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Chapter 2

Genetic Disorders of Bilirubin Metabolism*

FRANK B. JOHNSON

Between 1900 and 1907 Gilbert and co-workers[37-39] reported on a mild jaundice they called simple familial cholemia or chronic simple icterus. Dameshek and Singer,[28] on the basis of careful perusal of these articles, stated that the familial cholemia of Gilbert *et al.* was in reality mild-hemolytic jaundice. In contrast, Dameshek and Singer presented two families with some members having chronic mild nonobstructive jaundice without hematologic or other laboratory evidence of hemolysis. Unfortunately, no histologic studies of the liver were included in their reports. Meulengracht[57] made a noteworthy review of a condition he called *ikterus intermittens juvenilis*. This entity was characterized by variable but slight jaundice along with lassitude when the jaundice was most evident. He stated that this was undoubtedly the same disease described by Gilbert *et al.* Meulengracht gave a concise summary of the observations of other workers who had made similar descriptions. He cited the histologic observations of Krarup and Roholm,[53] Welin,[80] and Alwall.[2] These authors found evidence of neither inflammatory disease nor cirrhosis. In some instances there was slight fatty infiltration of the liver.

It was Meulengracht's vivid description of the clinical features of his cases of mild fluctuating jaundice in young people (more jaundiced than sick) that came to mind while I was reviewing, with Dubin, a series of liver biopsy specimens showing unusual pigmentation. We had the opportunity of studying liver tissue and clinical records of 12 cases that formed a distinct clinicopathologic entity we called chronic idiopathic jaundice. The usual clinical features were chronic or intermittent jaundice, along with abdominal discomfort, fatigue, dark urine, and possible liver enlargement. The liver specimens all showed conspicuous dark granular pigment with centrilobular distribution. Our preliminary observations[49, 50] were reported as abstracts for oral presentation. Four of our 12 cases were those of Sprinz and Nelson. There was much friendly exchange of ideas and information between Dubin and Sprinz, so it was agreed that our definitive report[32] would be published simultaneously with that of Sprinz and Nelson.[73]

* Armed Forces Institute of Pathology, Washington, D. C. The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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Regrettably, many neglect the important contributions of these workers when eponymic designation of the clinicopathologic entity is made

My task is not only to discuss chronic idiopathic jaundice but to deal with three other entities that share the features of familial disorders of bilirubin metabolism in the absence of hemolytic disease or obstruction of bile passages. The four conditions are fairly well defined, but there are nevertheless individual cases that defy attempts at precise assignment.

GILBERT'S DISEASE

Mention has already been made of the reports of Gilbert *et al.*[37-39] early in the 20th century. I realize that these early papers may have included more than one entity. Modern technical procedures and increased knowledge of bilirubin metabolism enable us to separate a group of cases of what is commonly known as Gilbert's syndrome. The subject has been reviewed by Arias[4] and Billing, Williams, and Richards.[13] The patients suffer from mild jaundice and may have abdominal discomfort, malaise, and nausea. Studies of liver function generally yield normal results, and levels of glucuronyl transferase were originally regarded as normal. Most of the elevation of bilirubin in the serum is of the unconjugated variety. There is no bile in the urine. Light microscopy discloses no significant abnormality in liver structure. A report of Arias and London[7] indicated the possibility of a deficiency in glucuronyl transferase, a microsomal enzyme, in Gilbert's disease. This has been confirmed repeatedly.[4, 14, 66] Schaff, Lapis and Sáfrány[70] have shown interesting changes in mitochondria and a decrease in the rough endoplasmic reticulum, along with an increase in smooth endoplasmic reticulum. Conrad, Crosby, and Howie[21] reported a group of 20 patients with hereditary nonspherocytic hemolytic disease with shortened survival of red cells. The laboratory findings in the individuals were otherwise typical of those in Gilbert's disease. Survival of red cells has been investigated in too few cases.

