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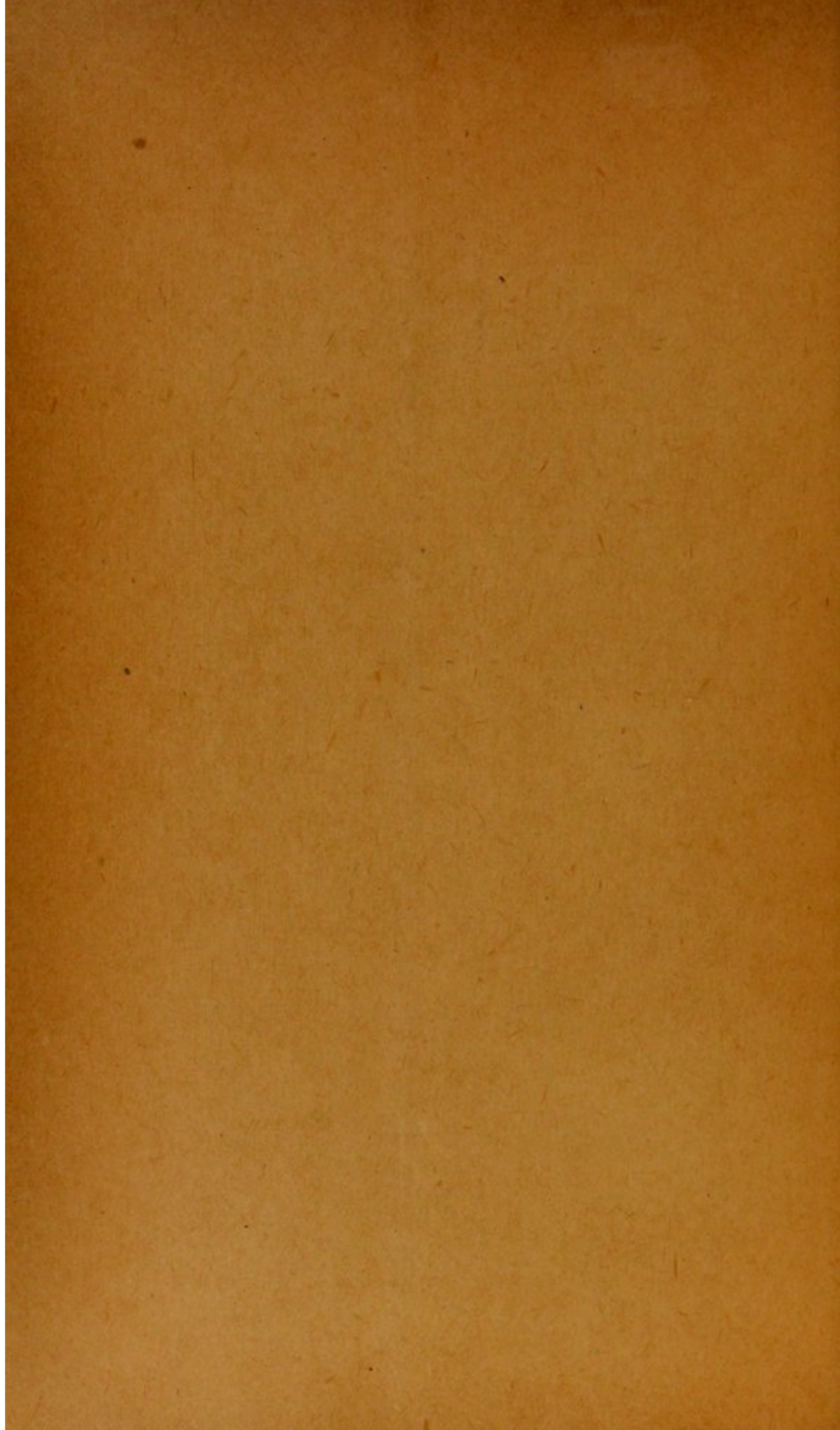
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**CONGENITAL FAMILIAL SPLENOMEGALY WITH
CHRONIC ACHOLURIC JAUNDICE**

ALSO A CONSIDERATION OF THE VARIOUS TYPES OF JAUNDICE
ASSOCIATED WITH SPLENIC ENLARGEMENT IN EARLY LIFE

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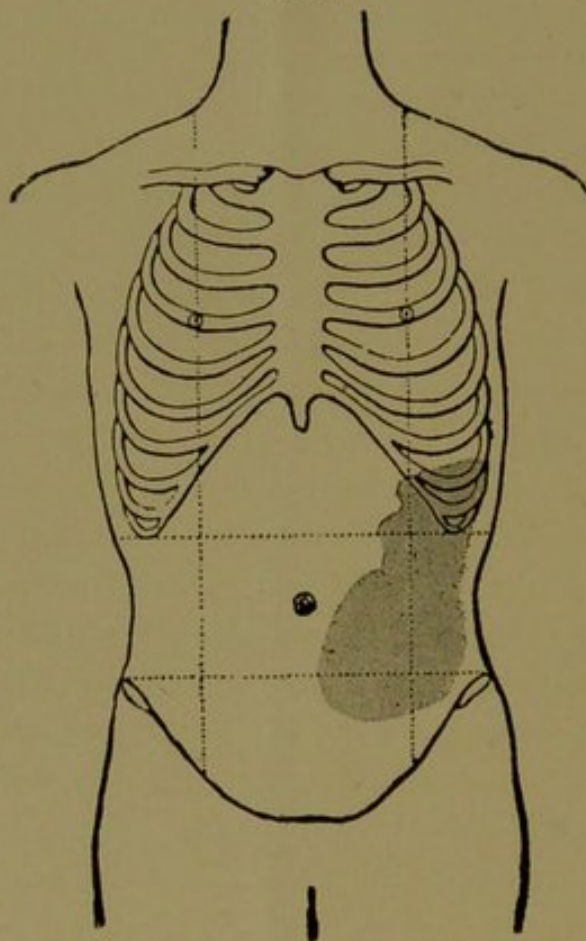
THE patient, Ernest N.,¹ is a fairly well developed boy, aged 14 years, but he looks somewhat anæmic, and his conjunctivæ have a slight but distinct icteric tinge. The spleen (see Fig. 1) is evenly enlarged and hard, reaching downwards to the anterior superior iliac spine. The liver cannot be felt and is apparently not enlarged; the fæces are not acholic. The urine is generally of rather low specific gravity, clear, pale, and free from albumin, sugar, and bile-pigment, but it sometimes shows excess of urobilin. The blood-serum was kindly examined by Mr. L. S. Dudgeon, in November, 1908, at a time when clinically the jaundice was scarcely recognizable, and was found to contain bile-pigment. The thoracic organs and other parts of the body do not show anything abnormal, excepting that on one occasion a systolic murmur was heard over the mid-cardiac area, probably not due to organic disease. The fingers are not clubbed; no enlargement of superficial lymphatic glands or tonsils is present; there is no pruritus or cutaneous affection.

