

Gastrointestinal Biopsies

How much is fact? How much is fantasy?

The emergence of the fiber optic flexible endoscope as the "veterinary toy of the 90s" was fostered by the belief that the ability to obtain biopsies from the gastrointestinal tract was going to be an important tool in the management of acute and chronic gastrointestinal disease in dogs and cats. Certainly, these endoscopes can do other tasks like visualize tumors or foreign bodies, but their ability to obtain tissue samples was the big selling feature.

Much has been said and written by various "gurus" of clinical gastroenterology about the uses of endoscopy, particularly its role in the diagnosis of inflammatory bowel disease in dogs and cats. Rarely does one have the chance to hear or read the opinions of the pathologists who, in the end, must interpret the tiny biopsies obtained. I know of many pathologists who treat such biopsies with great scepticism, and there certainly is a gap between what the clinical gastroenterologist would like us to say, and what we in fact are prepared to say, about these samples.

Over the last 20 years or so, I have looked at over 10,000 gastrointestinal biopsies...and this experience allows me to give you a perspective that may be different from what you may have heard at various meetings or read in clinical review articles.

Endoscopy versus full-thickness biopsy:

The greatest advantage of endoscopic sampling, in addition to the obvious advantages related to the ability to avoid invasive surgery, is the ability to obtain a large number of samples in a relatively short period of time. Typically, one would take 6-8 gastric samples, at least 2-3 duodenal samples, and another half dozen from the colonic mucosa. Endoscopic biopsies are limited to the mucosa, but are perfectly adequate when one is attempting to diagnose many types of inflammatory bowel disease, in which the ability to widely sample random areas of mucosa is more important than obtaining full thickness samples. They are also enough to diagnose most types of neoplasia...provided the tumor is in an area accessible to the endoscope.

In contrast, full thickness biopsies are more arduous and usually I receive only a single sample from each region of the gut. The small number of samples is a distinct disadvantage. Full thickness biopsies do have several advantages, however. The most obvious is that you are able to sample jejunum and ileum, which normally are not accessible to even the most skilled endoscopist. Secondly, there are a number of conditions for which sampling the full thickness of the gut wall is important. This is particularly true of lymphangiectasia (in which the dilated lymphatics are much more obvious in submucosa and tunica muscularis than they are in the mucosa), and some examples of intestinal neoplasia in which the transmural spread by the atypical cells is the only certain way to distinguish malignancy from a purely inflammatory proliferation.

Inflammatory bowel disease - is it real?

The gigantic supposition that underlies the clinical syndrome known as inflammatory bowel disease is that an increase in leucocytes within the intestinal lamina propria is somehow directly related to the production of vomiting or diarrhea. The supposition may be correct, but *in fact it is nothing more than a supposition that has been repeated so often that it is now assumed to be true.*

The normal cellularity of the dog and cat intestine has never been defined, so our ongoing struggle to pinpoint those patients in which the cellularity is “excessive” is doomed. I can guarantee you that the same intestinal biopsy, shown to 10 different pathologists, is likely to generate a 50:50 split in terms of who thinks it is inflammatory bowel disease and who would classify it as falling within the broad range of normal. Why, one must ask, has such an obvious question never been addressed?

The first and most obvious problem is one of the huge costs for such a study, which would require very large numbers of dogs and cats maintained for several years, so that we could study the influence of such things as diet, age, hormone fluctuation, concurrent disease, and previous or current subclinical parasitism on intestinal cellularity. It is undoubtedly true that the intestine of each animal is unique in its flora and unique in its cellularity, so that a biopsy that lies well within the normal range for the population as a whole may well be very abnormal for a particular individual - or vice versa.

The second flaw is the unproven and simplistic assumption that increased leucocyte numbers necessarily cause intestinal disease. A parallel argument would be that an increase in lymphocyte numbers within lymph node (lymphoid hyperplasia) signifies malfunction of that lymph node. This is clearly not the case, and in fact we assume that a hyperplastic lymph node is one that has been stimulated to do its job...and is to be congratulated. Why then do we assume that the intestine, which is the largest lymphoid organ in the body, is somehow malfunctioning when it undergoes lymphoid hyperplasia?

A valid alternative approach would be to examine the cellularity of intestines during active disease, and then do a repeat biopsy when the disease has spontaneously disappeared or when it has responded successfully to therapy to see what has changed. Alas, it is very difficult to convince owners to submit their pets to this second series of biopsies just to satisfy our curiosity...even when we have such a need to know! Unlike skin disease, where we have learned a great deal by charting the response of the skin to a single therapeutic protocol, we tend to use a wide variety of therapies when trying to control gut disease, and thus we cannot even use the response to therapy to speculate about the pathogenesis of most examples of canine or feline gastrointestinal disease.

In my judgement, when contrasted to so many other areas of diagnostic veterinary medicine, we have made virtually no progress over the last 20 years in addressing this most fundamental of all questions about intestinal disease: what is, and what is not, pathologic intestinal inflammation?

What is the correlation between endoscopic observation and histopathology?

