Unconjugated hyperbilirubinaemia in achalasia

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SUMMARY Moderate unconjugated hyperbilirubinaemia decreasing after pneumatic dilatation of the gastrooesophageal sphincter, so permitting a normal amount of food to be taken was observed in two patients with achalasia. Liver biopsy was performed, and hepatic digitonin-activated bilirubin UDP-glucuronyltransferase activity was decreased in both, as is usually found in patients with Gilbert's syndrome. In the patients examined the slight and variable hyperbilirubinaemia associated with Gilbert's syndrome seemed to have been aggravated because of the decreased food intake due to achalasia. This situation may be compared to the jaundice sometimes found in neonates with pyloric stenosis or other types of obstruction of the upper gastrointestinal tract. Observations in rats and man favour a complex mechanism for fasting-induced hyperbilirubinaemia.

Unconjugated hyperbilirubinaemia in adults has been observed in a great variety of diseases (Levine and Klatskin, 1964). Among these constitutional hepatic dysfunction (or Gilbert's syndrome) is a common disorder (Foulk, Butt, Owen, Whitcomb, and Mason, 1959; Powell, Hemingway, Billing, and Sherlock, 1967). It is associated with decreased liver bilirubin UDP-glucuronyltransferase activity (Arias and London, 1957; Metge, Owen, Foulk, and Hoffman, 1964; Black and Billing, 1969) and impaired clearance of bilirubin from the liver (Billing, Williams, and Richards, 1964; Berk, Bloomer, Howe, and Berlin, 1970). These abnormalities can be overcome by giving phenobarbital (Black and Sherlock, 1970; Black, Fevery, Parker, Jacobsen, and Billing, 1971).

Fasting-induced increases in serum bilirubin concentrations have been noted in patients with Gilbert's syndrome and to a lesser extent also in normal individuals (Felsher, Rickard, and Redeker, 1970; Barrett, 1971; Bloomer, Barrett, Rodkey, and Berlin, 1971) but the exact mechanism is not yet clear.

In the present study, two patients with achalasia, a condition in which the gastrooesophageal sphincter cannot relax, were found to have an unconjugated hyperbilirubinaemia. After pneumatic dilatation of the cardia (Vantrappan, Hellemans, Deloof, Valembois, and Vandembroucke, 1971), which restored to normal the patients' ability to take food, the serum bilirubin concentration promptly decreased. Further investigation showed that both had Gilbert's syndrome.

Methods

Serum bilirubin concentrations (total and 10 min direct-reacting) were determined by a modification of the methods of Jendrassik and Cleghorn (1936) Fevery, Claes, Heirwegh, and De Groote (see 1967). Bilirubin UDP-glycosyltransferases were assayed in a digitonin-activated liver homogenate according to the methods of Black, Billing, and Heirwegh (1970) and Fevery, Leroy, and Heirwegh (1972). Protein was determined according to the procedure of Lowry, Rosebrough, Farr, and Randall (1951).

Case Histories

Case 1

Patient W.J., a 44-year-old man, was asymptomatic until one year before admission. He complained of dysphagia for food, and to a lesser extent also for fluids. Physical examination was normal. Clinical chemistry showed only a moderate unconjugated hyperbilirubinaemia (table I) with normal haemoglobin and haptoglobin levels, reticulocyte count, osmotic and mechanical fragility of the erythrocytes, and normal liver function tests. On x-ray examination a normal gallbladder and bile duct system were found. The diagnosis of achalasia was
made by radiological examination and by oesophagogastrroduodenoscopy (Vantrappen et al, 1971). Liver histology was normal but hepatic bilirubin UDP-glucuronosyltransferase activity was decreased (table I).

After two pneumatic dilatations of the cardia (Vantrappen et al, 1971) the total serum bilirubin concentration fell due to a fall in the unconjugated bilirubin. A subsequent 24-hour fast nearly doubled the serum concentration (table I). He gained 4 kg over the following four months.

CASE 2
Patient V.D. was a 22-year-old housewife complaining for two years of progressive dysphagia for meat and solids, vomiting, retrosternal pain, and weight loss. Physical examination and clinical chemistry were normal except for an unconjugated hyperbilirubinemia (table I). No signs of haemolysis could be detected. Histology of the liver was normal but hepatic bilirubin UDP-glucuronosyltransferase was decreased (table I). The gallbladder functioned normally. X-ray and manometric examination established the diagnosis of achalasia. Treatment by three pneumatic dilatations restored food intake to normal with a weight increase of 9 kg over the following six weeks. The serum bilirubin decreased to 0·3 mg/100 ml.

Experiments on Rat Liver Bilirubin UDP-glycosyltransferases
On three occasions one litter mate of pairs of male Wistar-R rats was starved for 72 hr, but fluids were unrestricted. No significant changes in conjugating activities per mg of liver protein or per g wet weight of liver were found (table II). However, as a result of the marked decrease in liver weight, conjugating capacities for the whole liver were greatly lowered (table II).

Discussion
In patients with Gilbert’s syndrome and sometimes even in normal adults decreased caloric intake reduces plasma bilirubin clearance (Bloomer et al, 1971) resulting in unconjugated hyperbilirubinemia. The mechanism is not fully understood.

As far as metabolic events intervening in the production and metabolism of bilirubin have been studied, the effects of fasting appear to be many. In man, endogenous carbon monoxide production is increased 1·5-1·7-fold in normal controls as well as in patients with Gilbert’s syndrome (Lundh, Johansson, Merck, and Cavallin-Stahl, 1972; Kutz, Egger, Bircher, and Bachofen, 1972), whereas Bloomer et al (1971) reported values ranging from 1 to 1·5.

