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THESIS

SPLENIC ANEMIA

A CLINICAL AND PATHOLOGICAL STUDY OF SIXTY-NINE CASES OF SPLENIC ANEMIA OPERATED ON AT THE MAYO CLINIC FROM November 14, 1905 to September 1, 1920.

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Sir William Osler in his "Principles and Practice of Medicine" discusses splenic anemia under the heading, "Primary Splenomegaly with Anemia", which he defines as "a primary disease of the spleen of unknown origin, characterized by progressive enlargement, attacks of anemia, a tendency to hemorrhage, and in some cases a secondary cirrhosis of the liver, with jaundice and ascites. That the spleen itself is the seat of the disease is shown by the fact that complete recovery follows its removal."

According to this definition, Osler has included the cases of primary splenomegaly which Rolleston prefers to discuss under separate headings, - "chronic splenic anemia" and "Banti's disease".

According to Rolleston, chronic splenic anemia presents the following characteristics: "(1) Chronic splenomegaly which cannot be correlated with any recognized cause. (2) The absence of enlargement of the lymphatic glands. (3) Chronic anemia (with low color index). (4) The absence of leukocytosis and usually the presence of a leukopenia. (5) Liability of copious gastro-intestinal hemorrhages from time to time and (6) Prolonged course without any tendency to spontaneous cure, though splenectomy is usually curative."

In this same article, Rolleston tells what he considers the relation to be between Banti's disease and splenic anemia. Rolleston says, "The title, Banti's disease, is now often used as synonymous with splenic anemia even by those who fully recognize that it is a sequel or terminal stage of splenic anemia and does not occur in all cases even when unduly prolonged".

The term "splenic anemia" was first applied to a group of cases by Griesinger in 1866. The first American writer to call attention to the disease was H.C. Wood, who, in 1871, published a paper on the relations of leukemia and pseudoleukemia, describing two forms of the latter condition. He says, "I now desire to show that there is still a third form of pseudoleukemia - a splenic variety. Under the name of tumors of the spleen, splenic

cachexia, etc., from time far back, medical records furnish accounts of cases which I believe represent this affection." It was not until 1893, however, that a systematic study of the disease was undertaken due largely to the efforts of Banti.

According to Hollins in the "Practitioner", Banti describes three stages of the disease named for him. First, is the pronacitic stage in which splenic enlargement is present with or without anemia. Second, is the transitional stage of which the most prominent symptom is diarrhea; anemia and blood changes are found, the liver is somewhat enlarged and jaundice may be present. Third is the ascitic stage or Banti's disease proper.

In this study of splenic anemia it was thought advisable to first consider the pathology of the disease as revealed by the study of the spleen and then to take up the clinical characteristics as presented in a careful review of the clinical records of the cases. On account of the great confusion that now exists in the literature on this subject all of the cases will first be considered as a whole. A separate discussion will then be devoted to those patients who had, in addition to primary splenomegaly, a distinct hepatic cirrhosis.

This report is the result of a study of the pathologic findings and clinical records of sixty-nine patients with splenic anemia, on whom splenectomy was done at the Mayo Clinic from November 14, 1905 to September 1, 1920.

THE MICROSCOPIC PATHOLOGY

Variation in the normal spleen.

Before the pathology of any organ can be correctly investigated, it is essential that the pathologist have a clear conception of the normal. This is especially true in the case of the spleen for the gross and microscopic picture may vary widely under normal conditions. These normal changes

To show the average findings and the variations in the Microscopic Pathology of Splenic Anemia.

may be permanent, as in variations with age, or they may be temporary, as after a severe hemorrhage or sepsis. The pathologist must be familiar with those variations before he can determine accurately the changes that have been brought about by disease.

Before the study of the pathology of splenic anemia was undertaken, therefore, an effort was made to learn of some of the variations that could be ascribed to normal influences. This was accomplished by obtaining splenic tissue at necropsy in cases in which death had occurred rather suddenly and from some non-septic process such as injury or brain tumor and in which the necropsy was done within three hours of death.

Terminology.

By "sinus endothelium" is meant a specialized form of endothelium and not the lining cells of blood channels as the term is commonly employed. These specialized endothelial cells of the sinuses are probably reticular cells and to be correct should be so designated.

The word "pulp" is used to designate the cellular structures lying between the sinuses. "Pulp cords" would probably have been a more suitable term.

"Reticulum" refers to all the connective tissue not included in the capsule, trabeculae, or blood vessels.

Hyalin changes in the capsule and trabeculae are not included under the term "degenerations" which is reserved for degenerative changes in the reticulum, in the malpighian corpuscles, or within the pulp.

Method of study.

In order to express more accurately the degree of pathologic changes observed in the study of the spleen, figures have been used instead of descriptive adjectives. Normal findings were marked zero or simply

"normal". The degree of increase of the various pathologic processes above normal was designated on a scale -1, +2, +3, +4, while the decrease was graded -1,-2,-3,-4; +5 and -5 have been used occasionally in grading very unusual and extreme conditions.

A few words concerning the routine method in the selection of tissue for microscopic study are necessary. At least three blocks of tissue were taken from each spleen: one containing a portion of the capsule of the diaphragmatic surface, one from near the center of the organ, and one from near the hilus. The last block always included a portion of the wall of one of the large veins.

Microscopic sections were made by the frozen-section method or by embedding the tissue in paraffin. The routine stain was hematoxylin and eosin, but many of the specimens were also prepared with Dominici's and with nethyl-green pyronin stains.

A composite picture of the histopathology of splenic anemia is one of a generalized fibrosis. There are, however, no very definite and well defined characteristics which will enable the pathologist to say with certainty that the slide is one of splenic anemia.

The wide variations in the pathology of splenic anemia has been one of the arguments used in an attempt to prove that cases classified under this term belonged in closely related clinical groups and did not bear a sufficient clinical and pathologic resemblance to justify their being considered as a distinct disease entity. From the pathologic standpoint in the case of the spleen this argument is unfounded, for, while the pathologic variations are great, the microscopic and gross studies give results as characteristic of splenic anemia as similar studies made in the other groups of splenomegaly that present an accepted clinical syndrome: as pernicious anemia, hemolytic jaundice and others.

No small amount of the trouble in distinguishing the slides of splenic anemia from those of the other splenomegalies is due to the pathologic variations encountered in the individual types of splenomegaly. In splenic anemia these variations were found to be quite marked. For example, the capsule thickness varied from normal to plus 5, the reticulum and the arterial walls from normal to plus 4, the pulp from minus 3 to plus 1, the lymphoid tissue minus 3 to plus 3 and the endothelium of the sinuses minus 1 to plus 3. While these variations are very great, they are not at all surprising when the factors that may influence the spleen are recalled; as the duration and severity of the disease, the age of the patient, and the changes that may have been caused by previous diseases. Those great variations, while confusing, nevertheless suggest that the spleen plays an important role in the vital economy of the individual.

The average thickness of the capsule was found to be plus 1. The variations from plus 3 to plus 5 was caused by the extensive hyalin plaques found in some of the spleens. For the most part, however, the thickness of the capsule in any given specimen was uniform. As a rule the more fibrous the capsule the more prominent were the trabeculae throughout the splenic tissue. Lymphocytic infiltration of the capsule was not seen in any of the sections.

The reticulum may be distinctly prominent due either to marked fibrosis or to great cellular activity. The degree of fibrosis of the reticulum seemed to vary in a slight degree with the amount of thickening of the vessel walls, yet many cases were found in which the reticulum was very cellular and the degree of arteriosclerosis marked. The amount of lymphoid tissue present usually varied inversely to the prominence of the reticulum. The average amount of reticulum was found to be plus 2.

