Is Hypersplenism a Dead Issue?

By William H. Crosby

Hypersplenism became almost a household word about 15 years ago following publication by Dameshek and Estren of a book of that name.\textsuperscript{1} Objectors to the term say that it has no adequate definition, yet everyone grasps the concept of anemia or leukopenia or thrombocytopenia which can be cured by removal of the spleen. This practical definition is easy; obscurity lies in the area of pathogenesis. When Dameshek first used the word in its modern sense\textsuperscript{2} he stated his belief that the normal spleen exerts a mild inhibition on the marrow's hematopoietic activity; in hypersplenism the inhibitory effect becomes pathologically severe. Dameshek's concept resembled Weber's proposed analogy of splenic and thyroid activity\textsuperscript{3} with "hyposplenism," "eusplenism," and "hypersplenism" depending upon the amount of "splenin," the hypothetical hormone. Direct evidence to support the existence of splenin or other splenic humoral factors has not appeared and an alternative concept of hypersplenic activity due to sequestration has acquired considerable support. Doan became identified with this hypothesis which holds that blood cells are trapped in the spleen and prematurely destroyed. For several years the Damesheviks and the Doanites argued, pleasantly, but with conviction.\textsuperscript{4,5} However, much evidence favoring the concept of sequestration accumulated and, although the two are not mutually exclusive, the concept of marrow inhibition by the spleen seemed gradually snowed under. Warmth and vitality disappeared from the discussions of hypersplenism, and publications in recent years have become as stereotyped as the references to Galen's \textit{misterii plenum organum}.

Before inhibitory hypersplenism is buried it may be well to re-examine the concept for signs of viability. First, the evidence in favor of the hypothesis of sequestration can be briefly stated:

1. It has been observed in hypersplenism that the blood cell counts are lower in the splenic vein than in the splenic artery.\textsuperscript{6} Objections have been raised and contrary results (no difference in the counts) have been claimed. Certainly splenic function may be disturbed by surgical procedures, but the observations have been controlled by counts on normal splenic blood. The evidence favors sequestration.

2. When radioactive red cells are transfused into a patient with hemolytic anemia, surface counting may indicate that radioactivity has become concentrated in the spleen.\textsuperscript{7} In such cases splenectomy is reported to produce uniformly good results, indicating that the red cells were destroyed in the spleen.\textsuperscript{7,8} Some hematologists are so impressed with the accuracy of the procedure that they make a diagnosis of hypersplenism without recourse to...
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splenectomy. With regard to the results of splenectomy in patients who are negative for spleen localization, there is no adequate series because these people have been presumed to be free of hypersplenism. How many might be cured by splenectomy remains to be seen. The evidence favors the concept of red cell sequestration in hypersplenism in the cases which are positive for spleen localization.

3. Plasma from patients with idiopathic thrombocytopenic purpura produces a temporary thrombocytopenia when transfused into normal recipients. The "humoral factor" resembles an autoantibody but its origin is not splenic for the antiplatelet factor can be demonstrated postsplenectomy even in patients whose thrombocytopenia has been cured by the operation. Destruction of platelets in such cases requires the collaboration of antibody and spleen. Evidence favors the concept that the morphologic change in the marrow's megakaryocytes is probably not a consequence of splenic inhibition. Perhaps it represents immaturity associated with increased platelet production.

4. Studies with fluorescent antiplatelet antibodies have demonstrated a great excess of reactive material—presumably platelets—in spleens of patients with ITP. The work may be criticized because the control tissue was obtained postmortem, but the evidence favors the concept of splenic sequestration.

5. Studies of hemoglobin synthesis and reticulocytosis in clinical and experimental hypersplenic anemia have demonstrated a high output of red cells. This is inconsistent with the concept of splenic inhibition.

This pattern of evidence strongly favors the belief that cytopenias of hypersplenism are a consequence of sequestration and phagocytosis of blood cells. Some hematologists have concluded that the term depressive hypersplenism is misleading and that there is at present no proof of the existence of splenic hormones in hypersplenism. However, there are some observations which deserve consideration.

1. When autoimmune hemolytic anemia is cured by splenectomy the tests for autoantibodies usually remain positive or become negative rather slowly. Yet occasional cases of long duration have been cured immediately after splenectomy and at the same time the tests for red cell antibodies became and remained negative. This suggests—but of course does not prove—the existence of an anti-red cell humoral factor of splenic origin. But autoimmune disease may be directed at more than the red cell. When the erythroid marrow itself is injured by autoantibodies the picture comes close to fitting the concept of marrow inhibition. Restoration of the injured marrow following splenectomy is strong evidence in favor of hypersplenism.