The blood, examined during the periods in which the boy was nearest normal, sometimes shows the presence of a few normoblasts; of two rather large-sized normoblasts seen in a blood-film of January 21, 1909, one had a double nucleus. In another blood-film of the same date several normoblasts and one myelocyte were found. The red cells vary much in size ("anisocytosis") and staining ("polychromatophilia"). The average diameter of the red cells does not appear to be increased, as it often is in chronic obstructive

¹ The patient was shown at the Clinical Section of the Royal Society of Medicine in London on February 12, 1909.

jaundice, but if anything it is rather below the normal standard. A blood-count on November 6, 1908, gave 2,800,000 red cells, and 14,280 white cells to the cubic millimetre; the differential count of white cells (kindly furnished by Dr. A. E. Boycott) gave lymphocytes 20.6 per cent.; intermediates 4.8 per cent.; large hyalines 4.4 per cent.; neutrophile polymorphonuclears 68.4 per cent.; eosinophiles 1.0 per cent.; mast-cells 0.8 per cent. (no nucleated red cells seen

FIG. 1.



Showing size of the spleen on January 21, 1909, in the patient Ernest N.

on that occasion). A blood-count of a later date (January 21, 1909), gave 3,140,000 red cells and 14,500 white cells; hæmoglobin, 70 per cent. Examination of blood-films, as already stated, showed the presence of a few nucleated red cells. Dr. A. E. Boycott, who kindly looked over stained blood-films of that date, reported that there was a tremendous amount of variation in size and depth of staining amongst the red cells; most of the red cells were a good deal too small, but on the other hand, there was no poikilocytosis

to speak of.* There was much "anisocytosis" with very little poikilocytosis. The resistance of the red cells toward hæmolysis has been tested on various occasions by Ribierre's method²; it is found that hæmolysis occurs when a few drops of the patient's blood, diluted with normal saline solution, are added to a solution of between 0.40 and 0.48 parts per cent. of sodium chloride in distilled water (the resistance to hæmolysis was greatest on January 21, 1909). There does not, therefore, appear to be very decisive evidence that the chronic acholuric jaundice is "hæmolytic" in the present case; at all events, the evidence that it is due to congenital fragility of red cells is insufficient, though the fragility of the patient's red cells towards distilled water does really appear to be slightly greater than the average in normal individuals who were used as controls. In this connection an observation kindly made with the boy's blood by Mr. L. S. Dudgeon on November 25, 1908, is also interesting. Mr. Dudgeon found that the patient's blood-serum did not exert any hæmolytic action on the red corpuscles of a healthy individual, or on the red corpuscles of the patient himself (that is to say, it had no autohæmolytic action); nor had blood-serum from a normal individual any hæmolytic action on the patient's red cells.³

The history is that the patient was born at full term with the help of instruments, and was very yellow at birth. The jaundice never completely disappeared; his eyes (sclerotics) have always presented a slight yellowish tinge, but his complexion has generally

* From the blood-films taken from the boy Ernest N. on January 21, 1909, Dr. A. E. Boycott afterwards made the following differential count of 500 white cells: lymphocytes 20.4 per cent.; intermediates 5.6 per cent.; large hyalines 3.2 per cent.; neutrophile polymorphonuclears 66.8 per cent.; eosinophiles 3.2 per cent.; mast-cells 0.8 per cent. Whilst counting the 500 white cells he found 20 nucleated red cells: four of these were typical normoblasts; two were normoblasts with budding nuclei; and 14 were nucleated red cells of the ordinary type with polychrome cytoplasm, irregular in shape and about the size of a typical normoblast. There was much polychromatophilia present. The red cells showed marked variation in size (mostly on the small side), but hardly any poikilocytosis.

² I have to thank Dr. Chapuis, one of the house physicians at the German Hospital, for much assistance in the examination of the case, particularly in regard to the question of hæmolysis.

³ For Mr. Dudgeon's methods in this respect see his recent paper on the subject in the Proc. Roy. Soc., London, 1908, series B, vol. lxxx, p. 531.

been sallów rather than distinctly yellow. He has been always subject, however, to recurrent attacks of "depression," during which his urine becomes darker and he appears yellower and suffers from lassitude and drowsiness. These attacks recur about every three months on the average and last a few days. Recently he suffered occasionally from severe abdominal pains of uncertain character. Occasionally on blowing his nose he has noticed spots of blood on his handkerchief; but he has never had a regular attack of epistaxis and has never had bleeding from the gums or any other form of hemorrhage, excepting a mild attack of purpura in 1899, when he was four or five years old. At that time, according to Dr. Porter Parkinson's account (see later), the blood contained many small nucleated red cells (microblasts). His spleen was apparently first noticed to be large when he was three months old. He has always been subject to nocturnal enuresis. He has had no other illnesses except "croup" at one year of age.

