Hi Mrs. Mangle and Dr. Hilton,

Here is a summary of what we discussed on the phone this evening. The results of Whiskey's liver biopsies were consistent with a copper storage disorder known as copper hepatopathy. He does have a large amount of copper (grade 4 of 5), and some evidence of fibrosis. No evidence of cancer, infection (negative liver tissue culture), or immune-mediated inflammation in his liver, which is all excellent news. His intestinal biopsies were consistent with inflammatory bowel disease. I've attached his biopsy reports for your review. See below instructions for long-term management. I'm glad we caught this before he really got into trouble! I hope we can get his ALT (liver enzyme) back in normal range over the next 6-12 months. Please do not hesitate to reach out with questions.

Sincerely,
Dr. Cammarano

COPPER HEPATOPATHY

In most animals, liver cells take up ingested copper, store the metal inside the cell, and/or excrete it in the bile or plasma. Hepatic copper accumulation can result from (1) increased uptake of copper, (2) a genetic defect in copper metabolism, or (3) altered excretion of copper in the bile. In copper storage hepatopathy, excessive hepatic copper accumulation overwhelms the ability of the liver cells to store copper, resulting in oxidative stress, hepatitis, and eventually scarring of the liver (cirrhosis). Dogs with inherited copper-associated hepatitis begin to accumulate copper as early as six months of age, but it may be years before they manifest clinical signs. Symptoms are result from liver dysfunction and include inappetence, vomiting, nausea, increased drinking and urination, icterus, diarrhea, or they maybe asymptomatic. Lab work often reveals increases in alanine aminotransferase (ALT). A definitive diagnosis is made by histopathologic examination of liver biopsy samples. Several breeds of dogs have a presumed genetic risk for this disease including: West Highland White Terriers, Bedlington terriers, Skye Terriers, Dalmatians, Labrador retrievers and possibly Doberman Pinschers. This does not mean that the disease is limited to these breeds unfortunately and we can see it in any dog.

Treatment of copper hepatopathy is directed primarily at reducing copper accumulation in the liver. This can be done by reducing copper ingestion, and chelating copper. Diets low in copper, such as Hills L/d or Royal Canin hepatic, are necessary to decrease copper accumulation. However, due to Whiskey's concurrent inflammatory bowel disease, he will need a specially prepared diet. A home cooked diet that is both low in copper and hypoallergenic is recommended. Foods such as eggs, organ meats, and shellfish contain high levels of copper and should be avoided. The preferred chelation medication we use is called d-penicillamine, which binds copper and expedites its excretion from the body. Adjunctive therapy involves the use of antioxidants to decrease the free-radical formation and liver injury/fibrosis resulting from copper toxicosis, such as Denamarin, Vitamin E, and phosphatidylcholine. Based on the amount of copper seen in Whiskey's liver cells, we estimate he will be on therapy for 6-12 months, however this is highly dependent upon his liver values and clinical signs and tolerance of the treatment protocol.

INFLAMMATORY BOWEL DISEASE (IBD)

Inflammatory Bowel Disease is a disease of the intestine that is characterized by chronic, recurrent gastrointestinal signs, including vomiting, diarrhea, and weight loss in the presence of histologic evidence of inflammation (tissue samples evaluated under the microscope). The exact cause of IBD is unknown, but a breakdown in the immunologic tolerance to antigens within the gastrointestinal tract (from diet, bacteria or both) has been implicated. Waxing and waning vomiting and diarrhea are the most common clinical signs associated with IBD, although onset can be triggered by an event such as stress or diet change. Severe disease may be associated with blood in the vomit or diarrhea, weight loss, and protein losing enteropathy, in which the intestines become inflamed to the point that the protein that normally keeps water within the vasculature leaks through the mucosa and is lost through the digestive tract.

Treatment of IBD is often multimodal, requiring long-term management with a combination of diet, antibiotics, and potentially immunosuppressive therapy. Diets most effective in management of IBD patients are easily digestible and comprised of either a novel protein (containing antigens that a patient has not had the chance to mount an immune response against) or a hydrolyzed protein (in which proteins have been broken down into such small pieces that they are unrecognizable as antigens). In mild cases, dietary modification alone can be quite successful.

