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EVOLUTION OF THE AUTONOMIC INNERVATION OF VISCERAL AND CARDIOVASCULAR SYSTEMS IN VERTEBRATES

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I. INTRODUCTION

Comparative studies of the vertebrate autonomic nervous system are fragmentary. Nicol (401) wrote a general review of the early literature in 1952. Various specialised aspects of the subject have been reviewed since that time: for example, transmitter substances (185, 207, 518); nervous control of chromatophores (206); pharmacology (197, 284); bladder in amphibians (52); alimentary canal in fish (34), amphibians (449), birds (202), marsupials (515), and vertebrates in general (120); the cardiovascular system (296, 490); autonomic nervous system and swim bladder in fish (117, 198). Many other areas have been neglected; for example, there are very few reports on the innervation of blood vessels, genital organs, digestive glands, and lungs in lower vertebrates.

The comparative approach is useful, since many fundamental problems can be more easily and profitably studied on primitive systems and because a knowledge of the pattern of evolution may give new insight into the mechanisms operating in mammals, and in particular in man. For example, many deviations from Langley's classical concept of the mammalian autonomic nervous system (333) may become clearer as a result of evolutionary studies; some features may be recognised as retained relics of the primitive system, others as incomplete development of a device first seen in rudimentary form earlier in evolution, *etc.* The results may also indicate which parts of the autonomic nervous system are well established and which parts are more likely to show wide variation even between closely related species.

Previous generalisations about the pattern of evolution of the vertebrate autonomic nervous system are few. J. Z. Young (540, 542) raised an important issue when he stated that, "There is little evidence in fish of a differentiation into functionally antagonistic sympathetic and parasympathetic systems." On the basis of assays of catecholamines in various tissues from lower vertebrates, von Euler and Fänge (186) speculated that adrenergic fibres are a relatively late step in the evolution of the autonomic nervous system. Both these statements are examined in the present review in the light of a considerable body of conflicting evidence from recent work on the innervation of visceral and cardiovascular systems. However, it must be recognised that since physiological studies are limited to living animals at the latest stage in their evolutionary lives, any speculation about patterns of evolution make the dangerous assumption that current physiological mechanisms to a large extent reflect the primitive condition of that group.

Most early investigations of the autonomic innervation of various systems in lower vertebrates were made with the light microscope and with the use of relatively poorly understood drugs. Thus interpretation was difficult and for the most part the story that emerged was incomplete and generalisations were unsatisfactory. The recent application of modern techniques has given more insight into the nature of the vertebrate autonomic nervous system; these include the fluorescent histochemical method of localisation of monoamines, modern pharmacological studies, including the use of mechano-electric transducer recording systems, electronmicroscopy, and spectrofluorometric assay of tissue amines.

The vast bulk of research on the autonomic nervous system has been carried out on mammalian systems. Thus the mammalian system is used as a yardstick against which results of work on lower vertebrate systems are interpreted. However, it is essential that this is carried out with care. For example, many autonomic drugs can be used to elucidate the autonomic nervous components supplying various organs. This has been carried out exhaustively in mammals and it is generally recognised that particular drugs will have a known site and mechanism of action at a given concentration, with certain minor side actions. However, it is important not to assume when analysing components of innervation in nonmammalian systems that these drugs will have the same action, and thus wherever possible their specificity should be tested on the system being examined. The cholinergic blocking action exerted by low concentrations of a variety of adrenergic blocking agents on lower vertebrate systems is a good example of the problems involved (76). It is important also not to bend too far in the interpretation of results on lower vertebrates in an attempt to make the system fit within the classical definition of the autonomic nervous system established for mammals.

In this review, emphasis will be placed on the innervation of the lung, bladder, gut, and cardiovascular system, since much of the recent work has been carried out on these systems. Discussion of pharmacological studies in lower vertebrates will be restricted to the use of those drugs which give some information about the nature of the autonomic transmitter substances involved in the nervous control mechanisms. Models of the evolutionary pattern will be proposed for each system examined and some attempt to isolate overall evolutionary trends will be discussed in the final section.

II. ANATOMY OF THE AUTONOMIC NERVOUS SYSTEM

The classical picture of the autonomic nervous system in mammals (229, 333) is that it consists of two major divisions, the sympathetic and parasympathetic systems.

The sympathetic nervous system consists of a thoracico-lumbar outflow of preganglionic neurones passing *via* white *rami communicantes* to make synaptic connections with postganglionic neurones in the paravertebral or prevertebral ganglia. The sympathetic chain, which consists of a bilateral system of paravertebral ganglia joined by longitudinal connectives, extends rostrally to the upper cervical region and caudally to the lower sacral level, but receives no efferent contribution from the spinal nerves at these extremes. The postganglionic axons pass out of the sympathetic chain in several ways. Some pass *via* grey *rami communicantes* to the spinal nerves and run with them to supply peripheral vascular beds and other superficial structures such as sweat glands and pilomotor muscles. Some pass *via* connectives to join cranial nerves which supply systems such as the heart, iris, and salivary glands. Many, such as the splanchnic, cardiac, and hypogastric nerves leave the sympathetic ganglia and run directly to various visceral organs. Some of the preganglionic sympathetic nerves do not make synaptic connection with ganglion cells in the paravertebral chain, but pass straight

through into the various visceral nerves where they synapse with neurones in the prevertebral ganglia such as the coeliaco-mesenteric and hypogastric ganglia.

The parasympathetic system consists of portions of the outflows in the cranial (III, VII, IX, X and XI) nerves and the sacral spinal nerve outflows. Preganglionic neurones from the central nervous system make synaptic connections with postganglionic neurones in ganglia (*e.g.*, ciliary ganglion) lying in or near the innervated organs.

In general, autonomic fibres emerge in the ventral roots of spinal nerves and in the ventral root of the first cranial segment (oculomotor nerve), while in the bulbar region, autonomic fibres occur in nerves derived morphologically from dorsal roots (VII, IX and X cranial nerves) (237). Classically parasympathetic postganglionic neurones release acetylcholine, whereas the antagonistic sympathetic nerves release noradrenaline; preganglionic fibres whether sympathetic or parasympathetic are considered to be cholinergic (147). Detailed descriptions of the mammalian autonomic nervous system are available in a number of textbooks (for example, 328, 376); Nicol (401) gave a full account of the anatomy of the autonomic nervous system in lower vertebrates.

A. Cranial "parasympathetic" nerves

The arrangement of cranial nerves is relatively uniform throughout the vertebrates and parasympathetic autonomic fibres are usually found in III, VII, IX and X, although additional autonomic components are found in XI in mammals.

In cyclostome fish, the two vagus nerve trunks unite to form a cardiac plexus, which contains many nerve cell bodies. Autonomic fibres are distributed from this plexus to the heart, to the entire length of the intestine, the main blood vessels, and the gall bladder (200, 290, 300, 401, 436). The vagus nerves may contain fibres of sympathetic origin (359), since they run close to the mixed ventral rami of the anterior spinal nerves (see Peters, 436). Oculomotor and facial autonomic nerve components have also been identified (401).

The cranial autonomic outflow in elasmobranch fish consists of fibres leaving the brain stem in the oculomotor, facial, glossopharyngeal and vagus nerves. Although the sympathetic system does not extend into the head as it does in other vertebrates, there is often a connection between the first sympathetic ganglion and the vagus (132, 540). Since these connecting fibres are small and medullated, Young (540) concluded that they are neither postganglionic nor sensory, but rather represent preganglionic fibres from the vagus to the gastric (sympathetic) ganglion.

In teleost fish, the cranial autonomic outflow is restricted to the oculomotor and vagus nerves. It seems likely that the functions of the VIIth and IXth cranial autonomic nerves present in elasmobranch fish have been taken over by the vagus in teleosts. There are extensive connections of sympathetic with cranial parasympathetic nerves in teleosts (537). For example, the vagus nerve is joined by a branch from the cranial sympathetic chain, so that it is in effect a vagosympathetic trunk to most of the organs it supplies, *e.g.*, swim bladder (196), stomach (100–102), and heart (224). Many sympathetic fibres also run in the vagal trunks

of both urodele (newts) and anuran (frogs and toads) amphibians (136, 334, 335, 401, 529). In mammals, there are usually fibres passing from the superior cervical ganglion to the vagal, hypoglossal, and glossopharyngeal nerves and indirectly, *via* the carotid plexus, to the facial, trigeminal, and oculomotor nerves. The general opinion is that the majority of these fibres are sensory (237, 333). However, adrenergic fibres of sympathetic origin running in the vagus nerve branches supplying the heart have recently been demonstrated (405).

B. Spinal "sympathetic" nerves

The sympathetic nervous system is regarded, classically, as a preganglionic cholinergic outflow from the spinal cord, running through the ventral roots of the spinal nerves and making synapses with postganglionic fibres either in the sympathetic chains or in more remote ganglia outside the innervated organ. Even in mammals, this concept must be treated with some caution, since the number of known deviations is increasing (see Campbell, 116); *e.g.*, adrenergic fibres have been found leaving the spinal cord in the ventral roots (145). The situation in lower vertebrates is even less clear. In these groups, autonomic fibres may leave the cord in both dorsal and ventral roots. The peripheral synapses may occur within the substance of the innervated tissue, or may even be lacking.

In the cyclostome fish, there are no sympathetic chains or segmental sympathetic ganglia. Aggregations of nerve cell bodies are distributed along the cardinal veins in the abdominal cavity of lampreys and these may represent primitive sympathetic ganglia. Fibres appear to leave the spinal cord of the lamprey in both dorsal and ventral spinal nerves and run directly, without an intervening ganglionic synapse, to visceral structures (299). Thus, visceral branches of the spinal nerves run directly to blood vessels, genitalia, and kidneys while posteriorly there is a spinal outflow to the rectum, ureters, and cloaca, with many ganglion cells in the pathway (299). A similar visceral outflow has been demonstrated in the hagfish (200). It is not known, in the absence of experimental data, what proportion of these fibres is efferent, or whether many of the peripherally placed nerve cell bodies are sensory.

A subcutaneous plexus containing numerous nerve cells is a characteristic feature of cyclostome fish, which are unique amongst vertebrates in this respect. The nerve cells are supplied by spinal nerve fibres, which probably represent autonomic components concerned with the regulation of slime glands, chromatophores, and blood flow in subcutaneous sinuses (72).

In elasmobranchs, the sympathetic nervous system does not consist of a compact sympathetic chain but rather of a series of paravertebral ganglia, one or more occurring per spinal nerve, linked together by a loose plexus of nerve bundles. These ganglia are connected to the spinal nerves by white *rami communicantes*, but grey rami are absent (540). This implies that there is no entry of postganglionic fibres into the spinal nerves to reach dermal structures, although there is evidence for sympathetic nervous control of dermal melanophores (426). There are no cranial sympathetic ganglia and ganglia do not extend posteriorly beyond the mesonephros. Fibres from the paravertebral ganglia are concentrated

into anterior, middle, and posterior splanchnic nerves, most of which run with perivascular nerve plexuses to the viscera and probably also to cranial structures. Other nerve fibres run directly to urinary and genital ducts.

Most fibres pass out from the spinal cord in the ventral roots of the spinal nerves. Few, if any, efferent fibres run in the dorsal roots (379, 540). It would seem that there are three discontinuous regions of outflow from the cord: the anterior region, supplying the anterior splanchnic nerves, occurs in roots 3 to 7 in a dogfish (*Scyllium*) (540), 3 to 8 in another dogfish (*Squalus*) and 6 to 12 in the ray (*Raja*) (379); the medial region, supplying the middle splanchnic nerves, is found in roots 15 to 25 in dogfish (540); and the posterior region, supplying the posterior splanchnic nerves, is found in roots 27 to 30 in dogfish (540).

A thorough study of the structure of the autonomic nervous system in a teleost was carried out by Young (537). The sympathetic ganglia are well defined and resemble those of higher vertebrates (but not of elasmobranchs) in that they are connected with the spinal nerves by white rami consisting of medullated (preganglionic) fibres and grey rami composed of nonmedullated (postganglionic) fibres. The sympathetic ganglia are connected by a chain in which the medullated fibres may run forwards or backwards and may also cross in transverse commissures to the opposite chain. The two chains fuse to a variable extent in different species (132, 133) and extend backwards to the end of the tail. The extensive development of the sympathetic chain into the head of teleosts is an unusual feature among vertebrates. It extends into the head and bears sympathetic ganglia which are connected with the vagal, glossopharyngeal, facial, and trigeminal cranial nerves. The *rami communicantes* between these sympathetic ganglia and the cranial nerves consist almost entirely of nonmedullated (postganglionic) fibres; the preganglionic fibres for these ganglia run out in the white rami of the third and fourth spinal nerves and thence forward in the sympathetic chain. Young (537) regarded the cranial sympathetic ganglia as a special feature of teleosts and considered that the presence of more peripheral ganglia in the head of tetrapods is a new development in connection with the elaboration of salivary glands. This view is supported by the fact that they are poorly developed in amphibians, and less developed in reptiles than in mammals (526).

Sympathetic fibres from the chain are collected into a large anterior splanchnic nerve leaving the right sympathetic chain in teleosts, and a posterior splanchnic nerve has been demonstrated, at least in the trout (101). Some sympathetic nerves also leave the posterior chain and join periarterial nerve plexuses to supply urinary and reproductive tracts.

The situation in fish other than teleosts and selachians is not well known. Chevrel (133) found that in the sturgeon (*Acipenser*) there were connections between the anterior sympathetic "chain" and the vagus and glossopharyngeal nerves, but that there were no sympathetic ganglia in the head. Sympathetic chains appear to extend into the head of holostean fish (7, 414). In the lungfish, there is apparently no connection between the sympathetic chain and the vagus nerve (289a).

The macroanatomy of the sympathetic nervous system in amphibians was

established in the last century (231). In urodele amphibians it consists of paired longitudinal trunks extending from the first spinal segment into the tail. Four divisions of the sympathetic system, namely cephalic, cervical, abdominal, and caudal have been distinguished (12, 212). Their detailed pathways have been summarised by Nicol (401). It has been stated that in amphibians none of the efferent fibres supplying the gut runs in the dorsal roots of the spinal nerves (146, 276, 334). However, there is much convincing evidence that the excitatory nerve fibres emerge from the cord almost exclusively in the dorsal roots, down to about the level of the seventh spinal nerve (63, 252, 466, 484, 485). The origin of these fibres is not known. Bishop and O'Leary (63) were unable to find any evidence for efferent fibres to the gut when the dorsal roots were stimulated at a point central to the dorsal root ganglia. However, when nerves peripheral to the ganglia were stimulated, they observed strong contractions of the gut. On the basis of these experiments and of further experiments on degeneration they concluded that the excitatory fibres had cell bodies in the dorsal root ganglia but were not connected with the central nervous system *via* the dorsal roots. These results are consistent with the anatomical and physiological studies of Dale (146). However, Hato (252) was able to stimulate the dorsal roots central to the dorsal root ganglia and obtain a contraction of the stomach. Moreover, this response was abolished by painting the ganglia with nicotine solutions. In a subsequent paper (254) he found that the reactivity of the fibres in the dorsal root to stimulation central to the dorsal root ganglion was lost after central section of the root. His results therefore indicate that cholinergic fibres leave the cord in the dorsal roots and form synapses with excitatory nerve cell bodies in the dorsal root ganglia. These excitatory fibres do not make synapses in the coeliac plexus, since their action is not prevented by local application of nicotine (251, 466), but it seems likely that they synapse in the gut wall (77).

There is also an outflow of inhibitory adrenergic fibres in the upper spinal nerves of amphibians (5, 77, 251, 466, 543). These fibres are more typically "sympathetic" since they leave the cord in the ventral roots (252) and form synapses in the coeliac plexus (253, 466).

