THE CLASSIFICATION OF JAUNDICE with details of some of the causes of this condition.

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The division of the causes of jaundice into obstructive and non-obstructive, has for long been recognized as unsatisfactory. With increasing knowledge of the physiology of bile pigment formation and excretion, other classifications have been suggested. The most popular is probably that of McNee (1924) which is based upon his diagrammatic structure of the liver. The division here is into:—

Obstructive;

Toxic;

Hæmolytic.

This classification in which the middle term is based on etiology and the other two on pathogenesis cannot be quite satisfactory. Further, the term toxic is vague and though generally taken to mean toxic changes in the liver cells, might equally well mean the result of toxins causing increased blood destruction. It is easy to understand how the gross forms of obstruction produce jaundice, but when this is not present the position is far more difficult. Rich has given the theoretical possibilities:

- (1) If the threshold of the liver for blood bilirubin is raised.
- (2) If bilirubin were produced faster than normal liver cells could excrete it.
- (3) If the excretory mechanism of the liver were so disturbed that the amount of bilirubin normally produced could not be satisfactorily removed from the blood.
- (4) Any combination of the above conditions.

The first possibility is a purely hypothetical one for which there is no evidence. Rich (1930) has advanced many good reasons why it is unlikely that the excretory power of the normal liver could lag behind the bilirubin production. Just what is the reserve power of the human liver in this respect is uncertain but in dogs and monkeys the excretory power can be reduced to five per cent. by tying the ducts, without any development of jaundice. That the fæcal pigment in man may be greatly increased above the normal in the absence of jaundice shows that marked increases in the amount of bilirubin produced can be excreted by the normal liver well enough to prevent visible jaundice. As far as the third possibility goes, Rich points out that there is no form of jaundice which is known to result purely from a functional depression of the excretory powers of the liver without actual loss of cells through necrosis. The reserve power of the liver as mentioned earlier is so great that the liver cells can, so long as they are alive, deal with the normal quantity of bilirubin presented to them; it is only after there has been considerable necrosis that depression of the remaining cells can account for jaundice without excess of bilirubin. Any impairment, however, of the excretory function of the liver must diminish its reserve power and though such a liver could deal with normal quantities of bilirubin, if pigment is produced in excess such a liver may be unable to excrete it all and jaundice will result from retention of pigment. This is the fourth possibility and is quite common because most of the conditions which increase bilirubin formation would depress the excretory power of the liver.

As the result of these arguments Rich has proposed a classification based on pathogenesis into:—

- (1) Retention jaundice.
- (2) Regurgitation jaundice.

In the first group the liver is functionally unable to free the blood from bilirubin

produced in excess, the pigment is retained in the body and stains the tissues. In the second group the jaundice is the result of the escape of whole bile from the canaliculi into the blood stream either as the result of obstruction to the outflow through the ducts or because of the necrosis of liver cells. It must be noted that in the latter group it is whole bile i.e. bile pigment mixed with other biliary constituents which regurgitates from the ruptured bile canaliculi into the blood stream.

While most of the causes can by a little manipulation be pushed into one of these groups, combined forms can exist. A toxic agent which may at first merely depress liver function, with a tendency to retention jaundice, may go on to produce actual necrosis of liver cells with resulting loss of support for the bile canaliculi. These may give way and whole bile pass back into the blood stream and the picture of regurgitant jaundice be superimposed on the retention jaundice.

