If the patient does not have PLE, the next step is to eliminate maldigestion. Maldigestion principally means exocrine pancreatic insufficiency (EPI). Classic steatorrhea is not all that common in dogs with EPI; most of these patients have copious amounts of “oatmeal” consistency diarrhea without blood or mucus. You need to use the serum TLI test to establish the diagnosis of EPI; all the other tests (including fat absorption test and therapeutic trials with pancreatic enzymes) have a lot of false positive and false negative results; or, they are very inconvenient to use. Enzyme replacement therapy for EPI will not work in all patients; therefore, you need to establish a diagnosis of EPI with certainty using the TLI test (especially in almost any German shepherd). Failure to use the TLI may mean that you wrongly decide that EPI is not present and go on do tests that are unnecessary, inappropriate, and costly (e.g., intestinal biopsy). Most of the cases of EPI that I have seen have been referred for endoscopy and biopsy because EPI was "eliminated" after the animal did not respond to enzymatic supplementation. Conversely, incorrectly diagnosing exocrine pancreatic insufficiency in a dog that does not have that disorder results in prescribing expensive enzyme supplements that are not needed. Dogs may have EPI and not respond to pancreatic enzyme replacement because a) the enzyme product is poorly effective, b) the diet is too high in fat, and c) the dog also has antibiotic responsive enteropathy. Sometimes you need to address all of these issue before the dog with EPI will respond to enzyme supplementation. Sometimes feeding ground, fresh bovine pancreas with each meal is more effective than the commercial enzyme products. About 15% of dogs with EPI simply will not respond to enzyme supplementation no matter what you do. Dogs that are substantially hypocobalaminemic seem to have a more guarded prognosis, but it is not obvious that supplementing cobalamin helps these dogs.

Once maldigestion is eliminated, then malabsorptive diseases must be considered. Malabsorptive small intestinal disease is a common cause of diarrhea. A substantial number of dogs (and cats) with malabsorptive small intestinal disease have normal stools despite severe intestinal pathology. This is especially true in cats because they conserve water better than dogs. However, it is common enough in dogs that the practitioner must be very aware of the possibility. Small intestinal disease is a major concern in any animal with weight loss despite a normal (and especially an increased) appetite. If the appetite is decreased, one should still explore the possibility of small intestinal disease. In particular, explore the history to find out if the appetite was normal when the problem first began (a strong indication of small intestinal disease or feline hyperthyroidism). The most common causes of malabsorptive disease in dogs are probably parasites (e.g., giardiasis), bacteria (i.e., antibiotic responsive enteropathy), and dietary-responsive disease (i.e., either dietary allergy or dietary intolerance). Inflammatory bowel disease, lymphoma, and fungal infections are important, but are not the most common causes in the author's practice areas. Once parasites, protein-losing enteropathy, and maldigestion are eliminated (i.e., you have determined that the patient has a non-PLE malabsorptive disease), the question is whether to recommend therapeutic trials or a major diagnostic work up.

If the patient can tolerate a delayed diagnosis for the next 4-8 weeks without undue risk, then therapeutic trials are often reasonable. If therapeutic trials are performed, they must be
designed such that even if they fail, useful information is obtained and the clinician is further ahead than previously. Always ask yourself: "If this therapy fails, will I really know more about what the patient probably has, or will I be as confused as I was before treating it?".

An elimination diet for dietary responsive disease is often useful for non-protein-losing malabsorptive disease. While there are many excellent commercial diets that can be used, there are no commercial diets that will work in all dogs with dietary-responsive disease. We often see patients in which a dietary trial was performed, but it was done in such a poorly planned or implemented fashion that the effort was wasted. One must carefully investigate the history and see what the patient has eaten in the past. However, even when you have determined what dietary ingredients the patient has previously been exposed to, it is sometimes difficult to find a diet that works for that particular patient. In very rare cases, all of our well-planned hypoallergenic diets fail but a chance try at some commercial brand works.

When starting the patient on an elimination diet, one may use a homemade diet or a commercial diet. There are many excellent commercial diets, and they usually work. Homemade elimination diets sometimes work when commercial diets do not; however, this is very uncommon. Therefore, you will have to decide which is most appropriate in the patient that you are treating.

