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On the evolution of the spleen

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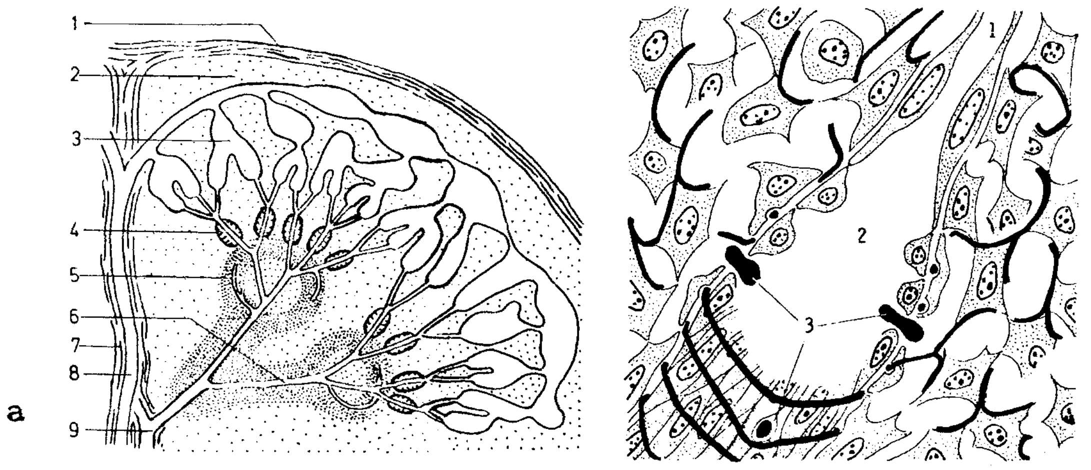
A. Definition of the mammalian spleen

The spleen, which arises from a mesenchymal proliferaiton in the dorsal mesentery or mesogastrium, embodies the most extensive continuous accumulation of 'active mesenchyme' in the organism. According to the nature of its tissue, the spleen belongs to the lymphoreticular organs; however, unlike the ordinary 'white' lymph nodes it is not inserted in the lymph- but in the blood-circulation. The spleen is part of the group of hemolymph organs, together with the real 'red' lymph nodes, but it differs from them in the special arrangement and the unique structure of its finer vessels.

The plan of the spleen in broad outline can be seen from sections; from a robust, serosa-covered capsule septa-like trabeculae enter the interior of the organ; some of the trabeculae carry vessels. The parenchyma itself forms a soft mass, the pulp, in which, normally, two parts can be distinguished with the naked eye; white and red pulp. The lymphoid tissue is dispersed as periarterial lymphoid sheaths and follicles, which, as white pulp, are embedded in the other tissue filled with vessels and blood; the red pulp. The common base of both parts of the pulp is formed by the spongy pulp reticulum, stretched across the spaces of the capsule-trabeculae framework.

Today, the spleen is generally considered to be one of the circulatory organs; this is based on its anatomical relationship to the circulatory system, which has been known for a long time (Tischendorf, 1970: History of research on the spleen[1]). However, it also corresponds to the more recent finding that the structure of the spleen, more than that of any other organ, is determined to the last detail by the vessels which, in the red pulp, even form the organ parenchyma itself. The lymphoid character of the spleen depends on the regular connection of its medium-sized and small arteries with specific mesenchyme derivates. The peculiar wall structure of the terminal capillary bed, moreover, marks the spleen as being a special, essential part of the reticulo-endothelial system (RES) and, at the same time, explains further functions.

The spleen is considered to be the most important site for production of lymphocytes, monocytes, and reticulo-endothelial cells. In mammals, including man, granulopoiesis is unimportant, erythropoiesis, too, is confined as a rule to the embryonic period, in contrast to the situation in Anamnia. Later, the spleen is involved in the turnover of blood cells as an organ supplementing the liver, in the breakdown of erythrocytes and in iron metabolism (and other metabolic processes). In this connection the spleen acts as a blood-filter and -reservoir, controls blood clotting and also the cellular and chemical composition of the blood, and produces antibodies and antiblastic substances. Among the correlations of the spleen with other organs those with the hematopoietic system, above all the bone marrow, come



a Structure of the (human) spleen (diagrammatic, magnification approximately × 10.). 1 = splenic capsule, covered by peritoneum; 2 = red pulp; 3 = sinusoid; 4 = ellipsoid; 5 = follicle; 6 = pulp artery; 7 = trabecula; 8 = trabecular vein; 9 = trabecular artery. – *b* Spleen, red pulp (semidiagrammatic, drawn by Prof. Dr. W. Specht, Homburg/Saar; magnification approx. × 450). 1 = capillary, opening into a sinusoid = 2; 3 = erythrocytes, which pass through temporary gaps in the sinusoid wall into the surrounding reticular tissue. Below left, tangential section of sinusoid wall with littoral cells and ring fibers. Reticulin fibers = thick black lines.

After Leonhardt, H. (translated by D.P. Winstanley), Human Histology, Cytology and Microanatomy, fig. 88/89. Georg Thieme Publishers, Stuttgart 1977.

