SPLENIC PANHAEMATOPENIA*

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The discovery of the Rhesus factor has elucidated the nature of haemolytic disease of the newborn. In recent years several other questions have arisen in regard to the haemolytic anaemias of childhood. The old controversy of the division between a congenital and an acquired form of haemolytic jaundice has been reopened by Loutit and Mollison (1946). These authors confirmed Widal's original idea that there are two different forms of haemolytic icterus: the familial form, in which abnormal red cells are rapidly destroyed by normal lytic processes; and the acquired form, in which normal cells are rapidly destroyed by abnormal lytic processes. Lysolecithin was indicated as being the normal lytic agent. The latter conception is in accordance with the theory of Bergenheim and Fåhræus (1936), who demonstrated that lysolecithin is formed and acts particularly in the spleen, when the blood is slowed in its passage through this reservoir.

In this connexion it is also of importance to mention a new theory, based upon experimental findings, of the cause of the physiological blood destruction after birth. Engelhardt (1947) recently demonstrated that more lysolecithin could be extracted from incubated serum or plasma of cord blood than from incubated adult serum. Owing especially to its lower cholesterol content, the serum or plasma of cord blood has less haemolysis-inhibiting effect than adult serum. In vitro, oestrone inhibits the formation of lysolecithin. The increased blood destruction which occurs after birth is due to the disappearance of oestrone during the first days of life, but this is counteracted by a rapid increase of cholesterol at this period.

Role of the Spleen under Normal Conditions and in Haemolytic Anaemia

Apart from these investigations the role of the spleen under normal conditions and in haemolytic anaemias has been studied recently from two opposing points of view. According to one conception, participation of the spleen in physiological blood destruction can be regarded as negligible. In certain haemolytic anaemias selective

splenic haemolysis is present, but is due to abnormal properties of the erythrocytes and not to primary haemolytic 'hypersplenism' (Singer, 1945). On the other hand Doan et al. (1946) hold that formation and destruction of blood elements in the normal spleen are balanced physiological functions. This equilibrium may be disturbed by a pathological dysfunction which may affect one of the cellular elements of the blood. A congenital hereditary disturbance of the physiological equilibrium may exist, or secondary dysfunction of the spleen may occur in a general constitutional disease. A combination of more than one disturbance is possible. Thus congenital and acquired haemolytic jaundice may be regarded as conditions in which destruction of the erythrocytes is an effect of disturbed splenic function. On the other hand in Werlhoff's disease the destruction of the platelets is paramount. In addition, new syndromes may be distinguished, or at least redescribed. They are: primary splenic neutropenia and primary and secondary splenic panhaematopenia.

It is known that haemolytic icterus may sometimes be combined with a moderate leukopenia, and very rarely also with a moderate thrombocytopenia, which disappear after splenectomy. In such cases the disturbed function of the spleen manifests itself primarily by increased destruction of erythrocytes. However, destruction of other blood cells may occur as a secondary phenomenon. Such cases are intermediate between simple acholuric jaundice and a condition in which all three types of circulating cellular elements of the blood are attacked, a condition called by Doan primary splenic panhaematopenia. This condition may be congenital or acquired, and in the latter case it may arise acutely or it may be secondary to pre-existing enlargement of the spleen. Proof that we are dealing with a primary dysfunction of the spleen is provided by the favourable effect of the removal of the spleen and any accessory spleens.

Primary Splenic Panhaematopenia Distinguished from other Anaemias

Primary splenic panhaematopenia is characterized by a striking decrease in erythrocytes, leucocytes,

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FIG. 1.—Changes in the blood before and after splenectomy in patient 1.

and platelets, but can be differentiated from aplastic or hypoplastic anaemia by the finding of hyperplastic bone marrow.

The fact that 'splenic panhaematopenia' may be secondary to splenic enlargement is of great clinical importance, but nevertheless it is not able to account for all of the extraordinary destruction of blood elements. Splenectomy does not as a rule remove the cause of the enlargement of the spleen in such cases, but it may nevertheless improve the clinical state and prolong life.

These conditions may be illustrated by a short description of two patients.