The anatomical arrangement of the sympathetic nervous system in birds and reptiles is close to that seen in mammals (526).

C. Sacral "parasympathetic" nerves

The concept of a sacral parasympathetic outflow in mammals is well established. There are well defined differences between responses of visceral organs to stimulation of the sacral nerve roots and of the thoracico-lumbar nerve roots. In lower vertebrates, this distinction is less clear. In anuran amphibians, Langley and Orbeli (334) distinguished between "sympathetic" and "parasympathetic" spinal autonomic nerves, largely on the basis of the gap in the outflow at the level of the eighth spinal nerve. This may represent the first appearance of a sacral parasympathetic system in vertebrates. Excitatory nerve fibres emerge from the cord almost exclusively in the dorsal roots down to the level of the seventh spinal nerve (63, 252, 466, 484, 485), but at the level of the ninth and

tenth spinal nerves, an excitatory outflow occurs in the ventral roots (77, 146, 276, 334). However, there do not appear to be any clearcut physiological differences between the "sympathetic" dorsal root cholinergic excitatory fibres and the "parasympathetic" ventral root cholinergic excitatory fibres, although differences of function might well occur. This point has been made with respect to the innervation of the toad urinary bladder (108) and rectum (77). In groups lower than amphibia, it seems highly likely that there are also gaps in the spinal autonomic outflow to the viscera, but this does not appear to be sufficient evidence in itself for defining a separate sacral parasympathetic system. A further complication is that many of the cranial parasympathetic nerves appear to be primitively inhibitory, releasing an as yet unknown transmitter substance. If such fibres emerge cranially, there is a possibility that they may also emerge caudally in a truly "parasympathetic" outflow. In this circumstance, it might be possible to use the presence of such fibres (inhibitory or possibly excitatory), which are distinct from typical adrenergic fibres, as a diagnostic feature of a parasympathetic outflow. However, this must remain conjectural until their presence in the mammalian sacral parasympathetic is proved or disproved.

A distinct sacral parasympathetic outflow, comparable to that known in mammals, appears to be present in reptiles and birds, but definitive evidence is lacking.

D. Summary

1. The cranial nerves are identifiable in all vertebrates and parasympathetic autonomic components are usually found in III, VII, IX and X. In mammals, parasympathetic fibres are also found in XI.

2. The spinal sympathetic outflow is not arranged in segmental ganglia in cyclostome fish. In elasmobranch fish there is a series of paravertebral ganglia, but they are not in the form of a compact sympathetic chain. A well defined sympathetic chain first appears in teleost fish and is retained throughout higher vertebrates.

3. In lower vertebrate forms, autonomic fibres leave the spinal cord in both dorsal and ventral spinal nerves. In higher vertebrates autonomic fibres emerge in the ventral roots, but some dorsal root outflow is retained in amphibians and possibly even in mammals.

4. In fish and amphibians, many fibres of sympathetic origin run in the vagus nerves. There is a clearer separation of sympathetic and parasympathetic nerves in higher vertebrates, but the presence of a few sympathetic fibres in the vagus trunks is retained even in mammals.

5. A sacral parasympathetic outflow appears in rudimentary form for the first time in anuran amphibians, and is strongly developed in reptiles and mammals.

III. NEUROTRANSMITTERS AND RELATED SUBSTANCES

This section summarises the results of assays of extracts of a variety of tissues from different vertebrate species and provides a useful reference point for the results discussed in other chapters. Fuller and more critical accounts of work in this field have been given elsewhere (184, 185, 207, 518).

A. Catecholamines

A comparison of the levels of noradrenaline and adrenaline found in the heart, urinogenital organs, gut, lungs, and spleen and in the adrenal gland of different vertebrates is summarised in tables 1, 2, 3 and 4. It can be seen that, in general, the predominant catecholamine in sympathetically innervated tissues in elasmobranch fish, reptiles, birds and mammals is noradrenaline whereas, in teleost fish and amphibia it is adrenaline. This distribution appears to be the reverse of the proportions of noradrenaline and adrenaline contained in the adrenal gland, *i.e.*, noradrenaline is predominant in amphibia, while adrenaline is the predominant catecholamine in the mammalian adrenal gland. An intermediate situation is found in reptiles.

In amphibia, where adrenaline is the predominant catecholamine in sympathetically innervated tissues there are very high levels of N-methyltransferase, which is the catalyst for conversion of noradrenaline to adrenaline, compared to tissue levels in other vertebrate classes (360). Another enzyme that can N-methylate noradrenaline to adrenaline has been isolated from toad parotid gland (and rabbit lung) and opens up the possibility of an alternate pathway for the formation of adrenaline in some species, *i.e.*, dopamine → epinine → adrenaline.

Catechol-O-methyltransferase activity has been found in fish, amphibian, and avian as well as mammalian tissues (26, 463). Monoamine oxidase has also been demonstrated in lower vertebrates (331, 363, 390).

There are very high levels of catecholamines and particularly adrenaline in the hearts of cyclostomes, but this is mostly localised in special chromaffin-type cells rather than in nerves (24, 65, 291, 302, 422, 423).

Apart from noradrenaline and adrenaline, high levels of dopamine have been found in the pacemaker region (sinus venosus) of the frog heart, and it has been suggested that dopaminergic nerve fibres may supply this region of the heart (15). Similarly high levels of dopamine have been found in the sino-auricular node in mammals (13a, 14).

From considerations of the distribution and metabolism of catecholamines in the nervous system of vertebrates, Pscheidt (438) has proposed that during phylogenetic development, the functional catecholamine has shifted from adrenaline through noradrenaline to dopamine. In mammals all three amines are present in nerve tissue, but each is found as the predominant amine in specialised structures. This was viewed as an evolutionary development designed to provide greater specificity in neurochemical function.

B. Acetylcholine

High levels of choline acetylase, acetylcholine and cholinesterase have been reported in visceral organs of all vertebrate classes (22, 30, 203, 437, 520), and acetylcholine has been established as a transmitter substance in the autonomic system of many species (245, 346, 397).

Amphibians contain a cholinesterase that is inhibited by neostigmine, but not by physostigmine (43). Several workers have noted that tissues containing pseudocholinesterase in mammals contain only true cholinesterase in lower vertebrates (23, 41, 43, 128, 469, 474), and it has been suggested that the appearance of en-

TABLE 1

Distribution of noradrenaline and adrenaline in heart

Class	Animal	Tissue	Assay Method	Noradrenaline μg/g	Adrenaline μg/g	Reference
Fish	*Myxine glutinosa* (hagfish)	Whole heart	Bio	0.83	5.0	422
Cyclostomes	*Myxine glutinosa* (hagfish)	Atrium	Fluorometric	18	8.1	186
		Ventricle		6.5	59	
	Lamprey	Whole heart	Bio	5.0	19.1	24
		Atrium		19.0	41.2	
		Ventricle		0.8	12.5	
Elasmobranchs	*Squalus acanthias* (dogfish)	Atrium	Fluorometric	0.78	<0.02	186
		Ventricle		0.09	<0.02	
		Whole heart		0.095	0.03	
	Raja batis (ray)	Whole heart	Bio	0.087	0.025	422
Teleosts	*Gadus callarias* (cod)	Whole heart	Fluorometric	<0.02	0.17	186
	Salmo trutta (trout)	Heart	Fluorometric	0.18	0.4	224
Amphibia	*Rana temporaria* (frog)	Whole heart	Fluorometric	0.1–0.3	0.8–1.0	15
		Ventricle		<0.1	17.0	
	Rana pipiens (frog)	Sinus venosus		0.9	2.49	
		Whole heart		0.01	1.38	
	Rana pipiens (frog)	Whole heart	Fluorometric		1.2	84
	Rana catesbeiana (frog)	Sinus venosus	Fluorometric	0.01	0.41	15
		Atria		0.01	0.41	
		Ventricle		<0.01	0.12	
		Whole heart		<0.01	0.12	
	Rana cinerea (frog)	Whole heart	Fluorometric		0.96	84
	Bufo terrestris (toad)	Sinus venosus	Fluorometric	0.13	3.58	15
		Atria		0.04	2.14	
		Ventricle		<0.01	2.08	
		Whole heart		0.01	2.09	
	Bufo americanus (toad)	Whole heart	Fluorometric		1.8	84
	Bufo marinus (toad)	Sinus venosus	Fluorometric	0.06	4.92	15
		Atria		0.08	3.89	
		Ventricle		<0.01	2.08	
		Whole heart		0.01	2.09	
	Bufo marinus (toad)	Whole heart	Fluorometric		7.6	84
	Newts	Whole heart	Fluorometric	0.57	0.01	15
Reptiles	*Tiliqua rugosa* (lizard)	Atria	Fluorometric	2.54	0.34	139
	Alligator	Heart	Bio and fluorometric	1.20	0.16	17
	Turtle	Heart		0.43	0.09	
	Snake	Heart		0.64	0.07	

TABLE 1—*Continued*

Class	Animal	Tissue	Assay Method	Noradrenaline μg/g	Adrenaline μg/g	Reference
Birds	Fowl	Heart	Fuorometric	0.24		185
	Magpie	Heart	Fluorometric	0.6–1.1	0.02	475
Mammals	Guinea-pig	Heart	Bio and fluorometric	1.80	0.20	17
	Nyctalus noctula (bat)	Whole heart	Fluorometric	0.92, 0.88		404
	Citellustri decemlineatus (ground squirrel)	Whole heart	Fluorometric	1.51, 1.03		404
	Erinaceus europaeus (hedgehog)	Whole heart	Fluorometric	1.18 ± 0.07		404
	Mouse	Heart	Bio and fluorometric	0.45	0.10	17
	Albino mouse	Whole heart	Fluorometric	0.65 ± 0.05		404
	Rat	Heart	Fluorometric	0.27	0.05	17
		Heart		0.6		268
		Heart		0.5		339
	Albino rat	Atrium	Fluorometric	1.19 ± 0.20		404
		Ventricle		0.46 ± 0.06		
	Dog	Heart	Bio and fluorometric	1.01	0.11	17
	Rabbit	Heart		0.17–0.54	0.045–0.094	274
	Sheep	Heart	Bio and fluorometric	1.05	0.17	17
		Heart		0.6–1.1		236
	Cow	Heart	Fluorometric	0.3–0.6		236
		Arteries and veins		0.3–0.5		
	Cat	Heart		0.5–1.0		185
	Cat	Atrium	Fluorometric	1.20 ± 0.11		404
		Ventricle		1.52 ± 0.08		
	Man	Heart	Bio and fluorometric	1.04	0.18	17

zymes with the properties of classical pseudocholinesterases is a relatively late evolutionary development (23, 128).

C. Other substances

5-Hydroxytryptamine has been found in the male reproductive tract of dogfish (358), in the skin of many amphibians (178, 179, 498, 519), in the frog and rabbit lung, in the intestinal mucosae of most vertebrates, in the lizard oviduct and in frog urinary bladder (84, 180, 519) (see table 5). However, it seems more likely that the 5-hydroxytryptamine is contained in chromaffin-type cells rather than in autonomic nerves.

High levels of *substance P* have been found in the intestines of teleosts (*Gadus callarias*), elasmobranchs (*Raja batis* and *Squalus acanthias*), and cyclostomes (*Myxine glutinosa*) (144, 187), as well as in mammal intestine (435, 454).

"*Darmstoff*," a biologically active lipid anion has been extracted from a num-

TABLE 2

Distribution of noradrenaline and adrenaline in urino-genital organs

Class	Animal	Organ	Assay Method	Noradrenaline μg/g	Adrenaline μg/g	Reference
Fish	*Myxine glutinosa*	pronephos	Fluorometric	6.3	<0.02	386
Cyclostomes	(hagfish)	Kidney		16	<0.02	
Elasmobranchs	*Squalus acanthias* (dogfish)	Kidney		19	1.9	
Teleosts	*Gadus callarias* (cod)	Kidney		<0.02	45	
Amphibia	*Bufo marinus* (toad)	Bladder	Fluorometric	0.17	1.4	386
	Rana temporaria (frog)	Bladder	Fluorometric	0.23	1.86	385
Reptiles	*Trachysaurus rugosus* (lizard)	Bladder	Fluorometric	0.40	0.11	387
	Turtle	Ovary	Bio and fluorometric	0.04	0.17	17
	Tortoise (greek)	Vas deferens	Fluorometric	17		475
Birds	Cock	Vas deferens	Fluorometric	9.1	1.4	475
Mammals	Guinea-pig	Ovary	Bio and fluorometric	0.74	0.15	17
		Vas deferens		10.0		475
		Testis	Fluorometric	0.02	<0.05	171
		Kidney		0.44	0.11	17
	Mouse	Vas deferens	Bio and fluorometric	6.0		475
		Kidney		0.32	0.06	17
	Rat	Ovary	Bio and fluorometric	0.20	0.05	17
		Vas deferens	Fluorometric	8.0		475
		Testis		0.01	0.01	17
		Kidney	Bio and fluorometric	0.10	0.03	17
	Dog	Ovary	Bio and fluorometric	2.83	0.41	17
		Vas deferens		1.0		475
		Kidney		0.32	<0.05	17
	Rabbit	Vas deferens	Fluorometric	7.0		475
		Testis		0.04	<0.05	171
	Cat	Vas deferens	Fluorometric	6.68	0.12	171
		Testis		0.21	<0.05	
	Sheep	Kidney	Bio and fluorometric	0.28	0.07	17
	Bull	Vas deferens	Fluorometric	7.0		475
	Man	Ovary	Bio and fluorometric	0.92	0.18	17
		Testicle		0.54	0.12	

TABLE 3

Distribution of noradrenaline and adrenaline in gut, lungs and spleen

Class	Animal	Organ	Assay Method	Noradrenaline μg/g	Adrenaline μg/g	Reference
Fish	*Squalus acanthias* (dogfish)	Spleen	Fluorometric	0.096	0.025	186
Elasmobranchs		Intestine		0.33	0.03	
Teleosts	*Gadus callarias* (cod)	Spleen	Fluorometric	0.06	0.16	186
		Intestine		0.06	0.08	
	Gastrophysis gaber (toadfish)	Stomach	Fluorometric	0.108	0.290	415
		Intestine		0.067 ± 0.01	0.169 ± 0.02	
	Salmo trutta (trout)	Stomach	Fluorometric	0.06	0.079	415
		Intestine		0.06	0.036	
	Carassius auratus	Stomach	Fluorometric		0.35	84
		Small intestine			0.64	
Amphibia	*Bufo marinus* (toad)	Stomach	Fluorometric	0.041	0.338	415
		Intestine		0.355	0.828	
		Rectum		0.196	0.663	
	Bufo marinus (toad)	Lung	Fluorometric	0.12	1.72	388
	Bufo marinus (toad)	Stomach	Fluorometric	1.1	1.2	84
		Small intestine			3.4	
	Bufo americanus (toad)	Stomach	Fluorometric	0.64	0.50	84
		Small intestine		0.95		
	Hyla aurea (frog)	Stomach	Fluorometric	0.126	0.381	415
	Rana pipiens	Stomach	Fluorometric	0.44	0.46	84
		Small intestine		<0.06	0.61	
	Rana crinerea	Small intestine	Fluorometric	0.44		84
Salamander	Desmognathus	Stomach	Fluorometric	1.1		84
		Small intestine		3.0		
	Axololl tigrinum	Stomach	Fluorometric	0.67		84
		Small intestine		0.38		
	Necturus maculous	Stomach	Fluorometric	1.3		84
		Small intestine		0.22		
Reptiles	Alligator	Spleen	Bio and fluorometric	2.00	0.03	17
	Snake	Spleen	Bio and fluorometric	0.43	0.10	17
		Lung		0.10	0.07	
	Trachysaurus rugosus (lizard)	Lung	Fluorometric	0.45	0.04	389
	Sauria cyanogenys (lizard)	Stomach	Fluorometric	0.76		84
		Small intestine		0.85		
Birds	Fowl	Stomach muscle	Fluorometric	0.063		185
		Small intestine		0.19		
Mammals	Guinea-pig	Lung	Bio and fluorometric	0.01	0.04	17
		Spleen		0.43	0.10	
	Mouse	Lung	Bio and fluorometric	0.03	0.08	17
		Spleen		0.23	0.04	

TABLE 3—*Continued*

Class	Animal	Organ	Assay Method	Noradrenaline μg/g	Adrenaline μg/g	Reference
	Rat	Lung	Bio and fluorometric	0.02	0.02	17
		Spleen		0.47	0.07	
	Rat	Stomach	Fluorometric	0.36		84
		Small intestine		0.35		
	Rabbit	Stomach	Fluorometric	0.19		471
		Small intestine		0.3		
	Dog	Spleen	Bio and fluorometric	1.31	0.05	17
	Sheep	Lung	Bio and fluorometric	0.22	0.09	17
		Spleen		5.75	0.40	
	Cow	Lung		0.05		185
	Man	Lung	Bio and fluorometric	0.04	0.03	17
		Spleen		0.08	0.02	

TABLE 4

*Distribution of noradrenaline and adrenaline in adrenal gland**

Class	Animal	Assay Method	Noradrenaline μg/g	Adrenaline μg/g
Amphibia	Frog	Bio and fluorometric	167.1	136.8
Reptiles	Alligator	Bio and fluorometric	321.5	373.05
Mammals	Guinea-pig	Bio and fluorometric	2.50	84.93
	Mouse		96.60	320.00
	Rat		172.00	600.00
	Dog		270.94	289.68
	Sheep		296.90	866.10
	Man		86.79	1173.20

* Figures taken from Anton and Sayre (17).

ber of mammalian intestinal preparations (508). It has been suggested that it may be an atropine-resistant postganglionic excitatory transmitter (9).

