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RELATION OF CHRONIC FIBROSIS AND THROMBOPHLEBITIS OF THE SPLEEN TO CONDITIONS OF THE BLOOD AND OF THE LIVER

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All red-blooded animals have spleens: their removal from the body does not cause appreciable permanent disturbance. The spleen has few functions that can be determined accurately, and it is quite evident that other organs with which it is associated in function readily assume its work. The changes in the spleen found in general necropsy service are seldom characteristic of the disease which caused death. The spleen has no known internal secretion and its nerve connection consists of unimportant fibers from the sympathetic and parasympathetic systems. It contains a small amount of nonstriated muscle, which, as in other portions of the body, has the power to originate contraction, and, like the heart, the uterus and the intestine, it originates certain rhythmic contractions, noticeably during the digestive period.

The spleen, according to Gross,¹ has characteristics referable to age. In early life, the germinal foci in the malpighian corpuscles and endothelial buds resembling granulation tissue are most active. In middle age these tissues atrophy. The spleen is oversupplied with blood for its own nutrition, as are the kidneys, the liver and certain other organs, and like these organs its action relates to the constituents of the blood stream. The blood supply of an organ gives a hint, and only a hint, of its possible function. The splenic artery is the largest branch of the celiac axis, and from the celiac axis comes the blood supply of organs such as the liver, the spleen and the stomach, which are concerned in the preparation and conversion of food products into material for the nutrition of the organism. The spleen is closely associated in function with the liver. Rowntree² compares the spleen and the liver with the kidney, believing that the spleen acts as the malpighian bodies and the liver as the tubules, the one straining out certain substances from the blood and the other acting on the material

1. Gross, L.: Studies on the Gross and Minute Anatomy of the Spleen in Health and Disease, *J. M. Research* **39**:311-338 (Jan.) 1918-1919.

2. Rowntree, L. G.: Personal communication.

brought to its vital laboratories. The material which is strained through the kidneys passes out of the body as urine, the purified blood passing back into the general circulation through the renal veins. The material which is strained out of the blood by the spleen is carried to the liver for further action. The liver has power to destroy micro-organisms and to detoxicate poisons as well as to eliminate through the bile function. In typhoid fever, the typhoid bacillus is found in the spleen and in the bile; if quantities of bacteria are fed to experimental animals in whose intestinal tract ulcers have been produced, the same type of bacteria will be found in the bile. Here, however, the analogy ends, since the kidney tissue lacks the destructive power of the hepatic cell, and the kidney filter frequently becomes involved in the specific type of infection which it is attempting to eliminate, especially pyogenic and tuberculous infections, while the liver seldom fails to destroy or eliminate the microbic or other noxious agents. The portal circulation of the liver includes the blood that has been acted on by the spleen, just as it includes the blood from the mesenteric vessels which contains unfinished products of digestion, all of which are subjected to the action of the hepatic cells before it is passed through the hepatic veins into the general circulation. The spleen initiates certain processes which it cannot finish; it is tied to the liver. Approximately one fourth of the total blood in the portal circulation comes from the spleen. The spleen is the one organ of the body in which normally the blood comes directly in contact with its constituent pulp, and the pulp cells are essential to the strainer action of the spleen, although other specialized cells aid the process. In intra-uterine life, up to the fifth month, the spleen, the liver and the lymphoid and adenoid structures of the body actively participate in the formation of the cellular elements of the blood, both red and white, a function which, so far as the red cells are concerned, is usually lost by the liver and spleen before birth, to be carried on to a great extent by other hemolymph bodies and by the bone marrow. After birth the spleen in health undoubtedly produces white corpuscles and it is believed by some observers that in life-emergencies it may produce red corpuscles, as after a severe hemorrhage.

