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Etiology, diagnosis and pathology of hemolytic jaundice

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The
Etiology, Diagnosis and Pathology
of
Hemolytic Jaundice

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INTRODUCTION

Hemolytic jaundice is a relatively recent clinical entity of unknown etioloty, and with classical symptoms, is readily diagnosed. It may, however, be one of the most confusing subjects in medicine, for in this field, the disease may simulate a variety of pictures which tend toward a wrong diagnosis. The reason for this confusion is not hard to find, for the disease, clinically, presents symptoms and complications not unlike other common diseases. The complications may alter the true picture, so that clinically, the diagnosis is difficult. On the other hand, the hematological picture may be confused with numerous blood dyscrasias. In these cases, fragility tests are at times, the only means of differentiation. Inadequate knowledge of blood diseases and insufficient laboratory equipment of the ordinary medical men, are further barriers to an accurate diagnosis of this disease.

Since the first accurate description of the disease by Minkowski in 1900, the disease has been called acholuric icterus, chronic familial jaundice, hemolytic splenomegaly, and chronic infectious jaundice with splenomegaly. This variety of terminology, undoubtedly, has offered some confusion in diagnosis.

The disease may be defined as a chronic microcytic

anemia, characterized by increased fragility of the red cells, reticulocytosis, acholuric icterus, and splenomegaly.

The importance of clinical features of the disease, in the presence of complications and the importance of laboratory studies, cannot be too strongly stressed. Without these studies, an accurate diagnosis many times cannot be made, especially when the disease simulates other conditions. For this reason, emphasis in this paper deals especially with the etiology, diagnosis, and pathology of hemolytic jaundice.

HISTORY

Murchinson in 1885 reported different members of the same families suffering from hereditary jaundice, without enlargement of the liver or spleen, but without data as to the blood picture.(1) From the clear clinical history he gave of these cases, he must have had the hemolytic form of jaundice in mind.(1) Several years later in 1890, Wilson of England gave a clear description of the syndrome in his report, representing three generations.(1) In 1898 hemolytic icterus was first established as a clinical entity by Hayem.(2) He stated, "That, aside from the types of chronic jaundice caused by obstruction of the bile ducts or compression by tumor and by hypertrophic biliary sclerosis, there were other types of the disease that were little understood." He then described five cases of icterus with very large spleens and a marked chronic anemia, the red cells varying in numbers from 2,493,000 to 6,320,000 per cu. mm., and he classified this variety as of a markedly hemolytic type with crises of varying intensity and duration. Bile pigment was present in the blood serum, but not in the urine, and the itching and clay colored feces found in other types of icterus, were lacking. He proposed to name the disease, "Chronic infectious splenomegalic jaundice of a paroxysmal type."(2)

According to Tiletson,(3) credit for the first accurate description of the familial disease is given to Minkowski in 1900. The outstanding freatures were hereditary, chronic icterus, without bile in the urine, persistant enlargement of the spleen; onset of symptoms at birth or in early childhood, lasting for years and as a rule not shortening life.(4) It was not until 1907 that Chaufford recognized the significant blood changes of excessive fragility of the erythrocytes, their deminution in size (microcytes) and the increased number of circulating reticulated red cells.(5)

Several years later, Widal 1909, believed all cases were not hereditary in origin and described an acquired form of the disease strongly stressing the hemolytic process. Since that time the disease has been divided into a hereditary (Minkowski-Chauford), and the acquired (Widal-Abrami), types. A few authors describe a congenital form but this group undoubtedly had the hereditary form in mind. The following important contributions to this disease were made by Tiletson and Griffin(3) 1910 and Thayer and Morris(6) 1911. Since this work, numerous articles have appeared in both foreign and Americal literature. Dawson (7) 1931 probably has made the most important recent contributions to this disease.

ETIOLOGY

The etiology is obscure. Sexes are affected equally and there is no racial or geographical distribution. There appears to be a distinct hereditary transmission being handed down equally by male and female. According to Sharpe(5), Naegeli, Haden, and others, believed that the bene marrow produces an abnormally small, thick, spherical fragile red cell, which is more susceptible to disruption and fragmentation that the ordinary erythrocyte. The spleen, thereby, becomes more hyperplastic, as a result of destroying these congenitally poor red cells of hemolytic jaundice; there fore, they believed that the anemia, jaundice, splenomegaly, reticulocytosis, and increased fragility, were all secondary to this inherit sphere shaped erythrocyte.

Doan, et al(8) 1934, believed that the phagocytic action of the spleen on the red blood cells, was the principle pathological agent that produced quantitative changes in the erythrocytes, and that the hyperplasia of the bone marrow was secondary, responding to the need of more red blood cells.

In England, Hawksley and Bailey, (9) believed there was already an abnormal red cell in the blood stream, that became further distorted by the spleen Sturgis, et al, (10) were of similar opinion, stating that the size

and shape of the red blood cell was an hereditary expression of the disease.

In view of the fact that there is a persistant high reticulocyte count, it is impossible to maintain that failure of the bone marrow, in the production of red blood cells, is the cause of this disease.(11) Opposing the primary hemolytic role of the spleen, is the fact that in many cases, increased fragility of the erythrocytes persists after splenectomy, and produces a virtual cure in every respect.(11)

Early observers believed the disease to be due to syphilis, congenital communication between the passages and lymphatics, infections, and unknown toxins. Acute hemolytic anemias also occur as a result of food intoxication, as in the disease known as "Fabismo" in Italy, and in certain infections such as those due to Bartonella muris, B. welchi, and possibly B. perfringens.(12) These conditions, although producing an acute hemolytic anemia, are distinct from the true chronic hemolytic anemia under discussion.

According to Thayer and Morris,(6) Troisier supported the hypothesis that the fragility of the corpuscles was dependent upon the fact that they had already become sensitized by union with a hemolytic amboceptor.

In my opinion, and in the opinion of several of the

staff of the University of Nebraska, the most logical cause of this disease, is the inherited abnormal red blood cell. McNee,(13) of the same opinion, stated that if would seem probable that the disorder existed in erythrocytes themselves and that the splenic enlargement was simply the hypertrophic responce of the over worked phagocytic reticulo-endothelial cells. Witts(14) further emphasized this fact by stating that acholuric jaundice was dependent upon the presence of an abnormal type of corpuscle that was ill-adapted to life in the blood stream, but the factors which determined the degree of variations of hemolysis were obscure.

Since the time of Widal's work in 1907, the disease has been divided into an hereditary and acquired type. Black, (15) as late as 1930, and others, even up to the present day, divided hemolytic jaundice into these two types. He stated that the general impression was that the acquired type resulted from some toxin or infectious process. Many theories have been expressed giving etiology to the acquired form of the disease. The majority of men, especially those who have done the most extensive work on this disease, believe that all cases have an hereditary background. Cheney and Cheney (4) agreed with Ganeslen's conclusion, that patients inherit a "hemolytic constitution". According to Cheney and Cheney

(4) Gansslen believed that the so-called acquired cases were born with a "hemolytic constitution", and that any kind of disturbance later on, such as unfavorable conditions of living, acute or chronic infections or trauma, may destroy the compensation by which health was maintained in spite of their defect, and so precipitate these symptoms and signs of hemolytic jaundice. Whitcher, (2) in quoting Naegeli, regarded these microcytes as belonging to a peculiar type of red corpuscle which was inherited, and concluded that these inherited microcytes indicated a distinct type of human species. All men agree with two rules, that inheritance is only through the affected and the corollary that once free, always free, is true of any branch of the family.(16) Campbell and Warner (16) stated that the abnormal fragility of the red cells may occur without the other signs and symptoms of acholuric jaundice both in oridnary cases after splenectomy and in latent cases. Where due allowance is made for these, acholuric jaundice is inherited as a "dominant Mendalian character". Smith (17) reported a case of four generations of jaundice of the hemolytic type. Tallerman(18) reported an hemolytic icterus family in which he found three and possibly four generations of manifestations of the disease.

