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The use of phenobarbitone to investigate the pathogenesis of unconjugated hyperbilirubinaemia

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An unconjugated hyperbilirubinaemia may result from increased bilirubin production, such as occurs in haemolytic disorders, or from defective uptake or conjugation of the pigment by the liver-cell. However, the factors causing hyperbilirubinaemia in many patients remain obscure, and even in haemolytic states it is difficult to correlate the depth of jaundice with the degree of haemolysis (De Gruchy, 1964). Patients with Gilbert's syndrome may show minor reductions in red cell survival time (Powell, Billing & Williams, 1967), but it is probable that the hyperbilirubinaemia found in the condition is more related to defective conjugation of bilirubin (Black & Billing, 1969) than to increased load. Investigation of four patients with haemolytic disorders revealed two with a defect of conjugation similar to that found in Gilbert's syndrome (Black, unpublished), and the co-existence of this defect in five of ten haemolytic patients studied by Berk, Bloomer, Howe & Berlin (1969) is suggested by their abnormal handling of ^{14}C-bilirubin. The levels of plasma bilirubin in these cases seemed to be dependent on more than a single factor.

The administration of phenobarbitone to patients with a proven, or suspected, deficiency of the bilirubin-conjugating enzyme, bilirubin UDP-glucuronyl transferase, leads to a reduction in the plasma level of bilirubin (Yaffe, Levy, Matsuzawa & Baliah, 1966; Whelton, Krustev & Billing, 1968). Matsuda & Takase (1969) have also shown a similar effect of phenobarbitone in two jaundiced patients with hereditary spherocytosis. Phenobarbitone has been shown significantly to increase biliburin-transferase activity in man (Black, Perrett & Carter, unpublished), and it is likely that its beneficial effect in these cases was by induction of transferase activity. Indirect evidence in favour of this hypothesis has been obtained by studying the effect of a 2 week course of phenobarbitone (180 mg/day) on the plasma bilirubin levels and ^{14}C-bilirubin disappearance curves of patients with mild unconjugated

hyperbilirubinaemia. In those patients with Gilbert's syndrome, in whom an enzyme defect had been demonstrated, a reduction in the level of plasma bilirubin and an improvement in the handling of ^{14}C-bilirubin was always observed. In a patient with congenital haemolytic anaemia and normal enzyme activity (and handling of ^{14}C-bilirubin) phenobarbitone therapy did not significantly alter either the plasma bilirubin level or the ^{14}C-bilirubin disappearance curve.

These observations indicate that a reduction in the level of unconjugated bilirubin in the plasma following phenobarbitone administration is suggestive evidence of a defect in bilirubin conjugation.

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Assessing reports of therapeutic trials

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The quality and reliability of clinical trials vary greatly, and before therapy is based on their results it is important to assess such trials critically, taking into account their design, methods and execution. We have developed a check list for examining reports of therapeutic trials systematically and for assessing their validity. The check list is intended to apply to any report of a prospective investigation of a therapeutic effect in patients. It is not suitable for the assessment of reports of pharmacological studies in man unless the drug was administered with therapeutic intent and the therapeutic effect was assessed. The check list is also unsuitable for reports of retrospective studies, and for case reports.

The check list first examines what information the report contains about the subjects studied, the drugs used, and the experimental design. The questions in this part of the list (sections 1 to 5) can all be answered by consulting the report of the trial. They are followed by questions which aim more directly at an assessment of the quality of the trial (sections 6 and 7); a subjective element is necessarily involved in answering these questions. The answers to all the questions in the check list can then be considered in relation to one another when it comes to assessing the trial as a whole.