In the study of the degree of arteriosclerosis the artery of the malpighian corpuscle was chosen. It was observed that the more marked the arteriosclerosis, the greater the tortuosity of the vessel so that it was often found that a malpighian corpuscle might show two to four cross-sections of the same artery. As mentioned in the discussion of the reticulum, marked arteriosclerosis was not necessarily associated with an extensive fibrosis and no evidence was found to even suggest that the fibrosis developed from the vessel wall. Indeed, oftentimes a marked fibrosis was found in which the fibrous tissue was conspicuously absent in the region of the malpighian corpuscle and the central artery. Arteriosclerosis was, to a slight degree, an exception to the rule that in any given spleen the pathologic changes were uniformly distributed. Some few spleens showed a variation of from plus 1 to plus 2 in the degree of arteriosclerosis in various sections of the organ.

The artery of the malpighian corpuscle was in almost every case eccentrically located. Its position with relation to the malpighian corpuscle was found not to be disturbed apparently by the thickening process of the vessel wall. There seemed to be at least one factor which helped to determine the size of the malpighian corpuscles and this was an encroaching fibrosis. The fibrosis, in turn, seemed to affect the position of the central artery by reducing in an irregular fashion the size of the malpighian corpuscle. It was a fairly constant finding that the greater the fibrosis the more eccentrically located was the artery. The average degree of arteriosclerosis was plus 1½.

In comparing the degree of thickening of the arterial walls in cases of splenic anemia with the other types of splenomegaly, the relation was as follows: syphilis plus 3, hemolytic jaundice plus 2, pernicious anemia plus 2, myelogenous leukemia plus 2, and splenic anemia plus 1½.

No marked abnormality could be detected in the splenic veins, but they were usually so closely associated with the trabeculae that a comparison of their walls was a very difficult matter. In many cases, however, distinct hyalin changes were seen in the walls of the veins. In not a single specimen were organized thrombi found, nor were other thrombi present.

In a spleen in which generalized fibrosis is a very prominent feature it would naturally be supposed that the amount of splenic pulp would be decreased. This was found to be true, and the average was minus 1. In a general way the amount of splenic pulp varied inversely to the degree of fibrosis and the prominence of the sinuses. This latter statement also bears out what would reasonably be inferred.

The endothelium of the sinuses or the true reticular cells showed a proliferative activity above normal and were rated as plus 1.

In nearly every slide the sinuses were prominent and dilated, but the other types of splenomegaly also showed it. The syphilitic spleens especially resembled those of splenic anemia in this particular. The prominence of the sinuses in splenic anemia averaged approximately plus 2.

The sinus endothelium or reticulum showed varying degrees of proliferation. In some slides the cells seemed especially inactive while in others the cells were very large and, as further evidence of activity, were free within the sinuses.

Downey in an unpublished article, "The structure and origin of lymph sinuses of mammalian lymph nodes" makes some very interesting statements:

"Both the embryological and anatomical studies have shown, therefore, that the tissue of the splenic sinuses is to be regarded as reticulum rather than endothelium....It is not identical with the endothelium of blood and lymph vessels."

With regard to the relation of the reticular tissue to the sinuses, he says, "The sinuses are closely associated with the reticular tissue of the organs concerned."

The amount of lymphoid tissue was found in many cases to be markedly below normal, but the average was estimated at minus 1½. In determining the amount present in any given slide the malpighian corpuscles, the perivascular lymphocytic infiltration, and the lymphocytes generally distributed throughout the slide were all considered. As a rule, the malpighian corpuscles were fairly well defined and small, but they did not stand out prominently in the slide nor were they frequently seen. Contrary to the findings of some authors, in this series the so-called germinal centers were very rarely seen and, when found, were small and inconspicuous. The intermediate zone of the malpighian corpuscle, "the zone of expansion" which in normal splenic tissue stains deeply and is prominent, was poorly defined and scarcely noticeable.

Case 18026. Splenic Anemia -
A small artery and not a
capillary.

Case No. 50096. Splenic Anemia. A small capillary near a trabecalum.

Case 13028. Splenic Anemia.

A capillary may be seen.

An attempt was made to study the minute capillaries which are connected with the splenic sinuses. In normal splenic tissue these small blood channels consist of but a single layer of endothelial cells, the media and the adventitia disappearing as the vessel approaches the size of a capillary. In splenic anemia as well as in the other splenomegalies, the spleens showed an increase of fibrous tissue about these vessel walls. Due allowance, however, must be made for the fact that the venous capillries enter the trabeculae soon after their formation. In many instances the walls of these vessels showed a decided hyalin change so that the lumen became quite small and irregular. Could this condition be a factor in the production of hemorrhages?

In the spleens of splenic anemia the low power objective of the microscope showed small, infrequent and inconspicuous malpighian corpuscles, a generalized fibrosis and practically no perivascular lymphocytic infiltration. The sinuses were fairly prominent.

The intermediate power verified the large size of the splenic sinuses. Lymphocytes were not conspicuous in a general survey of an average microscopic section.

The oil immersion objective showed the large sinuses with their prominent reticular cells. Care was required in finding the smallest blood channels and in disregarding the larger vessels which were very conspicuous. These small capillaries, directly related to the sinuses, were found to have their walls markedly thickened.

In attempting to make a differential diagnosis between the various groups of splenomegaly the greatest difficulty was experienced with the slides of syphilitic spleens, which resembled those of splenic anemia very closely. The sinuses in the syphilitic spleens were equally as prominent as those in cases of splenic anemia and the fibrosis was as great.

On account of the relative prominence of the malpighian corpuscles and the accuracy with which they can be studied they were given special consideration. They have been considered from the standpoint of relative size and number and general structure as compared to normal malpighian corpuscles.

While the malpighian bodies of splenic anemia were fairly promient in the slide and were well circumscribed, yet they were not nearly so prominent as in the normal or in cases of pernicious anemia. There were only two or three specimens, however, in which the boundaries of the corpuscles could not be marked out with a fair degree of accuracy.

Contrary to many reports on the subject of splenic anemia, areas of degeneration or fibrous nodules were not found within the malpighian corpuscles. This statement is entirely in accord with the ideas of Cushing and MacCallum who, in discussing splenic anemia, said: "No progressive sclerotic process such as Banti described is seen in those malpighian bodies nor has it been

A chart showing the microscopic pathologic findings in splenic anemia, myelogenous leukemia, pernicious anemia, hemolytic jaundice and spyhilis.

Case No. 50096. A malpighian corpuscle with a great amount of fibrosis about it. The central artery is cut obliquely.

Case No. 136357. Relatively a small amount of fibrosis, a slight degree of arteriosclerosis and a very small malpighian corpuscle.

possible to find any fibrous nodules which might have resulted from such a sclerosis."

The larger the malpighian corpuscle the greater was its tendency to be round or oval in shape and the nearer the center the artery seemed to be, although it was invariably located in an eccentric position. This statement was made after due consideration of the normal variations. As the generalized fibrosis increased in amount the malpighian corpusoles became smaller and were more irregular in outline.

As the fibrous tissue encroached upon the periphery of the malpighian body, it seemed to cut off groups of cells in a rather irregular fashion. A continuance of this process resulted many times in the malpighian body being composed of a group of cells without a perceptible central artery, the vessel lying entirely outside of the corpuscle.

Before entering on a discussion of the size of the malpighian body in splenic anemia the size of the normal should be considered. In Gray's Anatomy the size of the malpighian corpuscles of the spleen is said to vary from 0.25 to 1. mm. in diameter. Morris, in his Anatomy, gives the average size of the normal as 0.25 to 1.5 mm. Mall says the splenic lobule in a normal spleen is about 1 mm. in diameter and states: "The malpighian corpuscle usually lies in the proximal end of the lobule, but in case it is very large it may distend the lobule and cause it to bulge."

