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THE FUNCTIONS OF THE SPLEEN.

BY

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Early this year I was asked the question, What is the function of the spleen? Not knowing what the answer to the question was, I thought I had better try and find out. The subject, I thought, was a suitable one to put before the Society, for the spleen is an organ which almost every Fellow has daily to examine in the pursuit of his profession. I thought that it would be of service to them to try and set forth the evidence for the current opinions regarding some of its supposed functions. The results of my researches in the literature I have ventured to put before you to-night.

The dimensions of the spleen are approximately 12 by 8 by 4 cm., giving a volume of 384 c.cm. Its weight is about 200 g., about one-quarter per cent.
of the body-weight. At birth the weight is about 10 g. As, according to Barcroft (1925), in death from drowning or haemorrhage the spleen of a cat may shrink to half or even a quarter of its original size, the above figures should be applied with caution to the living body.

I. The General Anatomy.

The Albuginea in man is inseparable from the serosa except at the hilum. It is about 0.1 mm. thick and contains relatively few pale muscle fibres. Elastic fibres are also scanty, but they are more abundant in the trabeculae.

The Trabeculae may be as much as 1.5 mm. in thickness and thus form a thick sheath for the splenic artery and vein.

Lymphatics occur beneath the capsule (albuginea) only.

The spleen contains two tissues—(1) white pulp, (2) red pulp.

WHITE PULP.

When the trabecular artery is about 200μ in diameter it leaves the trabecula, and the sheath of connective tissue gradually changes its character, becoming lymphoid; it consists, that is, of a reticulum of fibres and branched cells in which lymphocytes abound, thus having the same structure as the Malpighian follicle; and, in fact, at birth this sheath forms a continuous layer around the artery, but in later life the thickened portions—the Malpighian follicles—are almost all that remain.

Stieda (1862) showed that the Malpighian follicles are not entirely isolated structures, but one follicle may be joined to another, or strands (follicular
cords) may still accompany the artery into the red pulp (cords of BILLROTH). The lymphoid sheath of the artery, the follicle, the follicular cords, all filled with lymphocytes, may be called "white pulp." In early life it is the predominating tissue, while in old age it has been replaced almost entirely by "red pulp."

**Malpighian Follicle.**

The Malpighian follicles have not always a defined contour, but may be diffuse without a germinal centre. About 0.5 mm. in diameter, they may be regarded as a collection of lymphocytes held together by a reticulum.

*(a) The Stroma or Reticulum* is variously described as consisting of (1) collagenous fibres (fibres which swell with acetic acid and yield gelatin on boiling) with here and there a connective tissue cell; or (2) as a reticulum of fibres and dendritically branched cells and a few elastic fibres, non-collagenous "reticulum" fibres (Gitterfasern or lattice fibres of OPPEN) being rare; or (3) as a reticulum of fibrillae and not of anastomosing cells; this reticulum is so fine at the margin of the follicle as to form a pseudo-membrane; in the centre the cells (and fibrillae) to some extent exist as a syncytium; or (4) Retterer (1915, 1916) regards the follicle as a solid syncytium permeated by haematoxylinophilous fibrillae, and nuclei 5μ in diameter, and attributes the ordinary descriptions to mal-fixation and postmortem changes. These nuclei, originally basophil, acquire oxyphil properties and when set free by liquefaction of the intervening cytoplasm become, or in fact are, red cells.

*(b) The Parenchyma or Cells.*—Here again there is much diversity of description. The cells of the germinal centre are undifferentiated cells (germinal cells of FLEMMING, lymphogonia of BENDA, basophil mononuclears of DOMENICI, haemocytoblasts of MAXIMOW). These large cells with basophil cytoplasm have an oval, vesicular nucleus containing a few chromatin masses (as seen in sections). The nuclei of these cells may be mitotic (implying multiplication) or pycnotic (implying destruction). The mitotic figures, in part, also belong to mesenchymatous (embryonic) cells of the central syncytium.

These haemocytoblasts may give rise to lymphocytes, monocytes, and myelocytes, while according to the dualistic view of the origin of blood these cells are lymphoblasts and give rise solely to lymphocytes. Normally, hyaline deposits and "epithelioid cells" may occur in the central zone. In the peripheral zone are found, (1) small lymphocytes with scanty protoplasm, (2) mononuclear cells, the cytoplasm of which contains basophil "stainable granules" of FLEMMING, which by some are regarded as the remains of phagocyted leucocytes, (3) plasma cells very rarely, (4) mast cells; while (5) granulocytes (polynuclears, etc.), are also described in the marginal zone by WEIDENREICH.
RED PULP.

The Stroma.

From the mesenchymal syncytium of the embryo are developed, (1) an inner layer of primitive blood cells, (2) an intermediate layer of primitive endothelium, and (3) an external layer of adventitial cells.

The primitive endothelium gives rise to the sinus endothelium (vide later) and the adventitial cells develop fibres—"reticulum fibres" (Gitterfaser or lattice fibres of Oppel). These two groups of cells constitute reticulo-endothelial cells or fixed histiocytes. The reticulum, as stated, consists of non-collagenous fibres which do not stain with orcein as elastic fibres do, and according to Jolly (1923) are identical with those of the white pulp, but as has been seen the reticulum of the white pulp is said to be collagenous.

Intensity and frequency of phagocytosis is one of the characteristics which justified the collection of groups of cells in different organs into a special system, the reticulo-endothelium, or histiocytic system. Intra-vitam dye staining is another or allied character, and in order of dye-staining capacity we have (1) splenocytes, (2) sinus endothelium, (3) reticulum cells; though according to Robinson (1926) the sinus endothelium is non-phagocytic for vital stains.

The Parenchyma or Cells.

(a) Splenic or Pulp Cells, or Splenocytes.—The reticulum cells in their mobile, free, non-fixed form constitute the pulp cells. They are large mono-
nuclear cells and are phagocytic and may contain red cells or yellowish-brown pigment (hæmosiderin). They occur in the splenic vein but are filtered out in the lungs so that they form few of the cells found in the blood (Schittenhelm, p. 488). Nägeli (1923), however, does not recognize a special cell but says they are merely lymphocytes, and adds that monocytes occur in moderate number (p. 235).

