious causes appear to dominate the concerns. Turkey infected with *Bordetella avium* experienced trachea collapse which was attributed to copper mediated crosslinking [300] even though collagen content was reduced. This points to a role for copper but suggests it makes the trachea worse. A study of silver nanoparticle effects on broiler chicks infected with *Escherichia coli* found [14].

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

which includes possible results of copper deficiency. Interestingly, high dose silver has been documented to decrease ceruloplasmin synthesis and serum copper concentration [189] [250]. It is not surprising that silver could be confused with copper as analogs can be inhibitory but as discussed elsewhere ceruloplasmin synthesis can proceed without copper but the protein may not be properly metallized. The reduction in synthesis is surprising although perhaps only copper containing ceruloplasmin was assayed and details need to be considered. The authors also mention other means than mis-metallization that silver or other metals can create a copper deficiency.

There is a lot of literature on dogs with many causes and therapies discussed but little overt inclusion of copper. One author introduces the topic as [257].

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

Alternatively, it has also been introduced as [135]

Tracheal collapse (TC) is a congenital cartilaginous tracheal ring problem to which small-breed dogs are predisposed. It is usually diagnosed by performing radiography, fluoroscopy, and tracheobronchoscopy. Tracheobronchomalacia is a structural defect of the trachea and bronchial cartilages. It results in flattening of the trachea and bronchial lumen. Affected tracheae show hypocellularity of the cartilages, loss of hyaline cartilage, and deficiencies of chondroitin sulfate, calcium, and glycosaminoglycans [7]. Fifty-one percent of dogs with a chronic cough exhibit tracheobronchomalacia, a condition regarded as a common cause of cough. More toy-breed dogs than dogs of other breeds show tracheobronchomalacia when they have a

chronic cough [13]. Upper airway obstruction, infectious tracheobronchitis, heart enlargement, parasitic disease, obesity, and oral problems can exacerbate clinical signs of TC [12]. However, studies investigating TC in patients without a history of cough are lacking.

Therapies in dogs can involve surgical interventions but also some of the following [179]

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

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

This work is predicated on the idea that there is often a nutritional component to cartilage quality and quantity with amino acid limitation being one factor but also physiological crosslinking which depends on copper in lysyl oxidase [141]. This should be distinguished from pathological crosslinking which may occur through other mechanisms. While much is not known about cartilage crosslinking, turnover, and remodeling some recent results do point to unexpected beneficial effects of copper mediated cross linking over week time scales [169]. A role for LOXL in aggrecan processing has been described [258].

2.2. Heart Problems : DCM/HCM

Heart problems are common in dogs. Recently, diet-associated DCM has made headlines as an increasing threat with copper deficiency mentioned as a possible although unlikely contributor as it is "routinely supplemented" in commercial foods [173] . While it is thought to be diet related, no clear recipes have been identified for causing or preventing it. The heart is particularly dependent on continuous efficient energy production and mechanical properties to insure blood flow as needed. As copper is important in both functions, distribution within the heart could be expected to be critical to overall health and therefore signalling for copper regulation. Indeed this seems to be the case A recent review of diet related DCM mentions copper along with sulfur containing amino acids as possible issues While expressing a concern about interactions with other metals, it does not appear to mention a possible interaction with the sulfur reducing copper usage.

HCM, defined as " echocardiographically-demonstrated LV concentric hypertrophy in the absence of another known cardiac, systemic, or metabolic disease capable of producing the magnitude of LV wall thickening evident" [233]. It is considered rare although it was initially considered rare in humans whie now being fairly common with a wide spectrum of symptoms [264]. Energy depletoin is thought to occur due to causative mutations but as of 2019 no disease modifying or proven therapies exist although Mavacamten apparently reduced outflow obstructions in as little as 2 weeks [264].

As early as 1993, copper restriction in rats was observed to produce cardiomyopathy [177]. while reduced cytochrome c oxidase activity was observed in 1999 particularly with simultaneously high fat diets [107]. Altough confusingly copper chelation with trientine is also thought to show promise in HCM treatment [216] but its unclear exactly how it rearranges copper distribution.

The heart relies on 4 valves and a rapid contraction subsequent to depolarization to move blood through the body. Mechanical properties of the valves as well as energy efficiency may be expected to be important to maintain performance without desperate remodelling. These requirements motivate an interest in accurate protein translation, and copper dependent physiological crosslinking, removal of deposits such as mineralization, and mitochondria performance. Empirically, copper deficiency can lead to cardiac hypertrophy with increased mitochondria [178]. Dilated and hypertrophic cardiac myopathy can both be related to mitochondria with "oxidative stress" as a signal for more copper at cytochrome oxidase. "Oxidative stress" has been reported to increase muscle mass while reducing performance [4]. "Oxidative stress" is often blamed in the literature as a cause of various problems but it may in fact also be a signal. ROS signalling is well known by now but specifically it may help get sufficient copper to the mitochondria.

As early as 2008, a pressure overload mouse model of DCM regressed with copper supplementation [103]. An recent 2023 work demonstrated correlations between heart copper content and cardiac parameters in a group of identically fed mice while also pointing to the heart as a regulator of copper concentration overall [17].

Over the same time however, concerns about diet linked DCM in dogs have emerged. A genetic link is also being investigated and a recent GWAS in dobermans pointed to two genes, RNF207 and PRKAA2 as risk factors [193] but did not mention copper. However, RNF207 may mediate degradation of ATP7A [306] while PRKAA2 comes up in cuproptosis [144].

Dobermans are at remarkably high risk of DCM [59]. Interestingly, "standard Dobermans" are also at high risk for hypothyroidism [201].

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

Contrary indicators also exist. A study of DCM among people exposed to metals at a mining area suggested blood copper levels increase with DCM risk and found near 100 percent DCM rates above a threshold level [154]. However, even assuming blood copper is proportional to exposure, the x-axis in the graph is more likely a sum of exposures and not just copper. That it, is a partial derivative of DCM risk in a direction that includes copper but also other things like arsenic. This is a very common problem in association studies depending on the inputs and population. In reality blood copper is largely determined by an acute phase protein and it will be associated with stress until the total stores are too low which may be well below the deficiency amounts.

2.3. Infection

Combined copper and zinc deficiency was observed to reduce response to covid-19 mRNA vaccines with only minimal copper deficiency [43]. The present work considers copper status in light of other nutrients notably amino acids such as Trp and Tyr and with zinc being a possible competitor.

In human health, zinc seems to have taken precedence over copper most recently with some headlines related to the covid-19 pandemic [11] [67]. Some studies suggest copper is not a factor in covid-19 due to measurements like serum copper levels [223] although ceruloplasmin as an acute phase protein can elevate levels during stress even with a deficiency in copper [86]. In sample of 70 patients prescribed zinc, many had symptoms consistent with copper deficiency [55].

Copper may antagonize many pathogens including H pylori [22] and clostridium

Thinking outloud

Repression of toxin production by tryptophan in Clostridium botulinum type E [138].

Copper compounds may reduce the virulence of some organisms for short periods even if not completely able to clear a pathogen [85] and in particular Cu was recently shown to be effective against the toxin of one anaerobe [30].

One interesting work explored the impact of copper on virulence of some environmental communities finding decreased virulence at a higher dose with increased proactivity at a lower dose [131]. There are a number of limitations with this work but in general there is likely to be a beneficial zone in copper supplementation to in vivo communities such as in GI tract.

2.4. Hypothyroidism

Copper was shown to correlate negatively with TSH in one human study and may increase T4 levels [299].

Hypothyroidism is a common problem in dogs and has effected several here [163] including some unpublished results where it was thought to contribute to peritoneal effusion after heartworm treatment. It can be defined by elevated TSH for a subclinical condition or low free T4 or T3 [192] although even the latter remains as a biochemical definition rather than something relevant to the patient. Ingestion related (diet low in iodine or containing goitrogen or relevant drugs) has been described as a "Rare etiology" with "acquired primary hypothyroidism" being considered most common although iodine deficiency in dogs appears to be poorly defined [304]. In this work, there is some evidence that added components such as iodine, benzoate, tyrosine, and copper may help and could fit under the category "acquired."

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

Dobermans are at remarkably high risk of DCM [59]. Interestingly, "standard Dobermans" are also at high risk for hypothyroidism [201].

Interestingly, copper deficiency in rats can reduce thyroid hormone levels and body temperature [151].

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

2.5. Degenerative diseases AD, PD, ALS, Arthritis

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

Deficiency seems to effect preferentially proteins involved in neuronal projection and diabetes and iron handling [271].

Rats fed a copper deficient diet shows neurological symptoms by 7 weeks and had reduced tyrosine hydroxylase and SOD activity ZZ [183].

A 2017 study explored the effects of copper and vitamin C as well as other molecules such as clioquinol on abeta and in vitro neurons suggesting abeta could be cleaved by copper in the presence of oxygen as well as an anti-oxidant such as vitamin C although restoration of neuronal functioning was only partial [296]. Interestingly, copper-ascorbate oxidation of tryptophan may be suppressed by Trp chelation of copper at high trp concentrations [182] suggesting reduced amounts may give copper more ability to damage an already low supply. This is interesting in terms of a nutrient interaction hypothesis on copper toxicity. And in fact as early as 2012 it was determined that tryptophan intake could reduce copper toxicity at least in carp [100].

Some precedence for metal modulated toxicity existed back to 1999 when work with cultured neurons showed a dose dependent reduction in abeta toxicity with Zn [149]. 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 [25]. In 2021, Ni was found in important amounts in a commercial abeta40 preparation [21] and was found to mediate dityrosine crosslinks [23] similar to the dityrosine crosslinks induced by copper found in 2004 [13].

A 2013 work found in vitro physiological conditions caused copper to prevent fibril formation [181].

By 2022, work focusing on moving copper into the cell considered many aspects of copper misallocation and devised a copper specific shuttle peptide to deliver Cu from abeta [199].

At least one recent 2024 work identified copper dysregulation as a contributor to microbial contributions to Alzheimer's [180]. While brain copper accumulation has been observed in mouse models of AD and appears pathological [102] any relation to real disease would be questionable but accumulation may be a defense against pathogens or due to other cues that are more disease relevant. Copper distribution in the brain can modulate many functions from olfaction to adult neurogenesis [3]. One work in 2022 addressed AD as a consequence of copper deficiency because [123]

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

Interestingly, iron chelation has failed in AD even as iron overload is observed with ROS generation [156]. This set of conditions could easily reflect age related copper loss as mitochondria and iron transport systems are limited. Another possibility is raised by a recent work suggesting that iron accumulation in aortic valve calcification is a compensatory response to global iron deficiency [143]. In this case then iron chelation may have to be replaced with supplementation if this "compensatory hoarding" occurs in the brain which often has priority along with the heart during nutrient limitation. .

Folklore regarding copper persists and yet clinical trials for Cu in arthritis continue to show lack of any benefit [217] even as other controlled tests show some effects of Cu on processes related to collagen properties [84]

Remarkably, copper sulfide was shown to protect against ETC damage by MPP [224] suggesting some activity against toxic insults. Copper histidine is used to treat Menkes disease which is a defect in ATP7A [186].

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

Thinking outloud

this may not belong here but relevant to other Cu stuff, A recently published work suggests copper delivery is the important part of a new ALS drug but the work also suggests a "hyperreductive state" around hypoxic mito that promote release of Cu from the drug complex [96]/ pointing to a possible more general mechanism. The work goes onto suggest possible role in Parkinson's Disease but does not address AD. At least one observational study found a negative correlation between odds ratio for Parkinson's and copper intake [305]

2.6. Cancer

The relationship to cancer is probably the most confusing aspects of copper interactions. However, Copper deficiency does not effect proliferation of erythropoietic cells but it does reduce differentiation and alters metabolism from mitochondria to glycolysis [32] so it can produce two central features of cancerous growth. Copper accumulation has been observed in neoplastic cells and it stimulates angiogenesis [226]. While this suggests a role supporting tumor growth, "acute phase copper" and improved blood supply can be part of a healing response.

Copper has been studied in relation to cancer being considered both as a limiting nutrient and a source of cuproptosis in the overload state [255]. Copper is essential for many growth processes and can activate receptor tyrosine kinases without a ligand making it a target for cancer [89]. However, these processes are also essential for maintenance and healing in the organism and any net benefit would have to consider host fitness as well as cancer cells again using a clinical endpoint to decide on approach. In some studies, copper depletion was considered to be motivated by the observation that copper chelation reduced cancer growth and equating chelation with depletion. However, role confusion may have applied as the chelated copper could generate ROS's with obvious cytotoxic activity.

Copper storage diseases and in essence "overdose" are well known [69] and a role in cancer is suspected [26]. 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 [236]. Lysyl oxidase activation, the goal of this therapy, is also associated with cancer spread [254][212][282]. 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 [16] or [307] and the survival curve in figure 1). Incidence of liver cancer in Wilson's Disease patients is remarkably low [185] and a discussion of possible treatment effects [278] points out that the copper per se rather than removal is likely to help while also mentioning differences with iron overload. Indeed, extra copper that prevents iron overload may be therapeutic as originally intended.

We should note that complexed copper is not equivalent to copper deficiency as the complex may not be inert. However, when an ROS generating complex has been observed its effects were diminished by antioxidants [61]. This also suggests that copper depletion per se may not kill cancer cells as much as copper complexes and that concerns about copper supplements and cancer may not be significant.

3. SITES OF INTEREST

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

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

Location	site	Effect	time scale
Heart	mitochondria	energy production	maybe days
Heart	mitochondria	remodelling	weeks or months
Heart valves	lysyl oxidase	crosslinking [211]	weeks or months
Trachea	lysyl oxidase	proper crosslinking	months
Macrophage		phagosome	days
Macrophage		lysosome	days
ceruloplasmin		distribution	days
foreign ligand	variable	variable	

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

3.1. Cytochrome C Oxidase

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

Supplemental copper has been noted to improve symptoms in one case report including symptoms such as hearing loss [99] attributed to defects in cytochrome C oxidase copper loading and restore function in mutant yeast [76]. Cytochrome C oxidase levels in rat hearts were shown to be related to copper deficiency as early as 1998 [222]. 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 [272][303].

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 [200]), 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 [28] and [91] . Copper is decidedly pro-angiogenic and several studies have shown effects of copper consumption increasing tumor growth in animals while both chelators and ionophores are being investigated for treatments [39]. However, pro-growth and angiogenesis could also be expected during regeneration which itself may require copper.

Thinking outloud

Copper loading of cytochrome C oxidase relies on an oxidized Cox11 to interact with Cox19 [27] 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 [88] and indeed mitochondrial related signaling [241] . 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 [29] in [241]) . However, the enhancement by GSSG suggests that the presence of oxidized antioxidants may be beneficial but not in their reduced state.

Thinking outloud

engineering ahead of medical, protein quality

In some other context, engineering efforts to produce biological products such as bone in a reacor vessel can offer insights into factors in vivo. A 2021 work focused on similar systems by modelling the effect of amino acids and copper on antibody quality in a production setting [152],

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

3.2. Lysyl Oxidase

Lysyl oxidase family of copper dependent enzymes contributes to controlled crosslinking of structural proteins such as in injury recover [33]. They have a central role in organ development and some activity in disease [287] with the latter association contributing to the idea that inhibition would be beneficial in many cases. However, the details again point to "fixing rather than inhibiting" as with apparently pathological coagulation. In this case, one problem may be incorrect or incomplete metallization which would be fixed with more copper. Other deficiencies may similarly alter the overall function of the LOX enzymes and it may be a better solution to fix these problems than inhibit LOX. Notable functions for tryptophan and tyrosine exist and these have been identified as potential concerns before [162] .

Several works point to the LOX family as a good target due to persumed causal role in pathological results. Lysyl oxidase was considered to be bad for vessels [18] and calcification but this may be related to metallization issues [243]. Lysyl oxidase expression has been associated with degenerative mitral valve disease in humans[211]. It has been observed to upregulate in the injured newborn lung [308] 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 [253] although details on reactions catalyzed could not have been fully explored.

Regulation at transcriptional and translation and post-translational levels is confusing. For example, it has been described in 1998 as [244],

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, catabolically 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, [225]

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

However, metallization may not be complete and feedback systems may increase expression to achieve an activity level. Note too that "crosslinking" is a variable modification and physiological as well as pathological crosslinking can occur. While "quantity versus quality" will be the subject of another work, its important to remember that increased expression of lysyl oxidase genes and more patholoical crosslinking could occur in the absence of sufficient copper. Mature functional lysyl oxidase contains an unusual lysine tyrosylquinone (LTQ) which itself is formed in a copper dependent process [291]. Depence on multiple tyrosines or tryptophans can increase the odds of generating dysfunctional enzymes which may be inactive or perform unintended functions when these amino acids are limited. This theme of amino acid starvation also appears in concerns about ceruloplasmin and more generally with aging.

3.3. Ceruloplasmin

Ceruloplasmin is an acute phase protein [106] which serves as the dominant copper carrier in the blood delivering copper as Cu(I) for uptake by CTRP1 by reverting to apoenzyme at cell surfaces [50]. As an acute phase protein its concentration may correlate well with early disease stages but it generally has a productive role. Besides stress modulation, activity may depend on factors such as copper availability, estrogen and progesterone [147] and , in wilson's disease, retinoids such as ATRA may improve ceruloplasmin secretion [247]. Ceruloplasmin (regardless of how assayed) and blod copper levels and their fluctuations do not have to reflect overall copper sufficiency.

It is also a promiscuous enzyme [279]. While best known for ferroxidase activity, it can also has oxidize activity against cyclic hydroxylamines (used as ROS probes) [72] as well as various amino acid derivatives such as " catechol and its analogs, such as dopamine, epinephrine, norepinephrine, 5-hydroxytryptamine, and tryptophan" [147].

Thinking outloud

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

Ceruloplasmin contains 6 coppers and histidines needed for metallization [92]. as well as 2 tyrosines. Independent errors in metallization will multiple and reduce likelihood of functional enzyme.

The blood leveels of ceruloplasmin may correlate well with copper blood levels but it can vary in quality too. A chain of W and Y are thought important for enzyme preservation with ceruloplasmin containing a chain of two tyrosines [261]. As iron accumulation is related to AD, there is a question about the quality of the circulating ceruloplasmin. If there is high-infidelity translation due to W and Y depletion, there is also the question of how feedback mechanisms control the overall amount. First is has to metalize right which requires 6 coppers and 6 histidines and then survive with the 2 tyrosines. If any components are deficient quantity or quality may suffer. Ceruloplasmin KO mice gained weight and showed increased scatter in weight with lipid dysregulation only partially corrected wth exogenous replacement [213] sugesting tight control may matter.

3.4. Macrophage et al

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

While well known for a role in infection control, macrophages also have a complicated role in cardiovascular disease [41] although the impact of copper may be less apparent. Recently some work has suggested that lysosomal copper may be an important storage location [209].

The importance of copper for host-pathogen relations is well known as is a prticular usage by macrophages [130] [24]. Note that nutritional immunity may involve either an excess or limittation of copper to the patogen hinting at a common source of myths about which direction to move a quantity to achieve a given result (see a list in Appendix C) . Much is known about interaactions of copper in macrophages with particular organisms such as Mycobacterium tuberculosis and Salmonella typhimurium [97] as well as Streptococcus pneumoniae [113] . 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 [246]. As with attempts to control amyloid beta in AD, there may be some passing benefits but taking all the information together this is likely of limited value if the simpler approach of enabling the copper based response in a well regulated way is feasible.

3.5. Associated Entities - histidine and garlic etc

Copper can of course form associations, with many chemical groups and diverse roles. Role confusion however seems to be a recurring issue as specific componunds may not sequester or activate copper as may be expected. One recent review on anti-cancer mechanisms of copper dicussed various ligands and roles for both copper depletion and overload [15]. The combination of the garlic and copper, while sounding like a medieval concoction (suggested as a result from Bald's Leechbook [85]) , has been described as synergistic against fungus [198] and seems plausible for generating perhaps more volatile and diffusible copper that could find otherwise inaccessible lysyl oxidase and other targets.

Dogs fed a histidine deficiencnt diet eventually developed feeding resistance and lower whole blood copper and zinc [44].

4. CASES AND OBSERVATIONS

This section describes the results of adding copper to diets for a variety of dogs. Context and individual case interpretation is also included here instead of the discussion section which is reserved for general observations about the cases.



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

This work tracks a small part of the diet and outcome history of a group of rescue dogs. The larger effort is designed to understand their diet and supplement needs with the hope of optimized feeding for each dog. The subset of data considered here focuses on variations in copper intake after the arrival of a new dog, Trixie, with various health conditions. All dogs were fed suitable human quality food and vitamin supplements in addition to commercial kibble and canned dog food products. Relevant part of the diet and outcomes were recorded in MUQED format [166] immediately after feeding and as events occurred. While most supplements and medicines were recorded in good detail, several common diet parameters can not be inferred from this data. Snacks containing vitamins were generally consumed within minutes of preparation although in some cases snacks would be refrigerated and eaten 12 or so hours later sometimes with AM and PM snacks together. As stability is a concern with copper, this point may be important. Besides the meal or snack, most dogs received additional meals of commercial dog food and unfortunately uncontrolled scraps or treats while others routinely ate toys or yard debris. However, some results appear to relate to the vitamin mix and notably inclusion of copper. Total calorie intake is not reflected in the data although some details of the products are indicated in the MUQED data (see Supplementary Information). In particular normalization of the "dinner" amounts is variable between dogs. Some of the discussion will also reference unpublished notes on "Little Man" who was given copper and other nutrients before the MUQED system was operating.