2. Ferrata's concept of blocco splenogeno was based upon experience with patients whose marrow was aplastic but recovered following splenectomy. McFarland et al. have recently studied several patients with aplastic anemia and pancytopenia whose marrow promptly recovered postsplenectomy and who have remained well. More limited affections of the marrow have also improved after splenectomy. In a case reported by Strawitz the patient had chronic lymphocytic leukemia and developed purpura with absence of megakaryocytes in his bone marrow. Following splenectomy the megakaryo-
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...cytes appeared and the platelet count became normal. In O'Brien's case the patient had lymphosarcoma and absence of plasma cells with associated hypogammaglobulinemia. Following splenectomy plasma cells appeared in the marrow and gamma-globulin in the blood. Such cases as these are rare and the possibility of coincidence cannot be ruled out.

3. Improvement of erythropoietic function has been observed postsplenectomy in patients with myelofibrosis.

4. Studies of platelet life span with radioactive tagged platelets have been used to compute the rate of platelet production. In some cases of chronic thrombocytopenia the computations have indicated diminished platelet production with normal platelet life span. Cure following splenectomy suggests that there had been splenic inhibition of platelet formation. Such computations should be viewed with caution. The values were not based upon the total number of tagged platelets used in the study but rather upon the number which remained in the circulation 24 hours after the platelet transfusion. A large proportion of the platelets might be destroyed by the process of tagging in vitro and by the spleen during the first day. Their life span and loss would not be reflected in the figure for half-life with which the computation is performed. The computed platelet production would therefore be smaller than actual production. This problem requires further evaluation.

Studies in splenectomized rats have shown a slight increase in the concentration of marrow megakaryocytes. In splenomegalic, hypersplenic rats the concentration of megakaryocytes is diminished. On the basis of such information, together with platelet life span studies, Matter and his coworkers have concluded that "...the spleen exerts its effect on the level of circulating platelets through alteration in the rate of thrombopoiesis."

5. Methylcellulose (methocel) produces splenomegaly and hypersplenic cytopenias which can be cured by splenectomy. Review of the reported results reveals considerable variability of hematologic response. The anemia is hemolytic rather than aregenerative, but some evidence of a lack of erythropoietic response has been reported. The milk of hypersplenic methocel mothers produces anemia in suckling rats. It has been reported that the life span of the red cells in these anemic pups, measured by tagging the cells with Cr, is normal. This was regarded as evidence of a myelosuppressive material passed from the hypersplenic animal to the healthy one. However, in view of the technical problems that must be involved in measuring red cell life span in such a small animal with an expanding blood volume, evaluation of the data should await publication of the method. The urine of hypersplenic methocel rats has also caused anemia when fed to normal rats.

6. Routing of splenic blood into the systemic circulation is reported to cause anemia ascribed to splenic humoral factors which are normally destroyed when the splenic blood passes through the liver. When rerouting is done by ligating the splenic vein, this shunts the blood through anastomoses, but it also causes congestive splenomegaly which may cause the hypersplenism. Transplanting the spleen to a subcutaneous location is said to inhibit erythropoiesis, but the results are variable and seem not to have statistical validity.
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hand, direct anastomosis of the splenic vein onto the vena cava does not result in anemia. The evidence for humoral hypersplenism in this group of experiments does not seem substantial.

7. Following removal of the normal spleen, animals show increased resistance to the effects of x-irradiation and nitrogen mustard. Preliminary studies on our own service indicate that the bone marrow of splenectomized human subjects has a greatly increased resistance to the chemotherapeutic agent, metasarcolysin. The observations suggest that the spleen contributes something to the toxicity of these myeloinhibitory agents, but the mechanism of this triangular interaction is not known.

8. If there is an inhibitory hypersplenism it seems reasonable to suppose that the spleen would contain distinctive cells to provide inhibitory factors. Such cells, if they exist, have not yet been identified.

In summary: Evidence favoring the concept of hypersplenic sequestration seems solid indeed, but it does not exclude the possibility that other splenic mechanisms may also cause cytopenic diseases. Although the evidence in favor of inhibitory hypersplenism is fragile and loopholed, there is still reason to suspect the existence of splenic humoral factors; at least there is room for argument.

REFERENCES


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