HYPERSPLENISM*

WILLIAM DAMESHEK

Professor of Clinical Medicine, Tufts College Medical School, Boston, Mass.

SPLENIC enlargement is a common accompaniment of a host of infectious, non-infectious, and proliferative processes. In many of these some degree of anemia, leukopenia, or thrombocytopenia or all three together are found. Over the years the association of one or another of the blood cytopenias with splenomegaly has been termed, correctly or incorrectly, hypersplenism. It is the purpose of the present communication to define this term as accurately as possible within the bounds of our present relatively meager knowledge of splenic physiology and physiopathology.

HISTORICAL DEVELOPMENT OF THE CONCEPT OF HYPERSPLENISM

That the spleen was in some measure related to the blood did not become apparent until the era of histopathology was well advanced. In 1846, when Virchow,[1] the great German pathologist, described "Weisses Blut," he pointed to the very large size of the spleen and later used the term "Splenomyelogenous Leukemia"[2] for the condition. Apparently it was Gretsel[3] in 1866 who first used the term "Splenic Anemia" for cases in which there was both splenomegaly and anemia, thus implying that the anemia was splenic in origin. Banti[4] popularized the term in a long series of publications beginning 1882 and continuing for about thirty years. He concluded that the spleen was the site of a "noxa," which resulted in: 1) a low-grade febrile disturbance; 2) a certain degree of anemia and leukopenia; and eventually 3) cirrhosis of the liver. Although the nature of the "noxious" principle in the spleen was not defined, it was apparent from Banti's studies in these cases that a certain relationship was present between the spleen and the blood-forming apparatus. Banti's many descriptions of splenic anemia led eventually to the use of the term Banti's disease for almost all cases

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From the Blood Research Laboratory of the New England Center Hospital and the Department of Medicine, Tufts College Medical School.

in which splenomegaly and leukopenia, with or without cirrhosis of the liver, were present. More recently, however, there has been an increasing tendency to restrict the use of the term to those cases of splenomegaly with leukopenia which simultaneously presented the various indications of cirrhosis of the liver. Banti's idea of a "noxa" originating in the spleen and terminating as cirrhosis of the liver was eventually largely discarded when it was found that cirrhosis of the liver was in all probability the initiating factor of the splenomegaly by way of portal hypertension and that the leukopenia was a later phenomenon.*

Eppinger, whose writings on spleen-liver relationships were perhaps also ahead of their time, discussed the possibility in 1916 of "Aktiven Milztumor," i.e., of splenomegaly of an "active" type resulting in changes either in the white cells directly or in their relationship to the liver. In his textbook, "Hepato-Lienalen Krankheiten,"[5] Eppinger described several cases with enlargement of the spleen and various forms of cytopenia. At about the same time, Frank,[6] working in Germany, described cases with splenomegaly in association with leukopenia or thrombocytopenia and concluded that a definite relationship probably existed between an enlarged spleen and the bone marrow, the end-result being either a lowered white count or a lowered platelet level. Who first used the term "hypersplenism" is not accurately known, but it began to appear in Chauffard's writings from 1907 on[7] and subsequently, and in those of Morawitz[8] and Eppinger[5] at a later date. In 1939, Wiseman and Doan[9] described "Splenic Neutropenia," a condition which they characterized as presenting splenomegaly, marked leukopenia with neutropenia, frequent infections, and a favorable response to splenectomy. Dameshek[10] in 1941, and subsequently, indicated that hypersplenism might be either "selective" or "total"; i.e., that the splenomegaly might be associated either with anemia or leukopenia, or thrombocytopenia, or with combinations of these cytopenias. He also pointed out that "primary" and

* Banti was in many respects far ahead of his time. His first description of "Splenic Anemia" was made in 1882 at the age of thirty. He defined splenic anemia as a progressive idiopathic anemia, accompanied by idiopathic non-leukemic hypertrophy of the spleen with variable enlargement of the liver. His thinking on the subject may be summarized in the following quotation from that work (freely translated):

"The hypotheses that may be formulated are principally two: 1) that the spleen destroys large numbers of red cells; 2) that certain biochemical processes taking place in the spleen result in the development of abnormal metabolites which enter the circulation and have secondary effects on hematopoietic organs."

Even at that early date, Banti was a strong proponent of splenectomy. Later, in 1910 et seq., he performed crucial experiments in the production of hemolytic anemia by hetero-antibodies, pointed to the central importance of the spleen in hemolytic anemia, and continued his advocacy, with Micheli, of the operation of splenectomy for various blood cytopenias. It was largely through his insistence that the first planned splenectomies in the so-called blood dyscrasias were performed. The success of splenectomy in certain cases of hemolytic anemia led Kaznelson to suggest this operation in idiopathic thrombocytopenic purpura.

"secondary" forms might be present; that is, that hypersplenism could be either a primary disturbance of the spleen and of unknown origin, or that in the presence of splenomegaly due to some well-defined cause such as tuberculosis, sarcoid, etc., these various cytopenias might develop. Later, in 1946, Doan and Wright[11] described splenic "panhematopenia" or, as we term it, "pancytopenia." Doan and his group have concluded that the various types of cytopenias were due to selective sequestration of the various hematologic elements in the enlarged spleen and in their eventual phagocytosis.

Our own concept is that the enlarged spleen has an indirect or humoral action upon the bone marrow, either by preventing the growth or maturation of the various cells, or else by blocking their delivery from the marrow to the blood. That *selective* sequestration and phagocytosis occur has been denied by Dameshek and his group,[12] although they have conceded that in certain cases of hypersplenism with increased hemolysis, such a possibility may well be present. These divergent theories of hypersplenism, neither of them well founded on experimental evidence, have been under discussion for a number of years, and will be further discussed below. At this point, however, since hypersplenism is to be discussed, one may ask whether there are any indications of normal functional activity of the spleen, or "splenism."