If search is made into families of hemolytic jaund-

ice patients, and especially if fragility tests are made on other members of the family, usually an increased fragility is found with or without other manifestations of the disease in some member of the family. It is known in many cases that there is a trigger mechanism which converts latent into acute cases of acholuric jaundice.(19) Hawksley (20) made a diagnosis of hemolytic jaundice from an hemolytic jaundice family of an infant 4½ months old by following the fragility tests before clinical signs of the disease appeared. We can probably justly say, that the more closely hemolytic icterus is studied, the more does doubt grow as to whether in a strict sense, an acquired form of the disease exists.

DIAGNOSIS

In typical cases the diagnosis of this disease is relatively simple. The old rule of a thorough history, complete physical examination and a careful study of the blood still seems the best aid in differentiating hemolytic jaundice from other blood dyscrasias.(5) The characteristic findings are; an increase of bile pigment in the blood, but not in the urine, jaundice, increased fragility of the erythrocytes, splenomegaly, anemia, increase in erythropoiesis with marked increase of reticulocytes in the blood, fertile exacerbations and after a familial occurence.(11) Absence of one or several of these findings, latent cases and complications, which are not uncommon, many times make the diagnosis difficult. Cheney and Cheney(4) believed that the occurence of a pronounced microcytosis in the presence of jaundice, whether clinical or latent, may be considered almost diagnostic of chronic hemolytic jaundice. Doan et al(8) considered the pathognomonic trial of the disease to be microcytosis, increased fragility and a high sustained reticulocyte level. Sear, quoted by Wade and Steigrad,(21) found osseous changes in association with this disease and believed the three cardinal points of the disease to be, anemia, enlargement of the spleen and changes in the osseous system.

Probably a better understanding as to diagnosis of hemolytic jaundice may be obtained if symptoms and complications be discussed at this time without specific stress on laboratory findings, which will be considered later.

The disease may take on variable clinical manifestations. Some individuals hardly know they have the disease, while others become chronic invalids. Symptoms may vary in intensity in the same individual from day to day, and in different individuals of the same family. The disease may be divided into acute, latent and chronic cases. Many times the same individual will show acute, latent and chronic symptoms.

The acute cases are individuals that probably have had the disease all their life but suddenly have an acute exacerbation of symptoms that make the disease apparent. These acute exacerbations are known as "acute hemoclastic crises." The crises is characterized by a sudden onset of upper abdominal pain, nausea, vomiting and fever, accompanied by a marked weakness with an intensification of jaundice and pallor, an increasing enlargement of the spleen, and a sharp drop in blood count.(5) During these attacks, the degree of jaundice and size of spleen may vary from hour to hour.(22) Numerous causes have been attributed to this condition as dietary indiscretions,

acute infections, menstruation, pregnancy, high altitudes and surgical procedures. The crises may occur repeatedly or may be separated by long remissions. They are usually milder during childhood and more severe in later life.(23) The additional load of pregancy may serve to "light up" a latent case of hemolytic jaundice, or cause an acute exacerbation of a chronic form of the disease.(5) Dawson (7) believed that the liability to severe hemolytic crises with short or no warning in this disease should be born in mind. In his series seven cases showed this feature and three of these died during the crises. Cheney and Cheney(4) explained the crises as a result of destruction in the spleen of a larger amount of red blood corpuscles than ordinarily takes place, occuring more rapidly than the hyperfunctioning bone marrow can replace the loss. To emphasize the importance of emotional stress in these cases as etiological factors in bringing on a "crises", Scott(22) reported the serial onset of hemolytic crises in an entire family, probably accounted for by emotional excitement.

Since an hereditary abnormal red cell is considered the outstanding etiological factor in this disease, certain members of an hemolytic jaundice family may enjoy perfect health without showing any clinical signs of the disease; but when the blood of these people is examined,

the characteristic small red cells and an increased fragility of their red cells may be found. These cases are known as the so-called latent or "formes fruste" type. Certain people of this type may live a life time without showing symptoms of the disease, while others, anytime during their life time, may show an acute exacerbation of the disease or pass into the chronic stage. Aaron(1) stated that the diagnosis of the latent forms of hemolytic jaundice was made through the Van-den-Berg method, which shows an increased bilirubin content of the blood serum.

The chronic form of the disease is the usual type found, and the term "chronic hemolytic jaundice" was named after this type. Chronic cases may complain chiefly of undue fatigue and weariness, while in the presence of anemia, such symptoms are dyspnea, palpitation, and dizziness may appear.(5) Epistaxis may be noted, usually in children. Typical of the more severe cases, are jaundice and splenomegaly.(5) Occassionaly in the chronic form, the only complaint amy be pain over the spleen.(19)

Jaundice is one of the outstanding clinical signs of the disease. It may be the first symptom noted, or may be entirely absent for years(24). When present, it is never very intense and is not accompanied by toxemia, pruritis, bradycardia, or hemorrhagic tendencies, which

are so common with the obstructive type. The jaundice in this disease, is extra-hepatic in origin, resulting from the hemolysis of the erythrocytes by the reticulo-endothelial system, chiefly the spleen.(5) The blood contains an increased bilirubin content without the presence of bile salts. The jaundice depends on the excretory capacity of the liver cells, so that even in the presence of active hemolysis with a moderately severe anemia, jaundice may be absent if the liver function is efficient.(8) The jaundice is usually slight, more of a sallowness, rather than a true icterus. In other instances, however, it may be as deep as that seen in obstructive jaundice. It's intensity is changeable, varying at different periods like the anemia.(4) There is no parallelism between the jaundice and the anemia. In some instances they may agree, but in others, the deep pigmentation may be noted in the absence of anemia. The disparity of anemia and jaundice is explained by the fact that while hemolysis is responsible in this disease for both the anemia and the icterus, the visible degree of either depends upon the functional capacity at the time, of the bone marrow and the liver.(4) Factors which have b been described as being responsible for the acute exacerbation of the disease, may also be responsible for the intensification of the jaundice. Increase of the jaundice

has sometimes been noted in connection with pregnancy.(24)

Another classical sign of the disease is splenomegaly. As a rule the spleen is enlarged, though the degree varies greatly. Gansslen(39) reported asshigh as 30 per cent of his cases without splenic enlargement. Lower percentages are reported in American literature. Weber(24) stated that an enlargement of the spleen may be one of the first signs of the disease. It's size varies in the individual patient with the severity of the condition at the time, fluctuating with remissions and exacerbations of the disease.(14) During a crises, the spleen is always larger, firmer, and more tender; after the crises is over, it rapidly subsides.(4) The spleen, in definite cases, may be very large, though it is never enormous in size as the spleen of leukemia or splenic anemia. (25) With increase in size, and stretching of the capsule of the spleen, the patient may complain of a dull aching in the left quadrant and back.

