

## CASE REPORTS

### Jaundice induced by stanozolol hypersensitivity

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#### Summary

A 66-year-old male patient developed jaundice after 7 months of treatment with the anabolic steroid, stanozolol. When the drug was withdrawn he made a full and uneventful recovery. A liver biopsy showed the histology of a hypersensitivity reaction. This is believed to be the first time jaundice has been recorded with stanozolol therapy and the first time a hypersensitivity-type jaundice has been recorded with any anabolic steroid.

#### Introduction

CHOLESTATIC jaundice may occur as a complication of treatment with certain anabolic steroids, and this is generally accepted to be due to a direct toxic effect upon the biliary canalicular cells (Sherlock, 1968; Maxwell and Williams, 1973). This report concerns a patient who developed jaundice while taking the anabolic steroid, stanozolol (Stromba, Winthrop) during a trial of its effect upon fibrinolysis in patients with ischaemic heart disease (Davidson *et al.*, 1972). In this case the jaundice appeared to be the result of a hypersensitivity reaction.

#### Case report

The patient was 62 years old when he sustained a myocardial infarct. He was started on phenindione and remained well after the incident with very stable control of his anticoagulant therapy. This was discontinued 4 years later, and after 4 weeks off all therapy he was entered in a double-blind placebo-controlled trial of the effect of stanozolol, and of stanozolol plus phenformin, upon plasma fibrinolysis in patients with ischaemic heart disease. He was randomly allocated to treatment with stanozolol 10 mg together with a phenformin placebo daily. This was continued and he remained well for 7 months. The effect upon the fibrinolytic mechanism has been reported previously (Davidson *et al.*, 1972).

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During the eighth month of treatment he was admitted to hospital with a 1-week history of jaundice, pruritus and dark urine. His appetite was unimpaired and there was no nausea or abdominal pain, but he had lost 4.5 kg in weight during the previous 3 weeks. There was no history of transfusion or of a recent injection or known contact with jaundice, and he had been taking no other drugs. He was deeply icteric with an enlarged (3 f.b.), smooth and non-tender liver. There were no other physical abnormalities.

#### Investigations

Serum bilirubin 8 mg/100 ml (direct acting fraction 7 mg/100 ml), alkaline phosphatase 31 KA u/100 ml, SGOT 51, and SGPT 74 RF u/ml, thymol turbidity 0.3 Maclagan units, albumin 4.1 g/100 ml and globulin 3.2 g/100 ml. There was bilirubinuria. Prothrombin and kaolin cephalin clotting times were normal. Hb 14.1 g/100 ml, WBC 11,300/mm<sup>3</sup>, platelets 242,000/mm<sup>3</sup>, reticulocytes 2%, ESR 16 rising to 57 mm/hr, and there were target cells in the blood film. Urea and electrolytes were normal. Chest X-ray, barium meal and enema were all normal. L.E. latex and L.E. cell test, and tests for anti-nuclear factor, smooth muscle and mitochondrial antibodies were negative. Six days after admission he developed an itchy maculopapular rash and was given chlorpheniramine 4 mg four times a day.

Cholestatic jaundice due to stanozolol was suspected but as there was no convincing improvement after 12 days (Fig. 1), percutaneous transhepatic cholangiography was performed. Bile was not aspirated, suggesting that an extra-hepatic biliary obstruction was unlikely (George *et al.*, 1965). A percutaneous liver biopsy likewise revealed no positive evidence of large bile duct obstruction. Cholestasis within bile duct canaliculi was prominent in the centrilobular zones (Fig. 2), while an inflammatory exudate was seen within and immediately

adjacent to all portal tracts (Fig. 3). Eosinophils were a conspicuous component of these lesions and they were present also in some sinusoids. Small foci of inflammation were seen in relation to a few scattered hepatocytes showing acidophilic necrosis. These appearances were considered to be most consistent with a cholestatic jaundice of hypersensitivity type.

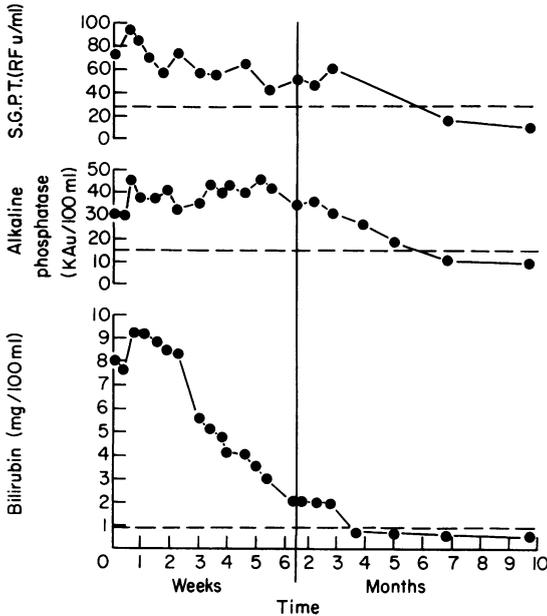


FIG. 1. Liver function tests from time of presentation to recovery (Interrupted lines = upper limits of normal).