Generally copper dosing was rotated leading to high doses some days with none on intervening days. A hard upper

limit of 3mg/kg body weight of supplemental copper per day was maintained based on quoted NOAEL's from an original source dated 1972 [46]. All of the dogs currently living here received increased copper shortly after the arrival of Trixie due to apparent spread of coughing. Trixie was later treated with Clavamox leading to cure suggesting indeed an infectious cause existed. Some of the dogs, notably Happy and Rocky, had varying cough levels previously as described below.

While all supplement data were recorded and many varied significantly over time, only a few are discussed here. Many of the dogs in this setting have had either symptoms that could be due to hypothyroidism or overt lab confirmed low thyronid hormone levels. As iodine intake flucuated wildly, it is included in some of the graphs as a putative factor confounding inferences about copper. The premise of this work is that the total diet is a "confounding factor" and readers are encouraged to check the MUQED data for other patterns. As copper chemistry in the GI tract may be impacted by sulfur, some attention should be given to sulfur sources such as amino acids including taurine.

Dog	Dates	Condition	weight(lbs)	Cu(mg/day)	Cu(mg/kg)	Outcomes
Cookie	21-09-10 22-01-21	Resp infection/azithromycin	13.5	2	.33	cleared
Happy	18-09-07 24-04-10	several	13.4 - 17.7			
Happy	18-09-07 19-05-30	heartworm/doxycycline	13.4	2	.29	cough gone
Happy	24-03-26	coughs	15.2 - 15.5	2	.29	rare coughing
Brownie	21-01-12 23-02-22		49 - 64	1 variable		pts due to cancer
Brownie	21-01-12 21-02-14	pregnant, fibroids, heartworm	≈ 60	1.5-2.5		uneventful
puppies	21-03-23 21-06-09	cough	104	4.5	.095	cleared
Trixie	23-12-16 24-04-10	resp infection/Clavamox	37.6 - 44.6	5	.276	cleared
Trixie	24-05-15 24-06-01	deep cough returned	44.2	6.7	.3	greatly reduced
Rocky	22-02-05 24-04-10		4.4 - 8.3	1	.37	subjectively better
Hershey	17-04-22 19-08-27	multiple	8.2 - 9	.2-6	.1	heart failure
Hershey	17-04-22 19-08-27	multiple	8.2 - 9	2	.52	transient improvements
LittleMan	2016	multiple			.8	honking stopped
Annie	2022-09-21	excessive sleep, apathy	7.74- 9.9	2	.5	active again
Dexter	2017-04-25	picky eating	5 - 6.8	variable low	"low"	see text

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

4.1. Dexter

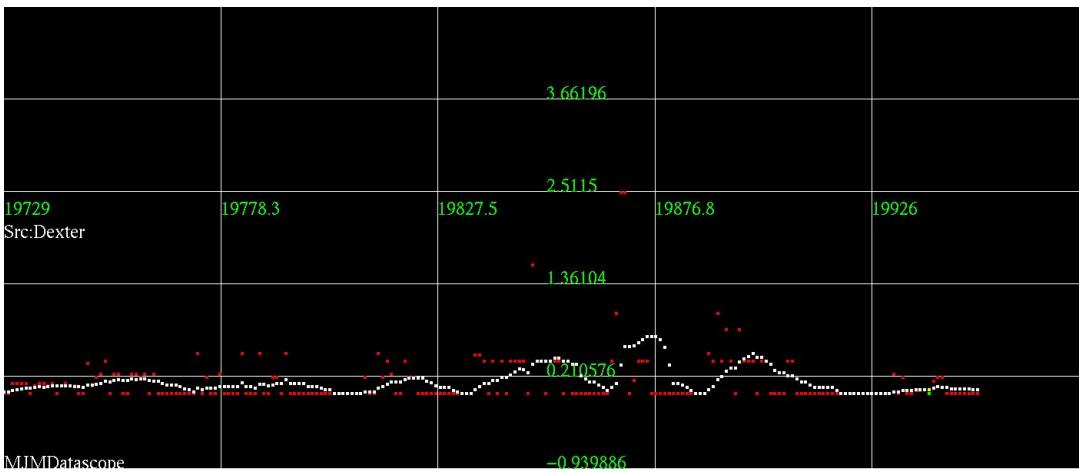


FIG. 2: Dexter daily copper intake around blood test on day 19926 . Daily amount in red 10 day trailing average in white.

Dexter was not originally part of the copper study but was included after showing signs of distress and elevated bilirubin. He had always been a picky eater but otherwise in good health with plenty of energy. Blood work on 24-07-22 was notable for elevated ALT of 140 (10-125 U/l) , total bilirubin of 1.8(0.9 ng/dl) and ALP < 10 (23-212

U/l). Low ALP with signs of liver failure may be diagnostic of Wilson's Disease but the copper intake pattern did not seem consistent with that. In Wilson's Disease, ceruloplasmin is low [297] and it may be a case of insufficiency coexisting with surplus leading to a supplementation dilemma introduced earlier. Low ALP activity may be due to zinc and magnesium deficiency [215]. Zinc and manganese did raise ALP levels in chicks although copper did not appear important under the conditions tested [231]. Based largely on the low ALP he was given a metal mixture along with KCl and various others components (see "DEXSNACK" in MUQED data) such as amino acids. The mixture added to kibble was well accepted by Dexter and others including Annie and Rocky. Metals included iron, magnesium, zinc, and rarely copper and manganese. He subjectively improved and he may be even eating better than before. The copper intake history did not suggest it was higher prior to the event during relevant time periods than it had been during prior times thought too distant to be relevant. His vet visit was on 2024-07-29 with last recorded copper intake of .4mg on 2024-07-04 and on 2024-07-03. He noted for spitting up yellow on 2024-08-09 after having .2mg on 2024-08-07 and -06. He had also been noted to spit up on 2023-08-08 after having no known copper since 2023-08-02. Its not real likely but he may be sensitive to copper and it was not a priority to give him more so follow on doses remain sporadic. Eventually he seemed to respond well to added vitamin D which was thought important due to bumps on his ribs and possible bone problems.

4.2. Cookie or Mixie

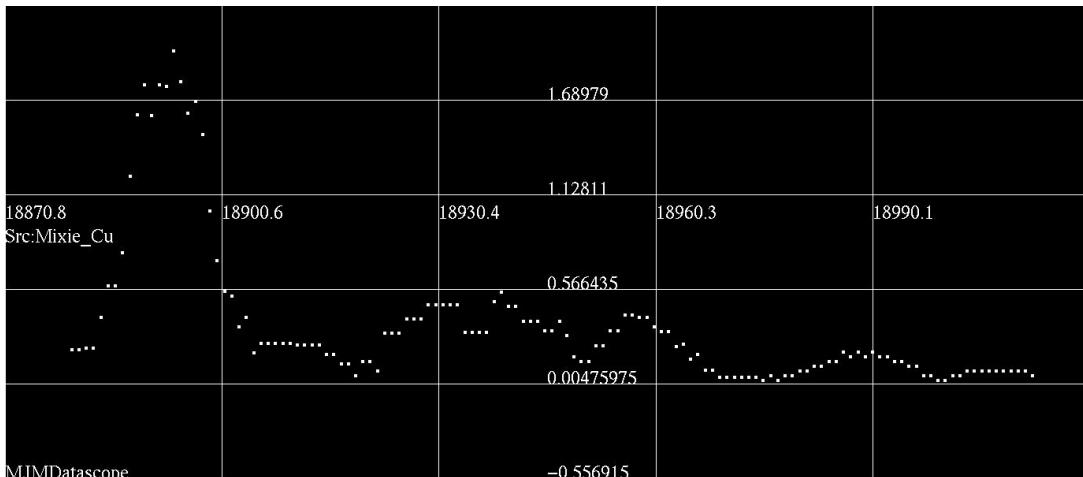


FIG. 3: Mixie daily copper (white) intake .

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

4.3. Brownie and puppies

Brownie was the subject of a prior work where her uneventful pregnancy was notable for vitamin K consumption while heartworm positive [167]. Subsequent to that work, her abdominal tumor was removed and diagnosed by vet as fibroids. Briefly, Brownie was determined to be pregnant shortly after arrival. Her heartworm was treated with Diroban after weaning and fibroids removed 2021-11-15 well after the puppies were gone. She was uneventful until being diagnosed with cancer and killed 2023-02-22. Prior to her diagnosis, she was observed to cough occasionally for no obvious reason and appeared to have some movement issues. X-ray confirmed tumors likely responsible for both problems.

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

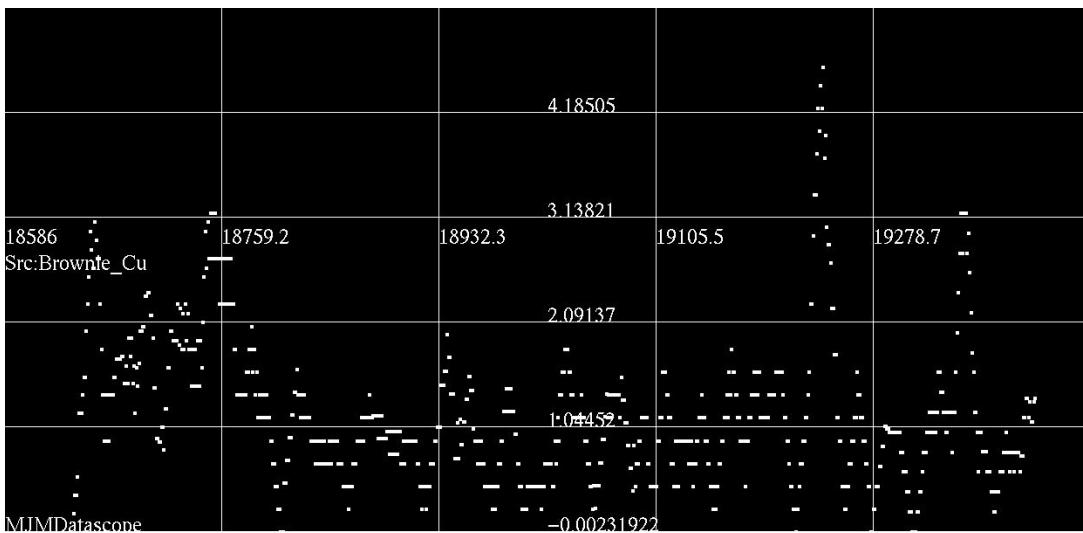


FIG. 4: Brownie 10 day trailing average copper (white) .

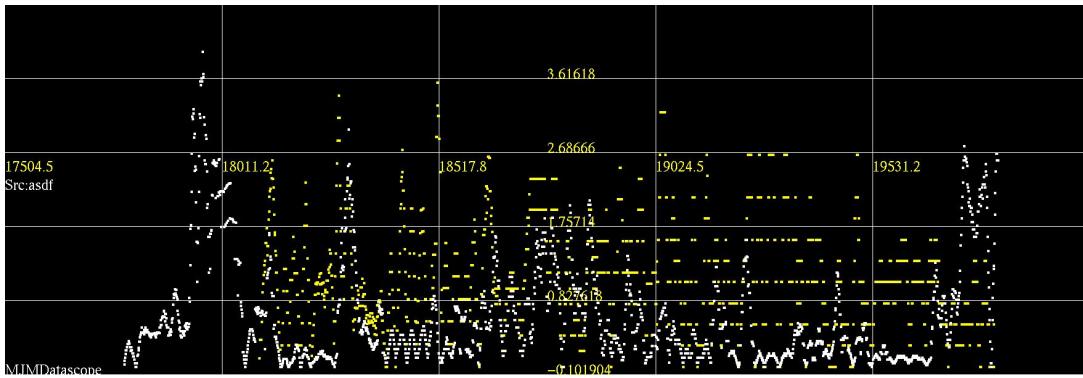


FIG. 5: Copper(white) and Zinc(yellow) dosing per day averaged over prior 10 day period as dosing was highly variable due to rotations of various nutrients. 18046 is 2019-05-30 when the cough was first noted to be gone for a few weeks. 19823 is 2024-04-10 the last date for which data was obtained. The cough stopped prior to the start of the Zinc and gradually increased to a notable background level over most of this interval although notes were incomplete. 19531 2023-06-23 notes the start of Cu depletion and chronic cough was noted by late Fall. During this time Zinc greatly exceeded copper dosing.

4.4. Happy

Happy arrived here in September 2018 heartworm positive. Her coughing was eliminated for a few weeks in 2019 and since then it has been coming and going to varying degrees. Over the years, she has experienced brief periods of sickness but generally been active and apparently healthy except for the cough. She has shown radiographic evidence of enlarged heart and possibly narrow trachea. Her heartworm recovery was described with vitamin K and other supplements [164] followed by an unusual episode which resulted in some investigation of possible role of vitamins B-2 and B-3 in her health [160]. She had two episodes resulting in emergency vet visits and blood work. On 2022-02-02 lab results were notable for elevated creatine kinase(609U/L, 10-200) slightly high glucose (123mg/dL, 63-114) , low normal Ca (8.5 mg/dl, 8.4-11.8) and Cl (108mmol/L, 108-119) with high normal bicarbonate(26mmol/L, 13-27). ALP(35 U/L, 5-160) was normal and total T4 low normal (1.2mug/dL , 1.0-4.0). On 2024-10-04 at a different clinic glucose was normal (111mg/dL, 70-143) and ALP was low normal (31U/L, 23-212) with no measures of creatine kinase or blood chemistry. The change in ALP appears to be largely due to reference ranges as numbers are similar between visits. For comparison, Little Man on 2016-12-29 while on steroids IIRC had elevated ALP (231 U/L, 0-140)i and high glucose (126ml/dL, 75-124) and low BUN (8.6 mg/dl, 9-29). ALP may have been elevated due to steroids as well as copper toxicity.

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

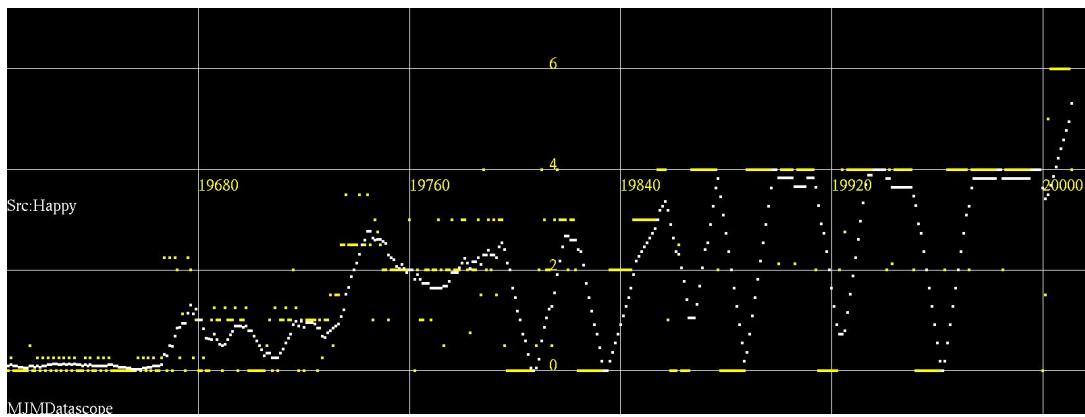


FIG. 6: Most recent with some passing progress

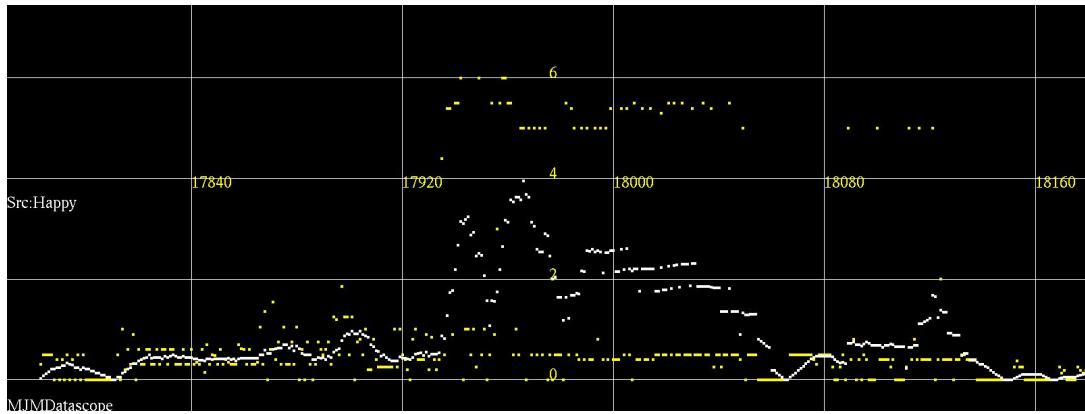


FIG. 7: Earlier when she was cough free for a whlie

Thinking outloud

Happy, like Brownie, was also the subject of two prior works. Initially her heartworm recovery was described with vitamin K and other supplements [164] followed by an unusual episode which resulted in some investigation of possible role of vitamins B-2 and B-3 in her health [160]. To summarize, Happy arrived heartworm positive coughing to varying degrees. She was treated with a slow kill approach including ivermectin and doxycycline as previously described. Years later she was acting sick but appeared to recover well with B vitamin supplements. Her coughing never returned to the very low levels seen after heartworm recovery until copper doses were increased with elimination of any zinc and care with tryptophan.

As copper was increased due to widespread coughing after Trixie's arrival, her cough was noted to decrease to lower than prior levels. Review of the copper dosing suggested it had fallen prior to Trixie's arrival. Often her excited cough appeared to be a honk on exhale suggestive of trachea collapse. She also would cough early in the morning when curled up. As outlined in the introductory material, it was later realized that earlier concerns about aromatic amino acids could be due to simple excitability rather than any disease worsening. This most recent effort considered some coughing increase normal and now she seems to have reduced coughing, good energy level, and maybe some aromatic amino acid sensitivity.

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

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

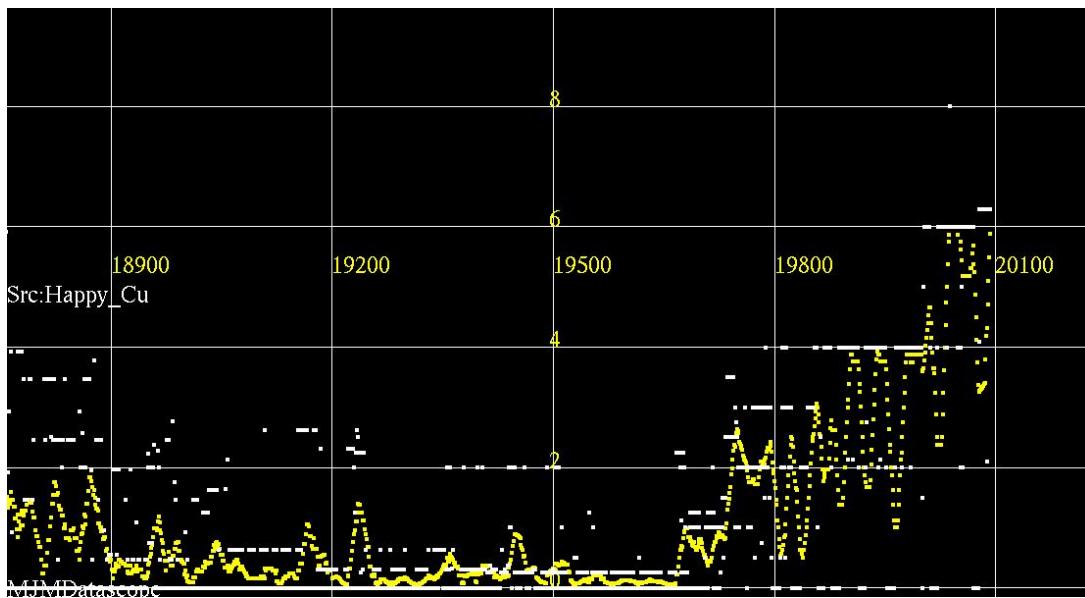


FIG. 8: Post script switch to Chinese citrate and increase dosing to no obvious benefit

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

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

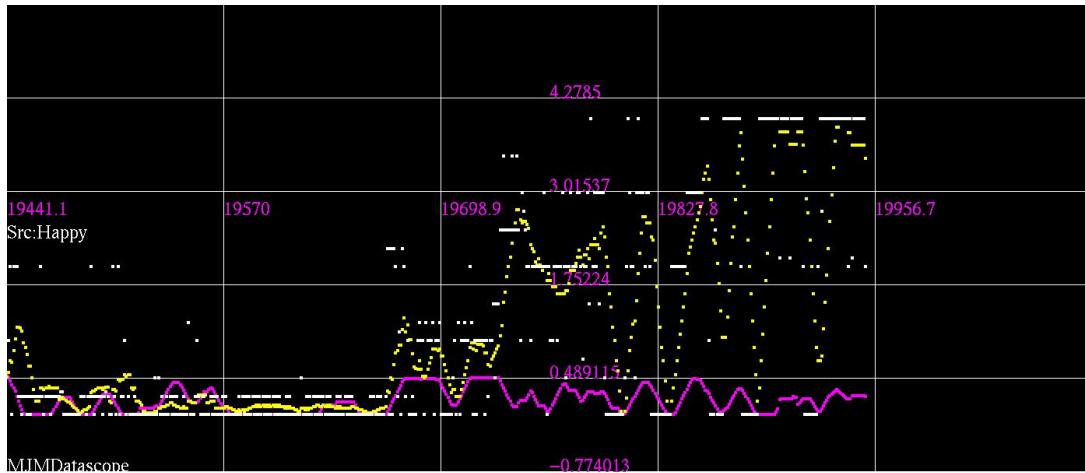


FIG. 9: Copper shown for daily and 10 day trailing average along with chicken thighs (magenta) as a measure of fat intake. Recovery from low fat diet appears to take longer than recovery from only copper deficiency.

