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 absorption of riboflavin which has resulted in a subsequently increased survival advantage against human Plasmodium spp infection. Available evidence (quoted by the authors) indicates, however, that such a deficiency exerts its influence 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 for 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 on the basis of superficial similarities alone would not be expected to result in 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 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 Hamite tribes of east, west, and central Africa (most adults possess persistence of the enzyme into their adult life) presumably migrated into northern Africa comparatively recently (within the last few thousand years) — and were thence ‘unprotected’ against Plasmodium spp. How then, did Hamite ‘malarialists’ survive falciparum infection? I know of no evidence that Hamites are, at the present day, more prone to P falciparum infection compared with Bantu with the exception that they lack certain major genetic diseases and persistent phenotype.5 But even here the degree of protection is only partial; riboflavin deficiency has probably exerted a comparably minimal effect, and certainly a lesser effect in terms of selective Darwinian pressure.

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. But even here the degree of protection is only partial; riboflavin deficiency has probably exerted a comparably minimal effect, 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 exerts its 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 ‘persistent’ 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’ existing initially, and therefore we did not envisage that it ‘developed’ later but that it continued to predominate in those areas. Even if, as some say, there is no evidence that the Hamite tribe (who possess the ‘persistent’ phenotype) are more prone to malaria than the Bantu, this does not necessarily show that our hypothesis is wrong, because the protection is not always exerted 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’ 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 bile stone

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-butyl 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 stones,2 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 glycine-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 outcome 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 stone provides further evidence on the beneficial effect of DMSO.4

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C VULLO


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 make the complete dissolution of bile duct stones with MTBE, or EDTA, or all three, a logical choice. Indeed, the use of DMSO for dissolving bile duct stones in humans has been described before but reports have been anecdotal.2 We are still very much interested in finding potentially toxic agents into human bile ducts. In contrast with topical dissolution of gall bladder stones, where the gall bladder drains the solvent into the gastro-intestinal tract, 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 others4 have found MTBE to produce much more local (haemorrhagic duodenitis) and systemic side effects (somnolentia, lethargy, nausea and other toxic effects) leading to temporary hospitalisation.5 In the present study with DMSO we have not observed such toxic side effects.

None of the patients included in our study had a history of previous dissolution therapy. As DMSO is known for its protective effect against leukocyte and platelet aggregation,6 we think it is justifiable to include DMSO in the solvent mixtures for direct dissolution of bile duct stones.

We conclude that multilayered solvent mixtures containing DMSO may be considered as a new treatment option for selected patients with bile duct calculi.

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Inflammatory bowel disease in married couples

ENTOR—We read with interest the article about inflammatory bowel disease in married couples by Comes et al (Gut 1994; 35: 1316–18). 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 arthropyathy and was found to have more than one small bowel strictures on a barium follow through. A ducal biopsy confirmed Crohn’s disease.

The male partner (now 48 years) was found to have sacridesis 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-consanguineous.

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.

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BOOK REVIEWS


The product of two Canadian pathologists of considerable experience and standing in gastrointestinal pathology, this is an excellent synopsis of the subject. The text is organised in a standardised way, covering the whole of the alimentary tract, with a high level of detail.

The emphasis is on the development of the book, as well as the key points of the text. The emphasis is on the development of the book, as well as the key points of the text.


'It is intended that this volume may be read in its entirety or as individual chapters detailing specific subjects important to the general practitioners, home healthcare professional, who is developing an interest in clinical nutrition, will use the textbook as a sole source of information...'. So says the preface to this well produced, 37 chapter, 60 author book. Do nutritionists want or need this book? Can they glean enough about nutritional support from the pages of Gut? Inspection of the index for the first three volumes of this journal suggest that they cannot. The book is intended for 'nutritional support', 'parenteral nutrition', 'enteral nutrition', and 'enteral feeding' indicate some abstracts, but very few main articles on how and why to nutritional support in humans, although the development of techniques for nutritional support has been one of the important therapeutic advances in the past two decades. Moreover this is not a field in which the untutored amateur does well: instead he is very likely to kill patients and waste substantial amounts of money.

I would not advise anyone developing an interest in clinical nutrition, except as a synonym for artificial nutrition support’ to start at the beginning of this book with a view to reading it straight through, if only because there are inevitably repetitious passages. For the methods for measuring energy expenditure are described on pp 43–47 ('Energy metabolism') by J Webber and I MacDonald, and then again on pp 138–141 ('Adult Macronutrient requirements') by H P Sarwar and J A Romijn). The index is comprehensive and well cross referenced, however, so it is easy to find the topic on which you want to read. The place to start is chapter 7, by S Allison, on ‘Malnutrition in hospital patients, and assessment of nutritional support’. Allison makes the vital distinction between malnutrition, which is an inevitable consequence of terminal disease, and protein depletion, which is not a temporary and remediable component of the patient’s illness. In the last case (but not the first) nutritional support may be very valuable. If the clinician who is a tyro as ‘clinical nutrition’ reads this chapter, and notes that some of his patients suffer from important and remediable malnutrition, then he should read the rest of the book, or else ensure that he can call on the services of a nutrition support team with the necessary expertise.
Reply

J J G H M Bergman

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