# Dubin-Johnson syndrome: A family study

*by A.K. Banerjee*

MBBS (Cal.), MRCP (Lond.) MRCP (Edin.), MRCP (Glas.)
Lecturer in Medicine,
University of Malaya,
Kuala Lumpur

## INTRODUCTION

IN 1954, Dubin and Johnson described 12 cases with a new form of hepatic disease characterised by chronic intermittent non-haemolytic jaundice since childhood with deposition of lipchrome-like pigment in the liver cells. Four similar cases were described independently by another group of workers, Sprinz and Nelson later in the same year. Since the original description, a number of cases of similar disease has been reported from various parts of the globe and quite a few of these have been found to be occurring in some families among siblings and in the members of two successive generations (Dubin, 1958; Beker & Read, 1958; Mandema, 1960; Arias, 1961; Blank et al, 1966 – Du & Rogers, 1967). Cases have also been reported from Malaysia (Burns-Cox, 1965; Dutt el al, 1968).

Recently, we studied a Malay family from a small locality about 30 miles east of Kuala Lumpur, and out of nine members from three successive generations, three were found to be suffering from this disease. Two of them, who are sibs as well, have the disease with all the features and the history is strongly suggestive that their mother, although not fully affected, is the carrier of the condition.

### The Family with Case Reports of the Affected Members

All the nine living members (fig. I) were clinically studied and investigated. The details of the affected ones only are mentioned below.

**Case 1:** The mother (Member 2 in the family tree), E.b.H.R., aged 70 years. She occasionally suffers from nausea after meals but there is no abdominal pain or discomfort. In the past, she has never had any serious illnesses or operations. However, she had suffered from frequent episodes of painless jaundice all through her life. These bouts had always been mild and lasted for a few days to a few weeks with spontaneous recovery. But the interesting feature here is that these 'attacks' were always precipitated by a "stress" situation, e.g. pregnancy or febrile illnesses. She had altogether 11 pregnancies and was noted to be mildly jaundiced during the later months of eight of these (see pedigree chart). Icterus used to clear spontaneously within a few weeks after the deliveries.

All deliveries were carried out at home and she had never been hospitalised before. The first pregnancy terminated in a stillbirth and the fifth child, who had never been jaundiced, died at the age of 35 of unknown cause. The last four children, two sons and two daughters, died very young, between the ages of four months to five years. However, none of them were noted to be icteric at birth or to be developing icterus later. Her husband, who is dead for many years, had never been "yellow" and so far as she

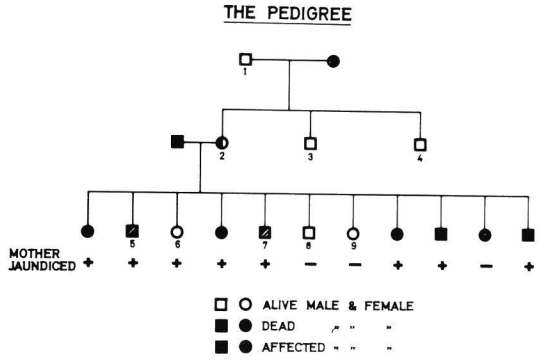


**Fig 1**

knew, no one in the husband's family had ever been jaundiced. Apart from being jaundiced in late pregnancies, she also complained of passing dark tea-coloured urine whenever she had a bout of fever. She was admitted into the University Hospital in November, 1969. On examination, her general condition was well. There was no jaundice. She had bilateral arcus senilis. Her liver and spleen were not palpable, and there were no clinical abnormalities.

The following investigations were carried out and the results were: haemoglobin 12.7 gm.%; total white cell and differential counts normal; no evidence of haemolysis; prothrombin activity 100%; urine (chemical and microscopy) normal; serum bilirubin 1.1 mg.%; unconjugated 0.7 mg.%; conjugated 0.4 mg.%; serum aspartate transaminase (AsT) 6 I.U/L; serum alauine transaminase (ALT) 25 I.U./L; serum alkaline phosphatase 9.6 K.A.U.%; B.S.P. excretion test (Sherlock, 1963) showed a normal excretory pattern with 2% retention at 45 minutes and 0% at 210 minutes; liver biopsy revealed a rather brownish yellow liver tissue. Histology (Dr. B. Ferguson): "Sections of liver show normal architecture. The hepatic cells are engorged 1-2 cells thick. There is no increase in fibrous connective tissue or fibrosis. Only occasional granules of yellow brown pigment are found in a few of the hepatic cells." With all this story and findings, a diagnosis of subclinical Dubin-Johnson Syndrome was made.

**Case 2:** I.b.H., male, aged 45 years, (Member 5 in the family tree) a motor mechanic by occupation and is married with one son and one daughter, both normal. He has been midly jaundiced since childhood, the degree of which fluctuates in intensity. He had been having recurrent attacks of right upper abdominal pain for some years for which he was admitted and investigated in another hospital in July 1968. Investigations then had suggested an obstructive jaundice, with a normal oral cholecystography. A laparotomy was carried out but no biliary stones were found; however, there was a small stricture in the cystic duct. A cholecystectomy was performed. He remained well for a few months but jaundice never disappeared. The right upper abdominal pain returned and he still complains of vague upper abdominal pain food.