There is no probability of a congenital syphilitic taint. The patient's father and mother both look healthy. The mother, now aged 48, has had thirteen children and no miscarriages. The eldest four children died early; the fifth, sixth, and seventh are living and healthy; the eighth is the present patient; the ninth, tenth, and thirteenth are living and healthy; the eleventh died as a baby; the twelfth, a girl with anæmia and splenomegaly without any jaundice, died at the age of one year and eight months. Both she and the present patient were shown in 1905, by Dr. Porter Parkinson, at the Society for the Study of Diseases in Children.⁴ Though there was no distinct jaundice in this girl Dr. Parkinson stated that the skin had a lemon-yellow color. Doubtless her blood would have been found to contain bile-pigment just as that of her brother does at present. Her spleen reached down to the anterior superior iliac spine and the liver could be felt one finger's breadth below the costal margin. Her red blood-corpuscles varied much in size (none very large) and numbered 3,393,000 to the cubic millimetre of blood. Her white corpuscles numbered 52,570, and the differential count gave polymorphonuclears 42 per cent., eosinophiles 10 per cent., small mononuclears 36 per cent., large mononuclears 9 per cent., and myelocytes 3 per cent. A most interesting point is that the

⁴ See the Society's Reports, London, 1906, vol. vi, p. 8.

mother says that all her children were born yellow and remained yellow for three to six months after birth, but the jaundice was permanent in the present patient only.

Before proceeding further I would state at once that the icterus neonatorum in these children was probably merely an exaggerated form of the so-called "physiological icterus neonatorum." The cause of "physiological" jaundice in new-born children is still uncertain; but whatever it may be, it seems to affect some families more than others. There have been families in which some of the children were affected with a harmless though prolonged form of icterus neonatorum, whilst others have succumbed to a fatal disease termed "icterus gravis neonatorum," which, according to Pfannenstiel,⁵ is certainly not septic in origin, but is merely an extremely severe form of the so-called "physiological icterus neonatorum"; in icterus gravis neonatorum, as in the physiological icterus neonatorum, the fæces are not acholic; and the results of post-mortem examination tend to show that the disease is to be distinguished from congenital obliteration of bile-ducts, with which it has probably sometimes been confused.

In order to illustrate the probable nosological position of the present case (Ernest N.) I shall now consider the main features of the various classes of cases characterized by chronic jaundice and enlargement of the spleen or of the liver, or of both of these organs, in early life. With few exceptions all such cases may be classified under one of the four following heads: (1) Congenital obliteration of bile-ducts and obstructive jaundice, probably connected with a congenital form of cholangitis; (2) inherited syphilis; (3) biliary cirrhosis; (4) chronic acholuric jaundice with enlargement of the spleen or of both the spleen and liver.

The occasional occurrence of very exceptional cases not coming under one of these heads can be easily imagined. For instance, hydatid cyst of the liver, causing enlargement of the liver, in a child may give rise to obstructive jaundice by pressure on the bile-ducts, or may be associated with a toxæmic catarrhal jaundice and splenomegaly. In the case of a boy shown by Dr. A. F. Voelcker at the Medical Society of London in November, 1907, there was en-

⁵ See J. Pfannenstiel: "Über den habituellen Ikterus gravis der Neugeborenen," Muenchener med. Wochenschrift, 1908, vol. lv, p. 2169 and p. 2233.

largement of the liver and of the spleen, together with a past history of jaundice (in 1902), which was recovered from. The hepatic enlargement was due to a hydatid cyst, which was afterwards successfully treated by operation; but a certain amount of splenomegaly remained in February, 1909, when Dr. Voelcker showed the boy again at the same Society.

1. *Congenital Obliteration of Bile-ducts and Obstructive Jaundice, Probably Connected with a Congenital Form of Cholangitis.*

In the cases generally termed "congenital obliteration of the bile-ducts," such as those so carefully collected and discussed by John Thomson⁶ in 1892, the jaundice is sometimes present at birth, but it may not be noticed till the second or third day, or may occasionally appear a few days later. It rapidly becomes intense and is distinctly obstructive in character. The urine is bilious. After the meconium, which is sometimes apparently normal, has been passed, the fæces are nearly always acholic,⁷ but as a rare exception they may be (*e.g.*, after a dose of mercury) slightly colored. The liver and spleen are both generally enlarged. Death always occurs within eight months. The lesions found in the liver and bile-ducts seem to be the result of a chronic cholangitis, but in some cases no actual obliteration of bile-ducts has been found. The exact site of the obliteration, when present, varies in different cases. Thomson⁸ says: "The inflammatory lesions follow the course of the bile so closely that we can scarcely avoid the conclusion that they are secondary to some irritating change in the character of this fluid. That inspissated bile and gall-stones should have been found is, therefore, of importance. The frequent occurrence of complete stoppage of the passage of bile before there is any absolute anatomical blocking of the lumen of the ducts is also worthy of note, and suggests the possibility of a descending catarrh from irritating bile, such as is said to occur from poisoning by toluyldiamine and other substances (Stadelmann, W. Hunter)." Rolleston and

⁶ J. Thomson: "On Congenital Obliteration of the Bile-ducts," Edinburgh, 1892.

⁷ In regard to fæces the epithet "acholic" is used to signify not merely that they are without bile-pigment, but likewise that they do not contain coloring matter derived from bile-pigment.

⁸ J. Thomson: Allbutt's System of Medicine, 1897, vol. iv, p. 256.

Hayne,⁹ in recording a case of the disease in a child who lived six months, suggested that the disease was primarily started by poisons derived from the mother and conveyed to the liver of the fœtus, and that a mixed cholangitis and cirrhosis was thus set up. This cholangitis, starting in the smaller biliary channels and descending to the larger bile-ducts, might lead, they thought, to the inflammatory obliteration of extrahepatic ducts.

