Reviewer’s report

Title: Iron behaving badly: inappropriate Iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases

Version: 2 Date: 14 October 2008

Reviewer: Tom Kirkwood

Reviewer’s report:

This manuscript is very much in a category of its own, both in the breadth of the synthesis that it undertakes and in the vast number of references cited. It is an advantage of online publication that it is even feasible to consider publishing it, so the number of references needs to be considered not as a physical obstacle but in terms of whether it might be useful to the reader.

The strengths of the manuscript are the inclusiveness of the approach taken by the author and the case that is argued for the value of an integrative, systems approach.

1. The background and introduction, with its concise discussion of the chemistry and biochemistry of iron is sound. The section on disease manifestations is comprehensive and well illuminates the unevenness of the attention that has been paid to iron and its potential role in pathogenesis. In some instances the number of references is very large indeed, presenting something of a barrier to easy reading of the text, but this is merely an inconvenience. It was a little odd to see aging and longevity included in this section, since there is some question generally about the relationship of aging to disease that is glossed over here, and longevity is surely not a disease. These aspects of presentation and organization could be improved by some light revision.

The sections on antioxidants and their links with iron are well written and thought provoking, although in some respects these merit treatment on their own as elements of a more focused review. Likewise, the material on iron chelators is a nice review though rather succinct.

2. The concluding remarks on systems and predictive biology are of course valid though tantalizing in their brevity. It would here be nice to see a bit more discussion of what a synthesis like the one attempted in this manuscript can deliver.

3. Overall, the review deals with many facets of iron and its roles in health and disease. In that respect it is highly integrative. On the other hand iron and its metabolism must be considered in the broader context of other processes that may be contributing to the disorders discussed. This is very much a question of how the cake of complex biology is cut. It would be good to see a bit more discussion along these lines.
Paragraphs numbered 1,2,3 indicate need for minor essential revisions.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No competing interests