The natural occurrence of *histamine* was first demonstrated by Barger and Dale (33) and it has since been shown to have a wide distribution. It is particularly abundant in the skin, lungs, and intestinal wall of adult mammals (164, 204) and has been shown to be present in sympathetic postganglionic nerves, although the existence of functional histaminergic nerves has not been established since mast cells are contained within the perineurium (184, 384). Mammalian foetal tissue contains relatively little histamine (307). There are few reports of histamine in lower vertebrate visceral organs.

IV. LUNG

The lungs of all vertebrates are homologous, since they develop embryologically from an evagination of the pharyngeal region of the gut (398). The air

TABLE 5

Distribution of 5-hydroxytryptamine in various species of vertebrates

Class	Animal	Organ	Assay Method	5-Hydroxytryptamine μg/g	Reference
Fish	*Carassius auratus*	Stomach	Fluorometric	1.1	84
Teleost		Small intestine		1.1	
	Amerurus nebulosus	Stomach	Fluorometric	0.15, 0.36	519
		Small intestine		0.40, 0.46, 0.74	
		Spleen		<0.02	
		Kidney		<0.04	
Holostean	*Amia calva*	Stomach mucosa	Fluorometric	1.6	84
		Small intestine		1.2	
Amphibians	*Rana pipiens*	Stomach	Fluorometric	3.0	84
Frogs		Small intestine		5.4	
	Rana cinerea	Stomach	Fluorometric	3.6	
		Small intestine		4.8	
	Rana catesbeiana	Small intestine	Fluorometric	1.9	
		Lungs		<0.03	
		Spleen		<0.08	
Toads	*Bufo americanus*	Stomach	Fluorometric	2.6	
		Small intestine		5.1	
	Bufo marinus	Stomach	Fluorometric	2.7	
		Small intestine		7.1	
Salamanders	Desmognathus	Stomach	Fluorometric	3.0	
		Small intestine		5.0	
	Axolotl trigrinum	Stomach	Fluorometric	1.1	
		Small intestine		2.1	
	Necturus maculosus	Stomach	Fluorometric	1.7	
		Small intestine		1.5	
Reptiles	*Sauria cyanogenys* (lizard)	Stomach	Fluorometric	2.2	84
		Small intestine		6.9	
Mammals	Rabbit	Stomach	Fluorometric	5.0	499
		Small intestine		10.0	
	Rat	Stomach	Fluorometric	0.6	84
		Small intestine		2.0	499

(or swim) bladder of fish also arises from a pharyngeal diverticulum and will therefore be dealt with in this section. Despite this homology, comparison of the innervation of the lung musculature of mammals with that of lower vertebrates is difficult, since according to Bronkhorst and Dijkstra (85), it is the mammalian interstitial muscle described by Baltisberger (31), rather than the bronchial muscle, which is homologous with the lung musculature of amphibians and reptiles. There is evidence that the interstitial musculature, like the bronchial musculature, is under excitatory vagal control (37), but there are no reports of the presence or absence of an inhibitory innervation of these muscles. The large body of literature concerned with the innervation of the mammalian lung is confined to the bronchial musculature.

A. Mammals

Many investigations of the innervation of the mammalian lung have been made, and it has been shown that the smooth muscle of the bronchi, bronchioles, and trachea is under the control of antagonistic vagal cholinergic excitatory and sympathetic noradrenergic inhibitory fibres (158, 522). The presence of some adrenergic fibres of sympathetic origin running in the vagal trunks to the lungs has also been suggested, as well as some cholinergic component in the sympathetic nerves (25). High levels of isoprenaline have been found in the cat lung. This was at first thought to represent inhibitory neurotransmitter (344), but was later shown to be of non-nervous origin (166, 452).

B. Fish

In some *teleost fish*, the air (or swim) bladder retains its opening to the pharynx and is filled by the fish gulping air. However, in the majority of teleosts, the air bladder has assumed a dorsal position, the pneumatic duct has closed off, and its role is switched to that of flotation, *i.e.*, it is a hydrostatic organ that controls the depth of the fish in the water. The air bladder is provided with special glands by which it is filled and the gas they secrete is mostly oxygen. In the more primitive forms gas is secreted all over the surface of the air bladder, but later special anterior oxygen-secreting and posterior oxygen-absorbing regions are developed. The mechanism of gaseous filling (secretion) and emptying (absorption) of the swim bladder is complex (117, 196, 198), and autonomic nerves are likely to be involved in controlling a variety of structures and processes, including the muscularis mucosae, the oxygen-secreting and -absorbing glands, the rate of blood flow through the secretory and resorptive epithelium, and the secretory cells themselves.

The muscularis mucosae of the swim bladder consists of two regions of smooth muscle, one of which is contracted by adrenaline and noradrenaline, but unaffected by acetylcholine; the other region is relaxed by catecholamines and contracted by acetylcholine. Both regions are supplied by fibres from the vagus nerve (196, 198). The vagus nerves contain nerve fibres that increase swim bladder secretion or filling (66). These fibres are probably cholinergic since atropine, like vagotomy, inhibits gas secretion into a deflated swim bladder (196, 198), but it is not yet clear what structures they act on. Other fibres in the vagus that produce emptying are adrenergic nerves; they act by contracting the secretory portion and relaxing the resorptive portion of the muscularis mucosae as well as causing vasodilitation in the resorptive region (196, 198). The adrenergic component in the vagus trunk is probably of sympathetic origin, joining the vagus intracranially (198). Recent fluorescent histochemical studies have confirmed the pharmacological evidence of Fänge (198) that there is adrenergic innervation of blood vessels throughout the swim bladder and of the muscularis mucosae (189, 190). Many, if not all, of the adrenergic neurones have their cell bodies in or near the swim bladder (190), and this explains why vagotomy does not alter catecholamine levels in this organ (186).

In addition to the adrenergic fibres to the swim bladder running in the vagosympathetic trunk, there is a direct sympathetic innervation by a branch of the

splanchnic nerve. These nerves appear to be concerned with the emptying rather than filling process, possibly by vasoconstrictor control in the gas gland (198), or possibly by peripheral inhibitory control of adrenergic neurones in the gas gland ganglion, since fluorescent varicose fibres have been shown to surround many ganglion cell bodies (190). Both *alpha-* and *beta*-adrenotrophic receptors have been demonstrated in the secretory part of the eel swim bladder, but only *beta*-receptors in the pneumatic duct (406).

In *lung fishes*, the air bladder has the form of a pair of lobes comparable to the arrangement of tetrapod lungs. There has been one pharmacological study of the lung of *Protopterus*, and this gives some indirect information about its innervation (298). Acetylcholine produced contraction of lung strips except when the muscle had been treated with atropine. Adrenaline and noradrenaline caused relaxation of the lung strips.

C. Amphibians

There have been several physiological studies on the innervation of anuran lungs (82, 125, 278, 387, 470, 505, 529). Carlson and Luckhardt (125, 126, 348–350) attempted to discern evolutionary trends in the control of amphibian and reptile lungs, with special reference to the central control of respiration.

Stimulation of the extracranial vagus nerve produced both contraction and relaxation of the lung of the frog (82, 125, 278) and of the toad (470, 529). Stimulation of the cervical sympathetic trunk above its union with the vagus nerve revealed that most, if not all, of the excitatory fibres to the frog and toad lung are sympathetic in origin, whilst all of the inhibitory fibres and possibly a few excitatory fibres are of vagal origin (125, 127, 470, 529). Wood and Burnstock (529) demonstrated that excitatory and inhibitory responses of the lung of the toad (*Bufo marinus*) could be obtained separately by varying the parameters of the pulses used to stimulate the nerve. The excitatory nerves appear to be cholinergic since: (i) the nerve-mediated contraction is readily abolished by atropine and potentiated by neostigmine; (ii) the rate of change of optimal frequency of stimulation with temperature, 2.06 pulses/sec/°C, is like that found for cholinergically innervated preparations (121); and (iii) low concentrations of acetylcholine cause contraction of the lung, mimicking the action of the nerve. Acetylcholine has also been shown to contract the lungs of other amphibians (80, 155, 278, 318, 505, 527).

Most of the excitatory fibres in the vagal trunk are probably postganglionic, since the ganglion-blocking agent mecamylamine had little effect on the nerve-mediated contractions of the lung (529). In their studies of the innervation of the frog lung *in vivo*, Carlson and Luckhardt (125) found that injections of nicotine abolished the inhibition, but not the contraction, caused by stimulation of the vagus nerve. Ganglia and isolated ganglion cells have been demonstrated histologically along the course of the main vagosympathetic nerve branches on the surface of the lungs of anurans (388, 477, 528), and ganglion cells have also been seen in the smooth muscle bundles of the lung (419). The response to stimulation of the vagus nerve stump 25 to 40 days after section of the nerve in a region just beyond the point of junction with sympathetic trunks was always excitatory

(529). This can be taken as evidence that the ganglion cells found within the proximal regions of the vagus nerve (388) are predominantly cholinergic. It seems likely too, that most of the fibres from the sympathetic nerves that join the vagus trunk near the cranium synapse with these cholinergic neurones, since there was no detectable change in the response of the lung to vagus nerve stimulation or in the composition of fibres in the vagus nerve trunk after degenerative section of the cervical sympathetic nerves. Further support for this conclusion is that stimulation of the amphibian lung *via* the cervical sympathetic nerves produces only contraction, which is blocked by atropine (125, 470).

Excitatory innervation of the lung of salamanders (urodels), the most primitive living amphibians, has not been demonstrated (348, 350).

There is evidence for the existence of inhibitory ganglion cells in the wall of the lung and within the portion of the vagal trunk proximal to the lung (529). Firstly, mecamylamine reduced the inhibitory response to stimulation of the vagus nerve. Secondly, transmural stimulation of the lung produced inhibition after either unilateral or bilateral degenerative section of the vagus nerves. Thirdly, the ganglion-stimulating drug DMPP (dimethylphenylpiperazinium) caused inhibition in both normal lungs and lungs examined after vagal denervation.

The inhibitory response of the lung to stimulation of the vagus nerves is not blocked by adrenergic-neurone-blocking agents (115, 119, 529). Furthermore, chronic treatment with reserpine and 6-hydroxydopamine, which deplete the nerves of noradrenaline, does not impair the inhibitory response (453). The large granular vesicles characteristically abundant in the many nerve fibres in the lung as well as in the gut, where nonadrenergic inhibitory fibres are known to be present, are still present after catecholamine depletion (453). Thus, it seems likely that most of the inhibitory responses of the lung to vagal stimulation are due to preganglionic cholinergic nerves forming synapses with intramural inhibitory nonadrenergic neurones in the wall of the lung that contain an unknown transmitter similar to that reported in mammalian and amphibian gut (108, 115). A small proportion of the inhibitory fibres may be adrenergic since: (i) the inhibitory response to vagal stimulation is reduced by adrenergic blocking agents (529); (ii) a small number of adrenergic nerves has been demonstrated in both the vagal trunks and in the lung musculature with the fluorescent histochemical method (388); and (iii) adrenaline and noradrenaline mimic the nerve action, *i.e.*, cause inhibition. Catecholamines also relax the frog lung (82, 125, 278), and adrenaline causes relaxation, sometimes preceded by a small contraction, of the isolated lung of the Japanese toad (318). The adrenergic inhibitory transmitter is likely to be adrenaline rather than noradrenaline, since it is the predominant catecholamine found both with spectrofluorometric assay of tissue extracts of the lung and with the fluorescent histochemical method (38). Many of the adrenergic inhibitory fibres are considered to be postganglionic, since mecamylamine blocked vagal inhibition incompletely and since the inhibitory response to transmural stimulation was reduced after vagal denervation. Some of these fibres may be axons originating from intramural adrenergic neurones (388).

D. Reptiles

The first observations on the nervous control of the lizard lung were made by Bert (58), who showed that stimulation of the vagus nerve caused contraction of the lung. In a study of respiration of lizards, Francois-Frank (214) investigated the effects of stimulation of the vagus nerve *in situ* and also concluded that it contained excitatory fibres to the lung musculature. There have been several physiological and pharmacological studies of the innervation of the lungs of turtles and tortoises (Chelonia) (126, 138, 213, 286, 349, 504) and of the lungs of a snake (126, 349). Several investigations of the anatomy of the innervation of reptilian thoracic viscera have also been made (2, 226, 230, 286). Chelonian lungs have been reported to receive excitatory fibres from the vagus nerve on the ipsilateral side only (126). However, in lizards, stimulation of either vagus nerve causes contraction of both lungs, so some crossing-over of the excitatory vagal fibres to the lungs occurs in this order (111,214).

Inhibitory fibres supplying the reptilian lung *via* the vagosympathetic trunk were reported only once in the early literature, in a turtle (504). It is possible that the recording conditions used *in vivo* by many of the earlier workers were not suitable to show inhibitory responses, since in a recent study by Burnstock and Wood (111) inhibitory fibres were demonstrated in the lung of the sleepy lizard (*Trachysaurus rugosus*). Stimulation of the vagus nerve usually caused a contraction of the lung followed by a relaxation. These responses were caused by separate excitatory and inhibitory fibres, since a contraction was obtained without any following inhibition by using appropriate strengths, durations, and frequencies of the stimulating pulses. Conversely, a nerve-mediated relaxation alone was obtained after abolition of the contraction by appropriate autonomic blocking drugs.

The majority of inhibitory fibres in the vagosympathetic trunk to the lung are of sympathetic origin (111). Jackson and Pelz (286) described nerves running from the sympathetic chain directly to the lungs in some species of Chelonia (although not in others), and stated that stimulation of the sympathetic chain in the neck caused relaxation and occasionally contraction of the lung in these species. However, Carlson and Luckhardt (126) could not detect any sympathetic fibres passing directly to the lung in chelonians, nor did they find any effect of stimulation of the sympathetic chain on the chelonian lung, a finding in agreement with that of Francois-Franck (213) and Burnstock and Wood (111). These differences in results may be species differences, or may be due to seasonal variations in the actions of the nerves (286).