A few patients may experience transient attacks of fever and abdominal pain, which may be due to perisplenitis or splenic infarction, in which case a friction rub may be heard over the splenic area.(24)

It has been estimated that sixty per cent of all cases of hemolytic jaundice are complicated by disease of the gall bladder, with or without stones.(26,27)

Because of this high incidence, symptoms referable to the gall bladder, bring these patients in for treatment. Previously, in many instances, cholecystectomies have been performed on these patients without apparent understanding of the true condition of the disease. Usually, gall bladder disease masks many of the clinical symptoms, so that it is important that careful histories and blood studies by made. It must also be remembered that abdominal pains in these subjects should not, however, be too readily regarded as due to cholelithiasis, since pain, due to perisplenitis or to splenic infarction, may confuse the picture.(24) The high incidence of biliary disease was best explained by Rich,(28) who pointed out that anoxemia, resulting from an associated anemia induces partial suppression of liver function, thereby diminishing it's capacity to excrete the increased bilirubin from the blood stream.(5)

Occasionally these patients have chronic ulcers, usually on the lower extremities, which are very resistant to treatment. Many times these ulcers are cured only by a splenectomy. With this fact in mind, chronic hemolytic jaundice should be considered, where no apparent cause of the ulcers can be found. Eppinger(29) has emphasized the complication of chronic ulcers that have occured about the feet, and believed they may be

the only outward sign in latent cases. In Weber's(24) series of seven cases, leg ulcers were present in three of these cases. McNee(13) believed that such ulcers occured in a number of cases of splenomegaly, and pointed out that Stuckeley in 1722, stated, "that even Hippocrates knew that ulcers in the legs of such, i.e., patients with splenomegaly, are difficultly healed.

Bone changes in these patients, although not common, may suggest diagnosis. According to Wade and Steigrad, (21) Sears, as previously pointed out, believed that changes in the osseous system to be one of the cardinal symptoms of the disease. Clinically bone changes are evident in parietal and frontal bones. These are greatly thickened, the degree of thickening being most pronounced in the central parts of the bones and gradually decreasing as the sutures are approached. The fronto-parietal sutures have undergone synostosis and the parieto-occipital sutures are partially obliterated.(21)

Feingold and Case(31) believed the occurence of "turmschadel" to be a common feature of the disease. They believed that the characveristic deformity in "turmschadel" resulted primarily from a hypoplasia of the base of the skull and secondarily from premature synostoses. They did not believe that it was pathognomonic for hemolytic icterus, but felt that it's high incidence should make

a valuable adjuenct in the diagnosis of this condition. Gansslen, who first described the condition and gave it the name "turmschadel" (tower skull), believed that the occurence of constitutional deficiencies indicated that hemolytic jaundice was only the link in the chain of a constitutional inferiority.(31) He concluded that numerous congenital anomalies occured in association with hemolytic icterus. Some of these were brachydactylia, syndactylism, and polydactylia of the osseous system; microphthalmia and heterochromia of the eyes; the ears; the skin; and endocrineglands (genital hypoplasia and hypothydoidism). The changes in the osseous system were the most outstanding.(31) Friedman(32) believed that the cranial and facial changes were consistant with the congenital nature of this disease, and were definitely pathognomonic. Radiographically, characteristic features are seen in the bones of patients with hemolytic jaundice, showing evidence of "turmschadel". The bones hsow no definite differentiation in the outer and inner tables and diploe, though there is a suggestion of a very thin inner table. No outer table can be seen, and the bones display a most peculiar vertical striation, more pronounced as the outer surface is approached. The whole appearance suggests that the osseous tissue would be soft and vascular.(21)

In studying the blood for calcium and phosphorus, no

definite changes have been found to suggest the etiology of this condition.(33)

Many of these patients first become aware of this condition during pregnancy. The additional load of pregnancy may serve to "light up" latent cases of hemolytic jaundice, or cause an acute exacerbation of the chronic form of the disease.(5) Claude Wilson mentioned a case of hemolytic jaundice that died of acute jaundice during pregnancy.(35) DeCarle(34) reported a case of hemolytic jaundice complicating pregnancy and he believed that chances were greatly in favor of recurrence of acute symptoms with a future pregnancy. Sharpe(5) reported a case of hemolytic jaundice which was definitely made worse during pregnancy. A case reported by Sharpe,(5) may well illustrate this point.

K. Y., a twenty nine year old female with typical familial clinical and hematological features of hemolytic jaundice for four years duration, became pregnant for the fourth time during the early fall of 1935. Six weeks before her pregnancy, the hemoglobin was 73 per cent; the erythrocytes, 4,110,000; leucocytes, 12,000; with a normal differential, the reticulocytes, 7 per cent, the fragility (0.50 to 0.35 per cent) and the icteric index was 10 units. Typical spherocytes were present in the blood smear. The spleen was not palpable,

though at times it seemed enlarged to percussion.

During the first and continuing through the second trimester, the hemoglobin remained at the same level but the red cells gradually decreased to 2,800,000. At the sixth month of pregnancy, the increased fragility and the icteric index remained the same, but the reticulocytes increased to 15 per cent. At this time weakness and drenching sweats made their appearance.

During the last trimester, these unpleasant symptoms were more prominent. However under iron-liver extract therapy, the hemoglobin increased rapidly to 86 per cent, with a delayed ans slower increase in the erythrocyte count up to 3,930,000. The increased fragility remained the same, with a reduction in the icterus index to 3 units and the reticulocyte to 3.2 per cent. The spleen was not palpable at any time. The delivery and puerperium are uneventful.

Splenectomy offers these women a chance to normal pregnancy. Cowen(36) reported one patient with four pregnancies, and another with seven pregnancies following splenectomy without ill effects to either mother or child. Mussey and Berkelsy(37) reported on cases of twenty three women who had thirty two pregnancies, and concluded that the course of pregnancy , confinement, and puerperium in this group of women showed no appreci-

able departure from normal.

As a rule, patients with hemolytic jaundice are free from fever. Fever, however, may be observed during intermittent infections, during attacks of gall stone colic, and during the crises.(38)

Hemolytic jaundice may simulate numerous other diseases, especially blood dyscrasias; therefore a differential diagnosis of this condition is necessary. The disease can be confused with pernicious anemia, aplastic anemia, ediopathic hypochromic anemia, splenic anemia, sickle-cell anemia, and chronic myeloid anemia.

In pernicious anemia, the megalocytosis, the absence of increased fragility, and the history, should serve to differentiate.(19) Although a lemon yellow color is seen in pernicious anemia, there is no definite icterus, as seen in hemolytic jaundice. The icterus index and van-den-Bergh studies are normal, while in hemolytic icterus these tests show definite evidence of increased serum bilirubin, Anesthesia, parasthesia, and irreversible neurological findings, frequently seen in neglected cases of this condition, are never seen in hemolytic jaundice. Griffen(25) states, "I have seen as confused a condition in the same patient as cirrhosis of the liver, marked splenomegaly, cholelithiasis, and a pernicious anemia type of blood picture, where only a definitely increased

fragility of the red cells indicated the way to a diagnosis of hemolytic jaundice." During a hemolytic crises, a blood picture of pernicious anemia may confuse the diagnosis.(41) Elliot and Jones differentiate pernicious anemia from hemolytic jaundice by noting a high color index, megalocytosis, evidence of achlorhydria, apparent non production of blood, and no splenomegaly in the former condition. Allen(40) reported a case of severe hemolytic jaundice of long duration, strongly resembling pernicious anemia, in which the usual increased erythrocyte fragility was possibly counteracted by long continued anemia. Splenectomy brought about a symptomatic cure. In any event, where the two conditions are confused, and where the fragility test is normal or near normal, the absence of response to liver therapy and the almost immediate relief of symptoms following splenectomy, will serve to differentiate hemolytic jaundice from pernicious anemia.

Idiopathic, hypochromic anemia may be differentiated from hemolytic jaundice by the absence of a familial history, a low reticulocyte count, absence of deeply staining microcytes, and a negative indirect Van-den-Bergh.(19)

A diangosis of splenic anemia is usually made after the various chronic splenomegalies are excluded. There

is no evidence of heredity, and the jaundice is of the obstructive type. The age of onset, leukopenia, and the chronicity, should lead one to suspect the diagnosis. Blood examination, however, is all important in it's differentiation from hemolytic jaundice. Blood studies that show increased fragility of the red cells, typical dark staining microcytes, a high reticulocyte count, and a normal or raised white cell count are sufficient to exclude the diagnosis of splenic anemia, and to suspect a diagnosis of hemolytic jaundice.(19)

There should be little confusion in differentiating sickle cell anemia from hemolytic jaundice. Clinically, both diseases are familial and both may show splenomegaly and ulcerations of the legs. However, sickling of the red cells in the presence of a normal fragility, is sufficient evidence to make a diagnosis of sickle cell anemia, and remove any confusion that might be present between these two conditions. Griffin(25) believed that hemolytic jaundice was always to be donsidered before a diagnosis of splenic anemia was made.