To determine the size of the malpighian corpuscle in splenic anemia a camera lucida was used with the low power of the microscope. Most of the corpuscles were not exactly round and for this reason the length and breadth were measured and the average was taken. When due allowance was made for the magnification, it was found that the average size of the malpighian corpuscle was 0.352 mm. in diameter or approximately 0.35 mm. The variation

in size was from 0.2 mm. to 0.6 mm. It is evident, therefore, that the size of the corpuscles in splenic anemia is within the limits of normal, but that the average size is much below the average in the normal.

The next step was the determination of the number of malpighian bodies in a given area of splenic tissue in splenic anemia. The dissecting microscopic proved to be very helpful in this work. A square 0.5 by 0.5 cm. was the size of the field chosen and three fields were counted in each spleen in order to get a general average of different portions of the organ. After determining the average for each spleen, the average for all of the spleens of the group was found. The average number of malpighian bodies per 0.5 cm. squared or 1/4 of 1 sq. cm. in the sixty-nine spleens was found to be 5.8, or nearly 6. The number of malpighian bodies in a square centimeter was estimated as 23.2, or approximately 23. Certainly this number is far less than the number of malpighian corpuscles in the same area in a normal spleen. In a series of about twelve normal spleens (far too few for calculating accurate averages), the number of malpighian bodies per square centimeter was approximately 40.

The relation of the number of malpighian bodies to the size and the weight of the spleens furnish interesting data. As in all statements concerning the pathology of splenic anemia, however, there are many exceptions.

These relations were illustrated in a chart from which the following conclusions were drawn. 1. The number of malpighian corpuscles per square area seemed to decrease as the size and weight of the spleen increased. 2. The size of the malpighian body became smaller as the weight and size of the spleen increased. By actual figures these statements were found correct in 70 per cent of the spleens. This would seem to indicate that the number of malpighian corpuscles in a spleen remains constant until a fibrotic or some other pathologic process becomes so marked that many of the corpuscles are completely destroyed or are made so small that they are not recognized.

An interesting question that may be asked at this point is: Can any relation be found between the blood count in the clinical records and the histologic findings in the spleens of splenic anemia? This question was taken up systematically in an effort to find a relation between the malpighian corpuscles and the lymphocytes of the blood stream. That the lymphocyte may have its origin in the bone marrow as well as in the various lymphatic structures seems to be an established fact.

The futility of trying to show a definite relationship was very obvious in view of the many conditions that may alter the blood picture in a very short time.

The average size of the malpighian bodies in each spleen was multiplied by the average number of corpuscles per square centimeter and these estimations were compared with the percentages given for the lymphocytes in the blood counts. In thirty-two cases a definite relationship was noted between the lymphocytes of the blood stream and the lymphocytes in the spleen, while in twenty-five no such relationship could be demonstrated. This subject was approached from another viewpoint. In the routine microscopic study it was found that eleven cases had been graded as having more than the amount of lymphoid tissue in a normal spleen. The number of lymphocytes in the differential count was increased in all except in three of them. The normal number of lymphocytes was taken as 20 per cent to 28 per cent, figures given by Pappenheim.

As in the microscopic study, a consideration of the gross pathology consisted in the study of the sixty-nine spleens of splenic anemia and a comparison with 175 specimens from the various other groups of splenomegaly.

The average weight of these spleens was found to be 980 grams approximately, and the variations in weight 120 gms. to 2200 gms. If patients less than ten years in age were excluded the average weight increased to 1015 gms. This figure is more nearly correct. Rolleston found the average

weight in twenty-one cases of splenic anemia to be 27.6 ounces or 782.15 grams.

When the average weight of these spleens was compared with that of the other groups of splenomegaly it was found that two other groups averaged higher in weight: those of Gaucher's disease and those in the lymphoma group. The spleens arranged according to their number and average weights were: Gaucher's disease, four, 7071 gm.; the lymphoma group, five 2240 gm.: splenic anemia, 33, 1010 gm.; pernicious anemia, 57, 940 gm.; myelogenous leukemia, 20, 937 gm.; hemolytic jaundice 32, 930 gm.; syphilis, 5, 775 gm., and tuberculosis, 4,501 gm.

In comparing these averages with weights given in other articles on this subject, the fact must be borne in mind that all of the spleens here considered were obtained at operation.

An effort was made to see if the weight or size of the spleens varied in any other pathologic conditions. Curves were made in order that any slight variation might be detected. When compared with the weight and size there was no constant change found in the capsule thickness, reticulum, arteriosclerosis, pulp, or endothelium of the sinuses. The heavier spleens showed a slight tendency to have thicker capsules or a greater degree of periplenitis.

The spleen of splenic anemia maintained to a rather remarkable degree the shape of a normal spleen. The preservation of the shape suggested that in the enlarging process the factors concerned exerted themselves equally in all parts of the organ. In a general way, however, it was found that the larger the spleen the less distinct were its gastric and renal surfaces. From the standpoint of perisplenitis, the average was found to be plus 2. Thirty-eight were plus 2, eighteen were plus 1, nine were plus 3 and four, plus 4.

An estimation of the gross thickness of the capsule showed forty to be plus 2, fourteen, plus 1, twelve, plus 3, and two, plus 4. The increase

in thickness effected all parts of the capsule equally with the exception of a few cases which showed marked localized thickening of the capsule with hyalinization. Apparently the prominence of the trabeculae varied with the thickness of the capsule.

Only five spleen showed macroscopic infarcts and these were very variable in size, the largest being 12 x 8 x 2 cm. and the smallest scarcely perceptible. In these five specimens the average arteriosclerosis was plus 1.5. In three cases there was a history of abdominal pain and in three, gastric hemorrhages. In three cases also, ascites was present. All the changes mentioned, arteriosclerosis, pain, hemorrhages and ascites were present in one case only. There was no constant clinical or pathologic finding in the spleen in all of the cases of infarct.

A typical spleen of splenic anemia bears the general shape of a normal spleen, but is about five times larger. When allowed to rest on the table it maintains its shape much better than the normal spleen which flattens out. The spleen of splenic anemia is very firm, being several times the firmness of the normal. Its capsule is a grayish white with a slight reddish or a purplish red tint. Hyalin plaques may or may not be seen on its surface, --in the average spleen they would not be present. Perisplenitis is very evident especially on the diaphragmatic surface.

The typical spleen of splenic anemia offers considerable resistance to cutting. The cut surfaces bulge outwards and present a red, beefy appearance. Fibrosis is very evident and the trabeculae are especially prominent. The malpighian bodies are not seen.

The cut surface of a specimen that has been preserved in formalin is quite pink in color and the trabeculae, which have become very white, form a promient network over the surface.

When the results of the pathologic study of splenic anemia are summarized and the findings are compared with a similar study of the other groups of splenomegaly, as pernicious anemia, leukemia, and hemolytic jaundice, the general impression obtained is that there is a very great pathologic variation within each group and that while some conditions seem to be more common in some groups than in others, there is a great overlapping in the findings. The points of similarity in the various groups are rather striking and suggest that the spleen may play a somewhat similar role in all of the diseases that produce splenomegaly.

THE CLINICAL STUDY

An investigation of the records of the patients who had splenic anemia resolves itself more or less into a statistical study. The accuracy of the results, therefore, depends upon the accuracy and completeness with which the data were recorded and the number of cases studied in a given series.

The histories of these cases of splenic anemia are far above the average in the amount of information they contain. The thoroughness with which these records have been kept is due to the personal care of Dr. H.Z. Giffin who is in charge of the department of diseases of the hemopoietic system at the Mayo Clinic.

The sixty-nine patients comprising the splenic anemia groups came to the Mayo Clinic after being in poor health for an average period of seven years. The possibility of inaccuracy in this statement is of course very great, because of the insidious onset of splenic anemia and the questionable reliability of the patient's memory. Moreover, this time period of seven years does not show the entire duration of the disease, but the period of illness up to the time of splenectomy.

