

Four cases of congenital acholuric (so-called 'haemolytic') jaundice in one family / by F. Parkes Weber and G. Dorner.

Contributors

Weber, Frederick Parkes, 1863-1962.

Dorner, G.

Royal College of Surgeons of England

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FOUR CASES OF
CONGENITAL ACHOLURIC
(SO-CALLED "HÆMOLYTIC")
JAUNDICE
IN ONE FAMILY

BY

F. PARKES WEBER, M.D. CANTAB., F.R.C.P. LOND.

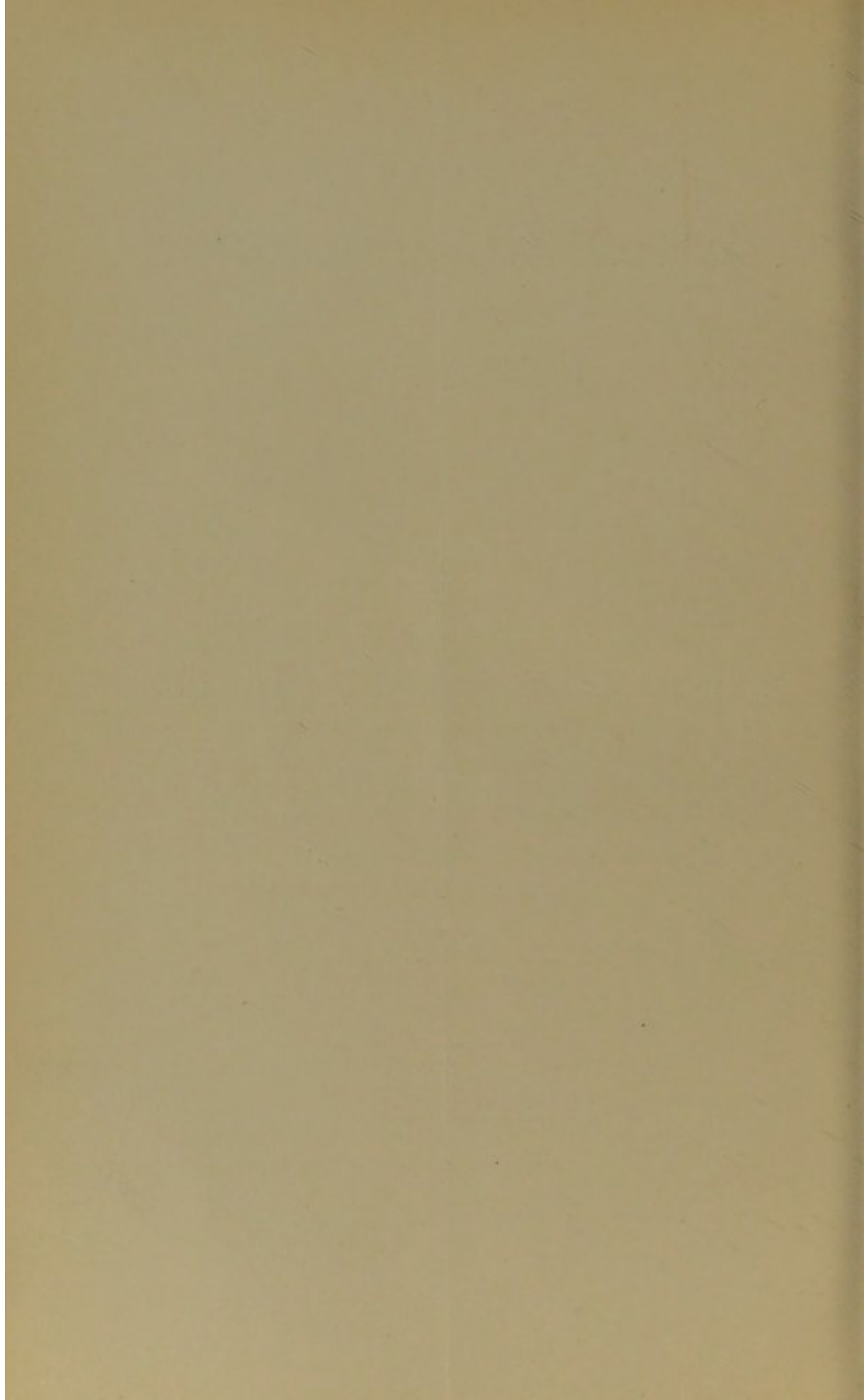
PHYSICIAN TO THE GERMAN HOSPITAL, LONDON;

AND

G. DORNER, M.D. KÖNIGSBERG

RESIDENT MEDICAL OFFICER TO THE HOSPITAL.

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FOUR CASES OF CONGENITAL ACHOLURIC (SO-CALLED "HÆMOLYTIC") JAUNDICE IN ONE FAMILY.

THE following examples of congenital and familial acholuric jaundice belong obviously to the same class as those recently described in England by H. P. Hawkins and L. S. Dudgeon,¹ R. Hutchison and P. N. Panton,² and F. J. Poynton and W. L. Scott.³ Amongst earlier English cases those of W. Moxon,⁴ Claude Wilson,⁵ Sir Thomas Barlow and H. Batty Shaw,⁶ J. A. Arkwright,⁷ W. T. Cocking,⁸ and H. A. Mason⁹ (Mason's patient was, however, the only jaundiced member of her family) probably belong to the same class. So also do the cases recorded in the German language by O. Minkowski,¹⁰ Bettmann,¹¹ Alois Pick,¹² H. von Krannhals,¹³

¹ Hawkins and Dudgeon: *Quarterly Journal of Medicine*, Oxford, 1909, vol. ii., p. 172. Includes many references to the literature of the subject.

² Hutchison and Panton: *Ibid.*, vol. ii., p. 432.

³ Poynton and Scott: *Transactions of the Medical Society of London*, 1909, vol. xxxii., p. 381. See also Poynton, *THE LANCET*, Jan. 15th, 1910, p. 153.

