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 low milk intake), which has evolutionarily 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*[1] (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 Australia) resulted from 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[2]; 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 into their adult life[3]) presumably migrated into northern Africa comparatively recently (within the last few thousand years) – and were thence 'unprotected' against *Plasmodium* spp. How then, did these Hamitic 'pastoralists' 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 diseases[4,5] (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.[4 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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1 Cook GC. Hypolactasia: geographical distribution, diagnosis, and practical significance. In: Chandra RK, ed. *Critical reviews in tropical medicine 2.* New York: Plenum Publishing, 1984: 117–39.
2 Bruce-Chwatt LJ. History of malaria from prehistory to eradication. In: Wernsdorfer WH, McGregor IA, eds. *Malaria: principles and practice of malariology.* Edinburgh: Churchill Livingstone, 1988: 1–59.
3 Cook GC, Kajubi SK. Tribal incidence of lactase deficiency in Uganda. *Lancet* 1966; i: 725–30.
4 Fleming AF. Hematologic diseases. In: Strickland GT, ed. *Hunter's tropical medicine.* 7th ed. Philadelphia: WB Saunders, 1991: 36–64.
5 Bruce-Chwatt LJ. Paleogenesis and paleoepidemiology of primate malaria. *Bull WHO* 1965; **32:** 363–87.

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 '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' existent 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 today, 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*-butyl ether (MTBE) and ethyl propionate in the presence of bile with or without dimethylsulphoxide (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[1] or brown pigment 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 state (nine of 22) or good disintegration 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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1 Dai KY, Montet JC, Zhoa XM, Amic J, Choux R. Dissolving agents of human mixed cholesterol stones. *Gastroenterol Clin Biol* 1988; **12:** 312–9.
2 Dai KY, Montet JC, Zhao XM, Amic J, Montet AM. Dissolution of human brown pigment biliary stones. *J Hepatol* 1989; **9:** 301–11.
3 Takacs T, Hajnal F, Nagy I, Montet JC, Lonovics J. Effective dissolution therapy of bile duct stones with a new multicomponent solvent. *European Journal of Gastroenterology and Hepatology* 1993; **35:** 867–70.
4 Guitaoui M, Montet AM, Takacs T, Montet JC. Contact solvents for common bile duct stones. Studies in an in vitro system. *Liver* (in press).

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 combined use of DMSO, 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.[1–3] We are still very reluctant to infuse potentially toxic agents into human bile ducts. In contrast with topical dissolution of gall bladder stones, where the gall bladder provides a reservoir enabling actual extraction 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[4] have found MTBE to produce much more local (haemorraghic duodenitis) and systemic side effects (somnolentia,

haemolysis) when used for ductal stones compared with its use for gall bladder stones.[5] However, Takacs *et al*[3] 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, infusion of any solvent into the bile duct 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 sphincterotomy 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*[3]) may also result from frictional forces between stones and the nasobiliary catheter as reported after treatment of bile duct stones with biliary endoprostheses.[6]

We feel that the use of topical dissolution therapy for bile duct stones should be limited to expert centres and to those patients in whom endoscopy and surgery are unsuccessful or contraindicated and in whom longterm endoscopic stenting is considered inappropriate.[7] In these selected cases the use of DMSO in combination with other solvents like MTBE may be considered.