The average age of the patients was thirty-three years, the youngest being two and one-half years and the oldest sixty-nine. If the average age is thirty-three years and the average duration seven years, then the

onset must have been about the age of twenty-six. The duration of the illness had been in all probability more than seven years, for many of the patients gave a history of "always being delicate". They dated the onset of their illness, however, from the time of some marked change in their condition, as a gastric hemorrhage.

The distribution was about equal in the sexes, there being thrity-six male patients and thirty-three female.

In none of them was a history of injury obtained as a possible cause nor did the records show any instance of two or more cases of anemia occurring in the same family. Occupation was apparently not a factor.

Most of the patients complained of more than one abnormal condition which they considered of great importance in their illness. Listed according to frequency, the clinical findings may be summarized as follows: Enlarged spleen and mass in left abdomen, twenty-nine, hemorrhages from the stomach, twenty, weakness, nineteen. Indigestion, pain in left side of the abdomen and anemia were each complained of in six cases. Diarrhea was mentioned three times, pallor three, pain in epigastrium, two, shortness of breath, two, and jaundice, two: while rheumatism, constipation, palpitation, headaches, bleeding from the bowels, pain and numbness in legs, nervousness and asthma were each mentioned but once. The most frequent complaints in these patients with splenic anemia were therefore: (1) Mass in the left abdomen, (2) gastric hemorrhages, and (3) weakness.

The frequency with which hemorrhage occurred was rather surprising. It was not only a very common complaint, but oftentimes the severity of it was so alarming that it was a common cause for seeking medical attention. The histories showed that forty-one of the sixty-nine patients had hemorrhages. Thirty-eight of these were recognized by the patients as having come from the stomach as they had vomited the blood, and twenty-seven, in addition to the

vomiting of blood, had recognized blood passed by the bowel. Of the three remaining patients one noticed blood in the bowel movements only and two had quite profuse nasal bleeding. From the standpoint of severity, these hemorrhages may be graded on a scale of 1,2,3,4. In five patients bleeding was graded 1, in eighteen, 2, in seventeen, 3, and in one, 4. Many of the patients spoke of the alarming nature of the hemorrhages and described the prostration following them as so great that they had to remain in bed from three days to two weeks.

Abdominal pain was rarely mentioned by the patient as the chief complaint. This was probably due to the fact that the relative infrequency of it caused the patient to consider pain of minor importance in his trouble. Nevertheless, upon being questioned, thirty-two patients told of having had one or more attacks of pain, most of which were of short duration but often rather severe. Four of these patients located the pain definitely over the spleen. Two had mid-epigastric pain, while another located the painful area in the lower right quadrant. There were twenty-five, therefore, who were indefinite as to the site of the pain. According to Giffin, "Pain in the region of the spleen in splenic anemia is common and is probably due to perisplenitis which is so frequently present".

Some of the patients who complained of left abdominal pain while under observation presented definite friction rubs over the spleen.

Evidence was found elsewhere than in the spleen that might explain the pain in fifteen of these thirty-two cases. Six of those who complained of abdominal pain and one of mid-epigastric pain had gall stones. Four with abdominal pain had diseased gallbladders and four had chronic appendicitis.

Eight patients gave a history of having had malaria. None of these had had recent attacks nor had the disease lasted over a very long period of time. In all of them a special search had been made in the blood smears for the malarial plasmodia with negative results.

With a very suggestive history as a guide, usually the first note made by the clinician in his physical examination was the size of the spleen. There was only one patient whose spleen could not be palpated and this might be explained by the fact that ascites was present. The spleen in this case weighed 390 gm. In two patients in whom the spleen could just be felt below the costal margin the weights were 250 and 425 gm. Another spleen, felt rather indistinctly and described as "a mass in splenic region", weighed 710 gm. A spleen of 530 gm. was designated as "one inch below the costal margin". On nearly every history chart a drawing was made by the examiner to show what he considered the relative size of the spleen. The size thus roughly designated varied in a general way with the weight in all except two instances. In these exceptions a spleen weighing 190 gm. and one of 320 gm. were outlined to suggest a much greater size. Judging from the diagrams on these histories a spleen that extended to the midline and down to about the level of the umbilicus should weigh approximately 1000 gm.

It would seem that the spleen maintained its relative position in the abdomen in spite of the enlarging process. As further evidence of this statement the notes with reference to the presence of adhesions are of interest. The adhesions about the spleen were so marked that special mention was made of them in thirty-three cases. There were, however, a very few spleens that showed an elongation of their pedicles. Only one surgical card referred to the presence of a twisted pedicle. The spleen in case A62017 showed one complete turn. This was a patient who had never had hemorrhages. The spleen weighed 610 gm.

In the physical examination the feel of the spleen was generally described by the clinician as "hard and smooth". A notch was felt in approximately 50 per cent.

Notes in the physical examinations regarding the size of the liver, referred to twenty-four as being enlarged. Some of these, however, were apparently just below the costal margin and were marked "questionable enlargement". According to the operative findings there were twenty-six patients who had enlarged livers. At operation thirty patients were found to have definite cirrhosis of the liver and in only thirteen of these, approximately one-half, was the liver larger than normal. The average weight of the spleen in the twenty-four cases in which the liver was described as enlarged was found to be 1016 gm.

It may be stated with a fair assurance of accuracy that the size of the liver in splenic anemia has no alyme relation to the size and weight of the spleen. The findings in this series of cases suggest that there is a steady progressive enlargement of the spleen during the course of the disease, but that the liver maintains its normal size until relatively late. It then enlarges and may remain enlarged, or it may return to its normal size or become even smaller than normal. It cannot be said just how early in the disease cirrhosis of the liver begins. In many respects therefore the physical findings in splenic anemia are the reverse of those in portal cirrhosis for in this latter disease a palpable spleen is usually found relatively late.

Ascites was present in twenty-four patients, twenty-three of whom had cirrhosis of the liver. In the remaining case the liver was enlarged, but apparently not cirrhotic.

Allbutt and Rolleston are of the opinion that in splenic anemia ascites may occur in the absence of hepatic cirrhosis.

As to the question as to whether the patient had lost weight during the progress of the disease only very general statements can be made, since there are so many sources of error. In most cases the disease had lasted so long that the patient was uncertain as to his weight before the onset.

It would seem, however, that in a series of twenty-two cases, the average loss of weight was only five pounds. The greatest loss was twenty-seven pounds, and three patients weighed more than what they considered their normal.

Bronzing of the skin is often spoken of as a frequent finding in splenic anemia. In this series the following notes were made concerning the appearance of the skin: twenty-one patients were described as "sallow" or "pale"; twelve showed "yellowness of the skin"; seven were described as "lemon yellow", five "brownish yellow", one "tanned skin", one "cachectic looking", and one "brownish pigment about the eyes". Twenty-seven then, showed some changes in the color of the skin. Twenty-one of the remaining forty-two patients showed sufficient pallor to attract attention. None of the patients showed a definite icterus.

In none of the histories was there a note concerning any enlargement of peripheral veins of the abdomen or chest.

From the standpoint of the laboratory work the blood count was undoubtedly the most valuable, but the reports on the coagulation time, fragility test, Wassermann reaction, and stool tests were not without some interest and value.

The Wassermann test was done in sixty cases and was negative in fifty-nine. The one positive reaction was later discredited as a result of four subsequent negative tests. Four patients gave a history of luetic infection, but in none of these could any evidence of syphilis be found.

Stool examinations were done infrequently. There were apparently two indications: a history of diarrheal attacks, or of residence in the tropics. Thirteen stool examinations were done with the following results: Nine were negative; two showed Amoeba histolytica, one Lamblia intestinalis, and one air-comonads and trichomonas. None of the patients, however, had diarrheal attacks.

The fragility test was done in twenty-nine of the patients. Fifteen of these were normal: only one showed a tendency towards an increase in fragility of the corpuscles while thirteen showed an increased resistance.

