HYPERSPLENISM

A Clinical Evaluation

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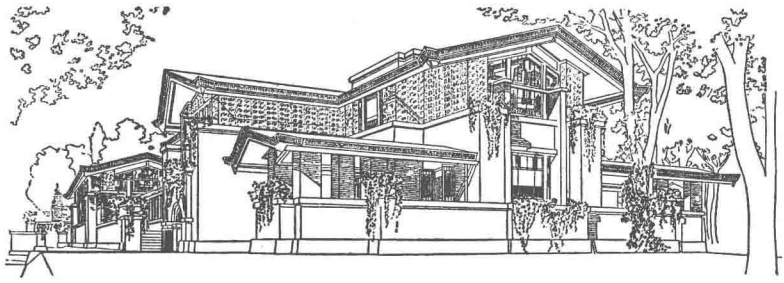

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Preface

FIRST, let me say that I hope you will pardon my justifiable pride in having been chosen to present this Beaumont Lecture. One of my earliest and most impressive recollections of medicine in this vicinity, when first coming to Michigan 25 years ago, was that there was such a lecture. I thought it was convincing evidence on the part of your organization of a fine progressive and scientific spirit. I am grateful, indeed, to have the opportunity to participate in such a program.

I wish also to pay tribute to my many illustrious predecessors who have given these lectures over the past years. A perusal of the names of the previous lecturers makes me feel very humble indeed.

Let me add also, at this time, a statement of admiration and praise for William Beaumont, pioneer Doctor and Physiologist, who in May of 1822 began his observations on the young French-Canadian, Alexis St. Martin, at Fort Mackinac. Great as were his additions to our knowledge of physiology, they were not all he gave to medicine and science. One of his finest contributions was the example of what can be accomplished by a physician who had the spirit of a great investigator; one who was isolated and working without apparatus, funds, associates, or a laboratory. Alone, guided and inspired solely by his own genius, he inaugurated a series of investigations which proved to be epoch making. William Beaumont had in him that inborn mental gift, that rare, precious talent combined with a deep-seated scientific curiosity which made him persue his chosen line of investigation and carry it through to a successful culmination. *Nothing* could have stopped him except death, and fortunately he was spared from this for 31 years after his studies had begun.

Just now one of the greatest problems which confronts all of us who are in medicine can be solved, in part, by even a small portion of that same element of human nature, namely an insatiable curiosity. The current problem is easy to define: how shall we keep abreast with the developments of medicine which are maturing at a rate faster than ever before in the history of medicine, and the tempo will not grow less.

No one physician can know all there is to know about medicine. Nor can any one faculty of medicine. If the latter did know all there was to know on one day, the next day their knowledge would be incomplete because new additional information would be available. Hence the spark of curiosity should urge us on. And let that spark, however feeble, never die. For if one's curiosity grows dull, the urge to keep on learning diminishes, and we have lost the essential progressive spirit of medicine which is so necessary to the welfare of every physician and his patients.

And finally, before I begin my remarks on "Hypersplenism," let me emphasize what I have to say here tonight is not by any means entirely my own although I must take the sole responsibility for my utterances. In the 25 years the Simpson Memorial Institute of the University of Michigan has been in existence, many diligent and brilliant investigators have worked there and I have learned much from them. I am especially indebted to Dr. Frank H. Bethell, the Associate Director, who has been with me for so many years, and more recently, to Dr. Muriel Meyers, Assistant Professor of Medicine, who devotes a major portion of her time to studies in the Institute. To all who have ever worked there, I gratefully acknowledge my indebtedness.

C. C. S.

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Introduction

THERE is no better introduction to the subject which I am to discuss than the following quotation from a lecture given before the medical students of Harvard University on November 6, 1861, by Oliver Wendell Holmes, Poet, Philosopher and Professor of Anatomy in that Institution. It is as follows:

"The best part of our knowledge is that which teaches us where knowledge leaves off and ignorance begins. Nothing more clearly separates a vulgar from a superior mind, than confusion in the first between the little that it truly knows, on the one hand, and what it half knows and what it thinks it knows on the other."

The truth expressed in this statement seems applicable to the topic which I have chosen tonight—hypersplenism. This mechanism presents an unexcelled field for stimulating speculation by the clinician and investigator; first, because undoubtedly the spleen, whose functions are incompletely known, plays an important role in the causation of this disorder; second, because there are no generally accepted pathological structural changes specific for the condition; and third, because our partial knowledge of both the formation and destruction of the formed elements of blood afford an unusual opportunity to play one process against the other, usually without fear of refutation, until there are substantial additions to our knowledge.