Occasionally, anemia associated with splenomegaly and malaria, may be confused with hemolytic jaundice. Both diseases may show a large spleen, a high reticulocyte count, and anemia.(19) The characteristic fever and the demonstration of the malarial parasites in the

blood, are suffieient evidence to make a diagnosis of malaria. Since patients with hemolytic jaundice may be complicated with malaria, blood studies showing an increased fragility of the red cells plus clinical manifestations of the disease, should suggest the diagnosis of hemolytic jaundice.

Hemolytic jaundice may be confused with chronic myeloid leukemia, only during a crisis, when occasionally numerous young cells are seen in the blood stream. A high reticulocyte count, a positive indirect Van-den-Bergh reaction, the presence of jaundice, and the typical deeply stained microcytes, suggest the diagnosis of hemolytic jaundice. These findings plus an increased fragility prove the diagnosis.(19)

Another group of conditions, though usually not considered in the differential diagnosis of hemolytic jaundice, may at times be confused with this disease. These are chlorosis, Hodgkin's disease, thromopenic purpura with splenomegaly, severe secondary anemias following infections, and erythroblastic anemia.

Chlorosis is of interest largely because of it's history. The disease is practically extince today, but when present, may have much the same blood picture as hemolytic jaundice. A normal fragility test and a ready response to iron eliminate the diagnosis of hemolytic jaundice.(42)

Hodgkin's disease, when primary in the spleen, may present a very similiar clinical picture as hemolytic jaundice. There would, however, be an absence of much evidence of active reproduction of erythrocytes and a normal fragility test would be obtained.(42) The prognosis in this condition is always poor, and a biopsy of enlarged lymph glands, showing the presence of Dorothy Reed cells, is sufficient evidence to make a diagnosis of Hodgkin's disease.

Rarely thrombopenic purpura with splenomegaly offers much confusion with hemolytic jaundice. A definite reduction in blood platelets during the active hemorrhagic stages is seen.(42) Usually spontaneous hemorrhage from mucous membranes, and a decrease in blood platelets, are sufficient evidence for a diagnosis of thrombopenic purpura. The bleeding time is prolonged, and blood platelets are decreased in this condition, while in hemolytic jaundice they are normal.

The usual severe secondary anemias following typhoid fever, pneumonia, acute rheumatic fever and dysentery, all give a very sallow complexion or anemia, and occasionally a palpable spleen. In these conditions, however, the etioloty of the process is usually evident and there should be no confusion in diagnosis.(42)

Erythroblastic anemia must be differentiated from

hemolytic anemia in infants and children. Bone changes in both conditions are similiar, less marked in hemolytic jaundice. "The absence of distinct racial incidence, the presence of a greater number of reticulocytes with relatively few nucleated erythrocytes, the increased fragility of the erythrocytes in hypotonic saline solution, the evidence of increased hemolysis, i.e., a high icteric index, visible jaundice, and a large amount of urobilin in the urine and stools, and finally the striking and usually lasting benefit obtained from splenectomy should differentiate hemolytic jaundice from erythroblastic anemia".(43)

PATHOLOGY

Laboratory findings are the most important in the study of this disease. Although the clinical signs may suggest the diagnosis of this condition, blood studies are necessary for the actual diagnosis. For this reason, special attention has been given in this discussion to these findings. Separate mention of each laboratory finding is to be considered in the following discussion.

As previously stated, the anemia may be absent, slight, or moderate in degree, depending upon the rival forces of blood destruction and construction.(7) Rarely does the anemia become severe unless it accompanies a hemoclastic crisis. The hemoglobin, except in crisis, varies from 60 to 80 per cent. Red blood cells average between 3 and 4 million. The color index is usually normal and the hemoglobin is reduced in proportion to the red blood cells.(3) During a crisis, anemia may first make its appearance or gradually increase, if already present, and may become fatal unless treatment is instituted.(44)

Poynten(35) stated, "that during paroxysms, there were marked changes in the red blood cells, the number rapidly diminished, they were altered in size and shape, and might lose much of their hemoglobin". This form of anemia is resistant to iron and liver therapy, and only remains at or near a normal level, after splenectomy.

According to American authors, Naegeli was the first to recognize the small red blood cell (microcyte). He noticed that these microcytes were smaller and thicker than the ordinary erythrocyte, and described them as globular or sphere shaped. Whitcher(2) believed that while the red cells appear abnormally small, they show an increase of hemoglobin content in each cell, and tended to approach an actual spherical form instead of the normal bi-concave form. He believed that the microcytosis was simply a characteristic symptom of the anemia in hemolytic icterus, influenced to a large extent by the condition of the spleen, and disappearing after splenectomy. The mean diameter of the red cell, though showing a striking decrease, may vary from case to case, and also vary in the same patient from abservation to observation.(9) Because of the small diameter yet greatly increased thickness of the erythrocyte, hematocrit determinations of the corpuscular volume and hemoglobin content do not give true values, i.e., a low red cell diameter with a normal cell volume and slightly increased content of hemoglobin.(45) The mean corpuscular hemoglobin concentration of the cells, or the amount of hemoglobin per unit volume of red cell, is definitely increased more so than in any other type of anemia.(2,46) Haden(47) attributed this spherical shape of the erythrocyte to the fact that the diameter of the mean cell was de-

creased out of proportion to the change in volume, so it was apparent that the thickness of the cell must be increased.

The normal mean diameter of red blood cells is 7.02 to 7.252 microns, and the normal mean corpuscular volume is 80 to 91.4 cubic microns. In Vaughn and Goddard's(46) study of red cell diameters and red cell measurements, in cases of hemolytic jaundice, they found that the mean corpuscular volume varied from 81.08 to 90 cubic microns and the mean corpuscular diameter varied from 5.927 to 6.618 microns. Haden(47) stated that Naegeli found in 11 patients a mean corpuscular volume of 100 cubic microns (his normal 88 cubic microns), Von Boras found a mean of 85 in 8 cases (his normal, 91) and Gansslen found a mean corpuscular volume of 92, 95, and 111 cubic microns in 3 cases. Paxton(45) found an average mean corpuscular diameter of 6.41 in a series of acholuric jaundice children. From these results we can conclude that there is a definite anisocytosis, shown as microcytosis, and corpuscles larger than normal are quite rare; and that the mean corpuscular volume is variable and is usually at or above normal. Paxton(45) defined mean corpuscular diameter, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration and gave has average results in normal children and in children with

acholuric jaundice as follows: (1)Mean corpuscular diameter (M.C.D.) is the average diameter of the red blood cells. (2)Mean corpuscular volume (M.C.V.) is the average volume of red corpuscles and is expressed in cubic microns. (3)Mean corpuscular hemoglobin (M.C.H.) is the average amount of hemoglobin by weight in the corpuscle and is given in micro-micrograms. (4)Mean corpuscular hemoglobin concentration (M.C.H.C.) given as a percentage of the amount of hemoglobin per unit volume of red cells.

