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Sepsis and cholestasis

Paediatricians know that in neonates cholestatic jaundice may be the sole manifestation of a serious infection, particularly with Gram negative organisms. The association used to be recognised in adults, too—for example, with lobar pneumonia¹—but it has become uncommon. A recent case report of gangrenous appendicitis presenting as cholestatic jaundice has highlighted the diagnostic dilemma.²

Cholestatic jaundice is most often due to mechanical obstruction of the biliary tract both inside and (more commonly) outside the liver, but it may also occur if for any reason conjugated bilirubin cannot be secreted from the liver cell or if flow along the canaliculi and fine bile channels is impeded. In such cases the cause might still be said to be "microscopic" obstruction to the secretory apparatus, but the number and variety of associations, which include inherited syndromes, pregnancy, many drugs, haemolysis, burns, operations, and sepsis, suggest that a single mechanistic explanation is unlikely. For the clinician the important point is that the key to diagnosis may lie elsewhere than in the biliary system, and an error may cost the patient dear, especially if cholestasis is the dominant feature.

The association with sepsis has been described repeatedly.^{1,3,4} Fever, rigors, and other signs of infection are followed within a few days by a mild to moderate obstructive jaundice without pain or itching. Alternatively, the doctor trying to make a diagnosis in a patient with unexplained malaise or fever may be surprised to find that the results of liver function tests suggest obstruction. Usually the serum concentration of bilirubin is moderately raised, up to perhaps six times normal (100 µmol/l; 5.8 mg/100 ml); exceptions are possible with both normal and very high values mimicking extrahepatic obstruction being recorded.^{5,6} A useful pointer in the absence of clinical jaundice is bilirubinuria. The activity of alkaline phosphatase is almost always raised, as are concentrations in the serum of substances such as bile acids and sulphobromophthalein that are usually excreted in the bile, while serum aminotransferase activities are normal or only mildly raised. Where liver biopsy specimens have been obtained the picture is characteristic of intrahepatic cholestasis, with bile in canaliculi around the central veins and in liver cells, a mild inflammatory cell response, and minimal hepatocellular damage. Material obtained at biopsy is invariably sterile on culture.

If occult sepsis is not borne in mind conditions such as cholangitis, liver abscess, Weil's disease, and tropical infections are likely to be considered. Where there is septicaemia (and results of blood cultures are by no means always positive), the organisms isolated have included *Escherichia coli*, *Klebsiella pneumoniae*, and *Haemophilus influenzae*⁴; but probably infection with any organism—and *Legionella* is one of the latest to be reported⁷—may result in cholestasis.

Among the recorded sites of infection have been the appendix, diverticula, the kidneys and lungs, endocarditis, and pelvic and subphrenic abscesses. A proper appreciation of the cause of the jaundice may be delayed because some patients are already suffering from the effect of operation, shock, haemolysis, and anoxia and may have been given multiple blood transfusions and potentially hepatotoxic drugs.

Many theories, none of them satisfactory, have been put forward to account for this type of cholestasis, ranging from the effect of bacterial endotoxins to local obstruction from inflammatory cells and swollen Kupffer cells. A much simpler explanation could be that a form of inspissated bile syndrome is induced by changes in the relative amounts of water, electrolytes, and larger molecules in the bile itself from factors such as fever, dehydration, and hypotension. Whatever the mechanism this type of cholestasis offers no threat to the patient provided that its identity is recognised; it does not require elaborate investigation. The clinical lesson to be learnt is that if an obstructive pattern of liver function values in seriously ill patients cannot be confidently attributed to disease of the liver or gall bladder a dangerous intruder must be sought in another part of the body.

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Cysticercosis: a new hope

Effective treatments are still needed for many infectious disorders common in the developing world, so a recent paper from Mexico is welcome in holding out a definite promise of such a treatment for cysticercosis.¹

Cysticercosis is produced when man becomes the host of the larval stages of the pig tapeworm *Taenia solium*. In the normal life cycle the adult worm lives in the human small intestine, and the eggs (or intact gravid segments of the worm) leave the body in the faeces. When the eggs are swallowed by pigs they hatch out to release oncospheres, which penetrate the gut wall and are carried by the circulation to the various tissues of the body, where they encyst as "bladder worms." Cysts may be found almost anywhere but are particularly abundant in the skeletal muscles and myocardium. When the pig's muscle is infected by these cysts the pork is said to be measly. Man becomes infected with the adult worms by eating inadequately cooked measly pork.

Adult tapeworms in the gut cause few symptoms apart from the uncomfortable sensation caused by an escaping proglottid. The serious effects of *T solium* are produced when man becomes host to the bladder worms (cysticerci). This may come about when he eats the eggs or by internal

autoinfection, in which reverse peristalsis or upward migration of an adult worm leads to gravid proglottids releasing eggs in the upper gut—tantamount to swallowing the eggs of one's own tapeworm. Direct infection from outside may occur when food or drink is contaminated by human faeces and also by sexual oroanal contact. In Southern Africa witch doctors may deliberately dose their patients with a gruel made from ground up segments of *T solium* and so produce massive cysticercosis.