Splenism

The spleen, although it may be removed with impunity from the normal individual without any apparent decrease in his well-being or general health, nevertheless appears to have a number of rather well-defined functions. The "reservoir" function of the spleen was pointed out by the British physiologist, Barcroft,[13] in a series of experiments using the cat. The spleen was exteriorized and its size noted following such procedures as hemorrhage, excitement and the like. These experiments, as well as others in which blood volume was measured, demonstrated conclusively that the size of the spleen fluctuated widely during the day and in response to specific "emergency" situations. With excitement and hemorrhage, a definite diminution in the volume of the spleen took place, indicating that a certain amount of blood was thrown into the general circulation by the contracting spleen. In other words, the body appeared to possess a mechanism for "auto"-transfusion which might be of value under such emergencies as acute blood loss, etc. Later,

Knisely[14] demonstrated by studying the surface of the living spleen of the intact animal with the cold quartz light that the sinusoids of the spleen were at times empty, at times full. Blood might "stagnate" in closed sinusoids for hours at a time (erythrostasis). This process, which could be likened to the incubation of blood in a warm test-tube, might conceivably result in modifications in the structure of the red blood cells including such changes as increased thickness, eventually leading to metabolic changes as well.

In addition to these mechanical functions, the spleen may also be thought of as a very large lymph node, or as a lymphoid filter, poised between an artery and a vein. The ordinary lymph node is situated between lymphatic channels, but in this unusual "lymph node," the organ is situated between a large artery, (the splenic artery), the largest branch of the celiac axis, and a large vein, (the splenic vein), the largest tributary in the portal vein. The large amount of blood going in and out of the spleen suggests its importance to the human economy.

The large collection of lymphoid tissue within the spleen indicates that it participates in the various functions of the lymphoid cells, although these are not too well known. The lymphocytes are probably concerned with combating infection with the production of antibodies. Undoubtedly, they have many other functions, including participation in fat and protein metabolism. The spleen is furthermore the largest single collection of reticuloendothelial cells in the body and as such must participate in the various functions of these phagocytic cells. The reticular and endothelial cells of the spleen have been known for years to be concerned with antibody production, perhaps in connection with their role as scavenger cells for red cell fragments, leukocytes, platelets and various other materials which must be destroyed before their end-products can enter the blood stream. In acute infections, the reticulo-endothelial cells may be said to participate as a "second line of defense." During many subacute infections, they become greatly increased and the entire reticuloendothelial system hypertrophied, thus accounting for the frequent splenomegaly under such circumstances. (Cf. typhoid fever, malaria, kala-azar, etc.)

Spleen an Endocrine Organ?

Of particular interest is the question as to whether or not the spleen is an endocrine organ. Although no definite statement regarding this can

be made at this time, there are many bits of evidence pointing in that direction. The literature to 1933 has been amply documented by Lauda.[15] Very little change has taken place since then with the exception of the relatively recent studies of spleen-adrenal cortical relationships.

A classical method for studying the endocrine function of an organ is to remove it and study the effects developing thereafter. Thus, thyroidectomy, adrenalectomy, and hypophysectomy have been studied extensively, and their effects noted. Various well-defined changes develop which can be traced to the deficiency or lack of hormonal factors derived from the organ removed. Similarly when splenectomy is performed a number of changes develop,[10] most of them detectable by rather subtle means such as blood counts and careful examination of hematologic changes. Thus, when the spleen is removed, there is a slight though definite increase in red cells, a well-defined increase in white cells, usually with a doubling of the white cell count, and a marked increase in the platelet level with usually a doubling or tripling of the original count. These changes might indicate either that the spleen, now missing from the body, did not destroy the various blood cells manufactured in the bone marrow or was not present in an inhibitory capacity to reduce or regulate the blood cells derived from the bone marrow. However, at least two other changes develop, one being the presence of Howell-Jolly bodies, and the second, the development of a relatively thin red cell population characterized by the presence of leptocytes or target cells.[10]

The Howell-Jolly body is a small fragment of nuclear material which is occasionally noted within the cytoplasm of the mature red cell. At times seen in severe blood dyscrasias, it is a constant phenomenon following splenectomy and is found in approximately 1 per cent of the red cells. Normally, the mature red cell in the circulation is completely devoid of nuclear material. That small fragments of nuclei may be retained in the relatively new red cells as they are produced from the bone marrow following splenectomy indicates that there is incomplete denucleation of the red blood cell in the absence of the spleen. This might indicate that the normal spleen has a remote effect on the marrow with respect to the final stop of complete denucleation of the red cell. Using the technique of parabiosis, in which two animals are joined, both Hirschfeld[16] and Lauda[15] showed that the appearance of Howell-Jolly bodies was controlled by a probably humoral factor

derived from the spleen. The removal of one spleen of a parabiotic pair of animals caused no modification of blood counts and no Howell-Jolly bodies were found. However, if both spleens were removed, Howell-Jolly bodies developed in the red cells of both partners. Similar observations were made in the case of bartonellosis, a peculiar bacterial infection which is present in many strains of splenectomized rats. The infection is not detected in the intact rat, nor in a parabiotic pair of rats if the spleen is removed from one partner. However, if the spleen is removed from both, bartonellosis develops in both, and the animals die of acute hemolytic anemia. These experiments, although by no means conclusive, indicate that the spleen is concerned in the ultimate denucleation of the normoblast of the bone marrow as well as with the tendency to keep Bartonella infection latent in the rat harboring this bacterium. These experiments do not rule out the possibility, however, that the spleen removes particulate matter from the red cell; thus, it is possible that the final remnant of the normoblastic nucleus or of the Bartonella bacterium within a red cell is removed by the spleen normally, while in the absence of the spleen these abnormal bodies are retained.