	M.C.D.	M.C.V.	M.C.H.	M.C.H.C.
Averages for normal children		78.54	25.17	32.06
Averages acholuric jaundice	6.41	79.08	28.20	35.46

The cell diameter was less than normal and the corpuscular volume, hemoglobin and hemoglobin concentration, were some greater than normal. Vaughn and Goddard(46) also found that the red cells were characteristically abnormally thick, with a mean corpuscular volume greater than the mean diameter, and a mean corpuscular hemoglobin concentration greater than in normal controls. Vaughn and Goddard(46) gave the following methods for calculation of the corpuscular constants:

Mean corpuscular volume (M.C.V. in cu. microns) $= \dfrac{\text{Volume of packed red cells (in c.c./1000 c.c. of blood)}}{\text{Red blood cells (in million per c.m.m.)}}$

Mean corp. hemoglobin (M.C.H. in m.m. grams) $= \dfrac{\text{Hemoglobin (grams per 1000 c.c. of blood)}}{\text{Red blood cells (in million per c.m.m.)}}$

$$\text{Mean corp. hemoglobin (conc. - M.C.H.C. \%)} = \frac{\text{Hemoglobin (grams per 100 c.c. of blood)}}{\text{Vol. of packed red cells (c.c. per c.c. of blood)}} \times 100$$

In rare exceptions which have been reported without microcytes and in those where they disappear after splenectomy, erythropoiesis is evidently not so heavily taxed.(4) Hawksley and Bailey(9) stated that fluctuations in mean diameter may in part, be dependent on the number of immature red cells present apart from the influence of splenectomy and transfusions. Masters et al(30) believed that the diameter of the red cells increased following splenectomy but Pemberton(27) and others believed that microcytosis of the erythrocytes does not disappear after removal of the spleen.(4,47,57)

According to Griffin and Sanford(48) Ribierre in 1903 was the first to devise a technique to test the fragility of red blood cells. Chauffard and later Buttler(49) used this test in the study of hemolytic jaundice, and found it of practical value as a diagnostic procedure. The test is now practically universally used, and a diagnosis of hemolytic jaundice is made only after an increased fragility is shown by this test. The method of testing decreased resistence of the red cells to hemolyzing agents or as it is sometimes called the increased fragility test is by mixing red cells, preferably after separation from the plasma, with hypotonic solutions of sodium chloride

of varying strengths, and noting the point at which hemolysis takes place.(3) According to Griffin and Sanford (48) most methods of testing fragility of erythrocytes depend on the observation of the breaking up of the cells in salt solutions of various percentage strengths, the chief difference lying in the method of making the various solutions, and of reading and reporting end points or degrees of hemolysis. Ribierre's method seemed to be the most satisfactory and simple method of accurately determining the fragility of red blood cells, so Griffin and Sanford(48) modified his method without altering its accuracy or simplicity and reported it as follows: "A stock solution is made by dissolving 0.5 grams of sodium chloride (chemically pure and anhydrous) in 100 c.c. of distilled water. A twelve hole Wassermann rack, with at least two rows of holes, is filled with three-inch by three eighths inch tubes. The front row is for the patients test the back row for a control. The tubes in the front row are numbered with a glass marking pencil, 25,24,23,22,21,20, 19,18,17,16,15, and 14. In each tube in the front row, and in the tube in the back row immediately behind it, is placed the number of drops of 0.5 per cent solution indicated by the figure marked on the tube in the front row. A capillary pipette drawn from soft glass tubing is used for putting the drops of salt solution in the

tubes, with the same pipette distilled water is added drop by drop to each tube so that there is a total of 25 drops; for example a tube marked '20' should contain 20 drops of 0.5 percent sodium chloride solution and 5 drops of distilled water, and the tube immediately behind it (control tube) should contain the same. Venous blood is taken with sterilized dry syringe and one drop of blood should be allowed to fall into each tube of the front row. The tube should be thoroughly shaken to make an immediate corpuscle suspension. The plasma is greatly diluted and usually no fibrin is formed. In the back row (control tubes) should be placed blood obtained in a similar manner from a normal person. The tubes are allowed to stand an hour or two at room temperature and then read." In case of normal hemolysis, the tube marked '20' showing beginning hemolysis reading consists as follows, 20/25 of 0.5 percent sodium chloride - 0.40 per cent sodium chloride. Tube marked '16' showing complete hemolysis contains 16/25 of 0.5 per cent sodium chloride or 0.32 per cent sodium chloride. Normally then hemolysis begins at 0.40 per cent sodium chloride and is complete at 0.32 per cent sodium chloride. According to Tiletson and Griffin,(3) normal hemolysis begins in salt solution of 0.44 per cent and is complete at 0.36 per cent, while in hemolytic jaundice, hemolysis may begin at 0.7 per cent and be complete at 0.5 per cent.

Increased fragility of the red cells is the most outstanding and persistent sign of hemolytic jaundice. Following splenectomy the increased fragility of the erythrocytes persists, where apparently the other signs and symptoms disappear.(52) Increased fragility is almost a constant feature of hemolytic jaundice, and according to Cheney and Cheney(4), it has been reported in other diseases of the blood such as pernicious anemia, post hemorrhagic anemia, and various forms of leukemia, which usually show an increased fragility but never to the same degree as in this condition. Patients with hemolytic jaundice occasionally may show a normal fragility of the red blood cells. According to Dawson(7), Gansslen reported that in 10 per cent of his cases of acholuric jaundice, there was no increase of fragility, and 5 cases of his own series, showed normal fragility. East(50), in 1935, reported a case of hemolytic jaundice with a normal fragility. Piney(51) believed that in all cases of acholuric familial icterus there was a general decrease of resistence of the red corpuscles. One probably can safely say that an increased fragility is necessary for an accurate diagnosis of this disease and those cases showing a normal fragility of red blood corpuscles, with other clinical signs of hemolytic jaundice, probably fall into what is termed the "waste basket" group of anemias.

The cause of the increased fragility is obscure. Doan et al(8), have shown the phenomena of erythrocyte fragility to be inherent in the red cells themselves and not secondary to any abnormality in the plasma. Haden (47) has shown that the spherocytes of hemolytic jaundice are similar to the globular shape of normal erythrocytes that have been placed in hypotonic salt solution just before the point of hemolysis. For this reason, he believed there was a direct relation between the increased thickness of the cells and the increased fragility. Increased fragility may vary in the same or different patients(5,7,8). The degree of fragility appears to have no relationship to the severity of the anemia, or to the jaundice, or to the splenomegaly(5,7,19).

Dawson(7) mentioned, and Thompson(53) reported a case of hemolytic jaundice in which the fragility of the red blood cells increased after splenectomy. Thompson (5) attributed this increase in fragility to the fact that after splenectomy, more fragile corpuscles may circulate in the blood stream, since they will not be removed by the spleen.

In normal blood, and even more in anemias, it is possible to find a number of red corpuscles in which, with so called vital staining, certain basophilic structures can be demonstrated(51). These red blood

cells, with basophilic properities, are called reticulocytes. According to Thayer and Morris(6), Chauffard first described the reticulocytes, and called them "granulo-reticulo-filamentous"(17). Brilliant cresyl blue is the most satisfactory stain used to demonstrate this reticular material in the red blood cells. In normal blood, the reticulocyte count varies from 0.1 to 0.5 per cent of red cells, and counts above 1 per cent are considered abnormal. In hemolytic jaundice, the reticulocyte count usually runs between 5 to 15 per cent, but may reach 40 to 60 per cent; no other disease gives such high findings(5). Higher percentages of reticulocytes have been reported. Baty(54) reported a case of hemolytic jaundice with a reticulocyte count of 70 per cent. Reynalds (55) reported a case who had 95 per cent reticulocytes, and Doan, et al(8), reported a case having 100 per cent reticulocytes. It is interesting to note that in these cases, the fragility of the red blood cells was at or near normal. Cheney and Cheney(4) stated that when reticulocytes, which are more resistant, were present in large numbers, the fragility of the red cells may be within normal limits. According to Hawksley and Bailey(9), reticulocytes are also of greater diameter than mature erythrocytes, thus, a fall in reticulocytes from a very high level may be accompanied by a fall in mean diameter. Thayer and Morris