The function of the spleen reaches its height in puberty, and senescence begins; in this period its disorders become manifest, although they may have existed in a nonrecognizable form for a long time. In general, the spleen may be considered to have three functions: first, the filtering of micro-organisms and toxic substances from the blood; second, the production of lymphocytes, especially as a defense phenomenon, and third, the destruction of worn out red corpuscles, the end products of which make up the bilirubin of the bile.

FILTERING OF MICRO-ORGANISMS AND TOXIC SUBSTANCES FROM
THE BLOOD

We know that during disease micro-organisms gain entrance to the blood in various ways. It would appear that under certain normal circumstances bacteria are permitted to enter the blood stream, and the reaction stimulates the development of lymphocytes and other forms of resisting agents. This vital process we speak of as immunization by the development of antibodies. The typhoid bacillus is at work during the prodromal period. What we call typhoid fever is the defense phenomenon following the development of specific antibodies. It is possible that the tonsils act as vaccinators in the maintenance of health,

Fig. 1 (Case 10324).—Photomicrograph of splenic tissue in splenic anemia.

permitting a few bacteria to enter the blood stream in the early stages of various diseases to start the immunizing process. These organisms may be eliminated from the blood by the urine without harm to the kidneys. When the elimination fails, the micro-organisms may be retained in the kidney filter, and the different varieties of hematogenous infections of the kidney result. Splenomegalia, occurring in chronic sepsis, typhoid, tuberculosis, malaria, syphilis and kala-azar, apparently is a result of the body's inability to send sufficiently rapidly to the liver for destruction the micro-organisms which the spleen has caught and is unable itself to destroy. A number of cases of chronic splenomegalia appear to be due to the hibernation of micro-organisms in the spleen, where, for some unknown reason, they may become more or less immune to even energetic and prolonged treatment and may become

a source of general reinfection because of our inability to reach them in the splenic pulp with remedies.

That white cells may pass out of the blood stream on the mucous surfaces of the body in health and return to the lymph channels is shown by the work of Stohrs and Adami,³ who demonstrated that the leukocytes pass out in the duodenum and upper jejunum, picking up bacteria and particles of fat, and that the pigmented areas in the liver are derived from killed bacteria. Hiss⁴ goes so far as to state that certain phagocytes of the body are dependent on specialized foods derived from micro-organisms, and thereby acquire, as a defense phenomenon against special micro-organisms, peculiar protective properties which may be retained for life. Each of the splenomegalias dependent on a type of micro-organism is specific, and the micro-organisms may be retained in the splenic pulp for long periods, perhaps for the life of the patient, as in tuberculosis and syphilis. Even if the micro-organisms eventually die, the changes in the spleen are permanent and the organ may continue unnecessarily to destroy the red cells and cause a grave secondary type of anemia, a true splenic anemia which at the time of subsequent discovery would be of unknown origin. That the spleen has definite reactions to specific organisms is well shown by the infrequency of abscess formation in septic splenomegalias. Yet the effect of the different organisms on the spleen is the production of a definite basic pathologic picture, fibrosis and thrombophlebitis, in addition to the specific changes due to the peculiar micro-organism which is responsible. This explanation is fair. The chronic anemia results from splenic fibrosis and thrombophlebitis without regard to the cause of the pathologic condition, and the terminal portal cirrhosis of the liver might be called a tertiary lesion resulting from the splenic anemia, itself secondary to a causative agent which may be no longer acting, while the accompanying bodily reinfections have their origin in an organism harbored by the spleen, as the organism of syphilis or of malaria.

We know much less concerning the ability of the spleen to filter toxins from the blood; our reasoning is largely an attempt to explain known phenomena. The group of so-called toxic splenomegalias is most interesting and includes the splenomegalias of unknown origin having the basic phenomena, however, of generalized fibrosis of the spleen and the thrombophlebitis, causing chronic anemias, and as a possible end-result, cirrhosis of the liver. These unexplained spleno-

3. Stohrs and Adami, quoted by Mayo, W. J.: *The Relation of the Spleen to Certain Anemias*, J. Ind. State M. A. 8:499-504, 1915.

