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Hemolytic anemia blood findings

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HEMOLYTIC ANEMIA

BLOOD FINDINGS

BY

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INTRODUCTION

In the past two years there have been several cases of anemia at the University Hospital which have lead to difficulty in diagnosis and treatment. Most of these cases have been characterized by spleneomegaly and since I have had the opportunity to follow these cases and work with them, a division of the subject has made a very suitable topic for a senior thesis. Hemolytic anemia , with which this paper is concerned, has numerous synonyms all of which are descriptive of some finding in the disease. The commonest are: acholuric jaundice, hemolytic jaundice, and hemolytic icterus. Splenic anemia is sometimes used to refer to this disease but is not correct in this usuage, and belongs to another group of disorders associated with Banti's disease. Hemolytic anemia is divided into two great groups about which there is some discussion as to whether they occur; there is the familial or congenital and the acquired types of the disease. Chauffard-Minkowski is the name associated with the familial type and Hayem-Widal with the acquired. The strong supporters of the familial tendency of the disease believe that if it could be properly traced back in all cases the disease would be found to be inherited.

This paper deals only with the findings related to the blood, and does not take up the clinical aspects of the disease. However, with a complete understanding of

the blood one will be acquainted with all the cardinal findings in the disease and should be able to have a working clinical knowledge from these findings.

HISTORY

The disease process known as hemolytic anemia although it is not new to the medical professional it can not be classified among the older disorders that the medical profession has dealt with. One point that makes it seem to be a more recent finding than it is is due to the fact that it is by no means common, and unless one is in a larger clinic he may never see a case. History reveals that is was first observed by Murchison in the year 1885. Following in chronological order it will be found that the first splenectomy for this disease was performed in 1887 by Sir Spencer Wells, and the second in 1895. Even though this occurred the disease was not established and adequately described until 1898 when Hayden wrote his paper. Minkkowski reported in 1900 a family in which there were eight cases. These last two events were what started things off and it was in 1903 that the first cases was diagnosed as hemolytic anemia and splenectomy was advised. In this same year, 1903, Ribierre first described a fragility test that was satisfactory for clinical use. This, however, did not bear relation to the disease until four years later when Chauffard discussed the increased fragility in hemolytic anemia, and then but a few months later he described the high reticulocyte count. This work was all being done in Europe and 1910 introduced it to the American literature by the paper of Tileston and Giffin whose later contribuare still cited. Contributions are still in order, however, for although the clinical picture of the disease is well

known and recognized the underlying pathology has yet to be adequately explained, and although splenectomy results in a symptomatic cure it does not return the blood to normal.

RED BLOOD CELLS

This disorder being an anemia, naturally the red blood cells a re of most importance and will be discussed first. Cheney(7) a recognized authority on the subject states that the red blood cell level is usually found around three to four million and the hemoglobin from sixty to eighty percent. However, the degree of anemia varies a great deal and the patient may run along at this level for long periods of time while others run a more varied course. Majority of the cases that are found to present themselves for treatment usually are suffering from a greater degree of anemia than this. A crises or exacerbation is what usually bring them to the doctor. These cause a sudden fall in the blood level and a patients red cells may drop two or three million during an attack. If spontaneous recovery occurs the return to normal blood level is much slower than the onset. Many cases are reported in which the count has dropped below one million before operation is performed. The fact that the degree of anemia varies so rapidly from time to time is one of the features of the disease.

The red cell level following splenectomy in tyoical cases is very striking. It used to be described that following operation the red cell level returned gradually to normal but in recent years it has been shown that this return that this return has started immediately and

in as early as the first hour after ligation of the splenic artery there has been a marked change. Glover and Fargo(17) noticed the change in a period of six hours. There cases showed and increase from 2,160,000 to 3,144,000 in this time. The hemoglobin increased from 46% to 74%. Doan(10) reports a case with an in - crease from 3,310,000 to 3,700,000 in fifty minutes after operation and at 9 PM on the same day the count was up to 5,500,000. In a later article (11) he states that major increases of one million or more occur immediately or before the patient leaves the operating table.

Accompanying this there is a tendency to rise above the normal level, Dawson(9) reports a case of in which the red count rose to 6,000,000 and Beer(4) sites one case going up to 13,000,000. This peak is usually reached in a few days to weeks after operation and then gradually returns to a more normal level, although it is common to have them remain high. Also other cases although they show a marked rise in red count following operation may come to rest below normal.(9)

Doan(11) has shown that the response of the leucocytes, red cells, hemoglobin, and platlets recorded following splenectomy are not the result of the operation or the anesthetic for in a series of miscellaneous operations under identical conditions they did not yield

similar results.

In the three cases described here it can be seen from the charts that there is a return toward the normal blood level, and although the onset of the rise is quite prompt the rapidity of the red cell increase does not agree with some of the just mentioned authors. It is true however, that the cases here were in a chronic state and if splenectomy had been performed in the presence of a crises that the results would have been more marked and the rise more rapid.