In several studies, the correlation between what you see with the endoscope and what I would eventually see with the microscope is not particularly good. It varies with the nature of the endoscopic observation. Things like ulcers or tumor-like masses are usually confirmed via histology, but observations of mucosal redness, edema, and granularity are seldom supported by histologic observation. This is not to say that the endoscopic observations are invalid, but merely that these changes reflect subtle hyperemia and edema that are not easily perceived microscopically. Conversely, the mucosal hypercellularity or subtle architectural disorganization that often forms the basis for our histologic interpretation may not be visible to the endoscopist.

Is endoscopy difficult to learn?

I certainly am no expert to answer that question, but I can tell you that the great majority of private practitioners who have purchased endoscopes are sending me good quality samples on their first or second attempt. Even experts will hit the occasional animal that seems most reluctant to give up any decent mucosal samples, but in general the learning time appears to be very short. It is not an instrument which one should fear...but buy a good one! Habitually poor samples are often eventually traced to the purchase of a “bargain” instrument.

If pathologists cannot diagnose inflammatory bowel disease, is it worth getting an endoscope?

I do not wish to paint too pessimistic a picture. There are many cases in which there are lesions like mucosal fibrosis, villus atrophy, epithelial ulceration, or massive eosinophilic or neutrophilic infiltration which are quite clearly the result of some kind of mucosal inflammatory disease. Endoscopic samples can also pick up unsuspected neoplasia, particularly intestinal lymphoma, and can diagnose some specific intestinal infectious diseases. My comments above were directed specifically at the vague entity known as inflammatory bowel disease, which is defined as a relatively normal intestinal morphology but with an excess proprial population of lymphocytes, plasma cells, or eosinophils. If I have portrayed the diagnosis of inflammatory bowel disease as a very subjective one, rather than as being based on well documented and widely accepted criteria, then I have portrayed exactly the correct message.

What about bacterial gastritis?

The discovery 20 years ago that the bacterium *Helicobacter pylori* is a major contributor to the syndrome of chronic gastric ulceration in people spurred a tremendous flurry of activity in the veterinary field. Part of the enthusiasm is driven by the desire to prove that gastric ulceration or chronic gastritis in dogs and cats also has an easily treated, bacterial pathogenesis. It is equally true that another major stimulus for the flurry of activity is the prospect of the huge dollars that would flow towards researchers who are able to establish dogs or cats as valid models for the human disease. Based on our current understanding, we know that *Helicobacter* and similar organisms are part of the normal flora of dogs and cats (as well as many other mammals). Colonization by these organisms results in an increase in overall cellularity within the lamina propria and in mucosal thickness, but in most experimental models there are no associated clinical signs. A similar phenomenon occurs throughout the intestinal tract at weaning, and seems to be a nonspecific response to increases in intraluminal antigen load.

We know that some dogs and cats with gastritis have an increased number of these organisms, but it is by no means clear whether the increase is the cause of, or the result of, the gastritis. There are many examples, throughout the gut, of shifts in flora that are the result of altered local environments, but we persist in assuming that any shift in flora must be the cause of the enteric lesions rather than simply the result. The jury is still out on this one. A diagnosis of helicobacter gastritis is, in some laboratories, the "flavor of the month". At the moment, it is my policy to carefully examine gastric biopsies for any evidence of overgrowth by spiral bacteria, and to report that observation when it occurs. It may be that specific antibiotic therapy in such cases will indeed be beneficial, regardless of whether the organisms are primary pathogens or are simply part of an opportunistic overgrowth.

When in doubt . . . ask!

If you have any doubts about whether endoscopic biopsy would be appropriate for a specific clinical case, I would welcome the chance to speak with you. I may not be able to answer your question, but it is sometimes prudent to consult the person who, in the end, will be looking at your biopsies! Perhaps here I can provide answers to a few of the more commonly-asked questions.

Do I need to put samples from each region in separate bottles?

The answer is no, because it is easy to distinguish the various parts of the stomach from one another, and from small intestine or colon.

Do I need to place the biopsies on pieces of cardboard?

The answer again is no, mostly because they all fall off anyway!

Why do I need to take so many samples?

There are two answers for this one. The first is that orientation of the biopsies is hit-and-miss, so that some of the samples will inevitably be maloriented and will not give me the information that I need. The second, and more significant, reason is that intestinal disease (particularly gastric disease) tends to be patchy, and it is quite common to have one very abnormal sample in the midst of 2-3 that are either completely normal or equivocal.

In addition, many gastrointestinal diseases have widespread histologic lesions even if the clinical signs seem to point to very local disease. Histologic changes in colon, for example, may greatly strengthen my faith in the validity of subtle gastric lesions, or vice versa.

Are there any diseases which cannot be diagnosed by endoscopy?

There is no easy answer to this one, in that most diseases are occasionally detected via endoscopy...but none are always detected!

1. Obviously, any disease which is purely functional will not be diagnosed by biopsy of any type.
2. Any disease in which the definitive lesions are habitually in submucosa or deeper layers, or in which lesions usually affect more distal small intestine, is a poor candidate. The most prevalent of these is **lymphangiectasia**. It usually is a difficult diagnosis based on mucosal

biopsies alone, because detecting dilated lacteals within the villi is neither sensitive nor specific. In most cases, the diagnosis requires visualization of dilated lymphatics and/or granulomatous lymphangitis in submucosa, tunica muscularis, or serosa. **Smooth muscle tumors** and other **gastrointestinal stromal tumors** are rarely accessible to endoscopic detection.