OBSERVATIONS ON A FAMILY WITH CHRONIC HYPERBILIRUBINAEMIA*

B. M. KENNELLY, M.B., CH.B. (CAPE TOWN), PH.D. (EDIN.), M.R.C.P. (EDIN.), H. KAVIN, M.B., B.CH. (RAND), DIP. MED. (RAND) AND S. J. SAUNDERS, M.D. (CAPE TOWN), M.R.C.P. (LOND.), F.C.P. (S.A.), *Liver Clinic, Department of Medicine, Groote Schuur Hospital and University of Cape Town, and Department of Medicine, Johannesburg Hospital and the University of the Witwatersrand*

The purpose of this report is to describe the case histories of 2 sisters with recurrent jaundice since childhood. Both have conjugated hyperbilirubinaemia, normal liver biopsies and other features in common with the cases first described by Rotor *et al.*[1] in 1948. Although bromsulphthalein (BSP) clearance was grossly impaired in each case, neither of the sisters showed the characteristic delayed peak in serum concentration of BSP which has been described in the Dubin-Johnson syndrome.[2-4]

CASE REPORTS

Case 1

M.S., a 50-year-old White housewife, first came under observation in 1965 when she was referred for investigation of recurring attacks of jaundice since the age of 6 years. Initially the attacks occurred 2 or 3 times a year and lasted several weeks. Over the previous few years episodes of jaundice had been more frequent and of longer duration until the jaundice became more or less continuous. During attacks she had vague abdominal discomfort, slight nausea, anorexia and intolerance of fatty foods. At no stage did she complain of pruritus, fever, rigors or abdominal pain. There was no history of exposure to hepatotoxins, nor did she take alcohol. The past history was non-contributory. Since childhood she had been aware of an asymptomatic goitre.

Examination showed an obese, euthyroid woman with moderately icteric sclera. There were no signs of anaemia, palmar erythema, spider angiomata or hepatic encephalopathy. Neither liver nor spleen was enlarged. A diffusely enlarged, firm, irregular goitre was easily palpable in the neck.

Laboratory investigations. The urine was dark and contained bilirubin and excess urobilinogen. Erythrocytic sedimentation rate was 30 mm./hr. (Westergren), haemoglobin 14 G/100 ml., packed cell volume 42%, reticulocyte count 0·9%, white blood count 12,800/cu.mm. with a normal differential white cell count and platelet count of 192,000/cu.mm. Liver-function studies were repeatedly done over the next 18 months. Total serum bilirubin ranged from 5·1 to 8·9 mg./100 ml. (conjugated 3·6 - 8·0 mg./100 ml.); alkaline phosphatase 5 - 14 King-Armstrong units; serum glutamic oxalacetic transaminase 14 - 31 Karmen units; serum cholesterol 254 - 292 mg./100 ml.; serum albumin 4·3 - 4·8 G/100 ml.; serum globulin 1·6 - 2·7 G/100 ml. Electrophoresis of plasma proteins was normal. The prothrombin index was 100%; zinc sulphate turbidity 9 units; thymol turbidity 1·0 units. No lupus erythematosus cells were demonstrated in preparations made from peripheral blood. Fig. 1 shows the retention of BSP in serum at intervals up to 3 hrs. after the intravenous injection of BSP in a dose of 5 mg./kg. body-weight. There was 57% retention of BSP at 1 hr., 43% at 2 hrs., 33% at 2½ hrs. and 29% at 3 hrs. An oral cholecystogram

*Date received: 13 February 1968.

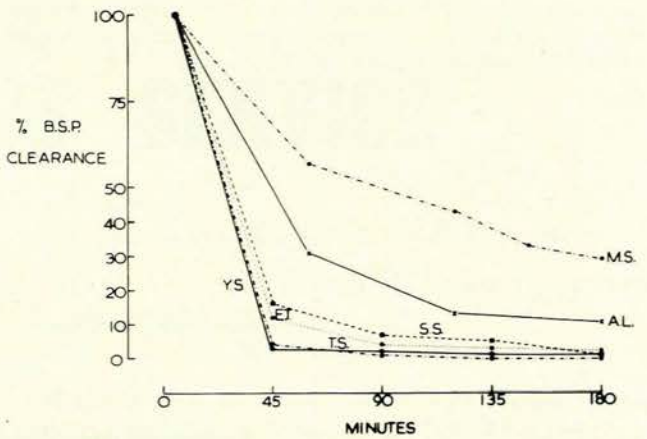

Fig. 1. Bromsulphthalein clearance curves for M.S. and her children, Y.S., S.S., T.S. and E.T., as well as for her sister, A.L.