The patient developed no further symptoms and required no treatment. His subsequent progress was entirely satisfactory with an eventual return of liver function tests and ESR to normal (Fig. 1).

### Discussion

Stanozolol is 17 $\alpha$ -methyl-17 $\beta$ -hydroxy-5 $\alpha$ -androstane (3,2-c) pyrazole (androstanopyrazole). Many patients will develop a degree of sulphobromophthalein retention when given an oral anabolic steroid. However, in many cases this returns to normal after 4 weeks despite continuing the treatment. Krüskemper (1968) carried out a quantitative comparison of the activity of oral anabolic steroids on sulphobromophthalein retention and found that stanozolol belonged to the group which had the least effect. He also reported that stanozolol had very little influence on the serum transaminases. To date, no case of cholestatic jaundice has been reported with stanozolol although it is a well known complication of other oral 17 $\alpha$  alkyl anabolic steroids (Sherlock, 1968; Krüskemper, 1968; Adlercreutz and Tenhunen, 1970).

Since the observations of Werner, Hanger and Kritzler (1950) on jaundice induced in man by methyltestosterone, it has been accepted that the cholestasis of anabolic steroid therapy is not a drug sensitization phenomenon. Schaffner, Popper and Chesrow (1959) studied liver biopsies in twenty-seven patients before and after the administration of norethandrolone. In none of their patients, including four who developed cholestatic jaundice, was there any hepatitis greater than the very minor degrees

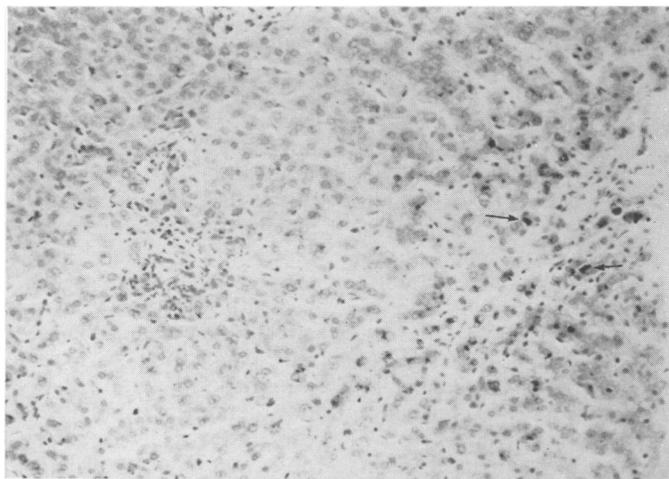


FIG. 2. Liver biopsy. In the centrilobular area (right) there are many small dark bile thrombi within bile capillaries (arrows). There is a mild inflammatory reaction in the portal tract (left). Neutral red  $\times$  250.

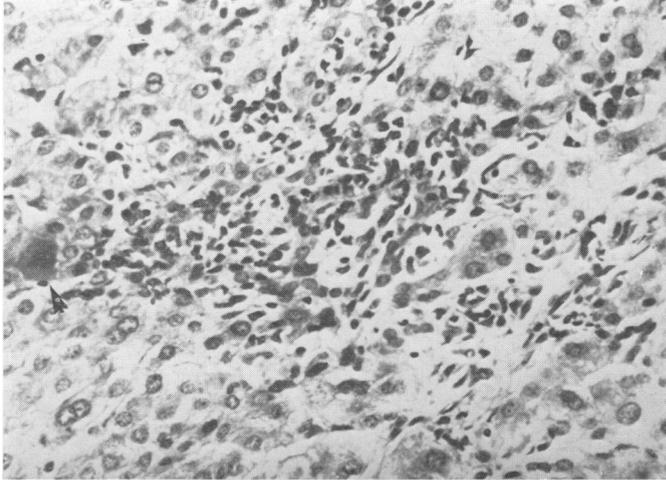


Fig. 3. Liver biopsy. A typical portal tract infiltrated with inflammatory cells including numbers of eosinophils. There is no cholangiolar proliferation. A pyknotic hepatocyte is present (arrow). Haematoxylin and eosin  $\times 565$ .