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[1] Tischendorf, F., Zur Geschichte der Milzforschung. Rückblick und Ausblick. Ergebn. Anat. Entw.-gesch. *42*/3 (1970) 1–64.

first. But there are also various interrelations with many other organs, not least the endocrine glands. The spleen itself is controlled by means of hormonal and nervous factors, and delivers active agents to the circulation which intervene everywhere in the neuro-hormonal system.

So the extremely complex structure of the spleen corresponds with a function that is no less complex. But because the several components of the spleen tissue, with the exception of the terminal circulation, represent nothing organ-specific, in mammals, after loss of the spleen its functions are largely taken over by other parts of the lympho-reticular and reticulo-endothelial apparatus according to the principle of decentralization. Although in mammals the spleen has reached the highest stage of evolution, it is not irreplaceable as in most non-mammals. An originally essential hemopoietic organ has become, in man, one of only limited vital importance; a highly differentiated regulation centre coordinated to the humoral system – so to speak a 'strategic reserve', the significance of which fully appears only in situations of unusual stress.

B. Phylogeny of the spleen

I. Comparative ontogeny and macromorphology of the non-mammalian spleen

The histogeny and topography of the vertebrate spleen – especially its dependence on the coelom – make a connection with the invertebrates conceivable; with the 'axial organ' of echinoderms or the 'cardiac body' of annelids (Hausmann, 1932, 1933).

Acrania *(Branchiostoma)* have neither erythrocytes nor a spleen. In the lowest Craniotes – the cyclostomes – the midgut contains a lymphoid tissue which structurally and functionally corresponds to the spleen and bone marrow of higher vertebrates. As a separate organ the spleen first appears in the Selachii. The epithelium of the peritoneal cavity (coelom) makes only a limited contribution to the formation of splenic tissue, which is an outgrowth of the mesenchyme traversed by sinusoidal capillaries. In Dipnoi the splenic tissue, which is only demarcated at a late stage, still lies within the gut-wall itself, as it does in Myxinoidei; it is in the submucosa and intermuscularis (in *Ammocoetes* in the subserosa, in the external furrow of the midgut formed by the spiral fold). As in *Petromycon* it arises from the mesenchymal coat of the subintestinal vein, near the pancreas-primordium.

In the full-grown state the spleen of Ganoidei, also developed from the perivenous, subintestinal mesenchyme, lies outside the gut, isolated by an omentum. Among the Teleostei, the connection of the spleen- primordium extending along the left side of the midgut with the subintestinal vein is especially marked in the Salmonidae; after loosening of the cranial pole the spleen is only connected at the caudal pole, via the pancreatico-splenic vein, with the subintestinal vein; the doubling of this (with an occurrence of 2–3%) also causes that of the spleen. In *Cyprinus* the spleen-primordium originally situated on the right moves to the left by the rotation of the gut, is pressed in a dorsal direction by the liver, and totally covered by it and the pancreas. Hence the concentric structure of the complete spleen; under the capsule demarcating it against the pancreas-liver there is a rind of red pulp, and in the middle white pulp.

The dependence of the size or weight of the spleen on various endo- and exogenous factors: species, race, sex, age, body weight, nutrition, activity, social behavior, time of day and season etc., is detectable in all vertebrates. In some fishes it is accompanied by a drastic change of form, as in *Salmo salar* (Mislin, 1941; cf. Zwillenberg, 1964: *Salmo trutta fario, S. gairdneri*) in the phase of maximal food intake (status devorans) or exclusively sexual activity (status prolificus).

In Gymnophiona the spleen is developed comparatively late, because it takes the place of the yolk-sac as a hemopoietic organ. Since at this time only the left vitelline vein still exists, the spleen develops on the left, close to the pancreas.

Marcus (1932/33, 1935) attributes the asymmetry in the vertebrate organism to the torsion of the cardiac loop, owing to which the cardio-enteric recess of the omental bursa is pushed in between heart and gut from the right.

In *Siphonops* and *Hypogeophis* a dorsal anastomosis (splenic venous arch) of the left vitelline vein with the liver-portal-vein furnishes the 'rete mirabile' of the splenic sinusoids. A portal-vein circulation exists here, since the spleen is joined not only with the liver-portal-vein but also with the mesenteric vein, by the side of which the smaller splenic vein later arises (see Weilacher, 1933, who considers the spleen as an originally entodermal, blood-forming and -destroying organ. On the question of which germ layer the spleen is derived from see Tischendorf, 1969, pp. 16ff., 31; contrary to older opinions the spleen undoubtedly is not a 'derivative of entoderm').

In urodeles the spleen arises on the left of the dorsal mesogastrium in the back wall of the stomach from an autochthonous mesenchymal condensation. In *Megalobatrachus* the vascularization occurs in four phases (Miki, 1963): I. The spleen-primordium covers the dorso-mesogastrial supply region of the mesogastric arteries near the major curvature of the stomach. II. Vessel loops which separate from the arterial network become concomitant veins. III. These mesogastric veins are divided into spleen-portal-veins, sinusoids and spleen-veins; at the same time the spleen is linked with the stomach branch of the liver-portal-veins. IV. Instead of the spleen-portal-veins a mesogastric artery takes over the blood supply. Stages I and II of the spleno-vasal metamorphosis – which in *Petromycon* last nearly the whole life-span – proceed very fast in *Megalobatrachus;* stages III and IV indicate the further path of evolution ot the mammalian spleen. In *Pleurodeles* (Hartmann, 1933) too, the spleen is cut off from the stomach only late, and is vascularized by a basal vessel which joins with the mesenchymal gaps. By remodeling of the reticulum this open blood circulation later changes into a closed one, so that arterial capillaries and venous roots communicate directly with each other. This is apparently a generally valid principle (although Hartmann has expressed a certain doubt). In urodeles and in anurans the spleen-primordium appears only in older larval stages with a typical spiral gut.