Nevertheless, the subject of the relation of the spleen to certain important blood dyscrasias, the immediate and

permanent curative effect which results from splenectomy, along with the newer significant additions to our knowledge concerning the relation of the adrenocorticotropic hormone and cortisone to the syndromes, compel us to give the process our serious attention.

——*II*——

Hypersplenism

Definition

A mechanism due primarily to an abnormal activity of the spleen, arising from unknown causes which results in a reduction in number of one or more of the cellular elements of the circulating blood, thereby causing an anemia, thrombocytopenia, or a neutropenia, or a combination of these conditions. In all instances, the bone marrow is hyperplastic, and prompt and permanent recovery frequently follows a complete removal of *all* splenic tissue. It is possible that the condition may be due to one, or a combination, of the following: 1) local splenic hypersequestration with increased destruction of the circulating blood cells and platelets; 2) to a hormonal influence emanating from the spleen and exerting its effect by inhibiting the release of the formed elements from the bone marrow; or 3) to the production of auto-antibodies chiefly by the spleen which causes abnormal destruction of erythrocytes, platelets and possibly white blood cells.

——*III*——

Structure and Function of the Spleen

The functions of the spleen are obscure but certain facts have come to light in recent years which are acceptable but

admittedly incomplete regarding its physiological activity in the body. There are some anatomical characteristics of the spleen which indicate that this organ has certain specific functions closely related to these structures. They are: 1) a smooth muscle reinforced capsul which surrounds the spleen and penetrates into the parenchyma as trabaculae. It is easy to understand that this structure is the basis for the rhythmic physiologic contractions and relaxations of the organ seen following exercise, hemorrhage, injection of epinephrine, etc. etc. This change in volume, which may attain 20 per cent of the total blood volume, is controlled by the autonomic nervous system; 2) a unique vascular system with relatively large venous sinuses which permits the storage of a considerable amount of blood. These two peculiar structural characteristics of the spleen combine to provide for one of its important physiological and perhaps pathological activities, namely, erythrostasis or the splenic "reservoir" function.

It is thought by some that the spleen is a major organ of blood cell destruction, that the red blood cells become sequestered there, are separated from the plasma, and as a result of stasis and body warmth become progressively spherocytic and hence progress to disintegration. Also, it is considered that by fragmentation the erythrocytes are broken down normally into small dust-like particles, and that these are disposed of by the spleen. It has been said, and aptly, that the spleen is "not the slaughter house but the grave yard" of the erythrocytes (1). A hyper-sequestration characterized by the withholding and destruction of red blood cells, white blood cells and platelets is the basis for the hypersplenic sequence of events as described by Doan (2), and discussed elsewhere.

Another feature 3) of the structure of the spleen is the large amount of lymphoid tissue in the organ which gives

rise to lymphocytes of the blood, as does lymphoid tissue elsewhere in the body. As Dameshek and Estren say, "the spleen is an enormous lymph gland between an artery and a vein." Another function of the spleen, therefore, must be related to the uncertain and incompletely known purpose of the lymphocyte in the body. Recent studies, however, give promise that the physiological activity of this cell and its participation in pathological changes in the body may be clarified. It has long been known that these cells 1) are active in the body's resistance to certain infections such as tuberculosis; 2) recent observations indicate that they are closely associated with antibody formation (3, 4); 3) that the release of the antibodies is at least in part controlled by the pituitary-adrenocortical system which has important therapeutic implications; and 4) evidence suggests that the lymphocyte is active in the destruction of toxic products of protein metabolism (5).

The Reticulo-Endothelial System

The cells comprising the reticulo-endothelial system have been given a variety of names, as follows: clasmatocytes (Ranvier), hemohistioblasts (Ferrata), resting wandering cells (Maximow), and macrophages (Evans). Such cells, arising from the mesochyme, are found in the sinuses of the spleen, the bone marrow, the intralobular capillaries of the liver (Kupffer cells), and the sinuses of the lymph nodes. They are also present in the serous membranes and perhaps in the endocrine glands. Furthermore, they exist as free macrophages. These cells were originally designated as the fundamental elements of the reticulo-endothelial system by Ashoff and Kiyono who demonstrated that they could be recognized by their capacity to take up vital stains such as lithium carmine. The cells of this system have in common their mesenchymal origin, the power of phago-

cytosis and of granular storage of electronegative colloids, the affinity for lipids, and the ability to become transformed quickly into the free ameboid forms.