More recent experiments point to the possibility that the spleen, the bone marrow, and the adrenal cortex are related through their hormones. Thus, the adrenal cortical hormones, cortisone and hydrocortisone, have well-defined effects on the lymphoid tissue, spleen and the thymus.[17] Following repeated administration of these hormones, there is a well-defined reduction in the weight of these tissues, due either to actual lysis of the lymphoid tissues, or to some other mechanism inhibiting lymphocyte production. Thus, it may be said that the adrenal cortex, through its hormone cortisone exerts an inhibitory effect upon lymphoid, thymic and splenic tissues. Conversely, there is some evidence, although not as clearcut, that the same hormones exert a stimulatory effect on the bone marrow, thus resulting in a well-defined increase in reticulocytes, erythrocytes, polymorphonuclear cells and blood platelets, all the elements in other words derived from the bone marrow. From these experiments, one may postulate a reciprocal effect between the lymphoid tissues, including the spleen and the thymus, and the bone marrow, at least in their relationship to cortisone. Such a reciprocal relationship has been discussed for many years and is well brought out in the acute infections. If it is postulated that the adrenal cortex has an inhibitory effect on the spleen and simultaneously a stimulating effect

on the bone marrow, a third angle of a hypothetical triangular "axis" can be built by assuming that the spleen has an inhibitory effect on the bone marrow.[18] This inhibitory effect is disclosed, as pointed out above, in the experiments with splenectomy which demonstrate a well-defined leukocytosis and thrombocytosis. It is brought out very strikingly by either hemorrhage or acute hemolysis in the splenectomized individual. Here, a very striking increase takes place in early red cells and white cells, with many nucleated red cells and myelocytes. These various features seem to indicate a regulatory function of the spleen upon the bone marrow.

In recent years some further, perhaps more direct evidence has been obtained indicating that the spleen is actually an endocrine organ with distant effects on other tissues. Ungar has extracted from the spleen two mutually antagonistic materials, splenine "A" and splenine "B". According to this worker, splenine "A" has an effect on the blood vessel wall, increasing its resistance, and splenine "B" an antagonistic effect on the bone marrow megakaryocytes, with the production of thrombocytopenia and thus the possibility of hemorrhage. In more recent experiments, Ungar[19] has demonstrated that splenine "A" is concerned with anti-fibrinolytic mechanisms and that splenine "B" may accelerate fibrinolysis; in other words, opposing activities.

Probably more definitive are the experiments of L. O. Jacobson[20] on spleen shielding which indicate a well-defined relationship between the spleen and the bone marrow. In these experiments, when rats were given a uniform large dose of x-ray, marked cytopenias developed as a result of bone marrow aplasia and all the animals died. However, when the spleens of another batch of animals were exteriorized and shielded from the effects of x-ray by a suitable lead covering, and the animals then given the same large dosage of x-ray, the cytopenias that developed were slight, and the mortality of the animals was low. With the exception that the spleen was shielded from the effects of x-ray, the conditions of the experiment were identical. The results of these experiments indicated that the spleen might contain a factor which protected the bone marrow against cytopenic effects of x-radiation. Further experiments tended to confirm this hypothesis. Thus, when the animals were given the same dosage of x-radiation without spleen shielding and either simultaneously or shortly thereafter a small transplant of splenic tissue was introduced into the abdomen, again the animals were protected from

the effects of x-ray. In further experiments, extracts were made from the spleen and cell-free material was injected into the animal either just before the x-ray exposure was given, or shortly thereafter, and again the cytopenias were slight and the mortality low. These and various other experiments indicated that lead shielding of the spleen prevented injury to the bone marrow and that a protective material was present in the spleen. Although not completely proved, all indications are present that the substance in the spleen is of humoral nature, which by its introduction into the circulation has remote (and protective) effects on the bone marrow.

In another series of experiments, suggestive evidence was obtained that a splenic hormone elaborated by the spleen might have a regulatory or cytopenic function on the leukocytes of the bone marrow. Thus, Palmer, Cartwright et al.[21] showed that splenectomy resulted in a doubling of the leukocyte count in rats. When only portions of the spleen were removed, no rise in leukocytes took place unless less than 10 per cent of the spleen was left intact. At this point, there was again an approximate doubling of the leukocyte count, as with total splenectomy. The leukocytic effect of splenectomy could be abolished by introducing into the peritoneal cavity a small transplant of spleen of approximately 10 per cent of the normal spleen in size. The transplant could be either "auto" or "iso" in type. It was concluded from these experiments that the spleen probably contained a hormonal or humoral factor which prevented the white count from rising or at least had some regulatory effect on the bone marrow leukocytic tissue, thus keeping the leukocyte count at normal values. In further experiments by the same group,[22] it was demonstrated that a hypersplenic effect could be produced by transplanting one or more spleens into the peritoneal cavity of the intact normal rat.

These and other experiments suggest that the spleen may have an effect on the bone marrow through some remote and as yet poorly-understood mechanism. If this is correct, the assumption must therefore be made that hormonal or humoral factors released by the spleen have an effect on bone marrow cells. The proof of this hypothesis is not yet at hand, since work with splenic extracts has thus far been inconsistent. Although splenic extracts have been prepared by a number of observers and injected in animals, the changes produced, whether on blood or other tissues, have been quite inconsistent, and in fact often-

times negative. This is quite in contrast with the positive results so readily obtained with extracts of thyroid or adrenal glands, and brings the matter of splenic hormones seriously to question. There is nevertheless the possibility that effective extracts of spleen have yet to be prepared.