and a barium meal were both normal. Liver biopsy was normal. There was no excess of pigment in the liver cells. Uptake of ^{131}I by the thyroid gland was 9% of the dose at 6 hrs. and 17% at 24 hrs. A thyroid scintogram showed patchy diffuse activity. Subtotal thyroidectomy was performed. The histology was that of diffuse follicular adenomata in a thyroid gland demonstrating the features of Hashimoto's thyroiditis. The density of the fibrosis in some areas suggested a process of long duration. No special precautions were taken pre-operatively and it is noteworthy that the jaundice was not aggravated by the surgery.

Case 2

A.L., sister of M.S., a White housewife aged 41 years, was first seen in 1947 following her first pregnancy, during which she had been jaundiced. Her clinical records in 1947 show that she, too, had been subject to recurrent attacks of painless jaundice from the age of 14 years, and that these attacks closely followed the pattern of jaundice in her sister. They were also associated with symptoms of lethargy, anorexia, nausea and aversion for fatty foods, with occasional abdominal pain and vomiting. At times she had slight pruritus. When jaundiced, her urine became dark, while her stools retained their normal colour.

On examination in 1947, she was obviously jaundiced but there were no other stigmata of chronic liver disease and the liver and spleen were not clinically enlarged. The thyroid gland was slightly enlarged but smooth and non-tender. The urine contained excessive amounts of bile and urobilinogen. Haemoglobin 16 G/100 ml., white blood count 7,400/cu.mm., peripheral blood smear normal and reticulocyte count 1·2%. Total bilirubin 6·0 mg./100 ml., serum albumin 4·1 G/100 ml. and serum globulin 2·1 G/100 ml. A cholecystogram was normal.

She had normal pregnancies in 1949 and 1950. However, because of deepening jaundice with each pregnancy, she was sterilized after her 3rd pregnancy. Despite moderate jaundice she remained fairly well for the next 12 years. In 1962 oral cholecystography and intravenous cholangiography failed to demonstrate the gallbladder or biliary tree. A barium meal examination was normal. A BSP excretion test was abnormal (Fig. 1). At 1 hr., 31% of the dye was retained; at 2 hrs., 13·5% and at 3 hrs., 10·6%.

In 1965 she had developed no new symptoms, and physical examination was again normal except for the jaundice. No clinical signs of parenchymal liver disease had developed over the period of 19 years since she was first seen. Jaundice no longer cleared completely, but merely fluctuated in intensity, and the smooth diffuse goitre observed in 1947 was not detectable. An intravenous cholangiogram was again attempted, but at no stage up to 5 hours after injection was any contrast visible in the biliary tree. The results of the other investigations done in September 1959, April 1962 and September 1966 were as follows: haemoglobin varied from 15·6 to 16·0 G/100 ml., and white blood count, peripheral blood smear and platelet count were normal. The reticulocyte count was under 1%, red cell survival (^{51}Cr) was normal, prothrombin index 100%, total bilirubin varied from 5·4 to 6·2 mg./100 ml. (conjugated 3·0 - 4·0), serum albumin 4·0 G/100 ml., total serum globulin 2·2 G/100 ml., alpha$_1$-globulin 0·28 G/100 ml., alpha$_2$-globulin 0·49 G/100 ml., beta-globulin 0·84 G/100 ml. and gammaglobulin 0·63 G/100 ml., serum cholesterol 204 mg./100 ml., alkaline phosphatase 6·6 King-Armstrong units, serum glutamic oxalacetic transaminase 16 Karmen units, zinc sulphate turbidity 4, thymol turbidity 1·0 units, serum iron 50 - 103 μg./100 ml. and PBI 8·9 μg./100 ml. No lupus erythematosus cells were detected. Liver biopsy was normal. Urine contained urobilin and bilirubin. Some of these results are shown in Table I.

