Reviewer's report

Title: Fatty metamorphosis and other patterns in fibrous dysplasia.

Version: 1 Date: 15 August 2003

Reviewer: M M Cohen

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I have had an opportunity to read this manuscript. I agree that the fatty metamorphosis is interesting. I cannot see the histopathology because I have a xeroxed copy of the manuscript.

I have had less trouble diagnosing fibrous dysplasia than the authors. This is because we obtain large biopsies and furthermore we see the patients and the radiographs. Thus, there are less equivocal answers than there are with small biopsies.

I do have concerns about some statements made in the paper.

The authors indicate that the McCune-Albright syndrome is associated with somatic mutations in GNAS1. However, the same mutation is present in monostotic fibrous dysplasia, which the authors are talking about, and also polyostotic fibrous dysplasia.

When making the diagnosis in an equivocal case, the activating mutations in GNAS1 are only two (Arg201Cys and Arg201His). All fibrous dysplasia lesions whether monostotic, polyostotic, or McCune-Albright syndrome have one of these two mutations. GNAS1 mutations are also found in some cases of osteosarcoma, pituitary adenoma, thyroid adenoma, thyroid carcinoma, parathyroid adenoma, Leydig cell tumor, intramuscular myxoma, and even some breast cancers (see Cohen, American Journal of Medical Genetics 98:290-293, 2001).

Fat is apparently partly-regulated by epinephrine receptors which signal through GNAS1 protein. Loss of function mutations result in fat accumulation. However, gain-of-function mutations, which are found in fibrous dysplasia, have been associated with uncontrolled fat production in thyroid tumor cells. Thus, it is at least possible that GNAS1 mutations could be associated with the fat accumulation in the stroma of fibrous dysplasia. At least the possibility should be considered by the authors.