4.5. Trixie

Trixie began coughing shortly after arrival and was very low energy. Her coat was notable for a sticky feeling that seemed to recur after a bath. Many other dogs began to cough or hack suggesting that she brought a communicable infectious disease which was the motivation for increasing copper again. Nutrient mix was modified to add more copper and most dogs' coughing returned to normal quantity and quality although her's did not entirely resolve. Copper stopped for a couple days (I was gone) and owner took her to the vet as she began coughing more. Clavamox was prescribed and her coughing stopped within a few days. Her energy level has improved but she did not run

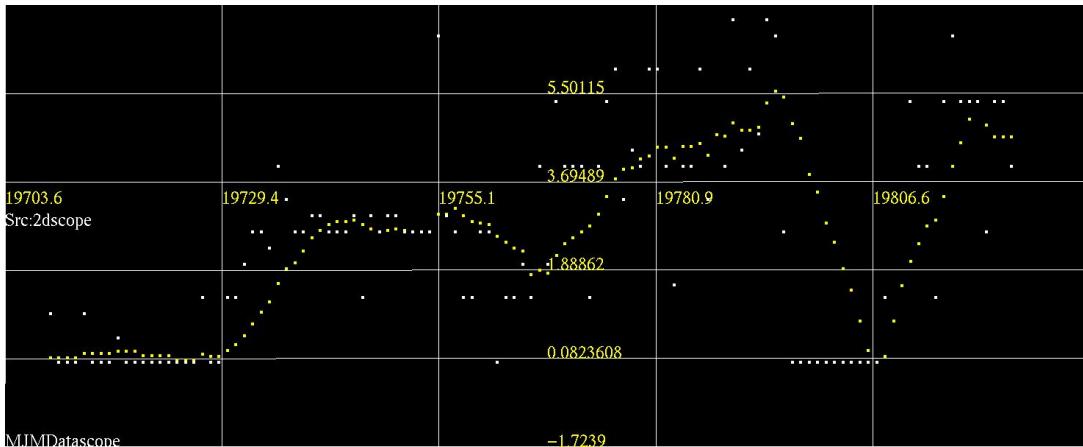


FIG. 10: Trixie copper consumption since arrival. Daily amounts (white)) and trailing 10 day average(yellow). Copper started to be significant around day 19730 in response to coughing. Day 19807 marked the end of the copper fast as well as the end of Clavamox which was prescribed due to worsening when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

until 2024-05-02 (19845) . She had a renewed cough around 2024-05-22 (19865) subsequent to copper withdrawl on 2024-05-15 (19858). Cough seems deep on excitement not honk/wheeze like Happy. Copper resumed 2024-05-27 and is greatly reduced by 2025-06-01 . She appeared more energetic than when I left and walked well although maybe still tired at end of walk. Her coat now feels clean.

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

4.6. Rocky

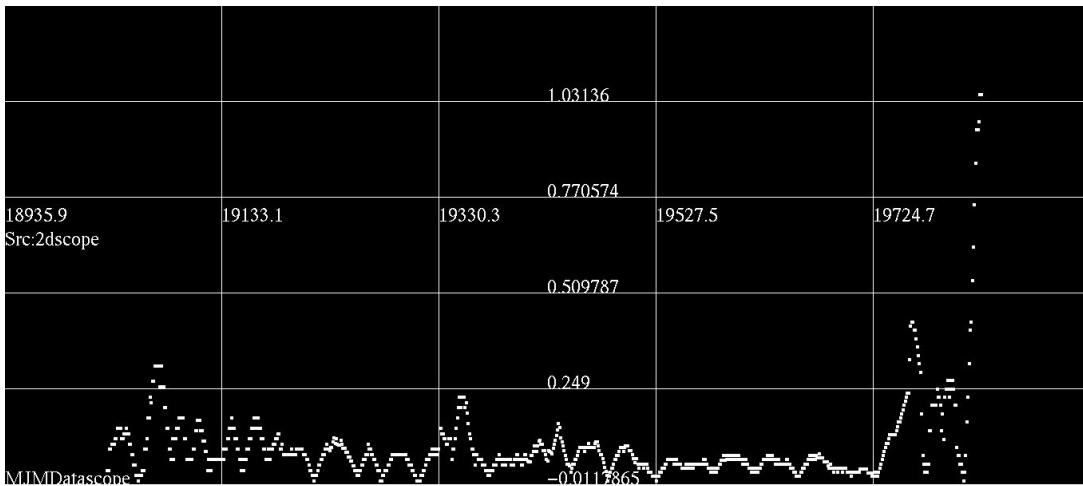


FIG. 11: Rocky 10 day trailing average copper (white).

Rocky arrived here on 2022-02-05 in generally good condition although notable for a "rubber block" or "plastic" body type feel. Notes on his condition including cough were sparse although he tended to stay covered up on the couch a lot as other small dogs tend to do. Rocky will hopefully be the subject of another work as he responded significantly to iodine and sodium benzoate which was attributed to, but never lab confirmed, low thyroid output. His "plastic" body type changed into a more normal "flexible" type and he began to feel like the other dogs when picked up rather than stiff. The addition of copper may have reduced his morning cough but he continued to have

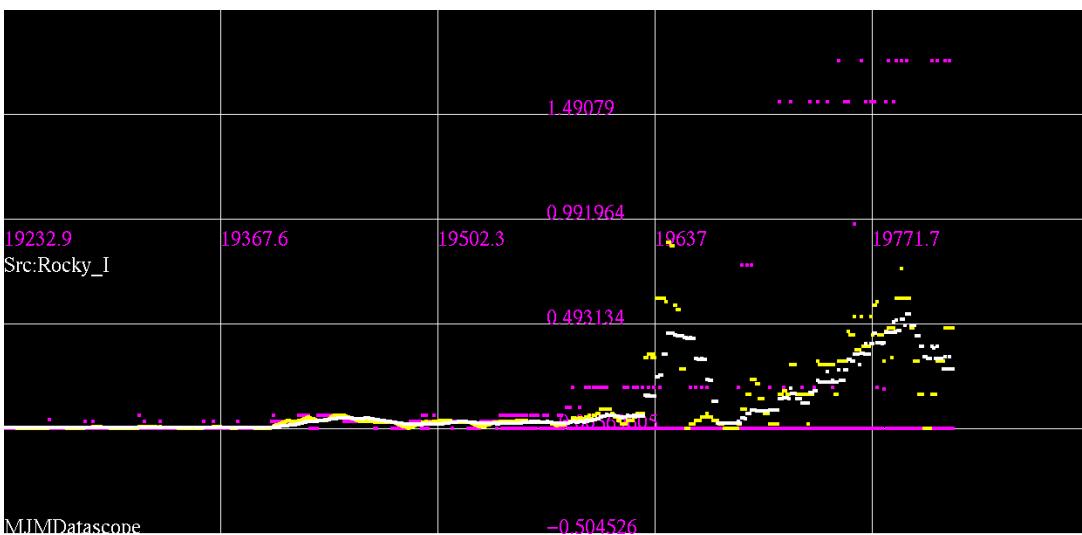


FIG. 12: Rocky iodine intake daily and with 10 and 30 day trailing averages. Patterns are difficult to discern with the pulsed dosing.

apparent congestion after eating sometimes breathing through his mouth and sneezing. That too has cleared up by 2024-06-01. Most recently he had notable muscle tone which had been lacking. His overall activity increased but that may be due to social factors such as feeding ritual. Some coughing now coincides with exposure to cigarette smoke.

Copper was shown to correlate negatively with TSH in one human study and may increase T4 levels [299].

As benzoate may be an important confounding factor, a brief digression here may be helpful. A recent study on rats fed benzoate demonstrated some insignificant indication of increased T4 and decreased TSH which the authors summarize as, [265] ,

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

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

4.7. Annie

Annie probably showed the clearest improvement coincident with increased copper (and a few other components described below) on two occasions. Annie arrived thin but in generally good condition although seemed old for stated age of 6 years . She ate well but had some limitations in sight and hearing. She seemed to get skin or paw irritations easily. Coughing was variable and not well documented. She feels a little "frail." She began to sleep excessively in early 2024 and a special copper snack was started on 2024-05-01 (19844). This consisted of 2mg of copper along with sodium benzoate, KCl, and B-6 in chicken broth which was more readily accepted than the full snacks for everyone else. As these other components had been quite common they were not considered significant although the sodium benzoate had also been stopped earlier. Lost vigor suddenly regained in a few days and seemed restored to her more typical self by 2024-05-05 (10948) with continuing improvements in energy and appetite. Her exercise interest improved and she walked and cried with good energy.

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

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

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

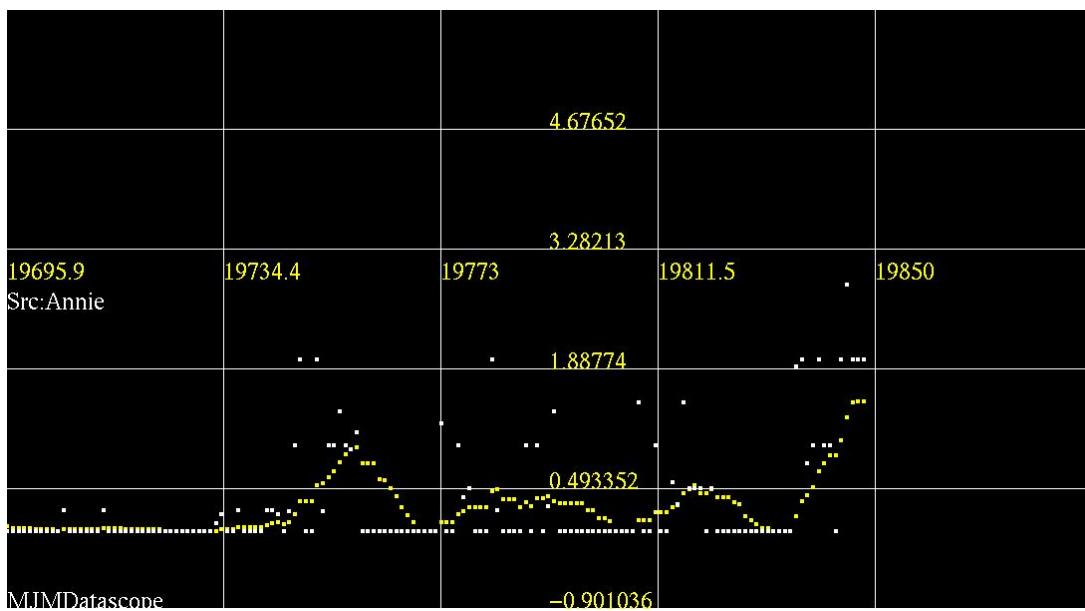


FIG. 13: Annie

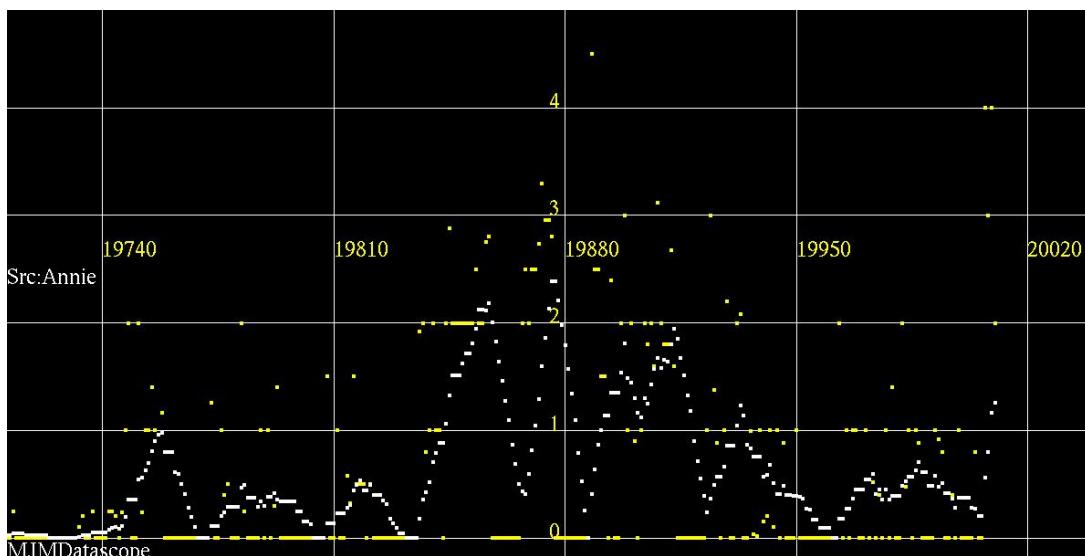


FIG. 14: Annie zoom in on recent days as copper was increased due to swelling under eye.

4.8. Hershey

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

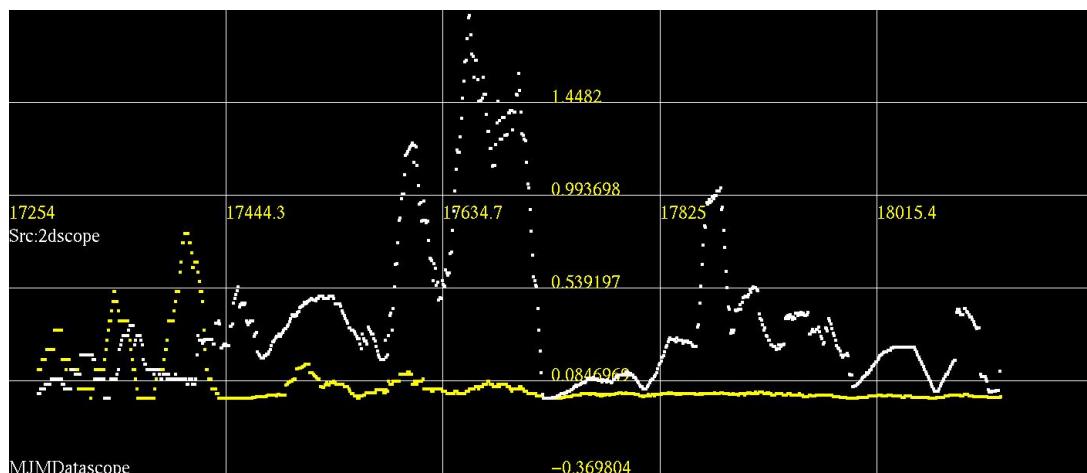


FIG. 15: Herhsey 10 day trailing average copper (white) and iodine (yellow).

Date	Day number	Comment
2017-09-25		developed skin problem, vet prescribed clavamox and miconazole chlorhexidine shampoo Malaseb
2017-10-13		blotches mostly gone yesterday Barb still notes some
2017-11-01		stumbled down steps did not come up until after PMSNACK restart lipoicacid
2017-11-13		struggles up deck steps but finally made it
2017-12-12	17512	seems to be coughing a lot
2018-03-06	17596	seems to cough less, continue copper
2018-04-19	17640	came up steps on own again cadence sounded good
2018-04-20		fur seems thicker except for small area on back behind neck. Still coughing though
2018-04-28	17649	appears alert more flexible and good up steps while still planning although he did stumble the other day
2018-04-29	17650	seems ok on steps, hair filling in.
2018-05-29	17680	not coughing much and energetic but refused to eat and diarrhea. Ate small amount indicated around 830AM. He seems ok at noon not coughing much but subdued.
2018-07-02	17714	lighter and not coughing except when really agitated. Made it up steps good. Could be just weight although not that much lost, something in yard wiped out with spraying, or something like potassium chloride or the lysine making him worse
2018-07-15	17727	had rear leg problem, Barb gave rimadyl
2018-09-04	17778	seems to be stumbling more on steps last day or 2 but yesterday later came up good with fish at top ...
2018-09-19	17793	left rear leg bad had to help up steps still limping in kitchen 5 mintues of so. Gave some b7ngnnnc rested ok. Made it up steps after PMSNACK ok although aborted on attempt but it is 95F out.
2018-10-12	17816	planning and cirling on bottom step then doing good up steps
2018-11-02	17837	walked up first few steps in the rain and then faster up last few no slipping. Rear left leg may be more useful now.
2018-11-26	17861	better again on steps walking up but coughing still
2018-12-04	17869	coughing a lot again try stopping Cu for day or two
2018-12-17	17882	probably made it up steps on own, saw he was gone then heard barking and clumsy step noise. Seems good still coughing on and off, went around shed today.
2018-12-27	17892	coughing less and went out to pee, maybe the extra copper yesterday helped quickly
2019-01-08	17904	seems generally more active maybe coughing less for all the barking with the other 2 BCAA's
2019-03-12	17967	pretty good up steps almost back to recent bests. Coughing like always but darted out the door to deck quite well went around shed etc.
2019-03-14	17969	leapt up some steps then stumbled near top, went around near side of shed ok and wandered yard for a while
2019-04-02	17988	good on steps leaping not slipping
2019-04-26	18012	came up steps without crying on his own.
2019-05-13	18029	Hershey slower than yesterday more normal
2019-06-03	18050	Vet found heart failure on X-ray and bladder stones.

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

Hershey quickly demonstrated several problems not long after arrival. He had problems with his fur, digestion, and coughing while ultimately being diagnosed with heart failure and bladder stones. During his time here, his diet was varied and he was observed for overall eating and behavior with specific interest in coughing and ability to make it up a short flight of steps from the backyard to the deck. Again, the notes were not sufficient to fully capture the dynamics of his condition but some representative ones have been edited into the above list. Some correspondence with copper intake is noted. In the last few days of his life, he would pass out and quickly regain consciousness until one day he did not recover presumably due to heart failure. As many initial features could be rationalized as related to thyroid output, his iodine intake was elevated. In retrospect, his initial response to increased copper may have been to be more energetic but that increased his coughing leading to a dosage reduction. Clearly the data are incomplete but suggestive now of some benefits.

5. DISCUSSION

Copper supplementation averaging around .2 to as high as .8 mg/kgBW/day appeared beneficial in this group of dogs as symptom improvement often followed weeks of dosing. In the case of Annie, two results appeared just a couple days after copper intake was increased. Several suspicious observations were noted but nothing robustly correlated with copper intake. As some symptoms such as coughing are the product of many factors, interpretation is difficult during the initial response phase. Most notably, increased general energy may increase coughing in the presence of a weak or collapsed trachea or with some heart conditions. Initial response would be to increased energy production and presumably a feeling of wellbeing but remodelling and stiffening may take longer to achieve more complete resolution. Another difficulty is due to pulsed dosing. This was chosen to allow rotation of various nutrients and make it easier to see short term effects of comparatively high doses. However, it did require that time series be averaged for analysis. Happy's copper intake dropped much lower than normal preceding a period of excessive coughing. It was only after copper was started due to Trixie's respiratory infection that the data were examined more carefully and the pattern noted. Ideally the filtering would be a lagging average weighted to some suspected biological parameters but even uniform moving average was useful.

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

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

The overall concern with Happy and aromatic amino acids is still not clear. Increased energy may lead to more coughing but pulmonary hypertension may be controlled by serotonin [5] and therefore tryptophan intake. Pulmonary hypertension is itself pathological and should be avoided while increased arousal state would be important for quality of life so investigation may be useful.

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

Reconciliation with various concerns and failures relies on the complex interaction with other dietary components which may be important over a large range of genetics. Copper was just one of many nutrients explored and it requires some of these for proper handling. Any optimization strategy would need to continually be finding the performance limiting nutrient in turn as each is tweaked.

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

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

Thinking out loud

repeated in intro

Besides the molecules already mentioned, it is worth noting that taurine was a consistent dietary component. Sulfates are observed to create copper deficiency in ruminants and the possibility exists that taurine exhibits related chemistry in the GI tract. Indeed, it has been observed to reduce copper toxicity in rats with increased fecal copper amounts [104] suggesting decreased absorption. Another work demonstrated taurine reduced ceruloplasmin only in rats fed a control diet but not a high-fat diet [125]. As taurine is being explored for various indications, including DCM [176], apparent limitations in supplementation could relate to induced copper deficiency which would likely cause some symptoms expected of copper deficiency.

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

Coughing and other subjective signs were often used to monitor progress and notes were not always sufficient. Coughing as described before can be produced by many causes. Here, we were concerned mostly with infection, trachea collapse, and heart enlargement. Honking related to trachea collapse may be more common when the dog is

excited. In this case, improving "energy" may produce more coughing even though the dog is largely healthier but the heart is still large or trachea still soft. This is further complicated with additions of vitamins that tend to promote alertness as was observed with histidine (indeed there was some concern about aggression when initiating it). This may not have been fully appreciated early on.

B-6 deficiency has been linked to excess copper excretion [36] possibly making copper a secondary excretion issue rather than a primary absorption problem. However, the concern with excess B-6 intake creating effective deficiency is a reminder to look more carefully at all data.

Iver a broad range of genetics, its likely that copper intake can be raised as long as other nutrients are also given to handle the copper beneficially. Candidate nutrients include tyrosine and tryptophan.

5.1. Aspects of Copper Chemistry

Thinking outloud

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

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

A central topic is copper speciation or oxidation state. Perhaps four copper oxidation states have been considered in the biological context. Solid Cu(0), Cu(I), Cu(II), and rarely Cu(III). Cu(I) and Cu(II) are probably the most relevant to food effects. Solid copper or Cu(0) has been claimed to have environmental remediation capabilities [51]. Cu(iii) is thought to be an intermediary in the copper Fenton reaction at near neutral pH with bicarbonate and sodium chloride present [207]. Cu(iii) production for degradation was also enhanced with histidine [203].

The first concern, the formation of insolubles that have decreased availability of the copper, is most clearly seen with sulfides but many other stable copper compounds are known. Copper minerals represent some compounds that exhibit low solubility in their native settings. Wikipedia lists several copper ore minerals [290] containing sulfur, iron, antimony, zinc, carbonate, hydroxide, aluminum, silicon, hydrogen, arsenic, and water. Of course an infinite number of organics could be formed with variable stability. Early XPS work suggested many copper minerals contain copper in the +1 state [187] although work continues to clarify specific issues [79]. Generally the minerals can be leached in acid to recover the copper and that chemistry may be useful here.