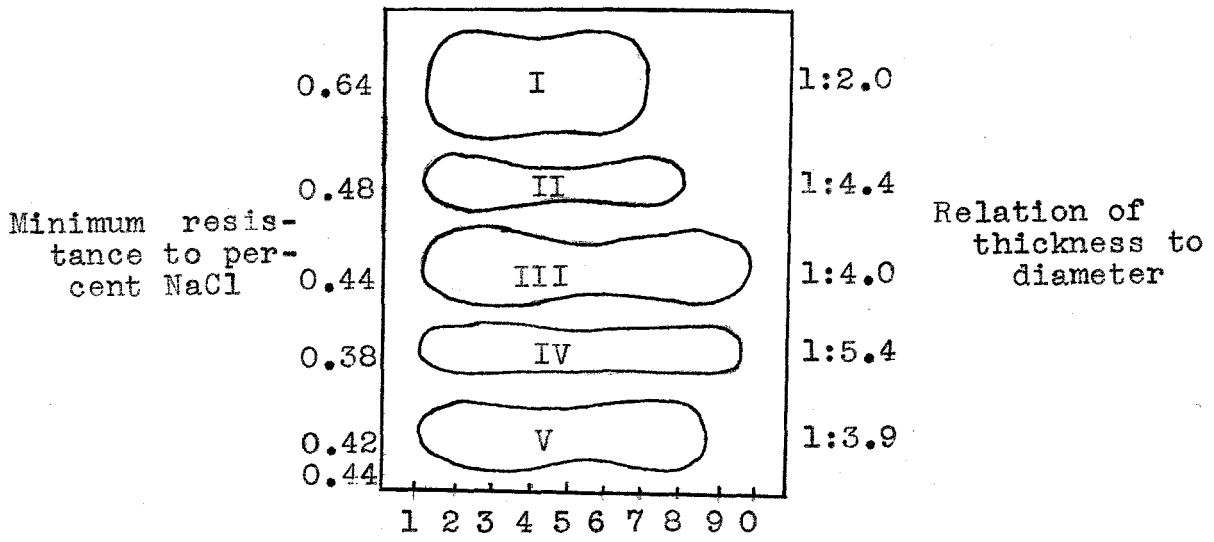
Krumbhaar(22) found that in working with experimental animals, dogs and monkeys, that following splenectomy there was an early anemia which started shortly after the operation and reached a maximum at a few weeks and disappearing after several weeks. Giffin(15) states that the anemia found in experimental animals following splenectomy is not observed in man for pathological spleens; however, mild anemia has been noted as a result of splenectomy for simple tumors in otherwise normal spleens. From this it appears that the sudden increase in red blood cells following splenectomy is quite typical for this disease process and is what makes the cure so striking.

In studying the pathology of hemolytic anemia most of our present knowledge is centered around the red blood cell. On first appearance it seems that this is a microcytic anemia but upon further examination and detailed

study it is found that it would be more accurately termed a macrocytic anemia. The cell instead of being a disc shape as is the normal cell becomes shorter in length but compensates by increasing in diameter.(41) As stated by cheney(7) while the normal cells are 7.5 microns in length the cells in this disease average from 6 to 7 microns. This variation in shape of the cell is illustrated in Fig. I. Associated with this there is an increase in the hemoglobin in the cells.(42) This particular form has been considered one of the distinguishing inherited characteristics; but there are several objections to this theory: (a) this has been abscent in some cases, (b) it is not peculiar to the disease but has been reported in others, (c) there are patients who after splenectomy this has disappeared.(7).

Since the chief characteristic of this disease is the excessive hemolysis, the inter-relation of the activity of the spleen the function of the bone marrow, the abnormal physical characteristics of the cell, and the increased fragility to hypotonic solutions has developed into a major problem about which there is a great deal of controversial discussion.

In many cases which seem to be quite typical of the disease do not respond to splenectomy. This incompleteness or lack of response to splenectomy according to Dawson(9) may be due to the bone marrow function failing to regain its full power or to the fact that the removal



I Chronic hemolytic anemia
Diameter 6.18
Thickness3.02
Volume 90

II Simple microcytic anemia
D 7.07
T 1.60
V 63

III Pernicious anemia
D 8.89
T 2.20
V 135

IV Obstructive jaundice
D 8.57
T 1.60
V 92

V Normal
D 7.7
T 2.0
V 90

Fig. I Cross-section and measurements of the mean erthrocyte in different clinical conditions
Taken from Haden (18)

of the spleen is insufficient and that there is a hemolysis which is excessive in other parts of the body. Beer(4) and other authors point out that splenules or accessary spleens are present and these after splenectomy enlarge, just as a remnant after resection and carry on the function of the spleen. Beer reports that many times they are numerous and there may be from thirty to forty through the omentum.

Momigliano and Baitat(26) demonstrated in their experiments the existence of an approximent normocytic reaction of the bone marrow, even in cases of hemolytic anemia which did not seem to have been completely cured after splenectomy, as evidenced by the persistence of microcytosis and erthrocytic fragility even though slight. They illustrated the capacity of the bone marrow to produce normal cells, at least from the view point of diameter. These observations were not favorable to the hypothesis that the spheroidal microcytosis represents a constitutional defect in erthropoieses. In their opinion it was evidence in favor of the view that with the cessation of hyper-hemolysis, that the state of affairs disappears which transforms into an actuality the potential disposition of the bone marrow to form pathologic erthrocytes.

Whitcher(42) also disagrees with the theory of the pathological condition of the red cell and states that there is a return to a more normal cell following splenectomy,

also a more normal blood picture. Therefore because of this disappearence of the microcyte, the feature maybe regarded as a concomitant manifestation of the anemia of the disease, rather than an inherent character of the erythrocyte of the individual. Cheney(7) states that it seems probable that the explanation of the microcyte in this disease is simply that these small round cells represent the subnormal response of an over stimulated bone marrow whatever the cause.

Then there is the opposite view point in which Weber(41) states that the fundamental abnormality is in the red blood cell and that this must not be confused with excessive blood regeneration.

Naegeles' conception, as described by Haden(18), of the microsperocytosis as the fundamental and probable contrast inborn error seems the correct one. Its presence after splenectomy as it may be found is important in evaluating it as a primary feature. In the same article be Haden he gives the views taken by other German authors. Von Boros pointed out that the capacity for absorption is less, instead of more, since such cells have a small surface in relation to volume. Gansslen stated that both (shape and fragility) are evidence of defect in the bone marrow and suggests that the microcytosis by reason of their size absorb water more readily from hypotonic solution. Meulengracht has disregarded the parallelism between the two

findings, shape and absorption, but concludes there is no relation between them.

In laboratory animals from Emmons and Vallery-Radont's studies, taken from Haden(34), as the cells change toward a globular shape in different species, the resistance to hypotonic saline solution decreases in almost direct porportion, so there seems a direct relation between the tendancy to spherocytosis and increased fragility in lower animals. The author showed that the cells went through these changes when placed in hypotonic salt and so that in the pathological cells the distance to hemolysis is shorter. He was able to show from charts of the findings that there was a close relationship between the point of initial hemolysis and the volume-thickness index.