ROTOR'S DISEASE

In 1948 Rotor, Manahan, and Florentin[63] reported cases with the familial occurrence of mild fluctuating jaundice along with abdominal pain and elevated conjugated bilirubin. In only a single subject was a biopsy made. This was a 19-year-old girl whose liver appeared normal on histologic examination. Following this there were a few additional reports of similar cases. The first 9 of these were reviewed by Porush, Delman, and Feuer,[65] who added another case. The usual features of what has been called Rotor's syndrome are mild and occasionally fluctuating familial jaundice, beginning in childhood, sometimes with fatigability or epigastric pain and an elevation in serum bilirubin, principally of the conjugated variety. The general range of bilirubin is from 2 to 20 mg. per 100 ml. There may be prolonged retention of Bromsulphalein, but other liver function tests are often not noteworthy. There is generally roentgen visualization of the gallbladder by oral cholecystography. The liver characteristically shows no histologic abnormality.[71]

The underlying mechanism of this disease has been thought to be a deficiency

in the ability of the liver to excrete conjugated bilirubin. Dollinger, Brandborg, Sartor, and Bernstein[29] have called attention to the possibility that there might be an additional factor, a hemolytic disorder as manifested by shortened red cell survival in the absence of other laboratory findings of a hemolytic process.

CHRONIC IDIOPATHIC JAUNDICE

In 1954 Dubin and I[34] and Sprinz and Nelson[73] called attention to the previously mentioned clinicopathologic entity that Dubin and I have called chronic idiopathic jaundice. A more comprehensive review was made by Dubin[30] in 1958. The clinical symptoms are similar to those of Gilbert's and Rotor's diseases. They include fluctuating jaundice, epigastric distress, and fatigability. The liver may be enlarged. The accompanying elevation of bilirubin in the range of 1.5 to 6 mg per 100 ml. is principally of the conjugated variety. Other outstanding features of chronic idiopathic jaundice that tend to distinguish it from the Gilbert and Rotor forms are dark urine, failure of gallbladder visualization on cholecystography, and conspicuous dark brown, iron-free pigment in centrilobular hepatic cells (Fig. 1). As in our original description, the pigment remains unidentified. Dubin stressed catabolic products of hemoglobin such as the mesobilifuscins as possible precursors. I favored the concept that the pigment was derived from oxidation and polymerization of unsaturated fatty acids and was thus related to the lipochromes (less ambiguously, the lipo-

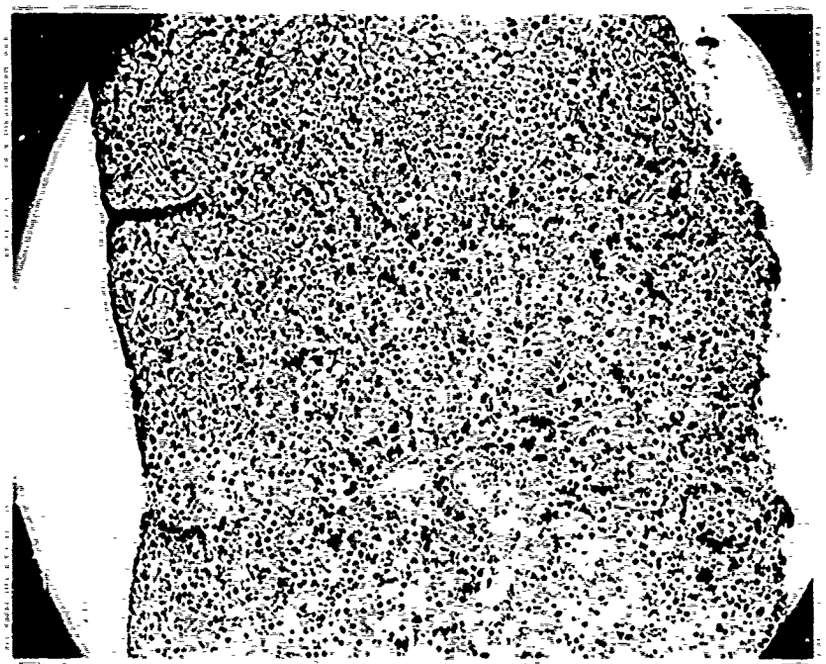

FIG. 1. Liver, chronic idiopathic jaundice. Ferric ferricyanide; × 240. (AFIP Neg. 54-1167-3.)