It has been noted that Cu(II) is converted to Cu(I) prior to transport and therefore some benefit may be obtained by making the conversion from Cu(II) earlier. However, as with some other nutrients, this may be counterproductive when normal mechanisms are operational. CTR1 for example will convert prior to transport [114]. This is likely similar to the situation with iron [229]

The two drawbacks of iron chemical characteristics, that is, Fe31 insolubility and toxic radical production by free iron, must be jointly addressed in some biological processes, such as the process of iron absorption by enterocytes at the duodenum. Iron is oxidized by stomach gastric juices, and most iron reaches the duodenum in the Fe31 form (32). As the stomach has a pH <3, Fe31 remains soluble until it passes to the duodenum where the pH is significantly higher. Thus, to enter into the enterocyte Fe31 must be reduced to Fe21. The absorption of the as-formed Fe21 must be done quickly to avoid the formation of hydroxyl radicals. To overcome this inconvenience, humans have developed a very efficient mechanism based on a protein pair. Iron transfer through the enterocyte membrane occurs due to the combined activities of two proteins: the DMT1 Fe21 transporter and the conjugated DcytB, which can reduce Fe31 to Fe21 (33). The DcytB/DMT1 pair is required for iron absorption since iron enters the small intestine lumen mainly as Fe31. DcytB, an ironregulated ferrireductase protein is highly expressed at duodenal enterocytes and reduces the Fe31. Upon reduction, Fe21 is transferred across the apical membrane of enterocytes by divalent metal transporters, mainly DMT1 (Fig. 6).

The same work [229] may be a good background for understanding copper more generally as a lot of issues with iron may be similar.

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

Copper "Fenton" reactions have been extensively explored for pollution remediation by destruction of toxic chemicals. Many of these reactions occur under mild nearly physiological conditions suggesting they may be able to degrade nutrients. In particular, bicarbonate in the 4mM range improves the degradation rates for a Fenton like Cu

system [205]. In fact, carbonate species are thought to be the active products not hydroxyl in neutral or alkali media [105]. Bicarbonate is being investigated for pollutant degradation optimization [283] as it apparently is quite active.

Thinking outloud

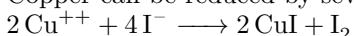
The photograph in Fig. 16 shows the side of a baking pan on the right which was representative of the surface to the left prior to heating for a while in baking soda water. The carbonate derived species may easily react with or make soluble the oxidized food grease which I thought was just a "like dissolves like" issue but may be as stated here. An ammonium bicarbonate electrochemical etch apparently optimized the mechanical properties of carbon fibers [120].



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

Cu(II) is the more common species but it can be reduced under relevant conditions by ascorbate, riboflavin leading to DNA damage [188](although maybe assisted with light [108]) or reducing sugars at elevated temperatures which may occur during food processing. It can be reduced and complexed with niacin [37]. It may be worth noting however even the interaction with ascorbate is controversial with redox competing with a catalytic mechanism leaving the Cu unchanged [237]. Generally copper absorption has been reported to decrease with higher dietary ascorbate with a confusing interaction with iron [112] which may be easy to rationalize a increased copper reduction prior to uptake.

Copper can be reduced by several things.

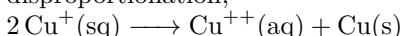


Once Cu(I) is formed, it can undergo undesirable reactions.

[228]



disproportionation,



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

Thinking outloud

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

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

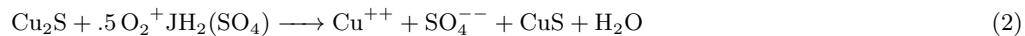
First its interesting to note that many high-school level chemistry examples are probably relevant. Copper is used to detect reducing sugars. This is one reaction that may damage other components such as sugars. Interactions with iodine are textbook illustrations.

Once a copper sulfide is formed, the copper may be recovered in processes such as commercial leaching that can go at 30C. In an acid environment both chloride and iron are important to getting optimal copper extraction from sulfide ore [227].

And some have observed chloride may be generally better for extractions of metals from sulfides, [94]

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

Some leaching reactions include [232]



(3)

FIG. 17: Some leaching reactions [232] at ambient or elevated temperatures

Ultimately food and stomach contents form a complicated variable mixture of chemical with varying ability to interact with copper and a survey of such properties such as [155] may be useful .

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

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

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

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

Copper sulfides can form varying large unit cell crystals with correspondingly high integer stoichiometry. They apparently are not molecular crystals. Unit cells may contain 24 or 62 distinct copper atoms and some phases contain a sulphur HCP structure with interstitial Cu that become fluid above 100C [58].

A phase diagram around Cu₂S was published in 1981 showing phase transformations above 72C [57] which is too high to be biologically relevant except for cooking but may be important in IC failure modes. A more complete phase diagram from CMU 1983 is also available [35]. Metastability may be common due to need to rearrange hcp.

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

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

5.2. Aspects of Copper Garlic Chemistry

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

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

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

The most well known sulfur compounds in garlic tend to be organic sulfurs with 1 or 2 sulfurs attached to an alkane or alkene a few carbons long. As these have an odor they likely have a high vapor pressure and may diffuse easily in some settings. A copper or other metal attached to the sulfurs would not likely be held in an insoluble solid

but rather allowed to move more freely. The question would then remain about getting to a suitable location and liberating the copper from the sulfur carrier.

Some works have cataloged and generalized the types of sulfur compounds prevalent in various food categories [54].

Empirically, organic polysulfides common in garlic, onions, shallots and related products are thought to have some cardioprotective effect but are difficult to analyze due to instability [263]. One small study suggested that garlic added to a diet could reduce some signs of copper deficiency in a fructose rich diet [64]. Interestingly, both copper and garlic demonstrated some favorable effects on cholesterol with copper reducing levels of fatty acid synthetase and garlic thought to slow the rate limiting step in cholesterol synthesis [124] although the interaction between copper and cholesterol (and fructose) relating to glucose intolerance has been known for decades has also been neglected [122].

Thinking outloud

this belongs in something on age related conditions too

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

5.3. Supplement Selection and Dosing Considerations

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

Common supplement forms include copper sulfate, copper gluconate, copper glycinate, and copper citrate. Glycinate appears to be popular due to solubility and reputed bioavailability. Sulfate appears to be common due to cost [293]. Gluconate was used in a lot of the latter part of this work as it was the only bulk form available in reasonable price and quantity. A priori and currently there is some reason to consider citrate as desirable. This was eventually purchased in kilogram quantities from China and had been used early on as it is a common form in small supplement capsules.

Sulfate, glycinate, and proteinate effects were compared in pigs and sulfate was found to be less absorbed and associated with reduced microbial diversity [289].

Citrate salts have been well studied in a variety of contexts. Calcium citrate in particular has been explored as it may have benefits for calcium handling in biological settings [145]. It appears to become more soluble with excess citrate although the Ca activity is reduced [268]. As most of the snacks formulated here included significant citric acid, the 'citrate dissolves citrate' notion may be applicable although the effects of complexing are not known. Reduced reactivity may be a benefit however.

Citric acid appeared to improve biological activity of copper as an algeicide in the presence of bicarbonate even when derived from copper sulfate [252].

Studies have also shown that mixing copper citrate with amino acids improves solubility [245] which may be relevant here as most snacks contained many amino acid supplements.

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

6. LIMITATIONS

While the other components were mentioned as important, it needs to be reiterated that the other snack components could have affected copper handling significantly and supplementation with another diet lacking these components may not be beneficial but copper restriction may not be either. Most food ingredients interact with metals to varying degrees and this notably contained citric acid and spinach along with amino acids.

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

like cough, the resulting outcome data was very sparse and relies on memory in some cases. The lesson remains that notes and data always need to be more complete.

7. CONCLUSIONS

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

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

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

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

Concerns about excess accumulation may be due to other dietary defects and not copper content per se.

8. SUPPLEMENTAL INFORMATION

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

8.1. Computer Code

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

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

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

9. BIBLIOGRAPHY

- [1] Alireza Abdolmohammadi and Vivek R. Sharma. Copper deficiency: A forgotten disorder? *Blood*, 118, 11 2011. Available from: <http://dx.doi.org/10.1182/blood.v118.21.5275.5275>, doi:10.1182/blood.v118.21.5275.5275.
- [2] Kazuki Abe, Yoji Hori, and Takao Myoda. Volatile compounds of fresh and processed garlic (review). *Experimental and Therapeutic Medicine*, 12 2019. Available from: <https://doi.org/10.3892/etm.2019.8394>, doi:10.3892/etm.2019.8394.

- [3] Sherleen Xue-Fu Adamson, Wei Zheng, Zeynep Sena Agim, Sarah Du, Sheila Fleming, Jonathan Shannahan, and Jason Cannon. Systemic copper disorders influence the olfactory function in adult rats: Roles of altered adult neurogenesis and neurochemical imbalance. *Biomolecules*, 09 2021. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8471899/>, doi:10.3390/biom11091315.
- [4] 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.
- [5] 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.
- [6] Muhammad Zain Akhtar, Ghias Nabi Tayab, Muhammad Imran Nawaz, and Iqra Seher. Excessive dynamic airway collapse after entecavir use in a patient with pegylated interferon-induced undifferentiated connective tissue disease and entecavir use to prevent hepatitis b virus reactivation upon giving rituximab. *Cureus*. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11260405/>, doi:10.7759/cureus.62835.
- [7] 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.
- [8] 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.
- [9] Seiji Aoyagi and David H Baker. Copper-amino acid complexes are partially protected against inhibitory effects of l-cysteine and l-ascorbic acid on copper absorption in chicks. *The Journal of Nutrition*, 124, 03 1994. Available from: <http://dx.doi.org/10.1093/jn/124.3.388>, doi:10.1093/jn/124.3.388.
- [10] MIGUEL ARREDONDO, RONNY MARTÍNEZ, MARCO T NÚÑEZ, MANUEL RUZ, and MANUEL OLIVARES. Inhibition of iron and copper uptake by iron, copper and zinc. *Biological Research*, 39, 2006. Available from: <http://dx.doi.org/10.4067/s0716-97602006000100011>, doi:10.4067/s0716-97602006000100011.
- [11] Anooshah Ata and Anthony Bradshaw. Zinc supplementation-induced copper deficiency myeloneuropathy: Another relic of the covid-19 pandemic (p8-11.014). *Neurology*, 102, 04 2024. Available from: <http://dx.doi.org/10.1212/wnl.0000000000208190>, doi:10.1212/wnl.0000000000208190.
- [12] Allah Nazar Atif, Atousa Hatefi, Asadullah Arven, Alireza Foroumadi, Sara Kadkhodaei, Alireza Sadjadi, and Farideh Siavoshi. Consumption of non-antibacterial drugs may have negative impact on helicobacter pylori colonization in the stomach. *Heliyon*, 10, 03 2024. Available from: <http://dx.doi.org/10.1016/j.heliyon.2024.e27327>, doi:10.1016/j.heliyon.2024.e27327.
- [13] 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.
- [14] M.H.H. Awaad, K. M.El. Moustafa, S.A. Zoulfakar, M.S. Elhalawany, F.F. Mohammed, R.M. El-Refay, and E.A. Morsy. The role of silver nanoparticles in the reluctance of colisepticemia in broiler chickens. *Journal of Applied Poultry Research*, 30, 2021. Available from: <http://dx.doi.org/10.1016/j.japr.2021.100155>, doi:10.1016/j.japr.2021.100155.
- [15] Maria V. Babak and Dohyun Ahn. Modulation of intracellular copper levels as the mechanism of action of anti-cancer copper complexes: Clinical relevance. *Biomedicines*, 9, 2021. Available from: <http://dx.doi.org/10.3390/biomedicines9080852>, doi:10.3390/biomedicines9080852.
- [16] 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/>.
- [17] Akhilesh Kumar Bajpai, Qingqing Gu, Buyan-Ochir Orgil, Fuyi Xu, Carolina Torres-Rojas, Wenyuan Zhao, Chen Chen, Athena Starlard-Davenport, Byron Jones, Djamel Lebeche, Jeffrey A. Towbin, Enkhsaikhan Purejav, Lu Lu, and Wenjing Zhang. Cardiac copper content and its relationship with heart physiology: Insights based on quantitative genetic and functional analyses using bxd family mice. *Frontiers in Cardiovascular Medicine*, 10, 2023. Available from: <https://www.frontiersin.org/articles/10.3389/fcvm.2023.1089963>, doi:10.3389/fcvm.2023.1089963.
- [18] Carme Ballester-Servera, Judith Alonso, Manel Tauron, Noemí 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.
- [19] Spyros Batzios, Galit Tal, Andrew T DiStasio, Yanyan Peng, Christiana Charalambous, Paola Nicolaides, Erik-Jan Kamsteeg, Stanley H Korman, Hanna Mandel, Peter J Steinbach, Ling Yi, Summer R Fair, Mark E Hester, Anthi Drousiotou, and Stephen G Kaler. Newly identified disorder of copper metabolism caused by variants in *ctr1*, a high-

- affinity copper transporter. *Human molecular genetics*, pages 4121–4130, Dec 2022. Available from: <https://pubmed.ncbi.nlm.nih.gov/35913762/>, doi:10.1093/hmg/ddac156.
- [20] 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.
- [21] 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.
- [22] 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.
- [23] 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 (A_β) 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.
- [24] Angelique N. Besold, Edward M. Culbertson, and Valeria C. Culotta. The yin and yang of copper during infection. *Journal of biological inorganic chemistry : JBIC : a publication of the Society of Biological Inorganic Chemistry*, pages 137–44, 01 2016. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5535265/>, doi:10.1007/s00775-016-1335-1.
- [25] Glenda M. Bishop and Stephen R. Robinson. The amyloid paradox: Amyloidupbeta metal 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.
- [26] 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/>.
- [27] 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.
- [28] 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/>.
- [29] 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/>.
- [30] 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.
- [31] George J. Brewer. Risks of copper and iron toxicity during aging in humans. *Chemical Research in Toxicology*, 23, 02 2010. Available from: <http://dx.doi.org/10.1021/tx900338d>, doi:10.1021/tx900338d.
- [32] Rodrigo I. Bustos, Erik L. Jensen, Lina M. Ruiz, Salvador Rivera, Sebastián Ruiz, Felipe Simon, Claudia Riedel, David Ferrick, and Alvaro A. Elorza. Copper deficiency alters cell bioenergetics and induces mitochondrial fusion through upregulation of mfn2 and opal in erythropoietic cells. *Biochemical and Biophysical Research Communications*, 437, 2013. Available from: <http://dx.doi.org/10.1016/j.bbrc.2013.06.095>, doi:10.1016/j.bbrc.2013.06.095.
- [33] Linyi Cai, Xin Xiong, Xiangli Kong, and Jing Xie. The role of the lysyl oxidases in tissue repair and remodeling: A concise review. *Tissue Engineering and Regenerative Medicine*, pages 15–30, 01 2017. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6171574/>, doi:10.1007/s13770-016-0007-0.
- [34] 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.
- [35] D. J. Chakrabarti and D. E. Laughlin. The Cu-S (copper-sulfur) system. *Bulletin of Alloy Phase Diagrams*, 4, 11 1983. Available from: <https://www.contrib.andrew.cmu.edu/~dl0p/laughlin/pdf/037.pdf>, doi:10.1007/bf02868665.
- [36] 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/>.
- [37] Jadwiga UrbaUx0144[bad char vv=324]ska and Halina PodsiadUx0142[bad char vv=322]y. Interaction of niacin with copper ions. *Polyhedron*, 60, 08 2013. Available from: <http://dx.doi.org/10.1016/j.poly.2013.05.023>, doi:10.1016/j.poly.2013.05.023.
- [38] HuiJun Chen, Mieko Kimura, and Yoshinori Itokawa. Changes in iron, calcium, magnesium, copper, and zinc levels in

- different tissues of riboflavin-deficient rats. *Biological Trace Element Research*, 56(3):311–319, Mar 1997. Available from: <https://doi.org/10.1007/BF02785302>, doi:10.1007/BF02785302.
- [39] Liyun Chen, Junxia Min, and Fudi Wang. Copper homeostasis and cuproptosis in health and disease. *Signal Transduction and Targeted Therapy*, 7, 11 2022. Available from: <https://www.nature.com/articles/s41392-022-01229-y>, doi:10.1038/s41392-022-01229-y.
- [40] Qiang Chen, Shaoqin Tu, Dongxiao Tang, Jiaming Wei, Nan Wei, Hong Ai, Bu Yang, and Zheng Chen. Amyloid-peptide treatment reverses bone loss in the mandibular condyle via wnt signalling pathway. *Bone Reports*, 07 2024. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11301219/>, doi:10.1016/j.bonr.2024.101788.
- [41] Runkai Chen, Hongrui Zhang, Botao Tang, Yukun Luo, Yufei Yang, Xin Zhong, Sifei Chen, Xinjie Xu, Shengkang Huang, and Canzhao Liu. Macrophages in cardiovascular diseases: molecular mechanisms and therapeutic targets. *Signal Transduction and Targeted Therapy*, 9, 05 2024. Available from: <https://www.nature.com/articles/s41392-024-01840-1>, doi:10.1038/s41392-024-01840-1.
- [42] Xinyue Chen, Qi Cai, Ruikai Liang, Deju Zhang, Xiao Liu, Meiyi Zhang, Yan Xiong, Minxuan Xu, Qi Liu, Pengyang Li, Peng Yu, and Ao Shi. Copper homeostasis and copper-induced cell death in the pathogenesis of cardiovascular disease and therapeutic strategies. *Cell Death & Disease*, 14, 02 2023. Available from: <https://www.nature.com/articles/s41419-023-05639-w>, doi:10.1038/s41419-023-05639-w.
- [43] 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.
- [44] 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.
- [45] 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.
- [46] 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.
- [47] Pellegrino Crafa, Marilisa Franceschi, Kryssia Isabel Rodriguez-Castro, Lorella Franzoni, Michele Russo, Giovanni Brandimarte, Antonio Tursi, Massimo Rugge, and Francesco Di Mario. Ppis and gastric cancer: any causal relationship? *Acta Bio Medica : Atenei Parmensis*, 06 2023. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10308480/>, doi:10.23750/abm.v94i3.14105.
- [48] 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.
- [49] S. E. Dale, R. C. Ewan, V. C. Speer, and Dean R. Zimmerman. Copper, molybdenum and sulfate interaction in young swine. *Journal of Animal Science*, 37, 10 1973. Available from: <https://doi.org/10.2527/jas1973.374913x>, doi:10.2527/jas1973.374913x.
- [50] Ramos Danny, Mar David, Ishida Michael, Vargas Rebecca, Gaite Michaella, Montgomery Aaron, and Maria C. Linder. Mechanism of copper uptake from blood plasma ceruloplasmin by mammalian cells. *PLOS ONE*, 11(3):1–23, 03 2016. Available from: <https://doi.org/10.1371/journal.pone.0149516>, doi:10.1371/journal.pone.0149516.
- [51] Paloma Ferreira de Sousa, André Fernando de Oliveira, Antônio Alberto da Silva, and Renata Pereira Lopes. Environmental remediation processes by zero valence copper: reaction mechanisms. *Environmental Science and Pollution Research*, 26(15):14883–14903, May 2019. Available from: <https://doi.org/10.1007/s11356-019-04989-3>, doi:10.1007/s11356-019-04989-3.
- [52] James J DiNicolantonio, Dennis Mangan, and James H O’Keefe. Copper deficiency may be a leading cause of ischaemic heart disease. *Open Heart*, 5(2), 2018. Available from: <https://openheart.bmj.com/content/5/2/e000784>, arXiv:<https://openheart.bmj.com/content/5/2/e000784.full.pdf>, doi:10.1136/openhrt-2018-000784.
- [53] Qin-Yun Dong and Zhi-Ying Wu. Advance in the pathogenesis and treatment of wilson disease. *Translational Neurodegeneration*, page 23, 11 2012. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3526418/>, doi:10.1186/2047-9158-1-23.
- [54] Dani Dordevic, Jana Capikova, Simona Dordevic, Bohuslava Tremlov, Mri Gajdcs, and Ivan Kushkevych. Sulfur content in foods and beverages and its role in human and animal metabolism: A scoping review of recent studies. *Heliyon*, 04 2023. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10130226/>, doi:10.1016/j.heliyon.2023.e15452.
- [55] Andrew Duncan, Calum Yacoubian, Neil Watson, and Ian Morrison. The risk of copper deficiency in patients prescribed zinc supplements. *Journal of clinical pathology*, pages 723–5, 06 2015. Available from: <https://pubmed.ncbi.nlm.nih.gov/26085547/>, doi:10.1136/jclinpath-2014-202837.
- [56] Charmaine D. Espinosa and Hans H. Stein. Digestibility and metabolism of copper in diets for pigs and influence of dietary copper on growth performance, intestinal health, and overall immune status: a review. *Journal of Animal Science and Biotechnology*, 12, 12 2021. Available from: <http://dx.doi.org/10.1186/s40104-020-00533-3>, doi:10.1186/s40104-020-00533-3.
- [57] H. T. Jun. Evans. Copper coordination in low chalcocite and djurleite and other copper-rich sulfides. *American Mineralogist*, 66:807–818, 1981. Available from: http://www.minsocam.org/ammin/AM66/AM66_807.pdf.

