CONGENITAL FAMILY CHOLEMIA.

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The following case was admitted into the Aberdeen Royal Infirmary
under Dr. Mackintosh on 31st October 1910.

H. T., male, aged 7.

Family History.—The father was alive, aged 37, and was quite
healthy. The mother was alive, aged 36. Until she was 20 her
colour was not good, but she was quite definite that she was not
jaundiced. Since then she had been quite strong. There had been
three children and no miscarriages. The first child, a female, died
of pneumonia at the age of 6 months. All her life she was
markedly jaundiced—“as yellow as a guinea.” The second child,
also a female, was aged 10, and was quite healthy. The third
child was the present case. The mother and sister of the patient
were examined; they showed no trace of jaundice, and no enlarge-
ment of the spleen; the blood, so far as the red and white cells
were concerned, was normal; the serum could not be examined
for bile pigment.

Personal History.—H. T. had been jaundiced since within a few
weeks of birth. Except for being rather more readily tired than
other children, he had been fairly strong. He had measles at the
age of 4, from which he made a good recovery. He had had
neither scarlet nor typhoid fever.

Present Illness.—The patient was referred for treatment by the
School Medical Officer. His parents considered him to be in his
usual health, and had ceased to lay much stress on his jaundice.
His mother stated that he had been yellow since within a few
weeks of birth. The jaundice varied in intensity; at some times it
was quite marked, at other times it diminished considerably. She
considered that on admission he was of unusually good colour.
When the jaundice was most marked he was more readily tired
and drowsy. He had never complained of pain in the abdomen.
He had never suffered from epistaxis or other haemorrhages.

State in Hospital.—The patient was a well-developed, bright,
intelligent boy. His general nourishment was excellent. His
skin was slightly jaundiced, and his conjunctivae were definitely
yellow. At irregular intervals the jaundice very definitely increased,
The visible mucous membranes were moderately pale. There were no haemorrhages in the skin or retina and no abnormal pigmentation of the skin. There was no clubbing of the fingers. Two or three small glands could be felt in the left axilla. Apart from changes in the spleen and blood, no further abnormality was discovered. The spleen was much enlarged and extended to one inch below the umbilicus. It was smooth, not tender, and it moved freely on respiration. The liver as a rule could not be palpated below the costal margin, but on certain days when he was more jaundiced it could just be felt, and he then rather resented palpation.

The Urine.—The urine was frequently examined during his stay in hospital; it never contained bile pigment, albumen or sugar. Urobilin could not be demonstrated on the two occasions on which it was tested for. The urine was, however, invariably high coloured—apparently due to excess of urochrome. As a rule the urine was free from a deposit of urates, which was, however, very marked on the days associated with an increase in the jaundice.

The Stools.—The stools were always well coloured and were usually of a deep brown colour. When the jaundice increased they became much more deeply pigmented, and were then of a very definite dark green colour.

The Blood.—Red cells, 2,800,000 per c.mm. White cells, 5800 per c.mm. Hb., 35 per cent.

Red Cells.—There was very marked anisocytosis, with numerous very large megalocytes, but the general tendency was undoubtedly to microcytosis. There was some polychromatophilic degeneration, especially affecting the megalocytes, but it was by no means general. Basophilic degeneration was also present in a small proportion of the cells. In one film, in counting 500 leucocytes, sixteen normoblasts and one megaloblast were seen. In other films the relative percentage of megaloblasts to normoblasts was considerably higher.

The white cells showed polymorphs, 58 per cent.; small lymphocytes, 35 per cent.; large lymphocytes, 2.2 per cent.; transit., 1.8 per cent.; eosinoph., 1.8 per cent.; mast., 8 per cent.; myelocytes, 4 per cent.