If these views be correct one can easily understand that abortive forms of the disease may occasionally occur from which recovery is possible. Thomson points out that "a few cases of infantile jaundice have been reported as ending in recovery which, from their symptoms, and from their occurring in the same families as other children with obliterated bile-ducts, seem possibly to have been cases of this disease (Anderson, Freund, Grandidier)." At a meeting of the Society for the Study of Diseases in Children on February 16, 1906, F. J. Poynton¹⁰ described two interesting cases of chronic obstructive jaundice in infants aged three months and one month respectively. In his first case the jaundice was present at birth; in the second it appeared on the third day. The liver in both cases was large and not tender. The spleen could not be felt. The stools were generally acholic, large, and fatty, but in both cases occasionally slightly colored. In both cases recovery ultimately took place. Poynton attributed the condition to excessive viscosity of the bile and possibly also unusual smallness of the biliary channels. It seems to me that (allowing Dr. Poynton's explanation to be correct) the viscid condition of the bile and narrowing of bile-channels in cases like those he described might result from a minor form of descending cholangitis of the same type as that which in more advanced degree might produce the characteristic symptoms and fatal progress of so-called "congenital obliteration of the bile-ducts."

It is quite possible that the following case now under my care at the German Hospital belongs to the same class. The patient, Willie W., when aged three months, was admitted (January 25,

⁹ Rolleston and Hayne: "A Case of Congenital Hepatic Cirrhosis with Obliterative Cholangitis," *Brit. Med. Journ.*, 1901, vol. i, p. 758.

¹⁰ Poynton: *Reports of the Society for the Study of Diseases in Children*, London, 1906, vol. vi, p. 173.

1909) suffering from malnutrition and jaundice of moderate degree. According to the mother the child had been jaundiced from birth. Both the mother and the father were said to be healthy. They had had only two other children, who were both living and healthy. There was no other history of jaundice in the family. The mother had had no miscarriages. In the hospital the child's liver was found to be enlarged but not tender to palpation. The spleen could not at first be felt. The faeces were acholic and rather copious. The urine was free from albumin and sugar, but gave a positive Gmelin's reaction for bile-pigment; one or two granular casts were found. The heart and lungs showed nothing abnormal. There was no enlargement of superficial lymphatic glands. No cutaneous, retinal, or other hemorrhages were noted. Blood-examination (January 30, 1909): Hæmoglobin (by Haldane's method) 90 per cent.; red cells 3,900,000 in the cubic millimetre; white cells 9375; the differential count of white cells (kindly made by Dr. J. C. G. Ledingham) gave small lymphocytes 1.4 per cent., large lymphocytes 25.6 per cent., large mononuclears and transitionals 8.4 per cent., neutrophile polymorphonuclears 61.0 per cent., eosinophiles 3.5 per cent., mast-cells 0.1; no nucleated red cells were seen. The average diameter of the red cells seemed to me distinctly above the normal (it was probably above ten micromillimetres, and this would correspond to the high color-index noted (nearly 1.2), and, according to French observers, might be connected with the obstructive jaundice. Moreover, the resistance of the red cells towards hæmolysis, as estimated by Ribierre's method, appeared rather above the normal standard; this again French authorities have maintained to be the general rule in cases of obstructive jaundice. Thus, on January 30, hæmolysis occurred (Ribierre's method) when a few drops of the patient's blood, diluted with normal saline solution, were added to a solution of between 0.34 and 0.36 part per cent. of sodium chloride in distilled water. After admission the child at first lost weight, but has lately gained weight, and looks less shrivelled and much happier. On January 25 the weight was 8 lbs., 8 oz.; on February 1 it was 8 lbs.; and on February 22 it was 9 lbs., 7 oz. The jaundice has very decidedly diminished, though it varies in degree from time to time. The stools are still practically acholic and the urine contains bile; but quite recently, the early part

of March, 1909, a very slight yellow coloration has been observed on several occasions in the faeces. The liver is decidedly enlarged, but not tender, and not much if at all of harder consistence than normal; in the right nipple line it extends downwards nearly to the umbilical level. The spleen seems to have increased in size since admission, for its lower border can be distinctly felt about one inch below the costal margin. The improvement in the child's general condition is, on the whole, so decided that the case may perhaps be one of mild congenital cholangitis with blocking of bile-channels by viscid mucus. Slight fever (up to 100° F.) was noted on four evenings during the first fortnight in the hospital, but lately the temperature has generally been subnormal, and has only once reached 100° F. A little sodium bicarbonate is being given in the hope of rendering the bile less viscid. Asses' milk (recommended by Dr. Poynton¹¹) is difficult to obtain for hospital cases in London.

2. *Inherited Syphilis*.—In the diffuse pericellular (intercellular) cirrhosis of intra-uterine and early postnatal life (a condition which is generally first recognized at post-mortem examination) jaundice may be present. The whole liver is infiltrated with small cells and the local presence of the *Spirochæta pallida* can be demonstrated by proper methods of staining.¹² In older children splenomegaly occurs as a late manifestation of inherited syphilis and is sometimes associated with enlargement of the liver and occasionally with jaundice. The diagnosis may be very difficult, but is sometimes facilitated by signs of syphilis in the bones (*e.g.*, nodes on the tibiæ, by the presence of Hutchinsonian teeth or other "stigmata" of inherited syphilis, by the past history of the case, or by the family history and by the presence of manifestations of inherited syphilis in other children of the same parents; sometimes the diagnosis is only cleared up by the results of antisyphilitic treatment. If Wassermann's serum-reaction for syphilis were found

¹¹ Poynton: *loc. cit.*

¹² The *Spirochæta pallida* was demonstrated in the liver of infants with inherited syphilis soon after the discovery of the organism in question by Schaudinn and Hoffman in 1905. Amongst the more recent papers on the subject see especially "The Occurrence and Distribution of the *Spirochæta pallida* in Congenital Syphilis," by James McIntosh, *Journ. of Path. and Bact.*, Cambridge, 1909, vol. xiii, pp. 239-247.

to give reliable results it would be of great diagnostic use in these cases. Dr. Robert Hutchison¹³ thinks that in children with splenomegaly as a late manifestation of inherited syphilis the splenic disease is sometimes accompanied by a gummatous enlargement or syphilitic cirrhosis of the liver. As a possible example of such an association and as illustrating the difficulty in diagnosis in the absence of undoubted signs of inherited syphilis, I will give the following short account of a case now under my care, though at the present moment the enlargement of the spleen and liver is not accompanied by jaundice.