Other Members of the Family

There is no history of consanguinity in the parents of the probands, but this cannot be excluded. Of the 8 children of this marriage, 3 daughters (M.S., A.L. and C.M.) have been affected. C.M. died in 1960 at the age of 36 years. She lived at a distance and was never fully investigated. She, too, had been jaundiced from early childhood, and jaundice tended to be constantly present. In addition she suffered from pruritus and epigastric discomfort, but had no anorexia, weight loss or fever. She had 9 children, and jaundice is said to have deepened during each pregnancy. Her death followed a caesarean section performed for obstetrical complications resulting from a hydrocephalic child.

All 7 children of M.S. and A.L. have been interviewed and examined. None of the children has had clinical jaundice or other symptoms and signs of liver disease. All the children have had blood counts and liver-function studies performed. E.T. and J.K. have bilirubin levels at the upper limit of normal (1·1 and 1·0 mg./100 ml.), while Y.S. has had readings of 2·7 and 1·3 mg./100 ml. on different occasions (Table I). Retention of BSP is markedly abnormal in E.T. and S.S., while it is at the upper limit of normal in Y.S. and T.S. (Fig. 1). A liver biopsy was obtained on only one of the children (T.S.) and is normal.

E.T. had a subtotal thyroidectomy in 1964 for a solitary nodule in the isthmus. Histology showed a well-differentiated and encapsulated papillary carcinoma. The remaining portion of the resected gland showed the features of Hashimoto's thyroiditis. The other 3 children of M.S. have slight thyromegaly, but are otherwise well.

Although no other members of this large family could be interviewed, enquiries have been reliable and consistent and have shown that none suffers from clinical jaundice.

None of our patients' sera had antibodies to thyroglobulin, liver or intrinsic factor, and cytoplasmic antibody to thyroid was absent. M.S. had gastric parietal cell antibodies, but these were absent in the other patients.

DISCUSSION

The 2 sisters described in this report have familial conjugated hyperbilirubinaemia. The absence of significant pruritus, and the normal serum alkaline phosphatase, prothrombin index and α_2- and β-globulins, together with normal liver biopsies taken during attacks of jaundice, exclude benign recurrent cholestasis.[5-7]

Although attempts have been made to subdivide the congenital conjugated hyperbilirubinaemic syndrome on the basis of differences in occurrence of lipofuscin-like pigment in the liver, level of alkaline phosphatase, and flocculation

TABLE I. BLOOD COUNTS AND LIVER-FUNCTION STUDIES

Patient	*Age (years)*	*Sex*	*Serum bilirubin (mg./100 ml.)*		*Serum alkaline phosphatase (King-Armstrong units)*	*Serum cholesterol (mg./100 ml.)*	*SGOT (Karmen units)*	*Serum albumin (G/100 ml.)*	*Serum globulin (G/100 ml.)*	*Zinc sulphate turbidity (units)*	*Thymol turbidity (units)*	*Serum iron (μg./100 ml.)*
			Total	*Conjugated*								
M.S.	50	F	6·6	5·2	9·0	292	18	5·8	2·7	4	1	110
Y.S.*	18	F	2·7	1·5	5·0	243	16	5·9	2·3	4	1	150
T.S.*	15	M	0·5	0	13·0	213	30	4·0	2·5	4	0	115
S.S.*	12	F	0·5	0	22·0‡	252	29	5·0	1·5	4	1	123
E.T.*	26	F	1·1	0·6	3·0	211	16	3·4	3·0	5	0	178
A.L.	41	F	5·6	4·0	6·6	204	16	4·0	2·2	4	1	50
H.L.†	19	M	0·4	0·2	19·6‡	—	—	3·5	3·2	5	2	—
J.L.†	17	F	1·0	0·2	4·8‡	175	25	4·6	2·6	4	1	158
M.L.†	16	M	0·4	0·2	32·6‡	—	—	—	—	—	3	—

* Children of M.S.
† Children of A.L.
‡ Pubertal values.