The hydrolyzed diets are often effective in patients with dietary-responsive disease, but they will not always be effective. Some animals respond better to a novel protein diet than a hydrolyzed diet, and vice-versa. Which ever elimination diet is used, one must be prepared to feed it and it alone for an absolute minimum of 3-4 weeks before its efficacy can be accurately determined. Rare cases need to be feed a diet for 6-8 weeks before they respond, but this is probably well less than 5% of GI cases. If a diet seems to be effective (i.e., weight gain plus resolution of diarrhea) then continue it for at least another 3-4 weeks to be sure that it was the diet that made a difference as opposed to the patient having some transient improvement due to any number of causes.

Small intestinal bacterial overgrowth (SIBO) is a term that refers to a disease process that has been well documented in people. Affected people have > 10⁶ CFU of bacteria per ml of fasting duodenal or upper small intestinal fluid. This large number of bacteria in an inappropriate place is attended with a constellation of clinical signs that may include weight loss, diarrhea, hypoalbuminemia, and various other changes. There are often structural problems (e.g., partial obstructions) or motility disorders that allow retention of ingesta, or there is decreased gastric acidity that allows excessive numbers of bacteria to enter the upper small intestine. This syndrome was extrapolated to dogs about 30 years ago, especially German Shepherd dogs. Since that time much as been written about this syndrome in dogs and cats, and multiple studies of the numbers of bacteria in normal and ill dogs and cats have been published.

At this time, the accuracy of the term “small intestinal bacterial overgrowth” is dubious, at best. Clinically normal dogs can have > 10⁸ CFU of bacteria in the upper small intestine, and this number is clearly in excess of what was initially accepted being definitive for SIBO (i.e., > 10⁶). Therefore, we will use the term “antibiotic-responsive enteropathy” (ARE) or “antibiotic-responsive diarrhea” instead of SIBO. “Dysbiosis” may also be a reasonable description.

Antibiotic-responsive enteropathy (ARE) seems to be a relatively common problem in dogs. It can best be described as a syndrome in which there are substantial numbers of bacteria in the upper small intestines AND the host responds to them in such a manner as to cause intestinal dysfunction. These bacteria are not obligate pathogens. Rather, they can be of any
species, and *E. coli* is a particularly common aerobic/facultative anaerobic bacteria found in the upper small intestines, while *Clostridium* and *Bacteroides* are especially common anaerobic bacteria. The signs they produce, if any, seemingly depend upon at least two factors: a) which bacteria are present and b) how the host responds to them. The relationship of ARE to IBD is unclear, but it seems very likely that bacteria are responsible for either initiating and/or perpetuating the intestinal inflammation that we call IBD in dogs and cats. The term “dysbiosis” has been suggested as the bridge between ARE and IBD (i.e., having bacteria that are somewhat prone to cause problems, such as *E. coli*, as opposed to having overt pathogens).

ARE is hard to definitively diagnose with laboratory tests. Histopathology and cytology of the intestinal mucosa are useless for diagnosing ARE. Serum cobalamin and folate concentrations are now known to be insensitive and non-specific for detecting ARE. There are many dogs with chronic GI disease that respond to antibiotic administration but which have normal cobalamin and/or normal folate concentrations. It is appropriate to treat for ARE regardless of whether the serum cobalamin and folate concentrations are normal or abnormal. Finding hypocobalaminemia or low serum folate levels is beneficial when looking for otherwise occult gastrointestinal disease.

In cats, supplementing cobalamin can clearly make the patient feel better and resolve chronic diarrhea. In fact, it is almost getting to the point where it is never wrong to give any sick cat cobalamin injections, regardless of blood values of the vitamin. Severe hypocobalaminemia has been suggested to be a poor prognostic sign. While the value of supplementing cobalamin to cats is clear (it is almost never wrong to give a sick cat supplemental cobalamin), relatively few dogs seem to substantially improve due to cobalamin administration. Currently, there is a lot of interest in whether measuring methylmalonic acid (MMA) might be as or more useful than measuring cobalamin.