The patient, J. B.,¹⁴ a boy aged 11 years, was admitted to the German Hospital in December, 1908, with chronic enlargement of the liver and spleen, and having a rather cachectic appearance, though not really anæmic. The liver bulged forwards in the epigastric region and its lower edge could be felt two finger-breadths below the costal margin in the right nipple line. The spleen was easily felt; it was of rather hard consistence, and reached two or three finger-breadths below the ribs. The thoracic organs showed nothing abnormal, except slight impairment of resonance at the apex of the left lung. Skiagrams (Dr. Finzi) of the lungs gave no evidence of disease at either apex. There was slight nasal obstruction, apparently due to chronic nasal catarrh and some dried blood in the nasal fossæ. No adenoid vegetations (Mr. G. F. Jenkins) or hypertrophy of tonsils were found. A few small lymphatic glands could be felt in the neck, but otherwise there was no enlargement of the superficial glands. The teeth were not well-formed, but were not distinctly "Hutchinsonian." There was a decided tendency to frequent slight bleeding from the lips or gums and from the nose (not regular epistaxis). There were a few hair-like telangiectases on the face and a small "spider-telangiectasis" on the chin. There was no jaundice and no œdema. Ophthalmoscopic examination showed nothing abnormal in the fundi (Dr. C. Markus). There was no fever. The bowels were regular. Urine:

¹³ See his remarks on splenomegaly as a late manifestation of inherited syphilis in the Discussion on Non-leukæmic Enlargements of the Spleen at the Annual Meeting of the British Medical Association, 1908 (*British Medical Journal*, 1908, vol. ii, p. 1156).

¹⁴ This patient was shown by me at the Medical Society of London February 8, 1909.

specific gravity 1016; acid; free from albumin and sugar. Examination of the blood (December 15, 1908) showed: red cells 6,000,000, and white cells 7000 in the cubic millimetre; hæmoglobin (by Haldane's method) 100 per cent. A differential count of 500 white cells (kindly made by Dr. A. E. Boycott) gave: lymphocytes 47.4 per cent.; intermediates 7.0 per cent.; large hyalines 4.0 per cent.; neutrophile polymorphonuclears 37.2 per cent.; eosinophiles 1.4 per cent.; mast-cells 3.0 per cent. No nucleated red cells were seen; the red cells seemed normal. Examination of the blood by Ribierre's method showed that there was no diminished resistance of the red cells to hæmolysis. Calmette's ophthalmoreaction for tuberculosis and Von Pirquet's cutireaction both gave a negative result.

In the hospital under treatment by a medicine containing iodide of iron and iodide of potassium the boy's general health has decidedly improved; he has put on flesh and has become more cheerful-looking; his liver has somewhat diminished in size and his spleen though still moderately enlarged does not feel hard. On different occasions the number of red cells in his blood has been found to vary between 5,500,000 and 7,000,000 to the cubic millimetre. This slight degree of polycythæmia may be in whole or part secondary to nasal obstruction, but it may likewise be in some way connected with circulatory obstruction from abdominal visceral disease.

According to the patient's mother the boy had pneumonia and pleurisy in the summer of 1907, and again in the summer of 1908. In 1907 his eyes had a yellowish color, she thinks. For a year or so his abdomen has been rather prominent. There is no history of a rash or skin-eruption during infancy, but he had rather a tendency to snuffles. The mother thinks she herself has always been healthy. She has been married twice. By her first husband she had three children, who are still living and healthy; none born dead; no miscarriages. By her present husband (said to be healthy) her first two children (seen by Dr. Weber) are apparently healthy; the third one is the present patient. Since his birth she has had one child born dead, and one miscarriage.

3. *Biliary Cirrhosis (Hanot's Disease).*—There is a form of hepatic cirrhosis, accompanied by jaundice and (usually great) enlargement of the spleen, which may be termed "biliary" cir-

rhosis, though in the livers from such cases when they finally come to be examined at necropsies the cirrhotic process is seldom or never strictly unilobular, excepting at spots here and there. The disease is mainly one of childhood and the period of growth, but may commence in later years (as in Hanot's original cases). The usual features are: Jaundice, which is generally deep, but varies from time to time, increasing with exacerbations of the disease; enlargement and hardness of the liver; enlargement (often extreme) of the spleen. There is generally a great tendency to bleeding from the nose, gums, etc. The fæces are generally not completely acholic, though the urine is rich in bile-pigment. Ascites, when it occurs, is usually a terminal phenomenon. When the disease commences early in life it leads to stunting of the child's growth by partial arrest of development or infantilism. In some cases "clubbing" of the fingers has been observed. This type of cirrhosis, like some other forms of jaundice and hepatic disease, occasionally occurs in two or more members of the same family.

