

# The spleen and its physiologic role; are we teaching for students?

Ayechew Adera Getu<sup>1\*</sup>

Department of Physiology, College of Medicine and Health Sciences, School of medicine, University of Gondar, Gondar, Ethiopia.

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**Abstract:** Despite having important clinical significance, the spleen is often a neglected internal organ especially in the medical physiology teaching. The present personal view is aimed to present the current understanding of the functioning of the spleen and the culture of teaching practices about spleen. The spleen is an intra-peritoneal organ located directly below the diaphragm connected to the stomach. It is one of the most perfused organs in the body. It consists of white pulp which is specialized in holding aggregation of lymphoid tissues, the red pulp having reticular mesh workings designed to destruct old, damaged and aberrant erythrocytes and the marginal zone lying between the red and the white pulp where foreign particles including microorganism are eliminated. The spleen, having such anatomical specializations, helps to perform wide arrays of activities ranging from successful induction of specific immunity through trapping, transportation, processing and presentation of antigens, recycling of iron and phagocytosis of senescent or damage red blood cells (RBCs) and pathogens. In conclusion, the basic knowledge of the anatomical and functional aspects of the spleen is essential for the assessment of its role in disease process and therefore, for the better understanding of the functions of spleen, teaching and incorporating the physiology of it in physiology syllabus is imperative.

**Keyword:** Spleen Structure and Function; Immune Function; Iron Recycling; Blood Flow to the Spleen

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## 1. Introduction

The spleen is considered as one of the seat of reticulo-endothelial system, a system which comprises of monocytes, macrophages and their precursors which are actually defending the body from infectious agents and tumorous cells.

Spleen is an intra-peritoneal organ located directly below the diaphragm connected to the stomach and perfectly situated for its role as a blood filter and an immune organ. It is structured in such a way that its arterioles end in a sinusoidal venous system originating from a 'tree' like branching of arterial system (14).

Immunologically, the spleen plays a great role in combating bacterial, viral, fungal infections and cancerous cells as it combines both adaptive and innate immune system. The anatomical and histological characteristics of the spleen allow it to be the site of filtering of incoming blood and removal

of senescent erythrocytes.

However, despite having important immunologic and physiologic roles, the spleen is not usually given well attention by both physiology educators and the physiology syllabus. Therefore, the present work is aimed to give information about the structural and functional organization and clinical significance of the spleen, which need to be incorporated in physiology curriculum.

## 2. Part I. Anatomical Organization of the spleen

The spleen is an intra-peritoneal organ located directly below the diaphragm in the left hypochondriac region connected to the fundal region of the stomach. In humans, it is about 12 cm long, 7 cm wide, and 3 cm in thickness, and weighs around 150-250 g even though its size and weight can be variable depending on the age, individual and the health status of a person (15). It is one of the highly vascular and perfused organs, about the size of clenched fist with purplish-red, soft in its texture.

\* **Corresponding author:** Ayechew Adera Getu, Department of Physiology, College of Medicine and Health Sciences, School of medicine, University of Gondar, Gondar, Ethiopia. P.O.Box-196. Email; [ayechevadera09@gmail.com](mailto:ayechevadera09@gmail.com); [Ayechew.adera@uog.edu.et](mailto:Ayechew.adera@uog.edu.et)

The size of the spleen can be varied depending on the nutritional status of the individual and functional activity of it. Its size is increased during and after digestion and becoming smaller after prolonged fasted state. It is also common for the spleen to be enlarged in size during certain inflammatory process like, malarial fever weighing occasionally as much as 9 Kilos. It has four important structures; outer covering capsule, red pulp, white pulp and marginal zone. Each structure shows a unique morphological structure each performing specific physiological functions.

### 2.1. The Capsule

It comprises compact connective tissues, elastic fibers and smooth muscle cells having sympathetic innervations arising from the splenic nerve plexus (15). The spleen is involved in the reservoir of blood in different circumstances. The reservoir blood may be pumped in to the circulation and contribute for the restoration of blood volume and oxygen supply to the tissues. This is possibly because of the organization in the capsular layer having few smooth muscle cells reflecting a minimal contractile role.