Among the Sauropsida, the spleen development in reptiles resembles that of the urodeles. The connection between the spleen-primordium projecting into the left abdominal cavity and the arterial system occurs through a branch of the dorsal aorta; the flow into the venous duct is at first through the dorsal pancreas. In birds the spleen primordium originally situated dorsally to the duodenum and the dorsal pancreas moves to the left side of the dorsal mesenterium and is penetrated by gastro-intestinal veins.

As in fishes, in other non-mammalian vertebrates 'an elongated spleen extending the entire length of the gut is considered as the ancestral form and the variations of the shape and position ... are explained on the assumption that the entire dorsal mesentery retains phylogenetically a development potentiality for forming splenic tissue, but an arrest of development either at the caudal or cranial portion ... usually takes place' (Murata, 1959). The amphibian spleen (Schabadasch, 1935) is still extended in Perennibranchiata, and lies close to the gut wall; in urodeles and anurans it is reduced at either the head or the tail end. The tongue-shaped spleen of urodeles lies, as in higher vertebrates, close to the stomach, but the bean-shaped or globular spleen of anurans lies near to the endgut. The spleen of reptiles, according to Klaatsch (1892), is reduced from the primitive state equally at the proximal and distal ends, to give rise to the forms found in the Rhynchocephala on the one hand, and in the Crocodilia on the other. A second line leads to the Sauria, among which the spleen is reduced, leaving only a small piece of its proximal end, and a third one to the Chelonia and Ophidia, where an endgut-spleen exists, strikingly similar to that of anurans. Murata also compares the situation in Chelonia and Ophidia with that in urodeles and anurans: 'The spleen of the tortoise ... lies in relation to the caudal part of the midgut, whilst the spleen of the snake ... is situated cranially near the stomach. In the lizard ... the position of the spleen resembles that of the snake, though situated somewhat more caudally.' Of course the phylogenetical conclusions of Klaatsch (cf. Sobotta, 1914; Klemperer, 1938; Osogoe, 1954; Kanesada, 1956) can be verified only by exact tracing of the primitive vessel-primordia and their relations to the spleen, and not by description of the definitive conditions (Hartmann, 1926, 1930). On the following higher levels of evolution, 'from Aves to Mammalia the spleen lies in the dorsal mesogastrium as a tongue- or bean-shaped organ and there is little variation in the position ...' (Murata).

II. Comparative micromorphology and histobiology of the non-mammalian spleen

1. Capsule-trabeculae-system

The 'pre-spleen' of cyclostomes is not yet demarcated by a capsule. In Selachii the multi-lobed, not yet trabeculae-containing spleen is enclosed by a thin capsule, serosa-coated as in all vertebrates, which besides strong collagenous and fine elastic fibers, in certain cases con-

Table 1. Quantitative characteristics of the capsule-trabeculae-system of the spleen in various vertebrates. After Murata, H., Comparative studies of the spleen in submammalian vertebrates. II. Minute structure of the spleen, with special reference to the periarterial lymphoid sheath. Bull. Yamaguchi med. School *6* (1959) 83–106 (cf. Tischendorf, F., 1969, table 12, p. 168).

Class	Order or suborder	Species	Capsule Thickness (μm)	Smooth muscle cells	Elastic fibers	Trabeculae	Septa
Pisces	Elasmobranchii	*Mustelus manazo*	10–20	–	+	–	++
		Dasybatus akajei	33–66	–	–	–	–
	Teleostei	*Cyprinus carpio*	10–20	–	–	–	–
		Carassius auratus	40–47	+	–	–	–
		Mugil cephalus	10–13	+	–	–	–
		Sebastodes tokionis	3–10	–	–	–	–
		Sparus macrocephalus	7–13	+	+	–	–
Amphibia	Urodela	*Megalobatrachus jap.*	17–40	–	–	–	–
		Triturus pyrrhogaster	7–12	–	–	–	–
		Hynobius lichenatus	10–20	+	–	–	–
		Hynobius dunni	5–10	+	–	–	–
		Hynobius nigrescens	7	+	–	–	–
	Anura	*Bufo vulgaris jap.*	7–13	–	–	–	–
		Rana nigromaculata	10–20	–	+	–	–
		Rana catesbyana	13–23	–	+	–	–
Reptilia	Chelonia	*Amyda japonica*	10–23	++	+	–	–
		Clemmys japonica	10–47	++++	+	–	–
	Ophidia	*Elaphe quadrivirgata*	23–53	++	+	–	++
Aves	Anseriformes	*Anas platyrhynchos domestica*	23–40	++++	+	+	–
	Galliformes	*Gallus domesticus*	50–80	++++	+	–	–
	Charadriiformes	*Columba livia domestica*	23–40	–	++++	–	–
Mammalia	Rodentia	*Oryctolagus cuniculus* var. *domesticus*	33–67	–	–	++++	–

tains also smooth muscle cells (e.g. *Chimaera*). In contrast to Ganoidei, in Dipnoi the spleen shows fibrous septa which reach from the capsule through the red pulp into the white. As a rule, there are no muscle cells in the capsule and trabeculae of the teleostean spleen, which frequently contain islets of pancreas tissue, as do the intralienal vascular sheaths. The lobules of the salmoidean spleen – which in the stage of hyperemia in *Salmo salar* (Mislin, 1941) are sheared off separately – are placed in compartments of connective tissue which, together with the capsule, form a concise functional system (for electron microscopic structure see Zwillenberg, 1964).