In regard to the size of the liver, though the organ is always enlarged in the typical cases, there seems to be no doubt that it may shrink, as in other forms of cirrhosis, provided that the patient lives long enough. This is, I believe, what took place in the following case:¹⁵

The patient, a girl, J. S., aged 14 years, was under my care at the German Hospital, where she died in February, 1895. She had, her father thought, been more or less jaundiced all her life, and had always been weakly and thin, though she had never had any serious acute illness. She had, I think, repeatedly had bleeding from the nose and gums. She was extremely ill-developed for her age, and looked very much younger than she really was. Her skin was jaundiced and likewise much darkened from chronic pigmentation; there were two or three capillary "stigmata" ("spider-telangiectases"). The liver could be felt considerably below the costal margin, but the spleen was excessively large, reaching a point below the anterior superior iliac spine. There was irregular fever

¹⁵ See F. P. Weber: "Simple Persistent and Congenital Persistent Jaundice, Family Biliary Cirrhosis, and Family Tendency to Jaundice," *Edinburgh Medical Journal*, August, 1903, pp. 111-120. This paper contains many references to French and other literature on biliary cirrhosis in children.

and, during the last weeks, ascites. One sister was said to have become jaundiced at about the age of thirteen years and to have died at nineteen years with symptoms somewhat resembling those of J. S. At the necropsy on the latter the liver was green, hard, and "hobnailed." Perhaps I ought to have described it as having an irregular, scarcely amounting to hobnailed, surface. It only weighed $26\frac{1}{2}$ ounces. Microscopic examination of the sections showed a large amount of fibrous cicatricial tissue, dividing the glandular substance into unequal compartments and sometimes invading the lobules, entering between the individual hepatic cells. There was a good deal of small-cell infiltration in the scar-tissue, showing the progressive nature of the disease. There was no very great increase of bile-canaliculi, but much green inspissated bile could be seen situated between or in the hepatic cells, which, on the whole, appeared to contain relatively little fat. The gall-bladder contained a moderate amount of clear, almost colorless, fluid. The common bile-duct was unfortunately not examined. There was no perihepatitis. The spleen, uniformly enlarged, weighed $20\frac{1}{2}$ ounces; on section its substance seemed rather firm, but otherwise normal; the microscope showed increase in fibrous tissue, and considerable deposit of pigment in some of the trabeculae. The lymph-glands, especially those at the hilum of the liver, were somewhat enlarged and much pigmented.

In the case (J. S.) the long duration of the disease and its early (possibly congenital or even antenatal) commencement are specially to be noted. Hence the growth and development of the whole body were impaired or partially arrested. The "hypertrophic" cirrhosis had time to become to some extent "atrophic" owing to the gradual contraction of scar-tissue. Doubtless the nodules which gave the surface of the liver an almost "hobnailed" appearance represented a compensatory attempt at regeneration of the glandular tissue of the organ.

In regard to the pathology of biliary cirrhosis I am in favor of regarding the disease as due to an "excretory" irritation of the hepatic glandular cells and minute bile-ducts resulting from the excretion by the hepatic cells of some toxic material or materials of unknown origin and unknown nature. H. D. Rolleston suggested that the "excretory" irritation in question might be due to

a poison arriving by the blood, as in experimental poisoning with toluylendiamine and other substances in animals (Stadelmann, W. Hunter). This theory amply accounts for the main difference between ordinary cirrhosis and cirrhosis of Hanot's type. In the latter form of cirrhosis large numbers of the minute bile-capillaries probably become blocked with plugs of inspissated mucus, so that, although bile from many hepatic lobules can usually still reach the intestine and for long periods prevent the fæces from becoming acholic, the clinical picture is as much one of chronic obstructive jaundice as it is of hepatic cirrhosis. One can also easily understand that (owing to secondary malnutrition and toxæmia) in the later stages of the disease the anatomical features of ordinary multilobular cirrhosis become grafted on those of unilobular cirrhosis; the irregularity of the cirrhotic process may be further increased by the development of nodular regenerative changes in the surviving glandular parenchyma. According to this view some of the features of Hanot's disease are those of cirrhosis of the hepatic parenchyma whilst some are those of exceedingly chronic obstructive jaundice, such as follow occlusion of bile-ducts by experimental ligature or otherwise, or rather, such as would follow occlusion of many of the minute intrahepatic biliary channels by chronic inflammatory changes and plugging with inspissated bile.

4. *Chronic Acholuric Jaundice with Enlargement of the Spleen or of Both the Spleen and Liver.*

A case of acholuric jaundice simply means a case of jaundice in which no bilirubin can be detected in the urine. In such cases urobilin is usually present in excess in the urine, and the term "urobilin icterus" was used (especially in Germany) to signify the condition in question when it was supposed that urobilin in the blood was the cause of the yellow coloration of the skin and conjunctivæ. Now that bilirubin, though absent (or only exceptionally and temporarily present) in the urine, has been shown to be constantly present in the blood is known to be the cause of the jaundice, the term "acholuric jaundice" or "acholuric icterus" has obviously become preferable to the term "urobilin icterus." Chronic acholuric jaundice is generally accompanied by enlargement of the spleen or both the spleen and the liver. It may occur in early life as a congenital or familial, or both congenital and

familial, peculiarity, or may be acquired in later life. Amongst cases of chronic acholuric jaundice without enlargement of the spleen or liver the series of congenital and familial cases described by Alois Pick¹⁶ is probably to be included. He recorded the case of a strongly built man, jaundiced from birth, who had one brother aged seventeen years, and one sister aged twenty-six years, both likewise jaundiced from birth. In all three the urine contained urobilin but no bilirubin, the faeces were of natural color, and there seemed to be no great, if any, enlargement of liver or spleen. The mother of these three patients, who died when thirty-five years old at her tenth confinement, was likewise said to have been jaundiced from birth.