and turbidity tests,[8-11] it is likely that the distinction is artificial and that the subdivisions merge into one another.[12,13] Indeed, varying intensity of pigmentation has been found on liver biopsy in families with congenital conjugated hyperbilirubinaemia.[3,13-15] In one patient reported by Taft and Earle,[16] liver biopsies 7 years apart showed considerable differences in the amount of pigment present. Even the more concrete distinction drawn between the conjugated and unconjugated groups of congenital hyperbilirubinaemia seems to be dubious in view of the findings of Billing *et al.*[17] They showed that some patients with conjugated hyperbilirubinaemia had defects of uptake and conjugation of bilirubin. Asymptomatic relatives of patients with the Dubin-Johnson syndrome may also have impairment of hepatic uptake of bilirubin. To confuse the issue further, patients with non-haemolytic unconjugated hyperbilirubinaemia may have livers containing lipochrome-like pigmentation to a degree consistent with the diagnosis of Dubin-Johnson syndrome.[10,18] Moreover, it is well established that the degree of pigmentation may vary considerably in normal livers.[19,20]

Characteristically, patients with familial conjugated hyperbilirubinaemia of the Dubin-Johnson type have a delayed peak in the clearance of BSP from the serum, the secondary rise occurring about 2 hours after intravenous administration of dye.[2-4] This is probably due to a selective defect in the excretion of conjugated BSP by the liver, whereas uptake and storage of the dye are normal.[9,21] Although clearance of BSP was grossly impaired in the 2 sisters described in this report, and was slightly abnormal in some of the children (Fig. 1), the characteristic late rise in serum BSP was not observed. The absence of the late rise in plasma BSP has been described in a case of Rotor syndrome,[22] but it is doubtful that this will prove to be of any diagnostic value in distinguishing between the Rotor and Dubin-Johnson syndromes.

It is noteworthy that the peripheral disappearance curves for BSP obtained in our patients resemble the BSP excretion pattern of a patient reported by Williams *et al.*[6] with idiopathic recurrent cholestasis during an attack of jaundice. The findings are consistent with a defect in the uptake and storage of the dye by the liver in addition to impairment of excretion in the bile. Further clarification of the behaviour of the liver in handling BSP and bilirubin in our family would require more sophisticated techniques.[3,4,9,15,17,21] Unfortunately our patients are reluctant to undergo further studies of this sort. Such tests would also help to explain the mechanism of the minimal hyperbilirubinaemia and abnormality of bromsulphthalein clearance in certain of the children in the family. This would be of considerable interest as these children may yet develop frank jaundice at a later date, or they may merely represent asymptomatic relatives who have difficulties in transport of bromsulphthalein to a lesser degree than their jaundiced mothers. Their situation at present seems analogous to the asymptomatic relatives of certain patients with the Dubin-Johnson syndrome.[13,17]

It is claimed that cholecystography is seldom successful in patients with the Dubin-Johnson syndrome whereas it usually succeeds in patients with the Rotor syndrome,[5,9,12,15,23] although exceptions to this generalization occur.[3,13,14] M.S. had a normal cholecystogram on the only occasion on which it was done. However, her sister, A.L., showed the interesting phenomenon of a normal cholecystogram in 1947, whereas in 1959 and again in 1966 both oral and intravenous contrast media failed to be excreted satisfactorily, despite little change in the level of serum bilirubin. While accepting that non-function on oral cholecystography and intravenous cholangiography may be a manifestation of gallbladder disease, it is possible that A.L. illustrates the overlap between the Dubin-Johnson and Rotor syndromes with respect to the function of the liver in excreting contrast media.

Studies on families with the Rotor syndrome have failed to define a consistent pattern of inheritance.[24] Genetic studies in these families are particularly difficult not only because of the wide range of expressivity but because arbitrary points are chosen to divide normal levels of serum bilirubin from abnormal.[25] Taking this into account, if both parents of the probands in this study were unaffected, both must have been heterozygotes in order to transmit the disease to 50% of their siblings. Unfortunately neither parent was available for investigation of possible subclinical manifestations of the syndrome.

Finally, the high incidence of thyroid disease in this family is of interest. Of the 9 members of the family examined, 6 had goitres and 2 were shown to have Hashimoto's thyroiditis histologically. The absence of serological positive reactions for thyroid in Hashimoto's thyroiditis with congenital conjugated hyperbilirubinaemia is probably a fortuitous one. No other 'markers' of an autoimmune process, as defined by Mackay,[26] were present. Thus the serum gammaglobulins were normal, LE cells were absent, tests for thyroid auto-antibodies were negative and there was no evidence of lymphoid infiltration in the liver biopsies.

