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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Key words. Spleen, fish; structure; function.

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.

fig. 2). The splenic veins join the hepatic portal system. The blood vessels passing through the capsule into the parenchyma are surrounded by some connective tissue[80], but usually no distinct trabeculae are found. The parenchyma contains the same elements as the splenic parenchyma of other vertebrates: blood vessels, ellipsoids, red pulp, lymphoid tissue (white pulp), macrophages. However, red and white pulp are less clearly defined than in the homeothermic vertebrates.

1.2 Vascular architecture and microcirculation

The splenic parenchyma is supplied by nonanastomosing arteries dividing into smaller branches. The terminal branches, considered as capillaries, usually have a sheath consisting of aggregated cells and fibres (fig. 1c). Such vessels with thickened walls, often termed ellipsoids, were first described in the porcine spleen[64] and have since been demonstrated in many vertebrate groups.

Ellipsoids occur in many fishes, but they may be indistinct or lacking in certain species[76]. Knisely[39] pioneered microcirculation studies of the living spleen (mouse, rat, cat) using quartz rod illumination and observation though water immersion lenses. The blood flow was regulated by rhythmic contractions of powerful sphincters, some of which seemed to be identical with ellipsoids. However, the results have not been confirmed. MacKenzie et al.[41] pointed out that Knisely paid no attention to rhythmic contractions of the splenic smooth muscles. They also remarked that in the spleen of mice, ellipsoids are absent or reduced, and therefore probably cannot act as sphincters. The splenic circulation in fishes is usually described as 'open'[28,80], but microcirculation studies have not been made.

1.3 Lymphoid tissue

In elasmobranchs (sharks, rays) and holocephalans (rabbitfish) lymphoid tissue (white pulp) is well devel-

Table 1. The weight of the spleen of fishes in percent of the body weight (ranges)

Species	Spleen weight	References
Holocephali		
Rabbit fish		
(*Chimaera monstrosa*)	0.42–1.82	Fänge and Sundell[22]
Elasmobranchii		
Nurse shark		
(*Ginglymostoma cirratum*)	0.21–0.36	Fänge and Mattisson[20]
Dogfish		
(*Scyliorhinus canicula*)	0.22–0.63	Fänge and Pulsford[21]
Various species	0.10–0.80	Fänge[18]
Shark		
(*Mustelus manazo*)	2.65–4.00	Murata[49]
Teleostei		
Bass		
(*Lateolabrax japonicus*)	0.05–0.14	Murata[49]
Mullet		
(*Mugil cephalus*)	0.12–0.34	Murata[50]
Salmon		
(*Salmo salar*)	0.04–0.86*	Miescher-Ruesch[45]
Various species of marine teleosts	0.02–0.18	This work

*Great seasonal variations (see text).