The blood-serum gave a very definite reaction for bile pigment. The Haig modification of Wassermann’s reaction was negative. The resistance of the washed red cells to hypotonic solutions of saline solution gave the following results. As controls, the red cells of a case recovering from an attack of jaundice due to gall-
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stones were used and also the red cells of a case of acute small-celled lymphatic leukæmia. The red cells of the leukæmia case showed marked changes on histological examination, including the presence of many nucleated red cells.

| Saline Sol. 1 per cent. | H. T. | Leukæmia. | Gall-Stones. |
|------------------------|------|-----------|-------------|
| " 9                    | "    | "        | "           |
| " 8                    | "    | "        | "           |
| " 7                    | "    | marked   | "           |
| " 6                    | "    | "        | "           |
| " 5                    | "    | complete | complete    |
| " 4                    | "    | "        | slight      |
| " 3                    | "    | complete | marked      |
| " 2                    | "    | "        | slight      |
| " 1                    | "    | "        | "           |

Neither iso- nor auto-hæmagglutinins were present in the serum, and it showed no hæmolysins either for its own or for foreign red cells.

We have here a case presenting the features of chronic icterus dating from a few weeks after birth, marked splenomegaly, an apparently normal liver, and very definite changes in the blood. We may further emphasise the fact that the boy, in spite of the profound changes discovered on examination, was considered by his family to be quite strong, and was referred for examination by the School Medical Officer.

That these cases are not very rare and represent a definite clinical entity is evidenced by a review of the fairly extensive literature of the subject. Minkowski, at the Congress of Internal Medicine at Wiesbaden in 1900, first accurately described the condition in a report headed “Ueber eine hereditäre unter dem Bilde eines chronischen Ikterus mit Urobilinurie, Splenomegalie und Nierensiderosis verlaufende Affektion.” In the family described by him eight cases occurred in three generations, all of whom presented chronic icterus and splenomegaly without impairment of the general health. There were no marked changes in the blood. On one of these cases an autopsy has been performed and will be referred to later. Hayem in 1898, under the title “Chronic Infectious Splenomegalic Icterus,” described familial cases which have since been shown to be of the same nature. The family reported by Wilson in 1890 also probably belongs to the same group. More recently, important articles on this subject have appeared, especially by Chauffard, Gilbert and Lereboullet,
From a consideration of the literature it is evident that the disease may appear in various types. Of these, the most striking is that in which it appears as a hereditary and familial affection occurring in several generations (e.g. three or four) and in several members of each generation. Examples of such cases are recorded by Minkowski, Hayem, Wilson, Krannhals, Barlow and Batty Shaw, Benjamin and Sluka, Hutchison and Panton, Tileston and Griffin (four families), and others. When occurring as a hereditary affection the disease affects males and females equally, and may be transmitted both by males and females. In some of the recorded families males only are affected, in others females only. So far no case has been recorded in which an unaffected member has transmitted the disease.

In a second type the disease appears as a familial affection, but no history can be obtained of its previous occurrence in the family. Examples of such cases are those recorded by Lereboullet and Hawkins and Dudgeon, and the present case.

In a third class we have isolated cases first appearing at birth or in early childhood, and there is a fourth type in which the disease first appears in early adolescence or adult life. This last type differs from the others only in the fact that the cases, as a rule, present much more severe symptoms than the hereditary or congenital cases. Strauss's and Oettinger's cases, in which autopsies have been obtained, belong to the acquired group.

The chief physical signs, viz. splenomegaly, changes in the blood and jaundice, will now be considered in greater detail.

The Spleen.—A splenic tumour is one of the most characteristic features of the disease, and has been present in the vast majority of the recorded cases, several of them having been reported as splenic anemia. As a rule the enlargement appears early and is considerable, the spleen reaching to the umbilicus. In a few cases the enlargement has been much greater. There are, however, a few cases, which apparently must be included in the same group, in which the spleen has not been enlarged. One of the most convincing of these is the family reported by Benjamin and Sluka. In this family the grandfather, his son and his granddaughter were all affected with the disease. The son and granddaughter both showed very large spleens, but the grandfather, although he had been very definitely jaundiced all his life and showed considerable blood changes, presented an apparently normal spleen.
Pick has described a family in which the mother, two sons and one daughter were affected, but none of them showed an enlarged spleen. Mason and Parkes Weber have each recorded an isolated example of acholuric jaundice in a young adult in whom the spleen was of normal size.

