*Clostridium tetani*, however, have been found in up to 40% of samples of human faeces.[2] Another of our patients developed postoperative tetanus, which was attributed to self-contamination, after removal of a tumour of the buttock. Since rubber-band ligation of haemorrhoids produces an avascular area, and since this is in contact with a potential source of *Cl tetani*, the tetanus in this case may reasonably be attributed the operation. Certainly the time relationship fits in with the incubation period of tetanus.

[1] Slack, W W, in *Diseases of the Colon, Rectum, and Anus, Tutorials in Postgraduate Medicine*, vol 1, ed B C Morson. London, Heinemann, 1969.
[2] Wilson, G S, and Miles, A, in *Topley and Wilson's Principles of Bacteriology, Virology and Immunity*, 6th edn, vol 2, p 2229. London, Arnold, 1975.

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**Princess Alexandra Hospital, Woolloongabba 4102, Queensland, Australia**
K J MURPHY, BSC, FRACP, deputy medical superintendent and medical director

# Primary biliary cirrhosis after long-term practolol administration

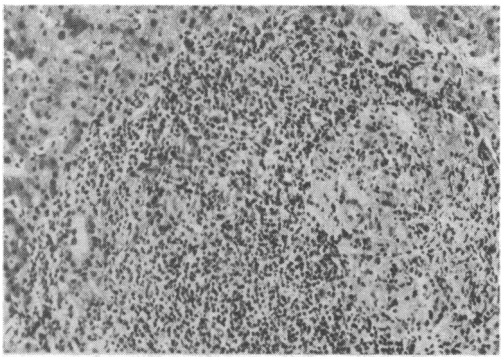
Oculocutaneous syndrome, sclerosing peritonitis, and pulmonary fibrosis may result from practolol treatment[1 2] but liver disease has not been implicated as an adverse effect. We have recently seen two patients with oculocutaneous lesions typical of practolol sensitivity who also had clinical and laboratory features of primary biliary cirrhosis (PBC, primary non-suppurative destructive cholangitis).

## Case reports

A 76-year-old man developed pruritus after four years' continuous treatment with practolol 300 mg daily for angina of effort. He had an eczematous rash with palmar erythema; dryness of the eyes was confirmed by Schirmer filter paper testing. Smooth, non-tender hepatomegaly was noted. The following measurements were made: serum bilirubin 25 μmol/l (1·5 mg/100 ml) (normal 1·7-17 μmol/l (0·1-1·0 mg/100 ml)), alkaline phosphatase (liver isoenzyme) 405 IU/l (normal 20-90), serum aspartate transaminase (SGOT) 12 IU/l (normal 4-20), serum albumin 36 g/l, serum total globulin 40 g/l, serum IgM 2·2 g/l (0·7-2·0), IgG 11·6 g/l (9·5-16·5). Hepatitis B antigen was absent. Antinuclear factor was present (titre 1/80) as was smooth muscle antibody (1/20) and mitochondrial antibody (1/80). Liver scan and histological examination of a needle biopsy specimen confirmed the presence of cirrhosis.

He remained well after practolol was stopped, but liver function tests showed persisting cholestasis. The development of cervical lymphadenopathy two years later, however, led to the diagnosis of nodular sclerosing Hodgkin's lymphoma. Despite radiotherapy he died after six months. Patent bile ducts were found at necropsy, and histology of tissue obtained a few minutes after death confirmed advanced cirrhosis with proliferating bile ducts and lymphocyte aggregates consistent with primary biliary cirrhosis. Staining with orcein and rubeanic acid showed hepatocytic metalloprotein complex as found in PBC.[3] Typical sclerosing peritonitis affecting the jejunum was also present.

