desoxycholate (10 ml. of 20% solution) which increases the emulsifying power of the blood and so reduces the size of circulating fat globules is limited because in larger doses it produces hæmolysis. Next, anticoagulant therapy has been advocated (Cobb and Hillman, 1961). Heparin is supposed to alter the lipoprotein density and would also prevent thrombosis if an occlusion did occur from the fat globules. From this small series, the impression gathered was that severe cases treated with anticoagulants recovered from the effects of fat embolism sooner than those treated without.

The treatment of these four cases has been discussed briefly; they are presented because they recovered in spite of prolonged unconsciousness, hyperpyrexia, respiratory and neurological involvement. It is also apparent that at the moment, beyond reduction of the hyperpyrexia, the quietening of the restlessness, and provision of a free airway for the patient with respiratory distress there is little to be done except to give anticoagulants, which did not interfere with fracture healing.

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INTRACTABLE PRURITUS DUE TO HEPATIC CIRRHOSIS RELIEVED BY CHOLESTYRAMINE

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PRURITUS due to liver disease is almost always due to biliary obstruction with associated retention of bile salts and other ingredients of the bile. The pruritus is always troublesome and its control is notoriously unsatisfactory. We report a case of hepatic cirrhosis whose pruritus was successfully relieved by cholestyramine.

Case Report

A married woman aged 47 attended the dermatological out-patient department on December 5th, 1962, complaining of severe generalised pruritus and tiredness for the last 5 years. At the beginning of her illness she had had bouts of violent sickness and vomiting at intervals of 6 to 7 months, but this had not troubled her much lately, although she had to avoid fried food because it made her feel sick.

She had scarlet fever in childhood. She had lived in N. Rhodesia from 1940 to 1946 where she suffered from enteritis and several mild attacks of malaria, from which she had been free since her return.

She was seen elsewhere for her skin complaint in 1960 and was put on Liq. Arsenicalis (Fowler's solution), which controlled her itching for the first time. She was kept on arsenic for about a year with reasonable control of pruritus, and thereafter this regime was stopped. Soon afterwards the pruritus returned, no other means could be found to control it, and it eventually got so bad that it interfered seriously with her sleep.

Physical examination revealed a thin, anxious looking woman with an earthy discolouration of the whole skin. There were numerous scratch marks on the body and limbs and some scattered superficial scars on the trunk and upper limbs. The provisional diagnosis was dermatitis herpetiformis and she was put on Dapsone 100 mg. b.d., which failed to control the pruritus. She was accordingly admitted on the 23rd April, 1963 for further investigation.

In hospital she was noticed to have pale coloured stools and dark urine occasionally, and her liver was palpable three finger breadths below the costal margin.

Investigations: Hb. 11 g./100 ml. PCV 35% MCHC 32%. The blood film was normal and Heinz bodies could not be found. Thrombotest 100%. ESR 37

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mm./hour (Westergren). Serum proteins: total 5.3 g./100 ml., albumin 2.5 g., globulin 2.8 g./100 ml. Thymol turbidity 3.6 units, alkaline phosphatase 43 K.A. units. Van den Bergh test: direct reaction positive. A cholecystogram showed normal filling, and no gallstones were visible. Clotting time 7 minutes. Bleeding time 65 seconds.

She was still thought to have dermatitis herpetiformis and the liver damage was provisionally attributed to the previous treatment with Liq. Arsenicalis. She was put on Cyproheptadine 4 mg. q.i.d. and discharged. The pruritus, however, failed to improve and she was readmitted on 10th September, 1963.

She described having had pale stools, flatulence and dark urine again, and we found a slight yellowish discolouration of the sclerae. Her itching was almost unbearable. The liver was as large as before, smooth and tender. The spleen was not palpable and there was no ascites. The skin was earthy brown over the whole body as before, there were numerous scratch marks, and on both upper limbs there were a few scattered erythematous-papular lesions.

Further Investigations: Bile was detected in the urine. ESR 37 mm./hour (Westergren). Hb. 10.3 g./100 ml., PCV 37%, MCHC 28%. Film—"the red cells show hypochromia with marked anisocytosis. The white cell series is normal in type and distribution". Thrombotest 100%. LE latex test negative, repeatedly. Serum proteins: total 6.9 g./100 ml., albumin 2.9 and globulin 4.0 g./100 ml. Thymol turbidity 3.6 units. Alkaline phosphatase 40.1 K.A. units. Electrophoresis showed a slight increase in the gamma globulin fraction. SGOT 71 units/ml. Van den Bergh test, direct reaction positive. Serum cholesterol 230 mg./100 ml. Bromsulphthalein test showed impaired excretion of the dye (30.5% remained). A 6-day faecal collection showed high fat excretion. Intravenous cholecystograph showed normally functioning gall bladder and no evidence of calculi. Skin biopsy, barium swallow and ECG showed no abnormality. Specimens of hair and nails submitted to activation analysis showed a normal arsenic content (hair 0.07 p.p.m.; nail 0.18 p.p.m.).

