

Responses to Reviewers

Reviewer 1 Comments

In this review article Charlesworth and Marsh discussed about some pitfalls in intraepithelial lymphocytes (IELs) count in duodenal biopsy samples. Indeed, they point out that a bidimensional biopsy may lead to an overestimation of IEL count. Therefore they propose a 3D model to overcome this shortcoming. The main problem of this manuscript is that it is hard to understand in several parts, especially for an audience of gastroenterologists. In particular, the last paragraph starting at page 6 is quite obscure and needs to be re-written in a form that could be widely understandable even by "non-experts". Authors must give a more simple, practical and understandable definition of "numerical digit preference" and "quotient of accumulative addition of values". These concepts are pivotal for the discussion of this paper, therefore Authors must explain how they are calculated or used for 3D analysis, even through a worked example. An "obscure" concept significantly limits the feasibility of a method and, therefore, its diffusion in practice. Additionally, they should discuss whether these parameters may rule out the problem of subjective interpretation of cell count. Page 3 line 9: please check the word "autolysed". Page 5 line 18: does figure 5 refer to the figure of another paper? This issue is repeated several times in this paper. If so, the reader is forced to look for other figures in other papers, and this may badly impact on the comprehensibility of the paper.

Response from the Authors

We are especially grateful to Reviewer 2 for the measured, insightful criticisms of our original MS. We have considerably simplified the definitions alluded to, and revised the text to simpler sentences. As required, we have also paid more attention to computerised image-analysis techniques used by us, and referred to those papers. We have added a further paragraph indicating that Computerised image-analysis can overcome many of the subjective drawbacks of routine histological analysis, and the resulting subjective errors in interpretation.

The paragraph (p6) has also been attended to and been re-written.

Finally, we both acknowledge the objective criticisms of our paper which have therefore resulted in a revised MS that is greatly improved. Thankyou!

Reviewer 2 Comments

Too many self citation 2. Please remove bibliographic references older than 5 years

Response from the Authors

The authors completely disagree with these reviewer's comments. In our last summary section, we reiterated that the main aim of this paper was to provide a definitive account of small intestinal structure and interpretation. As this is an area of study which has accrued over the past 60-70 years, we felt that it was important to include key historical references in our writing. To remove these references would completely change our central argument and fail to acknowledge the historical context of this field of research. We have also included self-citations as much of the work which we have previously performed is aimed at redefining mucosal interpretation in coeliac disease. To not include these works in what is a critical review of all the literature would therefore not be fully representative of this field of research.

In light of this, the authors have not made any changes. We note that Reviewer 1 did not express similar reservations: indeed, he rated the MS and its contents to be of a high scientific level. We agree with that opinion.