(b) Small Lymphocytes.—The most numerous cells, presumably derived from the Malpighian follicles.

c) Myelocytes.—Rare, their existence being denied by some. In the mole, on the contrary, distinct foci of these cells occur (Jolly, p. 775) and they arise after repeated hemorrhages (p. 792).

d) Granulocytes.—(Polynuclears, etc.) Rare; they come from the blood by diapedesis.

e) Red Cells.—Numerous; they may arrive in the pulp either through the walls of the venous sinuses or through the branches of the follicular artery (vide later).

f) Normoblasts.—Rare.

g) Megakaryocytes.—Rare in man, abundant in the mouse. All transitions from the hæmocytoblast occur.

(h) Plasmocytes.—(Plasma cells). Rare.

(i) Hæmocytoblasts.—Megakaryocytes, myelocytes, and normoblasts would, unless these arise metastatically from the marrow, be derived from the hæmocytoblast, which is described as existing scattered through the pulp and not in foci.

(j) Platelets.—These are granular, refractile bodies 1μ to 3μ in diameter, existing especially in young animals. It is not certain whether these bodies are platelets or broken down red cells. Le Sourd and Pagneiz (1912) state that, after bleeding, platelets are abundant in the spleen, around the Malpighian follicle.

WHITE AND RED PULP CONTRASTED.

That white pulp is essentially different from red pulp is shown, (1) by the action of X-rays. The Malpighian follicles are destroyed in twenty-four hours, while the red pulp cells are destroyed only after much longer exposure. (2) The different behaviour in leukæmias. In lymphatic leukæmia the follicles hypertrophy. In myeloid leukæmia the red pulp develops at the expense of the follicles (Eppinger, p. 21).

II. THE CIRCULATION OF THE SPLEEN.
THE ANATOMICAL FINDINGS.

Trabecular Artery.—When the artery leaves the trabecula it loses its muscle and elastic fibres and the sheath becomes lymphoid; the thickenings of this sheath form the Malpighian follicles.
**Follicular Artery.**—This supplies the Malpighian follicles, 100µ to 200µ in diameter, and is said by SOBOTTA (1914, p. 303) never to be central in their germinal area but always eccentric in the periphery of their cortical area. The eccentric “central” artery breaks up into follicular capillaries which ramify in the follicle and also in the lymphoid sheath of the artery itself. These capillaries are 8µ to 10µ in diameter, rapidly falling to 5µ. They consist of an intima of large endothelial cells and an adventitia containing elastic fibres but with no muscular layer. They are “lost” at the boundary between red and white pulp; that is, the circulation is no longer through closed vessels but through the red pulp, and injection fluid escapes here in a ring round the follicle. WEIDENREICH (1901) describes “lymphatics” as arising at this point (where the follicular capillaries lose themselves) which, after a short course, communicate with the venous sinuses.

**Pulpal Artery of WEIDENREICH.**—With a lumen of 15µ the artery has now lost its lymphoid sheath but still has intima, media, and a loose adventitia with elastic fibres (EPPINGER, p. 4). The intima is formed of long, spindle cells with bulging nuclei.

**Fusiform, Ensheathed or Husked Artery of SCHWEIGGER-SEIDEL (Ellipsoids).** 150µ to 250µ long, with a lumen of 6µ to 8µ. The walls of this portion of the artery are so peculiar that the structures are generally referred to as the **ellipsoids**. These appear in the first half of embryonic life before the Malpighian follicles, but in the second half they decrease again (SOBOTTA, p. 288). They are well seen in man, better in dog and pig, and best in birds, reptiles, and fish (JOLLY, p. 768). On the pulpal artery, before it becomes the ellipsoidal or sheathed

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**Fig. 3.**

**Ellipsoid: trans. section**

Endothelium
Connective tissue layer
Connective tissue reticulum containing irregular cells

**Fig. 4.**

1. Open circulation

Red pulp
Sinus

2. Open circulation

Ampulla of Thoma
Red pulp
Sinus

3. Closed circulation

Red pulp
Sinus

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artery, there may be a slight dilatation caused by an accumulation of red cells (? blood).
The structure is variously described. (1) The endothelium has large, bulging nuclei, and externally the walls consist of a syncytium with numerous nuclei. Between the nuclei there is a thick mass of very fine fibres, apparently non-medullated nerves. In this tissue also occur red and white corpuscles (Eppinger, p. 5), or (2) there is a bulging endothelium, then a thin layer of connective tissue, and then externally a reticulum, not of lymphoid, but of connective tissue fibres, in the meshes of which are cells with irregular outline. Jolly regards the structure as a reinforcement of the vessel wall against excessive pressure from within. On injecting the spleen through the artery the injection fluid accumulates here and does not go further (p. 769). (3) Robinson (1926) states that the ellipsoids have a length of 170μ to 240μ in cat and dog and a breadth of 34μ to 80μ. They consist of a reticulum of cells with shorter processes than those of the pulp. The diameter of the mesh is that of a red cell or half of one. The cells are phagocytic for colloid and particulate matter. Ellipsoids are permeable to injections, but carmine (partly) and Indian ink (entirely) are filtered out by them. Krumbhaar (1926) speaks of their "stop-cock" action.

Terminal Capillary Brush or Pencilillus of Ruysch.—Each brush consists of three or more branches. These short straight capillaries still have two layers, (1) an internal, with bulging nuclei (the only layer according to Jolly), (2) an external, of fine fibrillae.

The mode of ending of these capillaries is variously described. (1) They lose themselves in the pulp (open circulation). (2) They end in a conical, fenestrated end chamber—Ampulla of Thoma—thus permitting of blood entering the pulp (open circulation). The ampulla is regarded by Robinson (1926) as an "exaggerated pulp space." (3) They pass directly to the venous sinuses (closed circulation).

Fig. 5.

Venous sinus

1. Transverse section.

a. Endothelial fibre-cells cut transversely showing basal plates.
b. Circular fibres of Henle.