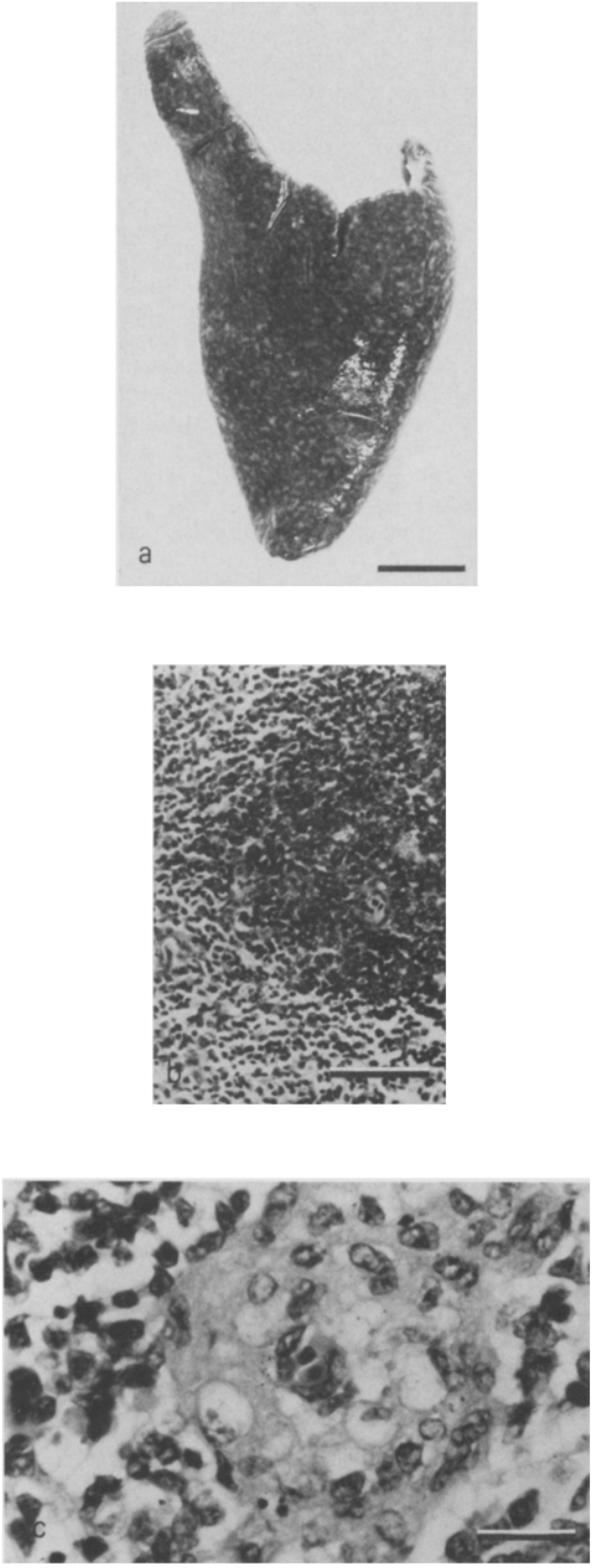

Figure 1. Spleen of the spiny dogfish *(Squalus acanthias)*. a) Ventral view of the isolated spleen. Whitish spots may represent lymphoid foci. Bar = 1 cm. b) Microscopic structure (paraffin section, Giemsa). To the left and below red pulp, to the right accumulation of lymphoid cells. Bar = 100 µm. c) Transversal section through an ellipsoid (haematoxylin-eosin). The endothelial tube (in the middle, containing blood cells) is surrounded by vacuolated sheath cells. Bar = 10 µm. (Original pictures.)

oped, especially around the arteries. But the periarterial lymphoid tissue is less distinctly outlined than in the mammalian or avian spleen, and germinal centres are lacking (figs 1b, 3). Electron microscopic studies show the presence of plasma cells in the shark spleen. Rosette-like contacts between macrophages and lymphocytes may be signs that immune processes are taking place in the spleen[20,59].

In teleosts splenic lymphoid tissue is poorly developed, but diffuse layers of lymphoid tissue may surround arteries and melanomacrophage centres, and scattered lymphocytes occur within the whole parenchyma[50,79] (fig. 3). Plaque techniques have demonstrated that antibody-producing cells occur in spleens of various teleosts[6,11,51,58,62,65]. But faster immune responses and larger numbers of antibody-producing cells are found in the teleost pronephros[51,65]. Teleosts, like higher vertebrates, may contain populations of lymphocytes which differ in surface globulins of the cells[40]. The spleen of the rainbow trout *(Salmo gairdneri)* contains lymphocytes which respond to different mitogens used to distinguish between classes of lymphocytes[17].

Along with other lymphohemopoietic tissues such as the pronephros, the spleen probably is an important source of immunoglobulins in elasmobranchs and teleosts. However, immunization experiments on splenectomized fishes have given contradictory results. Ferren[24] observed no effect on the intensity of antibody production after splenectomy in marine elasmobranchs and teleosts. On the other hand, Yu et al.[77] found that the absence of the spleen completely abolished the antibody formation in the teleost, the blue gourami *(Trichogaster trichopterus)* immunized against infectious pancreatic necrosis virus. Species differences may exist. Morrow et al.[48] suggest that in the dogfish *(Scyliorhinus canicula)* the spleen is the main immune organ. In the icefish *(Chaenocephalus aceratus),* a teleost which possesses practically no erythrocytes, the dominant cells of the spleen parenchyma are lymphoid cells and macrophages[71].