Haden in his conclusions agrees that in congenital hemolytic anemia cells have at the beginning a shape through which the normal cellspasses to hemolysis. One fundamental variation in hemolytic anemia is this cell and the anemia, jaundice, splenomegaly, reticulocytes, and the increased fragility are second to the globular form of the red cell.

Doan in attempting to determine whether the pathology was in the red cells or in the plasma in cases of hemolytic anemia has confirmed the fact that the erythrocytic fragility is inherent in the red blood cells. This

was done by testing the fragility of the cells in hypotonic saline and also with plasma or serum and he found that the fragility was present in both cases.

Another point of controversy although not much discussed is the presence of nucleated red cells or Jolly Bodies. Morris(27) reports one case of his and three cases of Roth in which nucleated particles have been found following splenectomy. They appeared within two weeks. Beer(4) in his article states that in view of the fact that some of the red blood cells contain so called Jolly's Bodies even as late as twenty years after splenectomy it is suggested that the spleen in some way influences the removal of the nucleus from the normoblast. There could be no other authors to support his suggestions. Krumbhaar(22) has done extensive work on this subject and reports that he has never seen these Jolly Bodies. He has experimented with animals, mostly the dog, and outside of an occassional normoblast he has never seen Jolly Bodies. An occasional normoblast may be seen in the normal. He has not been able to find them after splenectomy or before, during the anemia as it is occasionally reported to occur.

Vaughan and Goddard(39) made studies in the relation of the hemoglobin and the red cells. They studied cells shape and concluded that the average mean corpuscular hemoglobin concentration in this disorder was found to be greater than the normal controls. They suggested that the

finding is associated with the discrepancy between cell volume and cell diameter as discussed under the pathology of the red cell. The following is a chart of their findings.

	Red Cells (count)	HB gm.%	Mean Corp. Vol.	Mean Corp. HB.
5 controls	5.17	13.02	78.54	25.17
4 Hemolytic anemias	3.02	8.52	79.08	28.20

Other than this high hemoglobin concentration the hemoglobin follows along with the red cell level during the course of the anemia. It rises and falls along with the crises and follows the same level as the red cells after splenectomy.

The fragility of the red cell is one of the discussed characteristic of the disease hemolytic anemia, and although it is one of the cardinal findings its presence varies a great deal and may lead to much confusion. Thomson stated that repeated fragilities are necessary for diagnosis. This is because of the fact the fragility differs at different times in the same patient; it may be normal, or the cells may be more resistant. Giffin(15) makes note of the fact that an increased resistance may be present. The same author in another article(14) makes the statement that, "the increased fragility of hemolytic jaundice can be modified by long continued anemia to the degree that an increased resistance may be present".

Attention was first called to the fact that the

fragility can be normal in cases of hemolytic anemia by Gänsslen and he stated that it could be found normal in about 10% of cases. This figure still holds as about the average although different series vary to some degree. Giffin(14) in reporting a series of twenty-one cases found the fragility normal in three cases. Dawson(9) found the fragility normal in five of forty cases. Pepper(32), Thomas(38), and Van Ravenswaay(34) report a single case each with normal fragility. There cases were somewhat different in that Thomson found the fragility normal before splenectomy and increased after splenectomy. His explanation for this was that the spleen was removing the fragile cells before operation. Van Ravenswaay's case was normal before and after operation.

As to the effect that splenectomy has on the fragility of the red cells varies a great deal just as the occurrence of the condition. Campbell(6) in reporting four cases with increased fragility before splenectomy found that the average fragility curve was below that before operation but that it was still above the normal of four controls. Giffin(14) in reporting on twelve cases found similar results. In general the increased fragility was present after splenectomy although there was a slight decrease in the amount of fragility. Only two of the cases were normal. Dawson(9) reported that the fragility remains unchanged in half of the cases and is reduced in the re-

mainder after splenectomy. In the three cases reported here, there was one that at the end of a month showed an increase in the fragility, one that showed a decrease although still remained above normal, and the third that showed little change remaining slightly above normal fragility.

Increased fragility has been reported in pernicious anemia, post-hemorrhagic anemia and various leukemias, which usually show a decreased fragility but never to the degree that is found with hemolytic anemia. Cheney(7) states that an excessive number of microcytes in the blood tends to increase the resistance and it is not the small cells that hemolize. Size is used to explain the phenomenon and it this disease we have large cells apparently accounting for the increased fragility. He states that when there are more reticulocytes in the blood the fragility is nearer normal.

Dawson(9) states that the fragility varies in the same case. The extent of fragility is not an indicator of the clinical severity. It is a factor and not an essential feature; an adaptible part of a large mechanism.

Krumbhaar(22) with experimental work found that whether the spleen was removed from normal animals or for therapy in disease that there was always an increase in resistance of the erythrocyte to hypotonic saline as well as most other forms of damage. His experiments were with

men, dogs, and monkeys. In his article he sites Bottazzi as stating that the red cells emerging from the spleen appear less resistant, and indicates a hemoclastic effect on certain erthrocytes. This does not fit very well into our explanation of the disease process and as Pepper(32) states that although in many cases increased fragility persists, splenectomy has produced a virtual cure in every other respect. Also there is no satisfactory evidence to show that the spleen of such cases contains hemolysins. However that the fragility persists after splenectomy is the greater majority of cases seems to point to the primary implication of the bone marrow but the effect of removal of the spleen on the size of the red blood cells as Paxton(32) points out would suggest that there are two factors involved.

Neilson and Wheelon(28) in 1920 published an article on the hemolysis of the red cell and presented a vary different approach than is usually considered and although is does not coincide with the present pathways of though and research it is well worth noting. They stated that although the membraned cells and osmotic resistance naturally fall together as interpretive measures; the action of specific hemolytic agents, animal and vegatible poisens, cannot be easily explained for the destruction of the cells. They state that the stroma of the cells freed from its hemoglobin content is toxic and capable of producing intravascular clotting. Also that this stroma toxicity as they call

it is responsible, or at least leads to the hemolytic process in certain diseases where there is a break down of the red cells as in malaria, syphilis, and hemolytic anemia. The stroma of the normal cells or when in combination with the hemoglobin as it exists in the normal cells is perfectly inert.

