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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