seen in control biopsies. These drugs may interfere with the excretion of conjugated bilirubin from the hepatocyte, and electron microscopy of both human and experimental livers has shown some damage to bile canaliculi (Schaffner, Popper and Perez, 1960; Arias *et al.*, 1961). There is no hypersensitivity reaction such as characterizes the cholestasis due to the phenothiazine group of drugs (Sherlock, 1968; Maxwell and Williams, 1973). Kruskemper (1968) reported that allergic side effects to anabolic steroids had not been observed but postulated that a heterocyclic substitution in ring A, as is found in stanozolol, might cause allergic symptoms similar to those elicited by other pyrazole derivatives.

In this case the histological appearance of the liver was most consistent with cholestasis of the hypersensitivity type. The clinical presentation with a rash and a high ESR also favours this mechanism. It is possible, of course, that the jaundice was the outcome of a combination of direct toxicity and hypersensitivity. As far as can be determined, features suggesting hypersensitivity have not previously been implicated in the cholestasis associated with anabolic steroids. The risk of stanozolol causing cholestasis of a non-hypersensitivity type remains theoretical. None of the other eighteen patients in the trial who received it daily for up to 30 months developed any clinical or biochemical evidence of this (Davidson, Conkie and McDonald, 1974). Furthermore, Howard and Furman (1962) reported two patients who had a history of jaundice during methyltestosterone therapy and who remained well when converted to stanozolol.

Anabolic steroids are now widely used and recently have been considered worthy of further study in thrombosis prophylaxis (Prentice and Davidson, 1973). It is suggested that all patients on long-term anabolic steroid therapy should have regular assessment of liver function.

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## Gout induced by L-dopa and decarboxylase inhibitors

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### Summary

Two cases of clinical gout are reported in parkinsonian patients receiving L-dopa in combination with a decarboxylase inhibitor. Blockade of decarboxylation leads to major changes in the pattern of L-dopa metabolites. It is suggested that hyperuricaemia may result from accumulation of L-dopa itself or a transaminated product.

### Introduction

HONDA and Gindin (1972) have reported two patients who developed the clinical and biochemical features of gout while receiving L-dopa for parkinsonism. Elevation of the serum uric acid may occur more commonly without arthropathy though misleading measurements can result from L-dopa interfering with non-specific assay techniques (Cawein and Hewins, 1969). The mechanism by which L-dopa induces gout is not known. Two patients have recently been encountered who developed gout while taking L-dopa in combination with a decarboxylase inhibitor; one was receiving carbidopa and the other  $\alpha$ -methyldopa.

### Case reports

Case no. 1, aged 52 years, first noticed tremor in his left hand 10 years ago. This spread to involve the left leg and idiopathic parkinsonism was diagnosed. In 1968 he underwent stereotactic thalamotomy. His tremor improved but his speech and gait deteriorated. There was no family history of parkinsonism or gout

and no previous encephalitis or exposure to neurotoxic materials. He developed mild tremor on the right. Cogwheeling was present at both wrists and his tendon reflexes were brisk on the left. He was initially treated with benzhexol (4 mg/day) and then L-dopa (5.5 g/day). In March 1973 he started taking carbidopa 100 mg/day, the dose of L-dopa being reduced to 2.5 g/day because of dyskinesia.

Three months after starting carbidopa he developed acute pain, swelling and erythema in the left great toe. This resolved spontaneously over a week. After a week free of pain his symptoms returned. His serum uric acid was found to be 6.9 mg/100 ml. Gout was diagnosed and he was given allopurinol 300 mg/day. A week later the dose was reduced to 200 mg/day and pain returned in his left great toe. He returned to 300 mg/day and has been free of pain since. The dosage of carbidopa and L-dopa has not been changed. His serum uric acid in January 1974 was 4.2 mg/100 ml. Allopurinol was stopped for 1 week in order to estimate his urinary output of uric acid, which was found to be 0.98 g over 24 hr (normal up to 0.4 g).

Case no. 2, aged 75 years, offered a 20-year history of parkinsonism. His initial symptoms were tremor of both lower extremities which progressed slowly. He also experienced bradykinesia manifested by difficulty in arising from the sitting and supine positions. His gait displayed slowness, shuffling, festination, and propulsion. His balance was impaired. Speech was of low tone and poor quality. Sialorrhoea and dysphagia were present. There was no family history of gout. Previous routine blood tests had shown normal concentrations of uric acid.

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