The basal plates fix the fibre cells to the circular fibres of Henle (reticulum fibres).
The Venous Sinuses.—These form an intercommunicating system of sinuous cavities 10μ to 40μ in diameter. The walls differ so much from those of capillaries that they must be considered as "specific organs" (EPPINGER). Great diversity of opinion exists as to their structure. (1) According to JOLLY (p. 765) the wall of the sinus is perforated with narrow holes regularly arranged. Each hole is bounded by two circular fibres (of Henle), and by two "fibre cells"; in fact, the wall is a net of fine mesh. The description applies to man, monkey, rodent, and dog; but in sheep, horse, and pig the arrangement appears to resemble that described by MOLLIER. (2) WEIDENREICH's interpretation is similar. The internal, longitudinal cells he calls "rod cells" or "spleen cells" and considers that they are contractile. He differs, however, from JOLLY in this important respect, in that he regards them as attached to a structureless extensible membrane bounded externally by the circular fibres of

![Venous sinus. 2. Longitudinal section.](image)

**Fig. 6.**

**Fig. 7.**

*Venous sinus.*

2. **Longitudinal section.**

- a Endothelial fibre cells with basal plates.
- b Circular fibres of Henle (cut transversely).
- c Basal plate.
Henle. The venous sinus is, in fact, a closed tube, but here also there may be temporary stomata caused by the passage of leucocytes. (3) Mollier's (1910) interpretation is quite different. He does not consider rod cells and circular fibres as separate structures, but rod cells and circular fibres are the warp and the woof of a syncytial network and, in fact, the sinus is only part of the pulp or reticulum (syncytium) stretched out on the flat. The sinus wall is thus a net, though some of the meshes may be closed. In the horse, ox, pig and sheep, there is no regular arrangement of cords of Billroth and sinuses, and, moreover, the sinuses have no rod cells or circular fibres.

**FIG. 8.**

_**Venous sinus, according to Mollier.**_

*Pulpal Veins.*—These, consisting of intima only, enter the veins of the trabeculae through so-called "stigmata" in the latter, which are easily visible with a pocket lens in the wall of the slit vein. They represent points where the trabecular sheath is discontinuous, leaving gaps.

**THEIR INTERPRETATION.**

Assuming that the circulation of the blood is an open one:—*Entry* of blood into the pulp occurs at two points, (1) at the marginal zone of the Malpighian follicle, where the follicular capillaries "lose themselves," and (2) where the terminal capillaries of the "brush of Ruysch" lose themselves in the red pulp. *Exit* from the pulp is described as occurring through (1) the "lymphatic" tubes of Weidenreich, arising at the marginal zone of the Malpighian follicles running as short, narrow canals to the venous sinus, and (2) by trumpet-shaped openings in the venous sinus.

Assuming that the circulation is a closed one, blood can make its exit from and entry into the sinuses to and from the pulp by the stomata in the sinuses, if such exist.
EXPERIMENTS.

As the interpretation of histological appearances is conflicting, attempts have been made to determine the path taken by the blood in two ways.

(1) Injections.—When Prussian blue, Indian ink, or a suspension of hen’s corpuscles (Eppinger, p. 12) is injected from the artery, an almost constant finding is a leak around the Malpighian follicles, so that relatively little gets into the sinuses. Robinson (1926) does not mention this leak, but says the escape occurs through the ampulla of Thoma. In guinea-pigs, the sinuses can be injected from the artery, though they are surrounded by a zone of injection mass. The results obtained are not easy of interpretation, and a good deal apparently depends on the kind of injection mass used.
(2) *Ligature of Splenic Vein.*—If the ligature is left on for ten minutes the sinuses are filled but not the pulp, if for twenty minutes the pulp also. (EPPINGER, p. 12; JOLLY, p. 800). It is argued from this that the sinuses do not open into the pulp, as otherwise the escape would occur with a 10-minute stasis. The late entry into the pulp after a 20-minute stasis is explained by passage through the walls (pores) of the sinus. But, according to WEIDENREICH, owing to pressure in the terminal capillaries entering the sinus, the blood now escapes into the pulp by the follicular capillaries. (EPPINGER, p. 381).

The Spleen as a Reservoir.—GRAY (1854), in his classical treatise on the spleen, held that "the function of the spleen is to regulate the quantity and quality of the blood. The most satisfactory proof that we can possess is that the spleen really does contain, under certain circumstances, a varying amount of blood and that that amount is to such an extent as to justify us in concluding that the organ serves to regulate its quantity." (p. 343).

BARCROFT (1925, 1926) has shewn that when an animal has breathed carbon monoxide to the extent that its blood contains 20 per cent. carboxyhaemoglobin, yet there is none to be found for four hours in the "spleenic pulp," but if previously the animal has struggled, as when suspended by the ears, then carbon monoxide is found in the pulp.

BARCROFT and others (1925) found that during exercise the spleen may expel more than half its volume of blood. In man this implies from 100 c.cm. to 250 c.cm.

III. Hæmopoiesis.

**LYMPHOPOIESIS IN MALPIGHIAN FOLLICLES.**

Lymphopoiesis appears about the sixth month of foetal life, later, that is, than myelopoiesis in the red pulp. It is generally believed that this function continues in post-natal life. The histological evidence for this is the existence of mitotic figures in the (haemocytoblasts of the) germinal centres. Presumably by a *vis a tergo,* the lymphocytes are pushed to the periphery and reach the red pulp. They are said to pass from here to the sinuses by diapedesis (JOLLY, p. 795). Increased lymphopoietic activity is shown after haemorrhage, after food following a fast, and during gestation, the follicles enlarging and mitotic figures increasing. Pycnotic nuclei are also increased (JOLLY, p. 797).

**ERYTHROPOIESIS AND MYELOPOIESIS IN THE RED PULP.**

In the embryonic spleen there is evidence, histologically, of perivascular formation of erythrocytes, myelocytes, and megakarocytes, and at the same time there exist also erythrophages and pigmentophages. The activity of the pulp ceases about the time of birth or a little later, though, according to some authors, there still exist in post-natal life residues of erythropoietic and myelopoietic tissues as evidenced by the occurrence of normoblasts, myelocytes
(and granulocytes), and megakaryocytes (constantly present in rats and guinea-pigs), though all these appear to be rare in man.

PATHOLOGICAL CONDITIONS.