Hypersplenism

The concept of *hypersplenism* must be approached with a certain degree of caution since it is not definitely known whether "splenism" or "eusplenism" exists. Nevertheless, the concept has been a very useful one clinically and has tended to advance our thinking regarding the relationship of the spleen to the bone marrow and the blood cells, as well as to the practical merits of splenectomy in a given situation. What then is our concept of hypersplenism? As already stated, we have the relatively simple belief that hypersplenism is a condition in which the equivalent of two, three or more spleens (splenomegaly) is present and that this results in an unusually marked degree of inhibitory or depressant effect on the bone marrow. The greater the increase in splenic tissue, the greater, usually, is the degree of hypersplenism. Anatomic enlargement of the spleen is, we believe, productive in some obscure manner of physiologic hyperfunction. Thus, various conditions associated with splenomegaly are usually (not always) accompanied by neutropenia, anemia, or thrombocytopenia, or by a combination of these, including pancytopenia. The "proliferative" splenomegalies—polycythemia, leukemia, etc.—are, however, usually associated with leukocytosis. One or more cytopenias may be expected with almost any type of splenomegaly. Thus, a cytopenia with splenomegaly does not necessarily point to any specific diagnosis but merely to the fact that splenomegaly is present and with it the resultant physiologic or physiopathologic effects of the enlargement of this organ with its remote effects on the bone marrow. Hypersplenism can be further defined as showing the following features: 1) splenomegaly; 2) blood cytopenia or cytopenias; 3) a "full" marrow, i.e., a normally hypercellular marrow, free from proliferating cells. The full marrow may further show either maturation arrest of the affected cell type, or a normal appearance. The latter may be interpreted as "blocked delivery." An all-important fourth feature of hypersplenism is that splenectomy will result in the correction in the cytopenia or cytopenias; if it does not, and all the

other features are present, they can be discounted because "the proof of the pudding is in the eating."

Hypersplenism occurs in a variety of conditions with splenic enlargement. These may be listed as follows: 1) subacute and chronic infectious hyperplasia of the spleen; 2) portal hypertension, including cases with cirrhosis of the liver as the primary feature or those in which there is thrombosis of various parts of the portal circulation, or thrombosis of the splenic vein alone; 3) lipid cellular diseases, more particularly Gaucher's disease, in which the normal splenic tissue is almost completely occupied by lipid material stored principally in the reticuloendothelial cells in the spleen; 4) certain cases of lymphosarcoma, primary in the spleen; 5) other neoplasms including such relatively benign ones as hamartoma and splenic cyst; and finally, 6) conditions in which the spleen is enlarged and yet shows no particular disturbance; these are ordinarily classified as non-specific and might conceivably be the end result of a previous infection involving the spleen.

Hypersplenic syndromes may possibly induce a variety of effects, but the only ones that can be recognized at present have to do with the blood cells. Thus, hypersplenism may be associated with either neutropenia, thrombocytopenia, or anemia or with various combinations of these three. Furthermore, the hypersplenism may be "idiopathic" or "primary," or it may be secondary to some well-defined cause. Although the term "idiopathic" is unfortunate, its use must nevertheless be continued, since the cause for many cases of splenomegaly is still obscure. In the presence of the blood cytopenias, the bone marrow is characteristically "full" and usually hyperplastic. The cell type that is reduced in the blood is usually increased in the bone marrow. Thus with splenic neutropenia, there is usually a granulocytic hyperplasia in the marrow, and with splenic thrombocytopenia, the marrow megakaryocytes are usually increased. To a certain extent, this holds true for the occasional cases of splenic anemia due apparently to an inhibitory factor.

Although hypersplenism, as we have defined it, undoubtedly exists, there is no certainty that the "inhibitory" concept of its nature is the correct one. Doan and his group[23] have emphasized the phagocytic thesis to explain the various cytopenias, which they believe are due to selective sequestration and phagocytosis by the abnormal spleen. As evidence for this concept, Doan and his group point to the results of the adrenalin test. In this test, a small amount of adrenalin is injected subcutaneously

and blood counts are obtained before and after. In a positive test, the cell type low in the blood becomes definitely increased, indicating "selective sequestration" in the spleen. Our own observations with this test have been either completely negative, or if not negative, very questionable and often confusing.[24] Furthermore, following splenectomy in such cases, the post-adrenalin results have either been similar or even more striking than previously, thus indicating that adrenalin might simply result in a redistribution of cells from various tissues or organs into the blood stream and that the leukocytosis or other cellular increase might have little or no relationship to selective sequestration within the spleen. Another point emphasized by Doan and his group[25] is that counts obtained at operation from splenic arterial blood contain much larger concentrations of the cell type reduced in the blood than counts from the splenic venous blood, thus indicating that the spleen sequesters the cells coming into it by way of the artery. Again, however, our own results have failed to confirm these observations.[26] In our experiments, unusual care was taken to reduce agglutination and coagulation effects by the use of plastic tubing and siliconized apparatus. By these techniques, no significant alterations were demonstrated between blood counts obtained from the splenic artery and vein. Doan and his group also point to supravital studies of splenectomized material which show definite sequestration of the various cellular elements.[23] Curiously enough, fixed tissue sections of the same organ in the same condition usually show little or no evidence of sequestration or phagocytosis, and in our studies such evidence has ordinarily been lacking, except in certain cases of hemolytic anemia.

Our conclusions that hypersplenism is due to an inhibitory phenomenon induced in some manner by a large spleen mediated through a humoral mechanism, are based chiefly on bone marrow observations both before and after splenectomy. Particularly in the case of the megakaryocytes and thrombocytopenia, and to lesser extent, in the case of the granulocytic series with neutropenia, there is often evident a well-defined maturation arrest before operation, not present after operation. Proof of an inhibitory mechanism would be clearly provided by the preparation of splenic extracts, which when injected, would cause identical effects in animals. Unfortunately, such proof has until now been lacking, at least in any consistent degree, although we are now actively engaged in re-studying this problem with lyophilized extracts of spleen.