The determination of the coagulation time was done in thirteen only. All except one were between two and ten minutes. One patients showed a coagulation time of fifteen minutes. In this determination either the Biffi-Brooks Coagulometer, the Boggs Coagulometer or the Lee and Vincent test Tube Method was employed.

Probably the most important laboratory aid in the diagnosis of splenic anemia was a complete blood count. This study was done on all patients with splenic anemia before splenectomy, and on most of them at varying times after the operation.

A study of the relation between the number of red and white cells and the hemoglobin before operation showed a varying degree of anemia. This anemia in every case was of the secondary type, the color index in many cases being relatively very low. There was always a relative leukopenia and in some of the counts the number of white cells was very low in comparison to the number of red corpuscles. The average red blood count was 3,700,000, the hemoglobin 53 per cent, and the white blood count 4,900. In the thirty patients with definite cirrhosis of the liver the red blood cells were about 3,500,000, the hemoglobin 50 per cent and the white blood cells 4,600. In the thirteen patients with enlargement of the liver but without definite cirrhosis the red cells were about 4,000,000, the hemoglobin 56 per cent, and the white cells 5,800. The remaining twenty-six patients who had approximately normal livers had an average red cell count of 3,750,000, hemoglobin of 55 per cent and a white cell count of 5,000.

In many of the patients changes in the red blood cells were noted and were usually designated as "slight" or "moderate". These changes

were seen in patients with the greatest degree of anemia. Poiklocytosis and anisocystosis were noted in twenty-nine of the sixty-nine patients; anisocytosis, poikilocytosis and normoblasts in twelve; and anisocytosis alone in nine. Only occasionally, mention was made of polychromatophilia.

In most of the patients blood counts were made at varying intervals after splenectomy and in every case there was a marked increase in the number of white cells. A curve was made to show this relative increase. The normal was taken as 8000, and in each case the number of days after operation was considered. A composite chart showed that there was an initial rise in the white cells immediately after the operation and that the number gradually increased until about the forty-fifth day. There was then a gradual decrease until the count approached the normal line in seventy-five to one hundred days after splenectomy. Another curve was made to show the relative increase in the white cells after operation in comparison to the number before operation. A time relation was likewise considered in this curve. An abrupt rise occurring previous to the tenth day after splenectomy was demonstrated. Then from the tenth day to the thirtieth the increase was more gradual and was followed by a very gradual decrease until the normal line was approached.

An attempt was made to determine how long the secondary anemia persisted after splenectomy, but the results were rather inconclusive. It is certain, however, that after splenectomy there was an improvement in the hemoglobin and the number of erythrocytes. The degree of improvement varied greatly so that no time relation could be established. In only a very few cases were two or more blood counts made following splenectomy and, while these showed progressive improvement, the number was too small from which to draw any conclusions.

A differential cell count was made in sixty-three of the patients before operation. In the remaining histories the word "normal" was found in the space for the differential and, since the figures were not given, they were

discarded. If the normal number of polynuclears be considered as varying between 60 per cent and 70 per cent (Piersol) then from the standpoint of these cells in the preoperative counts there were twenty-four normal cases, ten below normal, and twenty-nine with a relative increase. According to Pappenheim the number of lymphocytes in a normal differential is from 20 per cent to 22 per cent. When the lymphocyte counts were compared with these standard figures the following results were obtained: Ten cases were within the limits of normal, thirty above normal, and twenty-five below normal. A comparison was next made between the preoperative and postoperative differential counts. There were thirty-five patients in whom one of the differential counts had been omitted. Ten patients showed an increase in the polynuclears after operation, and twenty-two showed an increase in the relative number of lymphocytes. Two patients showed practically no blood changes following the operation. The length of time that elapsed after the splenectomy seemed not have been an important factor. In patients who showed an inorease in the polynuclear cells, however the differential count had been made from seven to forty-three days after operation.

Most of the operative findings have already been discussed, but the condition of the gallbladder as found at operation has only been considered in part. Nearly every surgical card has some reference to the condition of this organ. In eleven cases it was described as either diseased, markedly distended, or as having a thick wall. In eight patients the gallbladder contained stones.

The condition of the vermiform appendix was frequently mentioned. It was found diseased in seven patients and the extent of disease was marked plus two or plus three.

The Group having Cirrhosis of the Liver.

At the present time there is considerable confusion in the literature as to the relation between Banti's disease and splenic anemia. Most of the American writers choose to consider the two terms as entirely synonymous, while foreign authors prefer to make a well marked distinction between them. On account of this confusion that now exists it was thought best to discuss separately those cases that were characterized by definite cirrhosis of the liver.

MacCarty, of the Mayo Clinic, has examined specimens of liver tissue obtained at operation in nearly all of these sixty-nine cases of splenic anemia and he is of the opinion that in none of them, no matter how short the duration, was the liver entirely normal. From the mildest case to the most severe, the liver showed varying degrees of hepatitis. In the more severe types a periportal fibrosis was evident, but there was no sharp line of differentiation between those that showed a well defined cirrhosis and those that did not.

For the purpose of comparison, the cases in which there was definite evidence of portal cirrhosis have been grouped together. Thirty such were found. From the standpoint of morbid anatomy these thirty spleens resembled very closely the remaining thirty-nine. Their average weight was a little greater, being 1027 gm. as compared to 1010 gm. of the entire series. There was a slight increase in the amount of fibrosis, but in all other respects no difference could be made out.

This close similarity was found also in the microscopic study. Each pathologic finding was graded and averaged as in all the other cases and the results were expressed in a curve. This curve was found to correspond exactly with that for splenic anemia, with the exception that the splenic pulp was minus 1.4 instead of minus 1.

The clinical study of this group showed some interesting varia-

tions from the entire series of cases. The average age was thirty-five. The duration of the disease was nine years. The same comment applies here as given in the previous discussion, however, that most of the patients dated the origin of the disease not from the time of the real onset, but probably from the time of some severe manifestation, as gastric hemorrhage.

Nineteen of these patients gave a history of hemorrhage the severity of which was no greater than that of the remaining twenty-two patients who also complained of hemorrhages. Eighteen of them had gastric hemorrhages, fourteen had also noticed blood passed by the bowels, and one had nasal bleeding. One patient complained of melena only.

In the chief complaints hemorrhages were mentioned eleven times, while enlarged spleen and abdominal mass, if considered together, were complained of twelve times. The less important complaints in order of frequency were stomach trouble, five, anemia, four, abdominal pain, four, weakness, four, jaundice, two, dyspnea, one, constipation, one and pain in the legs, one.

Ascites was of rather frequent occurrence in this group for it was noted in twenty-four patients; in ten of these it was sufficiently marked to be noticed before the operation. Thirteen of the thirty patients had an enlargement of the liver.

A comparison of the postoperative mortality in the patients with cirrhotic livers with the remaining cases was interesting. In the sixty-nine patients the highest mortality occurred within forty days of the operation. Twelve of the sixty-nine had died within this period, and seven of these were in the group that showed the marked cirrhosis. If these figures are expressed in terms of percentage it is seen that 23.7 per cent of the patients in the group with cirrhosis died within forty days of the operation, while only 12.5 per cent of the other patients died within the same length of time.

From the standpoint of operative prognosis, therefore, it would seem important to determine, if possible, whether the patient belonged in this group of marked cirrhosis or to the group of splenic anemias without much involvement of the liver.

While most writers consider true Banti's disease to include all patients with definite cirrhosis of the liver, according to Banti there should be an ascites in addition to the cirrhosis.

Twenty-four of the thirty cases that showed marked hepatic cirrhosis had ascites. There were twenty-four patients in this series, therefore, that could be classified as true Banti's disease.

