been interpreted as indicating that unknown intraluminal or mucus layer factor(s) might interfere with normal bacterial action. A recent report raises the possibility of antimicrobial resistance consequent upon previous suboptimal exposure, which emphasizes the need for an effective treatment regimen with a lower relapse rate.

Administration of bismuth subsalicylate (BSS) results in a high rate of H. pylori eradication (75% eradication after four weeks), comparable to that of bismuth substitute (CBS). As the subsalicylate salt is insoluble in the stomach and peak plasma concentration does not occur until 1-2 hours after ingestion, absorption must occur in the duodenum or jejunum. In contrast, CBS is a very soluble salt and is rapidly absorbed from the stomach, and the peak plasma bismuth concentrations occur 0.25 to 0.5 hour after the dose. The significant eradication of H. pylori by BSS tends to suggest that the anti-H. pylori effects are due to absorption of bismuth from the duodenum and subsequent exposure by way of systemic delivery. This is logically consistent with histological evidence which indicates that H. pylori inhabit the deeper part of the gastric mucosa and there may insinuate themselves between the epithelial cells [26] sequestering themselves from gastric juice by sitting deep to the mucus layer. This intimate adherence of the bacteria to the gastric epithelial cells and its histological implications for disease progression has been shown in a recent study. Systemic delivery only requires good contact with gastric secretion or intestinal fluid or diffusion into the gastro-duodenal lumen.

A further advantage of this hypothesis is that antimicrobial treatment should be given systematically to yield improved results (Figure). Currently effective treatments (amoxicillin, erythromycin, tetracycline, or metronidazole) might be given intravenously initially for several days before continuing with oral treatment. CBS can be given orally since a high initial postabsorptive plasma peak occurs particularly with the tablets, indicating rapid absorption of the gastric salt [27] being of necessity, contact with H. pylori. Enterohemorrhagic circulation of bismuth [28] could be of benefit as it would effectively prolong the exposure time of the bacteria to agents in the circulation.

We believe that the issue of luminal gastric drug delivery or systemic delivery is of critical importance for drug formulation and overall treatment strategy.

Letters

Diabetes and cholestilithiasis

SIR,—We read with interest the study by Laakso et al on serum lipids and lipidoprotein in patients with diabetes and patients with gall stone disease. One association between diabetes and cholestilithiasis has been defined also in the Italian population, but the reason for this association is not clear. It is generally held that patients with diabetes secrete a more lithogenic bile than non-diabetics. In the few studies that have compared diabetics with age, sex, and weight-matched controls, however, the difference, if any, is not significant. The secretion of a lithogenic bile by diabetics does not satisfactorily explain the observed frequency of gall stones in the diabetic population.

In one of our previous reports on 120 patients affected by type II diabetes we too observed an increased risk of gall bladder disease fasting plasma insulin concentrations and daily average plasma insulin concentrations were appreciably higher than in diabetics without gall bladder disease. But we failed to show any differences in serum total and high density lipoprotein cholesterol, triglycerides, fasting glucose, glycated haemoglobin HbA1c, body mass index, and duration of diabetes between patients with gall stones and those without gall stones. In our study, in non-diabetic patients the increased plasma insulin concentrations seemed to be associated with an increased risk of gall stones regardless of plasma triglycerides, plasma cholesterol, and obesity.

We believe that the issue of type II diabetes is necessary to take into account the effects of diet and, above all, prolonged use of oral hypoglycaemic agents which may bias the interpretation of plasma lipid pattern and the level of insulinemia. Furthermore, it is likely that the patient’s awareness of his gall stone condition (particularly if it is symptomatic) may cause pronounced changes in eating habits. In our study, in fact, all the patients were being treated with oral hypoglycaemic agents in addition to a restricted diet.

Because cholesterol gall stones are generally thought to be the result of an altered lipid metabolism information about the role of blood lipids in gall stone disease may provide indirect clues about the changes in lipid metabolism that are associated with their formation. But considerable controversy exists about the relationship between plasma lipid and gall stone compositions. Moreover, it is now generally recognised that a simple concept of lithogenic bile is inadequate to account for cholesterol gall stone development.

We agree with Laakso et al that changes in plasma insulin and serum lipid concentrations do not account for increased prevalence of gall stone disease in non-insulin diabetes. Abnormal gall bladder motility may play an important part in the pathogenesis of gall stone disease in these patients.

Recently, impaired emptying of the gall bladder in diabetes was shown and the presence of an autonomic neuropathy seems to be a risk factor for such an impairment.

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Reply

SIR,—Pazzi et al have shown an association between high insulin concentration and cholestilithiasis in non-insulin-dependent diabetes similar to what we have reported. In our study we also found a significant positive correlation between insulin concentration and very low density lipoprotein triglyceride concentration and a negative correlation between insulin concentration and high density lipoprotein cholesterol concentration [1]. Pazzi et al did not find any association between lipid and lipoprotein concentrations and gall stone disease. They proposed that the effects of diet and oral hypoglycaemic agents could explain the association of a high insulin concentration and gall stone disease. While we have presented similar explanations for this association, we have also proposed that a high insulin concentration in patients with gall stone disease is related to insulin resistance. Indeed, our preliminary unpublished data show that

References

17 Pazzi P, Trenzani L, Sartori S. 1st Medical Department, S Anna General Hospital, University of Ferrara, Ferrara, Italy.

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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, 1 and we have shown the association between insulin resistance and lipid and lipoprotein abnormalities in patients with non-insulin dependent diabetes. 1 Therefore, the correlation of a high insulin concentration with lipid and lipoprotein abnormalities which we found in patients with gall stone disease 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 colleagues 1 do not show any statistically significant increase in mucous secretory granules of the gall bladder epithelial cells in patients with cholesterol gall stones compared with control patients without gall stones but with polypos. 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 mm2 in diameter were obtained from each fragment. Transmission electron microscopy, using a specific method to stain glycoprotein and mucoproteins (Thiery'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. 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. 3 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. 3 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, several recent studies support the idea that protection against Cryptosporidium requires the presence of an appropriate humoral immune response. In particular, enteral administration of bovine colostrum containing Cryptosporidium-specific antibodies can diminish the intensity of Cryptosporidium infection in human subjects and in calves. 3 In addition, in mice infected with Cryptosporidium, the sporozoites for mice can be reduced or eliminated by incubating the sporozoites with antibodies that bind to their surfaces. 4 This particular finding raises the possibility that Cryptosporidium infection is caused by the presence of antibodies in the intestine that can bind to Cryptosporidium sporozoites in vivo.

The lifecycle of Cryptosporidium species is dependent on the gut epithelial cell. 5 Therefore, the sporozoites for mice are attached to intestinal epithelial cells, and are covered on their luminal aspect by an envelope of host cell origin. 5 Conceivably, this envelope may prevent luminal antibody from binding to Cryptosporidium sporozoites in vivo.

In summary, the authors should consider the possibility that T cell mediated immunity is not involved in the protection against Cryptosporidium infection, and that the humoral immune response is the major mechanism of host defence against this micro-organism.

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3 Heyworth MF. Intestinal IgA responses to Giardia murs in mice depleted of helper