Chronic acholuric jaundice is nearly always accompanied by more or less decided anæmia, but polycythæmia (excess of red blood-cells) has likewise been recorded. Thus Guinon, Rist, and Simon¹⁷ described the case of a girl, aged ten years, with chronic acholuric jaundice of variable degree, urobilinuria, and chronic splenomegaly; transitory cyanosis and polycythæmia (6,000,000 to 7,600,000 red cells in the cubic millimetre of blood) accompanied an exacerbation of the jaundice. Mosse¹⁸ described the case of a man, aged 58 years, with chronic acholuric jaundice, urobilinuria, and chronic splenomegaly, whose red blood-cells numbered 6,750,000 to 7,825,000 in the cubic millimetre of blood. The anæmia, in the acquired cases at least, may occasionally be of a very severe degree and associated with the presence of megaloblasts¹⁹ in the circulating blood so as temporarily to simulate the blood-picture of pernicious anæmia; the diagnosis of such cases from pernicious anæmia (with enlargement of the spleen) may of course be very difficult. Another difficulty which sometimes arises is to distinguish cases of chronic acholuric jaundice with splenomegaly from cases of splenic anæmia (that is to say, from the adult type of splenic anæmia). It is indeed almost certain that the jaundice

¹⁶ Alois Pick: Wiener klin. Wochenschrift, 1903, No. 17, p. 493.

¹⁷ Guinon, Rist, and Simon: Bull. de la Soc. Méd. des Hôpitaux de Paris, 1904, 3rd Series, vol. xxi, p. 786.

¹⁸ M. Mosse: Deut. Med. Wochenschrift, Berlin, 1907, vol. ~~xxxv~~, p. 2175.

¹⁹ Cf. F. P. Weber: "A Case of Acquired Chronic Acholuric Jaundice with a Blood-picture at One Time Resembling that of Pernicious Anæmia," Medical Society of London, Meeting of February 8, 1909.

may altogether disappear for a time so as to leave the case one of what can be termed "chronic splenomegaly with anæmia" or "chronic splenomegalic anæmia."²⁰ Thus, in the case (Ernest N.) described at the commencement of this paper it is to be noted that the boy himself suffers from a form of chronic acholuric jaundice with splenomegaly and anæmia, but sometimes the jaundice is hardly recognizable by ordinary inspection; moreover one of his sisters suffered from chronic splenomegaly with anæmia without actual jaundice. In other words, it appears almost certain that a form of "splenomegalic anæmia" without jaundice may alternate with "splenomegalic acholuric jaundice" in the same patient; and it is certain that in a single family one member may be affected with splenomegalic acholuric jaundice and another with splenomegalic anæmia (without jaundice).²¹ On the French "hæmolytic" theory, to which we shall subsequently allude, such cases without jaundice might be classified as representing an incomplete form ("*forme fruste*") of typical ("*complete*") cases with jaundice.

Amongst the clinical characteristics of chronic acholuric jaundice which have been specially investigated by French authors, including Hayem, Gilbert, Lereboullet, Herscher, A. Chauffard, Widai, Abrami, Vaquez, etc., there are several points which we have not yet sufficiently considered. The jaundice, besides being usually very slight, differs also from that of obstructive jaundice in not being associated with bilious urine, acholic fæces, icteric pruritus, or xanthoma. It seems as if a little bile-pigment (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, there may be temporary exacerbations of the jaundice, during which a trace of bile may (as a quite exceptional occurrence) be detected in the urine. According to A. Gilbert, P. Lereboullet, and M. Herscher²² the blood-serum of healthy

²⁰ Cf. Armand-Delille and Feuillié: "Un cas d'anémie splénomégaly avec fragilité globulaire," Soc. Méd. des hôpitaux de Paris, February 2, 1909, and discussion which followed the exhibition of the case.

²¹ Cf. Chauffard and Troisier: "Des rapports de certaines anémies splénomégalyques avec l'ictère hémolytique congénital," Soc. Méd. des hôpitaux de Paris, February 19, 1909.

²² Gilbert, Lereboullet, et Herscher: Bull. et Mém. de la Soc. Méd. des Hôpitaux de Paris, Séance de 15 Nov., 1907.

normal individuals contains on the average one gramme of bilirubin in 36 litres; but H. P. Hawkins and L. S. Dudgeon²³ say: "The experience of the Clinical Laboratory of St. Thomas's Hospital shows no such frequent presence of bile-pigment in the serum. From an examination of a very considerable number of sera obtained from all possible sources it may be said that bile-pigment is present only in the serum of patients obviously jaundiced or in the serum of patients in whom jaundice is just going to appear." Bile-pigment can always be found in the blood-serum of patients with acholuric jaundice.

The subjective symptoms of these patients are chiefly those of anæmia. 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 and sometimes by moderate fever. All the symptoms, as already mentioned, tend to be more severe in the acquired cases in adults than in the congenital and familial cases. It seems as if the cause of the disease (whatever this may be) is more successfully resisted or neutralized in the young patients (that is to say, in the congenital and familial cases that survive) than in patients who acquire the disease in adult life.

The blood-condition in this disease requires special attention. We have already alluded to the nearly constant presence of anæmia and to its variation in degree from time to time according to the severity of the disease; but there are other points which have been specially insisted on by French authors. In the first place there are nearly always a few, occasionally a good many, nucleated red cells to be discovered on microscopic examination of blood-films. These are mostly ordinary normoblasts, but there may likewise be microblasts and in very severe cases (especially in cases of the acquired class) there may be typical megaloblasts present of the "pernicious anæmia" type. The red corpuscles, though fairly normal in shape, vary too much the one from the other in size ("anisocytosis"), and a good many of them usually show polychromatophilia or granular basophilia. The average diameter of the red cells and the color-index are if anything below the normal standard, whereas they are if anything above it in cases of ordinary

²³ Hawkins and Dudgeon: *Quarterly Journal of Medicine*, Oxford, 1909, vol. ii, p. 172.

obstructive jaundice. According to French observations, at least in most of the cases, the red cells show abnormally low resistance to hæmolysis, whereas in chronic obstructive jaundice the rule is for the resistance of the red cells to be above the normal. That is to say, it usually takes a lesser proportion of distilled water to produce hæmolysis in blood withdrawn from these patients with chronic acholuric jaundice than it does in the blood of normal individuals. The abnormal tendency to hæmolysis can be best demonstrated, it is said, when the test is applied to the red cells previously freed from their blood-plasma.

