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Abstract
The common physical sign of jaundice is recognised by yellow discoloration of the skin and sclerae and it is confirmed and measured by estimating the concentration of bilirubin in the serum. Jaundice is rightly regarded as a sign of serious disease but like many other physical signs and biochemical deviations it may be of no pathological significance whatsoever. In such circumstances, to establish with certainty that no serious disease is present and to manage the patient accordingly is clearly more important than to make a precise diagnosis in an incurable case.

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THE MEDICAL STUDENT'S DISEASE

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The common physical sign of jaundice is recognised by yellow discoloration of the skin and sclerae and it is confirmed and measured by estimating the concentration of bilirubin in the serum. Jaundice is rightly regarded as a sign of serious disease but like many other physical signs and biochemical deviations it may be of no pathological significance whatsoever. In such circumstances, to establish with certainty that no serious disease is present and to manage the patient accordingly is clearly more important than to make a precise diagnosis in an incurable case.

The pathological causes of jaundice are classified, fundamentally, as.

1. **Overproduction jaundice**—due to excessive haemolysis.
2. **Hepatocellular jaundice**—due to defective biochemical processing of bilirubin by the parenchymal cells of the liver.
3. **Obstructive jaundice**—due to blockage of the bile duct system at any level from the finest intralobular canaliculi to the common bile duct leading to regurgitation of liver-processed bilirubin into the circulation.

A fourth class of jaundice is conceivable which may be termed constitutional jaundice and this can be redivided into three general types:

1. The congenital hyperbilirubinaemias which are genetically determined abnormalities of bilirubin metabolism. Further subdivisions are now well established.
2. Selective hepatic dysfunction in respect of bilirubin metabolism and excretion following viral hepatitis but without evidence of residual inflammation or diffuse hepatic fibrosis.
3. Subclinical jaundice of 1.0 mg./100 ml. to 1.6 mg./100 ml. may be explained in terms of the individual being placed in the "upper tail" of the normal distribution curve for serum bilirubin levels. The value of the upper limit of normal is highly controversial since the normal distribution curve suggests 1.6 mg./100 ml. as the extreme limit in healthy subjects although most values greater than 0.8 mg./100 ml. have a serious pathological significance.

In the past three years much attention has been devoted to the congenital hyperbilirubinaemias and to jaundice after acute hepatitis. This is a consequence of the recent clarification of the mechanism of bilirubin excretion and also of the development of tremendous activity in the fields of biochemical genetics and auto-immune disease.

THE CONGENITAL HYPERBILIRUBINAEMIAS

Benign familial jaundice was first recognised by Gilbert in 1900. His name is attached to the not uncommon syndrome which is estimated as

occurring in 1 in 300 (0.3%) of subjects of European stock although in practice detected in only a microscopic fraction of these. It is characterised by intermittent jaundice of up to 5 mg./100 ml. and occasionally higher. Biochemical findings are that the bilirubin is entirely unconjugated signifying that it has not been processed by the parenchymal cells. There is no evidence of increased haemolysis and the daily excretion of bile pigments is not raised. All liver function tests including BSP retention are within normal limits. The histology of the liver is normal. Investigation of the patient's family reveals at least one sibling or parent affected in 75% of cases.

Clinically the syndrome possesses certain extraordinary features. Although the condition is a genetically determined metabolic abnormality the vast majority of cases initially present between the ages of 14 and 30 years. Even more remarkable is that in several series more than half of the cases are medical personnel—nurses, residents and especially students.

While it is difficult to conceive that the same sort of genetic constitution makes for both interest in medicine and inability to conjugate bilirubin, a reasonable assumption is that the medical group is more likely to notice slight icterus and to meditate upon its significance. This implies that the great majority of cases of Gilbert's disease are undiscovered and this conclusion is borne out by researches which have sought symptomless jaundice in a healthy population.