An interesting side light has recently been thrown on this conception of liver dysfunction as a factor in the greater number of cases of non-obstructive jaundice. It is now believed that the liver is vitally concerned in the manufacture of prothrombin, because the plasma prothrombin level falls when the liver is partially excised or injured by chloroform. It has been shown that in the majority of cases of jaundice so far investigated the plasma prothrombin is diminished and that this accounts for the increased liability to bleeding which is present in these conditions. This deficiency of prothrombin may represent one of the manifestations of K-avitaminosis. This depends in part on a failure of absorption of fat soluble substance when bile is excluded from the intestinal tract or when the secretion of bile salts by the liver is reduced. There is another and perhaps more important factor namely the ability of the liver to utilize vitamin K in the formation of prothrombin. The practical point of this is seen in the response of the body to vitamin K. Where the liver is slightly damaged and the jaundice is the result of gross obstruction existing for a short period only, the common surgical case of jaundice, there will be a good response to vitamin K; but where there is more than minor damage to the liver the response is poor or non-existent. As the standard methods of determining the coagulation time of blood give little warning of the possibilities of hæmorrhage in cases of jaundice, it is advisable to use vitamin K concentrates and bile salts as a routine part of pre-operative and post-operative treatment in every jaundiced individual coming to surgery. The amounts of material required for prophylactic or curative treatment is still uncertain; for the former 400-800 mgms. of alfalfa concentrate with 1 gm. of bile salts; for the latter 1-3 gm. of concentrate and 2-4 gm. of bile salts are advised. One or two such doses is usually sufficient to raise the prothrombin to a safe level. There seems to be no advantage in parenteral administration over the oral route.

The poor response of the plasma prothrombin seen in many cases of retention jaundice is in favour of Rich's argument that liver damage is an important factor in causation.

Some Forms of Retention Jaundice.

Retention jaundice includes a most interesting group of cases. Rich suggests that the cause of the depression of liver function is in most cases a result of the anoxia produced by the anæmia of blood destruction. It is difficult to see how this can be the cause in every case but the main point is that there must be some form of functional depression present. The common features of cases with blood destruction as the cause of jaundice are:—

- (1) The immediate evidences of the increased blood destruction.
- (2) The compensatory hyperplasia and hyperactivity of the reticulo-endothelial system.

- (3) Evidences of the regenerative activity of the hæmopoietic blood producing tissues. These phenomena appear in various degrees and combinations in different cases, depending on, the severity of the blood destruction, the duration of the process, and the integrity of the blood forming tissues.

Blood destruction liberates hæmoglobin into the plasma in amounts proportionate to the number of erythrocytes destroyed. This pigment far in excess of the amounts produced by normal blood destruction tends to follow the normal course. It is absorbed by the cells of the reticulo-endothelial system including the Kupfer cells of the liver and is broken down to bilirubin. As much as possible is passed by the liver but some is retained. That which passes into the intestine is re-absorbed in the form of urobilin. Owing to the large quantity of pigment which reaches the intestine the amount of urobilin absorbed is apt to be great, and further it is not converted to colourless urobilinogen as it would be by a normal liver. It therefore escapes in the urine and may even tint the skin. This is a characteristic of all conditions of excessive blood destruction whether this be a true " hæmolytic anæmia " or so definite an entity as pernicious anæmia. If the hæmolysis is of still higher grade and the liberated hæmoglobin reaches a figure of 0.7 gm. per 100 c.c. then it is passed by the kidney and hæmoglobinuria results. In every case of hæmoglobinuria it is possible to demonstrate bile staining of the plasma but as these hæmolytic episodes are usually as brief as they are dramatic, the icterus does not attract attention.

Pepper (1938) has classified these conditions according to the mechanism of hæmolysis as far as it is known.

- (1) **Fault in the erythrocyte.**
 - (a) Acholuric jaundice—congenital and (if it exists) acquired type.
 - (b) Sickle cell anæmia.
 - (c) Hæmolytic factor in pernicious anæmia.
- (2) **Parasitic destruction of the erythrocyte.**
 - (a) Malaria.
 - (b) Oroya fever.
- (3) **Allergic hæmolysis.**
 - (a) Sensitisation to favus bean.
 - (b) Drug sensitivity: sulphanilamide.
- (4) **Chemical agents.**
 - (a) Exogenous: lead, snake venom, phenylhydrazine, etc.
 - (b) Endogenous: altered plasma pH.
- (5) **Bacterial toxin.**
 - (a) B. welchii infection.
 - (b) Streptococcal and staphylococcal infection.
 - (c) Some cases of acute hæmolytic anæmia caused probably by an unidentified infection.
- (6) **Mechanism unknown and not surely hæmolytic.**
 - (a) Cooley's anæmia.
 - (b) Erythroblastosis of infancy.
- (7) **Specific hæmolysins.**

Following incompatible transfusion.
- (8) **Physical agents such as cold.**

Paroxysmal hæmoglobinuria.

