THE DIFFERENTIAL DIAGNOSIS IN SPLENOMEGALY.

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The clinical features that differentiate an enlarged spleen from other swellings that may appear in the left hypochondrium are sufficiently well known to justify their omission in this article. Owing to the fact that splenic enlargement is usually due to a generalized disease any attempt to classify the causes of splenomegaly is extremely difficult. Whilst it is recognized that the following classification is artificial, it can be claimed that it is at least practical from the point of view of diagnosis.

The number of diseases that may be associated with enlargement of the spleen is so numerous that it has been considered expedient to limit the discussion to gross enlargement, arbitrarily defined by a spleen palpable half-way to the umbilicus or lower.

I. Associated with abnormalities of the red cells.

Familial Acholuric Jaundice.

Idiopathic Hypochromic Anæmia.

So-called Splenic Anæmia and Banti's Syndrome.

Polycythæmia Vera.

II. The Leukæmias, especially Chronic Myeloid Leukæmia.

III. Thrombocytopenic Purpura Hæmorrhagica.

IV. Splenomegaly of portal obstruction, usually referred to as splenic anæmia or Banti's syndrome.

Hepatic fibrosis—Hobnail cirrhosis or syphilitic fibrosis of the liver.

Thrombosis of the portal vein or splenic vein.

V. Hodgkin's disease, Lymphosarcoma, or Tuberculosis of the spleen.

VI. Tropical splenomegaly.

Malaria.

Leishmaniasis—Kala-azar.

VII. Cysts of the spleen.

Hæmorrhagic cyst or hydatid cyst.

VIII. Splenic Anæmia of infants.

Von Jaksch's Anæmia—Rickets—Congenital syphilis etc.

IX. "Metabolic diseases."

Gaucher's disease and Niemann-Pick disease.

X. Miscellaneous causes.

Chronic sepsis, lardaceous disease etc.

A study of the accompanying classification will convince one that no problem requires more thorough **clinical** or laboratory investigation than that of chronic splenomegaly. A detailed history will often reveal information of the greatest

importance. Symptoms of anæmia occur in most forms of splenomegaly and are therefore of little diagnostic value; spontaneous bleeding or purpura would suggest leukæmia or idiopathic thrombocytopenic purpura, whilst bleeding confined to the alimentary tract is more characteristic of splenic anæmia or Banti's syndrome. A familial or hereditary incidence is important evidence in the diagnosis of familial acholuric jaundice and also of the Gaucher and Niemann-Pick type of splenomegaly. A history of previous residence abroad would suggest the possibility of malaria, hydatid disease, or other forms of tropical splenomegaly, whilst a past history of syphilitic infection is of evident significance.

Physical examination should be equally thorough. The presence of enlarged lymphatic glands would suggest Hodgkin's disease, leukæmia, lymphosarcoma or tuberculosis. The signs of a hæmolytic jaundice are present in familial acholuric jaundice and those of an obstructive jaundice in splenic anæmia, Banti's syndrome, and Hodgkin's glands in the portal fissure; evidence of portal obstruction such as hæmatemesis or melæna, dilated veins over the abdominal wall, or ascites are important in establishing a diagnosis of splenic anæmia or Banti's syndrome; a prolonged septicæmia would suggest a chronic septic spleen or lardaceous disease; the combination of glossitis, dysphagia, brittle finger nails, achlorhydria, and anæmia in a middle aged woman would be almost diagnostic of idiopathic hypochromic anæmia.

Laboratory aids to diagnosis are indispensable in the complete investigation of any case of splenomegaly, but as in other conditions they must be interpreted only in conjunction with the clinical findings. *The blood count and examination of a blood film* will afford absolute proof of certain diseases such as leukæmia and polycythæmia; a moderate secondary anæmia with a leucopenia and relative lymphocytosis are found in most forms of chronic splenic enlargement and cannot be given undue diagnostic significance, although this combination is particularly frequent in splenic anæmia, Banti's syndrome, Hodgkin's disease, and tropical splenomegaly. *An increase of the fragility of the red cells* in hypotonic saline would be indisputable evidence of acholuric jaundice. *Persistent gross reduction in the blood platelets* is characteristic of idiopathic thrombocytopenic purpura. *A positive Wassermann or Kahn Reaction* would naturally favour a diagnosis of syphilis. In certain so-called metabolic diseases of the Gaucher type the *blood cholesterol* is abnormally increased. *The Van den Bergh Reaction* may give an indirect positive reaction in acholuric jaundice and a direct positive reaction in portal obstruction. It may be necessary to rely upon *histological examination* of an excised lymphatic gland to establish the diagnosis of Hodgkin's disease, tuberculosis, or lymphosarcoma.