The Blood.—In all cases bile is readily demonstrated in the blood-serum—it has been present in all the recorded cases in which it has been looked for. Urobilin is not present. One of the most characteristic features of the blood is a diminished resistance of the red blood cells to haemolyzing agents. This was first described by Chauffard, and it has been confirmed by practically all recent writers. It is best tested for by exposing the washed red cells to hyper- and hypo-tonic solutions of saline solution and noting the point at which haemolysis takes place. With normal blood, haemolysis begins at about -4 per cent. saline solution. In congenital cholæmia Chauffard has shown that haemolysis may begin with -7 per cent. or even -9 per cent. saline solution. This has been confirmed by Lereboullet, Möller, Parsons, Hawkins and Dudgeon, Hutchison and Panton, Vaquez and Giroux, Oettinger, Widal and Abrami and Brûlé, Tileston and Griffin, and others. Krannhals, using an imperfect method, also considered that in his family there was an increased fragility of the red cells. In most of the recorded cases haemolysis has commenced between -6 per cent. and -7 per cent. saline solution. Parkes Weber failed to demonstrate any definite increased fragility in his case, but the reaction was carried out, not with the washed red cells, but with a few drops of blood diluted with normal saline. Bettmann also failed to demonstrate any increased fragility in his case by the method of Hamburger and Limbeck. Widal and Ravaud describe a case of congenital jaundice in a male aged 24 with an increased resistance of the red cells to hypotonic solutions of saline, but, as this case showed a megalocytosis instead of the usual microcytosis and an absence of splenic enlargement, it probably belongs to a different group. This increased fragility of the red cells is the more remarkable as it has been repeatedly shown by many observers that the resistance of the red cells to haemolyzing agents is definitely increased in obstructive jaundice. Widal, Abrami and Brûlé have shown that the haemolysis depends solely on the fragility of the corpuscles, and that the plasma and serum are normal. Chauffard has further shown that the increased fragility is evident when tested with other haemolytic agents, such as eel and antihuman serum.
A second characteristic of the red blood cells which Chauffard first described is a very distinct tendency to microcytosis. This also has been generally confirmed, and is quite opposed to the megalocytosis usually observed in cases of obstructive jaundice.

Hæmoglobin has been found in the blood-serum in only two cases, those of Bettmann and Chauffard. In Bettmann's case attacks of paroxysmal hæmoglobinuria occurred on two occasions and the jaundice was always much increased by exposure to cold. Neither auto- nor iso-hæmoe-lysin have been found in the blood-serum, though frequently looked for. Hawkins and Dudgeon have described in two of their cases (sisters) the presence of a specific hæmagglutinin. No hæmagglutinin was found in our case or in the cases of Hutchison and Panton (two cases), Poynton (three cases), and Parsons.

In addition to the increased fragility of the red cells and the microcytosis, the blood as a rule shows further definite histological changes. In some of the older cases no very definite changes are described in the blood, but in the great majority of the more recent cases there has been a very definite anæmia with a red cell count ranging from 4,000,000 to 700,000 per c.m.m., an average count being about 2,500,000. The lowest counts occur in cases of the acquired type, which may closely simulate an advanced case of pernicious anæmia. Poikilocytosis is occasionally present, but much more frequent is marked aniso-cytosis, with a distinct tendency to microcytosis. Polychromatophilic and basophilic degeneration may also be marked. Nucleated red cells are frequent (Chauffard records them as high as 5·5 per cent. of total red cells), sometimes normoblasts and sometimes megaloblasts preponderating.

Guinon, Rist, and Simon have described one acquired case in a girl aged 10, who showed the usual symptoms of chronic acholuric jaundice of variable intensity, urobilinuria and splenomegaly, but who, in addition, suffered from transitory attacks of cyanosis and increase of the jaundice. During the attack the red cells rose to 6,000,000-7,600,000 per c.m.m. Mosse has recorded a somewhat similar case, but, as it developed in a male aged 58, there is considerable doubt if it belongs to this group.