(9) **Excessive destruction in the reticulo endothelial system.**

Reticulo endotheliosis: Hodgkins disease.

Some of these conditions are worth more detailed mention.

Acholuric jaundice. It is still usual to divide these cases into congenital and acquired forms, though considerable doubt is thrown by many authors on the existence of the latter. There is no doubt however that a considerable number of cases exist which are usually labelled chronic hæmolytic anæmia and should be included under the heading of acholuric jaundice. These may show minor increases of fragility and macrocytosis is common. There is no definite spherocytosis, the increase in thickness being part of the general macrocytosis. Owing to the macrocytosis and high colour index a diagnosis of pernicious anæmia may be made but the presence of free hydrochloric acid in the gastric juice should negative this. Marked reticulo-cytosis without treatment is a constant feature of the condition and should immediately indicate severe blood destruction. The crises in the "acquired" form are more severe than in the congenital and if these can be dealt with splenectomy may result in a successful alleviation of the condition. One has to be particularly careful in the use of transfusions in these cases because hæmolytic reactions are commoner than in the congenital type. Blood should therefore be most carefully matched not only for agglutination but also for hæmolysis. It should be run in very slowly and with these precautions may be a life saving measure especially during pre-operative preparation.

Sickle cell anæmia is a congenital hereditary familial defect in erythropoiesis. It is characterised by hæmolytic crises which occur for no known reason but it may go on for years without any manifestations. It is found mainly in negroes but cases have been described in Mediterranean and white American people. Sickling of the cells can be seen during the active phase of the disease and can be induced in vitro by reduction of the oxygen tension even when the disease is not active. This method may also be used to uncover sickling in other members of a family even if they have never had manifestations. There is a much greater tendency to abdominal pain and leg ulceration in this condition than there is in acholuric jaundice.

Paroxysmal hæmoglobinuria is now regarded as the name of a specific condition. It is rare and the attacks are associated with severe constitutional disturbances. The attack is in the nature of a paroxysm and it may occur with extreme rapidity. Syphilis is almost always present and the attack is excited by exposure to cold of even slight degree. Severe muscular exertion may excite an attack but this is probably more closely allied to the nocturnal type described later. The attack comes on abruptly a short time after exposure and is accompanied by severe pains in the back and legs, headache, abdominal cramps, vomiting, diarrhoea, and sometimes urticaria. There is usually a severe rigor with the temperature rising to 103—104° F. Paræsthesiæ, cyanosis of Raynaud type and sometimes gangrene of the extremities, may occur in severe cases. These manifestations suggest that hæmolysis is preceded by agglutination of the red cells or is accompanied by damage to the endothelial lining of the vessels with a consequent tendency to thrombosis and blockage. Lesions of the same type have been produced in animals by the injection of hæmolysin. There may be a transitory enlargement of the spleen and liver. The actual paroxysm usually subsides after a few hours.

After the attack the urine is full of hæmoglobin and in a well marked case may be port wine in colour—methæmoglobin may be present. There may be a sediment

of the remains of the red cells but the urine is neither turbid nor smoky; hæmolysis of the red cells is therefore complete. At the height of the attack the blood serum is tinged with hæmoglobin and when this disappears bilirubinæmia and jaundice persist for some days. Rarely mild attacks may pass off without any hæmoglobinuria and only mild jaundice is seen.

Donath and Landsteiner (1904, 1905) showed that the hæmolysis was due to a hæmolysin in the patient's blood. This has been found in 5—10 per cent. of cases of late syphilis even though the patients themselves have not exhibited hæmoglobinuria. This hæmolysin is rarely if ever found in non-syphilitics. It is suggested that there may be some constitutional individual peculiarity necessary to bring about the condition as well as syphilitic infection. The hæmolysin acts as an amboceptor and unites with the red cells, but only when the temperature is low. When the temperature rises again, the amboceptor-sensitized cells become lysed by the complement normally present in the blood serum (Donath-Landsteiner reaction). The treatment is naturally mainly prophylactic i.e. keeping the patient warm. Intense anti-syphilitic treatment should be tried but even if it is symptomatically successful the Donath-Landsteiner reaction remains positive.

