THE PLACE OF THE SPLEEN IN THE ENDOCRINE SYSTEM

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FROM being considered as of no use to the organism the spleen has come to occupy a rather insecure position as a gland of internal secretion. The purpose of this article is to try to show how this change has come about. A wide variety of functions has been assigned to the spleen from time to time, most of them involving the life cycle of the blood corpuscles. The spleen has been stated to manufacture red blood corpuscles and, on the other hand, it has been claimed that red corpuscles are destroyed in this organ. In the same way the spleen has been regarded by some as a place where white blood corpuscles are produced and by others as a place where they are destroyed. Evidence of an endocrine function of the spleen is still meagre and to some extent conflicting.

It is necessary to touch briefly on the background. The spleen was known to the ancients, the Greeks considering it as inessential to life. Aristotle refers to it and Erasistratus states that it is useless. It was regarded by the Greeks and Romans as detrimental to a runner and this idea persisted at least to the time of Shakespeare. It is frequently stated that the ancients removed the spleens of runners to increase their speed.

Splenectomy is said to have been performed in Europe in the sixteenth century. Moynihan gives an account of the operation performed by Zaccarelli as written by an Italian physician, Leonardo Fioravanti, for the removal of the spleen from a woman 24 years old. Apparently she made a prompt recovery and suffered no ill effects. Moynihan points out that the suggestion has been made that the mass removed was an ovarian cyst. At least two other removals of the spleen are stated to have taken place during this century. During the seventeenth century two splenectomies are recorded, both of which seem to be reasonably well authenticated. In both cases the reason for the operation was knife wound in the left side with prolapse of the spleen.

The first experiments known to have been performed on animals in a study of the spleen, as described by Moynihan, were carried out by Malpighi in 1669, Clarke in 1676 and Zambeccari in 1680. Malpighi ligatured the splenic artery and vein in a dog. Subsequently the spleen underwent complete atrophy and the liver enlarged. Both Clarke and Zambeccari performed splenectomies on dogs. No significant change was observed.

In 1841 Bardeleben published the results of the first carefully planned experiments directed toward elucidation of the function of the spleen. The results of complete removal of the organ were briefly these: a transitory decrease in the number of red, and an increase in the number of white, corpuscles in the circulating blood; an increase of activity of the bone marrow and lymphatic glands; no apparent ill effect on life. These experiments are particularly noteworthy because of the care with
which they were planned, the thoroughness with which they were carried out and the conclusions drawn.

It was at this time that general consideration began to be given to removal of the spleen as a therapeutic measure. The results of Bardeleben’s experiments gave support to the belief that the spleen was not necessary and splenectomy came to be employed more and more. Collier recounts 29 cases of splenectomy reported to 1882. Of these, 13 were for wandering spleen, enlargement (described as "simple") and hydatid cysts. Eight of these were regarded as successful. In the other 16 cases "leukocythemia" was present. None recovered. These results made it clear that splenectomy was neither a sound nor safe procedure for leukocythemia.

A relationship of the spleen to hematopoiesis was recognized as a result of Bardeleben’s experiments, which were confirmed by other investigators. The unsuccessful outcome of extirpation of the spleen in leukocythemia led to a turning of attention to the anemias. At the beginning of the twentieth century any syndrome of splenic enlargement and anemia was classified as a splenic anemia. If the spleen were responsible for destruction of red blood corpuscles then it seemed to follow that a condition such as pernicious anemia should be benefited by removal of the organ. Consequently, during the second decade of the century splenectomy was resorted to in a number of these cases. The results were inconclusive.

During this time Whipple, Hooper and Robscheit had been doing fundamental work on the anemias. Their report on the influence of meat, liver and various extractives on blood regeneration following simple anemia in dogs, produced by bleeding, is the foundation on which was developed our present knowledge of blood formation. From this study came the use of liver in pernicious anemia. Minot and Murphy found that feeding one-half pound of liver daily brought about improvement in patients with pernicious anemia. It later became clear that the fraction of liver which was curative in pernicious anemia was not the one which was effective in the anemia of bled animals. These discoveries led to the abandonment of the surgical procedure of splenectomy as a mode of treatment of anemia.