In the amphibian spleen a coherent capsule-trabeculae-framework as defined by the sauropsidean or mammalian spleen is missing, as is the muscular system needed for active volume alteration (Sterba, 1950). The fibre bundles – their rudiments are found already in urodeles – which branch off from the collagenous-elastic capsule of the gymnophionean spleen into the pulp are the first stages of the trabecular system of mammals (Weilacher, 1933).

Among the reptiles, in lizards there are not yet typical splenic trabeculae; the adventitial connective tissue entering the hilum with the vessels soon disappears. In leguans (Ferner, 1940) the splenic capsule contains plenty of muscle cells; in snakes the capsule forms a continuum with the pancreatic capsule and numerous septa come from it into the pulp. In reptiles and also in birds there is not yet a framework of splenic trabeculae forming chambers. In the capsule, which contains varied quantities of muscle cells, a thin, single-layered type (e.g. *Picus*) and a thick, double-layered type (e.g. *Dryocopus*) can be distinguished (Selymosy, 1936).

2. *Splenic pulp, hematopoiesis and -lysis*

In lower vertebrates the whole mesenchyma in both pre- and postnatal life carries out hematopoiesis. The secondary blood-forming organs (spleen, liver, bone marrow) of Amniota are only a territorially narrowed equivalent of the general circulation, in which erythropoiesis mostly takes place in Anamnia. The primary hemopoietic organ is the spleen; originally a common center for erythro-, leuco-, and thrombopoiesis, the spleen soon transfers the first to the bone marrow, as a secondary adaptation in higher vertebrates. Medullary hemopoiesis reduces the number and activity of the other blood-forming sites and restricts diffuse mesenchymal hemopoiesis to the beginning of development. When vitelline hemopoiesis is insufficient (certain birds, all mammals) a hepato-lienal intermediate phase guarantees adequate hemopoiesis during the changeover from mesenchymal to medullary hemopoiesis.

The spleen-like tissue in the adipose submucosa *(Myxine)*, or in the spiral fold *(Petromycon)* of the gut of cyclostomes has a lymphoid and a myeloid component, but still no separate white and red pulp. In the selachian spleen, too, where arteries and veins have lymphoid sheaths, white and red pulp cannot be segregated sharply. In the spleen of Holocephali the discontinuous periarterial lymphoid sheaths which form the white pulp are behind the red pulp, which coheres to form cords. The similarly hemosiderin-rich, blood-forming and -destroying spleen of Ganoidei has a lymphoid, white, and a myeloid, red, pulp region. The more diffuse white pulp of the teleost spleen, which ordinarily shows Malpighian corpuscles, produces erythro- and granulocytes like the surrounding red pulp. In Polyptera the spleen shows a central white and a peripheral red pulp; the lobed spleen of Dipnoi a central core of lympho-, mono-, and thrombopoietic white pulp and a rind of sinusoid-rich, erythropoietic red pulp, to which a granulopoietic mantle is added at the spiral fold, so that it combines the three blood-forming mammalian tissues (Jordan, 1935). Hemopoiesis largely stops by the end of the dry season, but quickly revives after the return to aquatic life.

In Gymnophiona the splenic white pulp forms a primitive Malpighian corpuscle, the inside of which contains lymphoblasts and moribund erythrocytes; the surrounding red pulp also shows only restricted hemopoiesis. In urodeles the spleen is the main producer of erythrocytes and thrombocytes; only in precipitate blood-forming, e.g. in spring, is there a falling back on the general circulation. The lymphoid tissue, without forming typical follicles, arranges itself in cords and heaps; white and red pulp are not sharply separated. In anurans the hemopoietic action of the spleen is less seasonal. In the periarterial lymphoid sheaths and follicles of the white pulp, lymphocytes and also eosinophils arise; in the red pulp the other granulocytes and the erythrocytes. The breakdown of blood takes place in the red pulp, which has twice the volume of the white pulp.

In reptiles, despite the well-developed periarterial and periellipsoidal lymphoid sheaths and follicles, the separation of the splenic white and red pulp is mostly much less distinct than in mammals. Altogether, in hemopoiesis reptiles are in an intermediate position between amphibians, in which the spleen is the main site of lympho- and erythropoiesis, and birds, in which erythropoiesis is confined to the bone marrow and lymph nodes appear as independent organs. In birds, the white splenic pulp has reached the highest state of evolution among non-mammals: 'The most striking feature of the lymphoid tissue of avian spleen is the occurrence of secondary nodules (germinal centers), which are never seen in the spleen of reptiles and other lower vertebrates' (Murata, 1959). In spring and summer – the peak of splenic lympho- and granulopoiesis – and under good nutritional conditions, the roundish-oval Malpighian corpuscles bounded by connective tissue are better developed than in autumn and winter or in bad nutrition. The thymus-dependent tissue corresponds to the lymphoid sheaths of the avian spleen *(Gallus)*, the bursa-dependent to the lymphoid follicles (Cooper, Peterson, Good, 1965). This is also valid for the mammalian spleen.