In there experiments they used sapotoxin to test the resistance of the red cells, and found it decreased in in hemolytic jaundice. They found that cholesterol had a relation to the fragility of the cells when tested with sapotoxin. They tested the blood in over a hundred cases of different diseases,nine of which were hemolytic anemia. They found a definite relationship between the blood cholesterol and the resistance of the cells. When the cholesterol was increased the resistance was high and when it was low the resistance was decreased. The cases of hemolytic anemia showed markedly decreased resistance and low cholesterol. They concluded that the cholesterol is an important protective element in the protection of the red cell against sapotoxin and that it is more practical therefore to determine the cholesteral level than the fragility.

RETICULOCYTES

Another cardinal finding in cases of hemolytic anemia is that of an increased presence of reticulocytes in the circulating blood. Even though it is a cardinal finding its presence may vary a great deal in different patients and may also vary in the same patient. It may be abscent. The usual level is from 5 to 30% and varies among authors.(10)(7)(17)(23) Higher figures are seen in many cases as for example Baty(3) reports a case with 92% over a long period of time. This may be disputed for the reticulocyte count varied from 30 to 70% for two years after splenectomy and the patient died in what was diagnosed as a crises. Wilkie(43) however, reports a case with 80% reticulocyte count which returned to 1% following splenectomy. Glover(17) reports a case with 18.25% and dropping to 1% by a month after splenectomy.

The reticulocyte count is generally associated with and is an indicator of the bone marrow response. Pepper(32) reports a case in which there was no increase in the reticulocytes which lead to a confusion of diagnosis and delayed treatment but it was later concluded that the case was in an aplastic state. Lewis(23) agrees with this that a low reticulocyte count indicates an aplastic state.

Piney(33) states that there is no relation be-

tween the reticulocytes and the degree of anemia. There is however, a close relation between the amount of hemolysis and the number of vitally stained corpuscles. This agrees with Cheney that the number increases in a crises.

Krumbhaar(22) in his experiments on normal mammalian spleens found that in from one to three days after splenectomy there was an increase in reticulocytes and may explain the increase in red cells after splenectomy, This rise was not present in controls. This increase lasted from ten to forty-two days, and sometimes over a year as did the bone marrow hyperplasia. This does not necessarily mean an increased rate of blood formation. It is well known that in cases of hemolytic anemia the reticulocytes decrease following splenectomy.(11)(43) Wilkie's case dropping from 80 to 1%. Krumbhaar did not explain or express an opinion as to why the reticulocytes increased after splenectomy in the normal mammalian but in the cases of hemolytic anemia in which there is a pathological process going on it is believed that the deman on the bone marrow is relieved and it is not forced into such over activity as to cause it to discharge these young and immature cells.

ICTERUS INDEX

Jaundice a striking symptom of the disease is quite constant although fluctuates a good deal through the course of the disease. It is a result of the increased bilirubin in the blood from the excessive red cell destruction; Barron(2) give a complete discussion of this process in his article in Medicine but which we will not go into here. Scott(36) reports that Gansslen found the presence of jaundice in 60% of his cases. Dawson(9) failed to find it in only four of his forty cases. This jaundice id dependant upon two factors: the rate of blood destruction or bilirubin formation, and upon the excretory ability of the liver. Cheney(7) states that while hemolysis is reponsible for the jaundice and anemia, the visible degree of either depends upon the functional capacity of the bone marrow and the liver. This idea is somewhat different that the first in the fact that he recognizes that if the bone marrow does not keep up the red cell formation, as it often doesn't in this disease, consequently hemolysis can not take place. Dawson(9) as well as Lewis(23) and others bring out the fact that there is no correlation between the intensity of the jaundice and the anemia. However, the hemolytic activity at the time and the presence of a crises will increase the jaundice. Chilling, gastro-intestinal disturbances, and emotional strains will increase it just as they bring on a crises. Scott(36) points

out that the jaundice may not appear at birth in the cases that are definitely congenital in type but appear in later life and from then on it may persist throughout the rest of the persons life in varying degrees.

The effect of splenectomy on jaundice and the icterus index as it is commonly determined is quite marked. Immediately following the operation the jaundice can be seen to decrease and the index recedes. Doan(10) reports a case that dropped from 46 to 31 on the day of the operation. He states that there is a progressive decrease following splenectomy. In cases where the operation is most successful the index will return to normal while other cases although clinically they are successful and clinical jaundice is not present the index still remains slightly increased. The normal icterus index is from 3 to 6 and Cheney (7) states that in hemolytic anemia it rarely runs above thirty except in a crises. Two of our cases reported here went as high as thirty and all cases showed a gradual decrease following operation. One dropping 17 in 48 hours.

Even though there is a high bilirubinemia it is quite characteristic of this disease not to find bilirubin in the urine. Dawson(9) holds,however, that it may be increased in the feces.

WHITE BLOOD CELLS

The white cells, as well as the red cells and the blood forming organs, are disturbed in this disease and are found to vary throughout its course. Lewis(23) states that the changes are not characteristic but that during the inactive stage the white count is usually normal. Cheney(7) agrees with this, stating the count is normal or a tendency to excess. Doan(10),however, points out that a lecopenia maybe found and that the more severe the anemia the more striking the lecopenia in general. In Case I that was presented in this paper seems to illustrate that point; the patient having an anemia of below one million showed a white count between one and two thousand. During a crises the white count will usually rise and there is a noticeable shift to the left.(23)(19)(7) This same leucocytosis is noticeable after splenectomy. Doan(10) reports a case that rose from 21,000 to 70,000 in less than two hours. This point is also brought out be Giffin.(15) In the cases presented here this was also meet with. One case running around a 15,000 white count increased to 73,000 in a few hours and although there was a marked drop the same day of the operation, five days later the count was still 26,500. It remained above the level of before splenectomy.