The *diagnosis* of hypersplenism is made on the features that we have already emphasized. These include: 1) The findings in history and physical examination of well-defined splenomegaly, the spleen being enlarged usually at least two to three fingersbreadth below the left costal margin. Many cases with hypersplenism show such features as vague aches and pains in the joints, with or without actual joint changes. Those with thrombocytopenia may show ecchymoses and petechiae. In general, however, the outstanding feature of a case of hypersplenism is the presence of a well-defined splenomegaly. 2) The blood changes; there are anemia and/or leukopenia with neutropenia, and/or thrombocytopenia, or a combination of these findings. 3) The marrow findings, which reveal a normally cellular or hypercellular preparation in which are present normal or increased numbers of nucleated red cells, normal or increased numbers of granulocytes, and normal or increased numbers of megakaryocytes. In the case of neutropenia, the granulocytes in the bone marrow are greatly increased, often at the expense of the nucleated red cells or the megakaryocytes; whereas in the case of splenic anemia, the nucleated red cells are increased and in thrombocytopenia there is usually a marked increase in megakaryocytes. In most instances, particularly in the case of the neutropenic and thrombocytopenic states, there is simultaneously some degree of maturation arrest of the affected cell series. Thus, with neutropenia, granulocyte maturation may proceed to the level of the myelocytes, the young metamyelocytes or the band-form myelocyte according to the case at hand. Mature polymorphonuclear cells are frequently conspicuous by their absence. In the thrombocytopenic situations, the megakaryocytes often show greatly diminished platelet production. In many cases, however, no evidence of maturation arrest is present, but the marrow shows the presence of normal or increased numbers of the cell type or types deficient in the circulating blood. It should be emphasized that the "full" bone marrow commonly found shows no evidence of the marked degree of primitivity of the leukocytes seen in leukemia, but the granulocytes are all of the normal mature or semi-mature variety with relatively few myeloblasts. It must be stated, however, that occasional cases of "aleukemic" leukemia may mimic hypersplenism very closely. Although in such cases a relatively large number of primitive cells is usually seen, we have observed others in which the leukemic nature of the condition became apparent only after splenectomy.

A diagnostic test that we have utilized more and more in recent years and that is particularly useful in the differential diagnosis of aleukemic leukemia from hypersplenism, is splenic puncture.[27] This is performed by the use of a 20 or 21 gauge needle, affixed to a 5 cc. syringe which is plunged very quickly into the body of the spleen as it extends below the costal margin, and as the patient holds his breath in inspiration. The entire maneuver takes a few seconds. A very small amount of splenic material, no more than 0.2 or 0.3 cc. is aspirated and quickly spread on a few glass slides. There is usually sufficient material to allow one to make the diagnosis between a normal cellular picture or that due to leukemia, myeloid metaplasia, or lympho- or reticulum cell sarcoma. Primary lymphosarcoma of the spleen may simulate hypersplenism quite closely and, in fact, may be associated with that disturbance. In the early stages, the bone marrow may show no infiltration with abnormal or primitive lymphocytes. This negative finding, in association with the splenomegaly, and the cytopenias, may lead to the diagnosis of primary hypersplenism. Lymphosarcoma should be kept in mind, however, particularly when there is any evidence of fever, night sweats, or other systemic manifestations, or when the sedimentation rate is considerably elevated. The diagnosis of lymphosarcoma can usually either be established or ruled out from the results of the splenic puncture. With lymphosarcoma or reticulum cell sarcoma, very large numbers of primitive cells with abundant nucleoli are readily evident in most instances. In some cases, the lack of "topography" as obtained with open biopsy sections, may make the diagnosis difficult, and the diagnosis may only be made by open biopsy or splenectomy. It is often wise, even in a case which seems to be quite typical for "primary" splenic neutropenia, to have the negative results from a splenic puncture before final resort to splenectomy is made.

Splenic Neutropenia

In considering more specifically the different types of hypersplenism, *splenic neutropenia* will be first discussed since in many respects it is the most clearcut of the hypersplenic syndromes. In this condition, the presenting symptom is often that of recurrent infections, at times very severe. During a period of years, there are frequent bouts of fever accompanied with sore throat, sores of the mouth, and possibly infected lesions of the hands and feet. Finally, a blood count demonstrates the

well-defined leukopenia and neutropenia. In cases due to hypersplenism, the spleen is ordinarily enlarged two to six centimeters below the left costal margin. There is usually little, if any, lymphadenopathy, and the remainder of the physical examination is ordinarily negative with the exception of ulcerative lesions of the gums and mucous membrane of the mouth and pharynx, which are present during the acute episodes. The cytopenia is usually quite selective for the granulocytic series, but a slight degree of anemia and thrombocytopenia may be present. The leukocyte count may fluctuate considerably, but in a typical case, it varies between 1,000 to 3,000 per cmm. with granulocytes from 0 to 20 per cent.

The cause for the splenomegaly and its associated cytopenias may not be apparent in most instances; however, in some cases there are definite indications of a primary disease. Such primary or fundamental conditions include rheumatoid arthritis, portal hypertension and cirrhosis of the liver, Gaucher's disease, sarcoidosis, brucellosis, chronic malarial splenomegaly, chronic syphilis and chronic tuberculosis. In undiagnosed splenomegaly with neutropenia, since the latter is non-specific, every attempt should be made to rule the presence of these various conditions in or out by appropriate clinical and laboratory studies. Some of these must be searched for by specific techniques, including, in a suspicious case of sarcoid, the removal of some tissue from above the clavicle in the region of the scalenus anticus muscle. Rheumatoid arthritis should be considered in every instance since the Felty syndrome may simulate so-called primary splenic neutropenia very closely and conversely the latter condition may be simply a variant of rheumatoid arthritis in which the joint manifestations are relatively mild. Finally, disseminated lupus may masquerade as splenomegaly with neutropenia and therefore in every case of suspected hypersplenism, the L.E. test should be performed.