Returning now to the case (Ernest N.) described at the commencement of this paper, we must on the whole regard it as a fairly typical case of splenomegalic chronic acholuric jaundice commencing in early life (probably congenital and familial), though the evidence as to the presence of an abnormally great tendency to hæmolysis is not decisive. It must be acknowledged that a "hæmolytic theory" of the disease, such as was first suggested by Minkowski²⁴ and later on was founded on a firmer basis by A. Chauffard²⁵ and others in France, best suits the facts observed in these cases. One can understand that in addition to the typical cases of chronic (permanent) acholuric jaundice (including those recently described by Hawkins and Dudgeon²⁶ with anæmia and splenomegaly (and possibly hepatomegaly), there are others really of the same pathogeny showing splenomegaly (and possibly hepatomegaly) with anæmia but without jaundice²⁷ or with only occa-

²⁴ O. Minkowski: "Ueber eine hereditäre unter dem Bilde eines chronischen Icterus mit Urobilinurie, Splenomegalie, und Nierensiderosis verlaufende Affection," *Verhandl. des Kongresses für inn. Med.*, Wiesbaden, 1900, xviii, p. 316.

²⁵ A. Chauffard, *Semaine Médicale*, Paris, January 16, 1907, p. 25; and later writings by himself and numerous other observers in France.

²⁶ Hawkins and Dudgeon: *loc. cit.*

²⁷ Armand-Delille and Feuillie: *loc. cit.* The sister of Ernest N. (the case described at the commencement of the present paper) was an example of splenomegaly with anæmia and without actual jaundice, according to Dr. Parkinson's description (already alluded to); but doubtless bile-pigment would have been found present in her blood had it been tested for, as it was later on in her brother's case. Similarly, A. Chauffard and J. Troisier (*loc. cit.*) describe the cases of a mother and son both showing splenomegaly and a blood-picture of "hæmolytic jaundice," but the son is not clinically jaundiced, though his blood-serum contains bile-pigment, just as does that of his mother, who is obviously jaundiced.

sional attacks of jaundice, as perhaps the cases described by Barlow and Batty Shaw,²⁸ and one or more of the family series described earlier by Claude Wilson²⁹ and yet others perhaps showing chronic acholuric jaundice without obvious splenomegaly or hepatomegaly (such as A. Pick's cases already referred to).

Of the pathological anatomy and histology of cases of chronic splenomegalic acholuric jaundice and of the allied cases of "splenomegalic anæmia" without jaundice very little seems to be known, specially in regard to the congenital and familial cases. It is by no means certain that all the cases are identical from the pathological-anatomical and histological point of view. In the congenital and family cases the question may be asked, Is the splenic enlargement ever of the "Gaucher type," that is to say, is it ever characterized by a diffuse growth of the kind of cells which have rightly or wrongly been described as "endothelioid," *i.e.*, cells characterized by a small pyknotic nucleus and apparent excess and unusual transparency of cytoplasm? The Gaucher type of splenomegaly has sometimes occurred in more than one member of the same family, and has moreover sometimes been associated with a yellow coloration of the skin.

In regard to familial cases of chronic acholuric jaundice it seems certain that, though cases of biliary cirrhosis (Hanot's disease) may probably occur in the same family, there is as yet no well-authenticated instance of a typical case of familial splenomegalic acholuric jaundice, or of the allied form of "splenomegalic anæmia," having subsequently developed hepatic cirrhosis and ascites. Therefore the splenomegaly of these families (whether accompanied or not by temporary or permanent acholuric jaundice), though associated with anæmia and constituting a form of "splenomegalic anæmia," must be sharply distinguished from the cases of "splenic anæmia" ("adult splenic anæmia") which ultimately develop hepatic cirrhosis and the symptom-complex of "Banti's disease."

²⁸ Barlow and Batty Shaw: "Inheritance of Recurrent Attacks of Jaundice and of Abdominal Crises, with Hepato-splenomegaly," *Clinical Society's Transactions*, London, 1902, vol. xxxv, p. 155.

²⁹ Claude Wilson: *Clinical Society's Transactions*, London, vol. xxiii, p. 162, and vol. xxvi, p. 163.

DIABETES *

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DIABETES—*diabetes mellitus*—is a disease characterized by glycosuria and hyperglycæmia due to hypoglycolysis, probably from insufficiency of the pancreatic and of the muscular or other glycolytic secretions.

Historically we may infer from the writings of Aretæus, Celsus, Galen and others that they were acquainted with diabetes as a rare affection in Rome in their day. Christie asserts that Cingalese physicians of the fifteenth century spoke of "honey urine." Willis taught at Oxford in the middle of the seventeenth century that the sweetness of diabetic urine was due to sugar, the actual presence of which was demonstrated by Dobson in 1775. The latter also stated that the serum of the blood in his case was sweet; but Ambrosius, in 1835, first extracted sugar from the blood of a diabetic, which others soon after showed to be an excess, rather than a mere presence. Disease of the pancreas with diabetes first appears in the literature with Cawley's report of a case in 1788, which connection has been further developed by Lancereaux, 1877; Von Mering and Minkowski, 1890; Opie, 1901. Rollo, in 1797, advocated a meat diet in the management of diabetes, and Warren, in 1812, extolled the virtues of opium in its treatment. Larrey, in 1820, observed glycosuria following cerebral injury; and Bernard, in 1849, regularly produced this result by injuring portions of the floor of the fourth ventricle. This acute observer also noted, in 1857, the glycogenic function of the liver. Cohnheim, in 1903, demonstrated the interdependence of the pancreatic and muscular glycolytic secretions.

Etiologically you may note that although diabetes is not common, yet it is increasing in prevalence and is an important malady.

* The substance of clinical lectures given in the Cook County Hospital, Chicago, Autumn, 1908.