Freud(25) has brought up the point of splenectomy in the present of chronic infection as depressing the defense mechanism against infection. Little actual clinical evidence is available to determine this point. Patek(29)

in his article on the effect of adrenalin on the blood of patients with and without spleens found that there was no difference in the two groups. He has studied the blood before and after the subcutaneous injection of adrenalin in two normal cases and nine with hemolytic anemia(5 spleneomegaly and 4 splenectomy) and five with various types of spleneomegaly. He concluded that no case showed a significant change in the concentration of the red blood cells, hemoglobin or hematocrit. In all cases there was a leucocytosis of myloid and lymphoid blood eliments. He concluded it was not from spleenic contraction and suggested the possibility of an alteration in the blood stream.

The presence of an eosinophilia is reported by many authors in reporting cases. It is usually found to be around 4% although it may be higher and some authors find no increase in the eosinophils. Keefer(20) makes a note of this condition and reports a case in which the eosinophils were present as high as 15%. This is as high as recorded but the fact that there is some increase of this type of cell in the circulating blood is a rather common finding.

PLATLETS

Experimentally and clinically the platlets have been found to increase after splenectomy. Krumbhaar (22) in studing the normal mammalian spleen found that in dogs there was an early rise in the platlets following splenectomy which dropped toward normal and was followed by a second and lasting rise. Galloway(12) followed the platlets in humans after splenectomy in cases of thrombocytopenia and splenic anemia. He reports on three cases and all showed a penia before operation. His curve differed somewhat from Krumbhaar in that it reached a maximum in eleven days and a gradual fall but which remained much above the original level. There was no reported second rise. Paxton(30) and Doan(10) report similar findings in cases of hemolytic anemia. Paxton in four cases reports an increase in the platlets to 7,000,000 to 8,000,000 per cubic millimeter and then returning to normal. Doan with two cases running below 200,000 reports an increase to a high point of 750,000 and a return to 300,000 to 500,000. These findings are in agreement with other authors following the condition.

Galloway examined the blood coming from the splenic vein in one case and found it to be 22% lower in platelets. He also found an increase in platlets in the spleen over the amount in the blood.

Although the platlets do not play an important

part in the cases of hemolytic anemia they follow somewhat the course of destruction as the red cells and respond similarly after operation. Evidence favors the thrombulytic action of the spleen, the histology of the spleen and the rise in platlets after splenectomy. It lasts for a lack of an inhibitor or a lytic organ. There has been no investigation as to the nature of the platlets in hemolytic anemia as to whether they are normal of abnormal as are the red blood cells. Until decisive evidence is available Krumbhaar states it would be reasonable to assume that the post splenic thrombocytosis in the normal mammalian spleen may be the result of both decreased thrombolysis and decreased inhibition of formation. This is probably also the case in hemolytic anemia.

PHYSICAL FACTORS

Giffin(16) and his co-workers have made a careful study of the blood volume before and after splenectomy to determine the change and show whether it is an actual or a relative anemia. He ran a fairly large group and compared them to normal controls. In his cases of hemolytic anemia, according to the surface area means of calculating the serum plasma volume, for the entire group it was 2200 cc. for each square meter. This is about 15% higher than normal. Following splenectomy there was a smaller variation.

His status for this disease is that there is a decreased cell volume and a normal blood volume. Or that there is an actual anemia rather than an apparent anemia in the plasma. This refers to total cell volume.

Following splenectomy there is a blood volume and a cell volume increase which is most striking and correlates well with the clinical improvement following operation.

His series consisted in the study of eleven patients.

Little material is present in the literature on the condition of the blood pressure in hemolytic anemia probably because it has no direct bearing on the pathological picture present. However, Giffin(13) experiences a noticeably low pressure in all but one of seventeen cases.

The systolic was frequently below 115 and the diastolic was constantly low, averaging 72, in the sixteen cases. This hypotension occurred irrespective of the degree of anemia or abscence of anemia. Doan(8), although he did not mention it but taken from the case historys, he shows a rather constant low blood pressure for his recent series.

Another mechanical factor in relation to the blood, which is found in hemolytic anemia after splenectomy, is the change in the portal circulation. Giffin(15) remarks that along with the decrease in jaundice there is an improvement in the portal circulation, probably an evidence of decreased volume of portal circulation, which is demonstrated by the disappearance of ascites and frequency of gastro-intestinal hemorrhage.

Little mention is made in the literature regarding the sedimentation rate in cases of hemolytic anemia. This also is probably due to it lack of relation to the physiological process of the anemia. Doan(10) mentions a case in which the rate was 70 mm. in two hours. Later on the same day of splenectomy the rate had dropped to 4 mm. in two hours. He did not explain this but stated that in the same period of time the red cell count had doubled itself. It is the opinion of some authors that the sedimentation rate will increase in cases of marked anemia due to the mechanical process of decreased blood eliments in the plasma. It has also been associated with the cholesterol of the blood.

LYSINS

The subject of lysins and agglutins is little touched on in the literature and there is little evidence to support this phenomina but for the sake of completeness the following paragraph is taken from Aaron(1); "Lysins and agglutins are present but auto-lysins and isolysins are not always found in the blood serum. It must not be forgotten, however, that isolysin is present in various diseases as well as in health. Auto agglutination of the red blood cells is considered characteristic of acquired hemolytic jaundice. If a drop of washed normal red corpuscles be added to ten drops of the serum of the patient agglutination occurs within a few moments".

PATHOLOGY

The spleen has long been considered the important pathological structure in hemolytic anemia. It is believed by most men at the present that hemolytic anemia is a pathological entity.(37)(10) Thompson quot," It is felt that hemolytic jaundice is a definite clinical and pathological entity and that no difference exists between the congenital and the acquired types of the typical disease". He states that the diagnosis can be made from the microscopic findings. Doan also calls it a specific clinicopathologic entity. In Doan's article in the Ohio State Medical Journal, he gives seven references to support his statement that the histopathology of the spleen is pathognomonic. Cheney(7) states that there is no universal agreement that it has not undergone any pathognomonic change. McCarthy of Mayos describes it as an excessive size from over filling with blood and no particular alteration on the structure of the spleen in any of its parts. It is this side of the question that is usually expressed by men on the Nebraska staff. Many men are of the opinion that the changes in the spleens of these patients can also be found in the spleens that are not from people suffering from hemolytic anemia.