There is strong pharmacological evidence that the excitatory fibres innervating the lizard lung musculature are cholinergic: the response to low concentrations of applied acetylcholine mimics the excitatory response to nerve stimulation, and atropine blocks and eserine potentiates the contractions caused by both nerve stimulation and by applied acetylcholine (111). Atropine also abolishes excitatory action of the vagus nerve on the turtle (213, 349) and snake (349) lung. Furthermore many of the axon profiles in the lizard lung contain only

agranular vesicles (107). Thus, the excitatory vagal fibres to the lung musculature in all reptiles appear to be cholinergic.

Many of the inhibitory fibres to the lizard lung are probably adrenergic. Noradrenergic nerves supplying the smooth muscle of the lungs of the sleepy lizard have been demonstrated with a fluorescent histochemical method (389). Noradrenaline is also the predominant catecholamine by spectrofluorometric assay of tissue extracts of the lung (0.47 μg/g noradrenaline; 0.04 μg/g adrenaline; 481). The pharmacological results described by Burnstock and Wood (111) are consistent with this view. Low concentrations of noradrenaline cause relaxation of the lizard lung. However, since the adrenergic nerve blocking agents guanethidine and bretylium reduce, but never block, the nerve-mediated inhibition, some inhibitory fibres that release a nonadrenergic transmitter are probably also present.

The excitatory and inhibitory responses of the lizard lung to vagus nerve stimulation were reduced by mecamylamine. This suggests that some fibres of each type may be stimulated preganglionically (111). Groups of ganglion cells have been observed along the course of the major branches of the vagus in the lizard lung, but specific noradrenergic fluorescence in such ganglia is rare (389). Jones (303) described ganglia in the base of the lungs of turtles and snakes from which postganglionic axons were distributed to the smooth musculature of the bronchi and lungs. Luckhardt and Carlson (349) found that ganglion-blocking doses of nicotine abolished the action of the vagus nerve on the lung of the snake, but not of the turtle. Veach (504), however, found that nicotine did block the excitatory action of the vagus on the turtle lung.

Few studies have been made on the nervous control of the lung in birds. However, it has been shown recently that stimulation of the vagus nerves to the isolated lungs of the bird (*Gallus domesticus*) produced contraction of the bronchial musculature, as did acetylcholine, while noradrenaline caused relaxation (141).

E. Summary

The data obtained so far on the innervation of the vertebrate lung shows the following evolutionary trends (see fig. 1).:

1) Excitatory nerves to the lung have been demonstrated in anuran amphibians, reptiles, birds, and mammals, where they are cholinergic. In anurans the excitatory cholinergic fibres run in the vagosympathetic trunks and are largely, if not entirely, of sympathetic origin. In contrast, in reptiles and mammals, the excitatory cholinergic fibres are largely, or wholly, of vagal parasympathetic origin. Excitatory innervation of the lung has not been seen in the salamanders (urodeles), the most primitive amphibian group.

2) Inhibitory innervation of the lung has been demonstrated in urodele and anuran amphibians, in some (but not all) reptiles, and in mammals. The inhibitory nerves in urodele and anuran amphibians are largely, if not entirely, of vagal origin. Most if not all, of these inhibitory vagal fibres are not adrenergic but release an unidentified transmitter substance to the amphibian lung. In reptiles, birds, and mammals, the majority of the inhibitory fibres are of sympathetic origin, and contain noradrenaline.

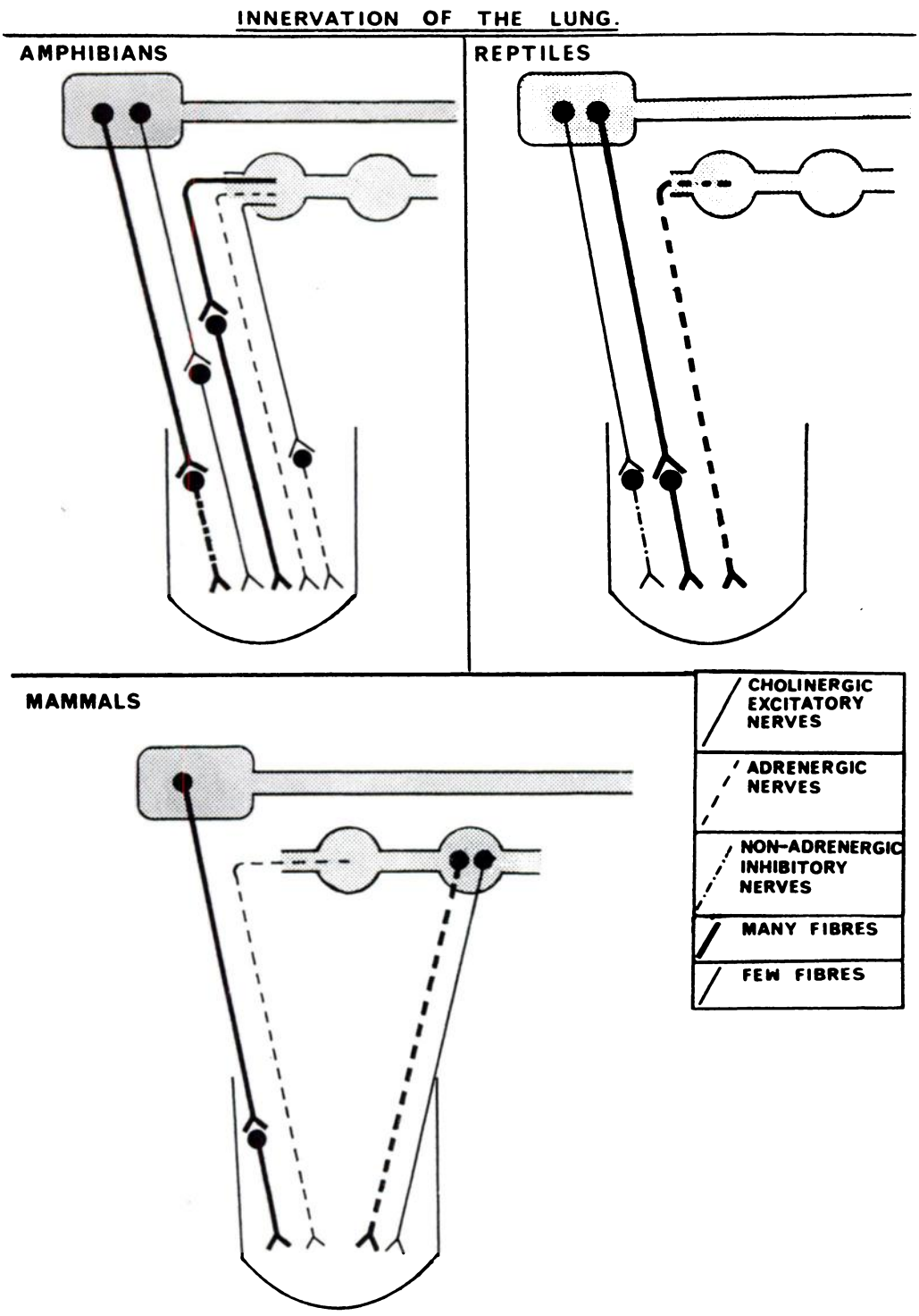

FIG. 1. Diagrammatic representation of the autonomic innervation of the vertebrate lung. Central nervous system and sympathetic chain are represented by the shaded areas. Note that all the fibres supplying the lung in amphibians and reptiles run in vagosympathetic trunks, whereas in mammals there are separate vagal and sympathetic nerves. The striking feature of the phylogeny of lung innervation is the exchange of cholinergic function from the sympathetic to the cranial parasympathetic outflow between the amphibians and reptiles.

3) The striking feature about this picture is that there is an exchange of sympathetic and parasympathetic function at some evolutionary stage between the amphibians and reptiles.

4) Autonomic nervous control of the air (or swim) bladder of teleost fish is complex and sophisticated in comparison with the nervous control of other systems in fish; in particular there is an extensive development of sympathetic adrenergic nerves to the musculature, blood vessels, and gas glands as well as pericellular networks about neurone cell bodies associated with the swim bladder, presumably concerned with modulation of ganglion activity.

V. URINARY BLADDER

The urinary bladder is not derived from the same embryonic tissues in all vertebrate classes. The bladders of mammals, reptiles, and amphibians are largely of endodermal origin, formed from ventral diverticula of the hind gut or cloaca (398). In addition, in mammals some parts of the neck of the bladder (the trigone) are derived from the mesodermal tissues of the ureters. In amphibians and most reptiles it seems unlikely that there is any contribution to the bladder from ureteral tissues, since the ureters open directly into the cloaca and do not at any stage enter the bladder directly. The bladder in teleost and ganoid fish is not homologous with the bladder of higher vertebrates, since it is formed by the expanded ends of the mesodermal tissues of the mesonephric ducts. There is no urinary bladder in elasmobranch fish or birds.

A. Mammals

There have been a large number of accounts of the physiology and pharmacology of the mammalian bladder (see Gruber, 244, Edvardsen, 168). The presence of a cholinergic excitatory innervation of the bladder is well established for placental mammals (131, 173, 247, 256, 279, 500,503), and has also been demonstrated in a marsupial mammal (103). The main evidence that the excitatory fibres are cholinergic in mammals (and also in other classes) is that atropine reduces and anticholinesterases potentiate the nerve-mediated contractions, and that acetylcholine causes contraction of the bladder. Many of the excitatory nerves to the bladder are considered to be postganglionic, since ganglion-blocking agents reduce the nerve-mediated contractions, and ganglion cells containing high levels of acetylcholinesterase have been demonstrated in the bladder wall (170). However, it seems unlikely that all excitation of the vertebrate bladder is due to cholinergic nerves. There have been many reports of only partial block of the excitatory response of the mammalian bladder to atropine (247, 500). This has also been reported in the bladder of teleost fish (542), amphibia (108), and marsupials (103). Some authors have interpreted this result in terms of "atropine-resistance" of cholinergic nerves to the bladder (*e.g.*, 279, 500). Other authors have suggested the alternative explanation that there are noncholinergic excitatory nerves with an unknown transmitter (131, 256). Atropine-resistant excitatory responses of the longitudinal muscle of the intestine have also been interpreted in terms of noncholinergic excitatory nerves (10). It is not yet known

whether the transmitter substance involved is the same as or different from that released by nonadrenergic inhibitory nerves in the gut, where recent work (461a) suggests that it is adenosine triphosphate or an analogue.

There has been much argument as to whether an adrenergic excitatory innervation of the mammalian urinary bladder exists. Various authors have demonstrated excitatory responses of the mammalian bladder to stimulation of the sympathetic innervation (173, 329, 365, 366), and some pharmacological evidence suggests that this contraction is mediated by adrenergic nerves (167). It has been claimed that the excitatory response occurs only in the trigonal area of the bladder (173), but Kuntz and Saccomanno (329) have shown contractions in what was apparently purely fundal tissue. This question has still not been answered conclusively. It is interesting in this context that the bladders of amphibians and reptiles do not contain a "trigonal" component, since the ureters do not enter the bladder directly. The lizard bladder, which may be regarded as purely "fundal," appears to have an adrenergic excitatory innervation.

The presence of a central or peripheral inhibitory mechanism to delay reflex micturition, initiated by distention of the bladder wall, is necessitated by the habits of many higher vertebrates. Adrenergic inhibitory fibres innervate the mammalian bladder (167, 173, 365, 366). Fluorescent histochemical studies of the cat bladder (248, 411) have shown that noradrenergic innervation is most dense in the trigone region, with both intramural adrenergic ganglion cells and abundant fluorescent varicose terminals about nonfluorescent ganglion cells. It has been suggested that fluorescent pericellular nerve endings on intramural nerve cells provide an adrenergic modulation of ganglionic transmission (413, 511). The fluorescent terminals on intramural ganglion cells of the cat bladder may be processes from intramural adrenergic ganglion cells (249, 413).

One feature of pharmacological interest is that the possum bladder is relaxed by low concentrations of histamine (103); relaxation by histamine has not been demonstrated in other visceral tissues, except the rat uterus (250).

B. Teleost fish

There is only one account of the innervation of the fish bladder. Young (542) demonstrated contraction of the bladder of the angler fish, *Lophius piscatorius* and *Uranoscopus scaber*, in response to stimulation of the vesicular nerves, which pass from the abdominal sympathetic ganglia to the viscera. The nature of the excitatory transmitter was not clearly resolved, but it may be acetylcholine. Low concentrations of acetylcholine mimicked the excitatory action of the nerves. Atropine partially blocked the nerve-mediated contractions in only a small proportion of the experiments, but did not rapidly inhibit the contractions produced by applied acetylcholine. Young (542) concluded that the action of acetylcholine on the bladder was "nicotine-like rather than muscarine-like." Ergotoxine did not inhibit the capacity of the nerve or acetylcholine to cause contraction.

Nerve cell bodies have been shown to be scattered along the vesicular nerves, so that many of the excitatory fibres are likely to be postganglionic. No inhibitory innervation was seen in the bladder of the angler fish (542).

C. Amphibians

Several workers have shown with both anatomical and physiological techniques that frog and toad bladders receive motor autonomic fibres from the sixth, seventh, eighth, ninth and tenth spinal nerves, although never from all these nerves in any one animal (146, 276, 317, 334, 335).

Cholinergic excitatory innervation of the bladder has been demonstrated in amphibians (43, 108, 385). Histochemical studies showing high concentrations of acetylcholinesterases localised in some intramural nerves in the bladder wall give further evidence for the presence of a cholinergic nerve supply (41, 385). These studies have also shown that many cholinergic nerves arise from neurone cell bodies in the bladder wall. Ganglia have also been demonstrated histologically in the wall of the frog bladder (39, 57, 262). Further evidence that many of the excitatory fibres that supply the bladder are preganglionic is that ganglion-blocking agents reduce the nerve-mediated contractions (108). The excitatory responses to nerve stimulation are only partially blocked by atropine (108), a result that could be interpreted to indicate that some noncholinergic excitatory fibres are also present.

No inhibitory responses to nerve stimulation were observed in the toad bladder (108), although a small number of adrenergic nerve fibres to the muscles have been observed histochemically and catecholamines usually reduce spontaneous activity (386). Many adrenergic nerves supply the muscles of the bladder of the frog (192, 385), and assays of tissue extracts of the bladder have shown high levels of catecholamines: 1.86 μg/g adrenaline and 0.23 μg/g noradrenaline (481). However, it is unlikely that these nerves have an inhibitory action, since directly applied catecholamines usually cause contraction (3, 385), and nerve-mediated contractions are blocked by phentolamine (385). It is possible that inhibitory control is mediated by circulating catecholamines in amphibians (and also in fish) or it may be that catecholamines are released locally from chromaffin tissue, which is distributed widely in lower vertebrates (13) and which more recently has been demonstrated with the fluorescent histochemical method (386). For example, large brilliant yellow fluorescent cells found along nerves are a prominent feature of the toad bladder, but not the frog bladder (386). These may form part of the scattered chromaffin tissue.

Neither fluorescent ganglion cells nor fluorescent terminals about ganglion cells were observed in the bladder of the toad (*Bufo marinus*) (386). The adrenergic innervation of the bladder of the frog (*Rana temporaria*) is more dense and some fluorescent ganglion cells are present, but no terminals about nerve cell bodies have been observed (385).

The transmitter substance in adrenergic nerves appears to be adrenaline in amphibians (15, 192, 386) rather than noradrenaline, as is the case in reptiles and mammals.

D. Reptiles

The only account of the innervation of the bladder of reptiles in the early literature is a brief description of some excitatory nerves to the bladder of the terrapin (480). More recently, cholinergic excitatory control of the lizard bladder

has been demonstrated (110, 121). Many of the cholinergic nerves appear to be preganglionic, since, in histochemical studies, high concentrations of acetylcholinesterase have been localised in intramural neurones in the bladder wall (102 a). Furthermore ganglion-blocking agents reduce the nerve-mediated contractions (110).