⁴ Moxon's cases of hereditary jaundice were described by Charles Murchison in his book on *Diseases of the Liver* (third edition, 1885, p. 481), and by G. Harley (*Diseases of the Liver*, 1883, p. 300). The later history of the same family (including Moxon's cases) has been quite recently published by R. Hutchison and P. N. Panton (*loc. cit.*).

⁵ Claude Wilson: *Transactions of the Clinical Society of London*, 1890, vol. xxiii., p. 162, and 1893, vol. xxvi., p. 163.

⁶ *Ibid.*, 1902, vol. xxxv., p. 155.

⁷ J. A. Arkwright: *Edinburgh Medical Journal*, 1903, new series, vol. xiii., p. 52.

⁸ *Quarterly Medical Journal*, Sheffield, 1903, vol. xi., p. 40.

⁹ *Ibid.*, 1903, vol. xi., p. 104.

¹⁰ Minkowski: *Verhandlungen des Congresses für innere Medizin*, Wiesbaden, 1900, Band xviii., p. 316.

¹¹ Bettmann: *Münchener Medizinische Wochenschrift*, 1900, Band xlvii., p. 791.

¹² Alois Pick: *Wiener Klinische Wochenschrift*, 1903, Band xvi., p. 493.

¹³ Krannhals: *Deutsches Archiv für Klinische Medizin*, Leipzig, 1904, Band lxxxi., p. 596.

Claus and Kalberlah,¹⁴ E. Benjamin and E. Sluka,¹⁵ and R. Pollak.¹⁶ Here likewise belong many of the cases of congenital or family splenomegalic cholæmia described in France by A. Gilbert and his pupil P. Lereboullet,¹⁷ Vidal and Ravaut,¹⁸ Lortat-Jacob and Sabaréanu,¹⁹ &c.; possibly also some of the cases without clinically obvious enlargement of the spleen. Since A. Chauffard's²⁰ well-known work on the subject most French cases have been published under the heading Congenital or Familial "Hæmolytic Icterus."²¹

Our patients are: (1) a man (B), aged 53 years; (2) his married daughter (C 1), aged 32 years; (3) another daughter (C 2), aged 14 years; and (4) a son (C 3), aged 12 years. Beyond the scabies, for which they all first came under our attention, and the signs and symptoms connected with their peculiar kind of jaundice, there is little that need be said about them. They all appear fairly well nourished and normally developed in body and mind. The father (B) has a pigmented scar on his right leg from ulceration due to an injury. The boy (C 3), the least jaundiced of the four, has slight enlargement of some of his cervical lymphatic glands and a scar on the neck left by an operation on lymphatic glands. The girl (C 2), who was for a considerable time under our observation as an in-patient, occasionally during that period had slight fever (at one time up to 99° or 100° F.). In none of the patients was there

¹⁴ Claus and Kalberlah: *Berliner Klinische Wochenschrift*, 1906, Band xliii., p. 1471.

¹⁵ Benjamin and Sluka: *Ibid.*, 1907, Band xlv., p. 1065.

¹⁶ Pollak: *Wiener Medicinische Wochenschrift*, 1908, Band lviii., p. 1489.

¹⁷ See especially the cases collected as examples of Ictère chronique splénomégaly, by P. Lereboullet, *Les Cirrhoses Biliaires*, Paris, 1902, pp. 447-464.

¹⁸ F. Vidal and P. Ravaut: *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris*, third series, 1902, vol. xix., p. 984.

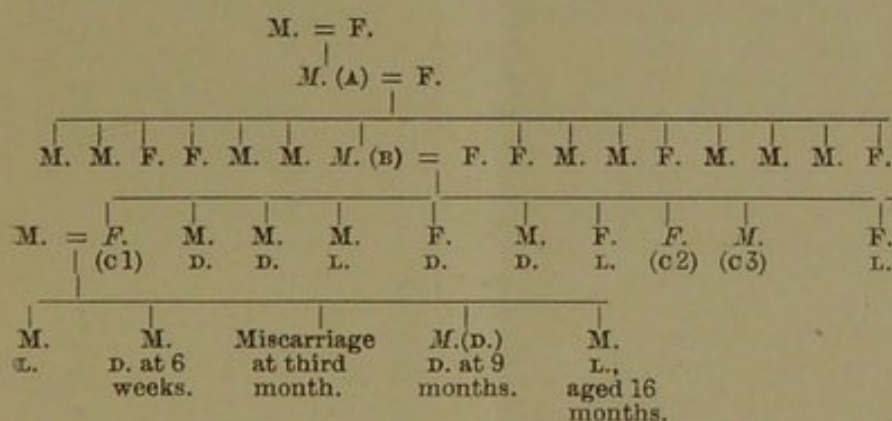
¹⁹ L. Lortat-Jacob and G. Sabaréanu: *Revue de Médecine*, Paris, 1904, vol. xxiv., p. 310.

²⁰ See especially A. Chauffard: *Pathogénie de l'Ictère Congénital de l'Adulte*, *Semaine Médicale*, Paris, Jan. 16th, 1907, p. 25.