The common findings pathologically are that grossly the spleen is enlarged from 800 to 2000 gm. Lewis reports a spleen waying 2,750 gm. The normal spleen is from

150 to 250 gm. The surface is smooth and does not show the perisplenitis or thickening that is seen in other diseases as Banti's. The surface is firm and may show a dark red color with mottling from increased pigmentation. The cut surface is relatively dry and dark red in color from excess blood. Malpighian bodies are not visible.

Microscopically the spleen shows small and widely separated Malpighian bodies. The venous sinuses are enlarged and widely dialated, someimtes they are empty although usually packed with red cells. The sinus endothelium is often prominent. The pulp also appears as a mass of closely packed red cells and a diffuse infiltration. Cases vary somewhat as to the degree of congestion of the sinuses and pulp with red cells, and authors vary in reporting the condition. There is no increase in the amount of connective tissue present. Although Thompson(37) states that there is no increase in the iron pigment most authors agree that there is an increase in the intra and extracellular pigment as one would ordinarily expect. There is no evidence of erythro or myelopoieses. Doan(10) has taken cultures from the organ but they have not produced growths.

From Klemperer's(21) most complete article on the pathology of the spleen he describes the condition as showing striking engorgement of the reticular meshes of the red pulp. Venous sinuses being less distended. The enormous number of erythrocytes obscures other cells in the pulp,

but in the less hyperemic portions one finds a hyperplasia of the reticulum cells. Thus the condition being one of hyperemia and hyperplasia. The evidence of increased blood destruction is not constant, erythrophagocytosis and siderosis which are conspicious in some cases are abscent in others.

Klemperer sites Eppinger as maintaining that the engorgement of the reticulum creates unusual conditions favorable for increased blood destruction by the macrophages of the spleen. This excessive immigration of erythrocytes into the reticular meshes is accounted for by an alteration of circulation of the blood. He agrees with Weidenreich who states that the blood circulates inside the spleen within closed as well as open pathways, and alteration of the closed tracks leads to a shunt of current into the open pathways. Eppinger observed hyaline changes in the intima and rupture of the clastica, etc. and this he believed proved his physiology of increased cell destruction. This change is seen in a varity of lesions and so is not satisfactory.

Lauda another German author cited by Klemperer(21) ran experiments to show an increased arterio-vaso-dilatation in the spleen in hemolytic anemia and produced it in dogs giving a similar picture. Yet this did not produce a greater blood destruction. He believed that in hemolytic anemia the cells may be abnormal and with this set up they may undergo

a more rapid degeneration. It maybe linked with a reflex to the bone marrow; that is abnormal cells cause a reflex and splenic hyperemia.

Klemperer in reviewing this author and from his own work concluded the following theory; that the increased blood destruction is dependant upon abnormal circulation, but this abnormal circulation as evidence of engorgement of the pulp is the result of a pathological condition of the erythrocytes and not the splenic arteries. This can be used to explain the persisting conditions after splenectomy.

Further remarks as to Lauda's work on the vasodilation and reflex control he showed the importance of the sympathetics on the spleen and their production of this condition. He stated that emotional conditions would effect the condition. It has been noted by many authors that emotional upsets may percipitate an exaserbation or crises. Cheney(7) said the crises are apparently brought on by emotional disturbances as fear, grief, worry as well as bodily factors as over exertion and acute infection.

The liver is thought not to have a primary or direct relation to the pathology of this disease, but changes that may be found in it are the result of its relation by its excretory function of the blood pigements. Cheney(7) states that changes in the liver are slight or abscent. In some few instances real hypertrophy has been noted, due to its effort to dispose of the excess bili-

rubin brought to it by the blood. Pemberton(31) in reviewing 188 cases found, 55 showed secondary liver enlargement, 32 being enlarged congested and hard, 7 cirrhosis, and in 6 ascites. Doan(10) states that the liver may show large quantities of hemosidern in the polygonal cells and an increase in the number and size of Kupffer cells.

McNee(24) a British writer bases the pathology of the disease on the reticulo-endothelial system, and states,"I am satisfied that it is the reticulo-endothelial phagocytic cells which are active in this disease". The function of the intracellular blood destruction is a function of the reticulo-endothelial system, of which the spleen is an important center, but not of any means the only one. He believes that the red cell is broken down and the iron free part of the hemoglobin is released into the blood stream as a bile pigment to be carried to the liver for excretion. Doan(30) also agrees with this theory and believes that there is an over activity of the phagocytic mechanism(reticulo-endothelial system, clasmatocytes) of the body, the center normally in the spleen. He is the strongest American author in support of this idea and in his recent article in which he presents six cases operated on in a crises, he showed in many of them that there was an increased phagocytic action noticed by the supra-vital method. Dr. Latta took the spleen from one of our cases and

put sections on a slide and sealed it with neutral red on the section. This was kept warm. The operation was performed about ten in the morning and the slides made immediately. Late that afternoon large vacules of neutral red could be seen in the cells. Phagocytosis could be seen in the afternoon late and there was still some present the next morning. This was considered normal.

On pathological examination of the bone marrow it is quite well agreed that there is a condition of over activity. Cheney(7) states that, "Guizette, 1912, reported a case in which he found signs in this structure of an enormous hyperactivity, with fatty marrow crowed by the red erythroblastic marrow". This was apparently the first case reported of this disorder. Cheney further remarks that from all evidence as hand it seems fair to conclude that the bone marrow is simply overworked, but condemmed by the hereditary factor to put out fragile erythrocytes. Doan(10) agrees with this hyperactivity of the marrow but states that it is predominately erythropoetic with normoblasts and erythroblasts rather than megaloblasts which would help to differentiate it from other anemias, as pernicious. Dawson(9) agrees with this using the phrases that there are haemoblastic more than leucoblastic, and normoblasts are more common than megaloblasts. He also mentions that mitotic figures show a varying prominence.