Table I Serum bilirubin and hepatic glucuronosyltransferase in two patients with achalasia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Serum Bilirubin (mg/100 ml)</th>
<th>Liver Bilirubin UDP-glucuronosyl-transferase Activity (μg bilirubin conjugated/g of liver/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Treatment</td>
<td>After Pneumatic Dilatation of the Cardia 24-Hour Fast</td>
</tr>
<tr>
<td></td>
<td>TB¹</td>
<td>DB¹</td>
</tr>
<tr>
<td>W.J.</td>
<td>1·5</td>
<td>0·2</td>
</tr>
<tr>
<td>1·7</td>
<td>0·7</td>
<td>0·2</td>
</tr>
<tr>
<td>V.D.</td>
<td>1·7</td>
<td>0·3</td>
</tr>
</tbody>
</table>

Table II Different parameters expressed as a ratio of values found with fasted versus fed rat litter mates

<table>
<thead>
<tr>
<th>Protein (mg)</th>
<th>Liver (g)</th>
<th>Total Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1·05 ± 0·25</td>
<td>1·19 ± 0·28</td>
<td>0·66 ± 0·15</td>
</tr>
<tr>
<td>1·33 ± 0·22</td>
<td>1·49 ± 0·25</td>
<td>0·82 ± 0·14</td>
</tr>
<tr>
<td>1·05 ± 0·12</td>
<td>1·15 ± 0·10</td>
<td>0·64 ± 0·02</td>
</tr>
</tbody>
</table>

¹Normal levels: 1100 ± 280 (1 SD)
²Determinations on consecutive days are given, before, and after treatment.
TB total bilirubin concentration; DB-10-min direct-reacting bilirubin concentration.
A two- to three-fold increase in hepatic microsomal heme oxygenase was noted in rats (Bakken, Thaler, and Schmid, 1972; Thaler, Gemis, and Bakken, 1972). As the enzyme activity per whole organ seemed to be highest in the liver (Tenhunen, Marver, and Schmid, 1968), these observations support the theory of a fasting-induced increase in bilirubin production.

In the rat, the intrahepatic uptake and conjugation of bilirubin are also impaired. Following fasting a two-fold decrease in the total amount of intracellular bilirubin-binding protein has been documented (Meuwissen, Fevery, and Heirwegh, 1971). Assays with rat liver homogenates showed a lowering of the total conjugating capacity of the liver (table II), mainly due to a marked decrease in liver weight. Similar results have been obtained by Bloomer et al. (1971) and also by Adlard, Lester, and Lathe (1969), who assayed liver slices of rats fed a protein-free diet for four days. Even more pronounced decreases in bilirubin conjugation were found in liver homogenates of neonatal rabbits (Flint, Lathe, and Ricketts, 1963). In contrast, total glucuronidation rates of p-nitrophenol and o-aminophenol were unchanged (Woodcock and Wood, 1971). Differences in the conjugation of bilirubin versus other aglycones (Dutton, 1971) may explain this discrepancy. It is noteworthy that restricting protein in rats caused a decreased conjugation of sulphobromophthalein in vivo (Whelan, Hoch, and Combes, 1969).

In normal man no direct evidence for a fasting-induced alteration of hepatic uptake, conjugation, or biliary secretion of bilirubin is available, nor of competitive substances eventually released during fasting. However, kinetic data indicate a reduced ability of the liver to extract bilirubin from the plasma (Bloomer et al., 1971).

In patients with Gilbert's syndrome endogenous carbon monoxide formation is normal and, on fasting, is increased to the same extent as in normal controls (Lundh et al., 1972; Kutz et al., 1972). The more pronounced increase in the serum bilirubin levels during fasting may be related to the markedly decreased bilirubin UDP-glucuronyltransferase activity of the liver (Black and Billing, 1969). The two patients reported had decreased glucuronyltransferase activity and could thus be considered as having Gilbert's syndrome. The achalasia seemed only to have functioned as inducing caloric restriction.

Unconjugated hyperbilirubinaemia is sometimes observed in neonates with pyloric stenosis or other types of obstruction of the upper gastrointestinal tract (Chaves-Carballo, Harris, and Lynn, 1968; Van Horenbeek, Kerremans, Bax, and Eggermont, 1972). In the majority of cases described, the infant remained icteric from the first week of life (Chaves-Carballo et al., 1968) and some showed a marked decrease in serum bilirubin levels when adequate calories were given intravenously (Giraud, Louchet, and Bernard, 1964; Van Horenbeek, et al., 1972). This situation resembles that which was found in the present adult patients with achalasia and decreased glucuronyltransferase activity, as the neonate has an immature transferase system. Deprivation of food due to pyloric stenosis may result in prolonged or increased hyperbilirubinaemia. The administration of adequate calories or removal of the stenosis converts bilirubin metabolism to normal.

We are grateful to Professor Vantrappen for allowing us to study patients under his care and to Professor Desmet for interpreting the liver biopsies.

**Addendum**

Since the above observation was made, the presented hypothesis with regard to jaundice in neonates with upper gastrointestinal obstruction has been documented by Felsher et al (Gastroenterology, 64, 1973, p. 151, abstract). These authors found a marked decrease in UDP-glucuronyltransferase in association with caloric deprivation in icteric neonates.

**References**


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