- [58] Howard T. Evans. The crystal structures of low chalcocite and djurleite. *Zeitschrift für Kristallographie - Crystalline Materials*, 150, 1979. Available from: https://rruff.geo.arizona.edu/doclib/zk/vol150/ZK150_299.pdf, doi:10.1524/zkri.1979.150.14.299.
- [59] 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, Åsa 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 Hundt, Matthias Hörtenhuber, Carsten Daub, César L. Araujo, Ileana B. Quintero, Kaisa Kyöstiälä, Maria Kaukonen, Meharji Arumilli, Riika Sarviah, Jenni Puurunen, Sini Sulkama, Sini Karjalainen, Antti Sukura, Pernilla Syrjä, Niina Airas, Henna Pekkarinen, Ilona Kareinen, Hanna-Maria Javela, Anna Knuutila, 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.
- [60] Sajjad Fatahi and Seyyed Morteza Hoseini. Effect of dietary tryptophan and betaine on tolerance of caspian roach (*rutilus rutilus caspicus*) to copper toxicity. *International Journal of Aquatic Biology*, 1(2):76–81, May 2013. Available from: <https://ij-aquaticbiology.com/index.php/ijab/article/view/29>, doi:10.22034/ijab.v1i2.29.
- [61] 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/>.
- [62] E Fedele. Anti-amyloid therapies for alzheimer's disease and the amyloid cascade hypothesis. *International journal of molecular sciences*, 24(19), 2023. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC10578107/>.
- [63] C K Fenger and C W Kohn. Tracheal obstruction from tracheal collapse associated with pneumonia in a horse. *Journal of the American Veterinary Medical Association*, pages 1698–700, Jun 1992. Available from: <https://pubmed.ncbi.nlm.nih.gov/1624350/>.
- [64] M Fields, C G Lewis, and M D Lure. Garlic oil extract ameliorates the severity of copper deficiency. *Journal of the American College of Nutrition*, 11, 06 1992. Available from: <https://doi.org/10.1080/07315724.1992.10718235>, doi:10.1080/07315724.1992.10718235.
- [65] H. Fieten, B.D. HooijerNouwens, V.C. Biourge, P.A.J. Leegwater, A.L. Watson, T.S.G.A.M. van den Ingh, and J. Rothuizen. Association of dietary copper and zinc levels with hepatic copper and zinc concentration in labrador retrievers. *Journal of Veterinary Internal Medicine*, 26, 2012. Available from: <http://dx.doi.org/10.1111/j.1939-1676.2012.01001.x>, doi:10.1111/j.1939-1676.2012.01001.x.
- [66] T. Fong, R. Vij, A. Vijayan, J. DiPersio, and M. Blinder. Copper deficiency: an important consideration in the differential diagnosis of myelodysplastic syndrome. *Haematologica*, 92, 10 2007. Available from: <http://dx.doi.org/10.3324/haematol.11314>, doi:10.3324/haematol.11314.
- [67] Zola Francis, George Book, Cara Litvin, and Benjamin Kalivas. The covid-19 pandemic and zinc-induced copper deficiency: An important link. *The American Journal of Medicine*, pages e290–1, 04 2022. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8970610/>, doi:10.1016/j.amjmed.2022.03.008.
- [68] Daniel E. Freedberg, Benjamin Lebwohl, and Julian A. Abrams. The impact of proton pump inhibitors on the human gastrointestinal microbiome. *Clinics in laboratory medicine*, pages 771–85, 09 2014. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4254461/>, doi:10.1016/j.cll.2014.08.008.
- [69] 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.
- [70] Hirohisa Fujikawa and Junji Haruta. Copper deficiency: An overlooked diagnosis. *Cureus*. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10733163/>, doi:10.7759/cureus.49139.
- [71] Mohammed D Gani, Vanessa C Rogers, Khalid H Sachak, and Joseph K Marzouk. Flat trachea syndrome: a rare condition with symptoms similar to obstructive airway disease. *BMJ Case Reports*, 02 2015. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4342702/>, doi:10.1136/bcr-2014-207063.
- [72] Douglas Ganini, Donatella Canistro, JinJie Jang, Krisztian Stadler, Ronald P. Mason, and Maria B. Kadiiska. Ceruloplasmin (ferroxidase) oxidizes hydroxylamine probes: deceptive implications for free radical detection. *Free radical biology & medicine*, pages 1514–21, 07 2012. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3448871/>, doi:10.1016/j.freeradbiomed.2012.07.013.
- [73] Erika Garay, Nils Schuth, Alessandra Barbanente, Carlos Tejeda-Guzmán, Daniele Vitone, Beatriz Osorio, Adam H. Clark, Maarten Nachtegaal, Michael Haumann, Holger Dau, Alberto Vela, Fabio Arnesano, Liliana Quintanar, and Fanis Missirlis. Tryptophan regulates *drosophilazinc* stores. *Proceedings of the National Academy of Sciences*, 119, 04 2022. Available from: <http://dx.doi.org/10.1073/pnas.2117807119>, doi:10.1073/pnas.2117807119.
- [74] T A Garrow, M S Clegg, G Metzler, and C L Keen. Influence of hypertension and dietary copper on indexes of copper status in rats. *Hypertension*, 17, 1991. Available from: <http://dx.doi.org/10.1161/01.hyp.17.6.793>, doi:10.1161/01.hyp.17.6.793.
- [75] Panos G Georgopoulos, Sheng Wei Wang, Ioannis G Georgopoulos, Mary Jean Yonone-Lioy, and Paul J Lioy. Assessment of human exposure to copper: A case study using the nhexas database. *Journal of Exposure Science & Environmental Epidemiology*, 16, 2006. Available from: <https://www.nature.com/articles/7500462>, doi:10.1038/sj.jea.7500462.
- [76] 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.
- [77] Natalia Giurgea, Mihaela Ioana Constantinescu, Ramona Stanciu, Soimita Suci, and Adriana Muresan. Ceruloplasmin - acute-phase reactant or endogenous antioxidant? the case of cardiovascular disease. *Medical science monitor : international medical journal of experimental and clinical research*, pages RA48–51, Feb 2005. Available from: <https://pubmed.ncbi.nlm.nih.gov/15668644/>.
- [78] Helly R. Goez, Francois D. Jacob, Robert D. Fealey, Marc C. Patterson, Vijay Ramaswamy, Rabin Persad, Edward S. Johnson, and Jerome Y. Yager. An unusual presentation of copper metabolism disorder and a possible connection with niemann-pick type c. *Journal of Child Neurology*, 26, 2011. Available from: <http://dx.doi.org/10.1177/0883073810383983>, doi:10.1177/0883073810383983.
- [79] Siew Wei Goh, Alan N. Buckley, Robert N. Lamb, Richard A. Rosenberg, and Damian Moran. The oxidation states of copper and iron in mineral sulfides, and the oxides formed on initial exposure of chalcopyrite and bornite to air. *Geochimica et Cosmochimica Acta*, 70, 05 2006. Available from: <http://dx.doi.org/10.1016/j.gca.2006.02.007>, doi:10.1016/j.gca.2006.02.007.
- [80] Ernst Graf. Copper(ii) ascorbate: A novel food preservation system. *Journal of Agricultural and Food Chemistry*, 42, 1994. Available from: <http://dx.doi.org/10.1021/jf00044a006>, doi:10.1021/jf00044a006.
- [81] Louise F. Gray and Louise J. Daniel. Effect of copper status on the urinary excretion of tryptophan metabolites and amino acids by the rat. *The Journal of Nutrition*, 103, 12 1973. Available from: <http://dx.doi.org/10.1093/jn/103.12.1764>, doi:10.1093/jn/103.12.1764.
- [82] Jung-Heun Ha, Caglar Doguer, and James F. Collins. Consumption of a high-iron diet disrupts homeostatic regulation of intestinal copper absorption in adolescent mice. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, 313, 10 2017. Available from: <http://dx.doi.org/10.1152/ajpgi.00169.2017>, doi:10.1152/ajpgi.00169.2017.
- [83] Iqbal Hamza and Jonathan D Gitlin. Hepatic copper transport. *Landes Bioscience*, 2013. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK6381/>.
- [84] 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/>.
- [85] F Harrison, AEL Roberts, R Gabrilksa, 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/>.
- [86] Linda J. Harvey and Harry J. McArdle. Biomarkers of copper status: a brief update. *British Journal of Nutrition*, 99, 2008. Available from: <http://dx.doi.org/10.1017/s0007114508006806>, doi:10.1017/s0007114508006806.
- [87] Nesrin M. Hasan and Svetlana Lutsenko. Regulation of copper transporters in human cells. *Current topics in membranes*, pages 137–61, 2012. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6365104/>, doi:10.1016/B978-0-12-394390-3.00006-9.
- [88] Yuta Hatori, Sachie 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.
- [89] 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.
- [90] 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/>.
- [91] 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/>.
- [92] 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.
- [93] 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.
- [94] O. Herreros and J. Viñals. Leaching of sulfide copper ore in a nacl-h₂so₄-o₂ media with acid pre-treatment. *Hydrometallurgy*, 89, 12 2007. Available from: <http://dx.doi.org/10.1016/j.hydromet.2007.07.011>, doi:10.1016/j.hydromet.2007.07.011.
- [95] C.H. Hill, B. Starcher, and G. Matrone. Mercury and silver interrelationships with copper. *The Journal of Nutrition*, 83, 1964. Available from: <http://dx.doi.org/10.1093/jn/83.2.107>, doi:10.1093/jn/83.2.107.
- [96] 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.
- [97] Victoria Hodgkinson and Michael J. Petris. Copper homeostasis at the host-pathogen interface*. *The Journal of Biological Chemistry*, pages 13549–55, 03 2012. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3340201/>, doi:10.1074/jbc.R111.316406.
- [98] Rebecca L. Holme, James J. Miller, Kay Nicholson, and Daisy Sahoo. Tryptophan 415 is critical for the cholesterol transport functions of scavenger receptor bi. *Biochemistry*, 55, 01 2016. Available from: <http://dx.doi.org/10.1021/acs.biochem.5b00804>, doi:10.1021/acs.biochem.5b00804.
- [99] R Horvath, P Freisinger, R Rubio, T Merl, R Bax, JA Mayr, Shawan, J Muller-Hocker, D Pongratz, LB Moller, N Horn, and M Jakob. 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/>.
- [100] 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.
- [101] Seyyed Morteza Hoseini, Amalia Pérez Jiménez, Benjamin Costas, Rita Azeredo, and Manuel Gesto. Physiological roles of tryptophan in teleosts: current knowledge and perspectives for future studies. *Reviews in Aquaculture*, 11, 02 2019. Available from: <http://dx.doi.org/10.1111/raq.12223>, doi:10.1111/raq.12223.
- [102] Md Selim Hossain, Archita Das, Ashiq M Rafiq, Ferenc Deak, Zsolt Bagi, Rashelle Outlaw, Varadarajan Sudhahar, Mai Yamamoto, Jack H Kaplan, Masuko Ushio-Fukai, and Tohru Fukai. Altered copper transport in oxidative stress-dependent brain endothelial barrier dysfunction associated with alzheimer's disease. *Vascular pharmacology*, page 107433, 09 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39317307/>, doi:10.1016/j.vph.2024.107433.
- [103] William Jr Hughes, Walter E Rodriguez, Dorothea Rosenberger, Jing Chen, Utpal Sen, Neetu Tyagi, Karni S Moshal, Thomas Vacek, Y James Kang, and Suresh C Tyagi. Role of copper and homocysteine in pressure overload heart failure. *Cardiovascular toxicology*, pages 137–44, Fall 2008. Available from: <https://pubmed.ncbi.nlm.nih.gov/18679830/>, doi:10.1007/s12012-008-9021-3.
- [104] D F Hwang, L C Wang, and H M Cheng. Effect of taurine on toxicity of copper in rats. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association*, pages 239–44, Mar 1998. Available from: <https://pubmed.ncbi.nlm.nih.gov/9609396/>, doi:10.1016/s0278-6915(97)00146-4.
- [105] Erzsebet Illes, Amir Mizrahi, Vered Marks, and Dan Meyerstein. Carbonate-radical-anions, and not hydroxyl radicals, are the products of the fenton reaction in neutral solutions containing bicarbonate. *Free radical biology & medicine*, pages 1–6, 11 2018. Available from: <https://pubmed.ncbi.nlm.nih.gov/30458276/>, doi:10.1016/j.freeradbiomed.2018.11.015.
- [106] Sachin Jain, Vidhi Gautam, and Sania Naseem. Acute-phase proteins: As diagnostic tool. *Journal of Pharmacy and Bioallied Sciences*, pages 118–27, Jan-Mar 2011. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3053509/>, doi:10.4103/0975-7406.76489.
- [107] Thunder Jalili, Denis M. Medeiros, and Robert E.C. Wildman. Aspects of cardiomyopathy are exacerbated by elevated dietary fat in copper-restricted rats. *The Journal of Nutrition*, 126, 1996. Available from: <http://dx.doi.org/10.1093/jn/126.4.807>, doi:10.1093/jn/126.4.807.
- [108] M M Jazzar and I Naseem. Genotoxicity of photoilluminated riboflavin in the presence of cu(ii). *Free radical biology & medicine*, pages 7–14, 1996. Available from: <https://pubmed.ncbi.nlm.nih.gov/8791088/>, doi:10.1016/0891-5849(95)02156-6.
- [109] 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.
- [110] 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.
- [111] Shujing Jin, Xun Qi, Bin Zhang, Ziqing Sun, Bingchun Zhang, Hui Yang, Tongmin Wang, Bo Zheng, Xingang Wang, Qiuping Shi, Ming Chen, Ling Ren, Ke Yang, and Hongshan Zhong. Evaluation of promoting effect of a novel cu-bearing metal stent on endothelialization process from in vitro and in vivo studies. *Scientific Reports*, 7, 12 2017. Available from: <https://www.nature.com/articles/s41598-017-17737-9>, doi:10.1038/s41598-017-17737-9.
- [112] Mary Ann Johnson and Cynthia Lee Murphy. *Effect of High Dietary Iron and Ascorbic Acid on Copper and Iron Utilization during Copper Deficiency*, pages 545–546. Springer US, Boston, MA, 1988. Available from: https://doi.org/10.1007/978-1-4613-0723-5_194, doi:10.1007/978-1-4613-0723-5_194.
- [113] Michael D. L. Johnson, Thomas E. Kehl-Fie, Roger Klein, Jacqueline Kelly, Corinna Burnham, Beth Mann, and Jason W. Rosch. Role of copper efflux in pneumococcal pathogenesis and resistance to macrophage-mediated immune clearance. *Infection and Immunity*, 83, 2015. Available from: <http://dx.doi.org/10.1128/iai.03015-14>, doi:10.1128/iai.03015-14.
- [114] Sumanta Kar, Samarpita Sen, Saptarshi Maji, Deepashri Saraf, Ruturaj, Rupam Paul, Sohini Dutt, Basudeb Mondal, Enrique Rodriguez-Boulan, Ryan Schreiner, Durba Sengupta, and Arnab Gupta. Copper(ii) import and reduction are dependent on his-met clusters in the extracellular amino terminus of human copper transporter-1. *Journal of Biological Chemistry*, 298, 03 2022. Available from: <http://dx.doi.org/10.1016/j.jbc.2022.101631>, doi:10.1016/j.jbc.2022.101631.
- [115] A.B. KASHANI, H. SAMIE, R.J. EMERICK, and C.W. CARLSON. Effect of copper with three levels of sulfur containing amino acids in diets for turkeys. *Poultry Science*, 65, 09 1986. Available from: <http://dx.doi.org/10.3382/ps.0651754>,

- doi:10.3382/ps.0651754.
- [116] Tetsuyuki KATAYAMA, Junko HAYASHI, Masato KISHIDA, and Norihisa KATO. Effects of dietary excess amino acids on the concentrations of cholesterol, α-tocopherol, ascorbic acid, and copper in serum and tissues of rats. *Journal of Nutritional Science and Vitaminology*, 36(5):485–495, 1990. Available from: https://www.jstage.jst.go.jp/article/jnsv1973/36/5/36_5_485/_article/-char/ja/, doi:10.3177/jnsv.36.485.
- [117] Louise Kelly, Matthew Macgregor Sharp, Isabelle Thomas, Christopher Brown, Matthew Schrag, Lissa Ventura Antunes, Elena Solopova, José Martinez-Gonzalez, Cristina Rodríguez, and Roxana Octavia Carare. Targeting lysyl-oxidase (lox) may facilitate intramural periarterial drainage for the treatment of alzheimer's disease. *Cerebral Circulation - Cognition and Behavior*, 5, 2023. Available from: <http://dx.doi.org/10.1016/j.cccb.2023.100171>, doi:10.1016/j.cccb.2023.100171.
- [118] B. G. Kim, D. Y. Kil, D. C. Mahan, G. M. Hill, and H. H. Stein. Effects of dietary sulfur and distillers dried grains with solubles on carcass characteristics, loin quality, and tissue concentrations of sulfur, selenium, and copper in growing-finishing pigs1. *Journal of Animal Science*, 92, 10 2014. Available from: <https://doi.org/10.2527/jas.2013-6323>, doi:10.2527/jas.2013-6323.
- [119] 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.
- [120] Kwan-Woo Kim, Jin-Soo Jeong, Kay-Hyeok An, and Byung-Joo Kim. A study on the microstructural changes and mechanical behaviors of carbon fibers induced by optimized electrochemical etching. *Composites Part B: Engineering*, 165, 05 2019. Available from: <http://dx.doi.org/10.1016/j.compositesb.2019.02.055>, doi:10.1016/j.compositesb.2019.02.055.
- [121] Yoon Jae Kim, Jeong Sang Lee, Kyung Sook Hong, Jun Won Chung, Ju Hyun Kim, and Ki Baik Hahm. Novel application of proton pump inhibitor for the prevention of colitis-induced colorectal carcinogenesis beyond acid suppression. *Cancer Prevention Research*, 3. Available from: <http://dx.doi.org/10.1158/1940-6207.capr-10-0033>, doi:10.1158/1940-6207.capr-10-0033.
- [122] Leslie M. Klevay. Metabolic interactions among dietary cholesterol, copper, and fructose. *American Journal of Physiology-Endocrinology and Metabolism*, 298, 01 2010. Available from: <https://doi.org/10.1152/ajpendo.00591.2009>, doi:10.1152/ajpendo.00591.2009.
- [123] 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.
- [124] VH Konjuufca, GM Pesti, and RI Bakalli. Modulation of cholesterol levels in broiler meat by dietary garlic and copper. *Poultry Science*, 76, 09 1997. Available from: <https://doi.org/10.1093/ps/76.9.1264>, doi:10.1093/ps/76.9.1264.
- [125] Ewelina Król, Monika Okulicz, and Justyna Kupsz. The influence of taurine supplementation on serum and tissular fe, zn and cu levels in normal and diet-induced insulin-resistant rats. *Biological Trace Element Research*, 198(2):592–601, Dec 2020. Available from: <https://doi.org/10.1007/s12011-020-02100-3>, doi:10.1007/s12011-020-02100-3.
- [126] Hedwig S. Kruijtwagen and Louis C. Penning. Preclinical models of wilsons disease, why dogs are catchy alternatives. *Annals of Translational Medicine*, Apr 2019. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6531654/>, doi:10.21037/atm.2019.02.06.
- [127] Meena Kumari and Kalpana Patel. Effect of sulfur-containing spices on the bioaccessibility of trace minerals from selected cereals and pulses. *Journal of the Science of Food and Agriculture*, pages n/a–n/a, 2016. JSFA-16-2048.R1. Available from: <http://dx.doi.org/10.1002/jsfa.8113>, doi:10.1002/jsfa.8113.
- [128] Yien-Ming Kuo, Bing Zhou, Dominique Cosco, and Jane Gitschier. The copper transporter ctr1 provides an essential function in mammalian embryonic development. *Proceedings of the National Academy of Sciences of the United States of America*, pages 6836–41, Jun 2001. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC34439/>, doi:10.1073/pnas.111057298.
- [129] Jagoda KUx0119[bad char vv=281]piUx0144[bad char vv=324]ska Pacelik, Wioletta Biel, Robert Witkowicz, and Cezary PodsiadUx0142[bad char vv=322]o. Mineral and heavy metal content in dry dog foods with different main animal components. *Scientific Reports*, 13, 04 2023. Available from: <https://www.nature.com/articles/s41598-023-33224-w>, doi:10.1038/s41598-023-33224-w.
- [130] Erik Ladomersky and Michael J Petris. Copper tolerance and virulence in bacteria. *Metalomics*, 7(6):957–964, 01 2015. Available from: <https://doi.org/10.1039/c4mt00327f>, arXiv:<https://academic.oup.com/metalomics/article-pdf/7/6/957/34785053/c4mt00327f.pdf>, doi:10.1039/c4mt00327f.
- [131] Luke Lear, Dan Padfield, Elze Hesse, Suzanne Kay, Angus Buckling, and Michiel Vos. Copper reduces the virulence of bacterial communities at environmentally relevant concentrations. *Environment International*, 182, 2023. Available from: <http://dx.doi.org/10.1016/j.envint.2023.108295>, doi:10.1016/j.envint.2023.108295.
- [132] D.R. LEDOUX, R.D. MILES, C.B. AMMERMAN, and R.H. HARMS. Interaction of dietary nutrient concentration and supplemental copper on chick performance and tissue copper concentrations. *Poultry Science*, 66, 08 1987. Available from: <https://doi.org/10.3382/ps.0661379>, doi:10.3382/ps.0661379.
- [133] Jaekwon Lee, Joseph R. Prohaska, and Dennis J. Thiele. Essential role for mammalian copper transporter ctr1 in copper homeostasis and embryonic development. *Proceedings of the National Academy of Sciences*, 98, 06 2001. Available from: <http://dx.doi.org/10.1073/pnas.111058698>, doi:10.1073/pnas.111058698.
- [134] Jennifer K. Lee, Jung-Heun Ha, and James F. Collins. Dietary iron intake in excess of requirements impairs intestinal copper absorption in sprague dawley rat dams, causing copper deficiency in suckling pups. *Biomedicines*, 9, 2021. Available