fuscins). Bynum[17] reported a case of chronic idiopathic jaundice in 1957 with repeated melanuria. He stated that his pathologist interpreted the liver pigment to be melanin. In 1964 Bernhardt[12] and Levrat, Brette, and Tissot[55] again reported on chronic idiopathic jaundice with melanuria. Sonnet, Steichen-Defalque, and Brisbois[72] also reported such an entity in 1969. Wegmann *et al.*[79] have made careful histochemical studies, including spectrophotometry, and concluded that the pigment in chronic idiopathic jaundice is a melanin (adrenochrome) not derived from tyrosine. We have isolated the pigment from a typically affected liver, by differential centrifugation, and examined it by infrared spectrophotometry and x-ray diffraction after prolonged lipid extraction, trypsinization, and acid hydrolysis. The results[48] are in agreement with the observations of Bonner and Duncan[15] in respect to the infrared spectra of melanins and with those of Thathachari and Blois[76] on the structure of catechol melanins.

Electron microscopy[9, 10, 34, 41, 45, 52, 60, 61, 63, 75, 77] has failed to demonstrate consistent morphologic defects to account for the deficiency in hepatic excretion of conjugated bilirubin as well as other organic anions. The electron microscope also fails to reveal the fundamental nature of the pigment. It is obvious that the latter is different from the usual form of hepatic lipofuscin and that it also differs from melanin identified in other sites. It appears to be confined to lysosomes and may be composed of two or more constituents. In individual cases in which serial biopsy samples have been obtained, the quantity of pigment remains essentially constant. Hunter, Sparks, and Flinner[44] report a case of severe hepatitis in a patient with chronic idiopathic jaundice whose regenerated liver cells lacked the pigment, which later, however, reappeared.

The fundamental biochemical lesion in chronic idiopathic jaundice is not known. It has been thought that the liver is fully capable of conjugating bilirubin but that there is an impairment in its secretion by hepatic cells. Billing, Williams, and Richards,[13] however, found a deficiency in hepatic uptake and conjugation in 2 of 5 cases designated as instances of Dubin-Johnson and Rotor syndromes. There is delay in excretion and regurgitation of Bromsulphalein.[18, 56, 81] Oral cholecystography results in no visualization or only faint visualization of the gallbladder.[83] Various anions exhibit diminished secretion.

Cornelius and associates have reported a useful animal model for the study of the disease in the form of a herd of mutant sheep.[1, 5, 22-26, 58, 59, 78] The histologic (Fig. 2) and chemical findings in these are almost identical with those in human patients except for the existence of photosensitivity in the former.

CRIGLER-NAJJAR DISEASE

In 1952 Crigler and Najjar[27] reported on a condition that they called "congenital familial nonhemolytic jaundice with kernicterus." The 7 patients were all infants from three consanguineous marriages. They had marked elevation of unconjugated bilirubin but showed no other evidence of altered liver function and no significant histologic changes except for intracanalicular bile thrombi. All also suffered from kernicterus. Childs and Najjar[19] reported 2 additional members of the kindred with elevated unconjugated bilirubin but no kernic-

