Author's response to reviews

Title: Evolutionary Explanations in Medical and Health Profession Courses: are you answering your students Why questions?

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Dear Editor BMC Medical Education

Attached we have submitted our manuscript entitles Evolutionary explanations in Medical and Health Profession Courses: are you answering your students why questions? based upon the 2nd round of reviews. We were delighted to see that the reviewer felt that our first revisions improved the paper and that he felt the paper will stimulate wide and productive debate. Indeed this is how the paper is intended. We would like to let you know that we greatly appreciate the extent of work that the reviewer went to in giving suggestions. We truly believe that the paper has been greatly strengthened by this interaction.

Nevertheless, the reviewer still had a number of comments and suggestions that he felt would strengthen the paper. We read these suggestions carefully, and we felt that most were constructive. We therefore present our new revised paper to you in which these suggestions have been incorporated. Following are our responses point-by-point concerning how we handled the reviewers suggestions.

Respectfully submitted,

Eugene E. Harris, PhD and Avelin A. Malyango, MD

1. The reviewer wished to see us take opportunities to address the testing of evolutionary hypotheses in medicine. In response we have taken several opportunities to do so. See below.

For example, on page 9 in the section Explaining Symptoms: To test the diarrhea-as-defense hypothesis persons were treated with and without the anti-diarrheal medication Lotomil [we now refer to that study]. This draws attention that these hypotheses can rather easily be scientifically tested.

We also refer to testing on pg 10: If each pathogen-host combination were to be analyzed separately, realizing that the balance of evolutionary forces acting on the host and pathogen may vary in different cases

We now directly include discussion of scientific testing with an example in the paragraph starting on pg 11 bottom and continuing onto pg 12: Such evolutionary hypotheses can be tested scientifically, for example, witness studies of cystic fibrosis (CFTR) [20, 21]. The gene was found to code for chloride ion protein channels on somatic epithelial cell membranes, and the bacteria See paragraph here.

Further, in many cases we point out where certain evolutionary hypotheses require further testing. For example, on page 15 middle we now say directly: Surprisingly, many such evolutionary hypotheses initially advanced a decade or more ago on the bases of observed biased inheritance patterns, because of the commonness of the disorder, and other circumstantial evidence, have not received rigorous scientific testing. In fact, for each disease or disorder, predictions could be made with respect to association with a hypothesized compensating advantage, and experiments designed to test the predictions. It would then be possible to determine the validity of the evolutionary hypotheses, and to clarify the proximate genetic and physiological mechanisms.
2. The reviewer suggests that we reference Wenda Trevathans book Evolutionary Medicine in the section concerning obstetrics Complications of Human Childbirth, Evolutionary Causes pg. 6.

First, we are glad the reviewer feels that our opening on childbirth works well after our first revisions. We have taken the reviewers additional suggestion and now point out Trevathans book on the bottom of page 6 (For further discussion of evolutionary obstetrics see Trevathans book Evolutionary Medicine[6]).

3. The reviewer has suggested toning down our discussion of the importance of big brains in humans.

We have now removed parts of this paragraph on pg. 6 that originally had phrases such as human brains being unrivaled in the animal world. While true, there is no reason to overly emphasize it here.

4. The reviewer comments that we mention rounding the pelvis repeatedly.

We have now changed our wording on pg 6 to birth canal and increasing the birth canal rather than saying rounding of the pelvis. This helps to clarify our meaning.

5. The reviewer queries why we have not cited Livingston for his work on sickle cell anemia in Africa.

This was an oversight. Livingston (1958) is indeed a classic paper of anthropological genetics that readers should be referred to. We now have cited Livingstons classic paper on pg. 8: and the relationships between mosquito ecology, agriculture, malaria, and frequencies of the sickle cell gene have been carefully studied [13].

6. Bottom of pg. 7: we now say alleles as suggested by the reviewer.

7. Following the reviewers suggestion, we now say on pg. 8: Thus, the allele for sickle cell has been maintained because heterozygotes have a higher reproductive success than either of the two possible homozygotes.

8. The reviewer suggests we cite Weatherall (2004) to back up our assertion. We do this now on pg. 9

9. We thank the reviewer for pointing out that we werent clear here. We now have worded the sentence more clearly on pg. 9: For example, Glader and Look [15] report that 41% of the South East Asian refugee population in the United States are carriers of, or have, one of the myriad hematological disorders.

10. The author has mentioned, as above in pt. 1, that it is important for us to mention possible testing of evolutionary hypotheses and that our discussion of the diarrhea symptom would be an opportunity. We agree with the reviewer. We have done this on pg 9. For further information on our changes see our response to pt 1 (above).

11. In order to indicate that Tay sachs hypothesis is controversial, we say on pg. 12: In contrast, it is unfortunate that the Tay sachs selective hypothesis remains largely untested almost two decades later. This also addresses the reviewers pt. 1 since we try to point out that these hypotheses can and should be tested.

12. The reviewer suggests we indicate to our readers how silly it is that evolutionary hypotheses, like the PKU hypotheses, have never really been followed up on.

We agree with the reviewer, therefore on pg. 15 we now say: Surprisingly, many such evolutionary hypotheses initially advanced a decade or more ago on the bases of observed biased inheritance patterns, because of the commonness of the disorder and other circumstantial evidence, have not received rigorous scientific testing. In fact, for each disease or disorder, predictions could be made with respect to its association with a hypothesized compensating advantage, and experiments designed to test the predictions. It would then be possible to determine the validity of the evolutionary hypotheses, and to clarify the proximate genetic and physiological mechanisms involved.

13. In order to qualify our remarks so as not to over-assert our interpretation of the leptin evidence, we now say on pg. 12: Although further research is required, evidence suggests that under increasingly obese body conditions

14. We have kept our insect example of semelparity in the paper, as we believe that readers can understand this. As the reviewer points out, other examples would also be good, but to properly describe
15. We have taken the reviewers suggestion and discussed a very important recent evolutionary hypothesis on Alzheimer's by Finch and Sapolsky 1999. On pg. 13 we start this discussion: Regarding Alzheimer's, another hypothesis [30,31] is built around recent findings of the neuroprotective functions of estrogen and apolipoproteins E2 and E3.

Likewise, we take the reviewers suggestion to discuss important new work on the evolution of hemochromatosis as protection against infection. We start this discussion on pg. 14: More recently, a different hypothesis has been advanced based on the finding that individuals bearing the hemochromatosis mutation (C282Y) show partial resistance to Yersinia.