He was admitted into the University Hospital in November, 1969 and on examination, his general condition was well. He was mildly jaundiced and his liver and spleen were not palpable. There was no other clinical abnormality apart from an old laparotomy scar on his right upper abdomen.

Investigations: haemoglobin 15.1 gm.%; prothrombin activity 100%; no evidence of haemolysis; urine normal, both on chemical and microscopic examinations; serum bilirubin 4.7 mg.%; conjugated 3.2 mg.%; unconjugated 1.5 mg.%; AST 9 I.U/L; ALT 9.5 I.U/L; Se Alk. Phos. 4.8 K.A.U.%; serum proteins normal; B.S.P. excretion test: abnormal retention and delayed excretion of the dye, 21.3% at 45 minutes, 36.2% at 120 minutes and 47% at 210 minutes. Straight abdominal X-ray did not reveal any abnormality. A liver biopsy was carried out. The microscopic appearance of the biopsy material was dark-brownish yellow tissue. Histology (Dr. B. Ferguson): (Fig. 2) "The hepatic areas are 1-2 cells thick and the size and shape of the hepatic and Kupffer cells are normal. Many of the hepatic cells contain granules of yellow brown pigment usually arranged in a perinuclear fashion, and is most concentrated in central lobular areas. The pigment stains positively for reducing substances, is P.A.S. positive and diastase resistant. The pigment is negative for bile stains and iron stains." This is beyond doubt a fully developed case of Dubin-Johnson Syndrome.

**Case 3:** S.b.H., male, aged 34. (Member 7 in the family tree), a married labourer, with no children. He has been mildly jaundiced since the aged of ten and for this complaint, he was admitted into Assunta Hospital in May 1967 and after investigation was found to be having mild obstructive jaundice. His gall bladder could not be visualised after oral cholecystogram. Following B.S.P. excretion test and liver biopsy, a diagnosis of Dubin-Johnson Syndrome was made. This case has been published earlier (Dutt et al, 1968). However, towards the later part of October

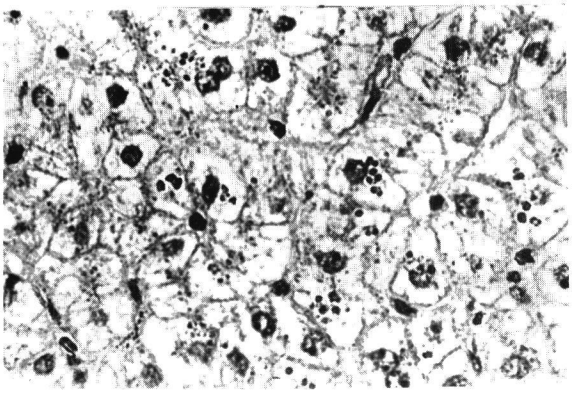

**Fig. 2**

1969, this patient was admitted into the University Hospital for a two-month history of irregular diarrhoea and bleeding per rectum for two days. On examination, he was mildly jaundiced, and there was first degree haemorrhoid to account for this recent P.R. bleeding. His liver was palpable, but the spleen was not palpable. His diarrhorae was found to be of non-specific origin, with normal stool culture and microscopy. This improved rapidly on symptomatic treatment.

Some of the previous investigations were repeated and the results were as follows:- serum bilirubin 3.0 mg.%; conjugated 2.0 mg.%; unconjugated 1.0 mg.%; AST 7 I.U/L; ALT 6 I.U/L; Ser. Ik. Phos. 5.4; K.A.U.%; serum proteins normal; B.S.P. excretion test revealed an abnormal and delayed excretion of the dye and a repeat liver biopsy (Fig. 3) was suggestive of Dubin-Johnson Disease. However, as this case has been reported earlier, no further details are mentioned.

The other members (Nos. 1, 3, 4, 6, 8, 9) were found to be completely normal. None of them has ever had jaundice. The female members had all been pregnant several times each, but none had any icterus during their periods of gestation. The following investigations were carried out on all of them: haemoglobin, reticulocytes, peripheral blood film, urine for bile pigments, prothrombin activity, serum bilirubin, AST, ALT, Serum Alkaline Phosphatase and Serum proteins. BSP excretion test was carried out only on member 8. The results obtained were all normal in each individual.

**Discussion and Comments**

Dubin-Johnson Syndrome is a rare form of congenital hepatobiliary condition characterised by mild non-haemolytic jaundice sometimes associated with vague abdominal pain, diarrhoea and passage of dark urine (Dubin, 1958). The disease commonly manifests under the age of 25 and tends to run in families. Both sexes can be affected and no case is known to be immune. The jaundice may be fluctuant with occasional exacerbation under stress situation e.g. pregnancy, infection, surgery, etc. The life long course is usually benign and the prognosis is excellent.