The presence of two peaks on the stimulation frequency-response curve indicates that two types of excitatory fibre innervate the lizard bladder (110). Furthermore, since atropine selectively reduces the peak at the lower frequency, the peak at higher frequencies may be due to stimulation of noncholinergic nerves. It has been shown that the frequencies of stimulation of cholinergic excitatory nerves that produce optimal contraction increase with temperature at a significantly lower rate than do the optimal frequencies of adrenergically innervated preparations (121). Analysis of the effects of temperature on the two frequency optima of the lizard bladder preparation showed that, while the lower peak moves with temperature at a rate comparable to that of the cholinergically innervated preparations tested, the upper peak moves at a higher rate and is comparable to that found in the adrenergically innervated preparations. However, the evidence for adrenergic excitatory fibres obtained with blocking agents is inconclusive, largely because so many of these adrenotropic drugs have atropinic side-actions (76). Some indication of mixed adrenergic and cholinergic excitatory innervation is the observation that adrenergic blocking agents reduce even further the excitatory response which remains after atropine, and *vice versa*. However, these experiments are not conclusive since the actions of the two blocking agents may be additive on the same receptor structure. Since catecholamines never caused contraction of the bladder, it seems unlikely that the noncholinergic excitatory fibres are adrenergic. There is no conclusive evidence as to whether ganglia occur in noncholinergic as well as cholinergic excitatory pathways in reptiles.

In the lizard bladder many muscle bundles are innervated by fluorescent fibres that contain noradrenaline (387) and play an inhibitory role (110). No fluorescent ganglion cells have been seen, but fluorescent terminals have been shown about some ganglion cells (387). Thus it seems likely the pericellular adrenergic terminals originate from fibres in the extrinsic nerves. No evidence is available as to whether the inhibitory nerves are pre- or postganglionic, but the inhibition caused by nicotine may indicate that there are some ganglion cells of inhibitory nerves present in the reptile bladder (110). However, this is not strong evidence, since it is known that nicotine can release noradrenaline from chromaffin cells and adrenergic nerve terminals.

The yellow fluorescent cells found throughout the lizard bladder wall have been shown to contain a primary monoamine (387). On the basis of their colour and reactivity, this could be 5-hydroxytryptamine or high concentrations of noradrenaline or dopamine (191, 194), but the presence of adrenaline within these cells cannot be excluded. The identity of these cells is not known, but their scattered distribution in the submucosa and their yellow fluorescence suggested that they may be mast cells. However, stains which have been used for the identification of mast cells did not support this view. The fact that similar cells

stained with silver may only confirm the presence of a reducing substance within them. Spectrofluorometric assay of tissue extracts of the bladder showed noradrenaline to be the predominant catecholamine in reptiles (386).

E. Summary

The pattern of evolution of nervous control of the vertebrate urinary bladder appears to be as follows (see fig. 2).:

1) The basic function of the urinary bladder is the temporary storage of urine, although in amphibians it has an additional function in the conservation of water and sodium. The bladder is therefore an expansible sac with muscular walls to provide for expulsion of the contents. The main requirement for the rapid emptying of the bladder would be an excitatory innervation to the muscle, and this has been demonstrated in vertebrates of all the classes possessing urinary bladders. Thus, cholinergic motor control of the bladder appears to be a primitive feature, which is retained throughout the vertebrate classes. There is evidence from vertebrate classes higher than fish that many of the cholinergic nerves to the muscle arise from intramural ganglion cells in the bladder wall, which are controlled by preganglionic cholinergic nerves in the extrinsic nerve supply.

2) "Atropine-resistance" of excitatory responses to nerve stimulation is characteristic of all vertebrate bladders. This has been explained in terms of the existence of noncholinergic excitatory nerves releasing an as yet unidentified transmitter, but there is no definitive evidence to support this interpretation.

3) Peripheral inhibitory control of the vertebrate bladder is not apparent in lower vertebrates; it appears first in the reptiles. Since no evidence is available concerning the presence or absence of reflex micturition in any groups lower than placental mammals, the significance of the absence of peripheral inhibitory nervous control in teleosts and amphibians is not obvious. It is possible that inhibitory control in these two groups is mediated by circulating catecholamines released from adrenal gland tissue or from catecholamines released locally from chromaffin tissue, which is widely distributed in lower vertebrates and has been demonstrated histochemically in both amphibian and reptilian bladders.

4) Adrenergic fibres to the bladder have been found in amphibians, reptiles, and placental mammals. They are excitatory in frogs, but have inhibitory action in higher vertebrates.

5) Progressively more elaborate adrenergic nervous control of the bladder has taken place during evolution. This includes the development of: (i) intramural adrenergic neurones in the bladder wall, probably controlled by preganglionic cholinergic fibres; although none have been seen in toad and lizard, a few are present in the frog, and many are present in the mammalian baldder; (ii) adrenergic terminals about nonadrenergic ganglion cells in the bladder wall; these terminals are absent in fish and amphibians, a small number have been seen in the lizard bladder, and they are abundant in the mammalian bladder.

6) The wide differences in pattern of innervation of the bladder in related species (*e.g.*, between frog and toad, and between cat and rat) may be related to ecological or behavioural differences, or both.

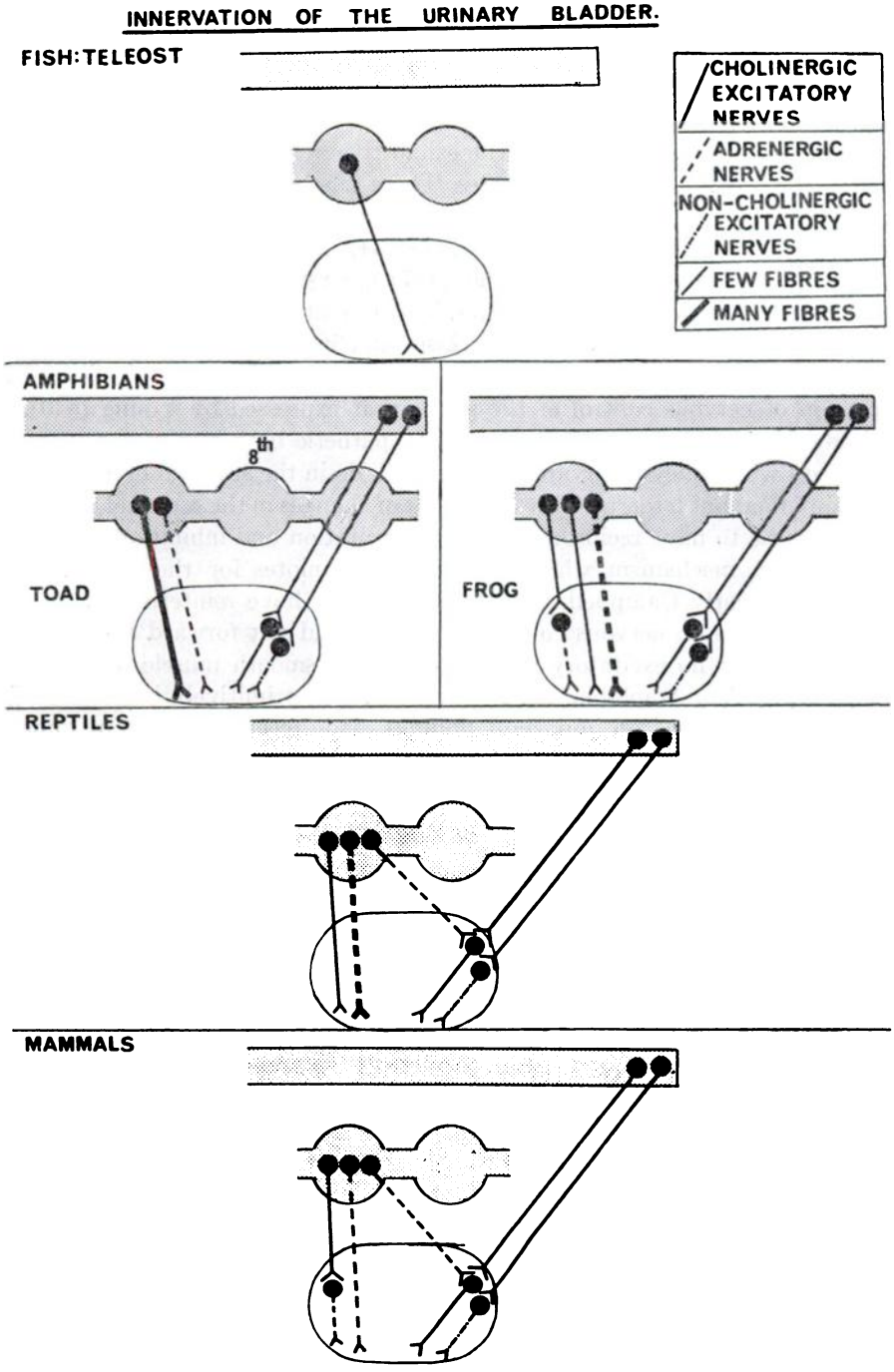

FIG. 2. Diagrammatic representation of the autonomic innervation of the urinary bladder. Central nervous system and sympathetic chain are represented by shaded areas. Although debatable (see section V A), noncholinergic excitatory fibres in the sacral parasympathetic outflow have been included. Note that adrenergic terminals around ganglion cells appear first in reptiles and become more extensive in mammals. Intramural adrenergic neurones have evolved independently in the frog and mammals. Note also the marked difference in innervation pattern between the bladder of the two closely related species of amphibians illustrated. A separate sacral parasympathetic outflow is depicted in amphibians, although this is not firmly established (see section II C).

VI. ALIMENTARY CANAL

This section is not intended to be an exhaustive survey of the literature dealing with gut activity in lower vertebrates. There has been a recent review on the comparative physiology of gastrointestinal motility (120) and others on the structure and activity of the gut in fishes (34), amphibians (449), birds (202) and marsupial mammals (515). Fänge (197) has reviewed the pharmacology of visceral muscles from lower vertebrates. The present review is confined to studies of the control of gut muscle by extrinsic and intrinsic nerves, excluding the nervous control of sphincter muscles. Currently the most common view of the evolution of nervous control of the gut is that expressed by Young (540). He suggested that "At first the vagus and sympathetic both had motor effects on the organs which they innervated, as they still do in the stomach of Teleostomes and Amphibia; but later, possibly as a result of changes in the terminal apparatus, the two came to have reciprocal effects of excitation and inhibition, giving the very efficient mechanism which is found in Amniotes for the control of the viscera." Recently Campbell and Burnstock (120) have reinterpreted many of the early results on nervous control of the gut and put forward the view that there is little or no excitatory cranial outflow to smooth muscle of the gut in groups lower than Amphibia and that the vagus is primitively inhibitory. This reappraisal was based on important findings made recently on the mammalian gut, which will be reported briefly below.

A. Mammals

The classical picture of mammalian gut innervation was that parasympathetic preganglionic cholinergic nerves form synapses in Auerbach's plexus with excitatory postganglionic cholinergic neurones and that these were opposed by the action of inhibitory postganglionic sympathetic adrenergic nerves running directly to the musculature. Intramural cholinergic neurones that were not connected with the extrinsic nerves and were involved in local reflex activity, as well as sensory neurones, were also considered to be present (261, 333).

Two major recent findings have made it necessary to modify this picture. Firstly, the existence of nonadrenergic inhibitory neurones in the enteric plexus which release an unknown transmitter has been established (45, 61, 88, 95, 103a, 104, 105, 151, 152, 272, 330). Satchell, Burnstock and Campbell (461a) have recently presented evidence that adenosine triphosphate or an analogue is the transmitter substance in nonadrenergic inhibitory neurones in the gut. These intramural neurones, at least those found in the stomach, are under the control of preganglionic cholinergic vagal nerves (113, 120, 332, 361). The nonadrenergic inhibitory nerves that have been shown to supply smooth muscle cells in the guinea-pig colon are not controlled by extrinsic nerves (221) and are presumably connected with other intramural neurones involved in intrinsic gut reflexes. A feature of the response of the gut to stimulation of the inhibitory nerves that is particularly pertinent to the interpretation of results in the gut of lower vertebrates is that there is a marked rebound contraction after cessation of stimulation; it may also occur after a long latency during prolonged periods of

stimulation (44, 108, 114). Especially when the tone of the muscle preparation is low, stimulation of the inhibitory nerves may cause an insignificant inhibition of activity, followed by a very large and long-lasting rebound contraction. Campbell and Burnstock (120) have suggested that many of the earlier records of the responses of nonmammalian gut preparations should be interpreted as rebound contractions following stimulation of inhibitory nerves rather than primary contractions caused by stimulation of excitatory nerves.

The second significant modification of the classical picture results from fluorescent histochemical studies. These have shown that most of the sympathetic adrenergic nerves to the gut form terminal networks about nonfluorescent ganglion cells in both Auerbach's and Meissner's plexuses (1, 36, 222, 271, 287, 410, 446, 448, 491). Kewenter (308) and Jansson and Martinson (289) have shown that a discharge in the sympathetic nervous system of cats inhibits vagal excitatory (but not inhibitory) transmission to the stomach and small intestine (but see 232, 234). It is therefore possible that the peristaltic reflex, or at least the emptying phase of the reflex, in mammals and to a lesser extent in birds and reptiles, is under the inhibitory control of sympathetic nerves that block synaptic transmission in Auerbach's plexus. This has recently been supported experimentally in the guinea-pig ileum (108a). The only part of the gut musculature that appears to be directly supplied by adrenergic nerves is the circular muscle coat of the large intestine, and the longitudinal muscle of the guinea-pig taenia coli (484).

It is generally accepted that peristalsis in the mammalian gut is a neurogenic process, mediated by intrinsic enteric neurones and only modified by the influence of the extrinsic nerves (319). Considerable attention has been paid to the possibility that 5-hydroxytryptamine contained in enterochromaffin cells acts as a sensory stimulant initiating peristalsis (89–91, 93, 94), but it is doubtful whether the presence of 5-hydroxytryptamine is essential for the maintenance of peristalsis (see Boullin, 75). More recently, Bülbring and Gershon (92) have suggested that 5-hydroxytryptamine participates in the vagal inhibition of the guinea-pig stomach.

Little information is available concerning the nature of peristalsis in the gut of lower vertebrates (8) with the exception of teleost fish (101, 102, 416). However, there is considerable evidence linking 5-hydroxytryptamine with the process of peristalsis in lower vertebrates. Thus Johnels and Östlund (301) found that the application of 5-hydroxytryptamine initiated peristalsis in the isolated rectum of the lamprey. Yung *et al.* (544) found that serosal applications of 5-hydroxytryptamine could initiate peristalsis in distended segments of tortoise intestine. Several workers have shown that low concentrations of 5-hydroxytryptamine have an excitatory action on gut segments from teleosts (101, 187, 502), amphibians (472, 509), and reptiles (496, 544). Inhibitory responses to 5-hydroxytryptamine have also been observed in amphibians (472) and reptiles (496). Furthermore, there is a ready source of 5-hydroxytryptamine in the mucosal enterochromaffin cells, which probably occur in all vertebrates (233, 343, 447, 506). Further studies of the effects of 5-hydroxytryptamine on gastrointestinal peristalsis in lower vertebrates may help to clarify the situation in mammals.