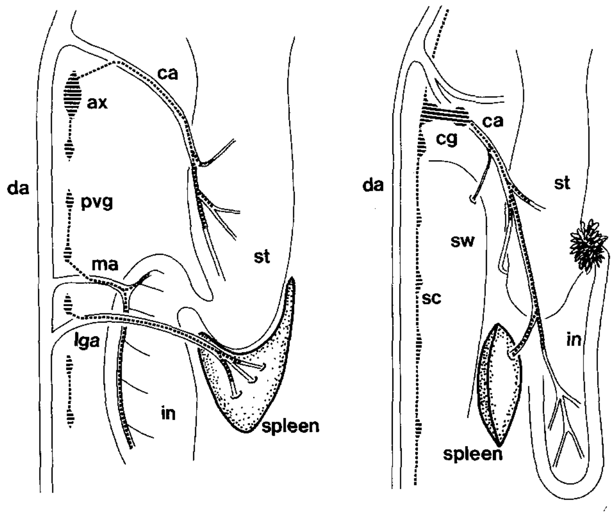

Figure 2. General arrangement of the arterial and nervous supply to the spleen of an elasmobranch, *Squalus acanthias* (left figure) and a teleost, *Gadus morhua* (right figure). In *Squalus* the dorsal aorta (da) sends off the coeliac artery (ca) to the stomach (st), the anterior mesenteric artery (ma) to the intestine (in) and the lieno-gastric artery (lga) to the spleen. The autonomic nervous pathways from the irregularly arranged paravertebral ganglia (pvg) run along or within the walls of the arteries. The most anterior pair of paravertebral ganglia, the gastric ganglia are associated with chromaffin tissue to form the axillary bodies (ax), from which a large anterior splanchinic nerve runs along the ceoliac artery to the stomach. It is possible that some of these fibres reach the spleen along the vessels connecting the stomach and spleen.

In *Gadus* the arterial supply to the anterior viscera is via the coeliacomesenteric artery, which branches soon after its exit from the dorsal aorta. Branches reach the swimbladder (sw), stomach, spleen and intestine. The autonomic nervous pathways are collected in the anterior splanchnic nerve, which runs along the arteries from the coeliac ganglion (cg). The paravertebral ganglia of teleosts are longitudinally connected to sympathetic chains (sc) of the type found also in the tetrapods.

1.4 Ellipsoid functions

Except having uncertain sphincter-like functions[39,42] ellipsoids have been ascribed several other functions such as supporting the blood vessels mechanically, or acting as valves or filters removing aged blood cells[15,68]. According to some authors the ellipsoid sheath contains highly vacuolated cells possibly functioning as pores. This should allow the blood from the splenic arteries to pass through the ellipsoids into the red pulp in two ways: through the vascular lumen as is the case with ordinary vessels, or through the loose-texture ellipsoid sheath.

In many vertebrates – mammals, birds and fishes – intravascularly injected materials (Indian ink, trypan blue) are taken up by ellipsoids. This has been shown in several fishes (skate, *Raja batis:* Tait[66]; lungfish, *Protopterus:* Dustin[14]; tench, *Tinca tinca:* Drăgotoiu-Untu[12]; turbot, (*Scophthalmus maximus:* Ferguson[23]). Studies on the avian spleen have shown that the ellipsoid endothelium is not phagocytic in the classical sense of the term but translocates material at the cell surface by a 'capping' process[72]. Antigen-antibody-complexes taken up by this mechanism are transported to the white pulp by macrophages. In the white pulp germinal centers appear. Similarly, according to Ferguson[23] in the teleost spleen macrophages transport materials from the ellipsoids to the so called melanomacrophages centers. One function of the ellipsoids in fish spleens may be trap-

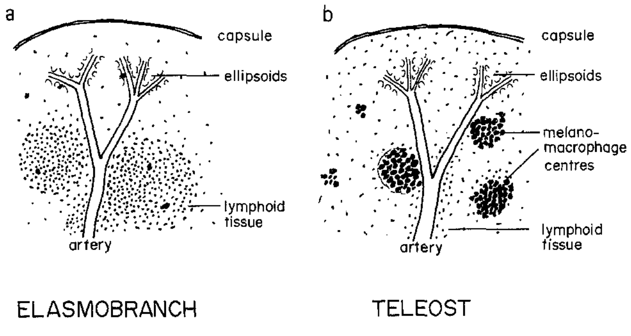

Figure 3. Diagrams of the microscopic structure of fish spleens. a) Elasmobranch type. Lymphoid tissue occurs around blood vessels and lymphocytes also are found elsewhere in the parenchyma. Melanomacrophages are distributed within the whole tissue. b) Teleost type. Lymphocytes are widely scattered and show only a slight tendency to accumulate around blood vessels and melanomacrophage centers. Germinal centers are not found in fish splenic tissue, or in other lymphoid tissues in fishes. (Veins and sinuses are not shown in the drawings.)

ping of antigens, or antigen-antibody complexes, as a step in immune responses, and in connection with degradation of material by macrophages[16,41]. It ought to be remembered, however, that ellipsoids vary in structure and may not exist in the spleen of all fish species.

