

# Gilbert's syndrome: evidence of morphological heterogeneity

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**SUMMARY** Hepatic ultrastructure was examined by electron microscopy in 25 patients with Gilbert's syndrome and the changes in the smooth endoplasmic reticulum quantified by grid technique. Thirteen patients showed gross hypertrophy of the smooth endoplasmic reticulum (SER). These were designated Gilbert's EM Positive. The remaining 12, designated Gilbert's EM Negative, did not differ significantly from normal controls. The EM Positive group showed a significantly greater percentage response to caloric restriction ( $P < 0.01$ ) and an exaggerated response to nicotinic acid stimulation when compared with the EM Negative group and normal controls. These results suggest that SER hypertrophy is not, as previously suggested, a constant feature of Gilbert's syndrome but rather a characteristic of a distinct subpopulation.

Gilbert's syndrome is usually diagnosed when a patient is found to have an isolated unconjugated hyperbilirubinaemia in the absence of overt haemolysis (Arias, 1962). However, as a raised bilirubin alone can be a manifestation of more serious disease (Levine and Klatskin, 1964), various tests have been proposed in an attempt to provide a firm diagnosis of Gilbert's syndrome. McGee *et al.* (1975) found gross hypertrophy of the smooth endoplasmic reticulum in all nine of their patients with Gilbert's syndrome and suggested it to be of diagnostic value. The present study assesses this feature in a larger series and compares the results with two other proposed diagnostic tests; the bilirubin response to (1) caloric restriction (Owens and Sherlock, 1973; Felsher and Carpio, 1975), and (2) to nicotinic acid stimulation (Fromke and Miller, 1972; Davidson *et al.*, 1975). The red cell half life was also determined, using radioactive chromium labelling, in view of the variable reports of shortened red cell survival in Gilbert's syndrome (Fouik *et al.*, 1959; Powell *et al.*, 1967; Berk *et al.*, 1970).

## Methods

Twenty-five patients (age 14-52 years) with Gilbert's syndrome were studied; 20 males and five females. They were selected from consecutive patients who presented to general medical outpatients with a variety of non-specific symptoms and in whom the only abnormality found on investigation was an isolated, predominantly unconjugated, serum hyperbilirubinaemia (range 18 to 105  $\mu\text{mol/l}$ ). All other tests of liver function, and cholecystography in those patients with vague abdominal symptoms, were normal. Extensive haematological tests excluded all common haemolytic diseases and the haemoglobin was normal in all cases.

A percutaneous liver biopsy was performed in all patients. A portion was immediately placed in ice cold Karnovsky's fixative (glutaraldehyde and cacodylate buffer) before processing for electron microscopy by standard methods. The remainder of the specimen was placed in formalin and processed routinely for light microscopy. Electron micrographs of several magnifications were prepared and examined by one of us (I.C.T.). The morphological characteristics were noted and the smooth endoplasmic reticulum was quantified by a modification of the method of Loud (1962). A grid, consisting of 11 parallel lines, spaced 15 mm apart and measuring 18 x 22 cm, was prepared. The grid was laid on

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Received for publication 6 June 1979

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