B. Cyclostome fish

The hagfishes (myxinids) and lampreys (petromyzontids) probably represent widely divergent evolutionary forms even though they are both grouped under the class Cyclostomata. It is therefore unfortunate that vagal action on the gut has been studied only in myxinids, and that even here the results so far do not permit any firm conclusion. Patterson and Fair (434) reported that stimulation of the vagi in a hagfish caused a slight relaxation of the intestine *in situ*. Fänge (195) and Fänge and Johnels (199) were unable to show any vagal effects on the intestine of another species of hagfish although the striated muscle of the pharyngeal sphincter was contracted. The results of Patterson and Fair (434) suggest that the vagal fibres are not cholinergic, since acetylcholine excites the intestine (187, 195, 301). On the other hand, they could be adrenergic, since adrenaline relaxes the gut (195, 301) and since high levels of noradrenaline have been isolated from the vagus nerve trunks (186). However, it has not been established whether the noradrenaline present is contained in neurones or in chromaffin cells, as is the case for the heart. If adrenergic fibres are present in the vagal trunks, it is likely that they are derived from the spinal "sympathetic" outflow, as suggested by Marcus (359), since the vagus nerves run closely with the mixed ventral rami of the anterior spinal nerves (see Peters, 436). Vagosympathetic trunks to the gut containing some adrenergic nerve fibres of sympathetic origin have been described in fish and amphibia (see later sections) but adrenergic fibres have not been shown in the cranial autonomic outflow of any vertebrate. Campbell and Burnstock (120) have postulated that the vagus nerve is primitively inhibitory to the vertebrate gut and is composed of nonadrenergic fibres. It is clear that further experiments are needed. In view of the thinness of the intestinal muscle coat in cyclostomes and the possibility that food movements are mediated by movements of the body wall, it would be preferable to work on preparations isolated from the body. Fluorescent histochemical studies of the cyclostome gut, especially of lampreys, would be useful.

There appears to be no separate spinal "sympathetic" autonomic outflow to the gut in myxinid cyclostomes (200), apart from those which might be running in the vagus trunks. However, in a lamprey, nerve fibres from both dorsal and ventral roots of the spinal nerves run to the rectal portion of the gut (299). Spinal branches may also reach the gut *via* blood vessels (see Nicol, 401). There are no physiological data concerning these nerves.

Peristalsis was reported to persist in the intestine of hagfish when the extrinsic nerve supply was sectioned (301, 420). The intestinal wall contains a nervous plexus with numerous cell bodies (Brandt, 79), some of which may be sensory neurones (372–374). Fänge *et al.* (200) have shown that neurones are less numerous in the posterior region of the gut, and that many of the enteric neurones appear to be innervated by vagal fibres.

C. Elasmobranch fish

There have been several studies of the effects of vagal stimulation on the gut of elasmobranchs. It is generally agreed that the vagal influence does not extend

beyond the stomach or the proximal portion of the intestine (74, 379, 540). The vagi are excitatory to the striated muscles of the oesophagus (74, 379, 540).

Botazzi (74) and Müller and Liljestrand (379) showed that the vagus nerve could cause inhibition of the stomach. The excitation that they recorded after a long latent period following stimulation of the vagus nerves to low-tone preparations, and also the excitatory response reported by Babkin, Friedman and MacKay-Sawyer (29), Lutz (354) and Young (542) were interpreted by Campbell and Burnstock (120) to represent rebound contraction after the stimulation of inhibitory nerves. Only Nicholls (399) has shown a clear record of primary excitation, and in view of the results of the other authors on the same species of ray it could be argued that this excitation was mediated by sympathetic fibres stimulated by current spread from the rather crude electrodes in use at that time. However, the presence of some excitatory fibres cannot be excluded on the basis of the available evidence.

With regard to the transmitter substance involved in the vagal responses, little is known. It is clear that acetylcholine is not the transmitter substance, even in the apparent primary contractions recorded by Nicholls, since the nerve-mediated responses are not reduced after treatment of the preparations with atropine (29, 399). In contrast, contractions caused by acetylcholine are abolished by atropine (187, 399). It is possible that the primary excitation found by Nicholls is mediated by adrenergic fibres, since adrenaline, like acetylcholine, can contract the gut in some elasmobranchs (29, 162, 187, 354, 399, 540). However, Nicholls (399) found that the excitatory effect of adrenaline on the stomach of some species of ray occurred only when low concentrations were used; higher concentrations caused an inhibition of spontaneous movements. Von Euler and Östlund (187) also found that adrenaline could relax contracted gut preparations from the ray while Lutz (354) found that adrenaline relaxed the rectum of the dogfish. It is therefore possible that the inhibitory vagal effects are mediated by an adrenergic transmitter substance. However, by analogy with the situation in higher vertebrate classes, where the existence of nonadrenergic inhibitory vagal fibres is better supported (113, 118, 361, 529), the inhibitory transmitter released from elasmobranch vagal nerves may also be nonadrenergic. Clearly further work is needed.

Several workers have shown what appear to be true primary contractions of the stomach and intestine in response to "sympathetic" nerve stimulation (29, 73, 399). In addition to these responses, the figures from some of these papers and those of Müller and Liljestrand (379) clearly implicate some rebound contractions following inhibitory nerve stimulation. The nature of the transmitter substances involved in either excitatory or inhibitory transmission is not known. Babkin, Friedman and MacKay-Sawyer (29) reported that atropine did not affect the excitatory responses to splanchnic nerve stimulation, but it is not clear whether they are referring to the primary contraction or to the rebound contraction. The inhibitory fibres may be adrenergic since catecholamines cause relaxation of the gut of a number of species (see Campbell and Burnstock, 120).

Müller and Liljestrand (379) were unable to elicit peristalsis by introducing a bolus into the gut of the ray. Young (540) reported that a nonspecific stimulus,

pinching the gut wall, could elicit contractions spreading anally in the intestine of the dogfish. However, he found that the same stimulus caused only local contractions of the stomach and oesophagus in this species, as had also been reported for the gut of the ray (379). These reports suggest that there may be regional differences in the mechanism of peristalsis of the gut of the same species. There also appear to be regional differences in the ease of initiation of peristalsis. There is a stratified enteric plexus between the muscle coats, but the nerve cell bodies lie diffusely in the meshes of the plexus throughout the gut (314) rather than in aggregations in the form of large ganglia, as in mammals.

D. Teleost fish

There are few reports of the effects of vagal stimulation on the gut of teleosts. In most species, the vagi innervate the striated muscles of the oesophagus and the smooth muscle of the stomach, but probably they do not extend to the intestine (101, 542). It should be noted that not all fish possess a stomach (34). The influence of the vagi does not extend onto the pyloric caeca (101, 542), which are found in most teleosts (421). However, in the tench, the vagus innervates both striated and smooth muscle coats along the whole length of the gut (357). The response of the teleost stomach to vagal stimulation was reported to be contraction (100, 357, 379, 542). However, in nearly every case, contraction occurred after a long latency in low-tone preparations, a result that strongly suggests rebound contractions after stimulation of inhibitory nerves (see Campbell and Burnstock, 120). In the paper by Burnstock (100) a small relaxation of the stomach of the trout was demonstrated preceding contraction.

If there are any primary contractions resulting from stimulation of the vagus trunk, they are likely to be due to the presence of sympathetic (cholinergic) nerve fibres, which join the vagus near the cranium (196, 537).

There is little clear evidence regarding the substance involved in the transmission of inhibition from the vagi to the smooth muscles of the teleost stomach. Since acetylcholine appears to have an excitatory action on all parts of the gut (56, 101, 162, 187, 223, 417, 542), the nerves cannot be cholinergic. Furthermore, the vagal responses are not affected by atropine (101). Burnstock (101) found that adrenaline causes contraction of the stomach of the trout. Thus, the inhibitory vagal fibres in this species do not appear to be either cholinergic or adrenergic. At least in the brown trout, the vagal fibres appear to be preganglionic when they reach the gut (101).

Very little work has been done on the spinal "sympathetic" outflow to the gut in teleost fish. However stimulation of the anterior splanchnic nerves causes excitation of the gut in the few species which have been examined (101, 379, 542). In the trout, this excitation was blocked by atropine; hence cholinergic excitatory fibres were postulated (101).

There is one clear example of an inhibitory response of the intestine in teleosts, namely, the relaxation of the large intestine of the trout following posterior splanchnic nerve stimulation (101). These inhibitory fibres are likely to be adrenergic since adrenaline (101, 187, 216, 223, 542) and noradrenaline (187, 223)

usually inhibit gut movements. Furthermore, adrenergic innervation of gastrointestinal muscle (particularly in the hind gut) has been demonstrated histochemically in trout, eel, and tench (36, 448). No physiological evidence concerning the distribution of these fibres in the roots of the spinal nerves is available. Nor is there any pharmacological evidence to indicate whether and where the fibres form synapses.

The fullest descriptions of peristalsis in the gut of lower vertebrates are of the brown trout (101, 102) and tench (416). It is interesting to see that many features of the mechanism appear to be the same as those described in mammals (38, 319, 497). For example, peristalsis can be initiated in both the trout and tench gut by distension (102, 416). In the trout gut, peristalsis usually spreads from centres in the antrum and in the anterior duodenum (102); these regions contain a greater density of nerve cell bodies in the enteric plexus than do neighbouring regions (101). By using the method of Trendelenburg (497), it is possible to separate the reflex in the small intestine of the tench into a "preparatory" contraction of the longitudinal muscle and an "emptying" phase of coordinated contractions of both muscle layers (416). In the brown trout, too, there is an initial phase of contraction of the longitudinal muscle followed by a contraction of the circular muscle during peristalsis (100, 101). Hexamethonium prevents peristaltic contr actions in the teleost fish gut (101, 416). This implies that the reflex is neurogenic and that there are cholinergic synapses in the nervous pathways to the circular muscle. This view is strengthened by the observation that rapid warming of the trout gut, which inactivates synaptic transmission (100), can prevent the phase of circular muscle contraction while leaving the longitudinal muscle contraction intact. It has been suggested by Burnstock (102) that the longitudinal contraction phase may be initiated by the effect of stretch on the arborising dendritic mesh, which is a characteristic feature of the large ganglion cells found in Auerbach's plexus of the trout, half embedded in the longitudinal muscle coat. It is well known that the emptying phase, but not the preparatory phase, of peristalsis in the mammalian small intestine is prevented both by ganglionic blockade (205, 430) and by temperature changes, in this case cooling (320). These similarities between peristalsis in fish and mammalian small intestine suggest that essentially the same mechanism is operating in both cases. There is no direct proof that Auerbach's plexus is the site of the ganglionic synapses involved in the excitation of the circular muscle layer during peristalsis. An alternative site for these synapses in the mammalian gut, in the absence of other evidence, could be the submucosal plexus of Meissner. However, in the gut of teleosts (102) and also in amphibians, the submucosal plexus does not contain nerve cell bodies. In these groups, Auerbach's plexus is the only region in which a great number of synaptic connections could occur. The motor innervation of the smooth muscle involved in peristalsis of the teleost fish gut, as in the mammalian small intestine, appears to be cholinergic since atropine always abolishes peristalsis in the stomach and usually abolishes it in the intestine (101). Atropine has also been reported to inhibit peristalsis in the tench intestine (416) although an earlier report denied this (216). There is evidence for choliner-

gic nerves supplying the smooth muscle of the gut wall in this species (216, 417). It may be that the apparently conflicting results can be explained in terms of regional differences, since even in mammals, atropine does not abolish peristalsis in the colon (340).

A detailed study has been made of the structure of the enteric plexus in different regions of the trout gut and a number of differences from those seen in mammals have been pointed out by Burnstock (102). Nerve cell bodies in Auerbach's plexus lie diffusely in the meshes of the plexus throughout most of the gut, and are not aggregated into large ganglia as in the mammals. The density of nerve cells in Auerbach's plexus in the trout (100 to 200 cells/mm^2) (102) is of the same order of magnitude as that reported in guinea-pigs (281), although considerably greater than the reported density in rabbits (17 to 35 cells/mm^2) (362). The total number of nerve cells calculated to be present in the trout gut (about 0.5×10^6) is considerably less than the figure given for mammals (5×10^6 in cat small intestine) (462). In addition to Auerbach's plexus there is a subserous plexus, a submucosal plexus (without ganglion cells and therefore different from Meissner's plexus in mammals), and a subepithelial plexus containing small multipolar cell bodies, which have not been described in the gut of other vertebrates (102, 314, 377).

E. Amphibians

The results of a large number of early investigations of the effects of vagus nerve stimulation on the gut of amphibians, especially anurans, showed that both excitatory and inhibitory fibres to the stomach are present in most species, although interpretation was often difficult because of the absence of knowledge about rebound contraction at that time (see Campbell and Burnstock, 120). The vagus nerve in amphibians is in fact a vagosympathetic trunk and it has recently become clear that the vagal component to the stomach is composed largely, if not entirely, of nonadrenergic inhibitory fibres, while the fibres of sympathetic origin are largely excitatory and cholinergic (118). Stimulation of the cervical sympathetic chain, which supplies the sympathetic fibre component in the vagosympathetic trunk, produced excitation of the stomach, which was blocked by atropine, whereas stimulation of the vagus nerve, above its junction with the sympathetic branch, produced inhibition of the stomach, which was not blocked by adrenergic or other cholinergic blocking agents. The fibres of vagal origin appear to be preganglionic cholinergic nerves forming synapses on intramural nonadrenergic ganglion cells in the stomach wall, since vagal inhibition is abolished by ganglion-blocking agents. Reinterpretation of many of the early results gives further support for this view. For example, destruction of the medulla oblongata in the frog caused an increase in the motility of the stomach (127, 137, 235, 484); this suggests that the vagal component contains inhibitory nerve fibres to the gut. Patterson (433) was also unable to obtain any excitatory responses of the stomach to stimulation of the vagosympathetic nerve in the urodele amphibian, *Necturus*, a result that suggests that there may be no distribution of excitatory sympathetic nerves with the vagal supply to the gut in this group.

The results of experiments concerned with discerning the nature of the trans-

mitter substances involved in vagal excitation and inhibition are confused. The intestine of the frog is contracted by acetylcholine (197, 464), but it has often been reported that vagal excitatory responses are not affected by atropine (127, 157, 507). It has also been reported that atropine can reduce but not abolish contractions caused by vagal stimulation (253). Singh (473) has presented evidence that the transmitter substances released by the vagus differ from one season of the year to another. In summer and winter, the transmitter is substance P; in early spring and late autumn, acetylcholine; in mid-spring and mid-autumn, histamine; in late spring and early autumn, 5-hydroxytryptamine. Although this suggestion is compatible with the results of other authors, it is so strikingly different from commonly accepted concepts of autonomic neuromuscular transmission that verification is essential.

The most commonly recorded effect of stimulation of the spinal autonomic "sympathetic" nerves on the gut of amphibians is excitation. It seems clear that the response is a primary excitation (5, 73, 137, 157, 251, 334, 466, 485, 543). The fibres are probably cholinergic since their action is prevented by atropine (77, 157). The splanchnic nerves originating from the third, fourth, and fifth sympathetic ganglia, which supply the stomach of the toad, have, at least in the summer months, an inhibitory action and appear to be adrenergic (118). However, stimulation of splanchnic nerves to the toad stomach in other seasons produces a predominantly excitatory action (251, 466). It appears likely that both inhibitory adrenergic and excitatory cholinergic fibres are present in the sympathetic nerves, but that changes in the balance of these antagonistic responses occurs with the seasons of the year.

At the level of the ninth and tenth spinal nerves, an excitatory outflow occurs in the ventral roots (77, 146, 276, 334). This outflow has been regarded as a sacral parasympathetic supply, on the grounds of the gap which occurs in the autonomic outflow at the level of the eighth spinal nerve (334). The nerves again appear to be cholinergic fibres, making synapses with post ganglionic cholinergic fibres in the gut wall (77).

An outflow of inhibitory nerve fibres in the upper spinal nerves is well established (5, 77, 251, 466, 543). The fibres leave the cord in the ventral roots (252) and form synapses in the coeliac plexus (252, 466); they probably keep the gut under tonic inhibition (431, 432). In addition, there appear to be inhibitory fibres which run through the body wall and then traverse the lateral vesicle ligament and the bladder, to reach the hind gut (208).