Splenic puncture was first employed by Bernstein in 1915 and although not often used it is undoubtedly of great value in the diagnosis of certain types of chronic splenomegaly, particularly in the Gaucher type of disease and in Leishmaniasis. It is performed by fixing the spleen firmly against the lower border of the ribs and plunging a needle attached to a syringe into the substance of the spleen. A portion of splenic tissue is then sucked up into the needle and syringe. After withdrawal firm pressure is applied with a sterile swab over the puncture site for a few minutes. The contents of the syringe are diluted with distilled water and transferred to a centrifuge tube where the preparatory processes for staining and fixing are carried out.

It is now proposed to discuss in more detail the individual causes of splenomegaly.

Familial Acholuric Jaundice.

The most characteristic feature is an *increased fragility* of the red cells in hypotonic saline solution. Although the disease is usually familial and hereditary no symptoms or signs may appear until the first or second decade or even later. In other members of the family the red cell fragility may be increased without producing other evidence of the disease, so the importance of estimating the fragility of the red cells in all members of the patient's family cannot be over-emphasized. The absence of such investigation in many recorded cases has led some authorities to doubt the existence of an acquired form of the disease. This was well illustrated in a case which I saw recently.

A married woman who had been previously healthy developed the disease at the age of 30, and careful enquiry failed to elicit any familial or hereditary incidence of the complaint. Routine investigation of her family, however, revealed an increased fragility of the red cells in two of her young children who were otherwise perfectly healthy and showed no clinical evidence of the condition.

The size of the spleen varies, the edge being usually felt at the level of the umbilicus, although it may reach as far as the pelvic cavity. The patient presents the features of a *hæmolytic jaundice*, namely lemon-yellow discoloration of the skin and conjunctive with *normally pigmented stools* and *without bile* in the urine.

The Van den Bergh reaction usually gives an indirect positive reaction. Gall stones of the pigment variety, are present in about 60 per cent. of cases, so the clinical picture may be complicated by the occurrence of *biliary colic* and *obstructive jaundice*. Further examination of the blood may reveal other important characteristics such as a *severe anæmia*, *marked reticulocytosis*, and an *apparent microcytosis*.

The course of the illness is typically chronic, but it is occasionally punctuated by alarming crises due to active hæmolysis of the red cells resulting in a severe and sometimes fatal anæmia. With thorough clinical and laboratory investigation there should be no difficulty in establishing the diagnosis of familial acholuric jaundice.

Idiopathic Hypochromic Anæmia.

It is sometimes forgotten that the spleen is clinically enlarged in a certain proportion of cases of idiopathic hypochromic anæmia or simple achlorhydric anæmia, so that the condition is occasionally mistaken for splenic anæmia or Banti's syndrome.

The presence of *glossitis*, *dysphagia*, *brittle finger nails*, a *low colour index* *microcytic anæmia*, and complete *achlorhydria* occurring in a woman of menopausal age should suggest the correct diagnosis. The anæmia in these cases responds rapidly to the administration of iron in adequate doses, but unlike some observers I have found that the anæmia in cases of splenic anæmia and Banti's syndrome often shows a marked improvement with this form of treatment, which should not be regarded as of diagnostic significance between the two groups. In idiopathic hypochromic anæmia the splenic enlargement disappears as the anæmia improves whereas the size of the spleen does not alter in splenic anæmia or Banti's syndrome.

Splenic Anæmia and Banti's Syndrome.

It appears that the term splenic anæmia was first employed in 1866 by Griesinger and Gretscl for cases of anæmia with chronic splenic enlargement, but the first systematic description of splenic anæmia was written in 1882 by Guido

Banti. In 1894 Banti first described a "symptom—complex and anatomic-pathological complex" which has since been known as "Banti's disease," and he made further observations on the subject in 1898 and again in 1910. For a clinical discussion on this subject one can do no better than refer briefly to Banti's original masterly description. Banti divided the course of the illness into three stages—

I. The Pre-Ascitic stage. (Usually termed splenic anæmia). The first thing to appear is *enlargement of the spleen* which is usually very big before it is discovered. Symptoms of *anæmia* follow; the red cells are generally reduced to between 3 and 4 million, the hæmoglobin is correspondingly low, and the colour index about half. The white cells are not increased, and often there is a *leucopenia*. The liver may be enlarged at the end of this stage. The commonest duration is 3 to 5 years, but it may be as long as 12 years.