With the rising interest in internal secretions the spleen was not neglected, though it did not receive as much or so wide-spread attention as some other endocrine glands. During this period among the most notable workers was the group headed by Pearce, with Musser and Krumhhaar and a large number of associates. Among others on this continent who were interested in trying to establish something definite as to the way in which the spleen functions were Leake, Holloway and Blackford, Eddy and Downs. In Europe probably Danilewsky, Stradomsky and Mouzon were particularly interested in the physiology of the spleen.

Investigation of the part that the spleen plays in the formation and in the destruction of blood cells has followed largely four lines: Microscopic examination of the spleen; the counting of the cells in the blood going to and coming from the organ; the results of splenectomy; and the effects of administration of splenic substance or extract.

During a period of about fourteen years centering on the second decade of this century Pearce and his associates carried out many experiments intended to throw light on the function of the spleen. Dogs were the animals used. In 1913 Musser and
Krumbhaar stated that after splenectomy anemia usually develops quickly and reaches its height in from three to six weeks; then the blood picture approaches the normal after about three to four months, with complete return to normal in five to ten months. Accompanying this is marked leukocytosis, which reaches its height in twenty-four hours but persists to a slight degree for several months. In 1912, Karsner and Pearce had reported an increased resistance of red blood corpuscles after splenectomy. This was confirmed the following year by Pearce and Peet who stated further, that the increased resistance cannot be explained on the basis of an increase in reticulated cells in the circulating blood. Practically all observers agree that after splenectomy the red blood corpuscles are less fragile than normally. Pearce, Krumbhaar and Frazier had concluded that the transient anemia following splenectomy is due to the loss of some substance that stimulates the bone marrow with a lack of blood formation, rather than to increased blood destruction. This conclusion was supported by the observation of themselves and others that it was relieved by the administration of splenic extract.

In 1920 Downs and Eddy published results of the subcutaneous injection of single doses of splenic extract in rabbits on the number of red corpuscles in the circulating blood. The immediate effect was a temporary decrease in the number. It was thought that the decrease might be due to a direct hemolytic action of a splenic agent. There was frequently a very transient increase in the number of white corpuscles. In 1921 Eddy enunciated the hypothesis that the spleen produces an internal secretion. This was based on the changes in the erythrocytes after splenectomy, the modification of the blood picture in hyperplasia of the spleen, and the specific effects on the red blood corpuscles of injection of splenic extract. Nothing was known of the chemical nature of the supposed hormone and it was difficult to formulate a consistent theory of its possible mode of action. He suggested that the chief function of the spleen is the removal from the circulation of disintegrated erythrocytes; that the splenic cells elaborate this material and thereby produce an internal secretion; that this internal secretion, possibly after modification by the liver, stimulates the erythrogenic function of the bone marrow and is used up in the manufacture of new corpuscles.

Danilewsky in 1895 was able to cause a marked increase in the number of red corpuscles in the circulating blood and also in the hemoglobin content of the blood by a single intraperitoneal injection of an extract of the spleen. Apparently he was the first to suggest that the spleen acts on the bone marrow. In 1916 Stradomsky had concluded that the immediate effect of the splenic agent was destruction of erythrocytes. The increase in production of red blood corpuscles by the bone marrow, however, went beyond the usual response to a reduction in the number of corpuscles in the circulating blood and he felt that this was explained by assuming the removal of a normal regulating action by a splenic hormone on the bone marrow.

In 1922 and 1923 Downs and Eddy reported further experiments in which splenic extract was administered subcutaneously to rabbits daily for periods of from four weeks to fifteen weeks. These showed the appearance of reticulated cells in the circulating blood in a proportion much greater than normal, the presence of
nucleated red corpuscles in the circulation, and an increase in the resistance of the circulating red blood corpuscles. These results agreed with those obtained previously and appeared to confirm the theory of splenic action that had been proposed.