²¹ On the whole subject of congenital and acquired hæmolytic jaundice see especially Vidal, Abrami, and Brulé, *Les Ictères d'Origine Hémolytique*, *Archives des Maladies du Cœur, &c.*, Paris, 1908, vol. i., pp. 193-231; Vaquez and Aubertin, *Sur l'Anatomie Pathologique de l'Ictère hémolytique*, *ibid.*, 1908, vol. i., pp. 609-623; Renaux and Verhoogen, *Ictère Hémolytique Congénital avec Splénomégaly*, *Société des Sciences Médicales et Naturelles de Bruxelles*, July 5th, 1909 (*Presse Médicale*, Paris, Sept. 25th, 1909, p. 680), and Renaux, *Journal Médical de Bruxelles*, 1909, No. 28, p. 440. In regard to acquired cases see also the recent German accounts by H. Strauss, *Ueber erworbenen Formen des Chronischen Acholurischen Icterus mit Splenomégaly*, *Berliner Klinische Wochenschrift*, 1906, Band xliii., p. 1590; and S. Möller, *Ueber Chronischen Acholurischen Icterus mit Splenomégaly*, *ibid.*, 1906, Band xlv., p. 1639; see also F. P. Weber, *Acquired Chronic Acholuric Jaundice*, *American Journal of the Medical Sciences*, 1909, vol. cxxxviii., p. 24.

any clubbing of the fingers. In all the cases, unless otherwise stated, the various examinations were carried out by Dr. Dorner.

Family history.—The father (B) of the other three patients tells us that he is one of a family of 15 children, eight of whom are still living, and that he is the only jaundiced one out of all the 15. His father (A), however, was jaundiced all his life, sometimes looking very yellow, sometimes less so. He died at the age of 70 years as a result of ulceration of the leg. The paternal grandfather and grandmother of the man (B) are said not to have been jaundiced. Of B's ten children (six living, four dead) only three—namely, our above-mentioned three patients—inherited the jaundice. Of these three, the married daughter (C 1), the eldest of his children, has had herself four children, one of whom is said to have been yellow and to have died ("anæmia") when 9 months old. In the accompanying genealogical table the italic letters indicate the affected members. M. stands for male, F. for female.



We confess that we are not quite satisfied as to the correctness of this family history, and should not be surprised to find that some of the brothers and sisters of B showed slight remittent or intermittent jaundice and a certain degree of splenomegaly.

The jaundice.—This symptom, which appears to have been congenital in the four patients, is as well marked in the skin of the body and the mucous membrane of the mouth as in the ocular conjunctiva. At present it is least noticeable in the boy (C 3), and very distinct, though not very deep, in his two sisters (C 1 and C 2),²² and in their father (B). The degree of yellowness varies occasionally from time to time, and is apparently deeper when they catch cold. The father (B)

²² When C 2 was seen on Jan. 3rd, 1910, the jaundice had almost completely disappeared.

says that he is yellower in winter than in summer, and that he feels weak and depressed during the exacerbations of the jaundice. His eldest child (C 1) says that her jaundice was increased during every pregnancy and whenever she caught cold. In none of the four cases has there been icteric pruritus or any xanthomatous change in the skin, such as is so often present in cases of chronic obstructive jaundice.

The spleen and liver.—The spleen can be felt abnormally hard below the costal margin and is decidedly enlarged in all four cases. In the father (B) and the girl (C 2) the lower edge is three fingers' breadth and in the married daughter (C 1) four fingers' breadth below the costal margin, but in the boy (C 3), although the area of the splenic dulness is distinctly in excess of the normal, the organ can only just be palpated below the ribs. The liver is slightly, if at all, enlarged. The lower edge can be felt just below the ribs in the father (B), the girl (C 2), and the boy (C 3), but not in the married daughter (C 1). There was never an attack resembling biliary colic in any of the cases, even during the exacerbations of the jaundice; and altogether there is no evidence pointing to any form of cholelithiasis, although on one occasion in the case of the father (B) during an exacerbation of the jaundice the faeces were said to be temporarily pale.

The faeces.—In the girl (C 2), whilst under observation in the hospital, the faeces were always normally coloured and very rich in urobilin (alcohol extraction, and in fresh faeces the perchloride of mercury test). So they have apparently generally been in the other patients, though on one occasion, as already stated, during an exacerbation of jaundice the father says that his motions became temporarily colourless.

The urine.—This has been examined in all four patients, and the only points to be noted are that in all of them it is of rather high colour, generally free from bilirubin but always containing abundance of urobilin (spectroscope and chemical tests) and urobilinogen. Occasionally, however, a very slight reaction for bilirubin was obtained.

Blood pressure.—The brachial systolic blood pressure in the father (B) was 115 millimetres Hg; in the married daughter (C 1) 115 millimetres Hg; in the girl (C 2) 125 millimetres Hg; and in the boy (C 3) 105 millimetres Hg.

THE BLOOD.

Colour of the blood serum.—In all four cases the blood serum was decidedly of an abnormal yellow colour and contained bile pigment (kindly tested by Mr. L. S. Dudgeon²³), but in none of the cases could the presence of urobilin be established by spectroscopic and ordinary chemical examination (Dr. Dorner).²⁴

The results of ordinary blood counts and differential counts are recorded in the accompanying tables. Microscopic examination of the fresh blood in these cases showed well-formed red cells, which, in a closed chamber, with few exceptions, retained their round contour (that is to say, did not become shrivelled and stellated or crenated in outline) for a long time; a "fresh" preparation from the girl (C 2) examined again after three days was found to show little change in the red cells, only an occasional one here and there having become crenated. For the special characteristics of the red cells, as seen in stained blood films, see the remarks in Dr. A. E. Boycott's report. Dr. Boycott kindly made blood counts (Nov. 30th, 1909) in all four patients and obtained the results expressed in Table II.

Dr. Boycott wrote that besides the details recorded in this table the most important features to note are: (1) abundant punctate basophilia in the red cells; (2) fairly frequent polychromatophilia; and (3) slight variation in shape and great variation in size of the red cells. The cells that are abnormal in size are too small. In the father (B) the ten largest cells averaged only 7.2μ , the ten smallest 4.6μ ; in the boy (C 3) the corresponding figures were 5.8μ and 4.1μ . Fig. 1 is a drawing to scale showing the outlines of the red cells in the father (B), and Fig. 2, drawn to the same scale, shows the red cell outlines in the boy (C 3). In Fig. 1 some of the cells are dotted to indicate the presence of punctate basophilia. The blood changes are most marked in the man (B), but are clear enough in the other three patients. Dr. Boycott calls attention to the high colour (denseness) of some of the red cells, a feature best marked in the boy (C 3), in whom the smallness of the red cells is specially noticeable.

