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 concept that hypolactasia is causatively associated with riboflavin deficiency (consequent upon the low milk intake) and has demonstratively produced a survival advantage against human Plasmodium spp infection. Available evidence (quoted by the authors) indicates, however, that such a deficiency exerts only a very mild 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 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) favours 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 persistency of the enzyme into 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 hypolactasia evolve to survive P.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 diseases5,6 (see later)!

P vifux 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.5,6 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


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 only a 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 ‘persistency 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 stated, 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-buty ether (MTBE) and ethyl propionate in the presence of bile with or without dimethyl sulfoxide (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 cholesterol or pigment biliary stones, however, in preliminary experiments we observed that DMSO solubilized cholesterol and that mixtures of DMSO and MTBE were much more effective. We have recently studied the bile duct stone dissolving capacity of multicomponent solvents in humans.2 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 state of the common bile duct over the stone(s) was achieved with these solvents. Only mild toxic side effects were seen during treatment. These mixtures containing DMSO proved effective enough to disintegrate not only cholesterol but also pigment or mixed stones, or all together.

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 make the comparison with dissolution of gall bladder stones, where the gall bladder contains a reservoir enabling the diffusion 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 others4 have found MTBE to produce much more local (haemorrhagic duodeniitis) and systemic side effects (somnia, lethalia, etc) which make this solvent unsuitable for humans.

haemolysis) when used for ductal stones compared with its use for gall bladder stones. However, Takacs et al used MTBE in much lower concentrations and reported only mild toxic side effects.

Furthermore, there are two important caveats concerning the efficacy of topical dissolution therapy for bile duct stones. Firstly, the solvent mixture is a dual solvent and stones may result in clearance of stones by its mechanical effect; stones are flushed from the bile duct into the duodenum. This is true especially for those cases in which a spincterotomy has been performed. Stone clearance may therefore result from spontaneous migration of stones or mechanical effect of infusion of solvents, or both, instead of true chemical dissolution. Secondly, fragmentation of bile duct stones (as reported in 50% of patients treated by Takacs et al) may also result from fricitonal forces between stones and the naso-biliary catheter as reported after treatment of bile duct stones with biliary endoprostheses.

We feel that the use of topical dissolution therapy for bile duct stones should be limited to experiment centres and to those patients in whom endoscopic surgery is unsuccessful or contraindicated. In whom longterm endoscopic stenting is considered inappropriate. In these selected cases the use of DMSO in combination with other solvents like MTBE may be considered.

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Inflammatory bowel disease in married couples

EDITOR—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 arthropathy and was found to have multiple small bowel strictures on a barium enema. 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-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, liver, hilum, spleen, lungs, bones, heart, spleen, and pancreas, and places particular emphasis on the appendix, the stomach, and the small intestine.

The text is easy to read and the authors have been careful to include relevant general information, for example, that appendicitis is the most common emergency in patients under the age of 40. The atlas is excellently illustrated with 100 line drawings, 120 photographs, and 10 tables. Overall, the atlas is very useful for the clinician, the radiologist, the general surgeon, and the gastrointestinal surgeon.

In the natural history of any disease, there are four parts: epidemiology, pathogenesis, clinical features, and treatment. This atlas satisfies each part of the story, but the volume that follows it, an illustrated synopsis of gastrointestinal disease, is even more useful.

I C TALBOT


‘It is intended that this volume may be read in its entirety or as individual chapters detailing specific subjects of interest to the 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, 600 author book, which is a goldmine for professionals who want or need this book? Can they not glean enough about nutritional support from the pages of Gut? Inspection of the index for the three volumes of this journal suggests that they cannot. The book contains sections on ‘nutritional support’, ‘parenteral nutrition’, ‘enteral nutrition’, and ‘enteral feeding’ indicate some abstracts, but very few main articles on how and why to use artificial 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 book 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 nutritional support to start at the beginning of this book with a view to reading it straight through, if only because there are inevitably repetitive passages. For example 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 Sauerwein 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 starvation, which is a truly significant and remediable component of the patient’s illness.

In the last case (but not the first) nutritional support may be very valuable. If the patient 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.