In view of the fact that there is divided opinion

as to whether the primary pathology is in the fragile erythrocyte or primary in the spleen comment will have to be made regarding Cheney's statement that the bone marrow is condemmed to put out fragile cells. He believed that there is no pathology present in the spleen other than an over activity.

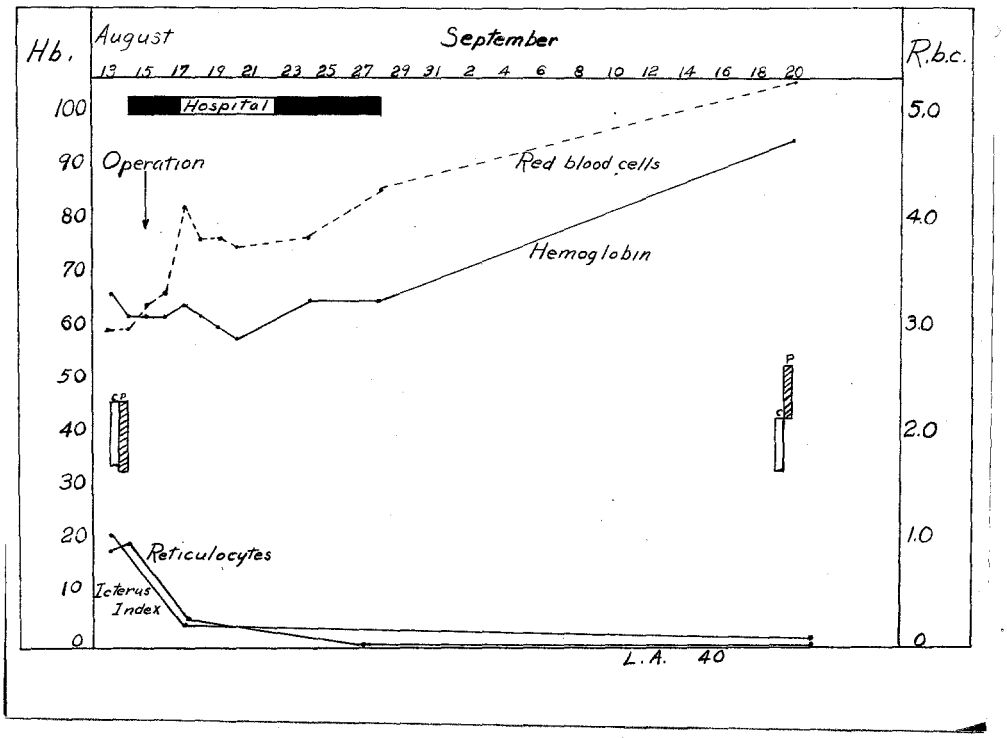
Organs other than the spleen, liver, and bone marrow show no change and play no part in the pathology. This is unless there is the presence of secondary spleens or the reticulo-endothelial system takes over the function of the spleen after splenectomy but no mention of this was found in the literature.

Case Report No. I

Mrs. LA a white housewife, age 40, was believed to be well and healthy until six years ago, at which time she had an attack of weakness associated with jaundice and pain in the left side. She has had varying degrees of a yellow coloration of the skin with weakness since that time. For the past year she has been conscious of a persistant dragging feeling in the left side. Also her weakness and jaundice have been worse during the past year.

Physical examination showed an icteric condition of the sclera and skin and a spleen that was enlarged to the midline and to the crest of the ilium. The liver was one finger below the costal margin.

Laboratory reports showed a hemoglobin of 49%, red blood cells 3,010,000, and white count of 6,650. The fragility was normal. The reticulocytes were 20.4% and an icterus index of 22. Splenectomy was performed with a prompt recovery.



Case Report No. II

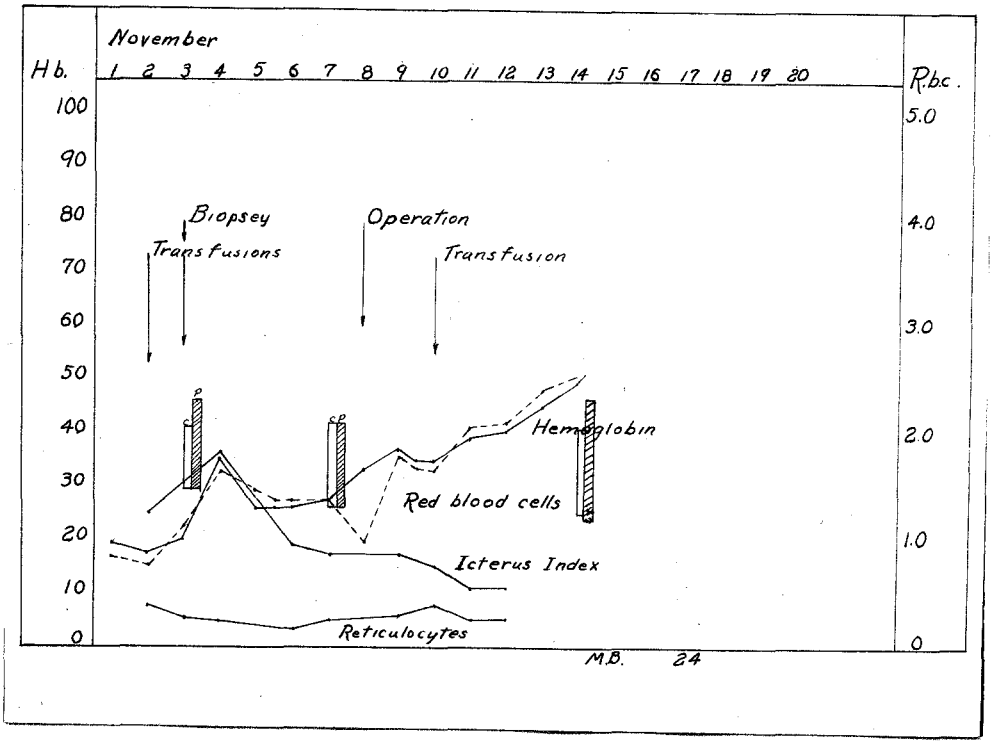
Miss MB a white houseworker, age 25, entered the hospital for the third time. On the two previous entries, the last of which was in 1932, or four years ago, she had been diagnosed as having pernicious anemia. She was given liver extract with questionable good results. Two months ago she was out of liver and had an attack of diarrhea and from this time she has been failing rapidly. Weakness and palor has been increasing. She has lost seventeen pounds of weight and complains of shortness of breath. There has been slight edema of the ankles for two or three weeks and she has been conscious of her heart going fast.