The viscosity of the blood and blood serum.—This was estimated by Determann's viscosimeter²⁵ and the results are

²³ According to Dudgeon bile pigment is present only in the serum of patients obviously jaundiced or in whom jaundice is just going to appear (see also later on).

²⁴ Dr. Dorner suggests that special chemical methods with larger quantities of blood serum might perhaps give a positive result in this respect (but see later on).

²⁵ See Determann, Ein einfaches Blutviskosimeter, Verhandlungen des Kongresses für Innere Medizin, Wiesbaden, 1907, Band xxiv., p. 533.

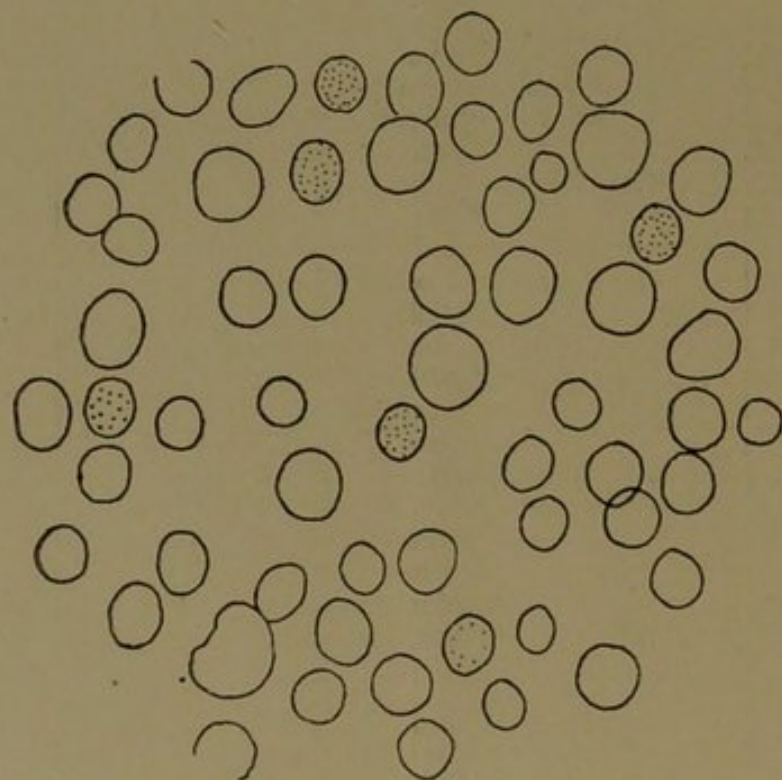
TABLE I.—*Showing the Results of Blood Counts made at the German Hospital.*

	Red cells per cubic millimetre of blood.	Hæmoglobin per cent. (Sahl's and Haldane's methods).	Colour index.	White cells per cubic millimetre of blood.	Differential count of white cells per cent.						Remarks.
					Neutrophile polymorpho- nuclears.	Small lymphocytes.	Large lymphocytes.	Intermediates.	Eosinophiles.	Mast cells.	
Father (B), (1) Oct. 25th	4,826,660	85	0.88	14,000	70.0	21.0	5.0	—	2.0	1.0	On this occasion the nucleated red cells (normoblasts) were counted amongst the white cells and con- stituted 1 per cent. of the differ- ential count.
" (2) Nov. 8th	—	—	—	—	65.6	23.7	5.3	1.8	2.6	0.9	
Married daughter (C 1), Nov. 8th	4,086,660	75	0.94	13,150	80.0	17.0	2.0	1.0	—	—	At this count no nucleated red cells were seen. No nucleated red cells seen.
Girl (C 2), (1) Oct. 19th.	4,453,330	71	0.81	12,600	78.0	15.0	7.0	—	—	—	
" (2), after taking iron, Dec. 18th	—	85	—	—	77.0	16.3	3.3	3.0	0.4	—	No nucleated red cells seen. Two normoblasts were seen in counting 500 white cells.
Boy (C 3), Oct. 30th	4,700,000	73	0.78	18,520	66.5	29.0	3.5	—	1.0	—	

TABLE II.—*Showing the Results of Blood Counts made by Dr. A. E. Boycott on Nov. 30th, 1909.*

	Red cells per cubic millimetre of blood.	Hæmoglobin per cent. (Haldane's method).	Colour index.	White cells per cubic millimetre of blood.	Differential count of 500 white cells per cent.						Neutrophile polymorpho-nuclears per cubic millimetre.	Remarks.
					Neutrophile polymorpho-nuclears.	Lymphocytes.	Intermediates.	Large hyalines.	Eosinophiles.	Mast cells.		
Father (B)	3,630,000	78	1.1	8,400	70.4	14.0	8.0	3.6	2.0	2.0	5900	Two nucleated red cells seen in counting 500 white cells.
Married daughter (C 1)	3,520,000	70	1.0	4,750	78.2	13.8	2.2	1.6	2.8	1.4	3700	Two nucleated red cells seen in counting 500 white cells.
Girl (C 2)... ..	3,460,000	77	1.1	3,800	77.6	14.8	3.2	3.4	1.0	0	2950	Two nucleated red cells seen in counting 500 white cells. Mast cells were present, though none were seen during the count.
Boy (C 3)	3,920,000	69	0.9	10,700	65.0	23.0	6.0	3.4	2.4	0.2	6900	One neutrophile myelocyte. 3 nucleated red cells seen whilst counting 500 white cells.