(6) believed that this phenomena was simply an indication of active blood regeneration, but there were apparently few conditions in which the frequency of these granular corpuscles compared with that in hemolytic jaundice. This fact seems to give them a real diagnositc value. Sharpe(5) regarded the reticulocytes as evidence of active bone marrow regeneration, in which young cells have reached the circulation in an immature state. Haden(47) believed the reticulocytes to be an expression of an over-stimulated bone marrow in attempting to compensate for the rapid destruction of erythrocytes. Reticulocytes may increase in the same patient from time to time, coincident with "crises", falling again to lower figures during remissions, even below 1 per cent, as in normal blood(4). It can definitely be stated that during the period of marked anemia in these patients, the number of reticulated corpuscles is high, but there is, nevertheless, no strict relationship between the number of these elements and the degree of anemia, as is shown in some cases with large numbers of these corpuscles and practically no anemia(51). Lewis (56) believed that a low reticulocyte count which remained consistently low, even though the patient was in a crisis, probably indicated an aplastic condition of the bone marrow. Piney(5) believed that periods of more intense jaundice are accompanied by an increased

number of reticulocytes, although the anemia does not necessarily increase. He further stated that it can justly be presumed that any case of jaundice in which reticulocytes were not increased in number was not due to hemloysis. The reticulocytes rapidly return to normal following splenectomy(57).

Polychromasia although not intense it most marked during periods of severe anemia(51). It is well known that staining with simple solutions of methylene blue shows slight degrees of polychromasia more distinctly than does any other method, and if this stain is used it is possilbe to find some polychromasic red corpuscles even at times when other stains do not reveal them(51). In stained smears of the blood, the red cells vary much in size (anisocytosis)(4). The anisocytosis is a more constant feature of stained blood smears than the polychromasia(51). There is no adequate evidence that poikilocytosis ever occurs(51).

Nucleated red cells (normoblasts) can usually be found, but the number seen will, of course, depend upon the time spent hunting for them; it is rare to find more than 1 or 2 per cent of the erythroblasts(51). These nucleated red cells may temporarily increase in number following splenectomy(53,58). Morris (26) found nuclear particles in the red blood cells following

splenectomy. He suggested that there may be some relationship between the occurrence of these nuclear particles in the erythrocytes and complete or partial loss of splenic function. Piney(51) believed that nuclear remnants, such as Joly bodies, were found just about as infrequently as were normoblasts and in some cases were absent for considerable periods of time. Cabot rings, usually found in slightly polychromasic corpuscles are found in the red blood cells of a small number of these patients(51). According to Piney(51) these characteristics must be regarded as evidence of intensified hematopoietic activity, possibly of a slightly atypical nature.

The leukocyte blood picture may be normal, or there may be a considerable leukocytosis with a shift to the left of the neutrophilic series(5). Cheney and Cheney(4) stated that the white blood cells were usually normal but that during a "crisis" and in exceptional cases a white blood count of 20,000 to 30,000 may be found. Thayer and Morris(6) believed that the differential count showed nothing remarkable beyond evidence of increased marrow activity as manifested by a high percentage of eosinophiles and the occasional presence of myelocytes and nucleated red cells. Poynten(35) also believed that there was some increase in the number of leukocytes, especially during attacks of "crises".

Piney(51) was of the opinion that either a leukocytosis or a leukopenia may occur, but usually the number of white cells was about normal. He also believed that it was quite common to find a slight degree of monocytosis and a few myelocytes and that during "crises" there were often a neutrophilic leukocytosis and an increase of myelocytes. As the anemia increases the leucopenia becomes more marked(8). From these opinions we can safely say that the leukocytic blood picture shows nothing characteristic to this disease and is only of value in eliminating other blood dyscrasias.

During the course of the disease the platelet count is normal(5). Cheney and Cheney(4), stated that the blood platelets usually were normal or increased but rarely were decreased in number. Paxton(45), believed that during the disease process the platelet count was normal, but as in all cases in which the spleen was removed a remarkable increase in the platelet count to 700,000 or 800,000 per cubic millimeter, occurred and was thereafter followed by a gradual return to normal numbers. Galloway(59), also found an immediate and great increase in number of circulating blood platelets, that reached their highest level in the eleventh day following splenectomy but in his series they still remained

much above the preoperative level even after one year. Bleeding and clotting times were normal in hemolytic jaundice patients(5).

Since jaundice is one of the cardinal symptoms of the disease, icterus is obviously a very important feature. The jaundice is usually of moderate degree, varying from a pale lemon hue to a well marked golden yellow (6). According to laboratory methods of diagnosis, an interic index of above normal is found, but it is rarely above 30 (5). The normal icteric index values are 4 to 6 either in adults or children (60). The Van-den-Bergh is indirectly positive and may reach as high as 5 to 6 units, the normal being 0.5 of one unit(4). Osgood and Haskins(60) gave normal indirect Van-den-Bergh estimations of 0.05 to 0.25 milligrams per 100 cubic centimeters. A direct reaction indicates obstructive jaundice and is usually associated with a high indirect reaction and an increased icteric index(60). An increased indirect reaction occurs in all types of hemolytic icterus whether latent or obvious.(60) Osgood and Haskins(60) believed that since the Van-den-Bergh reaction depended upon the concentration of bilirubin in the blood stream, rather than on the mode of production of the increase, it added little if any information to that derived from the icteric index.

Cases of jaundice are separable, on the basis of

pathogenesis into two main types(28). Retention jaundice, which results from an over production of bile pigment, usually associated with conditions, (anoxemia, fever, and immaturity), which tends to render the excretory power of the liver subnormal, and leaving enough bilirubin in the blood to stain the tissues(28). This form of jaundice is characterized by (a) indirect reacting plasma bilirubin, (b) increased amounts of fecal urobilin, and (c) urobilinuria(28). The second, regurgitation jaundice is caused by a reflux of whole bile from the canaliculi into the blood stream and is characterized by (a) direct reacting plasma bilirubin, (b) subnormal amounts of fecal urobilin, and (c) the presence of bilirubin and bile salts in the urine(28).

Retention jaundice in it's pure form, as seen in hemolytic jaundice, gives an indirect Van-den-Bergh reaction, because the bilirubin of the plasma has never passed through the liver cells and is therefore not mixed with the constituents of the bile(28). The stools contain an increased amount of urobilin because of the increased production of bilirubin. The liver is excreting more of the pigment than normally, even though it cannot excrete enough of the excess to prevent jaundice.(28) The urine contains an increased amount of urobilin, but no bilirubin; and it is free from bile salts, because

bile salts are formed in the liver and are absent from the urine unless they escape into the blood stream(28).

In regurgitation or obstructive jaundice, the plasma bilirubin gives the direct Van-den-Bergh reaction, because the bile canaliculi are altered in such a way that whole bile escapes into the blood stream(28). The stools contain less urobilin than normal, bacause the passage of bilirubin into the intestine is hindered, either by obstruction of the ducts, or by necrosis associated with rupture of canaliculi, which allows the bile to leak into the blood stream(28). The urine contains bilirubin, since the direct reacting plasma bilirubin escapes into the urine. Bile salts are usually present in the urine, because in this form of jaundice, whole bile finds its way into the blood and urobilinuria may occur, depending upon the balance between the amount of pigment reaching the intestine and the degree of damage to the liver(28).