### 2.2. White Pulp

The white pulp consists of lymphocytes, dendritic cells, plasma cells and macrophages, lying on a specialized reticular meshwork composed of concentric layers of stromal cells, now recognized to be specialized fibroblasts. Fibroblast cells are now known to produce several important proteins including type III collagen, laminin, fibronectin, playing an important role in the migration of lymphocytes during both fetal lymphatic tissue development and immune response in adulthood(1).

### 2.3. Marginal Zone

Is the region of the spleen located at the interface between the red pulp and white-pulp even though certain sources consider it as part of the non-lymphoid red pulp bordering the white pulp. The marginal zone is the site of termination of many arterioles, which frequently bifurcate just before their termination. It receives huge amount of blood because of the presence of large number of terminal arterial vessels. Lymphocytes and their accessory cells pass to the white pulp, platelets and erythrocytes pass into the red pulp. The marginal zone consists of sinus-lining reticular cells, marginal zone B cells, dendritic cells, marginal metallophilic macrophages, and marginal zone macrophages. Blood leaves the terminal arterioles into open sinuses, the blood flow is slowed down, and blood-borne particles are trapped with high efficiency(2).

The marginal zone is also the site of activation of B cells as a consequence of antigenic exposure due to the anatomical arrangement such a way that splenic arterial blood empties to this area. Because of this, the marginal zone is known to be the site where highest concentration of antigens is presented as compared to other areas in spleen.

### 2.4. Red Pulp

The bulk of human spleen is the red pulp comprising of four vascular structures in sequence: slender non-anastomosing arterial vessels (penicilli), the splenic cords, the venous sinuses; and the pulp veins(3). As described below because of the presence of specialized nature of the venous system in this particular part of the spleen, the red pulp is unique for its capacity to filter the incoming blood and remove old and damaged erythrocytes.

Blood and lymphatic organization:

Spleen receives considerable amount of blood flow (170 mL/min/100 gram of tissue), making it one of the most perfused organs in the body. It gets its blood supply through splenic artery and removes blood through splenic vein and lymph via efferent lymphatic vessels.

In rats and human being the blood flow through the spleen is unique in that it passes an open and a closed circulation in parallel(4).

In physiological conditions, more than 90% of the splenic blood flow goes through the white pulp bypassing the red pulp. The central artery supplies radial branches to the white pulp, marginal zone, and red pulp, and terminates in an attenuated vessel of variable structure supplying the red pulp. Lymph carries T cells, B cells, cytokines, chemokines, growth factors and peptide hormones.

### 2.5. Innervation

The nervous system directly or indirectly controls all body functions including the immune system. Primary and secondary lymphoid organs are directly innervated and their function is under the modulatory effect of the nervous system. Neuroanatomical studies demonstrated that all primary and secondary immune organs including the spleen receive a substantial sympathetic innervation from sympathetic postganglionic neurons. However, the spleen doesn't receive any sensory and vagal neural innervations(5).

Immune cells, once they are stimulated, can produce and secrete different of pro- or anti-inflammatory mediators, which in turn provide a controlled immune cell response. Neuron-immune systems communication is not unidirectional. It is widely accepted that the neurotransmitters released from neuronal ending supplying to the lymphoid organs affect those immune cell and certainly immune cell secretory products/mediators released from immune cells like cytokines can affect functions of the neural cells(6).

Sympathetic preganglionic neurons that innervate the spleen arise from the T1-T12 region of the thoracic spinal cord. These preganglionic neurons release acetylcholine as their neurotransmitter while the majority of the post ganglionic sympathetic neurons release the neurotransmitter norepinephrine. Lymphocytes (T and B cells) and macrophages residing in the marginal zone are influenced by the sympathetic discharges. Noradrenaline releasing sympathetic neurons particularly densely localized in T-cell zones and in areas of macrophages and mast cells(7).

### 3. Part-II. Functions of the Spleen

#### 3.1. The Spleen as Blood Reservoir

The spleen is a storage site for iron, erythrocytes, and platelets. It is also believed that it stores a minimal amount of blood in humans. In animals like cat, horse, dog and guinea-pig a sizeable amount of blood is stored in the spleen especially in the venous sinusoids. Whenever there is a need of blood to the circulation, considerable amount of blood can be ejected /squeezed from the spleen.