The leucocytes are generally present in normal numbers and show no constant abnormality in their relative proportions. In some cases a slight relative excess of the polymorphonuclears has been present (Tileston and Griffin, 80 per cent.) but in others there has been a relative lymphocytosis (Bettmann, Barlow and Batty
Shaw). Myelocytes in small numbers are frequently present, but they have been recorded as high as 9 per cent. (Möller). Mast cells also are frequently met with in small numbers.

The haemoglobin is diminished in proportion to the red cells, the colour index usually being about normal or rather less.

The Jaundice.—Jaundice is one of the essential features of the disease, without which the diagnosis cannot be made in any but familial cases. It varies considerably in intensity; in many cases it is stated to have been as marked as is usual in catarrhal jaundice, in others it has been much less marked, though the conjunctivae are always definitely coloured. In all, bile pigment is readily demonstrated in the blood-serum. It never passes into the green or black jaundice seen in malignant or congenital obstruction of the bile ducts. It seems possible, however, that there may be incomplete cases without definite jaundice, as some of the members of affected families have shown only anaemia and splenomegaly without jaundice (Chauffard and Troisier, Parkes Weber). In many cases the jaundice varies in intensity from time to time, and it is not unusual, as in our case, to find that the days associated with the more intense jaundice are accompanied by a heavy deposit of urates in the urine and a general sense of diminished well-being. In Bettmann’s case the crises of increased jaundice were distinctly related to excess in eating and drinking, mental and certain bodily strains, and, above all, to exposure to cold. In other cases the jaundice becomes more marked during the warm weather.

The Urine.—In the great majority of the cases, bile pigment is constantly absent from the urine, in a few it has been noted in small amount at rare intervals. Urobilin is generally present. Bettmann’s case occasionally suffered from attacks of paroxysmal haemoglobinuric, but this is no feature of the disease. In a considerable number of the cases it has been noted that the urine at irregular intervals showed a heavy deposit of urates, and at those times the jaundice increased and there was more or less impairment of the general condition. Apart from these abnormalities, the urine is quite normal.

The Stools.—In all cases the stools have been well coloured. Möller has shown that the total urobilin excretion in the urine and faeces is considerably increased. Tileston and Griffin have shown that the neutral fats, fatty acids and soaps are present in normal proportions. In our case we may emphasise the fact that, on the days associated with an increase in the jaundice, the
stools were always very definitely more deeply coloured with bile.

The Liver.—In the great majority of cases the liver has been found normal in size on physical examination; in a few cases it has been described as at times slightly enlarged, but very rarely has it extended more than a finger's breadth below the costal margin. In a case described by Claus and Kalberlah there was a very marked enlargement of the liver, which ultimately diminished in size. A brother suffered from chronic jaundice without hepatosplenomegaly. As there was no increase in the fragility of the red cells there is some doubt if the case belongs to this group. Roughness and irregularity of the surface of the liver have never been described.

General Features of the Disease.—One of the most remarkable features of the condition is the frequent absence of any symptoms of disease. Not a few of the familial cases, who were found to present all the characteristic features of the disease, were discovered only during a systematic examination of the family. Hawkins and Dudgeon's Case I. was a policeman, aged 27, who had shown all his life jaundice as intense as an ordinary catarrhal jaundice. His spleen extended to his umbilicus and his red cells were reduced to 3,676,000 per c.mm. and showed marked poikilocytosis and the presence of megaloblasts. In spite of this, he was, and—except for an attack of pleurisy five years before—had always been, in perfect health and able for full duty. He came up for examination solely on account of his colour, which had frequently given rise to remark.