1.5 Melanomacrophage centers

Nodules or centers of pigment-containing cells called melanomacrophages occur in lymphohemopoietic tissues and/or the liver of most teleostean fishes (fig. 3). Scattered melanomacrophages, not aggregated into centers, occur in the spleen and the liver of elasmobranchs and holocephalans. The pigment of melanomacrophages is assumed to consist of melanins, lipofuchsins, and hemosiderin[3]. In some teleosts (i.e. *Coryphaenoides rupestris, Argentina silus*) melanomacrophage centers are extremely well developed, in other species *(Lophius piscatorius, Cyclopterus)* such centers are indistinct or lacking (Agius[3] and own observations). The melanomacrophages are supposed to be filled with cellular debris of host or protozoal origin[23]. Bleeding reduces[77] and starvation increases[4] the appearence of these pigment cells in the fish spleen. Dendritic cells containing immunoglobulins have been demonstrated within melanomacrophage centers of the plaice, *Pleuronectes platessa*[16]. The centers are surrounded by aggregated lymphocytes and plasma cells (turbot, *Scophthalmus maximus*)[23]. The interactions observed between melanomacrophage centers and lymphoid tissue indicate that the centers are involved in immune responses. The centers have been suggested to represent primitive analogues of germinal centers of birds and mammals[3,23]. The structure and functions of the ellipsoids and the melanomacrophages centers, and the relationships between these structures and the lymphoid tissue of the fish spleen are insufficiently known and ought to be subject of further investigations.

1.6 Blood storage

Great seasonal changes of the spleen size have long been known to occur in the salmon *(Salmo salar)* and other salmonids[45,47,63]. Before and after spawning the spleen is large and hyperemic, but at spawning it shrinks and becomes anemic. These changes probably concern blood storage rather than lymphoid and hemopoietic activities. Miescher-Ruesch[45] calculated that the spleen of the Rhine salmon is able to store about ¼ of the total blood volume of the organism.

Blood stored in the fish spleen may be ejected during asphyxia or administration of certain drugs *(Gobius, Tinca)*[8,69]. It has been shown that a considerable part of the increase in hematocrit, that takes place during severe physical disturbance (produced by continuous chasing) in the teleost fish *Seriola quinqueradiata*, is due to release of erythrocytes from the spleen[74,75]. Opdyke and Opdyke[57] were unable to demonstrate any increase in the hematocrit of the elasmobranch, the spiny dogfish *(Squalus acanthias)* after adrenaline injection and interpreted this finding as due to lack of significant blood storage function in the spleen of this fish. However, later Nilsson et al.[56] demonstrated a release of erythrocytes from the in vitro perfused *Squalus* spleen, albeit smaller than from the spleen of the cod, *Gadus morhua* (see below and fig. 4).

1.7 Hemopoiesis

Erythrocytes and thrombocytes are produced in the red pulp of the elasmobranch spleen[25,78]. Granulopoiesis occurs in the spleen of the electric ray, *Torpedo ocellata*[25]. The erythropoiesis is an intravascular process taking place within the blood not only in the spleen but also in the circulating blood elsewhere[38,78]. Jordan[36] suggested that erythropoiesis is facilitated by a relatively stagnant circulation with low oxygen and high carbon dioxide concentrations, whereas granulopoiesis requires a sparsely vascularized mesenchymal tissue. Zapata[78] emphasized that studies of the elasmobranch hemopoietic organs may contribute to the understanding of microenvironmental conditions which lead to hemopoiesis.

In teleosts hemopoiesis goes on predominantly in the pronephros (head kidney), or in the kidney, but in some species the spleen is hemopoietically active (in *Scorpaena scorpus, Rutilus rutilus, Perca fluviatilis*)[9,25]. Lymphocytopoiesis probably takes place in lymphoid areas of the spleen of both elasmobranchs and teleosts[25]. Splenectomy influences only to a slight degree the cell composition of the blood of fishes[13,19,35]. In fishes with considerable splenic hemopoiesis, removal of the spleen may induce compensatory hemopoiesis in other organs than the spleen, and in the peripheral blood.