Culture of the small bowel was once considered the “gold standard”, but this test is no longer recommended. It is neither sensitive nor specific for ARE. There are very rare patients that appear to have ARE and yet are resistant to treatment with commonly used antibiotics. Seemingly, these dogs may have one or two very resistant bacteria in their GI tracts, and culture may be required to determine what antibiotic will be effective. However, we have only seen this scenario 2 or 3 times, and we believe it to be very rare.

Because of the apparent difficulty in diagnosing ARE with lab tests, empirical antibiotic therapy is often chosen as a means to diagnosis instead of laboratory tests. The obvious drawbacks to this approach are a) clinical “response” of the patient to the administered antibiotics may be due to the antibiotics or may be due to something else, b) if the patient did not respond to the antibiotic, it may be that you used the wrong antibiotics, and c) even if the patient does have ARE, there may be yet another disease present (e.g., a tumor causing a partial intestinal obstruction) which predisposed the patient to the ARE.

Broad spectrum antibiotics designed to lessen bacterial numbers seem to be more effective. You can never sterilize the GI tract. However, because clinical signs are due to a combination of large numbers plus an altered host response, simply lessening the numbers of bacteria often seems beneficial. Tetracycline is often effective; but, giving tetracycline is inconvenient. Tetracycline must be administered alone (i.e., without any food) and yet be washed down with water to ensure that the capsule to tablet does not stick in the esophagus and cause esophagitis. Tylosin powder has also been useful and is revered by many clinicians. Some clinicians like metronidazole; however, I have not been impressed with the efficacy of solo
metronidazole therapy for ARE in dogs. Metronidazole seems to have real benefit in many GI disorders, probably because it is so effective in eliminating many anaerobic bacteria. For patients that are EXTREMELY ill in which we need to know RIGHT NOW whether or not it will respond to antibiotics (i.e., that patient is so ill that you cannot take a chance of being 2-3 weeks from now and not having a response to therapy), I use a combination of enrofloxacin and metronidazole. I did not say that I used this combination for long periods of time. I use this combination when I absolutely have to know whether or not I will have a clinical response within the next 2-3 weeks or take a chance on losing the patient. Regardless of which drug is used, such a therapeutic trial should be performed for at least 3 weeks before a decision is made as to its efficacy. Remember, you must not only suppress the numbers of bacteria, but you must also allow the intestinal mucosa time to heal. Finally and very importantly, it appears that concurrently feeding a high quality elimination diet can substantially enhance the efficacy of the antibiotic therapy. Therefore, we now routinely use both in our therapeutic trials.

If the patient appears to respond to this therapeutic trial of elimination diet and antibiotics, then it is best to continue everything unchanged for an additional 2-4 weeks to be sure that the patient responded to this therapy (as opposed to the patient having some fortuitous, transient response to who-knows-what). If the patient is still doing well after this time, then you either a) stop the antibiotics and see if they diet alone is sufficient to control signs or b) slowly wean the antibiotics to their lowest effective dose (e.g., once a day or even once every other day). It all depends upon how frequently the clinical signs occur. If the signs occur once every few months, then it obviously makes sense to only treat when the patient is symptomatic. If the signs consistently recur within a few days of stopping the antibiotics, then you are probably stuck with treating almost constantly. Some patients that fall into this latter situation only need antibiotic administration every 2 to 3 days in order to maintain control. In very rare cases, the patient will breakthrough and re-develop clinical signs after several weeks or months, and a different antibiotic must be used. If the decision is made to stop administering the antibiotics, then the owners should be warned that it is possible that the signs are likely to recur at some point. For ARE to occur, there is probably some defect in host defense mechanisms that allowed the commensal bacteria to cause the clinical signs, and this defect is unlikely to disappear. The question is how severe is the defect (i.e., is the dog likely to have problems continually or only once in a while)? You should warn the clients that they are likely to have to deal with this problem repeatedly and you need to explain the difference between “cure” and “control”.

It is probably a good idea to routinely treat all dogs with chronic small intestinal, malabsorptive disease for ARE, even if you have histologic evidence of IBD or other disease. I will treat for ARE almost every time I diagnose a dog with a malabsorptive disease unless I find neoplasia or lymphangiectasia.