The condition appears to have little tendency to shorten life. One of Benjamin and Sluka's cases dating from infancy was alive at 81. Both Tileston and Griffin's cases died at 74. Minkowski's and Oettinger's cases died of an intercurrent pneumonia at the ages of 42 and 67 respectively; Wilson's case died in childbed, and Gandy and Brulés of typhoid fever; in the cases of Vaquez and Strauss death followed splenectomy and cholecystectomy respectively. The females can bear large families with impunity. At times, however, some even of the congenital cases show exacerbations, accompanied by slight pyrexia, a deepening of the jaundice, and an increase in the anaemia. At such times the cases may look very ill, and, unless a correct diagnosis be made, a very erroneous prognosis may be given. The acquired cases, as a rule, tolerate their condition much less readily than the congenital or familial, and in them it is the exception rather than
the rule to be without symptoms for any length of time. Pigmentation of the skin other than the jaundice is no feature of the condition. Repeated epistaxis is not infrequent, and, more rarely, haemorrhage from the gums occurs. Parkes Weber has recorded an acquired case which showed a few retinal haemorrhages and a few purpuric spots on the legs. Haemorrhages from the stomach and bowel, so frequent in the Banti syndrome, have not been observed. Attacks of pain over the splenic region, probably due to perisplenitis, have occurred in several cases. Attacks of true biliary colic due to complicating gall-stones have also been present in some cases. In not a few of the cases, as in our case, the urine at irregular intervals has shown a heavy deposit of urates. On those days the patients are "off colour," both literally and metaphorically. Ascites or any other sign of venous engorgement has not been noted.

Pathology.—Autopsies have been performed in eight cases. Six of those (Minkowski, Wilson, Vaquez and Giroux, Gandy and Brulé, Tileston and Griffin (two cases)) were of the familial type, while those of Strauss and Oettinger were of the acquired type. In both types the condition found has been the same. The liver has been found normal in size, or very slightly enlarged (Wilson). There have been no cirrhotic changes and no obstruction of the bile ducts. Except in Tileston and Griffin's second case, there has been no evidence of cholangitis; in their case the cholangitis was evidently due to complicating gall-stones. In Wilson's and Minkowski's cases there was also some fatty degeneration of the liver cells, which was probably associated with the terminal infection (vid. supra). In five of the cases gall-stones were present, and in Wilson's case the gall-bladder was not examined. In all, the spleen has been much enlarged. In most of the cases there has been more or less perisplenitis. The increase in size of the spleen was due mainly to an increase of the pulp, which was enormously engorged with red cells. In Tileston and Griffin's second case and in Wilson's case there was also some splenic fibrosis. In all there was a greater or less deposit of pigment in the spleen, mainly within the endothelial cells. In most of the cases there was also a variable amount of pigment in the kidneys, and in both of Tileston and Griffin's cases and in Wilson's case there was some fibrosis of the kidneys. The bone marrow in Tileston and Griffin's cases was in a state of intense reaction, with red marrow throughout the femur.

Pathogenesis.—Most of the recent writers are now agreed that
the condition is a haemolytic jaundice, associated with the diminished resistance of the red cells. All the features of the disease have been produced in rabbits by Lesnè and Ravaut by the injection of haemolytic agents. Whether this increased fragility of the red cells is due to a congenital defect in the blood-forming organs or is the result of a congenital defect of metabolism leading to the production of haemolytic toxins is unknown.

**Differential Diagnosis.**

*Splenic Anaemia, especially of the Family Type.*—Family cases of splenic anaemia of the ordinary type, although not common, have been described by Levy, Springthrope and Stirling, and Sutherland and Burghard. In this condition we have marked splenomegaly without hepatomegaly, accompanied by changes in the blood of a chlorotic type. The histological structure of the spleen in those cases is quite different from that seen in congenital family cholæmia. Clinically, the cases of splenic anaemia differ in the absence of jaundice, the presence of pigmentation of the skin, and probably, though this has not yet been sufficiently demonstrated, the presence of a normal fragility of the red cells. As a rule, also, the histological changes in the red cells are not so marked in splenic anaemia; this is not an absolute rule, as in the younger members of Springthrope and Stirling's family there were very definite changes in the red cells. In the cases which pass on to the full Banti syndrome, jaundice may develop, but there is then definite evidence of cirrhosis of the liver, and, generally, repeated gastro-intestinal haemorrhages occur.