Splenectomy should be considered in every case of splenic neutropenia when both the splenomegaly and the neutropenia are sufficiently severe, the neutropenia being marked enough to have resulted in frequent bouts of infection. The operation should be performed only after lymphosarcoma, disseminated lupus, syphilis, and malaria have all been adequately ruled out. One should also know the status of the liver function and whether or not sarcoid is conceivably present. It is thus safer to consider that every splenomegaly has a well-defined cause, which

should be ascertained by all possible means. Even with all these safeguards and unusually careful studies of the marrow, splenectomy may uncover a completely occult leukemia or sarcoma, or at the time of operation, a liver biopsy may demonstrate cirrhosis. It should be noted, however, that if well-defined cytopenias are present, splenectomy will almost always be followed in all of these entities (whether rheumatoid arthritis, lymphosarcoma, or cirrhosis of the liver) by well-defined increases in granulocytes and leukocytes. The rise in the total or absolute number of granulocytes is usually to normal or low-normal values (3,500 to 5,000 granulocytes), in the presence of a slight leukocytosis of 10 to 12,000. There is thus usually a well-defined lymphocytosis of 40 to 60 per cent following splenectomy; this should occasion no particular comment and is a common finding in normal individuals after splenectomy as well.

The term "splenic anemia," popularized by Banti, is used relatively little at the present time, although it might reasonably be used far more. Two main types may be discriminated, one hemolytic, the other non-hemolytic. In the hemolytic type ("hypersplenic hemolytic anemia") all the various features of a hemolytic process are present, including anemia, slight icterus, bilirubinemia, and a well-defined increase in reticulocytes of 3 to 10 per cent. There is simultaneously leukopenia and thrombocytopenia. The Coombs test is negative and no abnormal antibodies can be detected in the serum. The fecal urobilinogen content is high. Bone marrow examination reveals a markedly hypercellular preparation in which the nucleated red cells are conspicuous by their marked increase, but there are also increases in granulocytes and megakaryocytes. Splenectomy is followed by a striking and permanent increase in the blood counts to normal values. In some of the cases, the sections of the spleen show, in addition to congestion of the pulp, a well-defined erythrophagocytosis, indicating that the anemia is due at least partly to phagocytosis of the red cell elements in the spleen.

As for the non-hemolytic types of splenic anemia, these are generally associated with more fundamental disturbances, involving cirrhosis of the liver, Gaucher's disease, and possibly rheumatoid arthritis. Since there is no evidence of increased hemolysis in these cases, it is distinctly possible that the anemia is on the basis of splenic inhibition of the red cell elements in the bone marrow. Splenic pancytopenia, like splenic neutropenia, occurs in a variety of conditions, although in some cases it is

"idiopathic" and the splenic sections show non-specific hyperplasia. It should be noted that a fairly common cause for pancytopenia is sarcoid of the spleen, and that splenomegaly may be the only objective manifestation of that disorder.

Some note should be taken of Banti's syndrome, which is often used synonymously with congestive splenomegaly, although in Banti's original descriptions, he believed it was a "primary" condition of the spleen, with that organ producing a "noxa" which injured both the liver and the bone marrow. This concept that the spleen injures the liver has been well-nigh discarded, and it seems certain that most of Banti's cases were examples of cirrhosis of the liver with secondary portal hypertension and splenomegaly, and with ultimate leukopenia and neutropenia. In later years, Banti's disease was used to designate almost any splenomegaly with cytopenia, but as the diversity of the splenic histology became evident, it was realized that the cytopenias were simply the pathophysiologic end-products of an anatomical disturbance, i.e., the splenomegaly. If one still wishes to use the term Banti's syndrome, it should probably be reserved for those cases showing 1) chronic hepatitis associated with some degree of hepatic failure; 2) portal hypertension; 3) splenomegaly; and 4) the various hypersplenic effects of anemia, leukopenia, neutropenia, and thrombocytopenia. It is well to remember that splenectomy in these cases is followed by an improvement in the hypersplenic effects only, namely by increases in the white cells, granulocytes and platelets, and to some extent in the red cell count. There is usually little if any effect on the portal hypertension and certainly none whatever on the degree of hepatic failure. On the other hand, simple splenectomy may be followed by long-sustained improvement in the tendency to bleed from varices. This is perhaps due to such features as the reduction of blood in the portal circuit following splenectomy, and to a rise in the platelet count to normal or high values. For example, in one of our cases of juvenile cirrhosis with hematemesis, splenectomy was followed by a cessation of bleeding and a well-defined increase in red cells, white cells and platelets persisting for eight years after operation. Following another hematemesis, a portocaval shunt was performed, and the patient died within a week after operation. In another case well-marked anemia, neutropenia and thrombocytopenia were all relieved very dramatically by splenectomy and spleen-renal shunt. Unfortunately, however, the degree of hepatic failure became consistently and rapidly worse, and

the patient died about six months following operation.

In every instance in which the Banti syndrome is thought to be present, a consideration of simple splenectomy versus the spleen-renal or the portocaval shunt should be discussed and the limitations of each maneuver should be stressed. Splenectomy relieves the hypersplenism and is a relatively simple operation. The shunt operations are physiologically superior for their effects on portal hypertension. They are, however, much more serious operations and should not be performed unless all the *pros* and *cons* have been seriously considered.

Is there a condition of splenic thrombocytopenia? Certainly in the presence of splenomegaly a well-defined thrombocytopenia is present in most cases. Whether the thrombocytopenia of idiopathic thrombocytopenic purpura (ITP) is hypersplenic is now a matter of dispute, although some years ago this seemed reasonably clear. The association of thrombocytopenia in the blood with well-defined increases in megakaryocytes in the marrow, the latter cells showing but little platelet production, and the striking platelet production following splenectomy, all seemed to indicate quite clearly that the spleen was concerned in the thrombocytopenia. Recently, however, the immunologic nature of ITP has come to the fore,[28] and it is possible that most of the features of the disease are due to the immunologic abnormality and not to a more or less hypothetical splenic humoral effect. It is difficult, however, on this basis, to explain the striking thrombocyte production that occurs so quickly after splenectomy, possibly indicating the removal of an inhibitory factor. It is also likely that ITP may be a disease of variable pathogenesis, and that some cases may be immunologic and others hypersplenic.