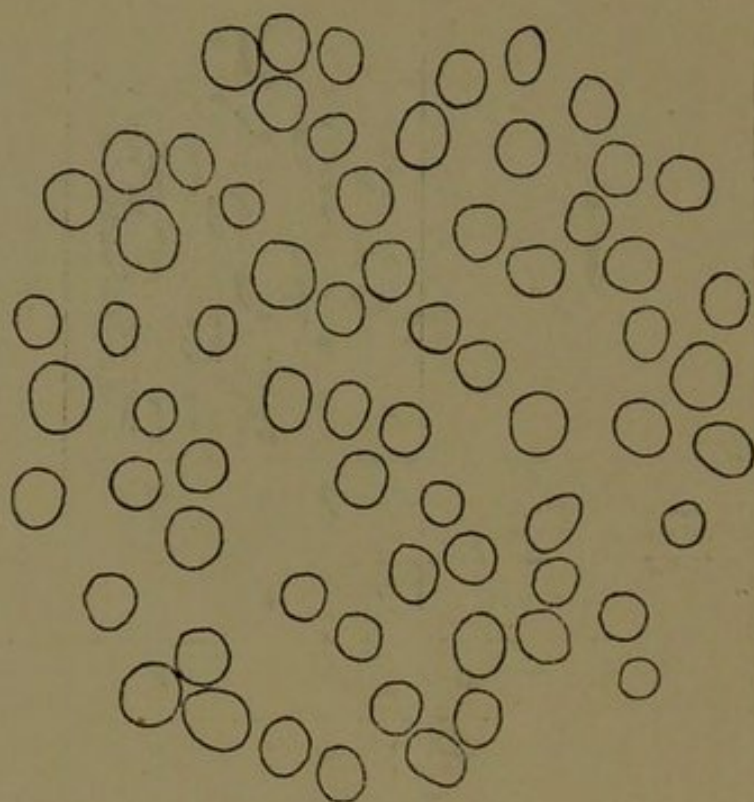
FIG. 1.



10μ

Red cell outlines in the father (B).

FIG. 2.



10μ

Red cell outlines in the boy (C 3).

shown (reckoned for a temperature of 20° C.) in the following table.

TABLE III.—*Showing the Viscosity of the Blood and Blood Serum.*

—	Father (B).	Married daughter (C 1)	Girl (C 2).	Boy (C 3).
Blood	5.0	4.72	4.86	5.8
Blood serum ...	1.88	1.88	2.0	2.08

The blood viscosity appears, therefore, to be practically within normal limits.

Resistance of the blood (red cells) to hæmolysis and the salt content of the red cells.—This was tested by means of graduated saline solutions, with (a) ordinary blood of the patients, and (b) their red blood corpuscles washed in normal saline solution. The results are shown in Table IV.

For comparison with these tabulated results Dr. Dorner examined the blood (the washed red cells) (1) of a normal person; (2) of a person suffering from veronal poisoning; and (3) of a person with aortic valvular disease. In all these three cases hæmolysis did not appear until the dilution of 0.45 per cent. sodium chloride was reached. It is interesting to note that the two methods (using blood and using washed red cells) gave exactly the same result in the case of the married daughter (C 1).

In our four jaundice cases Mr. L. S. Dudgeon and Dr. G. G. Butler likewise kindly tested the resistance of the blood (as blood, not the washed red cells) to saline solutions of various strengths. They found that hæmolysis commenced with a solution of 0.625 per cent. sodium chloride in distilled water and was complete with a 0.4 per cent. solution, whereas according to their experience by the method in question normal red blood corpuscles do not show hæmolysis until a solution of 0.375 per cent. sodium chloride is reached, and then very slightly only.²⁶

Mr. Dudgeon found in all four cases that the patient's blood serum did not exert any hæmolytic action on the red corpuscles of a healthy individual, or (as Dr. Dorner also found) on the patient's own red corpuscles (that is to say,

²⁶ Cf. Hawkins and Dudgeon: Congenital Family Cholemia, Quarterly Journal of Medicine, loc. cit. Mr. Dudgeon thinks that, strictly speaking, these hæmolysis tests indicate rather the salt contents of the red cells than the degree of resistance of these cells to hæmolytic agents generally.

TABLE IV.—*Showing the Effect of Graduated Saline Solutions in regard to Hemolysis.*

Sodium chloride solutions per cent. in distilled water.	Father (B).		Married daughter (C1).		Girl (C 2).		Boy (C 3).	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
0.9	0	0	0	0	0	0	—	0
0.75	0	Trace.	0	0	0	0	—	0
0.64	Trace.	Distinct.	Distinct.	Distinct.	Trace.	0	—	Distinct.
0.56	Distinct.	Almost complete.	Nearly complete.	Nearly complete.	Distinct.	Trace.	—	Nearly complete.
0.5	Almost complete.	Complete.	Complete.	Complete.	Complete.	Complete.	—	Complete.
0.45	Complete.	"	"	"	"	"	—	"
Date of the test	Nov. 14th.	Nov. 14th.	Nov. 14th.	Nov. 14th.	Oct. 19th.	Nov. 3rd.	—	Nov. 12th.

it had no autohæmolytic action); nor had blood serum from a normal individual any hæmolytic action on the patient's red cells. Furthermore, no hæmagglutinative action was observed on adding the patient's blood serum to a normal person's red cells, the patient's red cells to a normal person's serum, or the patient's serum to his or her own red cells.²⁷ The same remarks applied when blood plasma (citrated) was substituted for blood serum.

Wassermann's reaction for syphilis.—This test was kindly tried by Dr. J. Henderson Smith in the case of the father (B) and the girl (C 2), and by Mr. Dudgeon (using both long and short methods) in all four patients. The result was negative in every case.

It may likewise be mentioned here for what it is worth that von Pirquet's "cuti-reaction" for tuberculosis, tried in the case of the girl (C 2), gave a positive result.

REMARKS.