A 57-year-old man was treated with practolol 300 mg/day for angina. After seven months he developed a psoriasiform rash and two months later he complained of dryness of the eyes. Liver function was not tested until 16 months after discontinuing the drug. Findings were: serum bilirubin concentration 50 μmol/l (3·0 mg/100 ml), alkaline phosphatase concentration 144 IU/l, and SGOT 15 IU/l. Serum protein and immunoglobulins were normal as were autoantibody tests except mitochondrial antibody, which was positive to a titre of 1/160. A needle biopsy specimen of the liver showed normal lobular architecture, but near bile ducts were large epithelioid granulomata with surrounding lymphocytes (fig).



Epithelioid granulomata and lymphocytic infiltrate in the periportal area. (Haematoxylin and eosin. × 180.)

## Comment

These patients conform to the usual diagnostic criteria for primary biliary cirrhosis,[4] including cholestasis, a high mitochondrial antibody titre, and consistent liver histology. Chronic liver disease after drug administration usually resembles active chronic hepatitis. Only three cases of abnormal liver function after practolol administration have been reported to the Committee on Safety of Medicines in the United Kingdom, but the details are incomplete and difficult to interpret. Autoantibody abnormalities, however, are recognised with practolol rashes. Thus the serum in five out of 18 patients was reported positive for antinuclear factor but none of them had mitochondrial antibody.[1] A relationship between practolol and chronic hepatobiliary disease seemed likely but the presence of PBC-like histology and mitochondrial antibody in patients taking practolol could also have been fortuitous. We have therefore tried to calculate the probability of men with PBC being exposed to practolol. By making several assumptions, an estimate of the figure may be obtained from the number of prescriptions for practolol and the number of certified deaths from PBC a year. Two cases of PBC exposed to practolol in the northern region gives a much greater overall incidence than would be expected from annual prescription and mortality data. We therefore think that the association between PBC and practolol in our two cases was probably not fortuitous.

[1] Felix, R H, Ive, F A, and Dahl, M G C, *British Medical Journal*, 1974, **4**, 321.
[2] Erwteman, J M, Braat, M C P, and van Aken, W G, *British Medical Journal*, 1977, **2**, 297.
[3] Salaspuro, M, and Sipponen, P, *Gut*, 1977, **17**, 787.
[4] Sherlock, S, and Scheuer, P J, *New England Journal of Medicine*, 1973, **289**, 674.
[5] Committee on Safety of Medicines, personal communication.

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**Gastroenterology Unit and Department of Medicine, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP**
P J E BROWN, MB, MRCP, clinical registrar
MILENA LESNA, MD, MRCPATH, consultant histopathologist
A N HAMLYN, BSC, MRCP, first assistant in medicine
C O RECORD, DPHIL, MRCP, consultant physician in gastroenterology

# Malignant disease presenting as Addison's disease

Primary adrenal hypofunction—Addison's disease—is uncommon. Autoimmune destruction of the adrenals is now the commonest cause, other causes being due to metastatic carcinoma and tuberculosis. Vieweg *et al*[1] reviewed the published work and found only eight cases of Addison's disease associated with malignancy in which the diagnosis had been confirmed by the results of ACTH and cortisol estimations. It must be unusual for malignant infiltration of the adrenals to produce Addison's disease when there is no other evidence of malignant disease. Two such cases are described.

## Case histories

*Case 1*—A 75-year-old man presented in 1975 with prostatism. His medical history included tuberculosis at the age of 15; partial gastrectomy for duodenal ulcer in 1944; and syncopal attacks due to cardiac arrhythmias in1966. In the six months after prostatectomy for benign prostatic hypertrophy, he

developed anorexia, nausea, and vomiting associated with considerable weight loss. Initially gastric carcinoma was diagnosed, but the results of investigations confirmed the presence of Addison's disease (see table). Despite replacement therapy, three months later he had further nausea and vomiting, and died. Necropsy showed extensive carcinoma of the pancreas destroying both adrenals.

