Progress report

Bacteria and disease of the biliary tract

The biliary tract probably does not harbour bacteria at most times in normal individuals. It seems quite unlikely that there could be the same sort of sparse indigenous flora that is seen in the duodenum\(^1\) since complete biliary obstruction is rarely associated with bacterial cholangitis.\(^2,3\)

The conditions necessary for the development of infection of the biliary tract or for the production of infected bile are not in general known. It is agreed that infection regularly follows certain septicaemic illnesses, notably typhoid fever, and that infection so initiated may become chronic is indicated by the occurrence of the carrier state. The biliary infection occurring in typhoid fever is often regarded as a special case. But once typhoid is established in the biliary system and it has become chronic the disease resulting follows a pattern that is in no way remarkable when compared with infections due to other members of the Enterobacteriaceae. This is true whether the disease develops as chronic cholecystitis, as is common in Europe or America,\(^4\) or as recurrent pyogenic cholangitis on the Pacific coasts of Asia.\(^5\)

Cholera seems to behave similarly. Although a septicaemic phase is not well recognized in human disease it seems likely that it does occur. In the Rhesus monkey a septicaemia must be invoked in order to explain the biliary infection seen in experimentally infected animals which have previously had the bile duct ligated.\(^6\) The experimentally infected Erythrocebus monkey has provided evidence that pre-existing gallbladder disease is not a prerequisite for cholecystitis in experimental cholera.\(^7\) The recognition of chronic typhoid carriers in patients without gallstones argues, though less strongly, in favour of the possibility that chronic disease may develop in a hitherto normal gallbladder.\(^4\)

When gallstone disease is present in Europe or America there are bacteria in bile in up to a third of the patients while up to two-thirds show the presence of bacteria in or intimately associated with the gallbladder wall.\(^8,9\) It is often suggested that such infection follows rather than precedes the development of stones, and the attractiveness of this postulate lies in the explanation it appears to offer for this localization of ‘non-pathogenic’ bacteria. It has the consequence, however, of making the occasional occurrence of acute bacterial acalculous cholecystitis a phenomenon which requires a separate explanation. A common factor included in such explanations is ‘bile stasis’. Postoperative dehydration and fasting and the effects of narcotics are held to produce ‘bile stasis’ and explain the localization there of bacterial infection to produce acute non-calculous cholecystitis in the postoperative period.\(^10\) Any explanation of infection of the biliary tree in terms of bile stasis, however, runs counter to the experience already quoted that infection is uncommon in malignant duct obstruction, and in laboratory animals, too, obstruction of the common duct or cystic duct is not as a rule followed by infection.\(^2,3,11\) In the laboratory animal bacteria such as \textit{E. coli} introduced into the portal or systemic circulation may produce biliary
infection and the effects will be magnified by prior bile duct ligation. But infection is a consequence of bacteraemia itself. This conclusion is viewed with some disfavour, presumably because it implies some special affinity or tropism of ‘commensual’ bacteria for the biliary apparatus. It suggests, however, that the cholecystitis of typhoid or cholera might be best regarded as examples of a phenomenon seen in the behaviour of all the Gram-negative facultative anaerobes commonly or occasionally found in the bowels of man. In line with this hypothesis is the report in which extrabiliary sepsis, and by implication bacteraemia, has been emphasized as an association of acalculous cholecystitis in young Viet Nam casualties (though again it was felt necessary to postulate prior damage to the gallbladder from the pigment load resulting from massive blood transfusion and ‘bile stasis’ consequent upon dehydration in these patients).