Reticulo-endothelial cells give rise to the fixed reticulum and to the primitive free cells from which the monocytes of the circulating blood arise and mature. It is to these cells that Doan (6) attributes the principle hypersplenic activities of the spleen. He says . . . "there may be a tremendous increase in the number and phagocytic activity of the reticulo-endothelial cells in a normal-sized or greatly enlarged spleen with hypersequestration of entrapped, and, therefore, hypersusceptible blood cell elements, which can produce a circulating cell deficit despite attempts at bone marrow compensation." The fact that the spleen contains a large number of reticulo-endothelial cells may explain, at least in part, some of the abnormal changes associated with the mechanisms of hypersplenism. It should be kept in mind that the cells of this system have a widespread distribution in the body, and only a portion of the aggregate are removed by splenectomy. The remainder are left throughout the body to function, and perhaps to undergo hyperplasia to compensate for the loss of those resulting from splenectomy. This may explain why the operation fails to cure a certain per cent of patients in whom the mechanism of hypersplenism exists.

The Possible Hormonal Effect on the Bone Marrow

There is suggestive but not conclusive evidence to indicate that the spleen controls the development and emission of the formed elements of the blood from the bone marrow by hormonal influence. This belief is supported by changes which occur when splenectomy is done in certain pathologic states as thrombocytopenic purpura and splenic neutropenia. Before the advent of liver therapy, splenec-

tomy was occasionally performed in patients with pernicious anemia and it was not unusual to observe the immediate development of a remission which sometimes persisted for several months. It is suggested by Dameshek and Estren (7) that one of the functions of the spleen is a "bone marrow regulator" and by this is meant that there is control of emission of red blood cells, of denucleation, and of erythrocyte thickness. Furthermore, they believe that there is regulation also of the liberation of granulocytes, from the bone marrow and the formation of platelets from the megakaryocytes.

Complete proof of these statements is lacking but there is some experimental evidence in support of them. For example, it has recently been reported by Palmer and his associates (8) that splenectomy in the normal albino rat is followed by an increase of about 100 per cent in the total white blood cell count which persists for 70 to 90 days. This change is not observed in animals with control operations of similar magnitude (partial omentectomy and unilateral nephrectomy). The authors conclude that in the rat the spleen exerts an influence on the level of the circulating leukocytes, and hence the theory that this organ controls their production and rate of liberation in the bone marrow is supported but not conclusively proved. The fact that splenectomy is followed by an anemia in the normal mammal, as reported by Krumbhaar (9) is not entirely in harmony with this view. The anemia is transient, however, and accompanied by a reticulocytosis, the appearance of Howell-Jolly bodies, and of nucleated erythrocytes. These latter changes, however, would be in accord with the theory that the spleen normally has an inhibitory effect on the bone marrow, and when this is removed by splenectomy, the threshold is lowered and an increased number of immature cells reach the blood stream.

——IV——

Circulation of the Spleen and the Relation of the Sinus Filter to Deplasmatization

In 1936, Knisely (10) studied living transilluminated spleens microscopically in an attempt to learn how blood circulated through the organ. He points out that there have been two ideas concerning the circulating of blood through the spleen; 1) a "closed" circulation which considers that the blood is always inside of preformed, interconnected, lined channels; and 2) the concept of an "open" circulation which postulates that the arterioles or capillaries direct blood into the intercellular spaces of the splenic pulp tissue, and from these areas it is collected into the veins again. The studies by Knisely show, in his opinion, that the splenic vascular system of mammals consists of a "system of preformed, interconnecting channels." Of great importance are the venous sinuses which receive arterial blood from the central artery of the Malphigian bodies, conduct it to the arterioles, and thence to the arterial capillaries. These vessels then enter the venous sinuses which are definite anatomical units shaped roughly like cucumbers. The latter are considered to have a conducting phase during which time they are contracted to a narrow tube-like form and the blood passes through the sinuses rapidly and pulsation may be presesnt. Another stage is the filling-filtration one when the efferent sphincter of a sinus closes, causing the accumulation of blood which distends the sinus until it becomes a greatly enlarged curved oval-shaped structure, solidly packed with blood cells. Or, as he describes the state of the contained blood, it is "thick and pasty" and forms a "soft blood cast" in the sinus. During this storage phase, fluid passes through the sinus wall into the splenic pulp, and the deplasmatized red blood cells