In association with the bouts of jaundice certain subjective features are generally emphasised by the patient. The outstanding complaint is ready fatiguability. Gastro-intestinal symptoms—nausea, anorexia with loss of weight and particularly intolerance of dietary fat are next in frequency followed by vague abdominal discomfort often over the liver. The origin of these symptoms is wholly undecided. In favour of the psychosomatic explanation—that the symptoms are expressive of a fear of serious disease, perhaps aggravated by unwise medical advice is that precisely the same group of symptoms appears after acute viral hepatitis with complete objective recovery, the post-hepatitis syndrome as described by Sherlock. Here there is abundant evidence of a predominantly psychological origin.

However, in some cases of Gilbert's disease this typical symptom group is the reason for seeking advice before the icterus is detected and so a a biochemical basis for the fatiguability is not to be easily dismissed.

The marked periodicity of the jaundice and fatiguability is a most striking feature. Almost all of the mild cases have periods completely free of symptoms and of even latent jaundice. Each bout of jaundice lasts from about five to forty days and may occur spontaneously or be precipitated, according to the patients by physical exhaustion, emotional stress or over-indulgence in alcohol. Laboratory experiments have confirmed this effect of alcohol but have been inconclusive with respect to the effect of strenuous exercise.

THE AETIOLOGY OF GILBERT'S DISEASE

Recently much more information about the fundamental mechanisms of jaundice has become available and into this framework the pathogenesis of Gilbert's disease fits most beautifully.

To summarise, bilirubin is formed in the reticulo-endothelial system by the degradation of haemoglobin in a series of reactions involving the removal of the iron and the protein globin and the oxidative disruption of the porphyrin ring. It is quite wrong to assume that haemoglobin is converted quantitatively to bilirubin since it is known that some bilirubin is

derived from extraerythrocytic sources and also a variable proportion of haemoglobin is degraded along alternative pathways.

Bilirubin is transported to the parenchymal cells of the liver loosely bound to the plasm albumen. In these cells the all-important conjugation with glucuronic acid occurs as follows:

Blirubin + uridinediphosphoglucuronic acid = bilirubin glucuronide + uridinediphosphate.

This reaction is entirely dependent on the enzyme glucuronyl transferase and it is lack of this enzyme which is responsible for moderate and severe Gilbert's disease.

In the bile appears a mixture of the mono- and di-glucuronides of bilirubin. This modification of the molecule renders it much more water soluble and, at the same time, less lipophilic. Only in this form can bilirubin be excreted into the bile. This change is the basis of the conversion of the van den Berg reaction from indirect to direct and it also explains why bile does not appear in the urine with haemolytic jaundice as it does with obstructive jaundice since only the water soluble conjugated form is excreted by the kidney. It further explains the occurrence of kernicterus (bile staining of the basal nuclei in infants giving permanent neurological deficits, unless rapidly fatal) in haemolytic but not obstructive jaundice because only the lipophilic, unconjugated bilirubin reaches the site at which this damage may occur.

Now in cases of Gilbert's disease with a bilirubin level of above 5 mg./100 ml. a deficiency of glucuronyl transferase activity in liver biopsy specimens has been demonstrated by a brilliant in vitro method developed by Arias and London in New York. Furthermore the degree of enzymatic defect is roughly correlated with the bilirubin level and indeed the syndrome shows a continuous spectrum extending from the very rare cases with no detectable transferase activity and a serum bilirubin level of 15-20 mg./100 ml. However the majority of cases with a serum bilirubin level which never exceeds 5 mg./100 ml. have no detectable enzymatic deficiency and here the fault is widely supposed to lie in a reduced capacity of the parenchymal cells to take up bilirubin from the plasma. Another possibility is difficulty in breaking the albumen-bilirubin linkage.

THE GENETIC SIGNIFICANCE OF GILBERT'S DISEASE

These recent developments assume added significance in the great vista of human biochemical genetics. Several inborn errors of metabolism exist which are neither truly dominant nor recessive but in which there are important quantitative and qualitative differences between the homozygous and heterozygous state. A fine example is provided by the gene of sickle-cell anaemia. The homozygotes develop haemolytic anaemia because the majority of their haemoglobin is of the abnormal sickle-cell type. Heterozygotes on the other hand show the sickling phenomenon but do not develop anaemia because more than half of their haemoglobin is of the normal adult type and their condition is not biologically disadvantageous.