There can be no doubt that our cases are examples of the condition known as congenital and familial chronic acholuric jaundice, congenital familial cholæmia, or congenital familial hæmolytic jaundice. Little is known regarding the average duration of life in affected individuals, but that the disease is not inconsistent with longevity is shown by the case of the father (A) of our patient (B), who evidently suffered from the same affection as his son and lived to the age of 70 years. Syphilis seems (in spite of Hayem's suggestion) to play no part in the etiology of the condition, and it could be practically excluded in the present cases.

The most obvious signs of the disease are chronic jaundice, splenomegaly and (generally) a variable degree of anæmia. The jaundice is usually only slight and in some cases may probably be absent at times (see later on). It is never accompanied by icteric pruritus, xanthoma, or clubbing of the fingers. In many of the cases, however, occasional exacerbations occur, during which the patient sometimes complains of feeling weak and depressed. In one of our cases (the married daughter C 1) the jaundice was accentuated during her pregnancies. Cold weather or exposure to cold in some cases appears to intensify the yellow colour. In regard to exciting causes of the exacerbations of jaundice, Bettmann's case²⁸ was particularly interesting.

²⁷ For Mr. Dudgeon's methods see his preliminary report on the Presence of Hæmagglutinins, Hæmopsonins, and Hæmolysins in the Blood obtained from Infectious and Non-infectious Diseases in Man, Proceedings of the Royal Society, London, 1908, Series B, vol. lxxx., p. 531; see also his paper in vol. lxxxi. of the same series, p. 207, and his paper with Mr. H. A. F. Wilson in vol. lxxxii., p. 67.

²⁸ Bettmann: Loc. cit.

The patient (a man, aged 29 years) was very decided that the exacerbations could be induced by (1) unusually large meals; (2) mental excitement; (3) excessive walking or dancing; and especially (4) exposure to cold. His jaundice was (as in our patient B) more decided in winter than in summer. Another interesting point in Bettmann's case was that during the exacerbations his blood serum was occasionally coloured with hæmoglobin and he occasionally had temporary hæmoglobinuria. It may here be remarked that in typical cases of paroxysmal hæmoglobinuria true jaundice has very rarely been known to be associated with the hæmoglobinuric attacks.

The fæces are nearly always well coloured and the urine is nearly always free from bilirubin. But occasionally, during exacerbations of the jaundice, the motions become paler than natural and the urine may contain bilirubin in addition to the excess of urobilin which is nearly always present. Except during exacerbations, the patients seem to enjoy fairly good health and can work much like average individuals of their own size and age. They are not stunted in growth like patients affected with Hanot's so-called "biliary cirrhosis" in childhood.

The liver is usually not obviously enlarged, but occasionally can be felt a little below the costal margin. In uncomplicated cases the liver appears not to be cirrhotic. A necropsy on one of Minkowski's cases²⁹ showed both absence of any cirrhosis of the liver and absence of any mechanical obstruction to the bile-flow. A pigment-stone, which was found in the gall-bladder, could not have caused any obstruction. In one of Claude Wilson's cases the patient died with an exacerbation of jaundice during pregnancy, but no obvious hepatic cirrhosis was discovered at the necropsy.

The spleen is nearly always considerably enlarged and easily palpated; it generally does not extend downwards much beyond the umbilical level, but sometimes reaches the inguinal region. Neither liver nor spleen is ordinarily at all tender to pressure.

The blood shows characteristic changes. Bilirubin is always present in the blood serum and blood plasma (see later on). There is nearly always some anæmia (oligocythæmia), and the degree of this anæmia may vary considerably from time to time. The red cells are mostly fairly normal in shape—that is to say, there is seldom much poikilocytosis—but in size they usually vary very much more than those of normal individuals, so that there is a condition of decided "anisocytosis" present. The mean diameter of the red cells is somewhat less than that observed in normal persons, whereas in cases of chronic obstructive jaundice the mean diameter of the red cells is generally distinctly above the normal mean for healthy individuals. Polychromato-

²⁹ See O. Minkowski, loc. cit.

philia and generally punctate basophilia of red cells are observable to a greater or less extent, and the frequent presence of nucleated red cells (normoblasts) is characteristic. The red cells are found to undergo hæmolysis, when added to graduated weak saline solutions, more readily than do the red cells of ordinary healthy persons, and still more readily than those of individuals suffering from obstructive forms of jaundice (see later on).

In all probability persons affected with congenital acholuric jaundice ought as far as possible to be protected from great cold, especially in early life, and when decidedly anæmic should be treated by iron preparations.

In regard to the pathology of congenital acholuric jaundice (congenital family cholæmia), the disease seems, as supposed by French and other observers, to be due to a peculiar congenital abnormality or imperfect development of the bone marrow, which manifests itself by a kind of inferiority in the quality of the red blood corpuscles. These corpuscles yield more readily than those of normal persons to certain hæmolytic influences. Probably they are destroyed more rapidly than they should be by the action of even physiological hæmolytic influences. Such an abnormal fragility of red cells and the resulting excess of hæmolysis may be supposed to give rise to a chronic enlargement of the spleen, due to the great demands made on the hæmolytic functions of that organ.³⁰ According to this theory, the excessive hæmolysis must be also regarded as the cause of abnormally great production of bile pigment in the liver, leading to chronic jaundice and urobilinuria. Moreover, owing to the habitual excessive loss of red blood corpuscles the erythroblastic functions of the bone marrow (by a kind of "vicious circle") would be chronically more or less strained, and this would account for the frequent presence of unripe forms of red cells (nucleated red cells) in the circulating blood and likewise for the frequent presence of some anæmia (oligocythæmia) and the other blood features of the disease.