An effort was made to find some difference between the twenty-four cases which showed ascites and the remaining six cases of the cirrhosis group. Practically no difference would be made out and for this reason a separate discussion of the group of true Banti's disease would be but a repetition of that given on the group of cases that showed a decided cirrhosis of the liver.

In splenic anemia the condition seems to be one more of underfunction of the spleen than of overfunction. In the conflict with disease, while all the body tissues suffer, the spleen seems to bear the brunt of the battle. As the normal tissue of the spleen is destroyed it is replaced by fibrous tissue and the organ enlarges in an attempt to keep up its struggle against the disease. Finally, the spleen decompensates and, instead of being a help, it becomes a menace and may be a focus from which the disease is better able to attack the liver and the other organs.

This suggests the question of the most advisable time to do a splenectomy in cases of splenic anemia. From the standpoint of the operative mortality alone the spleen should certainly be removed before definite hepatic cirrhosis has occurred. In the future the development of some test of hepatic

function may indirectly be an index to the functional activity of the spleen.

The Mortality and the Post Mortem Reports.

A general summary of the deaths in this series of splenic anemia patients has been given by Giffin in his article: "Present Status of Splenectomy as a Therapeutic Measure". There were nine hospital deaths and six of these showed a definite cirrhosis of the liver. It would seem, therefore, that cirrhosis of the liver, especially if it be associated with ascites, is a very great factor in increasing the operative risk in this disease.

Autopsies were performed in ten of the cases. A few points summarized from these autopsy reports are worthy of consideration. They are as follows:

Case 1. (39673) A.C. Autopsy two years after the operation. Four liters of fluid in the abdomen. Mesenteric and aortic lymph nodes small and firm. Stomach contained bloody fluid and blood clots. Liver showed no gross evidence of cirrhosis. The bone marrow was exposed in the right femur and it was entirely red in color. The microscopic examination showed a hyperplastic marrow and a moderate cirrhosis of the liver.

Case 2. (150920) D.B.L. Twenty-two days after operation. Liver weighed 1350 gm. Its surface was very rough and the edges sharp. It was firm and fibrous and cut with resistance. Cirrhosis plus 3. The gall bladder contained five stones. The mesenteric glands were slight enlarged while the retroperitoneal glands were markedly increased in size.

Case 3. (231692) F.M. Autopsy twenty-one days after the operation. A thrombosis of the distal branches of the superior mesenteric artery was present associated with a gangrene of 45 cm. of the ileum. A subdiaphragmatic abscess was also found. The liver was normal in size and rather pale and the walls of the gallbladder were markedly thickened. Microscopically the liver showed pronounced fatty changes and slight perilobular round cell infiltration

Case 4. (246050) A.H. Fifteen days after operation. The liver showed a moderate degree of cirrhosis, cloudy swelling and fatty degeneration. The portal vein and the mesenteric vessels were thrombosed, but the radicles of the portal within the liver appeared normal. The splenic vein measured 2 cm. in diameter.

Case 5. (255355) R.P.R. The region which had been occupied by the spleen was in good condition. The liver was normal in size and of a pale pink mottled appearance. It showed no pathology grossly. Microscopically there was a cloudy swelling and a slight fatty degeneration.

Case 6. (230971) J.B. Eleven days after operation. The liver showed a marked cloudy swelling and fatty degeneration. Grossly it was slightly enlarged, pale and moderately firm. On section the markings were very indistinct.

Case 7. (242036) C.A Z. Four days after operation. The liver was slightly enlarged and showed a marked cirrhosis. It contained diffuse nodules throughout, which were not due to carcinoma. These nodules varied in size from a pin head to about 1.5 cm. in diameter, and through the capsule appeared of a light pinkish color. On section the liver presented a very granular appearance and the cells showed a slight cloudy swelling with some atrophy. There was an increase in the fibrous tissue and definite evidence of a portal cirrhosis. The abdominal lymph nodes showed a hyperplasia but nothing more.

Case 8. (99539) A.F.D. Three days after operation. Liver slightly increased in size, pale and anemic.

Case 9. (273017) V.S. Died the day of the operation. Anatomic diagnosis: Fibrous thickening of the walls of the portal and the inferior and the superior mesenteric veins with marked diminution in the size of the lumina. Varicosity and marked dilation of the venous plexus forming an anastomosis between the splenic and the left spermatic veins. Stone in the common duct.

Moderate fatty changes in the liver.

Histology: Slight bile retention in the liver.

Gross: Around the splenic area are many tortuous thickened veins. Some of these measure more than one centimeter in diameter. This plexus of veins could be traced to one large vein which ran downward posteriorly in the region of the renal artery and vein and emptied into the left spermatic vein and thence into the left renal. Both of these veins were also markedly dilated. The portal vein was very small and its lumen was not over five mm. in diameter. The wall of the portal vein was very thick. The splenic vein was found to be normal in size. The inferior and the superior mesenteric veins were normal in size and their walls somewhat thickened. The liver was very small, approximately two-thirds the normal size, and showed no gross evidence of cirrhosis

Case 10. (331245) W.P.P. Male 50. Admitted Aug. 26, 1920, operated on Sept. 2, 1920 and died thirty-nine days later. This is a case of splenic anemia associated with hematuria and is so unusual that a few notes from the clinical records are given. A similar case has been reported by Osler in one of his articles on splenic anemia. (Number XIV in his series of fifteen cases)

Family history negative. Past illnesses, none. The patient had had asthmatic attacks for many years. These attacks would come on gradually and would last from three to four weeks, coming at frequent intervals during this time. They were worse at night, were present whether in an upright or reclining position and were augmented by damp weather. There was a great deal of wheezing with a feeling of suffocation and as the attack was terminating there was coughing with a considerable amount of mucus. His appetite has been poor and in the last ten months he has lost twenty-seven pounds. During this same length of time he has had a gradually increasing constipation. He did not know how long he had been pale. In the last six months he has been troubled

with frequent urination. In the last five weeks the urine has been bloody. At no time has there been any pain referable to the urinary tract.

PHYSICAL EXAMINATION: There is some degree of anemia. Heart and lungs normal. The abdomen large and pendulous. The liver edge palpable about three fingers below the costal border. In the left upper quadrant a mass the size of one's fist was felt and this moved with respiration. There was a definite edge palpable but the mass descended atypically for a splenic tumor. Left sided irreducible inguinal hernia. Small hydrocele on the left.

Blood pressure 128- 70. Normal weight 220, at the time of examination 203 lb. Blood pressure just before operation: Hemoglobin 60 per cent R.B.C. 3,960,000 W.B.C. 2,600. After operation W.B.C. 3,300. Differential: polynuclears 71 per cent, small lymphocytes 24 per cent, large lymphocytes 3 per cent, eosinophiles 2 per cent. Urine: R.D.C. plus 1, pus, plus 4, pathalein 40 per cent, Wassermann, negative. Blood urea 22 mg. per 100 c.c. X-rays of the kidneys, ureters, bladder and of the chest were all negative.

Cystoscopic report: Tendency to reduplication and reversion to the mulberry type of kidney. Minor calices well outlined. Normal atypical kidney. Left hematuria. Tumor extra renal?"

Operation: Splenectomy. Decapsulation and exploration of the left kidney for cause of the renal hemorrhages. Space behind the left kidney was opened, the kidney loosened from its capsule and brought up into the wound where it could be carefully examined. Kidney was large, but no tumor was felt. If there was a stone or tumor present it was concealed within the kidney and could not be demonstrated.

Pathologic report at time of operation: "Chronic splenitis. Weight of spleen 330 gm."

The autopsy report: The liver was 7.5 cm. below the costal margin in the mid clavicular line. Liver and gall bladder weighed 2325 gm.

The liver was normal in color, increased in consistency and the cut surface had a distinctly yellow tinge. The markings were indistinct. Three stones were found in the gall bladder.