In phylogeny (v. Skramlik, 1927) the white splenic pulp falls more and more behind the red; the increasing separation of white and red pulp suggests a separate metabolism of formation (v. Herrath, 1958). The essential parts of the splenic parenchyme – perivascular lymphoid tissue and red pulp – already exist in cyclostomes. By the addition of pericapillary sheaths and the distinct development of all three components the selachian

Table 2. Lymphoid tissue in the spleen of various vertebrates. After Murata, H., Comparative studies of the spleen in submammalian vertebrates. II. Minute structure of the spleen, with special reference to the periarterial lymphoid sheath. Bull. Yamaguchi med. School *6* (1959) 83–106 (cf. Tischendorf, F., 1969, table 16, p. 258).

Class	Order or suborder	Species	Lymphoid tissue		
			Periarterial sheath	Secondary nodules	Periellipsoidal sheath
Pisces	Elasmobranchii	*Mustelus manazo*	+++	–	+
		Dasybatus akajei	+++	–	±
	Teleostei	*Cyprinus carpio*	±	–	–
		Carassius auratus	+	–	±
		Mugil cephalus	+	–	±
		Sebastodes tokionis	±	–	+
		Scomber japonicus	+	–	+
		Lateolabrax jap.	±	–	+
		Sparus macrocephalus	±	–	–
		Sillago sihama	±	–	±
Amphibia	Urodela	*Megalobatrachus jap.*	±	–	+
		Triturus pyrrhogaster	±	–	+
		Hynobius lichenatus	±	–	+
		Hynobius nigrescens	+	–	+
		Hynobius tokyoensis	+	–	+
		Hynobius dunni	±	–	+
	Anura	*Bufo vulgaris jap.*	+	–	–
		Rana nigromaculata	±	–	–
		Rana catesbyana	+/++	–	–
Reptilia	Chelonia	*Amyda japonica*	++	–	+++
		Clemmys japonica	++	–	+++
	Lacertilia	*Eumeces latiscutatus*	++	–	–
	Ophidia	*Elaphe quadrivirgata*	–	–	–
Aves	Galliformes	*Gallus domesticus*	+++	+	++
		Coturnix coturnix japonica	+++	+/++	++++
	Anseriformes	*Anas platyrhynchos domestica*	+++	+	++++
	Charadriiformes	*Columba livia domestica*	++	+	++++
Mammalia	Rodentia	*Oryctolagus cuniculus* var. *domesticus*	++++	++++	–

spleen comes largely to resemble the mammalian spleen. The lymphoid sheaths and follicles are very much reduced in Teleostei and amphibia; in Sauropsida they are well evolved again, except in the Ophidia, the spleen of which 'shows a peculiar structure quite different from ... other vertebrates' (Murata, 1959).

Lympho-, mono-, granulo-, and thrombopoiesis

Lymphocytes do not arise only in the white, but also in the red splenic pulp. Immature plasma cells belong to the white, mature ones to the red pulp. Monocytes arise in the whole of the pulp reticulum; granulocytes, as clearly myeloid elements, only in the red pulp. Granulopoiesis in cyclostomes is still mainly localized in the presplenic tissue; in higher vertebrates it is increasingly transferred into the bone marrow, but in many mammals the red splenic pulp – especially the follicular marginal zone – carries out only limited granulopoiesis. Eosinophil granulocytes are only sparse in fishes, a little more frequent in birds, but copious in amphibians and reptiles (Hartmann, 1926). Splenic megacaryocytes, which, with a few exceptions (e.g. goat, man) occur in most mammals, are generally absent in non-mammals. In urodeles thrombocytes are formed exclusively in the spleen; only during periods of extremely rapid hemopoiesis do they also arise in the general circulation, as they do in most non-mammals.

Erythropoiesis

In animals above the cyclostomes the spleen is not indispensable for erythropoiesis except in some teleosts and urodeles (Jordan and Speidel, 1929, 1930). The late-embryonic blood-formation in the bird spleen is far stronger in *Vanellus* than in *Uria*. In *Gallus* after involution of the yolk sac the bone marrow takes over its erythropoietic function unassisted, in *Sturnus* it is still supported by liver and spleen. The spleen is not a decisive organ for erythropoiesis for either nidifugous (e.g. *Gallus, Anas, Larus*) nor for nidicolous (e.g. *Melopsittacus, Columba, Turdus, Passer, Sturnus, Apus, Hirundo*) birds; however, the more intense splenic erythropoiesis of nidicolous birds could be of positive selective value for their evolution (Schmekel, 1962, 1963). The fetal splenic erythropoiesis of mammals as a phylogenic reminiscence is more evident in many other animals than in man. It usually stops at birth, but can be reactivated at any time if required. In certain carnivores it continues for some time in postnatal life; in some rodents, insectivores, and edentates for life (Hartmann, 1930; Hausmann, 1932, 1933; a.o.).