Very decided anæmia is not invariably present—that is to say, is not present at all times in every case. Indeed, by analogy with other chronic affections one is probably justified in expecting that the reaction of the erythroblastic functions of the bone marrow may occasionally be excessive, in which event an actual condition of polycythæmia would be set up in association with the chronic acholuric jaundice. In fact, Guinon, Rist, and Simon³¹ have described the case of a girl, aged 10 years, with chronic acholuric jaundice of variable degree, urobilinuria, and chronic splenomegaly; transitory

³⁰ During attacks of paroxysmal hæmoglobinuria the spleen sometimes, and the liver probably also occasionally, become temporarily enlarged. Vide G. H. K. Macalister, *Quarterly Journal of Medicine*, Oxford, 1909, vol. ii., p. 387.

³¹ Guinon, Rist, and Simon: *Bulletins de la Société Médicale des Hôpitaux de Paris*, 1904, third series, vol. xxi., p. 786.

cyanosis and polycythaemia (6,000,000 to 7,600,000 red cells in the cubic millimetre of blood) accompanied an exacerbation of the jaundice. Mosse³² has likewise described the case of a man, aged 58 years, suffering from acholuric jaundice (if not congenital, at least chronic), with urobilinuria and chronic splenomegaly, whose red blood cells numbered 6,750,000 to 7,825,000 in the cubic millimetre of blood.

Here we may also mention that the anaemia (that is to say, at least in acquired cases of chronic acholuric jaundice with splenomegaly³³) may occasionally be of a very severe degree and associated with the presence of megaloblasts ("gigantoblasts" with very large nuclei and polychromatophilic cytoplasm) in the circulating blood, so as temporarily to simulate the blood picture of pernicious anaemia; the diagnosis of such cases from pernicious anaemia complicated by splenomegaly and slight jaundice may be very difficult.

It is also highly probable that in some cases of the disease jaundice (at all events, obvious jaundice) may be intermittent instead of remittent—i.e., that (for a time at least) jaundice may be apparently absent, though the splenomegaly and characteristic blood features are present.³⁴ Such cases might be clinically termed cases of "splenomegalic anaemia" to distinguish them (A) from forms of anaemia with splenomegaly usually classified as "splenic anaemia of adults," and (B) from cases of so-called "infantile splenic anaemia" ("anaemia pseudoleukaemica infantum" of Von Jaksch). In other words, it appears almost certain that a form of "splenomegalic anaemia" without jaundice may occur (though perhaps only temporarily) as an incomplete form (*forme fruste*) of the chronic splenomegalic acholuric jaundice of which the family of the man (B) are complete examples.³⁵

The jaundice in cases of chronic acholuric jaundice (whether congenital, as in the present patients, or acquired), besides being usually very slight, differs also, as already stated, from that of chronic obstructive jaundice in not being associated with bilirubinuria, acholic faeces, icteric pruritus, or xanthoma. Chronic obstructive jaundice likewise differs from these cases in regard to hæmolysis, as estimated by the effect on the erythrocytes of graduated saline solutions of

³² M. Mosse: Deutsche Medicinische Wochenschrift, Berlin, 1907, vol. xxxiii., p. 2175.

³³ Cf. F. P. Weber: Acquired Chronic Acholuric Jaundice, with a Blood-picture at one time resembling that of Pernicious Anaemia, American Journal of the Medical Sciences, 1909, vol. cxxxviii., p. 24.

³⁴ Cf. Armand-Delille and Feuillie: Un Cas d'Anémie splénomégaly avec Fragilité globulaire, Société Médicale des Hôpitaux de Paris, Feb. 2nd, 1909, and the discussion which followed the exhibition of the case. See also Chauffard and Troisier: Des Rapports de certaines Anémies splénomégaly avec l'Ictère hémolytique congénital, Société Médicale des Hôpitaux de Paris, Feb. 19th, 1909.

³⁵ Cf. F. P. Weber: International Clinics, Nineteenth Series, 1909, vol. ii., p. 85.

various strengths. In chronic acholuric ("hæmolytic") jaundice, hæmolysis, as estimated in this way, occurs abnormally readily; on the other hand, in chronic obstructive jaundice the erythrocytes appear unusually resistant to saline solutions.

In chronic acholuric jaundice it seems as if a little bilirubin (possibly without the other constituents of the bile) passes into the blood, scarcely ever, however, in sufficient quantity to give rise to bilirubinuria. Occasionally, however, during exacerbations of the jaundice, as already mentioned, a trace of bilirubin may be detected in the urine.

According to Gilbert, Lereboullet, and Herscher³⁶ the blood serum of normal individuals contains on the average 1 gramme of bilirubin in 36 litres; but according to Hawkins and Dudgeon³⁷ bilirubin is by no means so frequently present. Dudgeon finds it present in the blood serum only of patients obviously jaundiced or in whom obvious jaundice is about to appear. Bilirubin can always be found in the blood serum of patients with acholuric jaundice.³⁸

In regard to the apparent absence of urobilin or urobilinogen from the blood serum in our present cases, Dr. Dorner suggests that special tests with larger quantities of blood serum might possibly give a positive result. On the other hand, S. Moeller has published two cases of acquired chronic acholuric jaundice (with splenomegaly) in which, though the urine was rich in urobilin, he was unable to detect the presence of any urobilin in the blood serum,³⁹ though he employed the method of Friedrich Müller and Gerhardt as modified by Syllaba. On the other hand, bilirubin was, as usual in such cases, present in the blood and absent in the urine.

The subjective symptoms of patients with chronic acholuric jaundice, when not very anæmic, are often very slight, or even apparently absent. Occasionally, however, there may be attacks of abdominal pain or of general depression, lethargy, or drowsiness, accompanied by temporary increase in the degree of the jaundice, sometimes also by moderate fever, and (rarely) by paleness of the fæces. All the symptoms usually tend to be more severe in the acquired cases in adults, such as the patient whom one of us showed at the Medical Society of London on Feb. 8th,

³⁶ Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris, séance de 15 Nov., 1907.

³⁷ Hawkins and Dudgeon: Loc. cit., p. 172.

³⁸ Cf. also S. Möller, Berliner Klinische Wochenschrift, 1909, vol. xlv., p. 2303.