It has been long time known that the splanchnic vascular bed constricts when the cardiovascular system is challenged by a variety of stresses. Since this region receives about 25% of the cardiac output blood volume, the resultant redistribution of splanchnic blood flow and mobilization of splanchnic blood volume can contribute significantly to the support of arterial blood pressure and cardiac output(8).

As described above, the discharge of the sympathetic nervous system to the splenic smooth muscle like cells during emergency situations like hemorrhage or exercises is believed to be responsible for discharge of the blood.

In experiment done on dog by occlusion of bilateral carotid arteries and inducing severe and moderate hemorrhage to measure the degree of blood distribution from spleen, liver and intestine showed that, the spleen exhibits the greatest ability to release blood in to the circulation(9). Spleen has smooth muscle fibers which are contractile upon several stimulatory factors like ingestion of food, exercise, hypoxia, bleeding, decrease in blood pressure, injection of catecholamines with a subsequent increase in hematocrit and hemoglobin concentration in the peripheral blood(10). This study showed that the human spleen acts as a reservoir for red blood cells, and contraction of the spleen leads to synchronous increases in hemoglobin content after exposure for diving-related interventions.

From the above animal studies, though the amount of blood redistributed is moderate and the time for mobilization is very short, splenic ejection may contribute significantly to the maintenance of blood volume and cardiac filling pressure especially during stressful situations and help to enhance tissue oxygenation.

#### 3.2. The Spleen as Blood Filter

The spleen is strategically located to remove abnormal and senescent erythrocytes and platelets, bacteria, and particulates from the circulation. Specifically the red pulp is responsible to filter the blood and remove old or damaged erythrocytes and platelets, apoptotic cells, and infectious agents from the blood(11).

As clearly demonstrated below, the red pulp is also associated with iron recycling because of its role in erythrocyte removal largely by the presence of densely aggregated macrophages in the splenic cords(12). About 240 ml of erythrocytes and 30 % of platelets can be stored and mobilized during splenic contraction in time of deficient in oxygen or a

decrease in blood volume. Due to its location on the blood mainstream, as opposed to other secondary lymphoid organs, the spleen filters approximately 5% of the cardiac output every minute(13).

#### 3.3. Immune Function of the spleen

Efficient control of pathogens by the immune system is promoted by a highly organized microarchitecture of secondary lymphoid organs. These structures form the basis for trapping, transport, processing, and presentation of antigens, a prerequisite for initial constraint of pathogens and successful induction of specific immunity.

The spleen is the largest secondary lymphoid organ, primary being the bone marrow and thymus, playing a great role in destroying old and damaged erythrocytes and phagocytosis of infectious microorganisms and cancerous cells. Its role in immunity is primarily through phagocytosis however cell-mediated immunity and humoral immunity are also most important functions of the spleen. Rapid removal of pathogens from the circulation by secondary lymphoid organs is prerequisite for successful control of infection. Blood-borne antigens are trapped mainly in the splenic marginal zone. The primary lymphoid organs control the production and maturation of immune cells and the spleen manipulates and presents antigens collectively eradicate pathogens and initiate adaptive immunity(14).

Spleen's role in fighting against infections and immunity was known at earlier times. Post splenectomy infection complications are now a well-known phenomenon. The risk of overwhelming infections is more than 50-times higher in post splenectomy patients compared to the general population. A retrospective study done by (15) indicated that splenectomy increases the risk for post-operative infectious complications. Their result showed that among patients who require abdominal surgery, splenectomy is associated with an almost 3- fold higher risk for development of early post-operative infectious complications and more than a 4-fold higher risk for developing an intra-abdominal abscess. Attention has also given for spleen in storing and disgorging monocytes whenever there are inflammatory injuries in the particular regions of the body and help to repair tissues. This is evident in the heart after suffering from myocardial infarction. The number of monocytes in the spleen is much higher than those found in the circulation. Even after myocardial infarction the amount of monocytes found in the heart exceeds those found in the circulation under normal conditions(16).

#### 3.4. Hematopoiesis

The process by which blood cells are formed occurs throughout life starting from early embryonic development to produce and replenish the blood system.