*Results of ACTH and cortisol estimations in two patients with Addison's disease due to carcinoma. Normal ranges for our laboratory given in parentheses*

| | Urinary free cortisol excretion (10-850 nmol/24 h) | Serum cortisol concentration (166-660 nmol/l) | | Serum ACTH concentration (10-118 ng/l) | |
|---|---|---|---|---|---|
| | | 9am | Midnight | 9am | Midnight |
| Case 1 | Nil | 168 | 104 | 260 | |
| Case 2 | 22 | 243 | 193 | 586 | 155 |

*Conversion: SI to traditional units*—Urinary cortisol: 1 nmol/24 h ≈ 0·36 μg/24 h. Serum cortisol: 1 nmol/l ≈ 0·036 μg/100 ml.

*Case 2*—A 60-year-old man was admitted in July 1976 with a three-month history of anorexia, nausea, vomiting, and weight loss. He had no family history of autoimmune disease and smoked 5 oz of tobacco per week. There was increased pigmentation over his legs and head associated with postural hypotension. The results of investigations confirmed Addison's disease (see table). No autoimmune antibodies were present and there was no evidence of tuberculosis, his chest *x*-ray film being normal. Replacement therapy resulted in rapid symptomatic improvement and he remained well on follow-up with normal chest *x*-ray films. Six months later the same symptoms recurred despite adequate replacement therapy. On this occasion the chest *x*-ray film showed an enlarged right hilum. He died shortly afterwards and necropsy showed a primary oat-cell carcinoma of the bronchus with a large abdominal tumour mass extending across the midline destroying both adrenals and directly invading the liver. No other metastases were seen.

## Discussion

Tiredness, nausea, vomiting, and weight loss are early symptoms of Addison's disease and are entirely non-specific. Not until later in the disease do postural hypotension and hyponatraemia occur, thereby facilitating the diagnosis. In both our patients the initial symptoms were identified as being due to Addison's disease and were relieved by appropriate replacement therapy. When similar symptoms occurred some months later these were shown not to be due to Addison's disease but to malignancy.

Over 90% of adrenal tissue has to be destroyed before symptoms of adrenal hypofunction develop. Bilateral adrenal metastases occur early in carcinoma and our cases show that the adrenals may be destroyed before the primary site can be identified. In the first case bilateral adrenal spread occurred nine months before pancreatic carcinoma was suspected. In the second case adrenal metastases must have been present bilaterally for at least six months before evidence of the primary tumour was found, despite repeated chest *x*-ray examinations. At necropsy the only evidence of tumour spread was a locally invasive retroperitoneal mass destroying both adrenals.

A careful search in patients presenting with Addison's disease may allow carcinoma to be diagnosed early, at a stage when the primary tumour is small and possibly amenable to surgery, radiotherapy, or chemotherapy. Furthermore, if the adrenals are the only site of tumour spread, resection of the primary tumour and bilateral adrenalectomy could be considered. Conversely, in some patients with obvious malignancy, symptoms often attributed to the non-specific effects of tumour growth may in fact be due to Addison's disease. Despite the common occurrence of tiredness, nausea, vomiting, and weight loss in patients with carcinoma, malignant destruction of the adrenals is thought to be uncommon and there are few reported cases of the results of ACTH and cortisol estimations in patients with Addison's disease due to carcinoma. If Addison's disease was diagnosed in some of these patients considerable symptomatic relief might be obtained by adequate replacement therapy.

[1] Vieweg, W V R, *et al*, *Cancer*, 1973, **31**, 1240.