³⁹ See S. Möller, Ueber Chronischen Acholurischen Icterus mit Splenomegalie, Berliner Klinische Wochenschrift, 1908, vol. xlv., p. 1639. Cf. also Möller, Zur Frage der Urobilinentstehung, ibid., 1909, vol. xlv., p. 2303.

1909,⁴⁰ than in congenital and familial cases, like those in the family now more especially under consideration. It seems as if the cause of the symptoms (whatever exactly that cause may be) is more successfully resisted or neutralised in the congenital cases—that is to say, in those of them that survive to adult age—than in patients who acquire the disease in adult life.

In regard to the diagnosis of congenital acholuric jaundice, the possibility of the presence of the so-called "Gaucher type" of splenomegaly may offer difficulties, as it did in the case of a boy (X), aged 14 years, whom one of us⁴¹ showed before the Clinical Section of the Royal Society of Medicine on Feb. 12th, 1909. In many of the recorded cases of the Gaucher type of splenomegaly more than one member of the same family has been affected; the disease, moreover, is a chronic one, and is not a primary diffuse epithelioma or endothelioma of the spleen, as by some it was formerly supposed to be; in several cases a yellowish colour of the skin during life has been remarked. In the boy (X) the size of the spleen was unusually large for congenital acholuric jaundice. When later on he was kindly examined by Dr. Boycott his anæmia was of a chlorotic type, and his total blood volume, as estimated by Haldane and Lorrain Smith's carbon monoxide method,⁴² was found (May, 1909) to exceed the normal for his body weight by 60 per cent.

A chlorotic type of anæmia is, however, probably not rarely associated with the congenital acholuric jaundice now under consideration, though it is, perhaps, a more constant feature in the Gaucher type of splenomegaly. In the boy (X) several points were in favour of the disease being the same as that of our present patients. His blood contained bilirubin and his urine was free from it. His fæces were well coloured. Examination of his red blood corpuscles (the mean diameter of which was rather below than above the normal standard for healthy individuals) showed hardly any poikilocytosis, but very marked anisocytosis, polychromatophilia, punctate basophilia, the presence of normoblasts (on one occasion 20 nucleated red cells were found during a count of 500 white cells), and a greater tendency to hæmo-

⁴⁰ F. P. Weber: Transactions of the Medical Society of London, 1909, vol. xxxii., p. 362.

⁴¹ F. P. Weber: Congenital Familial Splenomegaly with Chronic Acholuric Jaundice, Proceedings of the Royal Society of Medicine (Clinical Section), 1909, vol. ii., p. 117. See also F. P. Weber: Congenital Familial Splenomegaly, International Clinics, Philadelphia, Nineteenth Series, 1909, vol. ii., pp. 67-85 (regarding diagnosis of the condition, &c.).

⁴² See Haldane and Smith, Journal of Physiology, London, 1900, vol. xxv., p. 331; Smith, Transactions of the Pathological Society of London, 1900, vol. li., p. 311; Smith and McKisack, *ibid.*, 1902, vol. liii., p. 136; Douglas, Journal of Physiology, 1906, vol. xxxiii., p. 493; Boycott and Douglas, Journal of Pathology and Bacteriology, Cambridge, 1909, vol. xiii., p. 117 and p. 256, and Guy's Hospital Reports, 1908, vol. lxii., p. 157; Oerum, Deutsches Archiv für Klinische Medizin, Leipzig, 1908, vol. xciii., p. 356.

lysis than that proper to normal individuals. In this connexion we would remark that a point still requiring special investigation is the condition of the blood with regard to hæmolysis in undoubted cases of the Gaucher type of splenomegaly.⁴³ There seems to be no abnormality in the differential count of white blood cells by which a case of splenomegaly can be recognised during life as belonging to the "Gaucher type."

We have seen the patient (X) again quite recently. He looks sallow, but at present shows hardly a trace of jaundice. His enlarged spleen reaches almost to his groin. His liver cannot be felt. His urine is pale and clear, but contains urobilin and urobilinogen in excess. The last examination of his blood (Nov. 15th, 1909) gave the following results: hæmoglobin (Sahli's method), 50 per cent.; red cells, 3,533,330 in the cubic millimetre; colour index, 0.7; white cells, 23,000 in the cubic millimetre. Examination of the red cells in stained films showed the presence of much anisocytosis but relatively little poikilocytosis (though several oval and some pear-shaped forms were seen); much polychromatophilia. There were about three normoblasts to every 100 white cells. In about half of the normoblasts the nucleus was irregularly-shaped or split up. The cytoplasm of the normoblasts was generally polychromatophilic and sometimes contained basophilic granules. The differential count of white cells showed nothing special.

⁴³ On the Gaucher type of splenomegaly see especially: E. Gaucher, *De l'Épithéliome primitif de la Rate*, Thèse de Paris, 1882, and later writing by the same author; N. E. Brill, *American Journal of the Medical Sciences*, Philadelphia, 1901, vol. cxxi., p. 377; Brill, Mandlebaum, and Libman, *ibid.*, 1905, vol. cxxix., p. 491, and 1909, vol. cxxxvii., p. 849; F. Marchand, *Münchener Medicinische Wochenschrift*, 1907, vol. liv., p. 1102; F. Schlagenhauer, *Virchow's Archiv*, 1907, vol. clxxxvii., p. 125; J. C. G. Ledingham, in Allbutt and Rolleston's *System of Medicine*, vol. v., 1909, p. 766; W. Risel, *Ziegler's Beiträge zur Pathologischen Anatomie und Allgemeinen Pathologie*, 1909, vol. xlv., p. 241; P. Rettig, *Berliner Klinische Wochenschrift*, 1909, Jahrg. xlv., p. 2046; A. Plehn, *Deutsche Medicinische Wochenschrift*, 1909, Band xxxv., p. 1749.