4. Hiss, P. H., Jr.: *Some Problems in Immunity and the Treatment of Infectious Diseases*, Arch. Int. Med. 4:32-63 (July) 1909.

megalias comprise those conditions heretofore called splenic anemias, a lack of known etiology being one of the chief requisites for such classification. It should be borne constantly in mind that the basic pathology of the spleen, that is, generalized fibrosis and thrombophlebitis resulting in secondary anemia and liver changes, is essentially the same as the splenomegalias of known etiology such as syphilis, and the assumption of toxins acting to produce primary changes in the spleen and secondary changes in the liver is really an attempt to cover our ignorance of what the primary causes may be, or, it is only fair to say, have been. This is suggested by the similarity of the pathologic changes in the spleen in splenic anemia and in syphilis as shown by

Fig. 2 (Case 125899).—Photomicrograph of splenic tissue in syphilis of the spleen.

W. C. Chaney⁵ (Figs. 1, 2, 3 and 4). Assuming that there are such toxins filtered from the blood, are we to assume that all the blood must pass through the spleen by chance, or is there a peculiar attraction between those chemical bodies or living micro-organisms which by some process of chemotaxis are diverted to the spleen? Rosenow⁶ has shown experimentally that bacteria may be trained to attack certain organs, that organisms which have been found actively concerned in

5. Chaney, W. C.: Unpublished thesis.

6. Rosenow, E. C.: The Etiology of Cholecystitis and Gallstones and Their Production by the Intravenous Injection of Bacteria, *J. Infect. Dis.* **19**:527-556 (Oct.) 1916.

acute appendicitis or acute cholecystitis have, in many instances, appeared definitely to attack the appendix or gallbladder in animals.

The liver is the great agent of detoxication in the body. All the liver cells are alike and the pathologic processes of the organ are much simpler than of those organs containing various specialized cells which permit a wider range of pathologic variation. Detoxication of phosphorus, arsenic and chloroform, for instance, is found to take place in the liver, and if beyond the vital possibilities of the liver, ends in acute fatty degeneration of the hepatic cells; if the process is very acute, necrosis of the liver cells is the outstanding feature at necropsy. Chronic failure to detoxicate toxic material ends in portal cirrhosis which represents an attempt to encapsulate diffuse poisons which the liver no longer is able to render harmless and to eliminate. Cirrhosis of the liver in the terminal stage of splenic anemia is usually called Banti's disease, but does not differ in any important respect from cirrhosis of the liver without splenomegalia in chronic alcoholism. The alcohol cirrheses as well as pepper cirrhosis of curry-eating persons of India are examples of poisons derived directly from the alimentary tract. We may with reason assume that unknown toxic products filtered out of the general circulation by the spleen produce the splenomegalia of splenic anemia and that the liver finally, unable further to detoxicate the poisons carried to it from the spleen, develops cirrhosis just as happens in the liver cirrheses of alimentary origin. This would explain why removal of the spleen in some of the cases of splenomegalia of unknown cause results in betterment of the hepatic function by diverting the unknown toxin from the liver, although we are in a maze of speculation as to what becomes of the diverted toxic substance. It seems probable that the true explanation is that the chronic fibrosis and vascular changes in the spleen produce the agent which acts detrimentally on the liver cells without regard to the causes of the condition of the spleen. Another explanation which cannot be ignored is that by removal of the spleen the portal circulation is reduced by the amount of blood that the splenic vein carries to the liver, and there are sufficient uninvolved liver cells to care for the reduced volume. To the liver has been given the rare power of regeneration by cell hyperplasia. A considerable portion of the liver may be removed and hepatic regeneration take place, and this experiment can be repeated at intervals without causing death of the animal.

