Global Rates of Crohn's Disease

To the Editor:

Crohn's disease (CD) has conventionally been considered an autoimmune disease with a genetic predisposition. However, recent advances in clinical and fundamental research have challenged this classification, pointing instead to a state of impaired innate immunity to microbial exposures.[1,2] The epidemiologic observation that Crohn's rates are increasing in many parts of the world is also consistent with an infectious disease. As such, modeling rates of CD against putative determinants may help to predict the kinds of exposures associated with the increasing burden of disease. Because CD is not a reportable disease, until recently, data on CD occurrence were limited. An important first step to address this has recently been realized, with the publication of the first global atlas of Crohn's rates.[3]

As it is well recognized that CD is more common in industrialized countries, we plotted the incidence of CD in 27 countries on the Y-axis against each country's per capita gross domestic product (GDP) for 2005, reported by the United Nations (www.unstats.un.org). There is a positive association (Fig. 1A), with higher rates of CD in countries with higher productivity. Nonetheless, assuming a linear trend, the R^2 so generated is only 0.27, pointing to other determinants of CD incidence. Plotting CD against age-standardized cardiovascular mortality (www.who.int/infobase), a proxy for a Western diet, resulted in a weaker association (data not shown). We then explored the possible association between incidence of CD and antimycobacterial immunity, based on the hypothesis that a mycobacterial infection may have a role in the etiology of CD.

Mycobacteria are known to induce relatively nonspecific immunologic responses, with consequences for natural mycobacterial epidemics and BCG-induced protection.[4] Historically, tuberculosis (TB) and leprosy behaved as antagonistic epidemics and mathematical modeling has shown that a moderate degree of cross-protection would permit TB to eliminate leprosy.[5] Similarly, rates of human TB in England were lowest in counties where exposure to bovine TB was highest.[6] More recently, as TB rates have dropped, several countries discontinued BCG vaccination and soon after observed increasing rates of disease due to nontuberculosis mycobacteria.[7] To test whether declining rates of TB are associated with increasing risk of CD, we plotted the estimated incidence of CD against the incidence of TB in 2005 (http://www.who.int/tb/publications/global_report/en/). As seen in Figure 1B, there is a reciprocal relationship between these 2 rates, with $R^2 = 0.50$. To test the possibility that prior exposure to TB might be protective against CD, we compared Crohn's rates against 1990 rates of TB. Here, the inverse relationship is much more evident, with an $R^2 = 0.69$. Even removing the 2 countries with the highest Crohn's rates (Canada, New Zealand), $R^2 = 0.66$.

A number of hypotheses have been advanced for the rise in Crohn's rates, including improved hygiene, refrigerators, well water, or Western diets.[8] However, while most ecologic associations ascribe a higher or lower risk of disease to an environment or country, they do not permit one to target a particular group of microbial agents for investigation. The present analysis serves to stimulate quantitative investigation of the global incidence of CD and the potential role of certain microbial agents. For reasons that remain to be clarified, populations with the highest rates of CD have the lowest rates of TB.

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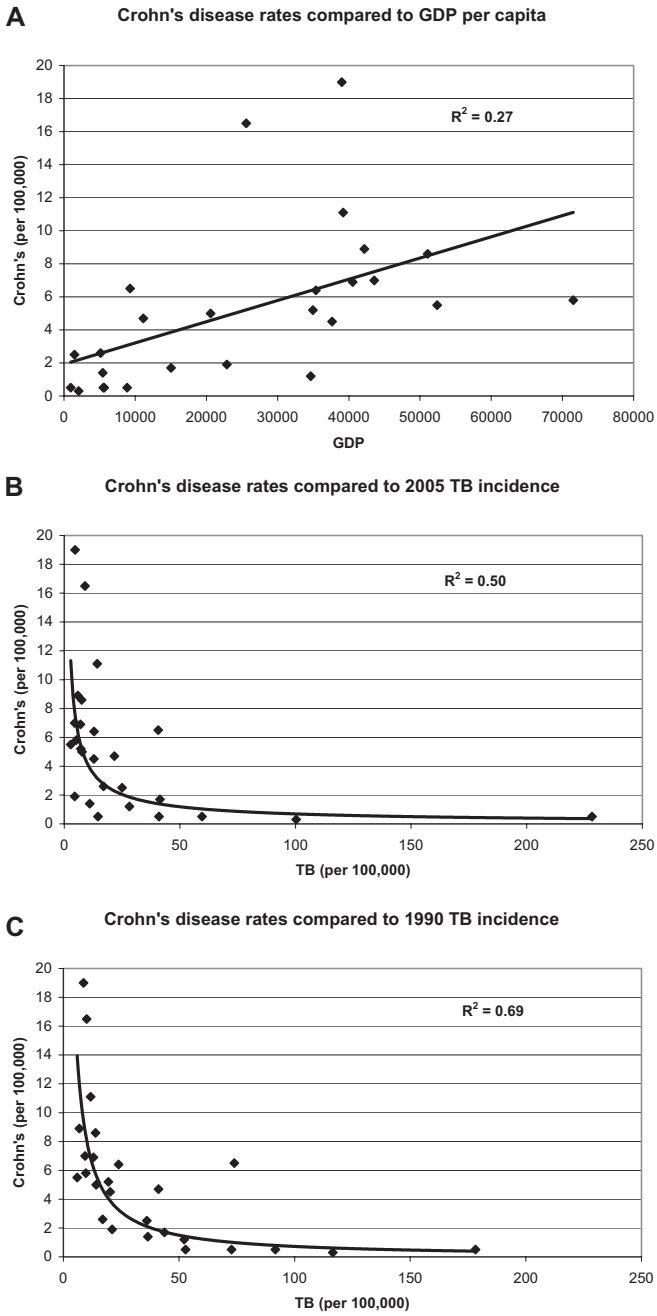

FIGURE 1. CD disease rates compared to (A) GDP per capita; (B) 2005 TB incidence; (C) 1990 TB incidence.