Past history shows she has been anemic since she was eighteen years of age. Has had a sore tongue occasionally. With attacks of anemia she has noticed that the spleen enlarges and her skin becomes yellow.

Physical examination shows a spleen that is below the level of the umbilicus and the liver two fingers below the costal margin.

Laboratory examination gives a hemoglobin of 20%, red cell count of 990,000, and a white count of 4,000. The fragility was slightly increased over the control and the icterus index and reticulocytes were increased to 20 and 8% respectively.

Splenectomy was performed and after a slight delay she showed good improvement.



Case Report No. III

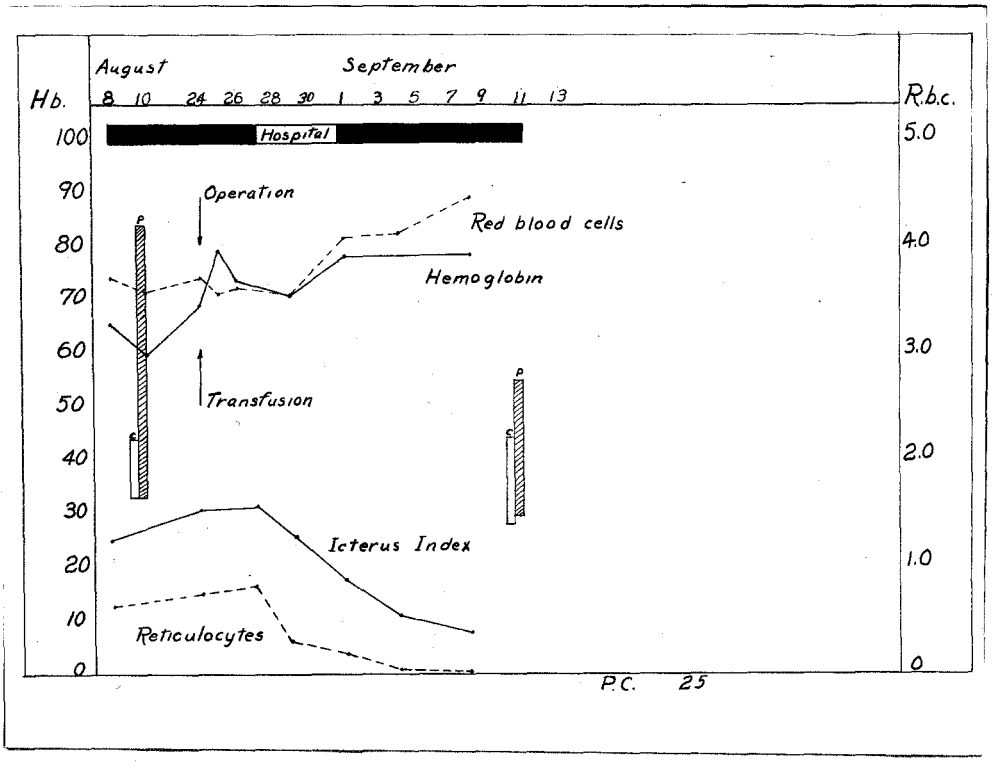
Mrs. PC a white housewife, age 25, entered complaining of jaundice, backache, and an enlarged spleen. She was in good health until June 1934 at which time she had an eight months pregnancy terminated because of high blood pressure, albuminuria, anemia, blind spots, etc. She recovered rapidly but in December 1934 she again took sick and was treated for anemia over a long period of time. She had noticed that her spleen enlarged with the amount of work she did and was subject to vary with her general physical condition. She had had some abdominal pain and diarrhea and with this she got yellow.

She also stated that at the age of ten she had a splenomegaly with an attack of pneumonia.

Physical examination showed an icteric tinge to the skin and a spleen four fingers below the costal margin.

Blood count showed the red cells to be 3,600,000 and hemoglobin 80%. There was a variation in the size and shape of the red cells with noticeable spherical forms. Reticulocytes 11.8% and icteric index 25. The fragility was much increased, hemolysis beginning at .85% and the control at .44%.

Splenectomy was performed with recovery.



SUMMARY

In summarizing we find that in hemolytic anemia we do not know the exact nature of the pathological process, however, much can be done for the patient by the recognized treatment of splenectomy. The pathology is centered around the red cell which we find is abnormal as to size, shape, and fragility. This cell is broken down in an excessive rate in the spleen which leads to an anemia and a high bilirubinemia giving the jaundice. The anemia results in an increased demand on the bone marrow and it is the opinion of some authors that this is why the red cells are abnormal.

Patients may go along for years with this condition present and have not symptoms. They are, however, subject to crises or flare ups of the condition which as the anemia occur in varying degrees. These may be brought on infections, other diseases, and emotional disturbances and result in a marked anemia causing symptoms of such. The recognized treatment is splenectomy which gives immediate and remarkable results. The red cell level will rise suddenly along with the hemoglobin, although the red cells still remain abnormal morphologically and as to fragility. The cells usually return to the normal level. The jaundice clears up and the demand on the bone marrow is decreased which results in a decline in the reticulocytes. This leads to permanent relief of the symptoms although the pathology.

of the red cells usually persists.

The pathology found is not marked. The bone marrow shows a hyperplasia of the erythroblastic tissue. The liver will show signs of hyperactivity from the increased amount of pigments to excrete. The spleen is enlarged and shows engorgement with signs of over activity, some authors describing increased phagocytosis.

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