THE HEMATOPOIETIC FUNCTION OF THE SPLEEN

Hematologists differ widely in their views on the origin of the blood. The first blood in the fetus and the blood in lower animals that have only one kind contain only leukocytes. The spleen, in its adult function, has power to destroy the worn out erythrocytes, leukocytes and

blood platelets, as well as to manufacture lymphocytes. In some indirect way the spleen acts as a regulator of red-cell production. Stradomsky⁷ suggests a twofold action of the spleen on the bone marrow. He believes that it inhibits the overproduction of red cells and stimulates underproduction, the two influences balancing each other.

Fig. 3.—Histologic findings in seventy-two cases of splenic anemia. The pathologic processes are graded from +1 to +5 to show the degree of increase of the various tissues above normal, which is rated as zero, and from -1 to -5 to show the decrease (Chaney).

Johnstone,⁸ working in the Mayo Foundation under Mann, has studied the blood following splenectomy in man and the bone marrow

7. Stradomsky, B. N.: The Spleen as a Regulator of Blood Production, *Russk. Vrach*, **15**:1122, 1916; abstr. *J. A. M. A.* **68**:885 (March 17) 1917.

8. Johnstone, E. M.: Unpublished thesis.

in splenectomized animals. He has obtained constant and comparable results in animals only by repeated studies on the bone marrow of the same animals, removed at various times following splenectomy. He has found that leukogenesis is very active immediately after splenectomy and reaches its maximum quickly. It decreases in from one to three months, until it has resumed its preoperative degree of activity. Erythrogenesis seems dormant at first in about half the animals. It then becomes more active until it exceeds the preoperative activity. In the other half of the animals, erythrogenesis begins almost immediately after splenectomy, but so slowly that it is difficult to determine. In both instances, it reaches its maximum in from three to four months, remains stationary for about two months longer, and then gradually decreases. The experimental marrow findings correspond to the blood picture after splenectomy. In disease, a disturbance of this balance takes place which promptly affects the blood picture. One might compare the splenic vein with the mesenteric venous radicles of the portal vein which pick up products and carry them to the liver, where final conversion into material for the body's needs is completed. According to this view it is assumed that the red corpuscles and other material strained out by the spleen have food value, which is undoubtedly true. On the theory once held that all the red corpuscles in the body are changed every seven days, it seems definitely established that the spleen does not indiscriminately destroy red corpuscles. Ashby,⁹ working in the laboratories of the Mayo Foundation, has shown that the red cells of transfused blood may last from one to three months and that the elimination of transfused blood seems to depend more on an intermittent activity of the body than on the condition of the corpuscles. The splenic vein contains an excess of leukocytes and of iron, and no doubt the spleen is an active agent in iron metabolism and in storage.

Much experimental work has been done which has to do with the blood conditions produced by the removal of the spleen. It is believed by some observers that the liver is permanently enlarged after splenectomy. Hirschfeld and Weinert¹⁰ found Howell-Jolly bodies nine years after splenectomy. Asher and Sollberger¹¹ found polycythemia

9. Ashby, Winifred: Some Data on the Range of Life of Transfused Blood Corpuscles in Persons Without Idiopathic Blood Diseases, *M. Clin. N. America* **3**:783-799 (Nov.) 1919; unpublished thesis.

10. Hirschfeld, H., and Weinert, A.: Klinische und experimentelle Untersuchungen über den Einfluss der Milz auf die erythroplastische Tätigkeit des Knochenmarks, *Berl. klin. Wchnschr.* **51**:1026-1028, 1914.