Erythrolysis

Erythrocytes mostly decay within the vascular bed, especially in lung and spleen. The breaking down of erythrocytes carried out by the reticulo-endothelial system (RES) which, in contrast to the breakdown of leucocytes, leaves characateristic traces (hemosiderin etc.), is not least an immunological phenomenon; normal autologous erythrocytes are tolerated, but altered or heterologous ones are eliminated. The mechanical stress undergone by erythrocytes passing the narrow passages of the splenic vascular bed favors the elimination of less resistant or older cells. In cold-blooded (poikilotherm) animals except fishes and lizards the destruction of erythrocytes occurs mainly in the liver; the RES of this organ is richer in hemosiderin than that of the spleen. Among warm-blooded (homoiotherm) animals, in birds it takes place to about an equal extent in liver and spleen, in mammals above all in the spleen (Schuchardt, 1966). In fishes (in Teleostei the iron content of the spleen is ten times greater than in Selachii) and in mammals the iron content of the spleen is higher than that of the liver and increases with age; the glutathione content is lower than that of the liver; in other classes of animals the situation is reversed (Kojima, 1939). As in many mammals, in most non-mammals the sheathed capillaries (ellipsoids), which are especially active parts of the RES as well as being pre-terminal narrows and regulators of blood flow, adjustable in lumen size and permeability, figure largely in the often seasonal breakdown of erythrocytes (for electron microscopic examination of the trout spleen see Zwillenberg and Zwillenberg, 1963; Zwillenberg, 1964).

RES of the spleen

The fixed reticulum cells whose lattice of reticular fibers serves as a support for the free cells of the spleen pulp accomplish important tasks in cellular defence owing to their phagocytic and storage activities; blood cell destruction, as well as iron-, protein-, lipid- and vitamin-metabolism. Together with the capillary and sinusoid endothelia they form the reticulo-endothelial apparatus of the spleen. The RES (see Tischendorf, 1969, pages 407–470) of mammals is not the same as that of non-mammals.

III. Intralienal vessels

Trabecular vessels as such can hardly be said to occur in non-mammalian spleens, since the trabecular framework found in mammals is absent. However, the large arteries near the hilum have strengthened connective tissue envelopes, and in birds – where the spleen also shows a special venous structure – an adventitial longitudinal musculature is added (Legait, 1951). As in sauropsidans, in many anurans the very thin-walled veins already surround the spleen like a net and on their radial path to the hilum form circular plexuses around the larger arteries.

The pulp arteries of non-mammalian spleens, enveloped in lymphoid tissue, correspond to the lymphoid sheath- and follicle-arteries of mammalian spleens (the latter, in spite of their eccentric position in the Malpighian corpuscle, are often incorrectly named 'central' arteries), but unlike those in mammals the ellipsoids in most cases also bear lymphoid sheaths. The ellipsoids or sheathed capillaries are still absent in cyclostomes, but are well evolved in Selachii, and even more so in Teleostei. The long, ramified ellipsoids of Polyptera and Holocephali resemble those of teleosts. Dipnoi, Urodela and Gymnophiona have less marked ellipsoids than teleosts; in anurans they are only demonstrable in tadpoles. Among the reptiles the ellipsoids are best developed in Chelonia and Crocodilia, in Lacertilia they gradually get lost, and in Ophidia they are quite absent. In birds the ellipsoids entirely surrounded by lymphoid tissue form a great part of the splenic parenchyma (Dustin, 1931–1939, 1954; Bargmann, 1941; Murata, 1959; Loreti, 1967; on the histochemistry of the Schweigger-Seidel sheaths of the spleen see Schlüns, 1964ff.).

Typical splenic sinusoids, clearly distinguishable from pulp veins, are not found in non-mammals (Hartmann, 1930). Murata (1959): "The true 'venous sinus' having characteristic annular fibers ... does not appear to occur in the spleen of submammalian vertebrates."

Like Weidenreich (1901) and others, Herrlinger (1949, 1950, 1957) and Tischendorf (1956, 1958, 1959, 1969, 1970), in mammalian spleen reject the old name '*venous* sinus' (Billroth) and interpret these 'specific vessels with circular bands and gaps' (Weilacher, 1933) as 'neutral blood flow zone' or 'formations sui generis' (cf. Knisely, 1936: 'specific anatomical units').

Terminal capillary bed of the spleen

In fishes the dissolution of arteries in the reticulum has been described, as well as a direct transition into veins. In anurans the reticulum stage between arteries and veins is much shorter than in urodeles; in the frog a 'regulated' circulation frequently and easily develops. Among sauropsidans, in tortoises and birds the arteries end free in the reticulum or turn into veins, in snakes and lizards the vascular system of the spleen is almost completely 'closed' (Hartmann, 1930).

It must be pointed out, that an interruption of the vascular wall within the spleen does not necessarily imply an interruption of the blood flow, i.e. an 'open' circulation (apart from artefacts simulating an interruption especially caused by irrigation and injection procedures used for elucidation of fine details of the vascular architecture). Even if one does not concede that all non-mammalian spleens have a structurally closed vascular bed, all the evidence points to a predominantly closed circulation (Sterba, 1950); a continuous, direct transition of blood from the arterial to the venous route. That is obviously also true of the mammalian spleen (Tischendorf, 1956, 1959, 1969, 1970)[2].