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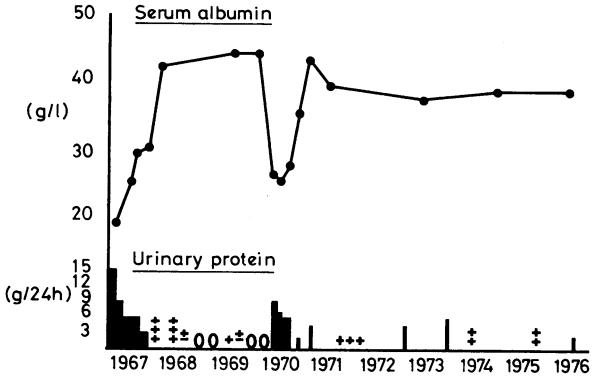
**Leicester Royal Infirmary, Leicester**
F D ROSENTHAL, MD, FRCP, consultant physician
M K DAVIES, MA, MB, senior house officer
A C BURDEN, MB, MRCP, senior medical registrar

# Spontaneous remissions of nephrotic syndrome in renal amyloidosis

The nephrotic syndrome caused by renal amyloidosis may remit when the disease underlying amyloid formation can be treated successfully.[1-3] Increasing knowledge about the nature of amyloid has recently led to the advocacy of new methods of treatment for the "primary" form of this condition. The value of any treatment for amyloidosis must be judged by comparison with the natural history of the disease. We describe spontaneous fluctuations in the clinical expression of renal amyloidosis that must be taken into account in the evaluating of treatment for it.

## Case reports

*Case 1*—An Englishwoman developed bilateral pulmonary tuberculosis in 1947 when aged 18. After a left artificial pneumothorax she was treated with sodium aminosalicylate and isoniazid. In 1966 she developed gross peripheral oedema with normal jugular venous pressure and blood pressure. There was no evidence to suggest reactivation of tuberculosis. The serum albumin concentration was 19 g/l and urinary protein excretion was up to 14 g/24 h. Blood urea concentration was 13·3 mmol/l (40 mg/100 ml). A needle renal biopsy specimen showed deposition of amyloid in relation to the glomerular basement membrane and in the blood vessel walls. She was treated with diuretics, and by July 1967 the nephrotic syndrome had remitted (fig).




Case 1: spontaneous remissions of nephrotic syndrome in 1967 and 1970.

During the next 21 months the urine was protein-free when tested on four occasions and showed only a trace on four other occasions.

The nephrotic syndrome relapsed in January 1970. The following measurements were made: serum albumin 29 g/l, urinary protein excretion 6-8 g/24 h, blood urea 4 mmol/l (24 mg/100 ml), serum creatinine 106 μmol/l (1·2 mg/100 ml), creatinine clearance 40-60 ml/min. The proteinuria was poorly selective, IgG/albumin clearance ratio 0·33. A second needle biopsy showed more extensive deposition of amyloid in the glomeruli and electron microscopy showed fusion of the foot processes which was particularly distinct in the region of amyloid deposition. Diuretic therapy reduced the oedema and proteinuria decreased. The serum albumin rose eventually to 48 g/l and has remained above 36 g/l to date. Diuretics were discontinued for 18 months. The development of hypertension and deteriorating renal function led to regular haemodialysis in December 1976.

*Case 2*—In 1937 a 16-year-old English girl developed pulmonary tuberculosis. After a right artificial pneumothorax her sputum became free of tubercle bacilli by 1938. In 1947 she developed ulcerative colitis which ran an intermittent course until 1957, since when her bowel action has remained normal. In 1965 she developed nephrotic syndrome with a serum albumin concentration of 28 g/l and urinary protein excretion of 6 g/24 hours. The blood urea concentration was normal. She declined renal biopsy and gradually lost her oedema with diuretic therapy. In outpatients urinary protein was subsequently recorded as a trace or one plus and the serum albumin rose to 44 g/l, indicating a trivial amount of proteinuria.

In 1967 the nephrotic syndrome relapsed. A renal biopsy specimen showed florid amyloid deposition. She was discharged on diuretic treatment but failed to attend as an outpatient. She reappeared in 1972 in advanced renal failure and was found to have unilateral renal vein thrombosis. After treatment with anticoagulants and peritoneal dialysis conservation management of the renal failure was possible for 10 months before regular haemodialysis became necessary in September 1972.

## Comment

Histological evidence of regression of amyloid is scanty in patients with amyloidosis who improve clinically with treatment of the under-