whole body insulin-mediated glucose uptake, evaluated by the euglycaemic clamp technique, tends to be lower in non-insulin dependent diabetic patients with gall stone disease than in diabetic patients without gall stone disease. Therefore, the risk of cholelithiasis could be in part due to defects in glucose metabolism. A high insulin concentration has been shown to be a good marker of insulin resistance,² and we have shown the association between insulin resistance and lipid and lipoprotein abnormalities in patients with non-insulin dependent diabetes.³ Therefore, the correlation of a high insulin concentration with lipid and lipoprotein abnormalities which we found in patients with gall stone disease¹ is expected.

In any case, the possibility that a high insulin concentration is only a marker of impaired insulin-mediated glucose uptake in diabetic patients with gall stone disease is a novel finding which deserves further study. The relation of insulin resistance and gall stone disease is, however, of biological importance only if this association can be shown in non-diabetic subjects.

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Gall bladder epithelium and cholesterol gall stones

SIR,—The ultrastructural findings by Sahlin and colleagues¹ do not show any statistically significant increase in mucous secretory granules of the gall bladder epithelial cells in patients with cholesterol gall stones compared

Figure 1: Ultrathin section uranyl acetate-lead citrate stained. An area of 'mucous metaplasia'. Many mucous secretory granules are recognisable in the apical part of the cells. Original magnification $\times 7000$.

Figure 2: Ultrathin section stained with Thiéry's method. A mucus layer is suspended above metaplastic cells. Original magnification $\times 45\,000$.

with control patients without gall stones but with polyps. Polyps of the gall bladder may be involved in the natural history of the gall stone disease,² and fragments of gall bladder mucosa taken from such patients do not seem to us appropriate control tissues. Sahlin *et al*, furthermore, do not say where 'a strip of the gall bladder wall was excised' and how many specimens were examined in each patient.

We investigated ultrastructural morphology of gall bladder mucosa in 15 patients with cholesterol gall stones (data submitted for publication). Fragments of tissue were taken from the fundus, body, and neck. Ten minute specimens of about 1 mm³ in diameter were obtained from each fragment. Transmission electron microscopy, using a specific method to stain glycoprotein and mucoproteins (Thiéry's method), showed at least one area of 'mucous metaplasia' (Fig 1) (similar to that which other workers have called gastric metaplasia) in at least one specimen from each patient. A layer of visible mucus was observed suspended only above the metaplastic areas (Fig 2), and intercellular spaces appeared much tighter in fully metaplastic epithelium than in the ordinary one, further indicating a progressive tendency to assume a secretory function. We suggested that the increase of mucous glycoproteins may be a zonal event: fully metaplastic zones may functionally represent 'nucleating areas' and the areas of gall bladder lumen near 'mucous metaplasia' might be the ones in which the onset of nucleation occurs.

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Immunological response to *Cryptosporidium* species

SIR,—The case report by Jacyna *et al* describing a patient with colonic *Cryptosporidium* infection and IgA deficiency, is informative.¹ Specifically, this report provides evidence that intestinal IgA antibody is important for protection against *Cryptosporidium* infection.

One comment by the authors—namely, that cell mediated immunity is the primary mechanism of host defence against cryptosporidiosis, is not well supported by currently available evidence. Clearance of an infection by cell mediated immunity means that effector cells such as macrophages or cytotoxic lymphocytes kill the responsible micro-organism. Recent studies with *Cryptosporidium*-infected mice indicate that clearance of the parasite is not inhibited by selective depletion of cytotoxic (CD8⁺) T lymphocytes.² This observation argues strongly against a role for T cell mediated cytotoxicity in protection against *Cryptosporidium* infection, at least in mice. By contrast, selective depletion of helper (CD4⁺) T lymphocytes prolongs murine cryptosporidiosis.² It can, therefore, be concluded that protective immunity against *Cryptosporidium* infection in mice is dependent on helper T lymphocytes, but this conclusion does not necessarily imply that the immunity is cell mediated.

Although it is unclear how CD4⁺ T lymphocytes confer protection against *Cryptosporidium* infection, a testable possibility is that they do so by triggering a *Cryptosporidium*-specific antibody response in the intestine.³ What is the evidence that antibody protects against *Cryptosporidium* infection? Besides the report by Jacyna *et al*,¹ several recent studies support the idea that protection against *Cryptosporidium* requires the presence of antibody. For example, enteral administration of bovine colostrum containing *Cryptosporidium*-specific antibodies can diminish the intensity of *Cryptosporidium* infection in human subjects and in calves.⁴⁻⁶ In addition, the infectivity of *Cryptosporidium* sporozoites for mice can be reduced or eliminated by incubating the sporozoites with antibodies that bind to their surfaces.⁷ This particular finding raises the possibility that protective *Cryptosporidium*-specific antibody acts mainly, or exclusively, against *Cryptosporidium* lifecycle stages that occur extracellularly, in the intestinal lumen (sporozoites and merozoites).⁸ Unlike these extracellular stages, *Cryptosporidium* trophozoites are attached to intestinal epithelial cells, and are covered on their luminal aspect by an envelope of host cell origin.⁹ Conceivably, this envelope may prevent luminal antibody from binding to *Cryptosporidium* trophozoites in vivo.