Not Hypersplenism

At this time, what is *not* hypersplenism should be discussed, especially since certain conditions resembling hypersplenism superficially, or which have been called hypersplenism by various observers may actually be examples of a more fundamental disturbance in which the spleen becomes enlarged secondarily. This is well exemplified in the cases of *hereditary spherocytosis*. Here, there is an hereditary defect of red cell production with the presence in the blood of variable numbers of small, unusually thick red blood cells called spherocytes. These cells, apparently because of their unusual shape, are trapped by the normal spleen,

sequestered there, and ultimately destroyed.[29] The life span of the spherocyte is, therefore, very short. Because the spleen is called upon to sequester and destroy more cells than is normal, it gradually becomes larger. This is not hypersplenism in the sense of our definition but is simple splenomegaly occurring in response to an outside factor, in this instance, the presence of spherocytosis. That hypersplenism is not a factor is indicated by the short survival time of the hereditary spherocytes when they are transfused into an individual having a normal spleen. Again, the transfused spherocytes are selectively trapped, and are removed quickly, even though by a normal spleen. Conversely, when the spleen is removed from a patient with hereditary spherocytosis, the red cell life span becomes normal, and the anemia previously present becomes completely corrected. Thus, in this disease, the fundamental disturbance is a defective red blood cell; there is no evidence, except possibly in a crisis, of an inhibitory mechanism,[30] and the phagocytosis is a normal splenic response to spherocytosis. In *auto-immune acquired hemolytic anemia*, the situation is quite different. Here, the red cells are produced in normal fashion by the bone marrow. They appear in the circulation as entirely normal cells, but are then attacked by antibodies which have the capacity of fixing themselves on the patient's own red blood cells, i.e., they are auto-antibodies. These abnormal protein materials are apparently produced by such antibody-producing tissues as the systems of the lymphoid, plasma cell, and the reticuloendothelial cells. As the result of the antibody attack, the red blood cells become injured and thus spherocytic to greater or less degree; they are then trapped by the spleen, as in the case of the hereditary spherocyte, phagocyted, and ultimately removed. Thus, their life span is distinctly shortened. This is not hypersplenism in the sense that we consider it, but simply splenomegaly on the basis of extra work by that organ, both by reason of phagocytosis and perhaps also on the basis of excessive antibody production. Here the fundamentally abnormal condition is the antibody productive mechanism and not a primary disturbance in the spleen.

Acute idiopathic thrombocytopenic purpura is also not hypersplenism. Here, the patient probably develops an abnormal immuno-allergic mechanism following either an acute infection or the intermittent use of a chemical. There is a rather sudden hemorrhagic disturbance characterized by petechiae, ecchymoses and bleeding from the mucous membranes. Because of apparent injury to the megakaryocytes in the bone

marrow, and the rapid destruction of the platelets in the circulating blood, the platelet level becomes very low. The spleen appears to have little, if any, relationship to the development of this disorder and most cases develop a normal blood platelet count spontaneously. We have concluded[31] that splenectomy is ordinarily not indicated in these cases, both because the operation in acute thrombocytopenia may be quite dangerous, and the patient makes a spontaneous recovery in at least seven cases out of ten. In the meantime, the patient is treated with blood transfusions given from plastic bags, in which the platelets are preserved, and by large doses of ACTH.[28b] With this procedure, the great majority of patients recover completely after several anxious weeks. Here, the fundamental disturbance is not in the spleen but rather in an immunologic mechanism. In chronic ITP the question of hypersplenism still remains, at least in those cases in which an immunologic mechanism cannot be demonstrated. Even when it can, however, the striking effects of splenectomy, as witnessed in the explosive production of platelets by the megakaryocytes, speak in favor of the possibility of a hypersplenic component.

Splenectomy

This brings us to a consideration of splenectomy, its indications, and its contraindications. When should splenectomy be performed? I have made three categories for this: "Yes," "No," and "Maybe." In the "Yes" category, the undoubted indication for splenectomy is splenic rupture, either following trauma, or in the course of an acute infection, such as infectious mononucleosis or malaria. Here, once the diagnosis is made, the patient should be operated upon as expeditiously as possible, else death may ensue. The other absolute indication for splenectomy is that of hereditary spherocytosis. Even in the presence of a relatively mild condition, splenectomy should be performed for two reasons: 1) Bilirubin production is greatly increased, even in the mildest cases, and as a result large amounts of bile pigment are constantly passing through the liver, bile ducts and gallbladder. Gallstone formation occurs in at least 75 per cent of the cases and sooner or later may cause trouble. 2) Each case of hereditary spherocytosis, however mild, is subject at some time during the patient's course to the development of crisis. This may occur early in life or not until the age of fifty or sixty. In the crisis, the red blood count may go from 4 million to 1 million in a period of twenty-

four hours. Occurring in a young child, this is serious enough, but in an adult it causes a considerable strain on the heart muscle and may even result in death. The fundamental cause of the crisis, whether it is related to hypersplenism or to "aplasia" of the red cell element, remains at present obscure.

Chronic ITP is a well-defined indication for splenectomy because no other good therapeutic method is presently at hand for the treatment of these cases. Splenectomy is curative in at least 60 per cent of the cases; in 20 per cent the remissions are slight, but in about 20 per cent, there is complete failure. In splenic neutropenia, splenic pancytopenia, hypersplenic hemolytic anemia, and hypersplenic thrombocytopenia, the indications for splenectomy are well-defined, and the results of operation are about 80 per cent curative. In those cases in which the results of the operation are either nil or very slight, the conclusion must be reached that the initial diagnosis of hypersplenism was in error. It is well to remember, however, that a certain statement as to the eventual result of splenectomy in a given case cannot be made for at least six months, as I have noted complete and sustained remissions that have developed at the end of that time.

As for the "No" group or the contraindications to splenectomy, in what at first glance appears to be hypersplenism (splenomegaly, cytopenias, hyperplastic bone marrow) leukemia is ordinarily a reason for not removing the spleen. This rule has its exceptions, however, and we have seen brilliant results following operation in occasional cases, particularly in those requiring numerous transfusions. In infections that can be reversed by appropriate therapy (malaria, subacute bacterial endocarditis) splenectomy should not be performed except for impelling reasons. It should also not be done in the acute self-limited type of idiopathic thrombocytopenic purpura, which we conceive of as a self-limited disease in the great majority of the cases, the fundamental mechanism being an immuno-allergic one. Splenectomy here entails a considerable risk for the patient; most cases have a completely beneficial result spontaneously.

