CORRESPONDENCE

COBALAMIN–FOLATE INTERRELATIONS

To the Editor:

I would like to comment on two points made by Dr Chanarin and his colleagues in their critical and comprehensive review of cobalamin–folate interrelations.1

First, they state that "megaloblastic erythropoiesis is unique to humans." They have overlooked completely the classic writings of Marston, who in 1952 described a profound macrocytic anemia in which the oxygen-carrying capacity fell to 30% or lower in sheep suffering from cobalt deficiency.2 Two further features were subsequently added to the picture: (1) the presence of abnormal primitive erythroblasts in the peripheral blood and (2) a spectacular response to folic acid. These were observed both in sheep reared on cobalt-deficient pastures and in experimental sheep rendered vitamin B12 deficient under carefully controlled laboratory conditions. In these animals "the blood picture proclaims a disorder of bone marrow very similar to that which is evident in pernicious anemia and like the latter responds dramatically to folic acid."3 In a further publication Marston described the anemia as megaloblastic and noted that it responds equally dramatically to vitamin B12 as well as to folic acid.4 True, the sheep is not the ideal experimental animal in which to study megaloblastic anemia because in it the effects of adenocobalamin deficiency are usually much more profound than those of methylcobalamin deficiency. It succumbs to the former usually before any serious degree of anemia develops.

Second, the authors state that "there is an unconfirmed report of increased urinary excretion of methylmalonic acid in patients anesthetized with N2O."5 Other important substances are metabolized along the propionyl–succinyl pathway. Notable among these are valine and isoleucine. Dietary loading with both these amino acids will increase the methylmalonic aciduria in untreated pernicious anemia, indicating that their metabolism also is impaired at the methylmalonyl-CoA mutase block.6 This is true also in patients under nitrous oxide anesthesia. Serum valine levels were significantly elevated in patients anesthetized with nitrous oxide for periods of three hours or longer. This was attributed to the inactivation of adenocobalamin by nitrous oxide, thereby inducing the methylmalonyl-CoA mutase block and resulting accumulation of valine in the blood.6,7 The urinary excretion of methylmalonic acid was not increased in these patients (unpublished observation). Isoleucine, which is only partly metabolized along the propionyl–succinyl pathway, as well as valine, and partly along a vitamin B12 independent ketogenic pathway, can also be elevated in patients undergoing nitrous oxide anesthesia, but the serum levels of both these amino acids show a pronounced fall in patients anesthetized without nitrous oxide.8 Three metabolites, valine, isoleucine, and methylmalonic acid, therefore accumulate proximal to the methylmalonyl-CoA mutase block in humans exposed to nitrous oxide.

This is convincing evidence that, unlike in the rat, the enzyme methylmalonyl-CoA mutase is inactivated by nitrous oxide in man. The serum valine levels measured by the highly sensitive microbiological method employed9 (mean recovery 99.4%, coefficient of variation ±3.2% in 12 experiments after adding 40.0 mg % of L-valine to normal serum) would appear to be a more sensitive indicator of the mutase activity than the urinary methylmalonic acid under these very short periods of exposure to nitrous oxide.

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REFERENCES

2. Marston HR: Cobalt, copper and molybdenum in the nutrition of animals and plants. Physiol Rev 32:67, 1952
4. Marston HR: Primary metabolic defect supervening on vitamin B12 deficiency in the sheep—Resume of experimental findings which led to the present investigations. Nature 190:1085, 1961

To the Editor:

In response to Dr T.E. Parry, the anemia in sheep reared on cobalt-deficient feed and hence developing cobalamin deficiency when examined by hematologists was reported to be normocytic and normochromic,1 and the marrow was hypoplastic.2 The assumption 30 years ago that the anemia in sheep was megaloblastic was not based on any supporting evidence.

We are not aware of any convincing evidence for the inactivation of methylmalonyl-CoA mutase by short-term exposure to nitrous oxide in man.

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Cobalamin-folate interrelations [letter]

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