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LETTER TO THE EDITOR: A REPLY

DIETARY MANAGEMENT OF SICKLE CELL ANAEMIA WITH VANILLIN

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Sir,

We agree with Dr. Arouma that the use of classical anti-oxidant compounds can be accompanied by pro-oxidant effects, at least in some *in vitro* systems.[1] It is not clear that the same concerns will pertain *in vivo*. For example, very high doses of ascorbic acid in normals are well tolerated.[2]

Sickle erythrocytes do exhibit evidence of oxidant injury, an effect likely related to iron contained in membrane associated hemoglobin[3,4]. Ascorbic acid or vanillin could conceivably exacerbate such damage, resulting in stiffer or more adherent red cells which might actually increase vascular occlusion and thereby worsen their sickle cell disease. Cell lysis might also occur, although this may be less important since patients with lower hemoglobin levels (and more severe hemolysis) often have fewer painful vaso-occlusive episodes than those patients with higher hemoglobin levels[5,6]. Such effects must be considered for employing pharmacologic doses of any anti-oxidant. On the other hand, vanillin's ability to inhibit sickle polymerization and to shift the hemoglobin-oxygen association curve[7] could decrease the amount of hemoglobin associated with the red cell membrane and thereby lessen the degree of cellular damage. Thus, while concerns over the pro-oxidant effects of drugs like vanillin and ascorbic acid in sickle cell disease remain largely theoretical, one should still be cautious in their use.

As vanillin seems to have less pro-oxidant action than does ascorbic acid, we have proceeded to initiate a Phase I trial in which we study the toxicity and pharmacology when vanillin is administered orally to normal human volunteers. In the initial trial,

we observed virtually no toxicity when oral vanillin (10 mg/kg) was administered to these normal volunteers, and additional studies at higher doses are planned. Once we have completed this normal volunteer study, we intend to carry out a similar Phase I trial in patients with sickle cell disease. We do recognize that because many of these patients do have some degree of iron overload, the pro-oxidant side effects of vanillin could be exacerbated in the sickle cell patient population.

Given the severity of sickle cell disease, prophylactic medications with significant potential side effects have been tried in humans. The current NIH funded Multi-institutional Trial of the anticancer drug Hydroxyurea[8] for treatment of sickle cell anaemia is one such study. We feel that the risk/benefit ratio for vanillin is sufficiently favorable to merit intensive investigation.

We wish to stress that vanillin remains investigational and is not appropriate for use outside of clinical studies. It is particularly important that patients not attempt to self-medicate with over-the-counter preparations (which may contain large amounts of the more toxic ethyl vanillin or ethanol), and that physicians, frustrated with this difficult disorder, do not attempt individual therapy outside a controlled research setting.

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