The goals of therapy for IBD are to reduce clinical signs (vomiting, diarrhea, promote appetite and weight gain), maintain quality of life, and prevent secondary complications (blood clots, edema). Treatment may consist of: 1) Hypoallergenic or novel protein or low fat diet: to prevent the body from overreacting to food antigens, and decrease associated inflammation in the intestines (such as Purina HA or home cooked diets) and to help with patients that cannot absorb fat. 2) Antibiotics: to help regulate the intestinal flora, to reduce the chance that the body is reacting to bacterial overgrowth in the GI tract (such as tylosin) 3) Immunosuppressant medications: to 'dampen' the overactive immune system, to help decrease inflammation in the intestines (such as prednisone, prednisolone, and dexamethasone). It is important to note that many animals require lifelong treatment with medications in order to keep

their symptoms under control.

MEDICATIONS:

1. **D-PENICILLAMINE 400 MG CAP:** Please give 1 capsule by mouth every 12 hours, 30-60 minutes prior to food or other medications. This is a chelating agent and should be given on an **empty stomach**. ***Please wear gloves if opening capsules to avoid coming into direct contact with this medication.*** This drug is a potential teratogen and should not be handled by anyone who is pregnant or may become pregnant. Side effects include GI upset, vitamin B deficiency. In humans, lupus-like syndromes have been reported. If vomiting or anorexia occur you may give this with a very small amount of food**. This prescription was submitted to Wedgewood Online Pharmacy**. Please contact us when additional refills are required. We recommend that Whiskey continues this copper chelation therapy for 6-12 months depending on response. He may need low dose chelation life-long.

2. **DENAMARIN 425 MG TABS**: Please give 2 tablets by mouth every 24 hours until directed otherwise. This medication must be given on an **EMPTY STOMACH** at least 1 hour prior to a meal. This medication is a liver protectant. It is generally well tolerated, but potential side effects may involve gastrointestinal upset (i.e. decreased appetite, diarrhea, vomiting). If you notice any potential side effects, please discontinue the medication and contact us for further guidance.

3**. ELEVATE 500 IU/mL (water-soluble vitamin E):** Please give 0.7mL (340 IU) by mouth or over food every 24 hours. This is an antioxidant and is usually well tolerated. **This will be shipped from the Cornell Pharmacy.**

4. **PYRIDOXINE HCL (VITAMIN B6) TABLETS**: Please give 25mg by mouth once a day. This needs to be supplemented while Whiskey is on d-penicillamine. This can be purchased at any human pharmacy as an **over the counter product**.

5. **PHOSPHATIDYLCHOLINE (PhosChol Brand) 900MG CAPSULES:** Please give 900 mg by mouth every 12 hours. This medication is an anti-fibrotic agent to prevent fibrosis of the liver. Side effects associated with this supplement are not currently reported. This medication can be purchased online or **over the counter.**

Please **CONTINUE** Tylosin, pancreatin supplementation as previously prescribed. Please request that vitamin B12 be added to his vitamin and mineral mix when your diet is formulated. You may use Visbiome as a probiotic if desired.

INSTRUCTIONS:

1. Please continue to administer the medications as directed above. Based on the amount of copper observed we expect chelation to take 6-12 months with good treatment compliance that includes: d-Pen, supplemental pyridoxine, antioxidants (SAMe, low dose vitamin E) and PhosChol TM with lifelong dietary copper restriction without protein restriction.

2. Please monitor Whiskey for decreased appetite, vomiting, diarrhea, coughing, lethargy, weakness, abdominal distension, or jaundice. If you notice any of these signs or are concerned for any reason, please contact us at 607-253-3060 or your primary care veterinarian for further guidance, or seek veterinary attention.

3. Please fill out the following form for **the Cornell Nutrition Service** so that they make formulated Whiskey's home-cooked diet. He will need to be on a low copper, hypoallergenic, with vitamin B12 diet life long. Please select "no commercial diet available to meet pet's needs ($325)."

http://www.loftuslab.vet.cornell.edu/nutrition-consult-form.html

4. FUTURE MEDICATIONS: It will be imperative to try to avoid giving Whiskey medications that could potentially be toxic to the liver, such as non-steroidal anti-inflammatory drugs (NSAIDs). Please inform any veterinarian who may treat him in the future of his condition.

5. **Please schedule a recheck with Whiskey's primary care veterinarian or Dr. Cammarano in 1 month to recheck his liver values with a chemistry or liver panel at an external reference lab**. Please have these results forwarded to Dr. Cammarano (vet-hosp@cornell.edu). Then every 3 months thereafter while on chelation therapy.

Thank you for entrusting us in Whiskey's care. He is such a sweet boy. He was a pleasure to work with! If you have any questions or concerns, please do not hesitate to contact us at 607-253-3060.