1.8 Destruction of blood cells

The spleen is one main site of destruction of aged red cells and other effete blood cells. Details of red cell destruction in the spleen of fishes are not well known. Zwillenberg[80] presented observations on the digestion

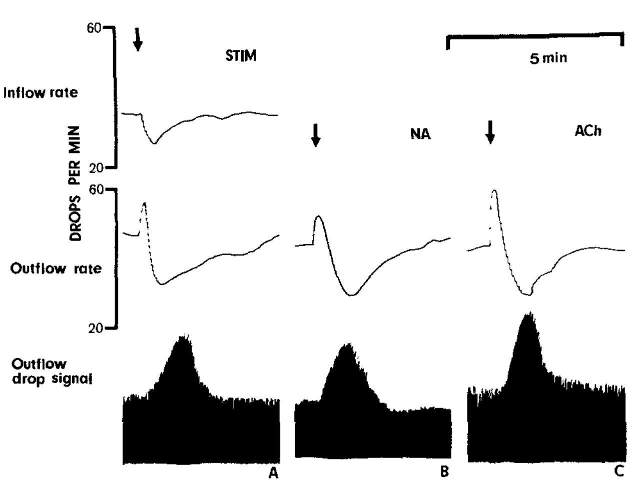

Figure 4. Recordings of changes in perfusion flow of the in situ perfused spleen of the cod, *Gadus morhua*. The figures show the effects of splanchnic nerve stimulation (A), and administration of noradrenaline (1 nmole) (B) and acetylcholine (1 nmole) (C). Note the close similarities in the responses to the different stimuli, and the increased amplitude of the outflow drop signal which reflects the increased optical density of the perfusion fluid due to expulsion of red blood cells. Reproduced with permission from Nilsson and Grove[53].

by macrophages of phagocytozed erythrocytes. The high content of iron in the spleen, probably stored mainly as hemosiderin within melanomacrophages[77], may be a consequence of red cell destruction[29,63].

2. *Innervation*

The spleen of elasmobranch and teleost fish is supplied by an autonomic innervation of spinal autonomic ('sympathetic') origin. The nerves reach the spleen in the anterior (teleosts) or middle (elasmobranchs) splanchnic nerves which, in contrast to the situation in mammals, consist of postganglionic fibers from the paravertebrate ('sympathetic') ganglia[53]. The possibility of fibers from the anterior splanchnic nerve reaching the elasmobranch spleen along the blood vessels connecting the spleen to the lower portion of the stomach cannot be excluded (cf. fig. 2). Similar to the situation in mammals[11] there are no indications of a vagal innervation of the spleen although, at least in teleosts, there are anastomoses between the right vagus and the splanchnic nerve. There are no descriptions of ganglion cells within the spleen.

It is reasonable to believe that one important function of the splanchnic nervous control of the fish spleen (and/or control via circulating catecholamines and possibly other hormones) is to release erythrocytes from splenic stores during various states of 'stress' such as hypoxia. As in mammals (see Davies and Withrington[11]) there may be considerable species differences in the magnitudes of volume change and erythrocyte release during nerve stimulation.

2.1 *Effects of drugs*

The fish spleen contracts in response to adrenoceptor agonists such as adrenaline and noradrenaline (fig. 5), and in those cases where the order of potency of the adrenergic agonists have been studied the results show that the excitatory effect is due to α-adrenoceptors. There are also some indications of the presence of inhibitory (spleno-dilatory) β-adrenoceptors in some fish species[1,7,32,52,54,56]. The pharmacological properties of the cod spleen *(Gadus morhua)* are typically those of an adrenergically innervated organ, and detailed descriptions of the pharmacology of the cod spleen can be found in Nilsson and Grove[54], Holmgren and Nilsson[32,33,34] and Nilsson and Holmgren[55].

Acetylcholine contracts the spleen of teleost fish (*Tinca, Gadus;* see table 2) and in these cases produces a maximal contraction force which is higher than that produced by adrenaline (maximal contraction in *Tinca* about 2–3 times that obtained with adrenaline[69] and in *Gadus* 1.55 times that of adrenaline[32]).

As in mammals[11] the effect of acetylcholine in most other fish is weak and inconsistent with considerable desensitization to repeated doses *(Squalus)* or absent (*Scyliorhinus*[56], *Lepisosteus*[52], *Huso*[7]. In the lungfish *(Protopterus)*, however, acetylcholine produces a strong contraction of isolated splenic strips but since the splenic tissue lies embedded in the gut wall, the smooth muscle of the spleen in this species may not be directly comparable to that of the other fish[1].