Now in 1952 Crigler and Naajar described a new syndrome occurring in seven infants from three different but related families. All seven infants had developed deep jaundice after birth with serum bilirubin levels of 10 to 44 mg./100 ml. of which nearly all were unconjugated. There was no excessive haemolysis or significant hepatic pathology in any case. In fact the condition is well described as an extreme infantile form of Gilbert's disease. Five infants developed kernicterus and soon died. Extraordinarily

the other two have survived well into childhood showing no neurological abnormalities and are apparently healthy apart from deep jaundice.

The really interesting feature, however, is that all these children had consanguineous parents which signified that a recessive or homozygous state is responsible. The gene which in a double dose produces a complete failure to conjugate bilirubin as in the Crigler-Naajar syndrome may be identical with the gene which in heterozygous individuals shows variable degrees of dominance resulting in the continuous spectrum of severity notably found in Gilbert's disease. The factors responsible for this variation of dominance, a phenomenon seen in many other genetically determined features, may involve the influence of other genes or may depend on the nature of the external or internal environment. In fact this is an outstanding problem in fundamental biology.

THE OTHER CONGENITAL HYPERBILIRUBINAEMIAS

These new ideas have resulted from improved laboratory techniques. At the same time epidemiological methods have borne fruit by revealing two variants of classical Gilbert's disease which are also classifiable as congenital hyperbilirubinaemias.

The Dubin-Johnston syndrome (1954) is much less common than Gilbert's disease and has the following distinctive features:

1. Jaundice is due to a mixture of conjugated and unconjugated bilirubin. In consequence bilirubinuria is the rule.
2. The liver is also unable to excrete certain dyes including BSP and the media used for cholecystography leading to a non-visualising gall-bladder.
3. There is a very prominent granular black pigment in the parenchymal cells which renders the liver black macroscopically. Its nature has excited much interest for it appears to be a lipochrome—a "wear and tear" pigment—and is definitely not iron-containing.

Like true Gilbert's disease this syndrome is familial, it is associated with fatiguability and it has an excellent prognosis. However it is more likely to be confused with obstructive jaundice because of bilirubinuria and the presence of conjugated bilirubin in the serum. An unnecessary explorative laparotomy is the typical consequence. Clearly a widespread disturbance of hepatic function is involved which is still compatible with normal health and longevity.

Very recently still another variety has been reported which is identical with true Gilbert's disease except that, as in the Dubin-Johnston syndrome, the excess of bilirubin in the plasma is largely conjugated and there is retention of BSP.

Post-hepatitic Jaundice

Acute infective hepatitis is usually followed by complete clinical and histological recovery but there exists several possible sequelae which may begin at once or be manifest only after a variable interval. Of these the most important is diffuse hepatic fibrosis developing into portal cirrhosis. Alternatively persistent or recurrent hepatitis is found which is typified by round cell infiltration of the portal tracts and which produces persistently abnormal liver function tests. The third important consequence is the post-hepatitis syndrome—the diagnosis when the symptoms of the acute attack fail to abate yet liver function tests and liver biopsy reveal no abnormality. Two physical signs are invariably present—mild, fluctuant

jaundice and an easily palpable liver. The latter occurs without hepatic enlargement in some introspective patients who have developed the knack of depressing their diaphragm to an extreme degree thus showing off their lower hepatic border.

Although most of the features of the post-hepatitis syndrome are certainly psychogenic there is little doubt that the virus of infective hepatitis can somehow modify the enzyme systems of the liver to bring about a selective dysfunction in respect of bilirubin metabolism. Consideration of these uncommon cases may shed light on the really important problem of infective hepatitis—why persistent inflammation and fibrosis occur. The old concept that the virus survives in the liver cells, flaring up intermittently over a long period, has gone out of fashion and evidence for the auto-immune theory has accumulated but has still a long way to go. Briefly the theory envisages that during the acute phase of hepatitis the protein components of the liver cells are somehow modified so that they are not recognised by the antibody producing mechanism as "self." Appropriate antibodies are produced over a long period and these have an adverse effect on healthy liver cells. Clearly a self-perpetuating type of situation may arise.