Is emergency splenectomy ever indicated?[32] We believe it is, but only in the case of rupture. In the hemolytic crisis of hereditary spherocytosis, it is best to place the patient in as good condition as possible by the use of transfusions and fluids to restore the water and electrolyte balance. Splenectomy can then be performed at leisure, in the presence of a

"quiet" patient. In acute idiopathic thrombocytopenic purpura, as already stated, splenectomy is best left alone. In the hemorrhagic crisis of the chronic form of the disease, the patient is best treated with ACTH and plastic bag transfusions. When the usual state of mild purpura and thrombocytopenia have then ensued, splenectomy can be performed as an elective procedure. This precaution has been very beneficial in improving the mortality rate of the operation.

In the "Maybe" group of cases, one must now list myeloid metaplasia of the spleen in association with myelofibrosis of the marrow, although at one time this condition was considered an absolute contraindication to splenectomy. This concept was based on the idea that the marrow had become almost completely fibrotic and that the spleen contained almost all the blood-producing tissue in the body. However, from a number of sources, it has become evident that splenectomy in this disease need not necessarily be fatal,[33] and that a well-defined remission may occur with operation, perhaps through the removal of the inhibitory factor of the enlarged spleen, perhaps through some other means. The operation should be considered only if the transfusion requirement is becoming more and more marked, or the platelet level relatively low. Under these circumstances, splenectomy may be followed by striking remissions. A complication of great significance is the tendency to thrombosis, often quite striking because of the marked increase in platelet level. This must be realized before operation is attempted.

There can be no doubt from this and other considerations that in certain cases a gamble or a calculated risk in carrying out splenectomy may ultimately result in a striking benefit for the patient. Thus, in certain cases of hypoplastic anemia, particularly when the marrow is relatively cellular, and in cases of so-called "refractory" or "adynamic" anemia with pancytopenia in the blood and a cellular marrow, splenectomy may be of distinct value, even in the absence of splenomegaly. The results may not be obtainable immediately, but there may be a gradual improvement and ultimately normal or near normal hematologic values may be reached. In other cases in which the marrow seems totally fibrotic and the transfusion requirement is particularly great, too great for hypoplasia alone, splenectomy may be followed by a brilliant result. We have seen this not only in myelofibrosis of the idiopathic type, but in the fibrosis of certain cases of lymphocytic leukemia. Certain cases of pure red cell hypoplasia are also benefited by splenectomy, but which ones will be

benefited and which will not, can unfortunately, not be predicted in advance of operation.[34] In such cases, the administration of cortisone may be temporarily effective, and if this occurs, as Loeb and Moore have indicated, splenectomy may be permanently so. Selected cases of Mediterranean anemia, particularly those in which anemia of moderate degree of severity is present in association with well-defined splenomegaly, icterus, and the indications of increased hemolysis, may be moderately well-controlled by removing the spleen. In this disease it is well to realize that the fundamental disorder is unmodified but the need for transfusions may be considerably diminished. In some cases of auto-immune hemolytic anemia not responding well to ACTH and cortisone, splenectomy should be considered and may eventually be followed by a complete remission. In certain cases of leukemia, removal of the spleen may be of distinct benefit;[35] for example, some cases of lymphosarcoma and leukemia are associated with continued pancytopenia and with the need for numerous transfusions. In these cases, the survival time of introduced red cells may be distinctly shortened, even though no gross evidences of increased hemolysis are present (occult hemolytic anemia). Careful studies in such cases will reveal 1) a shortened red cell survival time of introduced blood; 2) a slight though definite reticulocytosis of 2 to 5 per cent; and 3) an increased amount of urobilinogen in the feces. The transfusion requirement in these cases may be distinctly benefited to a greater or less degree by splenectomy. How much benefit will accrue in an individual case cannot be stated, but if the gamble is taken, some cases may show a striking and even remarkable effect. In one such case requiring transfusion at weekly intervals, removal of the spleen was followed by a rise in the red cell and hemoglobin values to normal and in a complete cessation of the need for transfusions.

Finally, the statement should be made that splenectomy may be undertaken in various peculiar hematologic cases characterized by varying cytopenias in the absence of splenomegaly. It is well to remember, however, before the final decision on splenectomy is made, that all fundamental diseases such as leukemia, the collagen disorders, certain infections like malaria, etc. should be ruled out as far as possible; otherwise, the end-result might be embarrassing. Each case should be carefully evaluated and judged on its merits and a thorough going-over of the pros and cons should be made.

SUMMARY

In this lecture we have discussed at some length our concept of hypersplenism, which is based chiefly on the possibility that a large and presumably abnormal spleen exerts an undue effect on the marrow blood cells. It is possible that hypersplenism represents simply an accentuation of the normal regulatory effect of the spleen (splenism) on the bone marrow. Thus, the spleen tends to have an inhibitory effect on the red cells, granulocytes and on megakaryocytes-platelets. In the presence of splenomegaly of many types these inhibitory effects are exaggerated with the result that various cytopenias occur. Under such circumstances the marrow is hypercellular but the blood is cytopenic. In the presence of marked degrees of cytopenia as with neutropenia, thrombocytopenia, anemia, or combinations of these three, the individual's life may be placed in jeopardy. Under such circumstances splenectomy must be seriously considered as a therapeutic procedure and in many cases is followed by highly beneficial result. Hypersplenism, although unproved as a definite entity, is nevertheless an important clinical concept from the diagnostic and therapeutic standpoints. Until medical measures are advanced for dealing with it, the necessarily crude operation of splenectomy will have to be continued as a prime method of therapy.

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