The erythropoietic and myelopoietic functions of the red pulp can be resumed under various conditions; thus, in myeloid leukaemia the whole spleen becomes myeloid at the expense of the Malpighian follicles, though EHRlich held that this condition was metastatic, the myeloid cells (myelokinetic) being derived from the marrow, and hence the term myelogenous leukaemia. A myeloid pulp is also seen after sepsis, haemorrhages, blood poisons, malaria, infectious diseases, etc. (JOLLY, p. 798). The origin of these myeloid cells is from the perivascular adventitial cells of MARCHAND, (the hæmocytoblasts of MAXIMOW). They are described as wandering into the vessels (NAGELI and SCHMINCKE). SCHRIDDE, on the contrary, derives them from the endothelial cells of the vessels.

**BLOOD OF SPLENIC ARTERY AND SPLENIC VEIN.**

KÖLLIKER and FUNKE found an extraordinary abundance of white cells in the splenic vein. WEIDENREICH (1911, p. 328), found seventy times as many leucocytes per c.mm. in the vein as in the artery. PEARCE (1917, p. 92) found no constant difference in splenic artery and vein counts, though he records normoblasts in the splenic vein in two of eight cases. MORRIS'S (1914) results in rabbits are summarized in the following table:

<table>
<thead>
<tr>
<th>Artery</th>
<th>Vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red cells, average</td>
<td>5,000,000</td>
</tr>
<tr>
<td>Leucocytes, average</td>
<td>6,000</td>
</tr>
<tr>
<td>Relative count</td>
<td>Polynuclear 47</td>
</tr>
<tr>
<td></td>
<td>Mononuclear 53</td>
</tr>
</tbody>
</table>

The blood was taken from between two clamps on the vein. JOLLY (1923) considers the method, namely that of counts of arterial and venous splenic blood, erroneous.

**IV. Hæmolysis.**

**Hæmocatatonistic Action of Spleen (BOTTAZZI).**

The red cells of the splenic vein are more fragile (less resistant), *e.g.*, to salt solutions, than those of the circulation.

Thus, hæmolysis begins at the following percentage of salt concentration.

<table>
<thead>
<tr>
<th>Peripheral Red Cells</th>
<th>Splenic Vein Red Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>I 0·48</td>
<td>0·52</td>
</tr>
<tr>
<td>II 0·48</td>
<td>0·5</td>
</tr>
<tr>
<td>III 0·48</td>
<td>0·52</td>
</tr>
<tr>
<td>IV 0·5</td>
<td>0·5</td>
</tr>
</tbody>
</table>
The inference is that the red cells have been injured in their passage through the spleen. The blood of the splenic vein is not tinged with haemoglobin, and the latter probably reaches the liver for conversion to bilirubin not simply as free haemoglobin but in (1) red cells of lowered resistance and (2) in red cells of normal shape or in fragmented cells contained in splenic macrophages (Eppinger, p. 58).

Bolt and Heeres (1922) found that this lowered resistance of splenic vein blood held good for sheep in twenty cases and also for man as established at splenectomy (for hæmolytic icterus). Pearce (1917) found in five dogs no difference, in three the resistance of splenic vein blood was less (p. 93). He suggests that peculiarities in venous blood of the spleen are shared by other venous blood.

The action of hæmolytic serum when injected into an animal is to increase the fragility of the red cells as a whole, but here again the increased fragility to salt solutions is more marked in the blood of the splenic vein. (Eppinger, p. 138).

<table>
<thead>
<tr>
<th>Time of Injection</th>
<th>Peripheral Blood</th>
<th>Splenic Vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normally</td>
<td>Hæmolysis begins in 0·48 per cent. salt ... ... ...</td>
<td>0·56 per cent. salt</td>
</tr>
<tr>
<td></td>
<td>Hæmolysis ends in 0·32 per cent. salt ... ... ...</td>
<td>0·36 per cent. salt</td>
</tr>
<tr>
<td>1½ hours after injection of hæmolytic serum</td>
<td>Hæmolysis begins in 0·88 per cent. salt ... ... ...</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Hæmolysis ends in 0·56 per cent. salt ... ... ...</td>
<td>0·6 per cent. salt</td>
</tr>
</tbody>
</table>

Aubertin and Chabanier (1922) find that the resistance to salt solutions of red cells from the splenic pulp is less than that of the general circulation. If now an animal be poisoned with tolulendiammin the resistance of the red cells of the circulation falls, but the resistance of the red cells of the pulp is still less. The inference is that the pulp exerts an erythrolytic function.

Barcroft (1926), using blood from the splenic pulp obtained by tying the splenic artery and stimulating the splenic nerve, found that pulp red cells are distinctly less resistant to salt solutions than red cells of the general circulation. But the reverse holds good for saponin; the pulp corpuscles are more resistant to this drug (p. 545).

Effects of Splenectomy.—After the removal of the spleen there is an increased resistance of red cells to salt solutions and to hæmolytic agents, such as saponin, cobra venom, and immune sera. (Pearce, p. 38).
Salt Solutions.

<table>
<thead>
<tr>
<th></th>
<th>Normally</th>
<th>After Splenectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hæmolysis begins at</td>
<td>0·42 per cent.</td>
<td>0·35 per cent.</td>
</tr>
<tr>
<td>Hæmolysis complete at</td>
<td>0·3 per cent.</td>
<td>0·23 per cent.</td>
</tr>
</tbody>
</table>

That is to say, in the case of a series of salt solutions, hæmolysis after splenectomy as compared with normal conditions does not begin (or end) until the weaker dilutions are reached. Possibly this increased resistance is due to the greater choles-terin content of the red cells which is found after splenectomy. (EPPINGER, pp. 46, 106, 138). JOLLY (1923, p. 794) states that the resistance after splenectomy is generally normal. PEARCE (1917) considers that the increased resistance following splenectomy may be due to several factors:

(a) To the anæmia.

(b) To young resistant cells from a rapidly proliferating marrow.

(c) To the removal of the supposed function of the spleen in diminishing the resistance of the red cells.

Hæmolysis was classified by HUNTER (1892) into (1) active, where the red cells are “dissolved” in the blood stream and (2) passive, where the process is due to erythropagocytosis.

Saponin is a poison which hæmolyses in the first way; it acts directly and immediately on red cells.