A few inhibitory fibres may also occur in the posterior spinal nerves, but their effect is outweighed by the excitatory fibres (77). The most likely candidate for the inhibitory transmitter substance is a catecholamine, probably adrenaline since this causes relaxation of the gut (77, 127, 175, 217, 275, 464, 543). The toad rectum is 30 to 200 times more sensitive to adrenaline than to noradrenaline (445). Furthermore, adrenaline is the transmitter substance in autonomic nerves supplying other visceral organs in the Amphibia (15, 192, 385, 386), and nerves containing adrenaline have been demonstrated in the gut of the toad (446–448). Singh (472) has presented pharmacological evidence, based on the use of the

anti-5-hydroxytryptamine drug bromolysergic acid diethylamide (BOL), that implicates 5-hydroxytryptamine in the inhibitory response; however, frog intestine is contracted by 5-hydroxytryptamine (464).

Multiaxonal synapses with single smooth muscle cells of the circular muscle coat of the toad large intestine have been demonstrated with the electronmicroscope (457), but it is not known whether these represent several terminal branches of one axon or the terminal regions of several different neurones or even different types of neurone. It was also pointed out that the circular muscle coat of the amphibian intestine has a much denser pattern of innervation than the longitudinal muscle coat (457, 494), a feature it has in common with mammalian intestine (395, 493). Structures resembling the "interstitial cells of Cajal" are present in the gut of all vertebrates (102, 262, 368). It has been claimed that these cells play some intermediate role in neuromuscular transmission in the gut (181, 337). However, recent electronmicroscope studies of interstitial cells in mammals (451) and amphibia (456) suggest that they are fibroblast or macrophage cells. There are no ganglion cells in the submucosal plexus in amphibians (246).

F. Reptiles and birds

There are very few reports of vagal effects on the gut in reptiles. Both excitatory and inhibitory responses of the stomach have been reported but again some of the excitatory responses may have been rebound contractions (*e.g.*, 53, 126, 455, 504, 530). Since the excitatory responses are blocked by atropine and mimicked by acetylcholine, they are probably mediated by cholinergic nerves.

The identity of the transmitter in the inhibitory fibres is not known. Stimulation of the vagi in a turtle (*Chrysemys*) with frequencies in the order of 0.5 pulses/sec caused a relaxation of the stomach (53, 455). Carlson and Luckhardt (127) also found that vagal stimulation caused relaxation of the oesophagus and, provided that the stimulus was weak, of the stomach also. Bercovitz and Rogers (53) found that the relaxation caused by low frequency stimulation, or by high frequency stimulation, or by high frequency stimulation after treatment with atropine, passed off very rapidly at the end of the period of stimulation. Thus, in two respects, namely the efficacy of low-frequency stimulation and rapidity of offset of the relaxation, the inhibitory fibres in the reptilian vagus resemble the nonadrenergic vagal inhibitory fibres supplying the stomach of the guinea-pig (113).

The excitatory vagal fibres appear to be preganglionic, since contractile responses to stimulation are blocked by nicotine (53, 409, 504). However, the vagal inhibitory fibres may be only partly preganglionic, since nicotine does not block their action on the oesophagus (127) or the stomach (53).

There do not appear to have been any significant studies of the spinal autonomic outflow to the gut in reptiles, although the gut wall contains adrenergic fibres (446–448).

The classical studies of Trendelenburg (497) on eliciting peristalsis in the mammalian gut have been repeated on the gut of only one reptile, namely the intestine of the tortoise (544). Distension of this gut with fluid was not by itself a

sufficient stimulus for peristalsis. Peristalsis occurred when the intraluminal pressure was raised only if the serosal surface of the gut was exposed to a stimulant drug, such as acetylcholine or 5-hydroxytryptamine. Yung *et al.* (544) concluded that peristalsis in the tortoise intestine was largely myogenic, but their evidence, based on the use of a local anaesthetic drug, is not full enough to warrant this conclusion.

Fluorescent adrenergic terminals about ganglion cells have been demonstrated in Auerbach's plexus in both reptiles (446) and birds (46, 174). Some intramural adrenergic ganglion cells are also present in the lizard large intestine (446) and chick gizzard (46), although they have not been seen in the alimentary canal in any other vertebrate class (446).

The nature and extent of the vagal innervation of the gut in birds is like that in mammals. Both inhibitory and excitatory fibres are present; the earlier evidence for this, particularly the excellent work of Nolf, has been summarised by Farner (202). Recently structural, histochemical, and electrophysiological studies have been carried out on the autonomic innervation of the gizzards of the chick and the pigeon (46–49, 50, 51). In both species, nonadrenergic inhibitory fibres are present in the vagi together with both pre- and postganglionic cholinergic excitatory fibres. The few noradrenergic fibres running with the vagi appear to be sympathetic in origin. The perivascular sympathetic nerves to the gut contain excitatory and inhibitory fibres (47, 48, 161, 407, 408). The excitatory fibres appear to be cholinergic since their action is blocked by atropine (407) or hyoscine (47). There are both pre- and postganglionic excitatory cholinergic fibres in the perivascular sympathetic nerves to the gizzard (47). The inhibitory nerves running in the sympathetic trunks are of the nonadrenergic inhibitory type and appear to be derived from the vagus (47, 48). Adrenergic fibres running to the gizzard appear to be sympathetic in origin and terminate around ganglion cells in Auerbach's plexus (46). Those adrenergic fibres present in the musculature are associated with blood vessels (46). Repetitive perivascular stimulation after cholinergic excitation has been blocked by hyoscine evokes depolarisation associated with contraction of the muscle cells, which is blocked by guanethidine and mimicked by noradrenaline (47, 48). Thus the inhibitory nerves to the gizzard are not adrenergic.

Recent pharmacological studies on the innervation of the intestine have indicated that the perivascular sympathetic nerves contain cholinergic excitatory and both adrenergic and nonadrenergic inhibitory nerve fibres (188). There is no evidence concerning a sacral parasympathetic nervous supply to the gut in either reptiles or birds.

G. Summary (See figs. 3 and 4)

1) The vagal supply to the gut in fish is mainly inhibitory, although the presence of a few excitatory fibres in some species cannot be excluded. In amphibians, reptiles, and mammals the vagus trunk contains mixed inhibitory and excitatory fibres. The vagus nerve in amphibians is in fact a vagosympathetic trunk and all the excitatory nerve fibres supplying the gastric musculature are of sympathetic

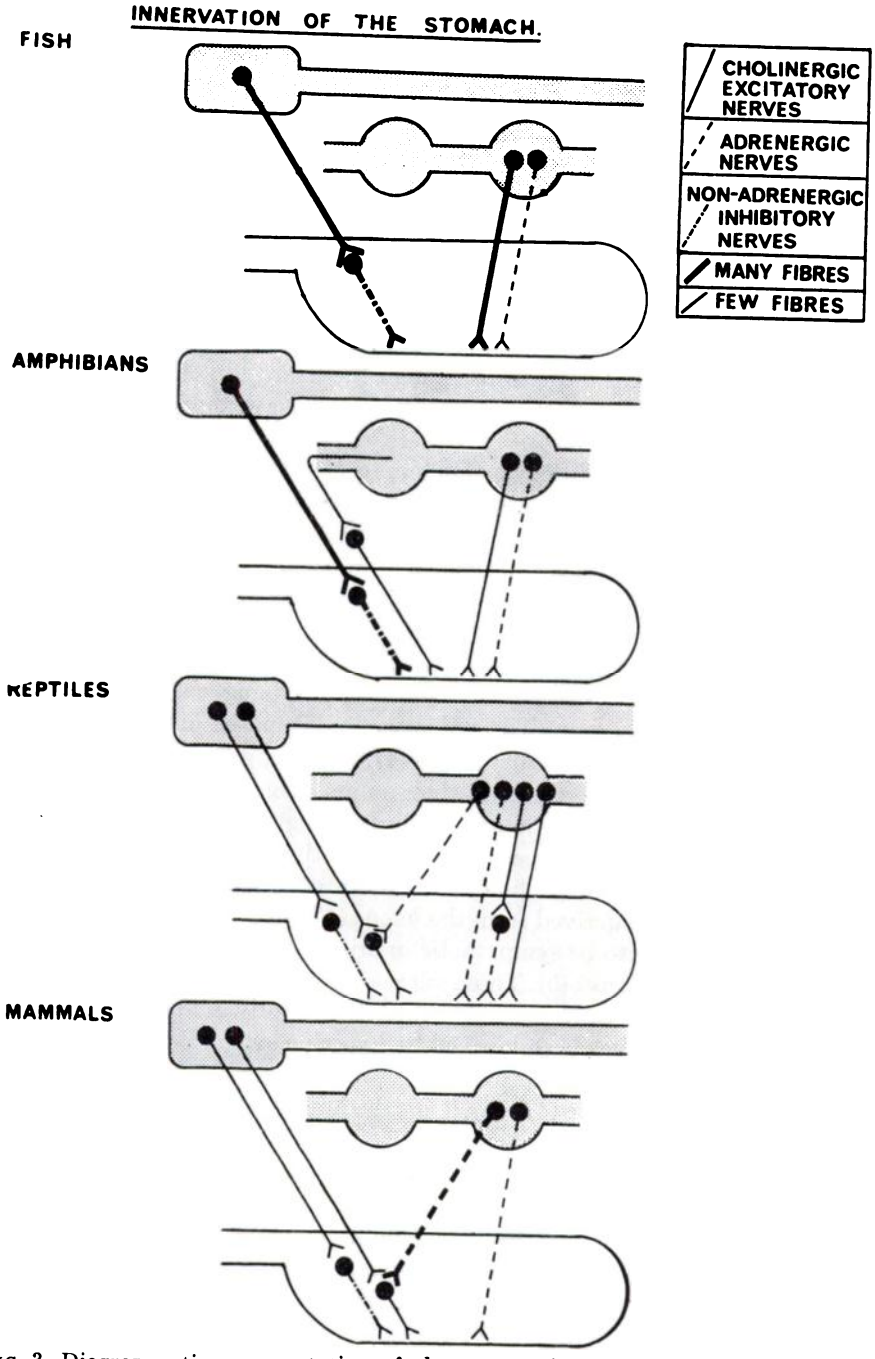

FIG. 3. Diagrammatic representation of the autonomic innervation of the stomach. Central nervous system and sympathetic chain are represented by shaded areas. Note that the vagal parasympathetic outflow is purely inhibitory to the fish and amphibian stomach and is opposed by excitatory cholinergic sympathetic fibres. In reptiles and mammals the cholinergic excitatory nerves have been switched to the parasympathetic outflow, sympathetic fibres becoming adrenergic and inhibitory. Adrenergic modulation of intramural ganglion cell activity is rudimentary in reptiles and strongly developed in mammals. The diagram depicting the innervation of the reptile stomach is largely conjectural. Intramural neurones that are independent of the extrinsic nerve supply are not included in the diagrams.

origin and cholinergic. In reptiles and mammals the excitatory nerves are preganglionic fibres of classical parasympathetic origin, which form synapses with cholinergic neurones in the wall of the gut. The transmitter released by the inhibitory fibres running in the vagus trunks in all vertebrate classes is not a catecholamine, but it may be adenosine triphosphate or some related nucleotide.

2) The sympathetic supply to all regions of the gut in both elasmobranchs and teleost fish contains a mixture of predominantly excitatory (probably cholinergic) and some inhibitory (probably adrenergic) fibres. In amphibia and reptiles sympathetic nerves are still mixed, but a much greater proportion are adrenergic, while in mammals they are almost exclusively adrenergic. It is interesting to note in terms of the old axiom that "ontogeny repeats phylogeny" that the sympathetic nerves that supply the intestine of rabbits 3 days after birth are predominantly excitatory and cholinergic (97, 150). A few intramural adrenergic neurones have been seen in the gut of reptiles and birds, but not in any other vertebrate.

3) The vagus nerve exerts an influence as far down as the large intestine in mammals but it has a more limited innervation in lower vertebrates. In teleost fish the vagus nerve does not extend beyond the stomach while in elasmobranch fish and amphibians it is limited to the anterior intestine. In the absence of preganglionic vagal fibres forming synapses with inhibitory nonadrenergic neurones in the hind gut region, the musculature in the hind gut is directly supplied by inhibitory adrenergic nerves of sympathetic origin.

4) Peristalsis occurs in the gut of all vertebrates and continues even after the gut is isolated from the central nervous system. The presence of the inhibitory phase of peristalsis known in mammals has not been demonstrated directly in any lower vertebrate. The excitatory phase, on the basis of observations made on teleost fish, appears to be neurogenic and is comparable to that occurring in mammals. The deviations from "typical" mammalian peristalsis may be no greater than the differences which are already known to occur in different regions of the gut in different mammals. Extrinsic inhibitory control of the peristaltic reflex (in the form of sympathetic adrenergic nerve terminals on enteric ganglion cells) appears to occur in mammals, birds, and to a rudimentary extent in reptiles, but has not been demonstrated in lower groups. Some evidence suggests that 5-hydroxytryptamine is implicated in the initiation of peristaltic activity in all vertebrates. Some intramural nonadrenergic neurones as well as cholinergic neurones are present in the large intestine of mammals, which are not connected with extrinsic nerves.

5) Although the basic plan of the enteric plexus appears to be constant throughout these vertebrate groups, some of the lower vertebrates do show significant anatomical deviations from the arrangement described in mammals:

a) Auerbach's plexus is present between the muscle coats in all lower vertebrates; nerve cells of various types are present but it is difficult to equate them between the different classes. The nerve cell bodies in fish and amphibia lie diffusely in the meshes of the plexus, rather than in aggregations or ganglia as in mammals and birds.