Most points in favour of the auto-immune theory are found in a peculiar type of post-hepatitic cirrhosis (lupoid hepatitis) occurring in young women and having several features in common with systemic lupus erythematosus. These patients have a complement-fixing antibody which reacts with an antigen consisting of normal human liver cells. Also suggestive of an auto-immune mechanism is the very high gamma-globulin level and the frequent clinical response to cortisone.

The crux of this problem is how does a virus modify the proteins of the liver cells to produce alterations in their enzymatic activity and antigenic properties.

Mode of Presentation and Differential Diagnosis of Constitutional Jaundice

The mode of presentation deserves particular emphasis. The majority of cases have a typical attack of infective hepatitis. Months later they are investigated because of persistent jaundice which is suspected to be due to serious liver disease. If the thorough investigation, which should certainly be undertaken, reveals no other abnormality then the alternatives are that the patient has Gilbert's disease, to which the hepatitis was incidental, or that he has an acquired hepatic dysfunction. In a number of cases the search for latent jaundice in the parents and siblings proves negative and then the doubt always remains but the distinction is academic since in both cases there is no treatment and the prognosis is alike excellent.

Since constitutional jaundice is not really common and other cases of jaundice are very common the diagnosis is only tenable after the most rigorous investigations to exclude a less benign cause. Differential diagnosis is from the following conditlons:

1. The haemolytic anaemias have in common with Gilbert's disease mild intermittent icterus, often a familial incidence and normal liver function tests. However they are easily excluded by finding normal values for the haemoglobin level, the reticulocyte count and the osmotic fragility test of erythrocytes.
2. Obstructive jaundice may be diagnosed in cases of Dubin-Johnston syndrome. In the latter the jaundice is intermittent over a long period and the level of serum alkaline phosphatase is usually within

the normal range. Liver biopsy is essential for the diagnosis of Dubin-Johnston syndrome yielding laparotomy unnecessary.

3. Persistent mild hepatitis and well compensated diffuse hepatic fibrosis are, of course, the most likely sources of confusion. The comparatively safe procedure of liver biopsy is always necessary when doubt exists, and of the biochemical tests the thymol turbidity test, the E.S.R. and the BSP excretion test are the most sensitive indices of serious disease. The ACTH test produces a lowering of the bilirubin level in some cases of Gilbert's disease and in obstructive jaundice as well as in active hepatitis for which it was once believed to be specific.
4. Chronic gastro-intestinal disease, particularly chronic duodenal ulcer, may produce mild jaundice through some unknown mechanism. This must be carefully excluded in all relevant cases.

Conclusions

Most cases of congenital hyperbilirubinaemia and harmless post-hepatitic icterus are misdiagnosed for many months or years as chronic hepatitis. This is particularly likely if there has been an initial episode of infective hepatitis. The object of this article is to emphasise the necessity for properly investigating these cases. A brief glance at the literature of this subject yields two most striking impressions. Firstly, all of the recent series have come from Scandinavia and the Eastern United States where the standards of medicine are sufficiently advanced to permit these advanced diagnoses. Secondly, it is grievous that such a high proportion of these intelligent, healthy, young people are consigned to pseudo-hepatic crippledom, a characteristic organ neurosis, which may be life long. This is because of the attitude of the physician who is under the impression that he is dealing with a case of chronic hepatitis. The hapless victim is daily reminded that "he has only one liver" or else that he must "put his liver first now." Even the threat of the dreadful cirrhosis may be used to bully the victim into submission and rest.

In the practice of medicine it behoves us that if we cannot do a patient any good then at least we should at all costs avoid doing him any harm. When dealing with the benign causes of jaundice only the highest diagnostic skill can avoid doing genuine harm in the form of prolonged incarceration, albeit in bed, an unnecessary surgical exploration or an iatrogenic psychoneurosis.