been interpreted as indicating that unknown intraluminal or mucus layer factor(s) might interfere with antimicrobial action. A recent report raises the possibility of antimicrobial resistance consequent on previous suboptimal exposure,[9] which emphasises 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 subcitrate (CBS).[10] 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.[11] 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 mucus film and often insinuate themselves between the epithelial cells[7 12] sequestering themselves from gastric juice by sitting deep to the mucus layer.[1] This intimate adherence of the bacteria to the gastric epithelial cells and its histopathological implications for disease production has been shown in a recent study.[13] Systemic delivery only requires good contact with gastric secretion or interstitial fluid or diffusion into the gastroduodenal lumen.

A practical extension of this hypothesis is that antimicrobial treatment should be given systemically 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 at the gastric site[11 14] hence, of necessity, contact with *H pylori*. Enterohepatic circulation of bismuth[15 16] could be of benefit as it would effectively prolong the exposure time of the bacteria to agents in the circulation.

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

SHAMSUL ISLAM
ALLAN J McLEAN
Clinical Pharmacology Department, Alfred Hospital, Melbourne, Australia

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Diabetes and cholelithiasis

SIR,—We read with interest the study by Laakso *et al* on serum lipids and lipoprotein in patients with non-insulin diabetes and with gall stone disease.[1] The association between diabetes and cholelithiasis has been defined also in the Italian population,[2 3] but the reason for this association has not yet been clarified. It is generally held that patients with diabetes secrete a more lithogenic bile than non-diabetics.[4] In the few studies that have compared diabetics with age, sex, and weight matched controls, however, neither the insulin dependent diabetics nor the insulin independent diabetics had a bile cholesterol saturation index higher than that of control subjects.[5] Therefore, 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[6] on 120 patients affected by type II diabetes we too observed that in diabetics with 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, glycated haemoglobin HbA_1, body mass index, and duration of diabetes between patients with gall stones and those without gall stones. In our study, in non-insulin dependent diabetes 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, however, that it 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 insulinaemia. 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 lipoprotein 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 relation between plasma and biliary lipid 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 diabetics was shown and the presence of an autonomic neuropathy seems to be a risk factor for such an impairment.[6]

P PAZZI
L TREVISANI
S SARTORI
1st Medical Department, S Anna General Hospital
D SIGHINOLFI
V ALVISI
Institute of Internal Medicine, University of Ferrara, 44100 Ferrara, Italy

Correspondence to: Dr P Pazzi, 1st Medical Department, S Anna General Hospital, Corso Giovecca, 203, 44100 Ferrara, Italy.

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Reply

SIR,—Pazzi *et al* have shown an association between high insulin concentration and cholelithiasis in non-insulin dependent diabetes similar to what we have reported.[1] 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. In contrast, 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 prolonged use of 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.[2] Indeed, our preliminary unpublished data show that