Toluylendiamin, on the contrary, is a poison which does not hæmolysse in vitro and which only acts in the body after many hours.

EPPINGER (p. 130) considers that it acts above all through the agency of the spleen which destroys by its phagocytes (reticulum and endothelium cells) the cells debilitated by the poison. Evidence of the debility exists in the increased fragility of the red cells.

The splenic factor in the action of toluylendiamin and similar poisons is shown (1) by blocking the reticulo-endothelial system (of which the splenic reticulum forms a part) by giving iron or choles-terin previously; the effect of the poison is now slight; neither anæmia nor icterus ensues (EPPINGER, p. 156).

(2) By the result of splenectomy; while normally a dose of 0·5 g. of toluylendiamin will kill an animal in twenty-four hours, in a spleenless animal the same dose does not endanger life (vide later).

It need only be added that other observers deny any connection between the activity of the spleen and toluylendiamin poisoning, and the difference in spleen and spleenless animals is attributed to the anæmia in the latter (PEARCE).

RETENTION OF RED CELLS BY SPLEEN.

In pyrodin poisoning, the red cells of the general circulation show Heinz bodies (i.e., granules probably lipoidal in nature, staining red with Giemsa, etc.). Such cells are absent in the splenic vein while the red pulp is packed with them. (EPPINGER, p. 137).
RED CELLS IN PULP.

Kölliker (1847) stated that red cells that escape into the pulp become smaller and darker and break up into small particles (? hemosiderin) and that this process may be extra-cellular as well as intra-cellular.

PHAGOCYTOSIS.

In the hæmo-lymph glands, it would appear as if all red cells were fated to be destroyed in the reticulum which traverses the blood sinuses or lacunæ. All transitions from red cells to débris and pigment can be found. Analogy with the structure of the splenic pulp suggests similar functions for the spleen.

Levaditi (1902) stated that when red cells are being destroyed, as in disease or by the action of a poison such as a hæmolytic serum, there is a great accumulation of red cells and erythrophages in the splenic pulp. In toluylendiamin poisoning (0.02 g. per kilo), the spleens swells in a few hours, and the swelling persists long after the giving of the drug has stopped. Red cells crowd the pulp, but the sinuses are comparatively empty and the lumina of the pulpal capillaries and ellipsoids cannot be distinguished. The follicular capillaries on the contrary are gorged. If the ellipsoids are blocked, the route through the follicular capillaries is the only one available. Phagocytosis then sets in. The red cells stain normally and are not to be regarded as ghosts, though this is contradicted. (Eppinger, pp. 136, 141, 155).

In poisoning after splenectomy, the injured cells remain in the circulation, and consequently also there is not available the hæmosiderin necessary for the formation of a pleiochromic bile and icterus (vide infra).

PHAGOCYTOSIS AND SIDEROSIS.

(a) Transfusion.—Erythrophages are found in the swollen spleen on the day after transfusion; two days after, the spleen is yet larger and displays numerous phagocytes, some containing nearly a dozen red cells; three days after, the phagocytes contain almost only hæmosiderin.* (Eppinger, p. 17, and Jolly, p. 795).

Jolly (p. 799) states that the pulp makrophages contain an excess of hæmosiderin after hæmorrhages, in infectious diseases, and also in hæmolytic icterus.

Eppinger (p. 491) states that in the latter condition the hæmosiderin exists in a diffuse form (diffuse blue staining of cell) and never in the form of granules. The relationship of hæmolysis to siderosis appears, however, to be a more complex one.

(b) Blood Poisons.—Normally a rabbit’s spleen contains very few erythrophages and still fewer siderophorous cells. After poisoning for several days

* Hæmosiderin, a yellow or brown pigment containing iron. In the brown state the pigment may not give the Prussian blue reaction (Jolly, p. 777).
with toluylendiamin, erythrophages abound, but sideropherous cells are almost entirely absent; forty-five days later the erythrophages have disappeared and the pigmentophages are numerous. If the spleen alone were the site of the hæmolysis, at the height of the poisoning it would be natural to expect all gradations from erythrophages to sideropherous cells.

(c) Venous Stasis (experimental) induces splenic tumour and an abundance of erythrophages but no sideropherous cells.

BIONDI (1895) concludes that (in poisoning) the sideropherous cells (siderocytes) do not arise from local hæmolysis but simply collect in the spleen.

Again, while globuliferous cells are distributed uniformly through the pulp, sideropherous cells occur always around the Malpighian follicles, but EPPINGER (pp. 68-69) states that the red pulp is the chief site, the pigment occurring partly in free histiocytes, partly in reticulum cells the fine processes of which are encrusted with it.

Although it is generally held that siderosis is a measure of hæmolysis, yet, though intimately connected with the latter, it appears to be dependent on other factors than increased red cell destruction.

Thus, in hæmochromatosis (bronzed diabetes), where there is no evidence of blood destruction, hæmosiderosis is extreme, occurring, for example, in the pancreas, sebaceous glands, and muscles. (EPPINGER, pp. 71, 490).

The view has also been held that hæmosiderin does not represent a degradation product of hæmoglobin, but that it arises from iron circulating in an inorganic form, and that the function of the sideropherous cells, the "siderocytes" of CHEVALIER, is to bring about the change (EPPINGER, p. 113). Normally the "splenocytes" are mainly concerned, but other reticulo-endothelium cells have the same function.

In hæmochromatosis, the siderocytes normally concerned in the transport of iron are for some reason or other unable to disgorge it, and the increased iron excretion in the faeces, which is a characteristic result of splenectomy, is attributed to non-functioning of siderocytes generally. (EPPINGER, pp. 114, 490.)

Bilirubin Formation.—SAKS (1926) states that blood leaving the spleen and marrow has more bile pigment (as measured by a spectrophotometer) than blood entering.

ERNST and SZAPPANYOS (1922) have shown that if a haemoglobin solution is transfused through the spleen, postmortem, bilirubin is formed (giving positive diazo, Hammarsten, and Gmelin reactions).