Case Reports

PRIMARY SPLENIC PANHAEMATOPENIA

The first case concerned a boy two years and eight months old, who entered the paediatric clinic of the University of Amsterdam with the probable diagnosis of aleukaemic leukaemia or aplastic anaemia. Following an attack of measles ten weeks before entering the hospital, the child had become very pale. He did not give the impression of being ill. The family history was unimportant. The liver was palpable one finger's breadth below the costal margin. The spleen was large and firm, and reached in the mid-line four fingers' breadth below the xiphisternum and in the anterior axillary line three fingers' breadth below the costal margin (Plate III a). The skin showed remnants of purpuric haemorrhages varying from 0.5 to 1 cm. in diameter.

In the urine, urobilin was nearly always present. No blood, pigments, ova, or parasites could be found in the stools. The luetic tests of the blood serum were negative, and its content of bile pigments was not increased. There was an isochromic anaemia with marked leuco- and thrombocytopenia, and a slight decrease of the mean diameter of the erythrocytes. During the first weeks in the hospital anaemia, leucopenia, and thrombocytopenia increased; the leucocyte count fell to 1,100, the blood platelets once to as low as 14,000 per c.mm.

Three diagnostic possibilities were considered: aplastic anaemia, aleukaemic leukaemia, and so-called megaloblastic anaemia of childhood. However, puncture revealed a hyperplastic bone marrow, and all three diagnoses had to be rejected. Diseases in which splenomegaly is secondary had to be considered. Portal obstruction was regarded as improbable because there was no history of umbilical infection, there had never been a haematemesis, and no signs of varices could be found in the oesophagus. The diagnosis of Gaucher's disease was rejected, as no special indications of this disease were found in radiographs of the bones, in the skin, or in the family history.

We thought that in this boy the cause of the enlargement of the spleen lay in the organ itself or in its neighbourhood. In view of the existing haemorrhagic diathesis, splenectomy seemed justified. At operation a large spleen was found with a somewhat knobby surface. Microscopic examination of the spleen (Plate III b and c) showed preservation of splenic architecture. The sinuses

of the pulp were much dilated and filled with a strikingly large number of cells. Among these cells were normoblasts and leucocytes, most of the latter being eosinophil. There was fibrosis of the pulp, with some increase of collagen.

FIG. 2.—Adrenaline test (Doan) in patient 2, with secondary splenic panhaematopenia (acholuric jaundice). (Feb. 12, 1947, before operation.)

The follicles showed fibroadenosis and peri-arterial haemorrhages. There was also a strikingly large number of Malpighian corpuscles with proliferation of reticulo-endothelial elements and a fairly large number of neutrophils.

Biopsy of the liver did not show anything special.

The results of haematologic studies at various times after the operation are summarized in fig. 1.

At present, one year after the operation, the boy is in excellent condition.

The etiology of the splenomegaly was obscure. The deviations of the hilar vessels, established at operation, could not fully explain the enlargement. We regarded the case as an example of primary splenic panhaematopenia.

SECONDARY SPLenic PANHAEMATOPENIA

The girl Y. came into the paediatric clinic for the third time at the age of four and a half years. During the second admission a diagnosis of haemolytic icterus was made; the mother also suffered from chronic haemolytic anaemia. When the child was discharged from the clinic for the second time the blood, and also urine and faeces, showed all the characteristics of haemolytic jaundice, but at this

time there was no leucopenia and no thrombocytopenia. The liver was felt about 3 cm., the spleen about 4 cm., below the costal margin.

At present the girl is six years old. She is a poorly developed child with yellow-brown skin. The radiograph of the wrist shows delayed skeletal development; in each wrist only two carpal bones are present. The protruding eyeballs are remarkable, and moreover there is a slightly mongoloid expression. On the skin many petechiae are present, and some purpuric spots about 1 by 2 cm. across. The abdomen is asymmetrically enlarged; the spleen occupies about the whole left part of the abdomen and protrudes (Plate IV a). The liver is palpable 4.5 cm. below the costal margin. The blood, urine, and faeces show the characteristics of haemolytic icterus with leucopenia (5,600) and marked thrombocytopenia (2,600) in addition. The icteric index is not increased.

