

by the discovery of cases among the relatives, to belong to the congenital group, as in Hayem's case (40). In one of Giffin's cases (31) the finding of increased fragility in the mother, though she was free from symptoms, was the only sign leading to the correct interpretation.

The age at onset is an unreliable criterion, it being by no means uncommon to have the congenital type begin in the second decade or even somewhat later. Cases beginning after thirty, however, and these form a minority of the cases reported as acquired, apparently never show any evidence of a hereditary factor.

The third point, the lack of hereditary influences, is not of much value as a distinguishing sign. For many of the hereditary diseases, such as progressive muscular dystrophy, occur at times in only one member of a family. The fact, however, that in cases of the acquired type recovery may occur constitutes an important difference.

The most valid reason, however, for separating the two types appears to rest in the etiology. For while the cause of the congenital type remains obscure, in many of the acquired cases the treatment of some associated condition, such as lues, malaria, a stricture of the intestine, has resulted in a cure of the jaundice. This is never the case in the congenital type, even in those rare cases accompanied by hereditary syphilis.

To sum up, it is best for the present to distinguish a congenital and an acquired type. But it will be safer to consider all cases as congenital unless it can be shown that they belong to the secondary group, with undoubted relation to some infection, intoxication, or malignant disease, or unless they begin late in life, after the third decade.

PATHOLOGY OF HEMOLYTIC JAUNDICE

Our knowledge of the pathology has been derived partly from autopsy reports, partly from the examination of excised spleens. Since no differences have been found between the congenital and the acquired types, the two may be considered together.

The spleen. The gross appearances are as follows: The organ is greatly enlarged, the average weight of 12 excised spleens being 1070 grams according to Giffin, (31), and of nine spleens at autopsy 716

grams. The capsule is often thickened and there may be adhesions to the diaphragm, both the result of old perisplenitis. The trabeculae are not thickened, the follicles appear few and small. The striking thing is the marked engorgement with blood, Guizzetti (38) remarking that the organ became reduced to one third its former size after the blood was squeezed out. Infarction has been noted in a few cases, in the absence of heart disease.

On microscopic examination the most striking thing is the marked congestion. This may be general, but often it is confined to the pulp (or "cords of Billroth"), the sinuses being empty. This peculiar distribution of the congestion was first noted by Vaquez and Giroux (88). It is unusual in other conditions; in chronic passive hyperemia for example the sinuses are engorged.

The trabeculae and reticulum show no marked degree of thickening. This constitutes an important point of distinction from Banti's disease.

The follicles appear fewer because they are widely separated owing to the congestion. They are usually normal except for the condition of the follicular arterioles, which often show a hyaline thickening, as described by Guizzetti (38), Sisto (82) and others. This change may be found also in the arterioles of the pulp, but to a lesser degree. A moderate degree of fibrosis of the follicles is sometimes encountered.

Pigment is present in the organ in varying amounts, being often very abundant, at other times scanty, or even absent, as in the case of Goldschmidt, Pepper and Pearce (33). It is chiefly within endothelial cells in the sinuses, and usually gives the iron reaction. The amount of pigment does not depend entirely on the duration of the disease, for Elliott and Kanavel (26) found very little in a man of fifty-seven years, jaundiced since birth. Phagocytosis of red cells is sometimes observed. The endothelial cells lining the sinuses may be changed from the normal flat type to an oval shape, as noted by Guizzetti and Sisto.

Liver. The size is about normal. There are no signs of cirrhosis, except in the rare cases of acquired hemolytic jaundice secondary to cirrhosis. The bile ducts are always normal, except where changes due to gall stones have occurred, as in Sisto's second case (82) with marked cholangitis and calculi in the common duct, and in the second

case of Tileston and Giffin (85). There is no deposit of bile pigment in the liver cells. Pigmentation to a greater or less degree is the rule, being absent only in the case of Marchiafava and Nazzari (56). It may be so abundant as to compare with that of hemachromotosis; as in an unpublished case recently seen by the writer. The pigment occurs in the form of coarse brownish granules, which usually give the iron reaction. It is situated mostly in the hepatic cells, especially at the periphery of the lobules, and in the stellate or "Kupffer" cells, though some may occur in the periportal spaces. Otherwise there are no changes, except those due to intercurrent diseases. Gall stones are present in a little over 50 per cent of the cases.

Bone marrow. The bone marrow of the long bones has been found red and in a very active state, with numerous normoblasts and myelocytes, in all the cases, with the exception of case II of Sisto, in which the anemia was not marked. Pigmentation is not noted in the records.

The lymph nodes. Pigmentation has been found in a few instances; in the writer's unpublished case it was extreme, the pigment being within endothelial cells in the sinuses and giving the iron reaction. Three cases have shown the change to hemolymph nodes, with congestion, phagocytosis of red cells and pigmentation.

Kidneys. There was a very marked siderosis in the case of Minkowski (60), who isolated $\frac{1}{2}$ gram of iron from one kidney; also in the case of Marchiafava and Nazzari (56), and to a lesser degree in that of Oettinger (67). The pigment is chiefly deposited in the convoluted tubules. In Marchiafava's case the pigmentation was exclusively confined to the kidneys, and the urine showed casts containing hemaglobin. This variation in the place of deposition of the pigment is interesting, suggesting that in such cases the hemaglobin is set free in the general circulation and reaches the kidneys, while as a rule the hemolysis takes place in the spleen and the pigment is deposited here, or is transported to the liver.

To sum up, the spleen shows marked congestion, often of a peculiar sort, involving the pulp but not the sinuses. The reticulo-endothelial apparatus, as Aschoff calls it, namely the endothelial cells of the spleen, liver, bone marrow and lymph nodes, shows signs

of hemolytic activity, such as phagocytosis of red cells and pigment deposit. The bone marrow shows the usual change from fatty to red marrow, as met with in most severe anemias.

DIFFERENTIAL DIAGNOSIS

Since most of the cases belong to the congenital type, a careful history, with special inquiry into the occurrence of jaundice among the relatives is of the greatest importance. The history of crises with pain and anemia is very suggestive. Any case of chronic non-obstructive jaundice, with or without enlargement of the spleen, should have the resistance of the red cells tested, and if this is lowered, the diagnosis of hemolytic jaundice is practically certain. If the resistance is normal, this does not exclude the diagnosis, provided the picture is otherwise typical. The resistance should also be tested where there is chronic anemia with splenomegaly, because hemolytic anemia without jaundice sometimes occurs. The presence of a considerable number of reticulated red cells, e.g., over 4 per cent, is valuable confirmatory evidence. The other important signs are anemia, increased urobilin excretion, the absence of bile pigment in the urine, highly colored stools and splenomegaly. Occasionally, however, any one of the above signs may be absent, and the diagnosis must rest upon the clinical picture as a whole.

In general, the diagnosis is to be made from other diseases accompanied by jaundice, diseases with splenomegaly and diseases with anemia.

1. Diseases with jaundice

Obstructive jaundice. This is excluded by the increased urobilin content and absence of decoloration of the feces, by the absence of bile pigment and bile salts from the urine, and by the absence of fatty stools. The resistance of the red cells is increased rather than diminished in obstructive jaundice.

Cholelithiasis. This is the most frequent source of error in diagnosis, owing to the fact that no less than sixty per cent of the cases of hemolytic jaundice are complicated by gall-stones. Many patients have undergone operation on the gall bladder, under the mistaken belief that the jaundice was due to calculi. It should be