V. SPLENOMEGALY.

During digestion the spleen gradually enlarges, reaching a maximum about the fifth hour, returning slowly to normal by the twelfth hour. The significance of this in regard to digestion is unknown. It has been regarded as part of the general splanchnic high pressure (SCHMINCKE, p. 1083).
Adrenalin causes a contraction of the spleen when all its nerves are cut. The view has been held that "the rod cells" of the sinuses are contractile.

Swellings of the spleen may be classified into:

1. Passive (spodogenous tumour of Pöntick): (σπόδος = waste products). The spleen cells take up dyes, colloidal iron, malaria parasites, red cells, pigment, etc., whence arises a passive swelling. The spleen is the lymph gland of the blood stream.

2. Active: Pathological spleens, where red cell débris is absent. (Eppinger, p. 116.)

**Splenomegaly in Infectious Diseases.**

This may be due to (1) hyperæmia; (2) inflammation of pulp tissue with resulting cell hyperplasia; (3) but mainly to œdema of inflamed tissue.

Why the spleen is enlarged in some infectious diseases and not in others is unknown.

The enlargement in certain diseases is regarded as myelotoxic. These diseases are characterized by leucopenia. Such are kala-azar, malaria, enteric, Banti's disease, Hanot's hypertrophic cirrhosis, and others. In a general way the leucopenia in these conditions is regarded as due to increased activity of reticulo-endothelial tissue and to excessive production therefrom of a marrow-inhibiting hormone.

**Splenomegaly and Lipoids.**

Diabetes.—In certain cases the reticulo-endothelial cells become so hyperplastic and laden with cholesterol esters that splenomegaly results.

Niemann's Disease.—In this disease in children the reticulo-endothelial cells of the spleen are infiltrated with lipoid matter, which occurs also in the reticulum cells of lymphatic glands, Kupffer's cells of the liver, thymus, etc.

Gaucher's Splenomegaly, while associated with disturbance of lipoid metabolism, is not associated with lipoids in the reticulo-endothelial cells (Sacks 1926, pp. 520-524).

**VI. Splenectomy.**

The effects of removal of the spleen are as follows:

**Red Cells.**

Pearce (1917) found that in dogs the normal count of 5,000,000 falls to about 4,000,000 in one month and returns to normal in three months (p. 12). A rise in the count was occasionally found immediately after splenectomy (p. 22). Asher, Vogel, and Sollberger (1912, 1913) found a hemoglobin and cell count fall if the diet contained too little iron, but a hæmoglobin and cell count rise if the diet contained enough iron. This is attributed to the elimination
of the hæmolytic action of the spleen and the increased marrow activity. Freytag (Eppinger, p. 97) found that the first-day effect of splenectomy was an increase in the number of red cells, followed by a fall for the next two days, then a gradual return to normal. He interprets the initial increase as being due to the removal of a hæmolytic organ, but it might equally well be explained on the assumption that the spleen secretes a hormone which keeps the hæmopoietic function of the marrow in check. The removal of this hypothetical hormone would then be followed by a rise. Jolly (p. 794) states that a fall in the red cell count and in hæmoglobin is not a constant result, and that when it does occur it is not to be attributed with certainty to red cell production, owing to the elimination of the spleen.

Polycythæmia.—Nägeli (1923) states that this is fairly common. It is attributed to absence of hæmolysis or to stimulation of the marrow by removal of a regulatory hormone for marrow.

Reticulocytes.—Gates (1916) describes an increase in reticulocytes when the cell count is lowest. Pearce (1917) states that they are very slightly if at all increased after splenectomy (p. 16).

Normoblasts.—Nägeli (1923) states that normoblasts may occur a few hours after operation and last for years (p. 273). He attributes their occurrence to absence of the splenic hormone. Pearce (1917) states that their appearance in seven splenectomized dogs was inconstant, in some cases none being found.

Howell-Jolly Bodies.—Hirschfeld (1915) records as a permanent effect of splenectomy the appearance of Jolly bodies (nuclear remains) in the red cells. The spleen, on this view, regulates the output of red cells by a hormone. Splenectomy is followed by the output of immature cells, i.e., those with Jolly bodies, and there may follow in "many cases" a polycythæmia (Schittenhelm, p. 183). Nägeli (1923) states they may occur a few hours after operation and last for years. Pearce (1917) did not find them in splenectomized dogs.

LEUCOCYTES.

Kurloff (Eppinger, p. 99) found the following condition in guineapigs:

<table>
<thead>
<tr>
<th></th>
<th>Before Operation</th>
<th>One Year after</th>
<th>Two Years after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total leucocytes per c.cm.</td>
<td>12,000</td>
<td>20,000</td>
<td>23,000</td>
</tr>
</tbody>
</table>

In the first year there was lymphocytosis, in the second year eosinophilia; but the monocyte count was unaltered. Pearce (1917) found that the normal count of about 12,000 in dogs rises on the day after splenectomy to 34,000 and then rapidly falls, reaching normal in about a month. Jolly (p. 793) attributes the leucocytosis to the effects of operative trauma or infection.

Lymphocytosis.—Pearce (1917) found after splenectomy only a slight degree of relative lymphocytosis (p. 18). Jolly (1923) states that moderate increases of lymphocytes and eosinophils have often been recorded in man.
and animals (p. 793); Nägeli (1923) that lymphocytosis in man is recorded by some authors as a permanent change (p. 236).

Noguchi (1912) in man finds a polynuclear fall and a corresponding lymphocyte rise. At the end of the first year the lymphocytes fall and the eosinophils rise, attaining a maximum after some years. The increase of lymphocytes is attributed to general swelling of the lymph glands after splenectomy.

Monocytosis.—Nägeli states that this change occurs.

Eosinophilia.—Pearce (1917) found that in dogs the result was variable. In two cases there was an eosinophilia of 6 to 30 per cent. In three cases eosinophil cells disappeared entirely for three to eleven weeks, but subsequently there was an eosinophilia of 6 to 20 per cent. (p. 20). Nägeli (1923) states that (in man) eosinophilia may persist for two years. Noguchi and Kurloff's results have already been mentioned.

ENLARGED LYMPHATIC GLANDS.

This change occurs in about 25 per cent. of cases after splenectomy (Nägeli, p. 236). Lymphocytosis is attributed to hyper-activity of the lymphatic apparatus. On the other hand, it has been attributed to the removal of an inhibitory hormone.