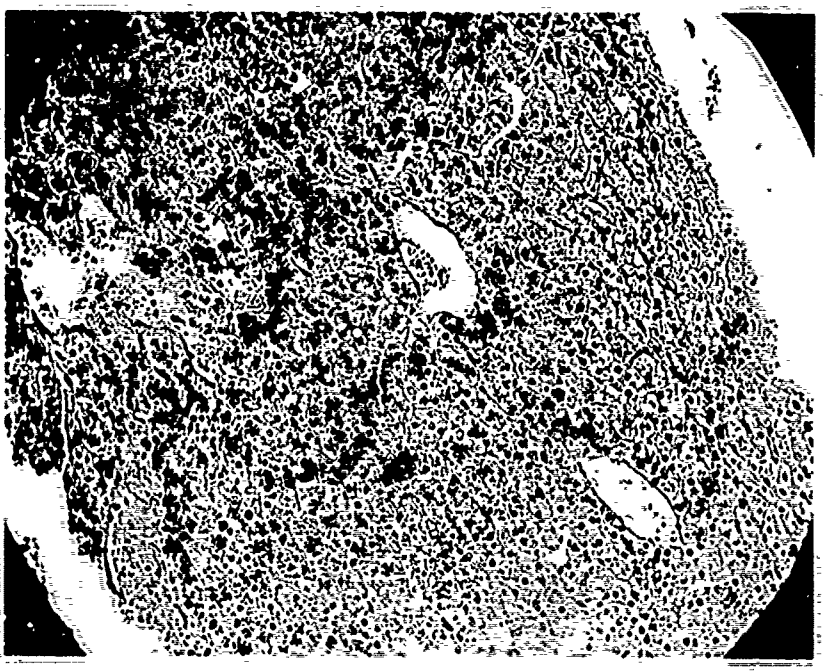

FIG. 2. Liver, mutant Corriedale sheep. Ferric ferricyanide; × 240. (AFIP Neg. 54-1167-4.)

terus. A few other cases have also been reported.[5, 36, 42, 43, 47, 74, 82] Hematologic studies have shown no abnormalities related to the jaundice, and significant structural abnormalities have not been demonstrated. Minio-Paluello, Gautier, and Magnenat[62] regarded the enlarged intercellular spaces they observed by electron microscopy in their case as evidence of hepatic immaturity. The significant abnormality in the disease is a deficiency in glucuronyl transferase activity.[20] There are, in fact, two forms of the disease: one in which there is severe jaundice and that fails to respond to phenobarbital stimulation; the other is mild with some glucuronyl transferase activity and a reduction in levels of circulating unconjugated bilirubin on treatment with phenobarbital.[84] In the first form, death in infancy is likely. In the latter, survival to adult years is possible.

A promising form of therapy is exposure to a bluish white fluorescent bulb to provide photochemical destruction of bilirubin.[51, 54] A mutant Wistar rat (Gunn) strain has proved to be a convenient animal counterpart[3, 6, 35, 40, 46] serving as a model for studies of hyperbilirubinemia caused by deficiency in glucuronyl transferase in the first form of the disease.

EPILOG

The hereditary characteristics of the familial diseases of bilirubin metabolism have not been discussed in this paper, though many of the references cited give some of the details, and some include pedigrees. Definitive studies have not yet been made. Some reports[11, 16, 61, 69, 83] cite examples of what

appear to be different disorders in the same family or of persons having features of more than one disease. Edwards[33] reported the possibility of more than one form of chronic idiopathic jaundice. It is hoped that the situation will be clarified in the future, with full investigation of families, including liver biopsy, bilirubin fractionation, studies of red cell survival, assessment of glucuronyl transferase activity, studies of Bromsulphalein excretion, and cholecystography.

I subscribe to the views of Price[37] opposing eponymic nomenclature. I also agree with Dubin,[31] however, who made the following statement: "I know that hybrids exist, but until I know the exact parentage of our strange hepatic animals I prefer to be mulish enough to suspend judgment about their ancestry and to call them by their original names."

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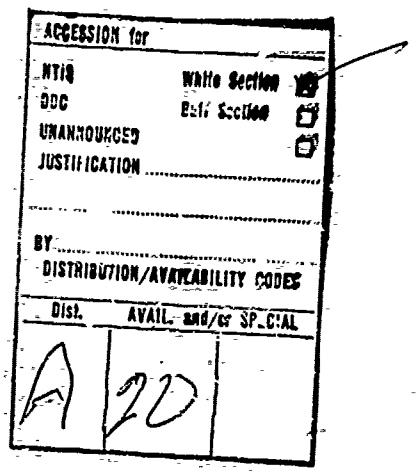
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