Some very interesting work has recently been done on another form of hæmoglobinuria. This is the syndrome commonly called after Marchiafa and Micheli. This condition may begin as a paroxysmal hæmoglobinuria or as a hæmolytic anæmia but when fully established it is characterised by paroxysms of hæmoglobinuria and the persistence of hæmolysis, jaundice, and anæmia between the attacks.

The illness usually begins insidiously with gradually increasing anæmia and it may be years later before the hæmoglobinuria appears. The onset is most commonly in the second or third decade and once the disease is fully developed death occurs in three to five years. The paroxysms are most often seen at night and the interval between attacks is very variable. They tend to disappear in the day and it has been found that posture or temperature have no effect. The degree of jaundice is usually mild and often less than is expected from the degree of anæmia. A few patients have developed a dark bronze pigmentation of the skin. The diet, the tongue, and the gastric secretion are normal, the stools are properly digested and contain no occult blood. The spleen is usually palpable as may be the liver. Gall stones may develop as the result of exaggerated pigment excretion. The anæmia is macrocytic and hyperchromic, but the red cells are not as large or so variable as in pernicious anæmia. There is a constant reticulocytosis of between ten and twenty per cent. Nucleated red cells are few and there is moderate leucopenia and thrombocytopenia. The Wassermann and Donath-Landsteiner reactions are negative, and no abnormal hæmolysins have ever been detected. The fragility of the red cells is normal and splenectomy has no effect. At autopsy the characteristic finding is an intense hæmosiderosis of the kidneys, the pigment being deposited in the convoluted tubules and the descending loop of Henle. There is no excess of hæmosiderin in other organs. Ham (1937) in America and Dacie, Israels and Wilkinson (1938) in England have been able to show that the nocturnal hæmolysis was related to the elevation of the carbon dioxide content of the arterial blood and the associated decrease in the pH which occurs in sleep. Counteracting this shift with sodium bicarbonate reduced the hæmoglobinuria while ammonium chloride produced the reverse result. This would seem to prove that the red cells of these patients are abnormally susceptible to hæmolysis in plasma of increased acidity within physiological limits. Unfortunately alkali medication while temporarily beneficial did not cure the condition and excessive blood destruction followed the cessation of sodium bicarbonate.

There is one other condition which resembles these two in showing paroxysms of hæmoglobinuria and that is the hæmoglobinuria of muscular exertion. This is a harmless abnormality occurring in young males and like postural albuminuria is often associated with lordosis. It disappears in adult life.

Lederer's anæmia. The acute febrile anæmia usually called after Lederer (1925) is an acute hæmolytic episode which closely resembles an infection. No causal organism has yet been isolated and it is suggested that the condition is more frequent in pregnant women. Though it may occur at any age there is greater frequency in younger people. In this condition the icterus though mild is a definite feature though usually overshadowed by the general collapse and the severe anæmia. The diagnosis is based on the extremely good response to blood transfusion.

Incompatible transfusion. The transfusion of incompatible blood can produce the most alarming symptoms and if sufficient blood is given death results. If the patient survives the immediate reaction death may occur later from suppression of urine due partly to blocking of the renal tubules and partly to poisoning of the kidney by the products of hæmolysis. Bordley (1931) analysed a series of cases of incompatible transfusion and concluded that no case receiving less than 350 ml. of incompatible blood died from suppression of urine and no case receiving more than 500 ml. recovered. The amount of lysed blood may be much greater than this figure in certain diseases such as Blackwater fever without death occurring. The extent and nature of the reaction therefore must depend on the rate as much as on the extent of hæmolysis.

The extent of jaundice in all these cases is a variable factor and the extent of hæmolysis is no guide to the icterus index. The hæmoglobinæmia soon gives place to bilirubinæmia, but as the amounts of bile pigment are well within the capacity of the liver to excrete there need be no visible jaundice. It does usually occur however owing to the effects on the liver of the general reaction and the anæmia. Rich (1930) has demonstrated the fact that in cold hæmoglobinuria the less anæmic the patient (and therefore the more cells available for destruction) the less likely is jaundice to occur for the liver has not yet been damaged by prolonged anoxia.

