Johne’s Disease and Crohn’s Disease: Are They Related?

A report from the National Academies recommends a closer look at the connection between Johne’s disease (pronounced Yo-knees), an intestinal disease found in cattle and other animals, and Crohn’s disease, an intestinal inflammatory disorder that affects humans. Crohn’s disease is a devastating illness of unknown cause that is lifelong and currently has no cure. Certain similarities between the two diseases have fueled increasing concern of a possible link.

The report, Diagnosis and Control of Johne’s Disease, is primarily focused on the effective diagnosis and control of Johne’s disease, but also addresses the possible connection to Crohn’s disease. If evidence of a link were found, it would transform Johne’s disease into a serious public health problem. The report breaks new ground in suggesting that scientists looking at the relationship of the diseases have been asking the wrong set of questions and should significantly shift the focus of their research.

The Potential Link

To understand the human health implications of Johne’s disease, researchers must resolve a central question: Is the underlying bacterial agent of Johne’s disease, referred to as Map (Mycobacterium avium subsp. paratuberculosis), a significant cause of disease in humans? More specifically, is Map a cause of Crohn’s disease, or is it an incidental bystander? Despite intense interest in Map, there is not enough evidence to prove or disprove that Map is a cause of Crohn’s disease or a significant human pathogen.

There have been, however, two well-documented cases of Map infections in humans. One is a young boy with scrofula (a bacterial infection affecting the lymph nodes) who subsequently developed Crohn’s disease. This case that has been cited as supporting evidence for a causal (etiologic) role of Map in at least some cases of Crohn’s disease. The second case is an adult male with AIDS with Map bacteria widely spread throughout his body. Because Map infection will be diagnosed only if it is specifically considered and if appropriate laboratory tests are performed, it is possible that Map has passed unrecognized in similar cases.

There are many similarities between Crohn’s and Johne’s disease. Both are diseases of the intestines that primarily affect the ileum (the portion of the intestines just above the colon), and both cause chronic diarrhea and weight loss. However, when they are compared clinically (symptoms) and pathologically (lesion sites and specific damage), several significant differences can be seen. Experts have interpreted these similarities and differences both in favor of and in opposition to the view that Map is a cause of Crohn’s disease.

The Search for Evidence

There have been several human studies aimed at finding the cause of Crohn’s disease. Researchers have examined cultures of bacteria from Crohn’s tissues, looked at the blood’s antibody responses to Map, and charted patient response to therapeutic treatments directed at Map infections. Unfortunately, these studies...
have produced highly variable and conflicting results. Most of the studies have been small and there has been no standardized patient selection criteria or laboratory methods. A large-scale therapeutic trial is now underway in Australia that, if properly designed and large enough, could help provide an answer to the question of therapeutic response.

What evidence would establish Map as a human pathogen? The generally accepted standard for establishing a specific infectious agent as the cause of a human disease has been the fulfillment of Koch’s postulates. Based on current evidence for Map in Crohn’s disease, Koch’s postulates have been only partially fulfilled as follows:

- **The microorganism must be found in all cases of the disease.** Partially fulfilled. Found in some cases, but not all.
- **It must be isolated from the host and grown in pure culture.** Fulfilled.
- **It must reproduce the original disease when introduced into a susceptible host.** Partially fulfilled. Experimental animals have been infected with human isolates but do not reproduce the syndrome.
- **It must be found in the experimental host so infected** – Fulfilled.

Partial fulfillment of Koch’s postulates support an association with disease but may or may not support causation. Different pathogens can be responsible for a single clinical syndrome. For example, Koch’s postulates are not fulfilled for a single organism in the general clinical syndromes of pneumonia, meningitis, hepatitis, and urinary tract infections, among other diseases. Koch’s postulates can be difficult or impossible to apply to many chronic diseases of complex origin. A notorious recent example was the claim that HIV did not cause AIDS because the human virus did not produce the disease in animal models. Only the tragic infection and disease of laboratory workers and recent responses to effective therapy has settled this controversy.

**The Right Research Questions**

The report recommends a new approach to resolving the question of whether Map is a cause of some cases of Crohn’s disease. A shift is needed from Koch’s postulates to fulfilling the Hills-Evans criteria, which are better suited to establishing the cause of complex chronic diseases like Crohn’s disease. The report also recommends convening an independent panel to establish standardized protocols and laboratory methods for the critical studies required to confirm or refute a causal role for Map in Crohn’s disease. This would allow direct comparison of results from different laboratories and facilitate attempts to repeat key experiments.

Epidemiologic evidence is an important element of the Hills-Evans criteria. Gathering such evidence for a causal connection will be difficult, however, because it is possible that exposure to Map is occurring in infancy but disease does not manifest itself for several decades. While fulfillment of all 10 of the Hill-Evans criteria would strongly incriminate Map, a lack of data makes this unlikely as illustrated by the following partial list of Hill-Evans postulates and an evaluation of currently available data:

- **Prevalence of Crohn’s disease should be significantly higher in those exposed than those not.** No systematic studies correlating exposure to Map to incidence of Crohn’s have been performed.
- **Exposure to Map should be more frequent among those with Crohn’s than without.** No studies specifically evaluate the exposure of patients with Crohn’s disease to Map.
- **Modifying or preventing the response should decrease or eliminate the disease.** Various therapeutic trials have been performed but the data are inconclusive.
- **All findings should make biologic and epidemiological sense.** Johne’s and Crohn’s diseases have many clinical and pathological similarities, but there are significant differences as well. It seems biologically plausible that Map could cause at least a subset of Crohn’s disease.

In addition to recommending a new research approach to the question of Crohn’s disease, the main body of the report outlines the steps that should be taken to control Johne’s disease, reduce the spread of Map, and minimize effects of the disease in animals. Johne’s disease is a significant animal-health problem that warrants the creation of control programs tailored both to specific animal species and segments of the agricultural industry. The report recommends an integrated, bottom-up approach to on-farm disease control that meets the needs of the livestock producers and motivates behavioral change, with support at industry, state and federal levels.

Diagnosis and Control of Johne’s Disease is available from the National Academies Press, 500 5th Street, Washington, DC, 20001; (800) 624-6242 or http://www.nap.edu. This study was conducted under the auspices of the National Academies’ Board on Agriculture and Natural Resources.

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