- from: <http://dx.doi.org/10.3390/biomedicines9040338>, doi:10.3390/biomedicines9040338.
- [135] Jeosoon Lee, Sookyung Yun, Inhyung Lee, Mincheol Choi, and Junghee Yoon. Fluoroscopic characteristics of tracheal collapse and cervical lung herniation in dogs: 222 cases (20122015). *Journal of Veterinary Science*, pages 499–505, 12 2017. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5746443/>, doi:10.4142/jvs.2017.18.4.499.
- [136] S. A. Lee, J. Dunne, T. Mottram, and M. R. Bedford. Effect of diet phase change, dietary ca and p level and phytase on bird performance and real-time gizzard ph measurements. *British Poultry Science*, 58, 05 2017. Available from: <https://doi.org/10.1080/00071668.2017.1293799>, doi:10.1080/00071668.2017.1293799.
- [137] S. Leeson. Copper metabolism and dietary needs. *World's Poultry Science Journal*, 65, 09 2009. Available from: <https://doi.org/10.1017/s0043933909000269>, doi:10.1017/s0043933909000269.
- [138] G J Leyer and E A Johnson. Repression of toxin production by tryptophan in clostridium botulinum type e. *Archives of microbiology*, pages 443–7, 1990. Available from: <https://pubmed.ncbi.nlm.nih.gov/2256780/>, doi:10.1007/BF00245225.
- [139] Hualin Li, Lijun Zhao, Tao Wang, and Y James Kang. Dietary cholesterol supplements disturb copper homeostasis in multiple organs in rabbits: Aorta copper concentrations negatively correlate with the severity of atherosclerotic lesions. *Biological trace element research*, pages 164–171, 03 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/33661473/>, doi:10.1007/s12011-021-02618-0.
- [140] 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.
- [141] Weiping Lin, Liangliang Xu, and Gang Li. Molecular insights into lysyl oxidases in cartilage regeneration and rejuvenation. *Frontiers in Bioengineering and Biotechnology*, 04 2020. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7204390/>, doi:10.3389/fbioe.2020.00359.
- [142] Changsong Liu, Yanfen Liao, Zongyuan Zhu, Lili Yang, Qin Zhang, and Li Li. The association between serum copper concentrations and elevated blood pressure in us children and adolescents: National health and nutrition examination survey 2011-2016. *BMC Cardiovascular Disorders*, 21, 2021. Available from: <https://doi.org/10.1186/s12872-021-01880-3>, doi:10.1186/s12872-021-01880-3.
- [143] Huiruo Liu, Zeyu Yang, Hourong Sun, Zerui Wang, Feng Xu, Yuguo Chen, and Chuanbao Li. Iron deficiency promotes intra-leaflet haemorrhage-induced aortic valve calcification: an experimental study. *International journal of surgery (London, England)*, 12 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39728514/>, doi:10.1097/JSS.0000000000002208.
- [144] 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.
- [145] Xiao-Chen Liu and Leif H. Skibsted. Citrate in calcium transport and biominerallisation. *International Dairy Journal*, 139, 04 2023. Available from: <https://doi.org/10.1016/j.idairyj.2022.105561>, doi:10.1016/j.idairyj.2022.105561.
- [146] 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.
- [147] Zhidong Liu, Miao Wang, Chunbo Zhang, Shigao Zhou, and Guang Ji. Molecular functions of ceruloplasmin in metabolic disease pathology. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, pages 695–711, 03 2022. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8901420/>, doi:10.2147/DMSO.S346648.
- [148] Marta López-Alonso and Marta Miranda. Copper supplementation, a challenge in cattle. *Animals*, 10, 10 2020. Available from: <https://doi.org/10.3390/ani10101890>, doi:10.3390/ani10101890.
- [149] Mark A. Lovell, Chongsong Xie, and William R. Markesberry. Protection against amyloid beta peptide toxicity by zinc. *Brain Research*, 823, 1999. Available from: [http://dx.doi.org/10.1016/s0006-8993\(99\)01114-2](http://dx.doi.org/10.1016/s0006-8993(99)01114-2), doi:10.1016/s0006-8993(99)01114-2.
- [150] Marta Lpez-Alonso and Marta Miranda. Copper supplementation, a challenge in cattle. *Animals : an Open Access Journal from MDPI*, 10 2020. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7602799/>, doi:10.3390/ani10101890.
- [151] Henry C. Lukaski, Clinton B. Hall, and Martin J. Marchello. Body temperature and thyroid hormone metabolism of copper-deficient rats. *The Journal of Nutritional Biochemistry*, 6, 1995. Available from: [http://dx.doi.org/10.1016/0955-2863\(95\)00062-5](http://dx.doi.org/10.1016/0955-2863(95)00062-5), doi:10.1016/0955-2863(95)00062-5.
- [152] Yu Luo, Robert J Lovelett, J Vincent Price, Devesh Radhakrishnan, Kristopher Barnthouse, Ping Hu, Eugene Schaefer, John Cunningham, Kelvin H Lee, Raghunath B Shivappa, and Babatunde A Ogunnaike. Modeling the effect of amino acids and copper on monoclonal antibody productivity and glycosylation: A modular approach. *Biotechnology journal*, page e2000261, 09 2020. Available from: <https://pubmed.ncbi.nlm.nih.gov/32875683/>, doi:10.1002/biot.202000261.
- [153] Naina Pakkir Maideen. Adverse effects associated with long-term use of proton pump inhibitors. *Chonnam Medical Journal*, pages 115–27, 05 2023. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10248387/>, doi:10.4068/cmj.2023.59.2.115.
- [154] Didier Malamba-Lez, Désiré Tshala-Katumbay, Virginie Bito, Jean-Michel Rigo, Richie Kipenge Kyandabike, Eric Ngoy Yolola, Philippe Katchunga, Béatrice Koba-Bora, and Dophra Ngoy-Nkulu. Concurrent heavy metal exposures and idiopathic dilated cardiomyopathy: A case-control study from the katanga mining area of the democratic republic of congo. *International Journal of Environmental Research and Public Health*, 18, 2021. Available from: <http://dx.doi.org/10.3390/ijerph18094956>, doi:10.3390/ijerph18094956.
- [155] Alain Manceau and Anthony Matynia. The nature of cu bonding to natural organic matter. *Geochimica et Cosmochimica Acta*, 74, 05 2010. Available from: <https://doi.org/10.1016/j.gca.2010.01.027>, doi:10.1016/j.gca.2010.01.027.

- [156] Pravat K Mandal, Joseph C Maroon, Avantika Samkaria, Yashika Arora, Shallu Sharma, and Ashutosh Pandey. Iron chelators and alzheimer's disease clinical trials. *Journal of Alzheimer's disease : JAD*, 07 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39031369/>, doi:10.3233/JAD-240605.
- [157] Mike J Marchywka. The paradox paradigm: When could amino acid supplements be beneficial? techreport MJM-2021-015, not institutionalized, independent, 306 Charles Cox , Canton GA 30115, 12 2021. Available from: https://www.researchgate.net/publication/357250784_The_Paradox_Paradigm_When_Could_Amino_Acid_Supplements_Be_Beneficial.
- [158] Mike J Marchywka. Update to covid-19 age distribution notes. Technical Report MJM-2021-007, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, 8 2021. Version .1, may change significantly if less than 1.00. Available from: https://www.researchgate.net/publication/353946686_Draft_table_comparing_expectations_to_recent_results_with_covid-19.
- [159] Mike J Marchywka. Experiences with a family of science based kitchen snacks for dogs. techreport MJM-2021-018, not institutionalized, independent, 306 Charles Cox , Canton GA 30115, 1 2022. Available from: https://www.researchgate.net/publication/357517852_Experiences_with_a_Family_of_Science_Based_Kitchen_Snacks_for_Dogs.
- [160] Mike J Marchywka. Happy again : Possible canine riboflavin deficiency. techreport MJM-2022-009, not institutionalized, independent, 306 Charles Cox , Canton GA 30115, 3 2022. Available from: https://www.researchgate.net/publication/359504498_Happy_Again_Possible_Canine_Riboflavin_Deficiency.
- [161] Mike J Marchywka. Vitamin d: Towards a conflict resolving hypothesis. techreport MJM-2022-010, not institutionalized, independent, 306 Charles Cox , Canton GA 30115, 7 2022. Available from: https://www.researchgate.net/publication/362303875_Vitamin_D_Towards_A_Conflict_Resolving_Hypothesis, doi:10.5281/zenodo.6922402.
- [162] M.J. Marchywka. On the age distribution of sars-cov-2 patients. Technical Report MJM-2020-002-0.10, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, 7 2020. Version 0.10 , may change significantly if less than 1.00. Available from: <https://www.linkedin.com/posts/marchywka-notes-on-aging-as-it-relates-to-covid19-activity-6684083706170265601-JMnN>.
- [163] M.J. Marchywka. Supplement history for a senior hypothyroid chihuahua. Technical Report MJM-2020-007, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, 12 2020. Version 0.50 , may change significantly if less than 1.00. Available from: https://www.researchgate.net/publication/355493547_Supplement_History_for_a_Senior_Hypothyroid_Chihuahua.
- [164] M.J. Marchywka. Canine heartworm treated with doxycycline, ivermectin and various supplements. Technical Report MJM-2019-001, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, March 2021. May be recycled in appropriate media. Available from: <https://www.linkedin.com/posts/marchywka-happyheart-activity-6781666969885167616--HfQ>.
- [165] 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.
- [166] M.J. Marchywka. Muqed: a multi-use quantitative event diary for dog diet analysis. Technical Report MJM-2020-004, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, April 2021. May be recycled in appropriate media. Available from: https://www.researchgate.net/publication/350636753_MUQED_a_Multi-Use_Quantitative_Event_Diary_For_Dog_Diet_Analysis.
- [167] M.J. Marchywka. Supplement usage including vitamin k by a heartworm positive pregnant pit bull and her puppies. Technical Report MJM-2021-003, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, 05 2021. Version 0.50 , may change significantly if less than 1.00. Available from: https://www.researchgate.net/publication/354924460_Supplement_Usage_Including_Vitamin_K_by_a_Heartworm_Positive_Pregnant_Pit_Bull_and_Her_Puppies.
- [168] Elizabeth A. Marcus and David R. Scott. *Gastric Colonization by H. pylori*, pages 25–37. Springer Nature Singapore, Singapore, 2023. Available from: https://doi.org/10.1007/978-981-97-0013-4_2, doi:10.1007/978-981-97-0013-4_2.
- [169] 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/>.
- [170] Edward B. Maryon, Shannon A. Molloy, Kristin Ivy, Huijun Yu, and Jack H. Kaplan. Rate and regulation of copper transport by human copper transporter 1 (hctr1)*. *The Journal of Biological Chemistry*, pages 18035–46, 05 2013. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3689948/>, doi:10.1074/jbc.M112.442426.
- [171] Shashank Masaldan, Sharneil 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.
- [172] Mary S. Matsui, Michael J. Petris, Yoko Niki, Nevena Karaman-Jurukovska, Neelam Muizzuddin, Masamitsu Ichihashi, and Daniel B. Yarosh. Omeprazole, a gastric proton pump inhibitor, inhibits melanogenesis by blocking atp7a trafficking. *Journal of Investigative Dermatology*, 135, 03 2015. Available from: <http://dx.doi.org/10.1038/jid.2014.461>, doi:10.1038/jid.2014.461.
- [173] Sydney R McCauley, Stephanie D Clark, Bradley W Quest, Renee M Streeter, and Eva M Oxford. Review of canine dilated cardiomyopathy in the wake of diet-associated concerns. *Journal of Animal Science*, 98(6):skaa155, 06 2020.

- Available from: <https://doi.org/10.1093/jas/skaa155>, arXiv:<https://academic.oup.com/jas/article-pdf/98/6/skaa155/33683311/skaa155.pdf>, doi:10.1093/jas/skaa155.
- [174] William Douglas McFarlane, Hugh Lehman Fulmer, and Thomas Hughes Jukes. Studies in embryonic mortality in the chick: The effect of diet upon the nitrogen, amino-nitrogen, tyrosine, tryptophan, cystine and iron content of the proteins and on the total copper of the hen's egg. *Biochemical Journal*, pages 1611–31, 1930. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1254774/pdf/biochemj01123-0023.pdf>.
- [175] Catherine C. McGowan, Timothy L. Cover, and Martin J. Blaser. The proton pump inhibitor omeprazole inhibits acid survival of helicobacter pylori by a urease-independent mechanism. *Gastroenterology*, 107, 11 1994. Available from: [http://dx.doi.org/10.1016/0016-5085\(94\)90582-7](http://dx.doi.org/10.1016/0016-5085(94)90582-7), doi:10.1016/0016-5085(94)90582-7.
- [176] Kathryn A. McGurk, Melpomeni Kasapi, and James S. Ware. Effect of taurine administration on symptoms, severity, or clinical outcome of dilated cardiomyopathy and heart failure in humans: a systematic review. *Wellcome Open Research*, 07 2022. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9257265/>, doi:10.12688/wellcomeopenres.17505.3.
- [177] D. M. Medeiros, J. Davidson, and J. E. Jenkins. A unified perspective on copper deficiency and cardiomyopathy. *Experimental Biology and Medicine*, 203, 07 1993. Available from: <http://dx.doi.org/10.3181/00379727-203-43599>, doi:10.3181/00379727-203-43599.
- [178] 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.
- [179] Raktham Mektrirat, Thareerat Rueangsri, Waraporn Keeratichandacha, Sasiwimon Soonsawat, Chavalit Boonyapakorn, and Wanpitak Pongkan. Polyunsaturated fatty acid eab-277 supplementation improved heart rate variability and clinical signs in tracheal collapse dogs. *Frontiers in Veterinary Science*, 07 2022. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9330478/>, doi:10.3389/fvets.2022.880952.
- [180] Jin-Hong Min, Heela Sarlus, and Robert A Harris. Mad-microbial (origin of) alzheimer's disease hypothesis: from infection and the antimicrobial response to disruption of key copper-based systems. *Frontiers in neuroscience*, page 1467333, 10 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39416952/>, doi:10.3389/fnins.2024.1467333.
- [181] 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.
- [182] 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.
- [183] R. F. Morgan and B. L. O'Dell. Effect of copper deficiency on the concentrations of catecholamines and related enzyme activities in the rat BRAIN¹. *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.
- [184] A Mudher and S Lovestone. Alzheimer's disease-do tauists and baptists finally shake hands? *Trends in neurosciences*, 25(1):22–6, 2002. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/articles/11801334/>.
- [185] 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: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4803712/>.
- [186] Mitsutoshi Munakata, Osamu Sakamoto, Taro Kitamura, Mamiko Ishitobi, Hiroyuki Yokoyama, Kazuhiro Haginoya, Noriko Togashi, Hajime Tamura, Shuichi Higano, Shoki Takahashi, Toshihiro Ohura, Yasuko Kobayashi, Akira Onuma, and Kazuie Iinuma. The effects of copper-histidine therapy on brain metabolism in a patient with menkes disease: a proton magnetic resonance spectroscopic study. *Brain and Development*, 27, 2005. Available from: <http://dx.doi.org/10.1016/j.braindev.2004.08.002>, doi:10.1016/j.braindev.2004.08.002.
- [187] Izumi NAKAI, Mihoko IZAWA, Yoshinori SUGITANI, Yoshio NIWA, and Kozo NAGASHIMA. X-ray photoelectron spectroscopic study of copper minerals. *Mineralogical Journal*, 8(2):135–138, 1976. Available from: https://www.jstage.jst.go.jp/article/minerj/8/2/8_2_135/_pdf, doi:10.2465/minerj.8.135.
- [188] I Naseem, M S Ahmed, R Bhat, and S M Hadi. Cu(ii)-dependent degradation of dna by riboflavin. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association*, pages 589–97, Aug 1993. Available from: <https://pubmed.ncbi.nlm.nih.gov/8349205/>, doi:10.1016/0278-6915(93)90209-h.
- [189] Ethan A. Natelson, Kelty R. Baker, and David W. Pyatt. Anemia and leukopenia following intravenous colloidal silver infusionsclinical and hematological features, unique peripheral blood film appearance and effective therapy with supplemental oral copper and apheresis. *Clinical Case Reports*, 7, 2019. Available from: <http://dx.doi.org/10.1002/ccr3.2316>, doi:10.1002/ccr3.2316.
- [190] New Hope Network. Top 100 supplements by 2023 u.s. sales. *Top 100 Supplements by 2023 U.S. Sales*. Available from: <https://store.newhope.com> and <https://store.newhope.com> and <https://store.newhope.com/products/chart-top-100-supplements-by-us-sales>.
- [191] Hoai Thanh Nguyen, Sarbast K. Kheravii, Shu-biao Wu, Julie R. Roberts, Robert A. Swick, and Mehdi Toghyani. Sources and levels of copper affect liver copper profile, intestinal morphology and cecal microbiota population of broiler chickens fed wheat-soybean meal diets. *Scientific Reports*, 12, 02 2022. Available from: <https://www.nature.com/articles/s41598-022-06204-9>, doi:10.1038/s41598-022-06204-9.
- [192] Ning Ning, Dengfeng Gao, Vincenzo Triggiani, Massimo Iacoviello, Judith E. Mitchell, Rui Ma, Yan Zhang, and Huijuan Kou. Prognostic role of hypothyroidism in heart failure: A meta-analysis. *Medicine*, 07 2015. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4540113/>

- //www.ncbi.nlm.nih.gov/pmc/articles/PMC4554113/, doi:10.1097/MD.0000000000001159.
- [193] 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 Hundt, 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.
- [194] Yasuhiro Nose, Byung-Eun Kim, and Dennis J. Thiele. Ctr1 drives intestinal copper absorption and is essential for growth, iron metabolism, and neonatal cardiac function. *Cell Metabolism*, 4, 2006. Available from: <http://dx.doi.org/10.1016/j.cmet.2006.08.009>, doi:10.1016/j.cmet.2006.08.009.
- [195] 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.
- [196] BL O'Dell. Fructose and mineral metabolism. *The American Journal of Clinical Nutrition*, 58, 1993. Available from: <http://dx.doi.org/10.1093/ajcn/58.5.771s>, doi:10.1093/ajcn/58.5.771s.
- [197] 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: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2018314/>.
- [198] 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/>.
- [199] 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 Fallar. 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.
- [200] 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.
- [201] 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.
- [202] 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.
- [203] Erwin Jongwoo Park, Ki-Myeong Lee, Taewan Kim, Donghyun Lee, Min Sik Kim, and Changha Lee. Trivalent copper ion-mediated dual oxidation in the copper-catalyzed fenton-like system in the presence of histidine. *Environmental Science & Technology*, 58, 06 2024. Available from: <http://dx.doi.org/10.1021/acs.est.4c03689>, doi:10.1021/acs.est.4c03689.
- [204] 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.
- [205] Jianbiao Peng, Chaonan Zhang, Ya Zhang, Dong Miao, Yaozong Zhang, Haijin Liu, Jinghua Li, Lei Xu, Jialu Shi, Guoguang Liu, and Shixiang Gao. Enhanced cu(ii)-mediated fenton-like oxidation of antimicrobials in bicarbonate aqueous solution: Kinetics, mechanism and toxicity evaluation. *Environmental Pollution*, 252, 09 2019. Available from: <http://dx.doi.org/10.1016/j.envpol.2019.05.148>, doi:10.1016/j.envpol.2019.05.148.
- [206] Ana Margarida Pereira, Margarida G. Maia, Antnio Mira Fonseca, and Ana Jordao Cabrita. Zinc in dog nutrition, health and disease: A review. *Animals : an Open Access Journal from MDPI*, 04 2021. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8066201/>, doi:10.3390/ani11040978.
- [207] A. Ninh Pham, Guowei Xing, Christopher J. Miller, and T. David Waite. Fenton-like copper redox chemistry revisited: Hydrogen peroxide and superoxide mediation of copper-catalyzed oxidant production. *Journal of Catalysis*, 301, 05 2013. Available from: <http://dx.doi.org/10.1016/j.jcat.2013.01.025>, doi:10.1016/j.jcat.2013.01.025.
- [208] 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.
- [209] Elena V Polishchuk and Roman S Polishchuk. The emerging role of lysosomes in copper homeostasis. *Metalloomics*, 8(9):853–862, 06 2016. Available from: <https://doi.org/10.1039/c6mt00058d>, arXiv:<https://academic.oup.com/metalloomics/article-pdf/8/9/853/34735754/c6mt00058d.pdf>, doi:10.1039/c6mt00058d.
- [210] 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/>.
- [211] 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.
- [212] C Rachman-Tzemah, S Zaffryar-Eilot, M Grossman, D Ribero, M Timaner, JM Mäki, J Myllyharju, F Bertolini, D Herskowitz, 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/>.
- [213] 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.
- [214] Perungavur N. Ranganathan, Yan Lu, Lingli Jiang, Changae Kim, and James F. Collins. Serum ceruloplasmin protein expression and activity increases in iron-deficient rats and is further enhanced by higher dietary copper intake. *Blood*, 118, 09 2011. Available from: <http://dx.doi.org/10.1182/blood-2011-05-352112>, doi:10.1182/blood-2011-05-352112.
- [215] Chinmaya Sundar Ray, Bratati Singh, Itishri Jena, Sudeshna Behera, and Subhashree Ray. Low alkaline phosphatase (alp) in adult population an indicator of zinc (zn) and magnesium (mg) deficiency. *Current Research in Nutrition and Food Science Journal*, 5. Available from: <http://dx.doi.org/10.12944/crnfsj.5.3.20>, doi:10.12944/crnfsj.5.3.20.
- [216] Anna Reid, Christopher Miller, John Peter Farrant, Rahul Polturi, David Clark, Simon Ray, Garth Cooper, and Matthias Schmitt. Copper chelation in patients with hypertrophic cardiomyopathy. *Open Heart*, 9(1), 2022. Available from: <https://openheart.bmj.com/content/9/1/e001803>, arXiv:<https://openheart.bmj.com/content/9/1/e001803.full.pdf>, doi:10.1136/openhrt-2021-001803.
- [217] 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.
- [218] WILLIAM W. RILEY and RICHARD E. AUSTIC. Influence of dietary electrolytes on digestive tract ph and acid-base status of chicks. *Poultry Science*, 63, 11 1984. Available from: <https://doi.org/10.3382/ps.0632247>, doi:10.3382/ps.0632247.
- [219] Elise Brochner Rischel, Michael Gejl, Birgitte Brock, Jorgen Rungby, and Albert Gjedde. In alzheimer's disease, amyloid beta accumulation is a protective mechanism that ultimately fails. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, 06 2022. Available from: <https://pubmed.ncbi.nlm.nih.gov/35673950/>, doi:10.1002/alz.12701.
- [220] KELLY R. ROBBINS and DAVID H. BAKER. Effect of high-level copper feeding on the sulfur amino acid need of chicks fed corn-soybean meal and purified crystalline amino acid diets. *Poultry Science*, 59, 05 1980. Available from: <http://dx.doi.org/10.3382/ps.0591099>, doi:10.3382/ps.0591099.
- [221] Mariangela Rondanelli, Milena Anna Faliiva, Vittoria Infantino, Clara Gasparri, Giancarlo Iannello, Simone Perna, Antonella Riva, Giovanna Petrangolini, Alice Tartara, and Gabriella Peroni. Copper as dietary supplement for bone metabolism: A review. *Nutrients*, 06 2021. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8308383/>, doi:10.3390/nu13072246.
- [222] 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.
- [223] Sander Rozemeijer, Henrike M. Hamer, Annemieke C. Heijboer, Robert de Jonge, Connie R. Jimenez, Nicole P. Juffermans, Romein W. G. Dujardin, Armand R. J. Girbes, and Angélique M. E. de Man. Micronutrient status of critically ill patients with covid-19 pneumonia. *Nutrients*, 16, 2024. Available from: <http://dx.doi.org/10.3390/nu16030385>, doi:10.3390/nu16030385.
- [224] Moisés Rubio-Osorio, 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>.
- [225] 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.
- [226] Lina M. Ruiz, Allan Libedinsky, and Alvaro A. Elorza. Role of copper on mitochondrial function and metabolism. *Frontiers in Molecular Biosciences*, 08 2021. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8421569/>, doi:10.3389/fmolb.2021.711227.
- [227] Karina E. Salinas, Osvaldo Herreros, and Cynthia M. Torres. Leaching of primary copper sulfide ore in chloride-ferrous media. *Minerals*, 8, 08 2018. Available from: <http://dx.doi.org/10.3390/min8080312>, doi:10.3390/min8080312.
- [228] Amram SAMUNI, Jacob ARONOVITCH, Dina GODINGER, Mordechai CHEVION, and Gidon CZAPSKI. On the cytotoxicity of vitamin c and metal ions. *European Journal of Biochemistry*, 137, 12 1983. Available from: <http://dx.doi.org/10.1111/j.1432-1033.1983.tb07804.x>, doi:10.1111/j.1432-1033.1983.tb07804.x.