*Splenic Anaemia of the Gaucher Type.*—The Gaucher type of splenic anaemia has a much more definite tendency to a familial incidence. Family cases have been reported by Brill, Collier, Bovaird, and Schlagenhaufer. So far, no case has been reported showing hereditary transmission. These cases show a unique pathology, and clinically they differ from cases of congenital cholæmia in the immense preponderance of females affected (thirteen out of fourteen), in the presence of marked enlargement of the liver, and in the absence of definite blood changes. A brownish-yellow discoloration of the skin, differing from that of true jaundice, is frequently present; it was marked in one of Brill's cases in which there was no trace of bile pigment either in the urine or in the blood-serum. Jaundice was present in Gaucher's case and was marked in Risel's case, which showed
the constant presence of bile pigment in the urine during three months' observation.

*Hypertrophic Cirrhosis of the Liver.*—This condition also appears as a family disease, presenting the features of chronic jaundice with enlargement of the liver and spleen. Family cases have been reported by Finlayson, Boinet, Osler, Dreschfeld, Hasenclever, Parkes Weber, and others. Clinically these cases show, in contradistinction to chronic family cholæmia, marked liver enlargement. Further, when it occurs in children the development of the child is usually retarded, both mentally and physically. Itching of the skin is much more pronounced, and clubbing of the fingers is frequently present. The jaundice is more marked, and bile pigment is practically always present in the urine. The blood changes are insignificant.

**Congenital Obliteration of the Bile Ducts and Obliterative Cholangitis.**—Familial and isolated cases of congenital obliteration of the bile ducts, more or less complete, are not very uncommon. These cases show marked jaundice developing within a short time of birth, spleno- and hepatomegaly, and a tendency to haemorrhages from various parts of the body. The great majority of the cases die within ten months of birth, but a few cases in affected families have been known to recover. They are readily differentiated from cases of congenital family cholæmia by the intensity of the jaundice, the presence of large amounts of bile pigment in the urine, the acholic stools, and hepatomegaly. Further, as in other forms of obstructive jaundice, the blood tends to show an increased resistance to haemolytic agents and a definite tendency to megalocytosis.

**Inherited Syphilis.**—In congenital syphilis, cases, frequently familial, are met with presenting the features of splenomegaly, hepatomegaly, and anaemia. These cases do not show jaundice without definite changes in the liver; the presence of other syphilitic stigmata and a positive Wassermann reaction would be decisive.

**Pernicious Anaemia.**—Congenital cases of congenital family cholæmia do not, as a rule, present an appearance suggestive of pernicious anaemia, but some of the acquired cases in which the general condition is much more adversely affected may closely simulate the rare cases of pernicious anaemia with marked splenomegaly. Such cases of congenital family cholæmia have been described by Chauffard and Parkes Weber. A recent case reported by Rudolf and Cole, which they consider to be probably
a case of pernicious anæmia or atypical splenic anæmia, appears to us to be of this nature. The diagnosis from pernicious anæmia must depend upon the long duration of the illness and the presence of acholuric jaundice. Whether any great stress in differential diagnosis can be laid on the presence of increased fragility of the red cells in congenital chalæmia is still doubtful, as the evidence as regards the fragility of the red cells in pernicious anæmia is contradictory. ¹

Leukæmia.—This condition was described by Leub, who considered it a combination of leukæmia and pernicious anæmia. It is now more generally believed to be an atypical form of leukæmia. In these cases we have splenomegaly and marked changes in the red blood cells without any very great increase in the white cells. There is no tendency to a family incidence in this disease. The cases are much more acute than those of congenital family chalæmia, the leucocytes on the whole tend to be definitely increased in number and show a higher percentage of myelocytes, and there is an absence of jaundice or chalæmia.

Treatment.—Many of the congenital cases are in a condition of equilibrium and require no treatment. Arsenic has been found to be of little use, if not actually harmful. Splenectomy has been done in only one case (Vaquez), with fatal result. Operation for the relief of complicating gall-stones has been performed in two of Tileston and Griffin's cases with success. In Strauss's case, cholecystectomy was followed by death on the third day.

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