II. The Intermediary stage. This stage is characterized by the onset of *gastro-intestinal disturbance*. Hæmatemesis may occur. The urine is diminished in amount and contains *bile pigments and urobilin*. The anæmia increases, the liver enlarges, but the size of the spleen remains about the same. This phase usually lasts a few months although it may be longer.

III. The Ascitic stage. This begins with the appearance of *ascites*, whilst the liver *decreases* in size and recedes behind the costal margin, and the anæmia becomes more pronounced. Death usually occurs within 6 months, the commonest causes being hepatic insufficiency or hæmatemesis. Banti stated that patients in this stage cannot be distinguished from those suffering from the advanced portal cirrhosis of Laennec. Banti added that the above disease in its first stage cannot be distinguished from splenic anæmia. He also gave a lengthy account of the pathological changes in the spleen, which he claimed were constant and characteristic in all these cases and distinguished them from other forms of splenic enlargement.

It is not practical to enter into the many controversies that have arisen since Banti wrote his accounts of the condition, except to state that it has since been generally recognized that there is no constant pathological picture in splenic anæmia or Banti's disease. The clinical syndrome may be reproduced by many different conditions, of which the most common is hepatic fibrosis and thrombosis of the portal or splenic vein, so that the term Banti's syndrome is preferable to "Banti's disease." It should be emphasized that tertiary syphilitic fibrosis of the liver is an important cause of the syndrome, and no investigation should be considered complete without a Wassermann or Kahn reaction.

Conditions that simulate so-called splenic anæmia or Banti's syndrome, such as leukæmia, Hodgkin's disease, lymphosarcoma, tuberculosis, purpura, idiopathic hypochromic anæmia, tropical splenomegaly, etc., are referred to and discussed more fully in other sections of this article. A diagnosis of splenic anæmia or Banti's syndrome is justifiable only after careful attention to the foregoing details and an exhaustive investigation to exclude other forms of splenic enlargement. One is strongly advised to keep an open mind and be prepared to revise the diagnosis if subsequent events warrant it.

Leukæmia.

In typical cases of leukæmia, when the *enormously enlarged spleen* is associated with a severe *anæmia*, *spontaneous hæmorrhages*, *retinal hæmorrhages*, *purpura*, and *generalized glandular enlargement* the diagnostic possibilities are considerably reduced. A blood count showing an increase in the number of white cells to possibly *hundreds of thousands*, and a blood film packed with *myelocytes* or *myeloblasts*, will establish the diagnosis beyond all shadow of doubt.

Occasionally, however, the disease may be very insidious and chronic and the splenic enlargement may exist without any other clinical evidence to suggest the nature of the complaint. I have seen two cases of this type which on clinical grounds were confidently diagnosed as splenic anæmia, until a routine blood count revealed the presence of chronic myelogenous leukæmia. Even greater difficulty is encountered in the extremely rare condition of aleukæmic leukæmia, where the blood count may be difficult to interpret. Difficult cases such as these, however, are very uncommon.

Idiopathic Thrombocytopenic Purpura.

The spleen is often but not invariably *considerably enlarged* in idiopathic thrombocytopenic purpura. During the acute phase of the disease which is characterized by *spontaneous bleeding, purpura, a persistent reduction in the blood platelet count*, to a very low level (60,000 to 1,000), with *prolongation of the bleeding time* and a *normal coagulation time*, the cause of the splenic enlargement is seldom in doubt.

During the relatively quiescent chronic phase of the disease, which is ten times more common than the acute, cases are sometimes confused with splenic anæmia, especially as the latter condition is sometimes accompanied by bleeding and a moderate thrombocytopenia.

In thrombocytopenic purpura the platelet count is more definitely and more persistently reduced, the splenic enlargement is seldom so great, and evidence of hepatic fibrosis or a positive Van den Bergh reaction never occur. Bleeding other than from the alimentary tract is uncommon in splenic anæmia.

Hodgkin's Disease, Lymphosarcoma, and Tuberculosis of the Spleen.