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1 Igimi H, Asakawa S, Kataoka A, Shimura H. Clinical trials of DMSO on the cases with intrahepatic stones. *Gastroenterology* 1984; **88:** A1666.
2 Patty I, Javor T, Past T, Deli J, Horvath L. New solubilizing mixture for pigment gallstones. *Gastroenterology* 1987; **93:** 665–7.
3 Takacs T, Hajnal F, Nagy I, Montet JC, Lonovics J. Effective dissolution therapy of bile duct stones with a new multicomponent solvent. *European Journal of Gastroenterology and Hepatology* 1993; **35:** 867–70.
4 Neoptolemos JP, Hall C, O'Connor HJ, Murray WR, Carr-Locke DL. Methyl tert butyl ether for treating bile duct stones: the British Experience. *Br J Surg* 1990; **77:** 32–5.
5 Allen MJ, Borody TJ, Thistle JL. In vitro dissolution of cholesterol gallstones. *Gastroenterology* 1985; **89:** 1097–103.
6 Goldberg M, Huck HV, Ruchim M. Clearance of choledocholithias with indwelling biliary stents. *Am J Gastroenterol* 1993; **88:** 1530–5.
7 Bergman JJGHM, Rauws EAJ, Tijssen JGP, Tytgat GNJ, Huibregtse K. Biliary endoprostheses in elderly patients with endoscopically irretrievable common bile duct stones: report on 117 patients. *Gastrointest Endosc* (in press).

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 meal follow through. 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

Atlas of Gastrointestinal Pathology. By D A Owen, J K Kelly. (Pp 258; illustrated; £138.00.) Philadelphia: WB Saunders, 1994. ISBN 0 7216 6730 9.

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 hollow organ alimentary pathology but not liver or pancreas, under the headings 'Biology of Disease', 'Clinical Features', 'Gross Pathology', 'Microscopic Pathology', 'Special Diagnostic Techniques', and 'Differential diagnosis'. The result is an admirably succinct review of gastrointestinal pathology, useful for both clinical gastroenterologists and pathologists. With the very comprehensive index and the clear style of the text, I am impressed with how easy it is to quickly find information that might be more difficult to locate elsewhere (for example, the distance of the landmarks in the oesophagus from the incisor teeth, or a brief biographical sketch about Harald Hirschsprung). There are important messages for clinical diagnosis and treatment. For example, with regard to tumours of the ampulla of Vater, the authors are quite right to state that 'superficial biopsies may reveal only an adenoma and miss the more deeply located malignancy. The presence of jaundice favors a diagnosis of malignancy'.

The reference lists at the end of each section are short and references are not cited in the text. The emphasis is on some of the classic papers rather than the more recent advances. The topics covered by the book are arranged into site specific chapters, with the exception of chapters on 'Diseases of Lymphoid Tissue', 'Stromal Lesions', and 'Neoplasms' and a further chapter entitled 'Diseases That May Affect Multiple Organs'. This includes graft *v* host disease, eosinophilic gastroenteritis, ischaemia, vasculitis, Kaposi's sarcoma, etc. These are the least successful parts of the book. The section on lymphomas, particularly, is somewhat lacking in clarity.

Paradoxically, in a book, which calls itself an atlas, the weakest part is in the illustrations. Their small size and number and quality compare unfavourably with many extant standard textbooks with no pretensions to be atlases. The choice of topics illustrated is sometimes questionable. For example, six figures illustrate acute appendicitis, a condition surely familiar to every reader, while adenocarcinoma of the appendix and pseudomyxoma peritonei, much more difficult diagnostic problems, are each given only one figure, of indifferent quality. The illustrations of dysplasia in inflammatory bowel disease are inadequate.

Despite the last criticism, this is a beautifully organised quick reference source, particularly suitable for clinical gastroenterologists and pathologists in training, as well as experienced gastroenterologists who wish to see their patients in a clear light. I warmly recommend this book. Its high price means that it is more for departments to buy than for individuals to own.

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Artificial Nutrition Support in Clinical Practice. Edited by J Payne-James, G Grimble, D Silk. (Pp 573; illustrated; £85.00.) London: Edward Arnold, 1994.

'It is intended that this volume may be read in its entirety or as individual chapters detailing specific subjects. We hope that any 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 gastroenterologists want or need this book? Can they not glean enough about nutritional support from the pages of *Gut?* Inspection of the index for the past three volumes of this journal suggest that they cannot. The entries for 'nutrition', '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 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' (here used as a synonym for 'artificial nutritional 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 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 malnutrition, which is an important 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.