At this time Leake and Leake\textsuperscript{17} demonstrated that both extract of spleen and extract of red bone marrow are hematopoietic agents and that a combination of the two is more powerful than either one alone. In their opinion they act first by increasing the rate of production and second, by causing an extension of functioning red marrow. Leake and Evans\textsuperscript{18} followed the treatment of various types of anemia in humans by the use of desiccated spleen and red bone marrow combined in equal quantities. Improvement was obtained in grave secondary anemias, both active and chronic, in dietary anemias of infants and in menorrhagic anemias.

The development of the concept of the spleen as a gland of internal secretion has taken place gradually during the past quarter century. During later years it has been based almost entirely on pathologic and clinical observations. In 1916 Kaznelson\textsuperscript{19} showed that removal of the spleen was followed by a rise in the platelet count and clinical improvement in some cases of thrombocytopenic purpura. He concluded that the spleen had been exerting an excessive cytolytic action on platelets. Whether Kaznelson's conclusion was sound or not his recommendation that splenectomy be performed in cases of thrombocytopenic purpura was followed by the report of excellent results in 16 cases.\textsuperscript{20} Troland and Lee\textsuperscript{21} in 1938 described a substance obtained from spleens that had been removed from patients suffering from thrombocytopenic purpura which caused a reduction in the platelet count when injected into animals. Wiseman and Doan\textsuperscript{22} in 1942 described a condition that they ascribed to hyperactivity of the spleen. The spleen was enlarged and the white blood corpuscle count low. They named it primary splenic neutropenia. Splenectomy was followed by an increase in the leukocyte count and improvement in the condition of the patient. They believe excessive activity of a splenic hormone to be the cause, without being able to determine what has led to this disturbance of splenic processes. In 1946, Doan and Wright\textsuperscript{23} described primary splenic panhematopenia, in which there is a reduction of all formed elements of the blood, red corpuscles, white corpuscles and platelets. In these cases also splenectomy caused marked improvement.

This study of the spleen is not unmindful of the useful purpose served by the spleen as a reservoir of quickly available red blood corpuscles with their hemoglobin. Nor does it overlook the phagocytic activity of the gland. It is, however, concerned with a different problem. Moreover, it has been pointed out that the phagocytic action and the production of one or more agents affecting the red blood corpuscles in active circulation and the bone marrow may be closely related.

**Conclusion**

An attempt has been made to trace the scientific study of the function of the spleen from the time of ancient Greece to the present. Modern theory and experimentation have linked the organ with the formed elements of the blood. Gradually a theory of endocrine activity has been developed which relates the spleen to the corpuscle content of the circulating blood. A normal blood picture is due, in part at
least, to a normally functioning spleen. There is then the possibility of hyper- or hypoactivity and it seems reasonable to regard certain clinical entities as due either partly or wholly to disordered splenic activity. Those conditions in which it seems to be fairly well established that removal of the spleen should be considered are thrombocytopenic purpura, splenic neutropenia and primary splenic panhematopenia. Cases so far reported suggest strongly that the prognosis is much improved by splenectomy. What the later effect of absence of the spleen may be remains unknown. A clinical manifestation of hypoactivity of the spleen does not appear to have been recognized as yet.

SUMMARY

While the evidence for an endocrine function of the spleen is meagre and the exact nature of this action is not clear it does seem to be fairly well established that the spleen must be considered as an important part of the mechanism whereby a normal corpuscle, and possibly platelet, content of the circulating blood is maintained.

This regulation seems to be due to the production by the spleen of one or more hormones.

These hormones appear to affect the processes of the bone marrow and also may act upon the corpuscles in the circulating blood.

The conception of hyperactivity of the spleen in the human being seems to be firmly established but little is known of the clinical appearance of its hypoactivity.

REFERENCES

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