An Enigma Wrapped in a Mystery – Inflammatory Bowel Disease

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It's a mystery to confound Hercule Poirot or Sherlock Holmes, or both. More than that, it's one that might send them off together to plan a career switch, or at least a long change of scenery.

IBD – inflammatory bowel disease – is a syndrome that has engendered far more questions than answers. It's not new in veterinary or human medicine, but has been recently recognized in ferrets, and its impact on ferret health may be far more widespread than we know. The only thing we know for certain about this disease is that our knowledge is sorely lacking. Today, most of our knowledge of IBD comes from human research, and a little (but not much) from other animal species such as dogs, cats, horses, and some species of rodents and monkeys.

The alias

"Monsieur Poirot, every killer leaves a signature – it is their very nature." Holmes bent down for a closer look. "Here it is," he exclaimed triumphantly. "The killer's name is Hilfiger – Tommy Hilfiger."

Like any master criminal, this syndrome travels under an assumed name. Even the name - inflammatory bowel disease – demonstrates our almost total ignorance about this disease. *Bowel* is another name for the GI tract, and that's about as specific as it gets. While we call it a *disease*, it is likely simply the end point of a number of different diseases, which all result in a similar picture – diarrhea, weight loss, and ill thrift. Finally, for an absolute lack of specificity, you can't do much better than *inflammatory* – it doesn't tell you anything at all about the cause, the lesion, or the symptoms.

The symptoms

Poirot completed his examination of the victim. "It is quite clear to me what caused the death of this poor unfortunate", he said. "What?" said Holmes, drawing deeply on his pipe. "A total absence of life", answered Poirot with all of the confidence of a man who had spent years finely honing his craft.

Like Poirot, many vets and owners fail to recognize the symptoms of IBD, as they are mild and intermittent until advanced disease is present. Unlike many other ferret diseases, there are no "classic" signs of IBD, so the diagnosis is often overlooked. Initially, affected animals have intermittent soft stools, and they may show a lack of appetite or a shift in food preference. Over a period of weeks to months, stools may progress to a grainy or birdseed appearance, indicating the intestine's inability to properly digest protein, starch, and fat.

The modus operandi

Holmes puffed his pipe again. "Ingenious", he said. "It appears the victim was driven to choke himself to death. Hence, I suspect the killer may be a telemarketer or a purveyor of life insurance." "Fiendish", opined Poirot.

Abnormal stool is the most common presenting sign of IBD in ferrets.

At its most basic, IBD is an affliction in which the body turns against itself – the normal defenses of the GI tract overload so that the gut itself becomes damaged. To properly understand IBD, you must first understand the natural protective mechanisms of the gastrointestinal tract.

Most people are unaware of the very important role that the immune mechanisms of the intestine play in protecting the body from disease. In fact, over half of the total lymphoid tissue of the body resides in the gastrointestinal tract. Every day, an amazingly complex network of cells sifts through all of the substances in the gut, deciding what is normal and what is a potential threat. Previously recognized substances (antigens) such as dietary components are allowed free passage, and new antigens are evaluated for threat potential.. Threats may come in the form of ingested bacteria, viruses, toxic or allergenic substances; even developing tumor cells may elicit a protective inflammatory response. Another amazing part about this system is that once a "threat" antigen is eliminated, it not only shuts itself down, but also creates a line of specific "memory cells" which provide a rapid response should that same antigen reappear months or years down the road.

So what happens when the body identifies a threat antigen? Like any good offense, it employs a number of weapons against the enemy. Once a threat antigen is detected, lymphocyte "generals" spring into action, assuming two important roles: "helper" cells which are responsible for inciting and maintaining the inflammatory response, and "suppressor" cells, which turn it off. The lymphocytes secrete cytokines, chemical messages that not only tell other cells what to do, but also make the area inhospitable to the invaders. Cytokines recruit other types of inflammatory cells to the site, to gobble up some invaders and release destructive enzymes to kill others (and unfortunately, anything else in the area.) More lymphocytes arrive and join the fight. Lymphocyte "killer" cells engage in close combat with invaders, punching holes in their membranes with lethal force. Other lymphocytes produce antibodies, which coat the invaders, and packaging them for destruction.

In most cases, the battle is violent and swift, and when the invaders are conquered and the debris is removed, suppressor lymphocytes take over. Surviving inflammatory cells depart, memory cells are created to watch vigilantly for the return of that invader, and cellular regenerative processes begin repairing the damage.

In this particular case, lymphocytes are the primary cells orchestrating the inflammatory reaction. In another, less common form of IBD, known as eosinophilic enteritis, eosinophils, which normally function primarily in allergic or anti-parasitic reactions, are the primary cells, multiplying madly and spewing their destructive enzymes throughout the gastrointestinal tract.

As you might surmise, the war is very damaging to the gut lining and extensive repairs are required for proper digestion to resume. The normal intestine is lined by millions of small finger-like projections (villi). These villi increase the surface area of the intestine many hundreds of times, which is important for extracting as many nutrients and water as possible. IBD's unrelenting inflammation causes loss of villi, and up to 90% of the absorptive area of the intestine, as well as the digestive enzymes contained on the villi. Nutrients now pass through the gut undigested and unabsorbed, diarrhea inevitably results.

We don't know exactly why the inflammatory response does not shut down in affected animals – it may be due to a continual presence of a true threat, or the aberrant recognition of a harmless substance, such as a normal bacterial inhabitant or a common dietary component,

as a threat. A second popular theory is that there is a problem with the suppressor lymphocytes, rendering them unable to turn off the inflammatory response. Regardless of the cause, the end result is a persistent inflammatory response that cannot be shut down without medical intervention, and ongoing bowel damage.

