LETTERS TO THE EDITOR

Hypolactasia and protection against Plasmodium spp infection in Homo sapiens

Editor,—Anderson and Vullo’s hypothesis (Gut 1994; 35: 1487–9) is based on the contention that hypolactasia is causatively associated with riboflavin deficiency (consequent upon the low milk intake), and postulated that this condition naturally produces a survival advantage against human Plasmodium spp infection. Available evidence (quoted by the authors) indicates, however, that such a deficiency enzyme may only develop under certain unfavourable conditions on the metabolism of the malarial parasite.

The overwhelming consensus of current opinion is that the hypolactasia phenotype represents the normal state for Homo sapiens (and virtually all other mammals), and that persistence of the enzyme into adult life in certain groups before ‘artificial’ mass population movements (for example, northern Europeans to the USA and Australians from Polynesia) cannot have a significant survival advantage; by involving malaria as the major ‘driving force’, Anderson and Vullo are thus interpreting the scenario in ‘reverse’ fashion.

Plasmodium spp are extremely ancient organisms; before they infected the earliest mammals, they utilised more primitive organisms, including reptiles, birds, etc, as reservoir hosts. The Anderson and Vullo hypothesis therefore implies that the very widespread prevalence of the hypolactasia phenotype in the animal kingdom developed as an exceedingly early protective mechanism against Plasmodium spp, and persistence of the enzyme into adult life only developed very much later in areas where Plasmodium spp was not a major environmental hazard affecting survival. The Hamitic tribes of east, west, and central Africa (most adults possess persistence of the enzyme in their adult life) presumably migrated into northern Africa comparatively recently (within the last few thousand years) — and were hence ‘unprotected’ against Plasmodium spp. How then, did the Hamites survive P. falciparum infection? I know of no evidence that Hamites are, at the present day, more prone to P. falciparum infection compared with Bantus with the exception that they lack certain major genetic diseases45 (see later) P. vivax infection was certainly a problem in northern Europe until recent times; however, it never caused the widespread acute mortality associated with human P. falciparum infection — which probably originated in Africa also comparatively recently.

The approximate parallel outlined in the hypothesis between the geographical areas incorporating the hypolactasia phenotype and those in which major haemoglobinopathies (which clearly possess a selective advantage against P. falciparum infection) are comparatively common, is of interest.5 But even here the degree of protection is only partial; riboflavin deficiency has probably exerted a comparatively minimal, and certainly a lesser, effect in terms of selective Darwinian pressure.

Therefore, although this hypothesis seems superficially attractive, I have grave doubts that it explains the human lactase polymorphism more satisfactorily than several of the previous theories.1

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Reply

Editor,—We thank Dr G.C. Cook for his interest in our hypothesis and would like to reply to some of his points.

Dr Cook says that ‘available evidence (quoted by the authors) indicates, however, that such a deficiency enzyme only exists under very mild influence on the metabolism of the malarial parasite’. We believe that the crucial point is not whether the influence of flavin deficiency on the parasite metabolism is ‘mild’ or ‘very mild’, but whether its effect is sufficient to prevent excessive multiplication of the parasite as it has been shown in vivo and quoted in our paper, so protecting the host from death.

Dr Cook also says that our hypothesis implies that ‘persistence of the enzyme into adult life only developed very much later in areas where Plasmodium spp was not a major environmental hazard affecting survival’. It is possible that we have not made it clear that the basis of our hypothesis is that the ‘persistent’ phenotype was the ‘wild type’ existed initially, and therefore we did not envisage that it ‘developed’ later but that it continued to predominate in those areas.

Even if, as it seems likely, there is no evidence that the Hamite tribe (who possess the ‘persistent’ phenotype) are more prone to malaria than the Bantus, this does not necessarily show that our hypothesis is wrong, because they could be protected by other factors, known or unknown.

We hope that the validity of our hypothesis might be supported if further detailed demographic studies are done on the ‘persistent’ and hypolactasia phenotypes in relation to malaria within suitable countries. The main purpose of publishing our hypothesis was to encourage such studies.

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In vitro dissolution of cholesterol biliary stones

Editor,—We read with great interest the article by Bergman et al (Gut 1994; 35: 1653–8) who reported on in vitro cholesterol gall stone dissolution with methyl-tert-buty1 ether (MTBE) and ethyl propionate in the presence of bile with or without dimethyl-sulphoxide (DMSO). We would like to comment further on the important role of DMSO on stone dissolution.

We have experience with the clinical use of different solvents containing DMSO. Based on previous studies by Montet’s group in which it was shown that the addition of DMSO to MTBE improved the dissolution rate of cholesterol1 or biliary calculi2 we have recently studied the bile duct stone dissolving capacity of multicomponent solvents in humans.3 In these mixtures, DMSO was present both in solvent 1 (aqueous glycerine-NaOH buffer solution of EDTA, sodium deoxycholate and 30% DMSO) and in solvent 2 (DMSO/MTBE 70/30). Solvent mixtures were infused continuously and alternately for 16–24 hours through a nasobiliary catheter placed into the common bile duct over the stone(s). In 20 of 22 patients with pigment or mixed biliary duct stone(s), or both, which were too large to be removed after endoscopic sphincterotomy, a stone free state or decline of 22 or good dissolution of stones (11 of 22) was achieved with these solvents. Only mild toxic side effects were seen during treatment. These mixtures containing DMSO proved effective enough to dissolve not only cholesterol but also pigment or mixed stones, or all three.

Our recent in vitro investigation in the field of contact dissolution therapy of bile duct stones provides further evidence on the beneficial effect of DMSO.4

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Reply

Editor,—We thank Drs Takacs and Montet for their comments. Although our interest with the clinical use of topical dissolution therapy has mainly focused on the treatment of gall bladder stones, we would like to comment on side effects and efficacy of topical dissolution for bile duct stones.

We do agree with Takacs and Montet that the multilayered composition of bile duct stones made the complete dissolution of these stones difficult. But, we think that potential toxic agents to human bile ducts. In contrast with topical dissolution of gall bladder stones, where the gall bladder contains a reservoir enabling the use of the solvent after infusion, topical dissolution of ductal stones lacks the opportunity to recover the solvent from the patient. This increases the risk of toxic side effects. We and others have found MTBE to produce much more local (haemorrhagic duodenitis) and systemic side effects (somnialectis, hypolactasia, parum, produced a low...
Inflammatory bowel disease in married couples

EDITORS — We read with interest the article about inflammatory bowel disease in married couples by Comes et al (Gut 1994; 35: 1316–8). We have under our care a married couple who both developed Crohn's disease after marriage.

The female partner (now 32 years) presented in 1988, one year after her marriage, with abdominal pain and arthropy and was found to have multiple small bowel strictures on a barium study. A duodenal biopsy confirmed Crohn's disease.

The male partner (now 48 years) was found to have sarcoidosis 24 years ago with a positive lung biopsy. He presented one year ago, five years after his marriage, with colitis of the sigmoid colon. Biopsy showed Crohn's disease with granulomas. Both patients are white. Their marriage is non-consanguinous.

The female partner's aunt is also a known case of Crohn's disease. The couple are therefore similar to the cases described by Comes et al in that symptoms of Crohn's disease developed in both after marriage.