The right and left kidneys weighed 220 and 230 gm. respectively. The right showed suggestions of a few lobulations. The markings were indistinct. At the lower pole a small cortical cyst measuring 7.0 cm. in diameter was found. Punctate hemorrhages were seen in the pelvis. The left kidney presented the same suggestion of lobulation as the right. The capsule had been separated. There was some replacement of the renal substance by peripelvic fat. The cut surface was congested. Both ureters were normal. The prostate was of normal size and consistency.

The bone marrow from the left femur was intensely red in color and soft in consistency.

Microscopic study: The prostate showed areas of lymphocytic infiltration in the muscle tissue. The vermiform appendix showed infiltration with lymphocytes within the serosa.

The liver contained focal areas of lymphocytic infiltration in the interlobular tissue. There were a large number of vacuoles found both at the periphery and center of the lobules. The sinusoids were slightly dilated.

The bone marrow was hyperplastic being made up mostly of fat with a relatively large number of cellular structures. These cells were chiefly plasma cells and myelocytes. The leukocytic cells predominated. The normoblastic production was relatively small.

The mesenteric lymph nodes showed a marked diffuse fibrosis which separated the lymphoid tissue into small islands. Germinal centers were absent. The capillaries were markedly engorged with blood.

A bronchial lymph node showed many healed tubercles. These tubercles showed a peripheral fibrosis and within them many giant cells. This

gland did not show an increased cellular activity.

The report on the microscopic study of the kidneys was very incomplete. No mention was made as to what each kidney showed, but one of them was described as follows: The tubules were found dilated. There was a diffuse lymphocytic infiltration and these lymphocytes were mostly about the vessels. A few of the glomeruli showed sclerosis.

Possible Factors in the Production of Hemorrhages

Hemorrhages occurred in forty-one of the sixty-nine patients or in 59.4 per cent. The severity of these has already been referred to. Many attempts have been made to explain the underlying factors responsible for this serious complication of splenic anemia, but none of them have been altogether satisfactory and the underlying causes still seem to be unexplained.

A few of the notes relative to this subject gleaned from the clinical histories and the surgical records will be given along with some observations made in the pathologic study.

The splenic artery is the largest branch of the celiac axis, but a considerable amount of this blood is sent to the stomach by way of the vasa brevia and the gastro epiploica sinistra. Osler says that from estimates of Wall and Erdman about 40 per cent normally goes into the gastric circulation. Under normal conditions, therefore, a large amount of blood goes to the spleen. According to W.J. Mayo approximately one-fourth of the total blood of the portal circulation comes from this organ.

It is very easy to speculate as to the factors that could upset the normal splenic circulation. For example any embarrassment of the circulation beyond the point where the vessels of the gastric circulation are given off will cause a larger amount of blood to be sent to the stomach. If this partial obstruction were permanent then the vessels about the stomach would

enlarge in proportion to the increase in the circulation. If in addition to this the return of the blood from the gastric vessels were interfered with then the vessels about the stomach would probably become even larger. Whether the hemorrhages of splenic anemia can be explained upon a purely mechanical basis cannot of course be said. This disease may for example produce some toxic material which might produce hemorrhages by its action upon the gastric mucosa.

The vessels that make up the gastric circulation do, however, become enlarged in this disease. Cushing and MacCallum say that in one of their cases hemorrhage seemed to have originated from the rupture of a small vessel in the lower end of the esophagus. Dock and Warthin said that in the second case of the two they reported the coronary veins of the stomach were markedly enlarged and that all of the veins of the stomach wall were greatly dilated and tortuous. One of these enlarged branches of the coronary veins showed a rupture.

Some of the notes made by the surgeons relative to the condition of the blood vessels in the region of the spleen and stomach during the operation for splenic anemia may be quoted briefly.

Case 99539. "Large veins leading to the stomach." (Liver was enlarged without evidence of cirrhosis. Hemorrhages: Gastric, plus three, bowel, plus two.)

Case 150920. "Veins very large and very friable." (Post mortem showed esophageal varices. Cirrhosis of liver. Hemorrhages: Gastric, plus four, bowel, plus one.)

Case 196877. "Huge blood vessels coming to the spleen and in its vicinity." (Liver apparently normal. Hemorrhages: Gastric, plus three, bowel, plus two.)

Case 231532. "Enormous blood vessels." (Liver apparently normal, Hemorrhages: Gastric, plus three, bowel, plus two.)

Case 236960. "Huge vessels running onto stomach which was enlarged." (Liver showed cirrhosis. Hemorrhages: Gastric, plus two, bowel, plus three.)

Case 237095. "Enormous blood vessels along the diaphragm. One group of veins about the size of two fingers." (Cirrhosis of the liver. Hemorrhages: Gastric, plus three, bowel, plus two.)

Case 245113. "Enormous veins." (Cirrhosis of the liver. Hemorrhages: none.)

Case 250373. "Enormous veins throughout its posterior attachement." (Spleen) (Cirrhosis of the liver. Hemorrhages: Gastric, plus two.)

Case 50096. "Veins of tremendous size." (Cirrhosis of the liver. Hemorrhages: Gastric, plus three, bowel, plus two.)

Case 76654. "Enormous veins, one as large as the small intestine." (Liver apparently normal. No hemorrhages.)

Case 105779. "Accessory veins near the pancreas very large." (Liver apparently normal. Gastric hemorrhage, plus three.)

Case 231814. The history shows that two years before the patient came to the Mayo Clinic a gastrotomy had been done to determine the source of severe hemorrhages the patient had. According to the patient's statement the surgeon found five large veins on the inner wall of the stomach. The three largest were tied off and the other two were not disturbed. The patient's condition was not improved by this procedure. This case showed cirrhosis of the liver. Hemorrhages: Gastric, plus three and bowel, plus one.

A careful study of the splenic artery was made to determine the possible relation between arteriosclerosis and hemorrhage. It was found that the degree of arteriosclerosis oftentimes varied in different portions of the same specimen but the average thickness of the vessel walls in splenic anemia was less than in many other diseases causing splenomegaly in which hemorrhage

does not occur. While there were many cases of hemorrhages that showed great thickening of both the large and the small arterial walls, there were equally as many that showed relatively little thickening.

The large veins like the arteries showed some thickening of the walls and in some cases hyalin changes, but evidences of a thrombophlebitis were entirely lacking. A special study of these larger veins was made together with a comparison of them with the veins in other fibrotic spleens not in the splenic anemia group, and no difference could be found between them.

The next question is whether fibrosis is related to hemorrhage. The cases were grouped according as the fibrosis is plus three or over, plus two, or plus one or below, the results obtained are as follows: Plus three or above, eighteen had hemorrhages and seven had none. In the plus two group fourteen showed hemorrhages and thirteen showed none. In the plus one group or below, six had hemorrhages and eight had none. Only two cases were graded as plus four and both of these gave a history of frequent and violent hemorrhages. Fibrosis therefore seems to be a factor.

No relation was found between the presence and absence of hemorrhage and the following: Size of the sinuses, size of the malpighian corpuscles, presence or absence of germinal centers, phagocytosis, and cell activity of the reticulum.

Attention has already been called to the thickening of the walls of the capillaries in splenic anemia. In most of the cases these small vessels not only showed a thickening of their walls but also apparently a narrowing of their lumina. For this reason the condition of these capillaries may be a factor in the production of hemorrhage.

Evidence has been presented elsewhere to suggest that the spleen in splenic anemia maintains fairly well its normal position during the process

of enlarging. If this is true, then hemorrhage does not occur as a result of the spleen twisitng at times on its pedicle. In this series of cases only one note was found in which the surgeon referred to any abnormal position of the spleen, and this one had made one complete turn on its pedicle. According to the history this patient had been free from hemorrhages.

In all probability a reduction in the constituents of the blood that have to do with clotting was not a factor in the causation of hemorrhage for the coagulation time was determined in thirteen of these patients with practically normal results as previously stated.