- [229] Manu Sánchez, Laura Sabio, Natividad Gálvez, Mercè Capdevila, and Jose M. DominguezVera. Iron chemistry at the service of life. *IUBMB Life*, 69, 06 2017. Available from: <http://dx.doi.org/10.1002/iub.1602>, doi:10.1002/iub.1602.
- [230] Parastoo Saniee, Somayeh Shahreza, and Farideh Siavoshi. Negative effect of protonpump inhibitors (<scp>ppi</scp>s) on *helicobacter pylori* growth, morphology, and urease test and recovery after <scp>ppi</scp> removal - an in vitro study. *Helicobacter*, 21, 04 2016. Available from: <http://dx.doi.org/10.1111/hel.12246>, doi:10.1111/hel.12246.
- [231] LFJ Santos, AM Gonçalves, LM Neira, VS Nakagi, M Macari, AC Laurentiz, and JM Pizauro. Effects of supplementation of zinc, manganese, or copper and different phytase levels in serum and bone acid and alkaline phosphatases of broiler chicks. *Brazilian Journal of Poultry Science*, 25, 2023. Available from: <http://dx.doi.org/10.1590/1806-9061-2022-1722>, doi:10.1590/1806-9061-2022-1722.
- [232] Mark E. Schlesinger, Matthew J. King, Kathryn C. Sole, and William G. Davenport. Hydrometallurgical copper extraction, 2011. Available from: <https://doi.org/10.1016/b978-0-08-096789-9.10015-0>, doi:10.1016/b978-0-08-096789-9.10015-0.
- [233] Karsten E. Schober, Phillip R. Fox, Jonathan Abbott, Etienne Côté, Virginia LuisFuentes, Jose Novo Matos, Joshua A. Stern, Lance Visser, Katherine F. Scollan, Valerie Chetboul, Donald Schrophe, Tony Glaus, Roberto Santilli, Romain Pariaut, Rebecca Stepien, Vanessa ArquedSoubeyran, Marco Baron Toaldo, Amara Estrada, Kristin MacDonald, Emily T. Karlin, and John Rush. Retrospective evaluation of hypertrophic cardiomyopathy in 68 dogs. *Journal of Veterinary Internal Medicine*, 36, 2022. Available from: <http://dx.doi.org/10.1111/jvim.16402>, doi:10.1111/jvim.16402.
- [234] Daniel Segna, Nele Brusselaers, Damian Glaus, Niklas Krupka, and Benjamin Misselwitz. Association between proton-pump inhibitors and the risk of gastric cancer: a systematic review with meta-analysis. *Therapeutic Advances in Gastroenterology*, 14, 01 2021. Available from: <http://dx.doi.org/10.1177/17562848211051463>, doi:10.1177/17562848211051463.
- [235] M. Alexis Seguin and Susan E. Bunch. Iatrogenic copper deficiency associated with long-term copper chelation for treatment of copper storage disease in a bedlington terrier. *Journal of the American Veterinary Medical Association*, 218, 05 2001. Available from: <http://dx.doi.org/10.2460/javma.2001.218.1593>, doi:10.2460/javma.2001.218.1593.
- [236] 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.
- [237] Jiaqi Shen, Paul T. Griffiths, Steven J. Campbell, Battist Uttinger, Markus Kalberer, and Suzanne E. Paulson. Ascorbate oxidation by iron, copper and reactive oxygen species: review, model development, and derivation of key rate constants. *Scientific Reports*, 11, 04 2021. Available from: <https://www.nature.com/articles/s41598-021-86477-8>, doi:10.1038/s41598-021-86477-8.
- [238] G. C. Shurson, P. K. Ku, G. L. Waxler, M. T. Yokoyama, and E. R. Miller. Physiological relationships between microbiological status and dietary copper levels in the pig. *Journal of Animal Science*, 68, 04 1990. Available from: <https://doi.org/10.2527/1990.6841061x>, doi:10.2527/1990.6841061x.
- [239] L.A. Sinclair, D. Johnson, S. Wilson, and A.M. Mackenzie. Added dietary sulfur and molybdenum has a greater influence on hepatic copper concentration, intake, and performance in holstein-friesian dairy cows offered a grass silage- rather than corn silage-based diet. *Journal of Dairy Science*, 100, 06 2017. Available from: <https://doi.org/10.3168/jds.2016-12217>, doi:10.3168/jds.2016-12217.
- [240] Girish Sindhwani, Rakhee Sodhi, Manju Saini, Varuna Jethani, Sushant Khanduri, and Baltej Singh. Tracheobronchomalacia/excessive dynamic airway collapse in patients with chronic obstructive pulmonary disease with persistent expiratory wheeze: A pilot study. *Lung India : Official Organ of Indian Chest Society*, pages 381–4, Jul-Aug 2016. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4948224/>, doi:10.4103/0970-2113.184870.
- [241] 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/>.
- [242] Daniel G.J. Smethurst and Natalia Shcherbik. Interchangeable utilization of metals: New perspectives on the impacts of metal ions employed in ancient and extant biomolecules. *The Journal of Biological Chemistry*, 10 2021. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8633580/>, doi:10.1016/j.jbc.2021.101374.
- [243] 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.
- [244] Lynda I. Smith-Mungo and Herbert M. Kagan. Lysyl oxidase: Properties, regulation and multiple functions in biology. *Matrix Biology*, 16, 1998. Available from: [http://dx.doi.org/10.1016/s0945-053x\(98\)90012-9](http://dx.doi.org/10.1016/s0945-053x(98)90012-9), doi:10.1016/s0945-053x(98)90012-9.
- [245] Sabrina Sobel, Allison Haigney, Michael Kim, Daniel Kim, Gregory Theophall, James Nuñez, Dionna Williams, Billy Hickling, and Joseph Sinacori. The complexation of aqueous metal ions relevant to biological applications. 2. reactions of copper(ii) citrate and copper(ii) succinate with selected amino acids. *Chemical Speciation & Bioavailability*, 22. Available from: <https://doi.org/10.3184/095422910x12692705325385>, doi:10.3184/095422910x12692705325385.
- [246] Stéphanie Solier, Sebastian Müller, Tatiana Cañequé, 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, Emmanuel 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.
- [247] Dan Song, Gou Takahashi, Yun-Wen Zheng, Mami Matsuo-Takasaki, Jingyue Li, Miho Takami, Yuri An, Yasuko Hemmi, Natsumi Miharada, Tsuyoshi Fujioka, Michiya Noguchi, Takashi Nakajima, Megumu K. Saito, Yukio Nakamura, Tatsuya Oda, Yuichiro Miyaoka, and Yohei Hayashi. Retinoids rescue ceruloplasmin secretion and alleviate oxidative stress in wilson's disease-specific hepatocytes. *bioRxiv*, 2021. Available from: <https://www.biorxiv.org/content/early/2021/08/10/2021.08.10.455792>, arXiv:<https://www.biorxiv.org/content/early/2021/08/10/2021.08.10.455792.full.pdf>, doi:10.1101/2021.08.10.455792.
- [248] Jerry W. Spears. Trace mineral bioavailability in ruminants. *The Journal of Nutrition*, 133, 2003. Available from: <http://dx.doi.org/10.1093/jn/133.5.1506s>, doi:10.1093/jn/133.5.1506s.
- [249] Barry Starcher, Charles H. Hill, and Gennard Matrone. Importance of dietary copper in the formation of aortic elastin. *The Journal of Nutrition*, 82, 03 1964. Available from: <http://dx.doi.org/10.1093/jn/82.3.318>, doi:10.1093/jn/82.3.318.
- [250] Karolina M Stepien and Andrew Taylor. Colloidal silver ingestion with copper and caeruloplasmin deficiency. *Annals of Clinical Biochemistry: International Journal of Laboratory Medicine*, 49, 2012. Available from: <http://dx.doi.org/10.1258/acb.2011.011199>, doi:10.1258/acb.2011.011199.
- [251] W.C. Supplee. Observations on the effect of copper additions to purified turkey diets. *Poultry Science*, 43, 11 1964. Available from: <http://dx.doi.org/10.3382/ps.0431599>, doi:10.3382/ps.0431599.
- [252] J.A. Swader and Wing-Yee Chan. Citric acid enhancement of copper solubility and toxicity in bicarbonate solutions. *Pesticide Biochemistry and Physiology*, 5, 10 1975. Available from: [https://doi.org/10.1016/0048-3575\(75\)90013-9](https://doi.org/10.1016/0048-3575(75)90013-9), doi:10.1016/0048-3575(75)90013-9.
- [253] 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.
- [254] 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/>.
- [255] Xiaolong Tang, Zaihua Yan, Yandong Miao, Wuhua Ha, Zheng Li, Lixia Yang, and Denghai Mi. Copper in cancer: from limiting nutrient to therapeutic target. *Frontiers in Oncology*, 06 2023. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10327296/>, doi:10.3389/fonc.2023.1209156.
- [256] Yiyang Tang, Zhenghui Liu, Qin Chen, Mukamengjiang Juaiti, Zaixin Yu, Benhui Liang, and Lihuang Zha. Association of sarcopenia with the long-term risk of atrial fibrillation: A prospective cohort study. *Aging cell*, page e14198, 05 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/38739369/>, doi:10.1111/acel.14198.
- [257] S. W. Tappin. Canine tracheal collapse. *Journal of Small Animal Practice*, 57, 2016. Available from: <http://dx.doi.org/10.1111/jsap.12436>, doi:10.1111/jsap.12436.
- [258] Mustafa M. Tashkandi, Saqer F. Alsaqer, Thabet Alhousami, Faiza Ali, Yu-Chiao Wu, Jennifer Shin, Pushkar Mehra, Larry M. Wolford, Louis C. Gerstenfeld, Mary B. Goldring, and Manish V. Bais. Loxl2 promotes aggrecan and gender-specific anabolic differences to tmj cartilage. *Scientific Reports*, 10, 11 2020. Available from: <https://www.nature.com/articles/s41598-020-77178-9>, doi:10.1038/s41598-020-77178-9.
- [259] L. P. Thornburg, G. Rottinghaus, M. McGowan, K. Kupka, S. Crawford, and S. Forbes. Hepatic copper concentrations in purebred and mixed-breed dogs. *Veterinary Pathology*, 27, 1990. Available from: <http://dx.doi.org/10.1177/030098589002700202>, doi:10.1177/030098589002700202.
- [260] 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:<https://dx.doi.org/10.1177/104063870001200201>, doi:10.1177/104063870001200201.
- [261] 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.
- [262] 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://europemc.org/abstract/med/1659568>.
- [263] Restituto Tocmo, Dong Liang, Yi Lin, and Dejian Huang. Chemical and biochemical mechanisms underlying the cardio-protective roles of dietary organopolysulfides. *Frontiers in Nutrition*, 02 2015. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC4428374/>, doi:10.3389/fnut.2015.00001.
- [264] C. Vaughan Tuohy, Sanjiv Kaul, Howard K. Song, Babak Nazer, and Stephen B. Heitner. Hypertrophic cardiomyopathy: the future of treatment. *European Journal of Heart Failure*, 22, 2020. Available from: <http://dx.doi.org/10.1002/ejhf.1715>, doi:10.1002/ejhf.1715.
- [265] Duncan Turnbull, Maia M. Jack, Pragati S. Coder, Catherine A. Picut, and Joseph V. Rodricks. Extended one-generation reproductive toxicity (eogrt) study of benzoic acid in sprague dawley rats. *Regulatory Toxicology and Pharmacology*, 122:104897, 2021. Available from: <https://www.sciencedirect.com/science/article/pii/S0273230021000374>, doi:<https://doi.org/10.1016/j.yrtph.2021.104897>.
- [266] S. Urtiaga, R. Terrero, M. Malumbres, and A. Pinel. Myelopathy secondary to copper deficiency: The great imitator. *Neurología (English Edition)*, 33, 2018. Available from: <http://dx.doi.org/10.1016/j.nrleng.2017.02.002>, doi:10.1016/j.nrleng.2017.02.002.
- [267] Gerrit J. Van den Berg, Shiguang Yu, Arnoldina G. Lemmens, and Anton C. Beynen. Ascorbic acid feeding of rats reduces

- copper absorption, causing impaired copper status and depressed biliary copper excretion. *Biological Trace Element Research*, 41(1):47–58, Apr 1994. Available from: <https://doi.org/10.1007/BF02917216>, doi:10.1007/BF02917216.
- [268] Martina Vavrusova and Leif H. Skibsted. Aqueous solubility of calcium citrate and interconversion between the tetrahydrate and the hexahydrate as a balance between endothermic dissolution and exothermic complex formation. *International Dairy Journal*, 57, 06 2016. Available from: <https://doi.org/10.1016/j.idairyj.2016.02.033>, doi:10.1016/j.idairyj.2016.02.033.
- [269] 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.
- [270] 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.
- [271] 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.
- [272] 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.scienmag.org/content/336/6086/1306>. full.pdf, doi:10.1126/science.1218632.
- [273] Misha F. Vrolijk, Antoon Opperhuizen, Eugène H.J.M. Jansen, Geja J. Hageman, Aalt Bast, and Guido R.M.M. Haenen. The vitamin b6 paradox: Supplementation with high concentrations of pyridoxine leads to decreased vitamin b6 function. *Toxicology in Vitro*, 44, 2017. Available from: <http://dx.doi.org/10.1016/j.tiv.2017.07.009>, doi:10.1016/j.tiv.2017.07.009.
- [274] Ahsan Wahab, Kamran Mushtaq, Samuel G. Borak, and Naresh Bellam. Zincinduced copper deficiency, sideroblastic anemia, and neutropenia: A perplexing facet of zinc excess. *Clinical Case Reports*, 8, 2020. Available from: <http://dx.doi.org/10.1002/ccr3.2987>, doi:10.1002/ccr3.2987.
- [275] Ahsan Wahab, Kamran Mushtaq, Samuel G. Borak, and Naresh Bellam. Zincinduced copper deficiency, sideroblastic anemia, and neutropenia: A perplexing facet of zinc excess. *Clinical Case Reports*, pages 1666–71, 05 2020. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7495772/>, doi:10.1002/ccr3.2987.
- [276] P.E. Waibel, D.C. Snetsinger, R.A. Ball, and J.H. Sautter. Variation in tolerance of turkeys to dietary copper. *Poultry Science*, 43, 03 1964. Available from: <http://dx.doi.org/10.3382/ps.0430504>, doi:10.3382/ps.0430504.
- [277] Helge L. Waldum, Øystein Sordal, and Reidar Fossmark. Proton pump inhibitors (ppis) may cause gastric cancer - clinical consequences. *Scandinavian Journal of Gastroenterology*, 53, 06 2018. Available from: <http://dx.doi.org/10.1080/00365521.2018.1450442>, doi:10.1080/00365521.2018.1450442.
- [278] 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.
- [279] Bo Wang and Xiao-Ping Wang. Does ceruloplasmin defend against neurodegenerative diseases? *Current Neuropharmacology*, pages 539–49, 2019. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6712297/>.
- [280] Peng Wang, Xiaohe Xu, Guisong Gu, Qianwen Guo, Yanzhi Rao, Ke Yang, Tong Xi, Yonghui Yuan, Shanshan Chen, and Xun Qi. Inhibition effect of copper-bearing metals on arterial neointimal hyperplasia via the akt/nrf2/are pathway in vitro and in vivo. *Regenerative Biomaterials*, 04 2024. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11256920/>, doi:10.1093/rb/rbae042.
- [281] Rui Wang. Hydrogen sulfide, microbiota, and sulfur amino acid restriction diet. *Frigid Zone Medicine*, 1. Available from: <http://dx.doi.org/10.2478/fzm-2021-0003>, doi:10.2478/fzm-2021-0003.
- [282] 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/>.
- [283] Yuqiong Wang, Zonghui Zhang, Lele Zhao, Chong Ma, Qi Hu, and Xiaohong Hou. Bicarbonate ions promote rapid degradation of pollutants in co(ii)fe(ii)/peroxyacetic acid systems. *Journal of hazardous materials*, page 136918, 12 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39708608/>, doi:10.1016/j.jhazmat.2024.136918.
- [284] 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/>.
- [285] Raul A. Wapnir and Cheryl Balkman. Intestinal absorption of copper: Effect of amino acids. *Nutrition Research*, 10, 05 1990. Available from: [http://dx.doi.org/10.1016/s0271-5317\(05\)80068-5](http://dx.doi.org/10.1016/s0271-5317(05)80068-5), doi:10.1016/s0271-5317(05)80068-5.
- [286] Cynthia L. Webster, Sharon A. Center, John M. Cullen, Dominique G. Penninck, Keith P. Richter, David C. Twedt, and Penny J. Watson. Acvim consensus statement on the diagnosis and treatment of chronic hepatitis in dogs. *Journal of*