If bacterial infection of the biliary system is a consequence simply of bacteraemia, and especially Gram-negative bacteraemia, it must be assumed to be commonly a transient event, as indeed it usually must be in typhoid or cholera. In both these diseases whether the biliary infection becomes chronic is thought to be determined by the presence or absence of pre-existing biliary disease. Thus the chance of becoming a chronic carrier appears to be related to age and therefore parallels the incidence of gallstone disease in the population. The observation is clearly open to alternative interpretations: it could be that with age the gallbladder favours the continuation of bacterial growth. Similarly the predilection of bacteria for the hepatic ducts of the patient on the western Pacific coasts may be too simply explained by invoking the frequency of fluke infestation, since such infestation is far from constant. Although there is no readily available alternative explanation, speculative hypotheses could invoke effects of climate or hyper-nutrition or malnutrition upon host resistance. Such factors have been shown to operate in determining the behaviour of other bacterial infections. But abnormalities in the biliary system, while probably not determining its occurrence, clearly do modify the clinical expression of an infection. Cholecystolithiasis, for instance, is commonly associated with infection involving all the large bile ducts together with the gallbladder and gallbladder wall. The most likely explanation of the association is that biliary obstruction favours the spread of infection from the gallbladder into the biliary system generally rather than that infection ascends the obstructed biliary system. The evidence is provided by the similar incidence of bacterial infection of the gallbladder wall in simple cholelithiasis and of bile in cholecystolithiasis, the uniformity of the infecting flora in the entire biliary system in these patients, and the low incidence of infection in malignant duct obstruction where cholelithiasis and hence an infected gallbladder is an infrequent finding. A crucial observation not yet made would be of the frequency with which cholelithiasis is present in patients with pancreatic carcinoma and jaundice, and the comparative frequency with which infection of the entire biliary tree occurs in these people and those with carcinoma but no gallstones. The prediction would be that generalized biliary infection would be rare in the absence of stones but present in a half to two-thirds of those with existing gallbladder disease. If gallstones are present in 10% of the patients who develop carcinoma of the pancreas the incidence of bacterial cholangitis in such patients with jaundice should be about 6% which seems in keeping with experience.
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The clinical importance of biliary infection varies. There is no doubt that what is clinically recognized as acute cholecystitis is often not associated with recognizable infection of bile or gallbladder. When infection is found to be present it is often an incidental consideration. However, it is clear enough that the association becomes increasingly important with increasing severity of the disease process.9,18,19

When obstruction of the common bile duct is produced by gallstones bile is found to be infected in between a half and three quarters or more of patients.2,3,8 The presence of such infection may be represented clinically by the occurrence of Charcot's intermittent biliary fever and two-thirds of patients with infected bile will describe the occurrence of such symptoms at some time. In the other third the presence of bacterial infection can only be determined bacteriologically.3 In other words, bacterial cholangitis is somewhat erratically revealed by clinical cholangitis. (Pathological cholangitis is a quite inconstant association of bacterial or clinical cholangitis and patients with bacterial cholangitis may show no changes other than those to be expected in large duct biliary obstruction of whatever cause.21) The intermittency of symptoms is usually assumed to be due to a self-limiting bacteraemia,22 though this is surprisingly difficult to show with any consistency.24

Again, however, the more seriously ill patients in this group have a clinical course dominated by the infection. Such patients are best referred to as having acute obstructive suppurative cholangitis.53,54,55,56 They are usually elderly, clinical signs of biliary obstruction are often indistinct, there is evidence of upper abdominal mischief, and with time the illness may become dominated by a Gram-negative bacteraemia. Pathologically 'cholangitis', in the sense of polymorphonuclear leucocytes infiltrating the wall of smaller bile ducts, is invariable and hepatic abscesses of miliary size are not unusual. (Emphasizing the conclusion that duct obstruction acts not as a determinant but as an aggravating factor are reports which show that an indistinguishable illness can occasionally occur without recognizable obstruction being present.27)

Along the western Pacific coast, and with a lesser frequency elsewhere, recurrent pyogenic cholangitis occurs.58 Although this too is a suppurative cholangitis it is worth preserving a separate title. The condition affects younger patients, the major site of bacterial attack is the bile ducts rather than the gallbladder, and once established the disease shows a striking tendency to relapse, the relapses being uninfluenced by cholecystectomy, which indeed in the view of some, is not an essential part of the surgical treatment.29 During a clinical episode recognized bacteraemia occurs in about a quarter of patients. In contrast with the experience of surgeons dealing with acute obstructive suppurative cholangitis is the view that the majority of patients can initially be handled conservatively.29 The disease is controlled by producing a wide stoma between common bile duct and intestine. This is effective in preventing the rise in biliary duct pressure which has been shown to determine the dissemination of bacteria from bile into lymph or blood.50 In this way systemic symptoms are controlled though asymptomatic 'bacterabilia' continues.5 An effective choledochostomy is similarly a vital early step in preventing or controlling septicaemia in the more aggressive acute obstructive suppurative cholangitis. There is general agreement that in this disease survival reflects the urgency with which this is undertaken.50