In humans, hematopoiesis begins in the yolk sac and transitions into the liver temporarily before finally establishing definitive hematopoiesis in the bone marrow and thymus. The spleen is an important hematopoietic organ during fetal

life. It produces erythrocytes until the fifth month of gestation and after birth it produces lymphocytes and is the center of multiplication of B and T lymphocytes and plays an important role in immune responses. After birth splenic role in production of erythrocytes ceases, though contributes in some hematological disorders such as leukemia. If there is any injury (e.g. tumor) to the bone marrow, the adult spleen can produce blood cells as hematopoietic stem cells circulate and reside in the spleen.

### 3.5. Role of the Spleen in Iron Recycling

Iron is an essential trace element for body functions playing important role in oxygen transport, electron transfer, and acting as a cofactor in enzyme systems. It is a component of several proteins including hemoglobin, myoglobin, cytochromes and enzymes involved in redox reactions. Under physiological conditions on average a person has about four grams of iron contained within hemoglobin(75%) and readily metabolized iron storage units(25%) known as ferritin or hemosiderin in the liver and other reticulo-endothelial systems(17). Iron is variably absorbed in the small intestine depending on dietary and host-related factors. Its absorption primarily occurs in the duodenum. In adult men approximately 1 mg/day of iron is absorbed in the small intestine with corresponding loss of 1 mg/day and recycling of it from macrophages with the rate of about 25 mg/day(18).

Senescent or in otherwise damaged erythrocytes are engulfed by macrophages in the liver and spleen. Once these erythrocytes are phagocytosed by macrophages hemoglobin degradation will follow. Degradation of hemoglobin releases Heme, which is then catabolized in to biliverdin, carbon monoxide, and iron as ferrous form ( $\text{Fe}^{2+}$ ). Macrophages in splenic red pulp are specialized for iron recycling, with increased expression of proteins for the uptake of hemoglobin, breakdown of heme, and export of iron. Recycling of iron from old and damaged red cells supplies the bone marrow with approximately 20 mg of iron per day for new red cell synthesis. It is believed that whenever the body needs iron, the splenic macrophages release the stored iron in to the plasma in response to the erythropoietic drive expressed by the bone marrow. A study done by Donovan et al (19) showed that a protein named Ferroportin-I which is found on the basolateral membrane of the duodenal enterocyte mucosa is known to be an exporter for Iron during absorption is also believed to be responsible for the transportation of iron from macrophages in the reticuloendothelial system like spleen.

## 4. Part III. Pathological Considerations

The spleen may show pathological changes due to a variety of causes, where splenomegaly becomes a major clinical diagnostic concern. Splenomegaly is a common nonspecific manifestation of variety of infectious and non-infectious conditions. The enlargement may be due to either the con-

sequences of disorder of internal organs as like liver cirrhosis or secondary to its contribution in the prevention of certain diseases such as malaria, sickle cell anemia, leukemia, and other conditions in which its primary route involving the spleen.

Several bacterial, viral, parasite infections as well as certain cancers are associated with splenomegaly. In Ethiopia, where the authors reside, malaria and visceral leishmaniasis are very common and patients usually experience enlargement of the spleen secondary to the effects of these infections. Malaria parasites induce an intense splenic response mainly characterized by enlargement of the organ. During the erythrocytic stages of malaria infection, the spleen is the main organ involved in the development of the immune response and in elimination of infected erythrocytes(20). In response, it becomes enlarged, weighing possibly as much as 9 kilograms.

As outlined above, the spleen receives considerable fraction of the cardiac output and significant amount of blood is accumulated in splenic sinusoids, traumatic and surgical injury and manipulation can lead to life threatening circulatory shock. Because of this risk, care has to be taken and sound practical skills, anatomical and functional knowledge of the spleen is needed in order to manage such type of surgical patients.

## 5. Conclusion

Spleen is a much neglected organ in physiological education even though it plays several important roles as it is strategically located where which huge amount of blood is flowing. It is the house for the efficient phagocytosis of old and damaged erythrocytes and recycling of iron, the uptake and destruction of pathogenic microorganisms, the induction of adaptive immune responses, production of new red blood cells in the embryo and reservoir of blood.

Partial or complete surgical removal of spleen either for splenic injury or hypersplenisms have significant pathophysiological consequences such as massive bleeding from the spleen in the acute phase, and subsequent immunosuppression that might lead to overwhelming infection in the postoperative periods for life.

Finally, even though splenic function was not given attention, it is worth to teach the important immunological and physiological roles of the spleen for medical students.

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