Reviewer's report

Title: Chemical and biomechanical characterization of hyperhomocysteinemic bone disease in a novel animal model.

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Version: 1 Date: 27 Dec 2002

Reviewer: Prof Scott Miller

Level of interest: A paper of considerable general medical or scientific interest

Advice on publication: Accept after discretionary revisions

This multidisciplinary study describes a new animal model for homocystinuria. The study is well conducted and the findings are interesting and appear to have similarities to the condition in human. The model is nutrition-based and has some obvious advantages over other models. Final growth rates were accelerated and there were obvious differences in the radiographs in the hCySH-supplemented animals. Growth and modeling rates appear to be accelerated in this model. Histological studies, which the authors state are in progress, will confirm some of the observations inferred from the radiographs and the biochemical data. Minor suggestions (not mandatory).

1. Page 7, line 12. "...known to be the most rapidly proliferating and...." Suggest that proliferating be replaced by "growing".

2. Page 9, line 3. A bit more detail on how the Ca/PO4 ratio was determined would be helpful.

3. One of the differences to this reviewer in the radiographs presented in Figure 3 A and B are the more obvious trabecular elements in the secondary spongiosa in B compared with A. This is not as apparent in the lateral views.

4. If the radiolucently areas were indeed unmineralized collagen "plugs", this raises the issue if there was a more generalized osteomalacia present (this could be confirmed later in the proposed histological studies). However, if there were unmineralized bone or collagen, it would seem that this would be reflected in the mineral content that was calculated as the ash to dry weight ratio. Alternatively, this is just a defect in cancellous bone as the mineral content appeared to be obtained from cortical bone. The lucent areas appear to occur in the cancellous but not the cortical areas (or do they?).

5. Page 15, first sentence. Suggest that the sentence be changed to read "....ossification front or the number or size of hypertrophic chondrocytes...." Growth at the plate is determined by the proliferation rate which will, in a normal plate, determine the number of hypertrophic cells in a column and the final size of the hypertrophic cells.
Competing interests:

None declared.