- Veterinary Internal Medicine, pages 1173–200, 03 2019. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6524396/>, doi:10.1111/jvim.15467.
- [287] Shanzun Wei, Liang Gao, Changjing Wu, Feng Qin, and JiuHong Yuan. Role of the lysyl oxidase family in organ development (review). *Experimental and Therapeutic Medicine*, pages 163–72, 05 2020. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7282176/>, doi:10.3892/etm.2020.8731.
- [288] Hailang Wen, Lin Feng, Weidan Jiang, Yang Liu, Jun Jiang, Shuhong Li, Ling Tang, Yongan Zhang, Shengyao Kuang, and Xiaoqiu Zhou. Dietary tryptophan modulates intestinal immune response, barrier function, antioxidant status and gene expression of tor and nrf2 in young grass carp (ctenopharyngodon idella). *Fish & Shellfish Immunology*, 40, 09 2014. Available from: <http://dx.doi.org/10.1016/j.fsi.2014.07.004>, doi:10.1016/j.fsi.2014.07.004.
- [289] Yang Wen, Runxian Li, Xiangshu Piao, Gang Lin, and Pingli He. Different copper sources and levels affect growth performance, copper content, carcass characteristics, intestinal microorganism and metabolism of finishing pigs. *Animal Nutrition*, pages 321–30, 11 2021. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8718720/>, doi:10.1016/j.aninu.2021.10.007.
- [290] Contributors to Wikimedia projects. List of copper ores. *Wikipedia*, 05 2024. Available from: https://en.wikipedia.org/wiki/List_of_copper_ores.
- [291] 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.
- [292] 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.
- [293] Min Wu, Guofeng Tan, Ruirui Shi, Dewen Chen, Yumei Qin, and Jianzhong Han. In vitro bioaccessibility of inorganic and organic copper in different diets. *Poultry Science*, 08 2024. Available from: <http://dx.doi.org/10.1016/j.psj.2024.104206>, doi:10.1016/j.psj.2024.104206.
- [294] Kuo Yan, Chen Zhang, Jongkyun Kang, Paola Montenegro, and Jie Shen. Cortical neurodegeneration caused by psen1 mutations is independent of abeta. *Proceedings of the National Academy of Sciences of the United States of America*, page e2409343121, 08 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39136994/>, doi:10.1073/pnas.2409343121.
- [295] 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.
- [296] Jing Yang, Xueli Zhang, Yiyi 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.
- [297] Yue Yang, Wenjie Hao, Taohua Wei, LuLu Tang, Nannan Qian, Yulong Yang, Hu Xi, Shijie Zhang, and Wenming Yang. Role of serum ceruloplasmin in the diagnosis of wilson's disease: A large chinese study. *Frontiers in Neurology*, 12 2022. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9768184/>, doi:10.3389/fneur.2022.1058642.
- [298] 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.
- [299] Yanshi Ye, Ye Li, Qintao Ma, Ying Li, Huxian Zeng, Yaosheng Luo, Yongqian Liang, Lan Liu, Lingling Liu, Xu Lin, Genfeng Yu, Cheng Song, Heng Wan, and Jie Shen. Association of multiple blood metals with thyroid function in general adults: A crossminutsectional study. *Frontiers in Endocrinology*, 14, 2023. Available from: <https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2023.1134208>, doi:10.3389/fendo.2023.1134208.
- [300] A.G. Yersin, F.W. Edens, and D.F. Simmons. The effects of bordetella avium infection on elastin and collagen content of turkey trachea and aorta. *Poultry Science*, 77, 1998. Available from: <http://dx.doi.org/10.1093/ps/77.11.1654>, doi:10.1093/ps/77.11.1654.
- [301] Hao Yu and Jie Wu. Amyloid-upbeta: A double agent in alzheimer's disease? *Biomedicine & Pharmacotherapy*, 139, 2021. Available from: <http://dx.doi.org/10.1016/j.biopha.2021.111575>, doi:10.1016/j.biopha.2021.111575.
- [302] 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.
- [303] 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/>.
- [304] Taesik Yun, Yejin Na, Dohee Lee, Yoonhoi Koo, Yeon Chae, Hyeyeon Nam, Byeong-Teck Kang, Mhan-Pyo Yang, and Hakhyun Kim. Case report: Technetium-99m pertechnetate scintigraphy findings in a dog with iodine deficiency-induced goitrous hypothyroidism. *Frontiers in Veterinary Science*, 9, 06 2022. Available from: <http://dx.doi.org/10.3389/fvets.2022.922456>, doi:10.3389/fvets.2022.922456.
- [305] Zhaoqiao Zeng, Yanmei Cen, Lijiao Xiong, Guo Hong, Yu Luo, and Xiaoguang Luo. Dietary copper intake and risk of parkinson's disease: a cross-sectional study. *Biological Trace Element Research*, 202(3):955–964, Mar 2024. Available from: <https://doi.org/10.1007/s12011-023-03750-9>, doi:10.1007/s12011-023-03750-9.
- [306] 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.
- [307] 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/>.
- [308] 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.
- [309] LiYe Zhou, RiJun Long, XiuYing Pu, Juan Qi, and WeiWei Zhang. Studies of a naturally occurring sulfur-induced copper deficiency in przewalskis gazelles. *The Canadian Veterinary Journal*, pages 1269–72, Dec 2009. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2777290/>.
- [310] 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.
- [311] Katarzyna Marta Zoltowska, Utpal Das, Sam Lismont, Thomas Enzlein, Masato Maesako, Mei Q Houser, Maria Luisa Franco, Burcu Ozcan, Diana Gomes Moreira, Dmitry Karachentsev, Ann Becker, Carsten Hopf, Marcal Vilar, Oksana Berezovska, William Mobley, and Lucia Chavez-Gutierrez. Alzheimer's disease linked abeta42 exerts product feedback inhibition on gamma-secretase impairing downstream cell signaling. *eLife*, 07 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39027984/>, doi:10.7554/eLife.90690.

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: Some Common Logical Fallacies and Misdirections

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

1. **first impressions last :** You see this even in physics. Once a mystery has been (partially) solved it becomes entrenched dogma. In some compression technologies its safe to assume the first thing you see is most common but that doesn't seem to work in science lol.
2. **people over data :** Thjis comes up in essays on long lived metdical myths. Opinions, votes, don't determine natural laws
3. **local optimum :** Moving some quantity in one direction perturbs the system in a sort of beneficial way preventing anyone from looking the other way for a better result.
4. **supply v demand :** An excess quantity is not inherently due to either supply or demand
5. **quantity may be due to a quality problem. :** The feedback that produces inducible effectors may not go away until the job is done. If the effectors dont' work you will get more of them. Getting rid of them will not fix the original problem that may be important if this control system evolved well lol.
6. **false dichotomy :** good and evil
7. **non-monotonic curves :** *show me a monotonic dose response curve and I'll show you a fool*
8. **fix or remove :** Often there are 2 approaches to getting the same result with a partially broken system.
9. **one extreme says nothing about the other :** Both invcreasing or decreasing some quantity may produce the same (beneficial or evil) effect.
10. **presumed antagonists may work together :** One example cited osteoclast activation as not be the opposite osteogensis and in fact vigorous remodelling may be important for healthy bones.
11. **hidden interaction :** The observed result requires some interaction partners
12. **X is a Y :** Role confusion leads to more untested assumptions.
13. **local optimum :** prohibits consideration of global optimum over rugged parameter space with bad figure of merit.
14. **rabbit trail :** Successive approcimations, even as advocated in this seris of works, can lead a strategy down the wrong path.

15. **platitudes** : better to be safe than sorry lol
16. **philosophy over dynamics** : feedback can be complicated and commonly observed associations misleading
17. **equations** : consider spherical horse linear approx
18. **proxies** : Almost only counts in horseshoes and handgrenades
19. **models** : This usually means cause and effect is tossed out and the premise of the work has nothing to do with the premise of the real disease and that is often not even known well.
20. **only relies on empirical observations** : no cause and effect established
21. **ignoring empirical observations** : "sanity check " Theory based on incomplete system topology needs to be consistent with empirical observations
22. **ignoring empirical observations** : Theory based on incomplete system topology needs to be consistent with empirical observations
23. **other state variables** : Hidden variables include a limiting nutrient that is needed to beneficially use the entity under test.
24. **regulatory landscape** : As life is generally robust control systems have evolved but may have non-obvious failure modes.
25. **trying harder** : If a preferred response is frustrated in attaining a survival relevant goal, there may be signals to try a less orderly response more vigorously. The disorganized response can be suppressed by enabling the effective one.
26. **narrow corridor** : Given host-other evolution, you could expect dose response curves with many features but more likely a tight tolerance means that the approach is missing something more robust.

Appendix D: Background Diet Summary

Name	2023-10 Oct	2023-11 Nov	2023-12 Dec	2024-01 Jan	2024-02 Feb
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	
egg03	0.065 ;0.12;23/23	0.062 ;0.062;30/30	0.055 ;0.12;20/24	0.062 ;0.062;31/31	0.062 ;0.062;29/29
eggo			0.01 ;0.062;4/24		
eggshell	0.13 ;0.25;23/23	0.12 ;0.12;30/30	0.11 ;0.25;21/24		
garlic	0.022 ;0.25;2/23	0.22 ;0.25;26/30	0.083 ;0.25;8/24	1.2 ;1;27/31	0.99 ;1;22/29
marrow	0.19 ;0.25;12/23	0.37 ;0.25;30/30	0.083 ;0.25;6/24		0.078 ;0.25;7/29
oliveoil(tsp)	0.035 ;0.12;8/23	0.014 ;0.12;4/30			0.039 ;0.12;9/29
pepper	0.36 ;0.25;23/23	0.38 ;0.25;30/30	0.35 ;0.25;24/24	0.36 ;0.25;31/31	0.38 ;0.25;29/29
pineapple			0.021 ;0.25;2/24		
raspberry	0.32 ;0.25;23/23	0.28 ;0.25;24/30			
salmon		0.043 ;0.25;8/30		0.025 ;0.25;3/31	
shrimp(grams)		3 ;38;5/30	4.9 ;16;9/24	2.8 ;16;8/31	1.8 ;13;4/29
spinach		0.15 ;0.25;12/30	0.36 ;0.25;24/24	0.38 ;0.25;31/31	0.36 ;0.25;28/29
sunflowerseed	0.23 ;0.25;21/23	0.25 ;0.25;30/30	0.21 ;0.25;20/24		0.034 ;0.25;4/29
tomato	0.36 ;0.25;23/23	0.23 ;0.25;19/30	0.18 ;0.25;12/24	0.17 ;0.25;15/31	0.19 ;0.25;29/29
tuna(oz)					
turkey	0.34 ;0.25;23/23	0.37 ;0.25;30/30	0.35 ;0.25;24/24	0.36 ;0.25;31/31	0.36 ;0.25;29/29
vinegar(tsp)	0.09 ;0.062;23/23	0.094 ;0.062;30/30	0.09 ;0.062;24/24	0.068 ;0.062;24/31	2.16e-03 ;0.062;1/29
VITAMIN					
B-1(mg)	4.09e-03 ;0.012;15/23	5.87e-03 ;0.0059;30/30	6.12e-03 ;0.012;24/24	5.69e-03 ;0.0059;30/31	5.87e-03 ;0.0059;29/29
B-12(mg)	0.033 ;0.25;5/23	0.029 ;0.25;5/30	0.047 ;0.25;6/24	0.024 ;0.25;5/31	0.034 ;0.12;8/29
B-2(mg)	5.7 ;16;15/23	7.9 ;8.1;29/30	8.1 ;16;24/24	21 ;32;30/31	43 ;65;29/29
B-3(mg)	8.3 ;24;15/23	12 ;12;30/30	12 ;24;23/24	31 ;48;30/31	60 ;48;29/29
B-6(mg)	6 ;12;11/23	12 ;12;28/30	11 ;12;21/24	8.9 ;12;29/31	5.8 ;12;26/29
B-multi(count)	0.022 ;0.062;8/23			2.02e-03 ;0.062;1/31	
Cu(mg)	0.11 ;0.25;10/23	0.76 ;2;19/30	0.86 ;2;19/24	1.9 ;2;30/31	1.9 ;2;28/29
D-3(iu)	91 ;300;7/23	60 ;300;6/30	62 ;300;5/24	58 ;300;6/31	52 ;300;5/29
Iodine(mg) ^(a)	2.3 ;12;8/23	0.1 ;0.78;4/30	0.065 ;0.78;2/24	0.1 ;0.78;4/31	0.13 ;0.78;5/29
K1(mg)	0.38 ;1.2;7/23	0.92 ;1.2;22/30	1.1 ;1.2;22/24	1.1 ;1.2;27/31	1.2 ;1.2;28/29
K2(mg)	1 ;1.6;15/23	0.3 ;1.9;7/30	0.47 ;3.8;3/24	0.91 ;3.8;8/31	0.81 ;3.8;8/29
K2MK7(mg)	1.63e-03 ;0.025;2/23	5.83e-03 ;0.025;7/30	2.08e-03 ;0.025;2/24		
MgCitrate(mg)	96 ;200;21/23	100 ;100;30/30	92 ;100;22/24	31 ;100;10/31	76 ;100;22/29
Mn(mg)			0.042 ;1;1/24	0.21 ;0.62;12/31	0.12 ;1;6/29
Se(mcg)		0.42 ;12;1/30			0.43 ;12;1/29

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

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

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

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

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

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

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

Appendix E: Notable Food Components with Copper Interactions

Entity	Comments
Cu	
Zn	
Fe	
Mo	
H/ OH	
S and amino acids	reduce toxicity [109]
PO4	
Fructose	
Tyr	
Trp	
His	
Pi-complex	
Fenton	
Ammonia, Amides, N	
Citrate	
Ascorbate	
garlic	enhance uptake [127]
Microbial products	
phytate	

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

Appendix F: Symbols, Abbreviations and Colloquialisms

TERM definition and meaning

Appendix G: General caveats and disclaimer

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

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

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

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

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

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

Version	Date	Comments
0.01	2024-04-12	Create from empty.tex template
-	January 12, 2025	version 0.00 MJM-2024-010
1.0	20xx-xx-xx	First revision for distribution

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

Version	Date	URL

```
@techreport{marchywka-MJM-2024-010,
filename ={copper} ,
run-date ={January 12, 2025} ,
title ={Copper Supplementation in Dogs: Listen to Her Heart } ,
author ={Mike J Marchywka } ,
type ={techreport} ,
name ={marchywka-MJM-2024-010} ,
number ={MJM-2024-010} ,
version ={0.00} ,
institution ={not institutionalized, independent } ,
address ={ 44 Crosscreek Trail Jasper GA 30143 USA} ,
date ={January 12, 2025} ,
startdate ={2024-04-12} ,
day ={12} ,
month ={1} ,
year ={2025} ,
author1email ={marchywka@hotmail.com} ,
contact ={marchywka@hotmail.com} ,
author1id ={orcid.org/0000-0001-9237-455X} ,
pages ={ 62}
}
```

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

```
322861 May 23 2020 ..../casesum/casesum.bib e3f31502ec3535aa4116c6682917678b
7283 Jan 7 18:54 comment.cut 06fe1c349b22e5f7d325b5acc0de759e
50083 Jan 7 18:54 copper.aux c1312b0ae7847e1a79ae9a1b70cc726e
143557 Jan 7 18:54 copper.bbl 02385d84443a927a43a221b4d6c49a86
1183344 Jan 7 18:53 copper.bib 60cad0870c4866dc15a793a78e994ca9
6817 Jan 7 18:54 copper.blg dc当地8dcb274b83df1bb6cd05b2ca871
0 Jan 7 18:56 copper.bundle_checksums d41d8cd98f00b204e9800998ecf8427e
2391 Jan 3 19:04 copper_doit_best.tex bf2fec4a83021f78d618198badbcee0a
34225 Jan 7 18:54 copper.flts 70d1444f98af9d618f00ce44184be621
12530 Dec 31 11:17 copper_food_chem.tex 47a15ff67b5ffda614c591e2b7660fa4
2928 Dec 31 16:52 copper_gralic_chem.tex e49f9ba2e4547ed47b37f5d48c5706fd
3 Jan 7 18:54 copper.last_page ecf27a776cdfc771defab1c5d19de9ab
63639 Jan 7 18:54 copper.log 760bf24de34340a000dbdbbeb381a8a56
11014 Jan 7 18:54 copper.out 054227e9e4c79e2d40d6710595c7317b
4892931 Jan 7 18:54 copper.pdf 4d421393a3d1ce416f5069bd943ce2da
158891 Jan 7 12:05 copper.tex 5eac1ce03ddfe0010be9858382a8511
4891 Jan 7 18:54 copper.toc 6ddd6a3d8d387432ea597aa19b7a05fe
46541 Aug 4 07:09 /home/documents/latex/bib/mjm_tr.bib fd19ef3f7d7042a135e45769b705efff
46905 Oct 31 2023 /home/documents/latex/bib/releases.bib 6312c37f3f52915692464bb77750d464
7331 Jan 24 2019 /home/documents/latex/pkg/fltpage.sty 73b3a2493ca297ef0d59d6c1b921684b
7434 Oct 21 1999 /home/documents/latex/pkg/lgrind.sty ea74beeadaa2b711ec2669ba60562c3
1069 Oct 15 2021 /home/documents/latex/share/includes/disclaimer-gaslight.tex 94142
bbe063984d082bff3b400abe0fb
425 Oct 11 2020 /home/documents/latex/share/includes/disclaimer-status.tex b276f09e06a3a9114f927e4199f379f7
3927 May 2 2024 /home/documents/latex/share/includes/mjmaddbib.tex d58183f98615737b38f9d6e03fc064de
117 Oct 16 2023 /home/documents/latex/share/includes/mjmlistings.tex c1c3bd564b7fb321b4d8f223c7d3cde3
4716 Jun 8 2024 /home/documents/latex/share/includes/mycommands.tex 4db8e7aaf06149a8a4e5067dc9daa805
990 Jun 8 2024 /home/documents/latex/share/includes/myrevtexheaders.tex 0b36736edafdf88ff428e1c7e2515eeef1
```

2919 Jun 9 2024 /home/documents/latex/share/includes/myskeletonpackages.tex 08
a01c33af793bf936c6684d2e792c
29313 Jan 27 2019 /home/documents/latex/share/includes/plainurl.bst dfacbfe6df173afc674ca07e6b8dad42
1538 Aug 14 2021 /home/documents/latex/share/includes/recent_template.tex 49763d2c29f74e4b54fa53b25c2cc439
7217 May 15 2023 /home/documents/latex/share/overrides/mol2chemfig.sty 5aa81c197d462c2153a794cceee9881ef
77648 Oct 28 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmmono10-
regular.luc 9781f5c8a34a4c0bc570a299d048fec7
77690 May 20 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmmono9-regular
.luc 96accec07e21c918c677d94556d7a487
124213 May 20 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmroman10-bold
.luc be24eb5b757919758e60aa4f6d6aeb1d
132135 Oct 12 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmroman10-
italic.luc 48267fd5932c239fb4bad361e29a6f1e
123142 May 20 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmroman10-
regular.luc d3b29489a8ffc91cd4e03357f67b2fc5
124110 May 20 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmroman12-bold
.luc 8287c14a46bbf501cc26dc995afe5943
123481 May 20 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmroman12-
regular.luc 43b95c7579b49c47160ac0c030902624
121774 Sep 15 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmroman5-
regular.luc c99e387d782447967e8d270ff980a91f
124323 May 20 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmroman6-
regular.luc 6f24b27a1b5aa4b0cc9bac3053577dc4
124198 May 20 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmroman7-
regular.luc 86fe133d3cae7b679738c113e6f1abb9
123949 May 20 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmroman8-
regular.luc 4c67e46bb33a79c15e883e91a392459c
124254 May 20 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmroman9-bold.
.luc d65daa4f1bfa8d8116e83ffdbe58b835
131665 May 20 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmroman9-
italic.luc 75ae5c563908ddf015a78b6a6c60e1f7
123771 May 20 2023 /home/marchywka/.texlive2019/texmf-var/luatex-cache/generic-dev/fonts/ot1/lmroman9-
regular.luc 389c904e3ac3a14fd699c9e66e0cad24
51122 May 5 2024 keep/annie_cu.jpg 521c60b7feaaa4ccfb8dbf4756a92e55
428861 May 9 2024 keep/annie.jpeg 13a4f3486683d7ae7ad27bd9e6e9a8fa
58718 Oct 20 10:33 keep/annie_swelling.jpg 0f059727d63694df3c637cce782e463f
115306 Jun 9 2023 keep/bakingpan.jpg d9eb5391d6416909d2b6cf8de7d84cf
62147 Apr 16 2024 keep/brownie_cu.jpg 81c3a362d84a404bf83657b8bea5c768
536210 May 9 2024 keep/browniepic.jpeg b11fa91314f2c17e2949c9ab981e3c51
519764 Aug 22 04:39 keep/dexter2020.jpg 510b5394d135191799e0826513f7649fa
59085 Aug 20 12:51 keep/dexter2_cu.jpg b59da700d050ccc534242f60318e47ed
130311 Apr 14 2024 keep/happy2seeyou.jpg 1bf34e471e34d5924ec77a056c39755f
73312 Jan 5 19:26 keep/happy_citrato.jpg 20d625ecffb85868809a016c7d070fd2
383062 May 9 2024 keep/happycu.jpeg ab19483a1a380bc1885b66653308bbda
71379 Oct 20 14:36 keep/happy_early.jpg acada03e8f385b1934633577f7693573
80244 Aug 21 09:16 keep/happy_misc.jpg 842bbadc85cdfef78496fe1999d20370
71576 Oct 20 14:35 keep/happy_recent.jpg cfb0d69a50a15dae01fc3b09f711b3c
75419 Apr 15 2024 keep/hershey_cu_i.jpg 0de9f65cf86e4425d1030bb260661c5f
53880 Apr 16 2024 keep/mixie_cu.jpg 11afe28d1457c0442d56602684512fe6
440047 May 9 2024 keep/mixiepic.jpeg dd241b517360a2c6eae24abb06b2cff4
13472 Apr 16 2024 keep/monthly.tex 5f5be103a23dbcfaf693b14aa65d6961
435321 May 9 2024 keep/rockycu.jpeg e8273d04abbdb6af5ee644d9fcc8bf1d
61570 Apr 16 2024 keep/rocky_cu.jpg 9762fd87dc7b086e9dd28a2695300120
20425 Apr 17 2024 keep/rocky_i.jpg 6ddb48b3895c24bb205d9601138d0fe1
61731 Apr 14 2024 keep/trixie_cu.jpg 0f3294b2513b37ea673b7b18c327b2fe
556497 May 9 2024 keep/trixiepic.jpeg 93fdf2303eed80a72f53812a1747b7f
812939 Jan 2 20:18 non_pmc_copper.bib ed2c0e9a2207e580872b8e88f5c76cf9
370004 Jan 4 14:40 pmc_copper.bib 5019cfc59b9c68ef0851f792ea5c8ec0
762281 May 2 2024 potusebib.bib 9d69c07c905fe1ea717d95d95c360c9b
413 Apr 12 2024 releases.tex 56213b8bd7e164dd6e668b62f5acf868
343782 May 9 2024 sbenzbib.bib 19b330e7dc1259065d1957d6a3c5ba2
15 May 20 2023 /var/lib/texmf/fonts/map/pdftex/updmap/pdftex.map -> pdftex_dl14.map
f177baa1c39a3ebd62c3096a43521a0d
2639651 Mar 16 2024 /var/lib/texmf/web2c/luatex/lualatex(fmt dc6e497e977effcd6b888a0f2c9952dc

4892931 Jan 7 18:54 copper.pdf 4d421393a3d1ce416f5069bd943ce2da