Antibacterial therapy and supportive measures in any suppurative
cholangitis should be appropriate to the septicaemia, which can be anticipated. Discussions of antibiotic therapy in this context often concentrate on drugs which can in normal subjects be shown to reach high levels in bile. These considerations are irrelevant in the life-threatening situations under discussion since it is likely to be generally true, that, as with rifamide, the mechanisms responsible for active secretion of the drug will themselves be impaired or destroyed by the disease.\textsuperscript{31} When bacteria are present in otherwise uncomplicated gallstone disease they are often sparsely so. Bacterial counts of greater than 10\textsuperscript{8} viable organisms per millilitre of bile are found in only 5 to 10\% of routine cholecystectomy samples.\textsuperscript{31} There is little or no information available recording the effects produced by infection on the constituents of bile or on the gallbladder wall, but it is known that in this case significant bacterial deconjugation of bile salts does not occur and phospholipid composition seems similarly unaffected.\textsuperscript{32} In patients with choledocholithiasis, on the other hand, bacterial cholangitis is usual, and the viable bacterial count ranges from 10\textsuperscript{6} to 10\textsuperscript{10}.\textsuperscript{2,5,8} In these circumstances bacterial effects become demonstrable with some regularity. These effects are recognized by the surgeon as ‘biliary mud’. Few of the effects that might be predicted have been accurately described but there is evidence that bacterial metabolism of bile salts in situ may lead to deconjugation and secondary bile acid formation\textsuperscript{33} and deconjugation of bilirubin may also occur.\textsuperscript{21} These effects are particularly common in patients with benign strictures of the bile ducts. Effects upon phospholipids have not been studied but bacterial lipo-phosphodiesterases might be expected to lead to the formation of diglycerides as well as other breakdown products of lecithin. The sum of these effects would lead to a reduction in the ability of bile to solubilize the water-insoluble substances present, notably cholesterol and bilirubin, and these will precipitate to form, with biliary mucus, biliary mud.\textsuperscript{21} Bacterial effects have also been shown to provide a plausible explanation for the development of calcium bilirubinate stones in Japan and may be the explanation for the similar stones that develop in recurrent pyogenic cholangitis.\textsuperscript{34}

Once chronic infection is established in the biliary system it becomes difficult to eradicate. If localized in the gallbladder infection may only rarely be eradicated by treatment with antibiotics, if results of treatment of the typhoid carrier state are generally applicable, and then only when gallstones are absent.\textsuperscript{4} Established bacterial cholangitis is rarely curable when it takes the form of recurrent pyogenic cholangitis\textsuperscript{5} though by a combination of T-tube drainage, cholecystectomy, and irrigation of the bile ducts with oxytetracycline cures of the typhoid intrahepatic carrier state have been achieved.\textsuperscript{35} Whether or not ductal infection is usually cured following choledocholithotomy in bacterial cholangitis determined by choledocholithiasis is not clearly established. Asymptomatic ‘bacterbilia’ may persist but what evidence there is suggests this is uncommon in the absence of stricture. In the patient with a benign stricture or in whom choledocho-duodenal or choledocho-jejunal anastomoses have been performed, bacterial cholangitis is usual.\textsuperscript{8} (Biliary to intestinal anastomoses are also usually complicated by bacterial cholangitis in dogs.\textsuperscript{30}) But clinical cholangitis or secondary effects upon the liver do not usually ensue in the animal model or human unless obstruction to bile flow occurs. Presumably obstruction has two effects: in raising the bacterial count in bile to high levels and in making
bacterial dissemination more likely by raising intraductal pressure.30

Only if surgical correction of the obstruction is not immediately feasible need antibiotics be administered. Probably the most reasonable aim in this instance is to prevent the formation of biliary mud, which may further contribute to obstruction, and to prevent the formation and hence the absorption of such toxic constituents of biliary mud as lithocholic acid which, speculatively, might contribute to the secondary sclerosing cholangitis seen in such patients. High concentrations of antibiotic in bile are then needed. Unfortunately there is no reliable way of determining the effect of any treatment of this kind that is undertaken, though duodenal bacteria may reflect the biliary infection when the latter is gross.33 The lack of a reliable clinical tool for the non-operative diagnosis of biliary tract infections remains the most important inhibitor of progress in understanding the interrelationships between bacterial infection and disease of the biliary tract.

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