SPLENIC HORMONE.

In support of the view that such exists is the fact that spleen extract will produce a leucocytosis, and diminished lymphocytes and eosinophils.

Pearce (1917) found that intraperitoneal injection of 10 c.cm. of splenic extract caused a rise in the red cell count of about a million, the rise lasting for a few days. The rise was greater than that caused by liver, kidney, or blood extract. There was a rise in the polynuclears and monocytes also (p. 97).

THROMBOLYSIS.

Normally, platelets occur in the spleen, but not in the marrow or glands. After splenectomy they are increased in the circulation. (Pearce, p. 17). While some hold that platelets are formed in the spleen, the above facts can be explained by supposing that they are destroyed there. The spleen then in the opinion of some authors terminates the career, not only of platelets and red cells, but possibly of leucocytes also, though it may be said, in the words of Rous, that much of the current theory upon blood destruction attests to the theorist's abhorrence of a vacuum. (P. Rous, 1923, p. 99.)

RECOVERY FROM ANÆMIA.

Pearce (1917) obtained the following results:—

The number of days taken for blood counts to return to normal in dogs rendered anemic.

<table>
<thead>
<tr>
<th>Source of Anæmia</th>
<th>Splenectomized Dogs</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hæmolytic serum</td>
<td>200</td>
<td>107</td>
</tr>
<tr>
<td>Sodium oleate</td>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>Bleeding</td>
<td>63</td>
<td>8</td>
</tr>
</tbody>
</table>
The anaemia produced in splenectomized dogs develops more slowly, is greater and of longer duration than in controls. Regeneration is less rapid, leucocytosis is greater, and the resulting decreased resistance of red cells persists longer. PEARCE says that the same obscure disturbance which causes the anaemia after splenectomy remains potent and delays recovery from induced anaemia (p. 111). The effect may be due to loss of the normal spleen's stimulating effect on marrow. EPPINGER (p. 97) and JOLLY (p. 791) found practically the same, but DUBOIS (EPPINGER, p. 97) on the contrary found the opposite, viz., that splenectomized animals when made anaemic recovered more quickly than controls.

DECREASED TENDENCY TO JAUNDICE.

PEARCE (1917) and EPPINGER (1920) record that jaundice normally following the giving of blood poisons is less easily produced in splenectomized dogs. The results that follow toluylendiamin poisoning may be tabulated as follows (pp. 136, 139, 529):

<table>
<thead>
<tr>
<th></th>
<th>With Spleen</th>
<th>Without Spleen</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 g. per kilo</td>
<td>Death in 24 hours</td>
<td>Life not endangered</td>
</tr>
<tr>
<td>Red cell count</td>
<td>Falls to about half</td>
<td>Transient anaemia</td>
</tr>
<tr>
<td>Hæmoglobinæmia</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Normoblasts and &quot;ghosts&quot;</td>
<td>Absent</td>
<td>Numerous</td>
</tr>
<tr>
<td>Platelets</td>
<td>Normal</td>
<td>In clumps in blood</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Intense</td>
<td>Absent or traces</td>
</tr>
<tr>
<td>Bile</td>
<td>Viscous</td>
<td>Thin, non-viscous</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.28 g. per 100 c.cm</td>
<td>0.093 g. per 100 c.cm</td>
</tr>
<tr>
<td>Urobilin in faeces</td>
<td>Abundant</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

PEARCE considers that the following factors may be responsible for the differences:

1. The anaemia which he found followed splenectomy. He finds that a hæmolytic serum does not produce jaundice as readily in an anaemic animal as in a normal animal (p. 72).

2. The hæmoglobin set free by the hæmolytic agent in a splenectomized animal does not arise in the portal system but in the general circulation. In support of this explanation he shows that hæmoglobin solutions injected into the mesenteric vein produce bilirubinuria, while if injected into the femoral vein bilirubinuria is absent. (In the latter case the hæmoglobin will arrive at the liver much diluted).

3. The increased resistance of the red cells following splenectomy. The red cells are presumably more slowly hæmolysed than normally. If this is so, the result would be the same as giving a hæmoglobin injection slowly instead of rapidly. If given slowly this substance is disposed of without producing hæmoglobinuria.
SPLENECTOMY COMPARED WITH AN ECK FISTULA.

Pearce (1917, p. 130) finds that the results of an Eck fistula, in which the portal vein is joined to the inferior vena cava, are very similar to those of splenectomy, namely, (1) anaemia, (2) leucocytosis, lymphocytosis, eosinophilia, (3) decreased tendency to jaundice following haemolytic agents. If the spleen contains a hormone then these results indicate that the liver is necessary for its activation. At any rate they probably imply that there is some bond between spleen and liver which splenectomy or Eck fistula upsets.

SPLENECTOMY IN PERNICIOUS ANÆMIA.

Splenectomy may be followed by a crisis-like return to normal of previously low leucocyte counts, platelet counts, and red cell counts, and by disappearance of urobilinuria. (Eppinger, p. 84.)

SPLENECTOMY IN HÆMOLYTIC ICTERUS.

Haemolytic jaundice is regarded as being either a primary disease of the spleen with increased haemolysis, or as due to an unknown toxin which acts on the marrow so that it produces fragile cells which are destroyed by the spleen. Splenomegaly is common, especially at crises, and there is evidence in the spleen of red cell destruction. The results of splenectomy are that the haemoglobin and cell counts return to normal, and the microcytosis diminishes; the urobilinuria and jaundice disappear, while the fragility of red cells may become normal, but usually is only decreased.

SPLENECTOMY IN BANTI’S DISEASE.

Banti’s disease is regarded as being due to a splenogenous toxin acting on the marrow. As there is no evidence of diminished marrow haemopoiesis it is supposed that the cells are not disgorged. Splenectomy may benefit or cure the condition.

SPLENECTOMY IN IDIOPATHIC THROMBOCYTOPÆNIC PURPURA (I.T.P.).

Splenectomy is followed by cessation of bleeding, and by rapid increase in the number of blood platelets, attributed to the removal of the hyperthrombolytic action of the spleen, but the thrombocytopænia may recur.