There is usually no difficulty in the diagnosis of Hodgkin's disease or lymphosarcoma.

Generalized glandular enlargement accompanies the *splenomegaly*, and the diagnosis may be definitely established in cases of doubt by the *histological appearances of an excised gland*. More rarely, however, the disease may apparently commence in the spleen with no evidence of glandular involvement until quite late. Such cases are usually diagnosed as splenic anæmia or Banti's syndrome.

During the course of an investigation on a large series of cases of splenomegaly I have seen a number entering this category. In some the exact diagnosis was not made until post mortem examination some time later; in others the true nature of the condition was not recognised until after histological examination of the spleen, which had been removed by operation on a mistaken diagnosis of splenic anæmia; in one outstanding case the excised spleen did not present any typical microscopic features and the diagnosis of Hodgkin's disease was not suspected until 3 years after the operation, when the superficial glands became enlarged. Similar remarks apply to lymphosarcoma, a condition closely resembling Hodgkin's disease. I have seen two cases in which the diagnosis was established only on the microscopic appearances of the spleen removed by operation; one of these patients lived four years after the operation.

Massive tuberculosis of the spleen is an extremely rare condition. I have recently seen a woman with the typical features of splenic anæmia, that is a spleen enlarged as far as the umbilicus and a moderate secondary anæmia and leucopenia with no evidence of other disease; the spleen which was removed on the assumed diagnosis of splenic anæmia, proved to be typical of tuberculous

disease of the nodular and miliary type; the patient made a good recovery and is in excellent health with no evidence of tuberculosis ten years after the operation.

Splenic anæmia is sometimes simulated by cases of chronic miliary tuberculosis. In most cases of these types the diagnosis is seldom suspected until the spleen has been removed or until further evidence of tuberculosis is forthcoming.

Other Forms of Splenomegaly.

The remaining causes of gross splenic enlargement are extremely rare and will be discussed only briefly.

Polycythæmia Vera. The diagnosis is usually quite straightforward, and may be confirmed by the *characteristic blood count* showing an increase in the red cells up to 12 million and in the hæmoglobin to 120 per cent. or so.

Tropical splenomegaly. The question of tropical splenomegaly comparatively seldom arises in this country. When the enlarged spleen is due to malaria the clinical history is usually so definite and clear cut that the diagnosis is strongly indicated; in endemic areas malaria should always be suspected in the presence of an enlarged spleen, particularly when occurring in infants and young children.

Leishmaniasis is an important cause of tropical splenomegaly, particularly in the Mediterranean and in India. The diagnosis may be established without doubt in suspected cases by finding the organism in the peripheral blood or spleen; *splenic puncture* is an extremely important method of diagnosis in this condition.

Gaucher's disease and Niemann-Pick disease. Gaucher's disease is usually familial but not hereditary. It is probably more common amongst Hebrews. The onset is insidious and although a disease of early childhood a diagnosis is seldom made until a much later period. The spleen is often found to be enlarged on routine examination of the patient; the liver is usually moderately enlarged; there is often a moderate anæmia with a persistent leucopenia. A peculiar brownish pigmentation of the skin and skeletal deformities involving the spine and long bones are found in some patients. The diagnosis is established by finding an increase in the blood lipo-proteins, and by the discovery of typical foam cells in a smear of the spleen obtained by splenic puncture.

Niemann-Pick disease closely resembles Gaucher's disease and is probably due to a disturbance of the phosphatide metabolism.

Spleen cysts. Cysts of the spleen are difficult to recognize, but their presence may be suspected when the form of splenic enlargement is atypical and when fluctuation can be elicited. Frequently they are mistaken for other conditions such as a mesenteric, pancreatic, or ovarian cyst. The commonest varieties are hæmorrhagic and hydatid cysts. A history of residence abroad and of past infection is important in establishing the diagnosis of a hydatid cyst, but this is not essential as I have seen the condition in a young child with no such history.

Splenic anæmia of infants. So-called splenic anæmia of infants, or Von Jaksch's anæmia, is a doubtful disease entity. Most cases are associated with other diseases such as hepatic cirrhosis, congenital syphilis, rickets, tuberculosis, malaria, etc. The diagnosis is usually made when an enlarged liver and spleen and a secondary anæmia with a leucopenia are discovered in an infant. In all such cases a thorough search for evidence of the above mentioned diseases should always be made.

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