11. Asher, L., and Sollberger, H.: Beiträge zur Physiologie der Drüsen. XIX. Fortgesetzte Beiträge zur Lehre von der Funktion der Milz als Organ des Eiweissstoffwechsels. Ueber die Kompensationsvorgänge nach Milzextirpation, *Biochem. Ztschr.* **55**:13-44, 1913.

after splenectomy and believed that splenectomy overstimulates the hematopoietic system. Definite changes in the number and kind of white cells have been described after splenectomy, and eosinophilia has

Fig. 4.—Histologic findings in six cases of syphilis of the spleen. The pathologic processes are graded from +1 to +5 to show the degree of increase of the various tissues above normal, which is rated as zero, and from -1 to -5 to show the decrease (Chaney).

been noted, usually after two years.¹² Stephan¹³ produces evidence to show that roentgen ray and radium applied to the spleen shorten

12. Giffin, H. Z.: Persistent Eosinophilia with Hyperleukocytosis and Splenomegaly, *Am. J. M. Sc.* **158**:618-629 (Nov.) 1919.

13. Stephan, R.: Ueber die Pathologie der Blutgerinnung, *Deutsch. med. Wchnschr.* **46**:684-686, 1920.

the coagulation time of the blood. On the contrary, Pearce, Krumbhaar and Frazier¹⁴ found that secondary anemia appeared after splenectomy, but disappeared in three or four months. It is evident that our knowledge of the exact relation of the spleen to the formation of the blood and of the maintenance of the blood in normal condition is in a confused state. But a large experience with splenectomies for injuries and acute diseases and the removal of the spleen for various pathologic conditions, sustains the view of Warthin¹⁵ that the spleen is only one of the hemolymph bodies and various other tissues which have the power to destroy the worn out red cells and to develop white cells; and that its changed function in disease does not so much concern the character of the red cells which occur in pernicious anemia as their reduction in value. The spleen is concerned with excessive destruction of the red cells rather than with the disturbance of their creation, and the regulatory effect on the bone marrow about which so much has been said is probably indirect rather than due to the as yet undemonstrated hormone. The anatomic structures of the spleen are involved in certain diseases somewhat differently, sufficiently to give rise to microscopic and macroscopic pictures which have some value. Such morphology as is shown in generalized fibrosis and thrombophlebitis, for example, without regard to the cause, can be looked on as the agent at least whereby the secondary anemia and probably the portal cirrhosis are produced.

The effect on the liver is quite the same as those forms of portal cirrhosis which have their origin in the alimentary tract.

With our present knowledge, therefore, satisfactory classification of the diseases of the spleen which are concerned in the anemias is not possible. One of the great difficulties in arriving at satisfactory data concerning the splenomegalias is that ordinarily we are unable to know that the spleen is enlarged until the enlargement is sufficient to be palpable beyond the free margin of the ribs, approximately twice the normal size. Percussion is an unreliable and overrated means of determining the size of the spleen. Roentgen-ray examination of the oxygen-distended abdomen, of course, has value, but we will not often apply this method to the ordinary anemias. Much of what little knowledge I possess of the subject has come from routine examination of the spleen during abdominal operations. I have taken great pains to compare the size of the spleen under diverse conditions with the blood condition of the patient and with the liver,

14. Pearce, R. M.; Krumbhaar, E. B., and Frazier, C. H.: *The Spleen and Anemia*, Philadelphia, J. B. Lippincott Company, 1918.

15. Warthin, A. S.: *The Changes in the Hemolymph Glands of the Sheep and Goat by Splenectomy*, Contrib. Med. Research (Vaughan), Ann Arbor, 1903, pp. 216-236.

and have removed many specimens from livers to obtain as early information as possible of changes in the liver in cases in which I have found the spleen more or less enlarged. In many cases of secondary anemia, the spleen was definitely enlarged but not sufficient in size to be palpated, and I have carefully observed some of the patients for months or years afterward without finding that a palpable splenomegalia developed. Early evidence, therefore, of the primary manifestations which take place in the spleens eventually developing splenomegalia of palpable size can seldom be obtained. My information has been fragmentary and inconclusive, but the mass of material which has passed through my hands has left me with the impression that generalized splenic fibrosis and thrombophlebitis are the result of many causes, and the pathologic changes in the spleen, the liver and the blood are regularly developed without regard to the primary etiologic factors.