2.2 *Nature of the splenic nerve fibers*

In *Protopterus* and *Scyliorhinus* no nervous control of the spleen has been described, and it is possible that the spleen in these species is controlled by circulating agents (e.g. catecholamines[1,56]). In *Squalus,* electrical stimulation of the splanchnic nervous supply to the spleen produced a polyphasic response, usually including a marked constrictor component. The response could be abolished by the α-adrenoceptor antagonist phentolamine, suggesting that the effect is due to an adrenergic innervation of the spleen[56]. Fluorescence histochemistry by the Falck-Hillarp technique demonstrated almost no adrenergic fibers in the spleen of *Squalus,* except in the walls of blood vessels, and it is possible that the main effector musculature in this species is the vascular smooth muscle[56].

In the cod *(Gadus morhua)* both acetylcholine and adrenaline/noradrenaline contract the spleen (perfused spleen or isolated spleen strips) and the responses to these agonists closely mimic the effect of splanchnic nerve stimulation (fig. 4)[54]. α-Adrenoceptor antagonists, such as phentolamine, reduce the excitatory response to splanchnic nerve stimulation, but never abolish the response. The same is true for the cholinoceptor antagonist atropine, and only if both the adrenoceptor and cholinoceptor antagonists are added simultaneously is the response to nerve stimulation completely abolished. It was thus concluded that both cholinergic and adrenergic elements are present in the splanchnic innervation of the cod spleen[54].

Later studies showed that treatment of the cod with 6-hydroxydopamine (6-OH-DA), a drug known from mammalian studies to destroy specifically the adrenergic nerve terminals, reduced the catecholamine content of the cod spleen to very low values[2]. The treatment also caused a presynaptic supersensitivity to catecholamines typical of an adrenergic denervation[33,34]. It was also seen that the 6-OH-DA treatment abolished not only the adrenergic component of the splanchnic innervation of the isolated perfused cod spleen, but that the cholinergic component was also destroyed. A supersensitivity to acetylcholine, probably linked to the

Table 2. Effects of adrenaline and acetylcholine on the spleen of some species representing different groups of fish. + indicates contraction; 0 indicates no effect

	Adrenaline	Acetyl-choline	Reference
Elasmobranchs			
Scyliorhinus canicula	+ +	0	Nilsson et al.[56]
Squalus acanthias	+ +	(+)	Nilsson et al.[56]
Dipnoan			
Protopterus aethiopicus	+	+ +	Abrahamsson et al.[1]
Holosteans			
Huso huso	+ +	0	Balashov et al.[7]
Lepisosteus platyrhincus	+ +	0	Nilsson[52]
Teleosts			
Tinca tinca	+	+ +	Vairel[69]
Gadus morhua	+ +	+ +	Nilsson et al.[54] Holmgren and Nilsson[31]

disappearance of cholinesterase associated with autonomic nerve terminals, was also demonstrated[33].

Studies by Winberg et al.[73] showed that the activity of choline acetyltransferase, an enzyme regarded as a 'marker enzyme' for the cholinergic nerve terminals in mammals, was reduced after 6-OH-DA treatment to the same degree as after surgical denervation of the spleen. Since very few nonadrenergic nerve cell bodies could be found in the coeliac ganglion (from which the splanchnic nerve runs in the cod), the findings were interpreted in favor of an undifferentiated adrenergic/cholinergic type of neuron as responsible for the splanchnic innervation of the spleen[33, 78].

2.3 Possible effector tissues

According to most authors there are no smooth muscles in the capsule of the fish spleen, nor does the system of muscular trabeculae (if at all present) reach the prominence of that in mammals[68, 76, 80]. It would thus seem that the major effector tissue for the autonomic innervation of the fish spleen is the vascular smooth muscle.

Some observations do, however, suggest the presence of a nonvascular smooth muscle element as being responsible for at least part of the contractile response of the fish spleen. In the cod *(Gadus)* there is a conspicuous lack of sensitivity of the vasculature to acetylcholine[31, 61, 70] and there are no signs of a cholinergic innervation of the coeliac artery[30] from which the splenic vasculature arises. Despite this, there is a very prominent constrictive effect of acetylcholine on the cod spleen (fig. 4), and there is good evidence for a cholinergic component in the splanchnic innervation of the cod spleen (see above). These observations tend to support the idea of a nonvascular smooth muscle component in the spleen, innervated by autonomic nerve fibers. The exact nature of this tissue is unknown, and it has been tentatively referred to as 'capsular/trabecular smooth muscle' as opposed to the 'vascular smooth muscle' (cf. Nilsson and Grove[54], Holmgren and Nilsson[32]).

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