SUMMARY

Two sisters with familial conjugated hyperbilirubinaemia and normal liver biopsies are reported. Abnormal bromsulphthalein excretion tests were obtained in them and in some of their children. One of the sisters showed the interesting phenomenon that despite a normal cholecystogram at the age of 21 years, 12 years later both oral cholecystography and intravenous cholangiography failed to demonstrate satisfactory excretion of the contrast media. It is possible that this patient illustrates the overlap between the Dubin-Johnson and Rotor syndromes in the excretion of contrast media by the liver. Finally, although there is a high incidence of Hashimoto's thyroiditis in this family, it is likely that this is a fortuitous occurrence.

We wish to thank Drs. J. G. Burger, H. van Wyk, H. A. Brown and M. Bailey for permission to publish; Dr. J. W. Irvine of the Department of Therapeutics, Royal Infirmary, Edinburgh, for the thyroid antibody studies; and Drs. J. A. H. Campbell and C. Abrahams for the histological reports on M.S., T.S. and A.L. This work was supported in part by the Staff Research Fund of the University of Cape Town and the F. Mellish Memorial Fund, and the Council for Scientific and Industrial Research.

REFERENCES

1. Rotor, A. B., Manahan, L. and Florentin, A. (1948): Acta med. philipp., **5**, 37.
2. Charbonnier, A. and Brisbois, P. (1960): Rev. méd.-chir. Mal Foie, **35**, 75.
3. Mandema, E., De Fraiture, W. H., Niewig, H. O. and Arends, A. (1960): Amer. J. Med., **28**, 42.
4. Vest, M. F., Kaufmann, H. J. and Fritz, E. (1960): Arch. Dis. Childh., **35**, 600.

5. Summerskill, W. H. J. and Walshe, J. M. (1959): Lancet, **2**, 686.
6. Williams, R., Cartter, M. A., Sherlock, S., Scheuer, P. J. and Hill, K. R. (1964): Quart. J. Med., **33**, 387.
7. Schapiro, R. H. and Isselbacher, K. J. (1963): New Engl. J. Med., **268**, 708.
8. Schiff, L. and Billing, B. H. (1959): Gastroenterology, **37**, 595.
9. Schoenfield, L. J., McGill, D. B., Hunton, D. B., Foulk, W. T. and Butt, H. R. (1963): *Ibid.*, **44**, 101.
10. Herman, J. D., Cooper, E. B., Takeuchi, A. and Sprinz, H. (1964): Amer. J. Dig. Dis., **9**, 160.
11. Reaves, L. E. (1966): Postgrad. Med., **39**, 270.
12. Dubin, I. N. (1962): Arch. Intern. Med., **110**, 823.
13. Butt, H. R., Foulk, W. T., Baggenstoss, A. H. and Dickson, E. R. *in* Taylor, W., ed. (1965): *The Biliary System*, p. 619. Oxford: Blackwell.
14. Wolf, R. L., Pizette, M., Richman, A., Dreiling, D. A., Jacobs, W., Fernandez, O. and Popper, H. (1960): Amer. J. Med., **28**, 32.
15. Arias, I. M. (1961): *Ibid.*, **31**, 510.
16. Taft, L. I. and Earle, E. (1959): Med. J. Aust., **1**, 486.
17. Billing, B. H., Williams, R. and Richards, T. G. (1964): Clin. Sci., **27**, 245.
18. Sagild, U., Dalgaard, O. Z. and Tygstrup, N. (1962): Ann. Intern. Med., **56**, 308.
19. Post, J., Benton, J. G. and Breakstone, R. (1951): Arch. Path., **52**, 67.
20. Tygstrup, N., Schmidt, T. and Winkler, K. (1965): Gut, **6**, 194.
21. Wheeler, H. O., Meltzer, J. I. and Bradley, S. E. (1960): J. Clin. Invest., **39**, 1131.
22. Dollinger, M. R. and Brandborg, L. L. (1967): Amer. J. Dig. Dis., **12**, 413.
23. Dubin, I. N. (1958): Amer. J. Med., **24**, 268.
24. Pereira Lima, J. E., Utz, E. and Roisenberg, I. (1966): *Ibid.*, **40**, 628.
25. Butt, H. R., Anderson, V. E., Foulk, W. T., Baggenstoss, A. H., Schoenfield, L. J. and Dickson, E. R. (1966): Gastroenterology, **51**, 619.
26. Mackay, I. R. (1961): *Ibid.*, **40**, 617.