Some Forms of Regurgitation Jaundice.

A. Jaundice due to rupture of canaliculi produced by toxic agents. There are many chemical, bacterial, and vegetable poisons which possess the property of producing damage and death of the hepatic cells. The cases are usually divided into acute and sub-acute forms. Each are sub-divided into severe and mild types.

Acute hepatitis: mild form. This usually begins with gastro-intestinal disturbance. Appetite is lost, nausea is felt and vomiting is frequent. Constipation is commoner than diarrhoea and the patient feels ill. The temperature may rise up to 100-102°. Leucocytosis is absent. This stage may last up to two weeks. There may be dull aching pain over the liver and this may become severe and increased on deep breathing or coughing. This is due to swelling of the liver which becomes palpable as a tender organ about an inch below the costal margin. About this time icterus develops, bile appears in the urine and disappears from the stools. As jaundice appears the general symptoms regress and the appetite returns, though dislike of fats may persist. Sometimes jaundice is the first sign to appear. It may go on to any degree though never the very severe greenish black of prolonged obstructive jaundice. The patient will remain jaundiced, tired, and depressed for two to six weeks and the liver is usually palpable the whole time. Occasionally the spleen is enlarged.

Severe form. This is fortunately a rare condition. The patient becomes gravely ill in a few hours or a day or two. There is intense headache with repeated vomiting. This vomit may show some altered blood. Jaundice appears but in the most severe cases it may be slight. The patient becomes restless, delirious, and passes into coma. This coma may be preceded by convulsions and other signs simulating meningitis. The tongue and mouth become very dirty and dry and the urine is scanty and contains casts. The breathing is increased in rate and depth at first but later becomes irregular. The temperature rises steadily throughout the disease and the liver shrinks continually. Once the patient passes into coma recovery is unusual. In this severe form there is such intense necrosis of liver cells that the bile canaliculi rupture and bile stained debris may be seen on section.

B. Jaundice due to obstruction of the bile ducts. Because of the reserve excretory power of the liver it is unusual for jaundice to appear in these cases unless the flow through the major part of the system is prevented. It has been shown by Baron and Bumstead (1928) that for a short time after acute obstruction of the common duct only the indirect van den Bergh reaction is found; later the direct reaction is given. This they say means that in the early stages bilirubin is accumulating which has not passed through the liver cells and they suggest that the liver temporarily stops taking up bilirubin. Later the excretion continues and the canaliculi become overfilled with bile. These canaliculi increase in size until their bulbous ends come into direct communication with the perivascular lymph spaces and drainage into these may take place before rupture of the canaliculi occurs. It has been shown that in acute bile duct obstruction bilirubin appears in the lymph before it is found in the plasma. Later the canaliculi burst and whole bile is discharged into the blood stream.

Differential Diagnosis.

It is not usually difficult to distinguish retention jaundice from regurgitation jaundice. In the former it is common to find evidence of blood destruction or of the peculiarity of the red cell or serum leading to this destruction. There is usually no bile in the urine, but excess of urobilin in the urine and the faeces. Haemoglobinuria is a feature of acute haemolytic episodes. The usual difficulty is to distinguish the jaundice due to toxic agents acting on the liver from pure obstructive jaundice. The pale stool indicates obstruction but intra hepatic obstruction may occur in toxic hepatitis. Hepatitis is likelier in younger patients. The previous history is important as biliary colic or cholecystitis point to obstruction whereas treatment of syphilis with arsenic, or gout with cinchophen, or the use of other hepatic poisons indicates hepatitis. In the first few weeks when the stools are pale the galactose tolerance test will usually give a normal result in obstruction, and an abnormal one in hepatitis; a high blood phosphatase is common in obstruction, normal or slightly raised in hepatitis. Gall stones may be seen on X-ray and a carcinoma of the head of the pancreas may give a deformity of the duodenum.

If jaundice, apparently obstructive, persists for more than six weeks in a patient over forty and the diagnosis cannot be otherwise established, then a laparotomy should be performed.

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