From the above discussion, it is easy to see that laboratory findings in retention jaundice are quite the reverse of those found in regurgitation jaundice. Retention jaundice is commonly known as hemolytic jaundice and regurgitation jaundice is known as obstructive jaundice. The follwoing table taken from Rick's(28) report on the pathogenesis of the forms of jaundice,

will further serve to differentiate these two types of jaundice:

	Urine		
	Bilirubin	Bile salts	Urobilin
Retention jaundice	○	○	+
Regurgitation jaundice	+	+	○

	Blood	Feces
	Van-den-Bergh	Urobilin
Retention jaundice	Indirect	Increased
Regurgitation jaundice	Direct	Decreased

In hemolytic jaundice, there is an excess destruction of red blood cells, which gives the retention type of jaundice in this disease. Jaye(61) stated that the indirect Van-den-Bergh was simply a quantitative estimation of blood bilirubin. He gave normal figures as 0.1 to 0.5 milligrams per 100 cubic centimeters of blood. The origin of the bilirubin is from the broken down red blood cells. By catabolism, the hemoglobin content is converted into globin(protein), and hematin(an iron containing compound) (61). Hematin is then changed by the cells of the reticulo-endothelial system to bilirubin; the iron of the compound being utilized by the bone marrow in the formation of the new red cells(61). The liver removes most of this pigment from the blood and secretes it as one of the constituents of the bile. If there is no liver damage, it can always keep pace with the increased amount of bilirubin brought by the blood(61). Bilirubin, when it

reaches the bowel, is changed to urobilin or urobilinogen(61). Part of the urobilin is reabsorbed and the remainder is lost in the stools. After a certain concentration is reached in the blood stream, urobilin is excreted by the kidneys. Normally, tests for urobilinogen are positive in the urine in dilutions up to 1 to 20,(61). Beyond this dilution, the finding of urobilinogen in the urine is pathological and indicates an increased urobilinogen content in the blood. According to Joye,(61) these findings are to be anticipated in hemolytic jaundice, since increased blood destruction results in increased bilirubin content of the blood, which accounts for the jaundice. Increased bilirubin of the blood means increased bile pigment to be excreted by the liver. Increased bile pigment in contact with the bowel, becomes increased urobilinogen of the bowel content, and when absorbed, it becomes urobilinogen of the blood stream. Eventually, when excreted by the kidneys, there is an excessive amount of urobilinogen in the urine(61). According to Cheney and Cheney(4), darkening of the urine is characteristic in obstructive jaundice, but in hemolytic jaundice the urine is usually normal. If the urine is dark, bile pigment is absent. Minkowski called the disease "acholuric jaundice" for that reason(4). Bilirubin may at times by found in the urine during

"crises" (4). Thayer and Morris(6) stated that the urine was rather a high color, often brownish or mahogany hue, but free from bile. They, however, agreed with the fact that urobilin was usually demonstrable in the urine. An abundance of urobilin in the intestine keeps the feces their usual color or even darker than normal(4). Sharpe(5) also believed that the stools and urine might be highly colored owing to the increased urobilin excretion. If at any time, in the course of chronic hereditary hemolytic jaundice, bile is found in the urine and none in the stools, a complicating obstructive jaundice, due to gallstones blocking the common duct, should be suspected(4).

Following splenectomy, the jaundice disappears almost immediately(7,36). Freund(62) reported six cases of hemolytic jaundice in which the jaundice and other clinical signs continued following splenectomy. Glover and Fargo(52) attributed the persistence of symptoms following splenectomy to the presence of accessory splenic tissue in the abdomen, that may take over the function of the removed spleen. Elliot(63) reported a case of hemolytic jaundice that remained jaundiced following splenectomy. He stated that in the absence of choluria and cholemia, the jaundice was interpreted as being due to the vital staining of the tissues, resulting from 54 years of continued jaundice. His case remained

clinically well except for the jaundice following splenectomy.

Transfusions tend to increase the jaundice and cause an anemia as a result of blocking of kidney tubules by masses of hematin pigment(5,7). Hartfall and Stewart(64) attempted to prepare a case of hemolytic jaundice for surgery with blood transfusions. The patient became more deeply jaundiced and died within 24 hours. We can justly say that transfusions are not indicated as a therapeutic procedure in this condition, and especially as a preoperative treatment where splenectomy is contemplated.

Gastric analysis shows a normal amount of free acid in the stomach contents(5).

The spleen is usually enlarged, weighing between 500 to 1500 grams(5). It is usually easily removed at operation, being relatively free from adhesions(65). On section, the fresh spleen presents a uniform and fairly characteristic appearance(65). The cut surface is relatively dry and it is of dark purplish-red color, hemogeneous in texture and bulging slightly above the capsule. The malpigian bodies are not seen(65). Thompson(65) believed that a diagnosis of hemolytic jaundice may be made from the microscopic study of the spleen alone. He gave the following microscopic description of the spleens removed

at operation and at autopsy: "The malpigian bodies are small and widely separated. The venous sinuses are enlarged, widely dilated, and frequently empty. The sinus endothelium is prominent, the outlines of these cells bulging into the lumen of the sinuses. The pulp is a mass of closely packed red cells and this diffuse infiltration is the most striking feature of the microscopic appearance. There is no increase of connective tissue and no visible increase of iron pigment. The so called iron crustations are frequently incountered, being usually within the trabeculae. There is no visible evidence of phagocytosis of the red cells and , except for an occasional lymphocyte, one finds nothing but red cells distending, distorting and dilating the pulp". Thayer and Morris(6) stated, "that there was a marked congestion of the spleen especially confined to the pulp. This engorgement was a rather striking contrast to the relative emptiness of the sinuses. There were few macrophages in the splenic pulp and more in the sinuses. The endothelial cells were filled with iron containing pigment". McNee(13) also pointed out that the spleen of these cases was seldom enormously enlarged, but had a most characteristic histological structure, quite unlike that of any other form of splenomegaly. He stated that by staining

sections for iron by the Prussian blue method, it was possible to separate the spleens that were removed during an active or inactive stage of the disease. In the active stage, hemosiderin is abundant, lying chiefly within the reticulo-endothelial cells of the pulp and in the large endothelial phagocytic cells lining the blood sinuses(13). In the inactive stage of the disease, stained splenic tissue shows practically an absence of iron pigment(13). Vaughn(19) believed that iron was found as a granular or a diffuse impregnation of the elastic, collogen and reticulum fibers of the spleen. When considerable iron was found between the impregnated fibers, densily fibrotic Gandy-Gamma nodules were ultimately formed(19). These Gandy-Gamma nodules appeared to be due to hemolysis, independent of hemorrhage(19).

Grossly, the bone marrow presents the appearance of a very active state(5). The bone marrow is hyperplastic because of the demand for red cells in this disease(5). Cheney and Cheney(4) stated that the bone marrow was simply overworked, but condemned by the hereditary factor to put out fragile erythrocytes. In the stage of exhaustion, the marrow becomes more normoblastic and eventually shows a tendency towards megaloblasts(7). Dudley(66) also showed that the hyperplastic bone marrow was chiefly normoblastic in character. Vaughn(19) has

observed megaloblastic changes. Sharpe(5) reported a case in which a sternal biopsy was done before, and one month after splenectomy. The bone marrow following operation was still moderately hyperplastic.

