strate no evidence of “nonspecific antibacterial effects.” Hence, the high remission rate is clearly a specific effect of the anti-MAP drugs on MAP. The Selby et al paper did intimate that metronidazole and ciprofloxacin may cause “nonspecific” effects but failed to mention that both drugs have known antimycobacterial activity and therefore their effect can be directly attributed to an anti-MAP effect rather than the nebulous “nonspecific antibacterial effect.”

We, as physicians currently treating patients with Crohn’s disease using anti-MAP drugs and seeing results not achievable with established therapies, are surprised that this GASTROENTEROLOGY paper—describing an effective, new “breakthrough therapy” with a high remission rate—was cast in a negative light. Nevertheless, we congratulate the journal for publishing this novel treatment so needed in an area crying out for effective therapies.

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2. ICH Harmonised Tripartite Guideline: General Considerations for Clinical Trials E8.

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Importance of the Australian Crohn’s Disease Antibiotic Study

Dear Sir:

The article by Warwick Selby, “Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn’s disease” and the accompanying commentary are well written and worth reading carefully. They contain important data and commentary. Unfortunately, despite data supporting the positive impact of properly chosen antibiotics in treating Crohn’s disease (CD) patients, the authors emphasize the negative. The authors report the data accurately, but their interpretations need to be challenged. It is true that atypical mycobacterial antibiotic therapy (AMAT) did not provide a cure for CD, and thus this trial was technically a negative study, but the antibiotic limb did significantly better than the comparison limb as long as antibiotics were being administered. At 4 months, 66% of patients on AMAT were in complete clinical remission. This response rate is better than any other therapy (including infliximab) to date. The data support another interpretation: AMAT provides a more effective treatment regimen with a more favorable side effect profile than current conventional therapy. This is indisputably true for a subset of patients who need to be better defined. Certain points need to be made.

1. The control arm was not a placebo arm; patients continued to receive treatment with mesalamine drugs and 6-mercaptopurine (6-MP).
2. Unknown at the time, but recently published by Robert Greenstein and Sheldon Brown is the fact that mesalamine and 6-MP have an antibiotic effect against Mycobacterium avium paratuberculosis (MAP) in vitro. They opine that conventional therapeutic regimens may be effective because of their anti-MAP characteristics and not because of their immune suppressive characteristics. Nevertheless, adding antibiotics to the treatment was associated with a significant improvement (66% vs 50%) in achieving complete clinical remission at 4 months, 42% versus 25% at 1 year, and 34% versus 18% at 2 years. The fact that the difference between the 2 groups no longer remained statistically significant at 3 years (1 year after the antibiotics were removed; 19% vs 12%) should not have been interpreted as showing that AMAT was not beneficial. The conclusion could have been that AMAT suppresses CD activity, but evidence for a cure in this group study was not achieved.
3. Important specific information on individuals was not reported. Clinical responses not achieving complete remission were considered to be failures. Physicians with experience with AMAT have all seen patients whose disease disappears and their bowels heal. The subset of patients for whom AMAT is a miracle therapy is completely unreported.
4. Conventional therapies do not provide a cure and are accompanied by predictable, serious side effects. Infliximab initially has a 60% response rate with only 20% achieving remission at 1 year. In this study, 42% of patients receiving AMAT were in clinical remission at 1 year. It is inconsistent to extol the virtues of one form of therapy that improves symptoms but does not cure the disease and then dismiss AMAT because it does not cure the disease, although it is safer and does a better job at achieving remission.
We are all seeking additional options to treat this disease. Antibiotics have been, and still are, first-line therapy for CD. Most choose single agents such as metronidazole or ciprofloxacin. They both seem to work for a while. The triple antibiotic regimen used in this study is an improvement on the monotherapy usually given. This is truly a situation where the glass is half full or half empty. Presenting the positive data in a negative manner is not helpful. Perhaps if the authors were to reevaluate their conclusions they would realize the true value of their efforts.

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Reply. Thank you for the opportunity to respond to these letters regarding our trial of antimycobacterial therapy in Crohn’s disease.1–4 Most of the comments and criticisms raised by your correspondents were addressed in our original article.5

The higher doses proposed by Drs Gitlin, Biesecker, Lipton, and Barash are derived from regimens used for treatment of Mycobacterium avium complex infections, not specifically for Mycobacterium avium paratuberculosis (MAP). We chose the same doses of clarithromycin and rifabutin that were reported to be effective in Crohn’s disease in the open-label study performed by Gui et al.6 Our placebo-controlled, double-blind study added clofazimine to this regimen, but did not replicate their results. To our knowledge, there are no published reports of the use of higher doses of these antibiotics in Crohn’s disease.

We were also concerned about the nonresolution of clofazimine in vitro (which may or may not have occurred in vivo). We performed a supplementary analysis, excluding patients who were exposed to the defective capsules. This demonstrated a higher relapse rate in the active treatment group, which is inconsistent with a loss of efficacy owing to failure to dissolve.

It is argued that the results of the trial are invalid because we did not identify MAP by culture or polymerase chain reaction testing. This is discussed in our paper and does not influence the findings that the antibiotic regime was not effective in the long term.

Dr Chamberlin states that “the antibiotic limb did significantly better than the comparison limb as long as antibiotics were being administered.” This is incorrect—the only statistically significant difference was at 16 weeks. It is not clear why there was a difference at 16 weeks, but it seems unlikely that it was due to elimination of MAP because there was no statistically significant difference at 12, 24, or 36 months despite continuing the antibiotics for 24 months. We have speculated that it may be due to a nonspecific antibacterial effect—the data do not permit any firm conclusions.

Dr Chamberlin cites recently published data suggesting that mesalazine and 6-mercaptopurine have an antibacterial effect against MAP in vitro.7 The extrapolation of in vitro data to the clinical arena is speculative and is not consistent with the well-established activity of other immunomodulators, such as corticosteroids and infliximab.

Dr Kuenstner suggests that the study required an unrealistically high response rate for a positive outcome. We disagree; the power calculation was based on demonstration of a difference of 40% in relapse rates between the active treatment and placebo arms. Dr Kuenstner also suggests that reexposure may have occurred. This should not have affected patients who continued to take MAP therapy. Dr Kuenstner comments that the study may not have had adequate power to detect a difference if only a proportion of patients were infected with MAP. This is true for any trial of any therapy for any infection. However, the results of the study do not support a significant pathogenic role for MAP in the majority of patients with Crohn’s disease. Dr Kuenstner’s advocacy of public health measures and development of better MAP therapies for Crohn’s disease is not supported by current evidence.

Drs Gitlin and Biesecker are critical of endpoints chosen for the study (proportion of patients experiencing at least one relapse at 12, 24, and 36 months), suggest that the proportion of patients achieving remission would be more appropriate, and compare the 66% remission rate at 16 weeks with a 39% response rate with infliximab. We believe the choice of endpoints is appropriate (the aim of the trial was to assess long-term anti-MAP therapy) and that it is misleading to perform such cross-trial comparisons. Their criticisms are contradictory; if the response to MAP therapy “ranks among the highest remissions generally achieved,” the dosage must have been adequate and the patients continuing in the active arm should have stayed in remission.

We conducted a randomized, double-blind, controlled trial comparing steroids plus 3 anti-Mycobacterial antibiotics with steroids alone. To our knowledge, this is the