The haemorrhagic diathesis which might be explained by the thrombocytopenia, is very unusual for (familial) haemolytic jaundice. Radiographic studies revealed widening of the marrow cavities and thinning of the cortex in tubular and flat bones (Plate IV b); the skull showed thickening without distinct striations. The changes were more or less similar to those found in Cooley's erythroblastic anaemia. The first puncture of the bone marrow, performed directly before a blood transfusion, showed few cells, and seemed to indicate a complicating hypoplastic anaemia. However, the increased number of reticulocytes was not in agreement with these findings. A second puncture, performed two weeks later, showed many blood-forming cells of the erythropoietic and of the leucopoietic system and also some megakaryocytes.

In our opinion this case could be explained as one of haemolytic anaemia, in which the extreme enlargement of the spleen had caused an increased destruction of leucocytes and thrombocytes. However, we had to collect more arguments in favour of our conception, as in hypoplastic anaemia no favourable effect can generally be expected from splenectomy. We began by giving repeated blood transfusions and in this way temporarily improved the child's condition. Then, following the method of Doan (1946), we performed an adrenaline test. After the injection of adrenaline a marked temporary increase of all cellular elements of the blood took place (figs. 2, 3, and 4). This was considered a further justification for the removal of the spleen. After some preparatory blood transfusions splenectomy was performed.

The spleen weighed 1,377 g. Microscopic examination (Dr. R. van Dam) revealed an increase in the number of follicles, some of which showed fibrous change. In some follicles there was haemorrhage round the central artery, with increase of connective tissue. The pulp showed thickening of the fibres, some of which stained red with van Gieson. The sinuses contained polynuclear neutrophils and also myelocytes; doubtful normoblasts

FIG. 3.—Adrenaline test (Doan) in patient 2, with secondary splenic panhaematopenia (acholuric jaundice). (Feb. 12, 1947, before operation.)

FIG. 4.—Adrenaline test (Doan) in patient 2, with secondary splenic panhaematopenia (acholuric jaundice). (Feb. 12, 1947, before operation.)

were present. A few megakaryocytes were found in the pulp. In one of the sections a Gandy-Gamma corpuscle was present (Plate IV c and d).

The girl made an uneventful recovery. Her haemoglobin, erythrocyte and leucocyte counts remained at the level obtained after the preparatory blood transfusions; the number of platelets rose immediately after the operation. The haemorrhagic diathesis disappeared, but the other characteristics of familial haemolytic jaundice are still present in the blood. The direct Coombs test was negative.

The fluctuation of the cell counts can be seen in fig. 5.

At present, five months after the operation, the girl is in perfect condition. Recently the adenoids were removed with hardly any haemorrhage. We think we are justified in presenting this girl with chronic haemolytic jaundice as an example of so-called secondary splenic panhaematopenia.

A second adrenaline test performed in this patient a few weeks ago again produced a temporary increase in the cell counts, but this increase was distinctly less pronounced than before the splenectomy (figs. 6, 7, and 8). The result of the second test corresponded to the results obtained in control tests.

Skeletal Changes in Chronic Haemolytic Icterus

There is another point to which we want to return before concluding. The skeletal changes found in chronic haemolytic icterus, like those found in the two other chronic haemolytic anaemias (erythroblastic anaemia and sickle-cell anaemia), are secondary changes, produced by the compensatory hyperplasia of the bone marrow. It is noteworthy that our second patient showed advanced changes in the tubular bones and in the flat bones. The changes resembled those seen in erythroblastic anaemia more than usual, and were analogous to those found in a typical case of chronic haemolytic icterus (Noordenbos, 1929). The retardation in growth and development in our patient is probably partly related to the extensive skeletal changes. In none of the other cases of chronic haemolytic icterus which we have observed were the skeletal changes so intense as in our case.

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(a)—Patient 1.

(b and c)—Photomicrograph of the spleen in patient 1 with primary splenic panhaematopenia.

PLATE III

(a)—Patient 2.

(b)—Radiograph of pelvis, patient 2.

(c and d)—Photomicrographs of the spleen in patient 2, with secondary splenic panhaematopenia.

PLATE IV

FIG. 5.—Changes in the blood before and after splenectomy in patient 2.

FIG. 6.—Adrenaline test (Doan) in patient 2. (Aug. 15, 1947, after operation.)

FIG. 7.—Adrenaline test (Doan) in patient 2. (Aug. 15, 1947, after operation.)

FIG. 8.—Adrenaline test (Doan) in patient 2. (Aug. 15, 1947, after operation.)