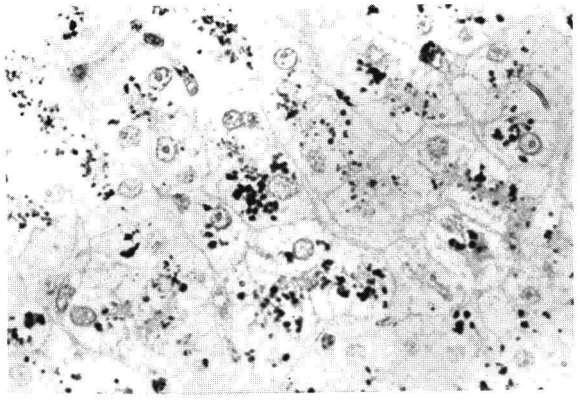

**Fig. 3**

There is no architectural change in the liver although the hepatic histology commonly reveals an excess of dark yellow pigment in the parenchymal cells. The other common denominators are elevated serum bilirubin mostly of the conjugated type, an abnormal retention and delayed excretion of the bromsulphalein dye (Dubin and Johnson, 1954; Dubin, 1958; Butt et al, 1966). However, these criteria are by no means constant or specific. Jaundice has been reported to be non-existent (Burka, 1960) or manifest only under stress (Dubin, 1958) and the degree of intrahepatic pigmentation to be grossly variable in amount (Wolf, 1960).

In the original discussion of this condition, Dubin and Johnson used the term "chronic idiopathic jaundice." Today, even after 16 years, this term still maintains its validity. Although a lot is now known about the bilirubin metabolism, the way it is handled by the liver cells and the pathogenesis of various other congenital hyperbilirubineamias, the basic pathology of Dubin-Johnson Syndrome still remains unexplained. However, available evidence suggests that the defect, which is probably genetically determined, lies in the biliary excretion. No evidence of bilirubin over-production, defective bilirubin uptake or inactivity of enzyme i.e. glucuronyl transferase has yet been demonstrated in this disease (Butt et al, 1966). On the other hand, the classical laboratory findings of an elevated conjugated bilirubin level in the serum, a poorly visible or non-visible gall bladder after oral cholecystogram, a secondary rise in the conjugated B.S.P. dye and low Tm. for B.S.P. (Arias, 1961) are all indicative of an excretory defect.

As regards intrahepatic pigmentation, there still exists a considerable amount of controversy and uncertainty about its nature. The majority (John, 1956); Brown, 1956) including Dubin and Sprinz themselves, regard this as lipofuscin. Others, however, consider this as of the melanin type and they put forward the clinical presence of melanuria in some of their cases (Bynam, 1957) as the supportive evidence.

The effect of pregnancy on the female sufferers of this disease is significant. Out of nine female patients

in a particular series, seven had become pregnant at some time or other and in six of them, pregnancy had precipitated or aggravated the disease. Although normal offspring was the usual outcome, quite a few pregnancies terminated in spontaneous abortions. Neonatal deaths due to unknown cause have also been noted. We can correlate these statements with the clinical history of Case 1.

Abdominal pain, especially over the right hypochondrium, is not uncommon and this is most probably due to pain in the liver. Development of biliary stones may occur in about ten per cent of cases but they virtually never produce obstruction. In one of Professor Sheila Sherlock's cases in Hammersmith Hospital, London, only narrowing of cystic duct, similar to our Case 2, was noted at laparotomy.

Genetically, the disease has been known to be transmitted as autosomal dominant (Dubin, 1958; Wolf, 1960; Arias, 1961). Wide variety in expression of the various features of the disease has also been reported. (Butt et al, 1966).

In the present family under study, there is little doubt that the disease has been in existence in two successive generations. The mother (Member 2) has got the disease in a subclinical form, presumably due to the low penetrance of her dominantly affected gene. As such, she manifests jaundice only under "stress" such as pregnancy and febrile states. However, two of her sons (Members 5 and 7) suffered from the full-blown disease with complete penetrances of the dominant genes they had inherited from their mother. The other live children studied have luckily escaped the disease, the reason for which is quite obvious and simple. Regarding the dead children, however, no one could say whether any one of them would have manifested the disease had he or she lived a few years longer. The three members (Members 1, 3 and 4) of the mother's family studied are all free of any feature suggestive of the disease and her deceased mother's clinical history is unobtainable; thus we cannot be sure of the mother's (Member 2) inheritance of the disease. This is extremely important before one accepts it as an incidence of mutation.

**Summary**

A Malay family resident in the district of Selangor, Malaysia, with three of its members affected by Dubin-Johnson Syndrome, is studied. The nature of the disease is breifly reviewed with some references.

**Acknowledgement**

I wish to thank Dr. A.K. Dutt of State Hospital, Kota Bharu and Dr. V. Rudralingam of Klang Hospital, the former for kind permission to include his already reported case (S.b.H. : Case No. 3) into this study and the latter for the previous clinical details of I.b.H. (Case No. 2) I am also indebted to Drs. S.C. Tan, B.K. Lim and A. Ambikapathy of University Hospital, Kuala Lumpur for their co-operation.

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