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[2] Guyton, A.C., Textbook of Medical Physiology, 6th edn W.B. Saunders Company, Philadelphia/London/Toronto 1981: 'Small vessels flow directly into the venous sinuses, and when the spleen distends, the venous sinuses swell, thus storing blood. In the splenic pulp, the capillaries are very permeable, so that much of the blood passes first into the pulp and then

IV. Extralienal vessels of the spleen

The 'simple' splenic artery of non-mammals is almost exclusively directed towards the spleen (Schabadasch, 1935); usually as a single small trunk (e.g. *Rana, Emys, Anser, Circus)*, sometimes 2–4 (e.g. *Raja, Lacerta, Tropidonotus, Passer*). The caliber of the splenic artery is small, so that the arterial value of the blood brought to the spleen in fishes, amphibians and reptiles is as small as its capacity for blood-storage. Neither in cold-blooded nor in warm-blooded animals (birds, mammals) is there a succession corresponding to the zoological order of precedence in the complexity or perfection of the arterial supply of the spleen.

In the magistral tape (e.g. *Equus, Sus, Bos*) of complicated splenic artery found in mammals all segmental branches successively spring from a joint trunk, whereas in the disperse type (e.g. *Erinaceus, Canis, Homo*) the trunk divides earlier into a few large branches. The magistral type means a total, continuous flow through the spleen; the disperse type (which supplies not only the spleen, stomach and greater omentum, but also the pancreas) a partial, discontinuous flow. Both types may appear in the same zoological family, and the allegedly more perfect (Ssoson-Jaroschewitsch, 1927) magistral type does not oust the disperse. V. Herrath (1958), who considers that the caliber of the splenic artery has a linear relationship to spleen size and weight, argues against the idea that the magistral type belongs to the 'storage' spleen which is rich in reticulum, and the disperse type to the 'defence' spleen which is rich in sinuosids. Because the vascular system is not rigidly determined by palingeny, but subjected to the most varied cenogenetic influences, the comparative-anatomical analysis of the splenic artery, like that of the spleen itself, has also to consider the evolution of all other systems functionally combined with it, and also the relevant environmental factors (see below).

The origin and branching type of the splenic vein, like those of the splenic artery, result from the site, size, and tributary region of the spleen, which vary with the species. According to Ceriotti (1948) the blood of the splenic vein may come from the spleen and stomach *(Amiurus, Triton, Lacerta, Meleagris, Gallus; Erinaceus, Talpa, Canis, Sus)*, from spleen and hindgut *(Rana, Bufo, Testudo)* or exclusively from the spleen *(Tropidonotus, Anas, Anser)*.

C. Adaptative differentation trends; types of mammalian spleen

If the variation in spleen structure found in different species is one of the criteria used for classification, the seemingly irregular variability in the relative spleen weight of mammals – which far exceeds that found in non-mammals – becomes a serial quantitative grouping in which the two extremes (elk, rabbit) can be understood as spleen types which have differentiated in opposite ways. The relatively and absolutely large spleens, which are rich in trabeculae and muscle but poor in lymphoid tissue, are storage-sites for erythrocytes and have a powerful effect on the circulation; these are 'storage' spleens. The relatively and absolutely small spleens are poor in trabeculae and smooth muscle cells but rich in lymphoid tissue, and can be contrasted with them as 'defence' or 'metabolism' spleens (v. Herrath, 1935–1939, 1941, 1946/47, 1953–1955, 1958).

The functional importance of the primitive type – the 'defence' spleen, which developed earlier in phylogeny and ontogeny – is greatest in early youth and decreases as with increasing age involution of the white pulp occurs. The 'storage' spleen – a new development among the mammalian spleens – in ontogeny first passes through a state corresponding to the 'defence' spleen, and only when growth is completed does it reach its full effectiveness, only to lose it stepwise in age. Immunological and metabolic stimulations which give rise to a vigorous growth of lymphoid tissue with corresponding increase of weight in the 'defence' or juvenile spleen are less effective in the adult 'storage' spleen. Here the effective stimulation derives from the circulatory and heat-regulation systems, as is shown by the stable weight ratio of spleen and heart. The 'series rule' of Hesse, which states that larger individuals of the same species have lower relative heart weights than smaller ones, is also valid for the 'storage' spleen (e.g. horse, dog). The 'defence' spleen (e.g. rabbit, man) does not follow this rule, and is not susceptible to the same stimuli. The extent of the erythrocyte-storage of a spleen not only depends on the relative weight, wealth of trabeculae and smooth muscle but also on the content of red pulp, which is decisive for the absolute spleen size, and its composition; in extreme 'storage' spleens there are only reticulum and sparse pulp veins, in 'defence' spleens with decreasing storage efficiency there is increasing 'sinusoidisation'. Thus 'the storage spleen is a reticulum spleen, the defence spleen a sinusoid spleen' (v. Herrath).