The lifecycles of *Cryptosporidium* and *Giardia* species have little in common with each other. None the less, evidence accumulated over recent years suggests that antibody plays a major part in the development of protective immunity against both these genera of intestinal parasite.¹⁻¹⁰

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Reply

SIR,—We thank Dr Heyworth for his comments. As we mentioned in our discussion, and as our case report clearly shows, humoral immunity is very important in achieving a successful resolution of infection, as is illustrated by the protracted cryptosporidial infections which affect patients with hypogammaglobulinaemia. The point we were trying to make was that T lymphocytes are also important for successful elimination of cryptosporidial infection, and that inadequate T lymphocyte numbers results in a protracted infection.¹ We are grateful to Dr Heyworth for pointing out the recently published data indicating that the helper T lymphocyte specifically seems to be the most important cell mediating this response,² but these data were not available to us at the time and were only published after our article had been accepted by *Gut*.

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Use of elemental diets in the treatment of Crohn's disease by gastroenterologists

SIR,—Several studies have been published suggesting that elemental enteral diets may have a part to play in the treatment of Crohn's disease, and the effects may be independent of the nutritional benefit.^{1–3} A survey of British Society of Gastroenterology members was undertaken to determine the current use of elemental diets in clinical practice. Altogether,

129 questionnaires were returned by consultant members of the society in clinical practice in the United Kingdom and Eire: 59% of respondents had used elemental diets for the treatment of Crohn's disease; 19% had used them as the sole treatment in newly diagnosed disease; 33% had used them as the sole treatment in relapsed disease; 39% had used them in combination with conventional treatment in newly diagnosed disease; and 55% had used them in combination with conventional treatment for relapsed disease. The number of patients treated with elemental diets per year by respondents was very variable, with a range of 1–50 patients (median six). Respondents to this survey treated a total of approximately 750 Crohn's patients with elemental diets in the United Kingdom per year. The median length of treatment was four weeks (range 5 days–16 weeks), although 5% of respondents using the diet would continue using it until remission of symptoms. The survey questionnaire deliberately did not define the term 'elemental diet.' Originally this term was coined to describe free amino acid and glucose containing diets,⁴ and was often prefixed by the phrase 'chemically defined.' In recent years the term has embraced diets whose nitrogen sources include peptides (often called predigested diets). We believe that 'elemental diet' should be used for either type, but that for simplicity those with an amino acid nitrogen source should be called 'chemically defined elemental diets,' and those with a peptide nitrogen source 'predigested elemental diets.' 'Polymeric diets' refer to those with a whole protein nitrogen source. Generally, the energy source is of secondary importance when classifying enteral diets. Using our criteria a chemically defined elemental diet was used by 70% of respondents; 45% had used EO 28 (Scientific Hospital Supplies Ltd, Liverpool, UK), and 25% had used Vivonex (Norwich Eaton, Newcastle-upon-Tyne, UK). In the last year Vivonex has been withdrawn from the UK market for commercial reasons, and is therefore no longer available. Eighteen per cent of respondents used predigested elemental diets; 13% reported the use of polymeric diets which have been shown in uncontrolled studies to have an apparent benefit on acute Crohn's disease.^{5,6} Several respondents commented on their uncertainty about diet classification; 14% of the respondents used a range of elemental diets.

This survey shows that elemental diets are recognised by an appreciable proportion of practising clinicians to have an important role in the treatment of Crohn's disease. The results of further controlled randomised studies examining the use of enteral diets as an alternative treatment are eagerly awaited.

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Vancomycin in resistant hepatic encephalopathy

SIR,—We were interested to read the paper of Tarao and colleagues (*Gut*, 1990; 31: 702–6) on the use of vancomycin in resistant hepatic encephalopathy. Neomycin is now used only relatively rarely in this context because of anxiety about nephrotoxicity and ototoxicity.^{1,2} Furthermore, there is no convincing evidence that neomycin with lactulose is more effective than lactulose alone.³ Tarao *et al* state that vancomycin is non-absorbable, which seems to be almost literally true in normal subjects, and oral use of the drug does not seem to be a cause of ototoxicity in patients.⁴ We, however, can find no equivalently authoritative reference that reassures us that oral vancomycin could not be cumulatively nephrotoxic. Indeed, appreciable systemic absorption has been reported during vancomycin use for pseudomembranous colitis,^{5,6} with transient fever and neurotoxicity apparently the result in one anephric child.⁷ The link with pre-existing renal impairment has special importance in hepatological practice since many patients with cirrhosis have clinical or subclinical renal disease, and there is also evidence for increased intestinal permeability. It is therefore disappointing that Tarao *et al* include neither systemic vancomycin concentrations nor serial data on the renal function of their patients. We would like such data before recommending this drug for prolonged use.

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