If changes in the blood vessel walls were a factor they are likewise only of minor importance and may be associated with the severe anemia. It is true that three of the patients had slight nasal hemorrhages, but bleeding from the nose is seen as frequently in other conditions producing anemia.

Cirrhosis of the liver may be a factor in some cases or even in all of them, but it does not seem to explain the whole problem. In the sixty-nine patients thirty showed a definite hepatic cirrhosis and nineteen of these had hemorrhages. Of the remaining thirty-nine thirteen had an enlargement of the liver without a definite cirrhosis and seven had hemorrhages. The livers in the remaining twenty-six patients were practically and relatively normal, but fourteen of these patients had hemorrhages. In considering these groups somewhat further, it is evident that the group of hepatic cirrhosis has a higher percentage of hemorrhage cases, but it must be borne in mind that most of these are of longer duration than the others and therefore have a greater chance for hemorrhages from the standpoint of time alone. The greater the degree of cirrhosis, however, the more of a factor it seemd to be. It seemed to be a factor when the portal radicles were sufficiently obstructed to produce ascites. There were twenty-four patients who had ascites and of these, seventeen had hemorrhages.

All of the patients that have had splenectomy done have replied to questionnaires sent them from the Mayo Clinic. Fourteen of the splenic anemia cases have had hemorrhages following operation, or 20.5 per cent. When this percentage is compared with 59.1 per cent of hemorrhages that occurred before operation it is readily seen that the patients are greatly improved by splenectomy when considered from the standpoint of hemorrhage alone.

Nine of the fourteen cases that had post operative hemorrhages had definite evidence of cirrhosis of the liver. Two of the fourteen patients gave no history of hemorrhages occurring before the splenectomy.

The cases that had bleeding following the splenectomy may be summarized as follows:

Case 20919. Tarry stools, none severe. All following exertion.

Hemorrhages from the stomach: First one, 3 yrs. 10 mos. Postoperative.

Second, 5 yrs. 10 mos.

Third, 8 yrs. 3 mos.

Case 19050. Hematemesis and tarry stools 5 mos. postoperative.

"Passed quantity of blood" 2 yrs. 7 mos.

Hematemesis 3 yrs. 1 mo.

Hemorrhage (severe) 4 yrs.

Case 53579 Moderate cirrhosis, ascites, hemorrhage into the stomach, extreme anemia 2 yrs. 1 mo. postoperative.

Case 58739 Some teeth extracted. Severe bleeding 1 yr. 10 mos.

Case 82918 Hemorrhage 9 mos. postoperative.

Slight hemorrhage 2 yrs.

Four hemorrhages, fetal hemetemesis 2 yrs. 9 mos.

Case 39075 Bleeding from the mucous membrane of mouth and throat. 5 yrs. postoperative.

Case 118013 During the second year he had three attacks of hemorrhage hematemesis, tarry stools.

Case 119568 Passed blood by stool 1 mon. postoperative.
Two severe hemorrhages, 7 yrs.

Case 77736 Severe hemorrhage from stomach 5 yrs. 8 mon.

Case 153035 Tarry stools 3 weeks postoperative.
Tarry stools 5 mon.
Tarry stools 8 mon.

Case 127319 Hematemesis 2 yrs. 7 mos. postoperative.

Case 211116 Recurrence of hemorrhages 2 yrs. 1 mo. postoperative.

Case 236962 Hemorrhages a few days before death, hematemesis and stool.

Case 273017 Postoperative hemorrhage. Died the same day of the operation.

With reference to the number of these postoperative patients that actually died as the result of hemorrhage in the form of hematemesis, Giffin says "It is an important observation that hemorrhage in the form of hematemesis was evidently the cause of death in eight cases."

Summary. (Pathological)

1. A composite picture of the pathology of the spleen in splenic anemia was found to be one of a generalized fibrosis. There were no findings in the splenic tissue that would enable the pathologist to make a positive diagnosis of splenic anemia, yet the pathology was as characteristic of this disease as in the other diseases producing splenomegaly.

2. The degree of fibrosis of the reticulum seemed to vary in a slight degree with the amount of arteriosclerosis. There was no evidence to show, however, that this fibrosis originated in or about the vessel walls.

7. The size of the malpighian corpuscle seemd to be effected by the degree of fibrosis and the greater the fibrosis the more eccentric was the so-called central artery.

4. The splenic veins presented no marked abnormality and there was no evidence of thrombi in them.

5. Dilatation of the sinuses was fairly constant and the reticular cells showed a proliferative activity. The syphilitic spleens resembled those of splenic anemia in this respect.

6. The amount of lymphoid tissue present was usually found to be below normal. The malpighian corpuscles were fairly well defined, but the so-called germinal centers were small and infrequently seen. Areas of degeneration or fibrous nodules were not found in the malpighian bodies.

7. As a result of an actual measurement it was found that the size of the malpighian corpuscles was within the limits of normal, but that the average size was below the average for the normal. The number of corpuscles per square centimeter was found to be twenty-three.

8. By actual figures 70 per cent of the spleens showed that the number of malpighian bodies per square area decreased and the size of the corpuscles became smaller as the size and the weight of the spleen increased.

9. The average weight of the spleens was found to be 1015 gms.

Summary (Clinical)

1. The average age of the patients with splenic anemia was found to be thirty-three years and the number of males was about equal to the number of females. There was apparently no familial tendency.

2. The most frequent complaints were three: Mass in the left abdomen, gastric hemorrhages and weakness.

3. While abdominal pain was rarely given as the chief complaint, the history brought out the fact that thirty-two of the patients had an attack at some stage of the disease. In many instances this pain was probably due to a perisplenitis.

4. In the physical examination spleens designated as just palpable weighed from 250 to 500 gm. while a spleen of approximately 1000 gm. extended to the midline and about to the level of the umbilicus.

5. The relation of the size of the spleen as given by the clinical records to the actual weight, and the fact that many adhesions were found at the operation suggested that the spleen of splenic anemia maintains its relatively normal position in the abdomen.

6. The physical examinations showed twenty-four enlarged livers while at the operating table twenty-six showed a definite cirrhosis, thirteen of which were larger than normal. The size of the liver seemed to have no relation to the size and the weight of the spleen.

7. Ascites was found in twenty-four patients at the time of the operation, twenty-three of whom had a definite cirrhosis of the liver.

8. In the sixty-nine patients the average red cell count was 3,700,000, the hemoglobin 57 per cent and the white blood count 4,900. The coagulation time and the fragility test were normal while the Wassermann tests and the stool examinations were negative.

9. A composite chart of the blood counts made after the operations showed an increase in the leukocytes and the number gradually increased up to the forty-fifth day. There was then a gradual decrease until the normal was reached in about seventy-five days. A similar result was obtained in a composite chart in which the number of white cells found in the counts made before the operation, was taken into consideration.

10. A comparison made of the number of lymphocytes in the differential count showed that the average was within the limits of normal. A lymphocytosis did not seem to be a characteristic in this series.

Summary. (Cirrhosis Group)

1. In the study of the liver tissue of the cases of splenic anemia thirty showed a definite cirrhosis, but in none of them was the liver entirely normal.

2. The chief complaints of the thirty patients that have hepatic cirrhosis were the same as those in the rest of the series; hemorrhage and abdominal mass being the predominating complaints.

3. Twenty-four of the patients with cirrhosis of the liver had ascites.

4. From the standpoint of mortality 83.3 per cent of the patients that had cirrhotic livers had died within forty days of the operation while within the same length of time the death rate of the remaining was only 12.3 per cent.

Summary. (Hemorrhages)

1. Hemorrhages occurred in forty-one of the sixty-nine patients or in 59.4 per cent.

2. Cirrhosis of the liver and fibrosis of the spleen may be factors in the causation of hemorrhage.

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