Other authors (e.g. Hoepke, 1951; Zwillenberg, 1958/59) reject such all-embracing correlations between spleen weight, morphology and physiology, and are content with a descriptive-histological classification, which makes no assumptions about function. Snook (1950; cf. Neubert, 1922; Watzka, 1937) distinguishes between sinusoidal and non-sinusoidal mammalian spleens. Hoepke (1951) instead of a storage 'type' prefers only to speak about a storage state; in some cases this state is so pronounced that the defence state existing at the same time can be neglected (as well as the metabolism, reaction and blood flow-regulating state, among others). On the other hand, the storage state can

oozes through this before entering the venous sinuses. Therefore, the net quantity of red blood cells in the general circulation decreases slightly when the spleen enlarges ...' (p. 352, fig. 29-6).

This description of the terminal circulation of the spleen agrees completely with that given by Tischendorf (1969, pp. 575–612, figs. 262–281): "The direct connection between capillaries and sinuses (seen under the light microscope) is without doubt the normal situation in the human spleen ... A closed circulation means that the so called 'intermediary circulation' depends on the peculiar structure of the walls of the splenic sinuses (fig. 282), and not on the presence of a gap between arterial capillaries and sinuses observable under the light microscope. This does not exclude the fact that the arterial capillaries of the spleen, observed using the electron microscope, show a special organ-specific ultrastructure; an increased permeability, as is also found in other organs of the lympho-reticular system."

also occur together with the blood-forming state (e.g. in the hedgehog). Tischendorf (1969, pp. 128ff., 201ff., 374) – in spite of fundamental objections to a far-too-inflexible handling of the terminology in general and the definition of the 'storage' spleen in particular – does not wish to renounce the principle suggested by v. Herrath as a classification. Even if the type theory is not convincing in all its aspects, its combined quantitative and functional approach has permanently influenced spleen research and will – especially in its more conciliatory last version (v. Herrath, 1963, 1965) – keep its heuristical worth as a working hypothesis.

The species-specific differences in the fine and coarse innervation of the mammalian spleen have unfortunately been neglected until now, and virtually nothing is known about the innervation of the non-mammalian spleen. Though many questions in the last analysis can be settled only by experiment, a specialized innervation or a favored kind of innervation allows us to draw conclusions about the functions of certain structures (Harting, 1952), because the nervous control (Hoff, 1931) is not less important than the humoral for the harmonious coordination of the numerous partial processes constituting the total function of the spleen. If the neuroarchitecture (Tischendorf, 1948, 1956, 1969, pp. 662ff.) of various spleens is considered in the light of v. Herrath's concepts, a considerable agreement results; i.e. the crucial points of innervation lie on the respective structural-functional key positions. But already the few innervation pictures known – which, moreover, like the quantitative histological findings are mainly confined to domesticated animals – show much greater differences (e.g. regarding the influence of the pulp muscle on the distribution of nerves within the spleen) than would be expected according to these ideas. Obviously a great many more factors – not least environmental (ecological) and peristatic-adaptative ones – must be considered, if we hope to achieve a better understanding of the spleen.

Literature

Owing to lack of space, many authors whose work is discussed in the foregoing article could not be cited in the text. The reader will find references to their work, as well as that of the few representative authors named above, in the relevant chapters or the bibliography of the book: Tischendorf, F., Die Milz, in: Handbuch der mikroskopischen Anatomie des Menschen, vol. VI, part 6, pp. 1–968. Ed. W. Bargmann. Springer-Verlag, Berlin/Heidelberg/New York 1969.

The literature in this bibliography is restricted to work published before 1969, but since then no major contributions to the phylogeny of the spleen have come to my notice.

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The fish spleen: structure and function

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1. Morphology, circulation, lymphoid functions

1.1 Comparative anatomy

Cyclostomes have no spleen, but spleen-like lymphohemopoietic tissues occur in the intestine (hagfishes: *Myxine, Eptatretus;* ammocoetes larvae: *Lampetra, Petromyzon*)[27,67].

In lungfishes (dipnoans) the spleen is enclosed within the stomach wall and the spiral valve of the intestine[37,60]. In holocephalans (rabbitfish, *Chimaera*) the spleen is associated with the pancreas and is lying free in the peritoneal cavity[22]. In other fishes the spleen generally occurs close to the stomach in the dorsal mesentery, where it forms a well-defined organ with a discrete vascular and nervous supply.

Scattered information is available on the spleen of holosteans (gar, bowfin) and chondrosteans (sturgeons, paddlefish)[26], polypterids (bichirs)[76] and the coelacanth *(Latimeria)*[46]. Cartilaginous fishes (sharks, rays, rabbitfish) have a large spleen, comparable in size with that of mammals (spleen weight in man is about 0.27% of the body weight)[6]. In the holocephalan *Chimaera* the spleen weighs about 1% of the body weight. In teleosts the spleen is usually smaller than in holocephalans and elasmobranchs (table 1).

Sharks and dogfishes have a lobated elongated spleen. In large sharks such as the basking shark *(Cetorhinus maximus)* the spleen is divided into up to 100 lobes[43]. In small-sized specimens the spleen is less lobated (figs 1a, 2) but occasionally consists of separate parts (*Etmopterus*)[44]. Rays *(Raja, Torpedo)* have a relatively small flattened round spleen. In teleosts the structure of the spleen varies very much. The fish spleen is surrounded by a connective tissue capsule, which is often very thin. The arterial supply of the spleen is derived from the visceral arteries such as the lieno-gastric artery (elasmobranchs) or the coeliac (mesenterial) artery (teleosts) (cf.