On October 11th, 1963, a percutaneous liver biopsy was performed under local anaesthesia, which showed a cirrhotic process with alteration of the liver architecture. The spurs of connective tissue between the hepatic cells contained chronic inflammatory cells suggesting that the lesion was not completely quiescent, but there was no evidence in the specimen of an obstructive process. The histological picture was reported as consistent with cryptogenic cirrhosis (Fig. 1).

Treatment: On October 25th, 1963, she was put on cholestyramine 6 g./day, in three divided doses, and ferrous gluconate 200 mg. t.i.d. Three days later the pruritus started to abate, and in a week it had completely disappeared. She was able to take the capsules easily and had no noticeable side effects. She never showed any bleeding tendency. The prothrombin time was checked on alternate days and found to be normal. Her bowel habits remained unchanged. She was discharged home on November 11th to continue the treatment.

She has been followed up regularly as an out-patient. She has remained free of itching, has maintained her appetite and weight, and has never shown any tendency to bleed. Two months after the treatment began she developed slight looseness of the stools. She is still under observation. A

FIG. 1.

(x33)

recent reduction of the dose to 4 g./day was followed quickly by a slight recurrence of pruritus.

Discussion

Hepatic cirrhosis, especially biliary cirrhosis (or chronic intra-hepatic biliary obstruction, term preferred by Sherlock), is well known to have an insidious onset, as our case demonstrates.

The intense pruritus, the skin lesions, and the fact that Liq. Arsenicalis brought relief suggested the diagnosis of dermatitis herpetiformis to begin with. She was therefore put on Dapsone and our failure to influence the pruritus with this drug led us to investigate the case further. The abnormal biochemical and haematological findings pointed to parenchymatous liver disease. The lack of evidence of extra-hepatic obstruction, the persistently high serum alkaline phosphatase, the behaviour of the serum proteins and bilirubin suggested biliary cirrhosis, but this diagnosis was not fully supported by the histological examination of the liver biopsy specimen, which showed hepatic cirrhosis without the specific features of biliary cirrhosis. Since our patient has neither had overt infective hepatitis, nor homologous serum jaundice, was not in the habit of taking alcohol and

had adequate diet, we considered whether the arsenic, a known hepatotoxic agent, could have been the cause of her cirrhosis, since she had taken it for about a year. We feel, however, that the normal values for arsenic in hair and nails weigh against this possibility. The cause of the cirrhosis is uncertain but we feel that the insidious onset, the persistently raised alkaline phosphatase, the absence of hypertension and the behaviour of the serum proteins are all in favour of biliary cirrhosis. Whether she also has dermatitis herpetiformis is hard to tell, but it would be difficult to explain the response to arsenic without making this supplementary diagnosis. At no time since we have had her under observation has she had the typical eruption of dermatitis herpetiformis.

It is well known that biliary obstruction is often associated with pruritus. The exact cause of this is not understood, but it is suspected that the accumulation of bile acids could be responsible, although no correlation between the degree of bile acidemia and the pruritus could be demonstrated (Osborn, Wootton, Da Silva and Sherlock, 1959).

Intermittent surgical drainage helps to relieve the pruritus of obstructive jaundice temporarily (Varco, 1947). Methyltestosterone (Lloyd-Thomas and Sherlock, 1952) and norethandrolone (Sherlock, 1959) are also effective, but they tend to deepen the jaundice in obstruction, and to cause bromsulphthalein retention in normal subjects, and hence their use is of doubtful value (Foss and Simpson, 1959).

An entirely new therapeutic approach was the introduction of cholestyramine, a strongly basic quaternary ammonium anion exchange resin, that forms insoluble compounds with bile acids in the gut which are neither digested nor absorbed (Tennent, Siegel, Zaretti, Kuron, Ott and Wolf, 1959). Hashim and Van Itallie (1960) successfully treated 4 cases of biliary cirrhosis. Itching disappeared within 2 weeks of starting cholestyramine 15 g./day. Steatorrhoea, accompanying high doses of cholestyramine, was the only side-effect noted. Carey and Williams (1961) came to similar conclusions in treating 4 cases of chronic obstructive jaundice, and found that the resin was ineffective in complete obstruction. Datta and Sherlock (1963) treated 10 patients (9 with primary biliary cirrhosis and 1 with congenital atresia) with cholestyramine. They noted that the pruritus was relieved in 4 to 11 days after the administration of 6.6 to 10 g. of cholestyramine daily. Bile acids usually fell and output of faecal fat increased. Visintine, Michaels, Fukayama, Conklin and Kinsell (1961), treating a case of xanthomatous biliary cirrhosis with cholestyramine, noticed relief of the pruritus in one week.

These successes with cholestyramine led us to use it in our patient, in whom it proved very helpful.

Summary

A case of intractable pruritus is described, which proved to be due to hepatic cirrhosis. The pruritus has been successfully controlled by the continued administration of cholestyramine in a dose of 6 g. daily. The literature on cholestyramine has been reviewed.

Addendum

The patient is still well controlled 14 months after starting treatment. She has needed vitamin K by injection.

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