The cause(s)

Poirot reached over and picked up a large bound ledger on the floor. "Our day is almost complete, Holmes", he said, "for this book contains the address of our killer." "You never cease to amaze me, Poirot", said Holmes, as he held out his hand for the volume, entitled The Complete Residential and Business Listings of London.

The list of potential and proposed causes for IBD is endless - viruses, bacteria, dietary antigens, and toxic substances have all been considered, and only a few agents have been conclusively proven or excluded. In humans, dietary gluten has been overwhelmingly implicated as the cause of a form of IBD known as celiac disease. Evidence is mounting that normal bacterial inhabitants of the intestinal tract may have a prominent role in IBD. Research in mice has shown that IBD-prone mice, when raised with sterile intestinal tracts do not develop IBD. In cotton-top tamarins, small monkeys that develop inflammatory colitis, a new bacteria has recently been identified which causes the disease in previously healthy individuals.

In the ferret, there is a growing body of evidence that microorganisms are a prime cause of IBD, although likely not the only causes. *Helicobacter mustelae*, a ubiquitous bacteria in the ferret stomach, causes profound lymphocytic inflammation which destroys the stomach lining, necessitating treatment in about 10% of all ferrets. In my own laboratory, recent research has shown a high incidence of coronavirus antigen (up to 40% in some areas) in the intestine of ferrets diagnosed with inflammatory bowel disease. While it would be nice to believe that these two infectious agents are the only causes for IBD in ferrets, the evidence for other types of agents in other species is far too compelling to ignore.

Diagnostic options

"Are you confident that the victim is dead?" asked Poirot. Holmes deftly removed the dead man's wallet and put it in his own pocket. Seeing no reaction, he nodded his head.

Currently, the options for the definitive diagnosis of IBD in ferrets or other animal species is limited to surgical biopsy. Today, however, biopsies may be obtained via endoscopy in ferrets, without requiring abdominal surgery and a prolonged recovery. There is currently no blood test for IBD, and imaging procedures, such as X-rays and ultrasound are notoriously poor for identifying inflammatory lesions of the bowel. A combination of appropriate clinical signs and several relatively non-specific indicators on routine bloodwork, may suggest a diagnosis of IBD. However, there are a number of other conditions, such as Helicobacter, coccidiosis, and proliferative colitis that can display an identical picture, and would be worsened by empiric therapy for IBD.

Treatment options

Based on incontrovertible evidence that the killer acted alone and out of their great respect for the recommendations of the two greatest detectives in the world, Scotland Yard locked up all men, women, and children in London who could not provide an alibi for their whereabouts on the night in question. While highly taxing to the British penal system, and profoundly impacting many businesses in and around the London area, it is safe to say that a similar murder was never again reported, and the case was closed.

In most cases, the treatment for IBD is immunosuppression. As we are unsure of

the causative agent in most cases, the typical approach is to shut down the inflammatory reaction with immunsuppressive drugs such as high doses of steroids. Treatment for *Helicobacter mustelae* is an exception – as a bacteria, it can be treated with antibiotics, and if the infection is cleared, the persistent inflammation will diminish as well. In cases of post-ECE inflammatory bowel disease, we do not have this option, as there are no effective antiviral drugs, and As there are no drugs which effectively treat viruses, and we are forced to immunosuppress the animal.

The administration of the steroid prednisone, one of the key treatments in IBD, profoundly affects the body's ability to mount a viable inflammatory reaction. Steroids inhibit the inflammatory response at a number of steps - migration of inflammatory cells, liberation of cytokines, and at higher doses, actually kill lymphocytes. A major concern with this approach is that prednisone is not selective for the gut, but affects the entire body, and may render the animal unable to fight off invaders in other organ systems.

Aziothioprine (Imuran) has recently been used in ferrets that do not respond well to prednisone, but there is much that still needs to be learned about the dosGE and effects of this drug in ferrets. Bone marrow suppression has been reported in several ferrets receiving this drug; so periodic monitoring of complete blood counts is strongly advised.

Dietary changes are also of great benefit in IBD ferrets. The severely damaged intestine requires a bland diet that is highly digestible. Chicken baby food continues to be my personal favorite for animals with chronic GI illness; however, the prescription diet a/d (available through your veterinarian), or a number of types of "duck soup" may be used to advantage in affected animals. Anecdotally, a switch to non-traditional kibbles such as turkey and barley may alleviate some clinical symptoms, possibly by eliminating offending dietary antigens from the diet. It is unlikely that simply switching brands of commercially available ferret chow would be of any significant help in the treatment of IBD, as most have a very similar array of ingredients.

The future of IBD

You don't have to be Sherlock Holmes or Hercule Poirot to see that there is a lot to be learned about IBD in ferrets. To date, only two causes have been definitively incriminated in its development – one bacteria (Helicobacter) and one virus (coronavirus). There is likely many more waiting to be discovered, but the trail is difficult and proof is hard to come by.

Further research is warranted in the extra-intestinal manifestations of IBD as well. Definite correlation between IBD and diseases of other organ systems in humans has been made, including immune-mediated anemia, hepatic lipidosis, clotting disorders, and skin disease (all of which are seen with fair regularity in ferrets). The possibilities are intriguing, to say the least.

The future certainly holds more research and likely some amazing discoveries about the origin of inflammatory bowel disease, its diagnosis, and treatment. That, my friends, is elementary.