A causal role for *Mycobacterium avium* subspecies *paratuberculosis* in Crohn's disease?

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Criteria for establishing a causal role of microorganisms in disease were first outlined by Henle and further developed by his student Koch in the late 19th century to establish the relationship of tubercle bacillus to tuberculosis. The Henle-Koch postulates state that the organism is always found with the disease, the organism is not found with any other disease and cultured organisms isolated from a diseased individual reproduce the disease in a susceptible animal (1). To broaden these criteria for chronic diseases as well as for infectious diseases with related asymptomatic or carrier states and/or multifactorial causes, a broader set of standards were outlined by Hill (2). While not all of the arguments in total, and only a few of the individual arguments, can be required as a sine qua non in any given circumstance, these standards provide a useful basis for discussion of causal inference.

In this issue of *The Canadian Journal of Gastroenterology*, Hermon-Taylor and colleagues (pages 521-539) address "Causation of Crohn's disease by *Mycobacterium avium* subspecies *paratuberculosis*". Elucidating the etiology of Crohn's disease is a major challenge. Crohn's disease exhibits the characteristics of a chronic disease (ie, indefinite onset, a presumed long latent period and crucial dependence on host factors), yet, as proposed by Hermon-Taylor and colleagues, the basis of disease may be microorganism infection. In their review, Hermon-Taylor and colleagues nicely highlight a number of issues that hamper efforts to study the role of *M avium* subspecies *paratuberculosis* (MAP) in Crohn's disease. These issues include difficulties in culturing MAP in vitro, the lack of knowledge related to the environmental distribution of MAP, the relatively high prevalence of sub-

clinical MAP infections in domestic animals and perhaps humans as well, and problems with antibody recognition to detect present or past MAP infection. Nevertheless, the authors present some interesting indirect evidence that suggests a role for MAP in Crohn's disease. While the evidence presented in the review is thought-provoking and indicates areas of future research interest, the evidence necessary for inferring a causal role of MAP in Crohn's disease is lacking in several key areas.

A cornerstone of many of the standards for causality outlined by Hill is direct evidence from human populations (2). The presumed association between MAP and Crohn's disease, or the ratio of Crohn's disease in those with and without active MAP infection, has not been established, nor has the temporality of the association, or evidence that MAP infection precedes the development of Crohn's disease, been established in human populations. The identification of MAP DNA in Crohn's disease tissue (3) only reveals that MAP infection and Crohn's disease can exist at the same point in time. MAP infection may occur before or after the development of Crohn's disease and in either case may have little influence on the natural history of the disease. There is also a lack of information about the impact of the occurrence of Crohn's disease on the elimination or reduction of MAP from environmental sources such as milk or water. Geographic variation in Crohn's disease incidence (4) must be interpreted with a great deal of caution. Variation may be due to many causal or modifying factors that may or may not be related to the presence of MAP in environmental sources. William Farr erroneously attributed cholera to fetid air in the 19th century based on the observation of a higher inci-

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dence of cholera at lower altitude (5), illustrating the need to guard against inferences or conclusions that are not based on direct evidence.

Hill (2) wrote,

All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer on us the freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

It would be unwise to ignore the indirect evidence presented by Hermon-Taylor and colleagues that supports further investigation of the role of MAP in Crohn's disease. It

would be equally unwise and premature to initiate primary prevention efforts at this time due to the uncertainty in the possible MAP-Crohn's disease link. Optimal utilization of limited time and resources requires reduction in the uncertainty of the MAP-Crohn's disease association before any primary prevention measures can be discussed.

REFERENCES

1. Rivers TM. Viruses and Koch's postulates. *J Bacteriol* 1937;33:1-12.
2. Hill AB. The environment and disease: Association or causation? *Proc R Soc Med* 1965;58:295-300.
3. Sanderson JD, Moss MT, Tizard MLV, Hermon-Taylor J. *Mycobacterium paratuberculosis* DNA in Crohn's disease. *Gut* 1992;33:890-6.
4. Bernstein CN, Blanchard JF. The epidemiology of Crohn's disease. *Gastroenterology* 1999;116:1503-6.
5. Langmuir AD. Epidemiology of airborne infection. *Bacteriol Rev* 1961;25:173-81.