Extra medullary bone marrow has been found in cases of hemolytic anemia. Dawson(7) found nodules of ectopic bone marrow in the costo-vertebral angle of one of his patients with hemolytic jaundice. Brannon (67) reported the occurrence of a large kidney sized mass of bone marrow tissue in the thorax of a man who died of hemolytic jaundice. The spleen had been removed sometime before death in this man. Extra-medullary bone marrow has also been found in other sites in the body, such as, the kidneys, suprarenal glands, broad ligaments and organizing thrombi. Brannon(67) believed that extra medullary hematopoiesis was a fairly common finding in certain anemias of infancy and childhood, and large tumor like growths of hematopoietic tissue particularly occured in the hilus of the kidney. This tissue, microscopically, was composed of all the blood forming cells except the large mononuclear, transitional or endothelial cells(67). A few lymphocytes have been found, but these cells have no conspicious part of the red masses(67). Hartfall and Stewart(64) described these extra medullary masses as follows: "Heterotopic tumors show the structure of

actively erythroblastic bone marrow. The preponderating cells are unquestionably the red blood corpuscles, of which nucleated and non-nucleated forms are about equally numerous. Here and there, groups of very embryonic nucleated red cells are seen with deeply basophilic ground-glass cytoplasm and large vesicular nuclei. They occur both singly and in small groups. The great majority of the nucleated red cells present are, however, normoblasts, often with small deeply staining pyknotic nuclei. Cells of the neutrophilic granular series, both mature and immature, are present in large numbers and there are many eosinophil cells, most of them mononucleated. Typical megakaryocytes are present in small numbers, but no mast cells are seen." The marrow of the bodies and processes of the vertebrae and the ribs in Hartfall and Stewart's(64) cases, was of deep red or maroon color and somewhat less dark than that of the paravertebral tumors.

Saleeby(68) believed that the occurrence of tissue resembling bone marrow in positions other than in the bony cavities, was uncommon and was usually found associated with bone, as a result of chronic inflammation, or appearing in some other organ of the hematopoietic system, as a result of a need for more blood cells in the circulation. Brannon(67) stated that it seemed logical to assume that, because of insufficient blood production,

a reversion back to foetal type of blood production may occur. He believed that since we have established evidence of the normal formation of blood outside the bone marrow during extra-uterine life, it seemed most probable that this original function of the liver, spleen, lymph nodes, thymus, and other tissues, may in life, when adequately stimulated again, assume a part of the load of blood production. Pauz, quoted by Collins(69), stated that bone marrow found in his cases in the supra renal glands arose from preexisting bone marrow found there at the time of birth.

The liver may show a slight degree of fatty degeneration(19). Vaughn(19) found granules of iron infiltrating the centers of the hepatic columns, with but little infiltration in the Kupffer cells. Vaughn(19) also noticed that erythroblasts and occasionaly myelocytes may be found in the sinusoids. Glover and Fargo(52) observed that in long standing cases hemosiderosis of the liver, kidneys and lymph nodes may be seen. Usually, however, it is rare to find any definite pathological abnormality of the liver (4) except for the high incidence of cholelithiasis of the pigment type, due to the persistant hyperbilirubinemia(5).

The kidneys, lymph nodes, and other organs do not show any important pathological changes, although in a

few instances, variable degrees of pigmentation have been noticed(5). Vaughn(19) stated that the kidneys may show a variable number of hyaline and a lesser number of pigmented casts.

Vaughn(19) gave the following microscopic description of the ulcers, found usually on the legs of these patients: "The ulcer is deep and almost reaches the subcutaneous fat, the base being formed by a narrow layer of dermis, which is moderately infiltrated with neutrophil leucocytes and shows areas of superfical necrosis. The margin is high and overhanging. The epidermis extends over the upper one third of the ulcer; beneath this it is superficially necrosed. The dermis for a considerable distance behind the margin is densily infiltrated with plasma cells and contains numerous macrophages loaded with granules of iron, whilest its vessels are greatly engorged. For a wide distance behind this all the dermis except a narrow zone at its base is replaced by a cellular fibullar scar tissue. There is no endarteritis."

A rather typical case of hemolytic jaundice may well illustrate the more important of the clinical and pathological findings in these patients. Elsie(70) reported this case as follows: "The patient, a girl, 12 years of age, was first seen three years before by

Dr. Russell Keiser in a routine school examination. At that time Dr. Keiser found an enlarged spleen and a red cell count varying from 1,620,000 to 2,840,000. The hemoglobin was 32 per cent at one time and 35 per cent at another time, and the leukocytes varied from 11,400 to 15,200. In differential count, the polynuclear neutrophils were 63.6 per cent, lymphocytes 29.9 per cent, large mononuclears 1.5 per cent, eosinophils 1 per cent, and myelocytes 4 per cent. There were a few nucleated red cells present.

The patient was again seen at the Elsie clinic in March 1932, at which time she stated that she had been in good health, had no complaints, but had not gone to school for three years, being kept out because of her condition. She stated that her paternal grandfather was dead and that he had had a large spleen. Her father was living and well at forty-eight years of age and also had a large spleen. No other family history of importance could be obtained.

Physical examination revealed a well nourished girl with pale skin. The physical examination was entirely negative except for a markedly enlarged spleen and mildly icteric sclera. The spleen was firm and moveable. The liver margin was felt at the costal margin, the edge was sharp and firm. The hemoglobin was 43.6 per cent, 6.91 grams

red blood cells 2,960,000, color index 0.71, volume index 0.63, icteric index 25, white blood cells 8,800, polynuclear neutrophils 62 per cent, eosinophils 3 per cent, small lymphocytes 23 per cent, monocytes 1 per cent, and staff cells 9 per cent. Fragility began at 0.60 and ended at 0.38, cell volume 15.97, nucleated red cells 3 per cent anisocytosis two plus, polychromatophilia two plus, reticulocytes 20 per cent, blood platelets 202,000, coagulation time three minutes and bleeding time three minutes.

On March 21, 1932 a splenectomy was done. The day following operation her hemoglobin was 100 per cent, red blood cells 5,490,000, white blood cells 38,000, polynuclear neutrophils 73 per cent, small lymphocytes 4 per cent, monocytes 3 per cent, staff cells 20 per cent, anisocytosis one plus. On discharge from the hospital the blood showed hemoglobin 86.5 per cent, red blood cells 4,620,000, white blood cells 12,900, polynuclear neutrophils 45 per cent, eosinophils 5 per cent, small lymphocytes 47 per cent, monocytes 2 per cent, staff cells 1 per cent, anisocytosis one plus. Fragility began at 0.56 and ended at 0.32.

Dr. Karl Martzloff examined the spleen and reported that it measured 5.5 centimeters by 12 centimeters by 20 centimeters. It weighed 770 grams. It was firm, uniform in consistency and the capsule purple to bluish

gray in color. On section it cut with resistence and presented a dark red surface with grayish strands. Microscopic examination revealed a nearly complete absence of the malpighian bodies and the normal splenic appearance. The sinuses were filled with blood. Occasional polynuclear, eosinophils, and giant cells were present. Lymphocytes were absent."

CONCLUSIONS

1. The etiology of hemolytic jaundice is obscure. Theoretrically, the most logical cause of the disease is the inherited abnormal red blood cell.
2. Hemolytic jaundice is an inherited disease. We probably can justly say that the more closely hemolytic jaundice is studied, the more do we doubt, as to whether in a strict sense, an acquired form of the disease exists.
3. The diagnosis is easy in typical cases, but the absence of one or several of the typical signs of the disease, latent cases, and complications, which are not uncommon, many times make the diagnosis difficult.
4. The cardinal signs of the disease are jaundice, splenomegaly, microcytosis, increased fragility and a hereditary background.
5. Hemolytic jaundice may be complicated by cholelithiasis, bone changes, ulcers of the legs, pregnancy, extra-medullary bone marrow, and "acute hemolytic crises".
6. Splenectomy cures most of these patients clinically, but a microcytosis and an increased fragility of the red cells persists.
7. Transfusions are not indicated and may exaggerate the conditon or prove fatal in certain cases.
8. The diagnosis of hemolytic jaundice may be made from the microscopic examination of the spleen alone.

9. There is nothing characteristic pathologically in the other organs of the body, except for a high incidence of pigment cholelithiasis and iron pigmentation of some of the organs in chronic cases.

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