MECHANISM OF IRON UPTAKE

To the Editor:

In the June 1, 1991 issue of Blood, Cochran et al. found that the primary pathway for initial uptake of Al-transferrin and Fe-transferrin by human fetal red cells (obtained from placentas) was through a high-affinity saturable receptor that did not distinguish between the two metallo-transferrins; that a process that followed initial uptake did distinguish between the two metallo-transferrins; and that as much as 20% of the uptake of metallo-transferrin, at physiologic concentrations of protein, was by way of a low-affinity, nonsaturable receptor.

The differential handling of Al-transferrin and Fe-transferrin after they have been endocytosed, as discussed by the Cochran et al. may be due to the differential release of Al and Fe from the endocytosed metallo-transferrins or differential transport of the two metals after their release. There is another possibility. Recent experiments have shown that mitochondria have receptors for iron. Al and Fe might compete for binding to these receptors.

The postulate of a low-affinity nonsaturable receptor seems at odds with the usual characteristics of a receptor, of which saturability is one. The low-affinity, nonsaturable uptake may perhaps be more easily explained by the receptor-independent endocytosis that is characteristic of fetal erythrocytes.

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2. Weaver J, Zhan H, Pollack S: Mitochondria have Fe(III) receptors. Biochem J 265:415, 1990

RESPONSE

We thank Dr Pollack for his comments and for drawing our attention to these recent publications. He refers to our finding that, when we compared the handling of diferric transferrin (FeTr) and aluminum transferrin (AlTr) by reticulocytes, after initial uptake, the cells appeared to distinguish between the two forms of metallo-transferrin. He raises the question as to whether the Al and Fe might compete at the mitochondrial receptor, which is an interesting possibility, especially as Al has a high affinity for ATP and it is the Fe-ATP receptor to which he refers. Competition at this point might explain the inhibition of heme synthesis that has been shown to result from exposure to Al. Our data did not examine in any way the internal fate of the Fe, so we are unable to comment on the likelihood of Al and Fe competing at this site. However, as far as AlTr and FeTr are concerned, our data showed that, once the indistinguishable surface binding of AlTr or FeTr to the classical high-affinity receptor had been accounted for, there was no competition for 59Fe uptake from excess AlTr. On the other hand, with regard solely to Fe accumulation, we found that an internal rate-limiting step existed. We tentatively suggested that this was at the point of binding to a transport protein in the vesicle membrane because with our procedure, which simply measured 59Fe accumulation, a rate-limiting step later in the pathway would not have been recognized; the iron in the cell, in whatever form, would still have been counted. Thus, the appealing idea that Al and Fe, bound to ATP, might compete for binding to the mitochondrion receptor remains speculative.

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Mechanism of iron uptake [letter; comment]

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