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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16885-Review.doc).

Title: Increased catabolism and decreased unsaturation of ganglioside in patients with IBD

Authors: John J Miklavcic, Tasha Hart, Gordon M Lees, Glen K Shoemaker, Kareena L Schnabl, Bodil MK Larsen, Oliver F Bathe, Alan BR Thomson, Vera C Mazurak, M Tom Clandinin

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 16885

The manuscript has been improved according to the suggestions of reviewers:

Reviewer: 02999941

Major points:

1 The discussion includes explanation and justification of sampling 10 cm away from tumour in CRC control. The discussion is expanded to include this as a strategy for avoiding measurement of ganglioside in cancer tissue which may be altered in tumourigenic state.

2 Based on the information collected from specimens, additional descriptors have been added to the description of BAP tissue sampled. The manuscript also includes discussion related to avoidance of measuring familial polyp cases.

3 The 2nd last paragraph of discussion discussed the strength of the study control groups and the high correlation of observations among BAP and CRC tissue with respect to relative ganglioside and phospholipid content. Discussion now also includes limitation/suggestion for future study pertaining to comparison of IBD intestine to other inflammatory conditions to ascertain whether observations in this study are specific to IBD or inflammation. As described, at reference 37, "less-" inflamed or "adjacent-to-inflamed" tissue was not sampled and the explanation has been expanded upon. Potential latent effect of anti-TNF biologic and/or immunosuppressant is further discussed in Methods.

Other points:

1 The 4th paragraph of introduction contains minor amendment to explain and justify the reasons for examining intestinal phospholipid (in addition to ganglioside). 4th paragraph of discussion also includes summary related to the new statement in introduction.

2 Introduction now includes information on IBD pathogenesis in addition to epidemiology, presentation, treatment, and complications. 4th paragraph of introduction is expanded upon to aid reader in interpretation of discussion (paragraphs 5, 6) pertaining to ganglioside and phospholipid composition.

3 Some disagreement among quantitative measures of GM3 and GD3 in Table 2 had previously limited reader interpretation. A new paragraph in discussion pertaining to standardized measure of ganglioside content (relative content, /phospholipid, /protein, /wet weight, ratio) in intestine is now included.

4 BAP was the smallest group (*n*=6); measurement and comparison of HEXA and NEU3 content (Figure 2) for comparison to IBD and CRC is under-powered. The authors elect to avoid presenting a figure including an apparently significant difference of enzyme content in BAP from IBD intestine when in fact, it would be under-powered. However, the authors anticipate a very high correlation between BAP and CRC control with respect to HEXA and NEU3 due to the high correlation of relative ganglioside content these groups, which is noted in the discussion.

5 2nd paragraph in discussion expands on possible functional consequence of ~2-fold increase in HEXA in bowel from patients with IBD.

6 To limit the 'busyness' of the tables, table 5 no longer includes data pertaining to PE and simply acknowledges no significant difference in the results and table legend. Table 4 has been shortened to no longer include data from ganglioside GM3 or ganglioside species of lower abundance in GD3 and GD1a.

Reviewer: 02999956

1 Statement in the first paragraph of discussion which originally proposed cause-and-effect has been softened and now indicates plausible correlation.

2 Discussion pertaining to whether microbiome or bacterial enzymes may have influenced findings is now included.

3 The 3rd comment from this reviewer is addressed as in "Other points #3" above.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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