MISCELLANEOUS RESULTS OF SPLENECTOMY.

Following splenectomy—(1) The total fat content of blood is always greater (in animals) as the transport of lipoids by spleen makrophages is eliminated (Eppinger, p. 145).

(2) The cholesterin content of the blood is always greater.

(3) The iodine number (which represents unsaturated fatty acids) is
always less; from which it is concluded that the spleen takes a part in the formation of unsaturated fatty acids.

Splenectomy in man may be followed by a rise in temperature and pulse, sleeplessness, lack of spirits, nervousness, gastric oppression, vomiting, loss of flesh (some attribute these symptoms to injury of the pancreas and resulting fat necrosis, and absorption of products), polyuria (Eppinger, p. 95), glandular enlargement, pains in bones.

I must apologise for having put before you a set of disconnected facts or statements the truth of which is in nearly all cases disputed by someone or another. I have not ventured to produce any summaries or conclusions; it seems to me hardly possible to do this, considering the bewildering conflict of evidence. There are other aspects of supposed splenic activity which I have not mentioned. The time is fully ripe for a "Monograph on the Spleen" (1854 was the date of Gray's work) in which the existing state of our knowledge could be set out in detail and in which the evidence, pro and con, so far as possible could be weighed. My task to-night would have been comparatively simple if the views of Paley were still tenable. A century ago in his "Natural Theology," he said, "It is possible in my opinion that the spleen may be merely a stuffing, a soft cushion to fill up a vacancy or hollow, which unless occupied would leave the package loose and unsteady." I think one may say of this view that it is not the correct one.

REFERENCES.


DISCUSSION.


Dr. Andrew Balfour: I have been asked, and I need hardly say I comply with the greatest pleasure—I have been asked, I say, to propose a very hearty vote of thanks to our President for the address he has given us this evening.

Greatly daring, very wisely and, as I hope to show in a moment, most generously, Professor Stephens chose as his subject “The Functions of the Spleen.” He might, I think, have suitably termed it “The Structure and Functions of the Spleen,” for we have had to-night a lesson in anatomy, a lesson in histology, and a lesson in physiology, and I am sure we all of us required these lessons. I am not certain but that we have not also had a much-needed lesson in modern scientific nomenclature.

I have said that Professor Stephens has been very daring, and it is true, because the spleen has been an enigma ever since the days when the ancient Greeks found that they could excise it with impunity, at least so far as life was concerned. You will remember that the athletes at the Olympic Games, keen to gain the coveted chaplets, were wont to burn out their spleens prior to engaging in the races. They thought that by this means they lightened their bodies and thus improved their chances. The spleen not being necessary to life, one cannot but wonder why nature has produced the complicated mechanism which Professor Stephens has so carefully described this evening.

You will have noticed how many diverging views there are about the spleen, and I would express the hope that the President himself may write the book on the subject which, as he tells us, is so much needed. I may say that I understand that work is now proceeding in London which may throw a flood of fresh light upon the spleen and its functions. We shall see.

I have said that Professor Stephens has been wise in his choice of a subject, and this is the case because, as you know, the spleen plays a great part in the pathology of many tropical diseases. The truth of that assertion is evident if you study the microscopes laid out on the table; but, quite apart from the slides of leishmaniasis and other conditions shown there, splenic pathology plays its part in malaria, schistosomiasis and a host of other diseases. We know very little about the subject, and that is no doubt one reason why the term “idiopathic splenomegaly” continues to grace out text-books. I am afraid it will continue to do so until further study has familiarized us with both the structure and the physiology of the spleen.
I have said that Professor Stephens has acted generously in compiling this address, and you will agree that this is the case when you think how very valuable it will be to many workers. The information which he has brought together is scattered through a wide literature, and I can imagine that when his paper is published in our Transactions it will prove most helpful to many a worker in the tropics who is anxious to gain information on this difficult subject. Professor Stephens has taken infinite trouble to bring together the various conflicting views. On all these grounds, therefore, his daring, his wisdom, his generosity and also on account of the trouble he has taken over this erudite address, I have pleasure in proposing that a very hearty vote of thanks be accorded to him, a motion which I understand is, very fittingly, to be seconded by Colonel James.

Lieut.-Col. S. P. James: I have the honour and great pleasure to second the vote of thanks to our President, which Dr. Balfour has proposed. Professor Stephens began his lecture by saying that he had only recently commenced to study the functions of the spleen. He has been too modest. If my memory serves me, Professor Stephens took an interest in the spleen and its functions as long ago as 1899 when he was on the Royal Society's Malaria Commission in India, and I feel that the lecture is really the result of a study during the thirty years which have elapsed since that time. I heartily endorse what Dr. Balfour has said about the usefulness of the address. Those of us who attended the British Medical Association meeting in Edinburgh last July, know how very conflicting are the views of eminent physiologists, not only on the functions, but even on the histological anatomy, of the spleen. They will remember the controversy between the professor who based his remarks on the structure of the spleen of the fish and the professor who had apparently been chiefly concerned with a study of the spleen of the cat. Unfortunately the fact that they had been studying different animals was not made known until the discussion had lasted an hour or more.

The information which Professor Stephens has collected in his paper will be indispensable to all workers in the tropics. Almost on every line there is a useful item of knowledge. For example, I was interested in the statement that during exercise the spleen loses half its volume of blood, and it occurred to me to wonder whether this might have a bearing on recrudescences of malarial attacks. At Horton we have a patient who remains free from parasites and fever as long as she remains at rest in bed, but who gets a recrudescence when she is allowed up and takes exercise. The lecture contains other valuable information which may have a bearing on enlarged spleens due to disease. During a recent tour in the United States it seemed as if the delicate methods used by malariologists in that country for detecting small degrees of splenic enlargement might give rise to fallacious estimates of the prevalence of malaria, and I therefore looked up the literature to ascertain what are the common causes of splenic enlargement in
non-malarious countries. Among them I will only mention enlarged tonsils, measles and recent vaccination for smallpox. The last has recently been found to be a significant cause of splenic enlargement among soldiers in England.

For these and many other reasons I feel that Professor Stephens’s address will be a constant source of assistance to workers. I second the vote of thanks to him with much sincerity and pleasure.