In man cysticerci are present in the subcutaneous tissues, where they can often be readily palpated; in the muscles, where they are easily visible radiologically once they have calcified; and in the brain and sometimes the eye. It is cerebral cysticercosis that is mainly responsible for the serious symptoms. Cysts vary in diameter from a few millimetres to over two centimetres.

The manifestations of cerebral cysticercosis include epilepsy, raised intracranial pressure, and focal neurological signs—determined by the precise location of the cysticerci and their numbers.^{2,3} Until recently the only treatment available was anticonvulsants to control the fits and steroids to control acute exacerbations brought about by the host reaction around the cysts.

Praziquantel is effective against many tapeworms and also has powerful antischistosomal activity.⁴ Its first reported use in cysticercosis was in pigs in 1978 and in man in 1980.⁵ Since then subjective evaluation has seemed to suggest a favourable response on several occasions.^{6,9} The present report is unique in providing for the first time in man objective evidence that treatment with praziquantel can reduce the number and size of the cysts.

The paper describes the treatment of 26 carefully selected patients at the Mexican National Neurological and Neurosurgical Institute. All were adults with a stable neurological state, and none had intracranial hypertension. All had intracranial cysts large enough to allow their progress to be monitored by computed tomography, and most had supporting serological findings. None had radiological evidence of surrounding inflammatory reaction, a factor which might have led to a spuriously favourable response. All cysts were counted and measured before treatment was started, this being praziquantel in three divided doses to a total of 50 mg/kg body weight a day for 15 consecutive days.

Twenty four of the 26 patients had adverse reactions during treatment, mainly severe headache. Twelve patients had fits, and two developed intracranial hypertension, though not severe enough to need steroids or other special measures. All reactions subsided spontaneously after treatment was completed.

Follow up was both radiological and clinical. Three months after treatment two thirds of the cysts had disappeared without being replaced by inflammatory tissue, and their total diameter had greatly decreased. The few patients followed up at six months showed little further improvement. Symptoms and signs at the three month follow up also showed improvement in nearly all patients. The pronounced rise in cells and protein in the cerebrospinal fluid that occurred during treatment had returned to normal by three months. In an untreated control series there was no spontaneous improvement, for new cysts had appeared and existing ones had grown larger. So the effectiveness of praziquantel has been shown beyond doubt, although whether cysts that remain require further treatment with praziquantel is still unanswered.

Nevertheless, the dramatic host reaction that develops around the cysts and in the cerebrospinal fluid during

treatment means that praziquantel should always be given with extreme caution under expert neurological and neurosurgical supervision. Inevitably some patients will develop more severe intracranial hypertension than was seen in this small series, and acute obstructive hydrocephalus is always a possibility.

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Oral gold for rheumatoid arthritis

Gold was first used for treating rheumatoid arthritis in the late 1920s in the belief that the heavy metal acted on an infectious agent responsible for the disease.^{1,2} It was introduced into Britain by the late S J Hartfall^{3,4} and several years later controlled trials throughout the world confirmed its efficacy.⁵⁻⁷ Careful studies showed that it improved both biochemical and clinical indices of the activity of the disease.⁸

Gold fell out of favour again with the arrival of the flood of new anti-inflammatory drugs, but there has been a recent resurgence of interest with the publication of two symposia, sponsored by Smith Kline and French, the makers of an oral gold compound (Auranofin),^{9,10} and of an extensive review.¹¹ This fresh interest has stemmed from several observations. Firstly, non-steroidal anti-inflammatory drugs are now generally recognised to be merely palliative in treating rheumatoid symptoms. Moreover, these drugs are only partially effective and many patients take more than one preparation. They have many side effects and in the long term they may increase joint damage. Secondly, clinicians persist in their desire for, and debate about, drugs which may alter the course of rheumatoid arthritis. Though preparations such as gold, penicillamine, hydroxychloroquine, and sulphasalazine are often termed "anti-rheumatoid" or "remission inducing," so many doubts persist that many prefer the term "second line agents." Early trials showed that gold treatment was effective against symptoms but had no effect on erosions.¹² More recently, serial radiography over five to six years has shown a less severe progression of destructive changes in patients treated with a full gold regimen than in those who discontinued the drug because of toxicity,¹³ and Sigler *et al* reported that gold slowed the rate of the appearance of new erosions.⁷ The third factor has been the development of an oral gold preparation which promises to be less toxic than the intramuscular drug.

Intramuscular gold is available in Britain only as sodium aurothiomalate. In the United States aurothioglucose is also