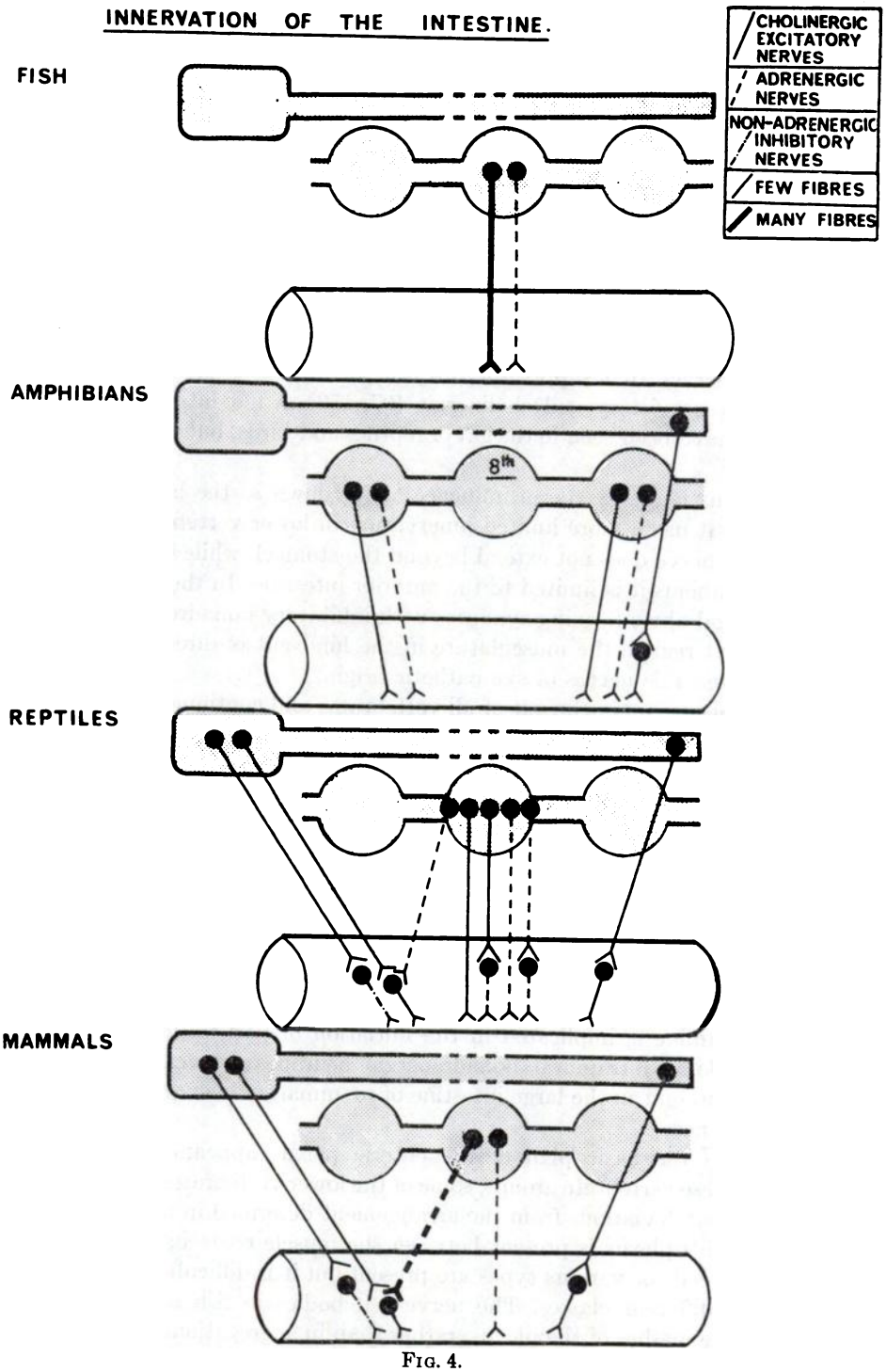
INNERVATION OF THE INTESTINE.
CHOLINERGIC EXCITATORY NERVES
ADRENERGIC NERVES
NON-ADRENERGIC INHIBITORY NERVES
FEW FIBRES
MANY FIBRES
FISH
AMPHIBIANS
8th
REPTILES
MAMMALS

FIG. 4.

b) Sympathetic adrenergic nerve fibers envelop ganglion cells in Auerbach's plexus in mammals and birds; only a few such terminal networks are seen in reptiles and none in amphibians and fish. Direct adrenergic innervation of the circular but not the longitudinal muscle coat (except the taenia coli of the guinea-pig) is present in all vertebrates, but is usually limited to the hind gut region.

c) The submucous plexus of Meissner in the adult mammalian gut is a meshwork of nerve fibres containing nerve cell bodies. However in teleosts and amphibians there are no nerve cell bodies in the plexus. It is interesting to note that in developing human gut neuroblasts are first established in Auerbach's plexus throughout the gut at about 3 months. It is only after this time that some ganglion cells migrate across the circular muscle to the submucosa where they form Meissner's plexus (418).

d) The mammalian gut contains a nerve fibre plexus lying just beneath the mucosal epithelium. This plexus is also present in the amphibian gut and is a particularly prominent feature of the teleost fish gut, where it contains small multipolar cell bodies, which have not been described in the gut of other vertebrates. A subserous plexus has also been described in the teleost fish gut.

e) As in mammals, nerve endings have been identified in the mucosal epithelium of amphibians and teleost fish, but there is no evidence to show whether some, or all, of these endings are sensory.

f) Structures resembling the "interstitial cells of Cajal" are present in the gut wall of all vertebrates. These cells have been examined with the electron microscope in mammalian and amphibian gut, and shown to be fibroblast or macrophage cells, which are unlikely to be concerned with the transmission of activity from the enteric plexus to the musculature.

6) The essential changes in nervous control of the gut during evolution are summarised as follows (see figs. 3 and 4). Available evidence concerning the vagal supply to the gut of lower vertebrates has been reinterpreted to show that the outflow is primitively inhibitory. Inhibitory fibres alone are found in the vagi of hagfishes, elasmobranchs, teleost fish and amphibians. In higher groups, the inhibitory fibres are accompanied by excitatory fibres. The excitatory fibres are probably cholinergic. The nature of the transmitter substance released from the inhibitory fibres is not known, but may be adenosine triphosphate.

FIG. 4. Diagrammatic representation of the autonomic innervation of the intestine. Central nervous system and sympathetic chain are represented by shaded areas. The diagram illustrating the reptile condition is partly conjectural, being based largely on the results of fluorescent histochemical studies. Note that the vagus nerve does not extend far enough down the gut in lower vertebrates to influence most of the intestine, while in mammals it extends at least as far as the ileocolonic junction. Adrenergic modulation of ganglion activity appears first in the reptiles and is strongly developed in mammals. It is not known whether adrenergic nerve terminals envelop postganglionic sacral parasympathetic neurone cell bodies. A separate sacral parasympathetic outflow in amphibians is depicted, although this is debatable (see section II C). Intramural neurones that are independent of the extrinsic nerve supply are not included, although it should be noted that in the large intestine, there is evidence that intramural nonadrenergic inhibitory neurones as well as cholinergic neurones are involved in local reflex pathways.

The available evidence concerning the spinal autonomic outflow to the gut in lower vertebrates is interpreted to indicate that the outflow consists, primitively, of a mixture of excitatory cholinergic and inhibitory adrenergic fibres. It appears that there is a greater outflow of excitatory fibres to the gut in lower vertebrates than there is in mammals. A complication is presented by the observation that, in anuran amphibians, the outflow is separated into a dorsal root excitatory system and a ventral root inhibitory system. It is not clear whether this arrangement is confined to the amphibians or is found in other groups, including the mammals (see Kure, Ichiko and Ishikawa, 329a).

VII. HEART

In fish there is a simple tubular heart with successive cardiac chambers; the venous blood drains into the sinus venosus, passes through the atrium into the ventricle and is pumped into the truncus arteriosus to enter the afferent branchial arteries. In the premetamorphic stage, the amphibian circulatory system and heart are much like that of the fish. However, after metamorphosis, a septum developing in the atrium divides the cardiac activity into two; the right atrium receives systemic venous blood from the sinus venosus, while the left atrium receives blood from the lungs. From the two atria, blood passes into a single ventricle into which the bulbus cardis is largely incorporated. In reptiles, the separation of the heart has advanced to include the ventricle, although, with the exception of crocodiles, the division of the ventricle into two chambers is incomplete. In warm-blooded vertebrates, the higher metabolic rate has necessitated a more efficient circulatory system. Thus in birds and mammals there is a complete separation of the heart into four chambers. Information on the innervation of the vertebrate heart is more complete than for most other organs (135, 296, 401). However very few of the papers describing the innervation of the heart of lower vertebrates differentiate between the action of nerves on different regions (*e.g.*, sinus or A-V node, atrium, conducting cells, ventricle) or on different physiological parameters (*e.g.*, rate, contractile force, action potential, conduction velocity, impulse production). Thus, although it would clearly be of great value to be able to make a more detailed comparison of these various actions of nerves in lower vertebrates with those known in considerable detail for the mammalian heart, this is not possible at the present time.

A. Mammals

In mammals, it is well established that the heart is controlled by inhibitory cholinergic fibres in the vagus nerve and excitatory noradrenergic fibres in sympathetic nerves reaching the heart by separate pathways (394, 442, 521, 523, 535). The vagus innervates the S-A node, which is the pacemaker region, and the atrium, but not the ventricle. The sympathetic nerves leave the stellate ganglion (= fused 1st thoracic and inf. cervical ganglia) to innervate the S-A node, atrium and ventricle. In the dog, there is also a contribution arising from the caudocervical ganglion, rostral to the subclavian artery (512a). The heart is sensitive to low concentrations of acetylcholine and noradrenaline, which mimic the actions of the nerves (523, 535).

Acetylcholine may also act on the "sympathetic ganglia" in the heart, *i.e.*, acetylcholine on an atropinised heart may cause cardioacceleration which is blocked by ganglionic and adrenergic blockers (439, 442). The existence of some intramural adrenergic cells in the heart has been demonstrated with the fluorescent histochemical method (169, 288, 404). However, whether these cells are rudimentary neurone cell bodies or chromaffin-type cells has not been clearly established. These cells are comparable to those described as special catecholamine-containing type cells (SIF cells) in sympathetic ganglia (176, 412) and are reminiscent of the primitive catecholamine-containing cells found in the heart of cyclostome fish (65).

The presence of pericellular adrenergic terminals on nonadrenergic ganglion cells in the heart was also reported recently (169, 404). It may be that these structures account for the modulation of vagal responses of the heart by sympathetic nerve activity (341a), although this modulation has also been explained in terms of adrenergic-cholinergic interaction at the muscle level (341b, 364a). The small number of adrenergic fibres in the vagal supply to the heart have been shown to be of sympathetic origin (405).

B. Cyclostome fish

The heart consists of a thin-walled sinus and atrium and a muscular ventricle. Branches of the visceral vagus run to the cardiac plexus near the hagfish heart but stimulation has no effect, so the heart does not appear to be controlled by extrinsic nerves (24, 123, 242). In support of these observations, no nerve fibres were found during an electronmicroscopic study of the heart of the hagfish (264). Furthermore, the heart does not react to acetylcholine even at concentrations of 10^{-2} g/ml (24, 290, 291). In addition, despite the fact that the hagfish heart contains very high levels of noradrenaline and adrenaline, contained in special chromaffin cells (65, 143, 238, 263, 264, 302, 423), it is insensitive to these catecholamines (129, 422). However, dihydro-ergotamine and reserpine both depress the activity of the heart, and in hearts treated in this way, noradrenaline has a marked stimulating effect (65, 201). It has been suggested that acceleration of the heart during mechanical distension is produced in part by release of catecholamine from the special chromaffin cells (197).

The lamprey heart, unlike that of the hagfish, is richly innervated (24). Stimulation of branches of the visceral vagus nerve in adult lamprey gives inhibition with secondary augmentation, but in larval lamprey there is no response to vagal stimulation (124). In contrast, the main response to stimulation of the medulla oblongata of another species is acceleration of the heart; when stimulation is intense, this is followed by a period of deceleration (24, 545). The heart of lampreys in contrast to that of hagfish is accelerated by low concentrations of acetylcholine (10^{-8} to 10^{-7}), which at the same time depress the force of contraction. Thus vagal innervation is probably cholinergic. The response to acetylcholine is blocked by hexamethonium and tubocurarine, but is unaffected by atropine (24, 193, 425). Thus the cholinergic receptors appear to be of the nicotinic type. There is no clear evidence in the lamprey that vagal fibres are preganglionic forming synapses with intramural ganglion cells.

No adrenergic nerve fibres were demonstrated in the lamprey heart with the fluorescent histochemical method but some monoamine-storing cells were seen (193). Catecholamines are reported to cause either a slight depression (425) or weak acceleration and augmentation (24, 193) of the heart beat.

C. Elasmobranch fish

The heart consists of a muscular sinus, an atrium, and a ventricle; a muscular conus is also present. According to Young (540) there is a vagal plexus on the sinus with a few fibres extending to the atrium and ventricle. There are no ganglion cells and only very few nerve fibres in the walls of the atrium and ventricle. Stimulation of the vagus nerves and acetylcholine produce inhibition of the heart (28, 96, 132, 201, 259, 294, 305, 315, 422, 540).

There have been several reports that there are no sympathetic accelerator nerves to the heart (285, 351, 352, 483, 540). High concentrations of adrenaline usually cause inhibition, sometimes followed by augmentation of heart beat (96, 352, 381, 422), while lower concentrations usually produce acceleration (28, 83, 201, 259, 294, 352, 422). However since there are no intracranial connections between sympathetic nerves and the vagus in elasmobranchs and certainly no separate sympathetic pathway, it seems unlikely that sympathetic adrenergic cardioacceleration of the heart will be found.

D. Teleost fish

The heart consists of a sinus, an atrium, a ventricle and a bulbus. Stimulation of the vagus nerves inhibits the sinus, atrium, and, indirectly, the ventricle (64, 112, 132, 224, 243, 305, 325, 326, 336, 391, 392, 440, 458, 468, 476, 483, 542). Acetylcholine mimics this inhibitory action (315) and atropine blocks the inhibitory response to vagal stimulation (224, 315). In early embryonic stages of the killifish (*Fundulus*) the heart is insensitive to acetylcholine (18).

There is both electronmicroscopic (533) and physiological (476) evidence that the sino-auricular junction is the primary cardiac automatism centre in teleost fish, and has a dense innervation. Yamauchi and Burnstock (533) suggested that the sino-auricular region in the fish heart is homologous to the sinus node in avian and mammalian hearts, and therefore that this system should be regarded as phylogenetically old.

Most workers have claimed that no sympathetic adrenergic nerve fibres supply the fish heart (64, 132, 296, 305, 336, 351, 401, 440, 476, 483, 537). It was suggested that regulation of beat was due to variation of the level of resting vagal influence on the heart (325, 326, 336, 458, 476). However, Gannon and Burnstock (224) have recently demonstrated many nerve fibres containing catecholamine in the sinus venosus and atrium and some in the ventricle of the trout heart with the fluorescent histochemical method, and have also shown that stimulation of the vagus nerves in the presence of atropine reveals excitation which is abolished by adrenergic blocking agents. Furthermore granular vesicles, which have been shown to be associated with catecholamines (109, 269), have been seen in nerves in the trout heart (533). Positive chronotropic and inotropic effects of adrenaline

and noradrenaline on the fish heart have been demonstrated (83, 193, 422, 441) and von Euler (183) has reported both noradrenaline and adrenaline in tissue extracts of fish heart (see table 1). Thus it seems likely that a small number of adrenergic nerves reach the heart *via* the vagosympathetic trunks.

Evidence for the presence of a small number of adrenergic ganglion cells in the trout heart has been discussed by Gannon and Burnstock (224).

E. Amphibians

The heart consists of a sinus, two atria, and a ventricle. The vagus nerves pass along the vena cava to the heart. Sympathetic nerves to the heart join the vagus at or peripherally to the vagal ganglion just outside the cranium. Together they form Remak's ganglion in the sinus, from which fibres pass along the atrial septum to Bidder's ganglion at the atrio-ventricular junction. Branches pass from the ganglion to the ventricle (230).

Acetylcholine and vagal nerve stimulation inhibit the heart of newts (393), toads and frogs (62, 172, 226, 227, 313, 346). There is a marked seasonal dependence on the response of the heart to vagal stimulation; in spring and early summer, stimulation of the vagus produces little response; throughout the summer vagal stimulation causes a progressively more marked response.

Stimulation of the sympathetic nerves causes acceleration of the frog heart (226, 227), and adrenaline mimics this action (172). Loewi (347) identified the substance released during stimulation of the sympathetic nerves to the frog heart as adrenaline. Adrenaline is 10 to 20 times more potent than noradrenaline in stimulating the frog heart (422). This is not surprising in view of the evidence that adrenaline rather than noradrenaline is the sympathetic neurotransmitter in amphibian hearts (15–17, 27, 32, 182, 184, 192, 346, 347, 422). Excitation resulting from sympathetic nerve stimulation is mediated by beta receptors, since the potency ratio for stimulation of the heart is isoprenaline > adrenaline > noradrenaline (177, 400, 422), and the beta blockers dichloroisoproterenol (DCI), pronethalol, and MJ 999 block action (154, 177).

The existence of a few small adrenergic ganglion cells within the ventricular myocardium, especially around the atrio-ventricular node, have been claimed but no micrographs shown (192).

F. Reptiles

The heart consists of a sinus, two atria, one ventricle partly divided by a septum, and a conus. Stimulation of the vagus nerve causes inhibition of the hearts of the tortoise, crocodile, lizard, and terrapin, and this response is blocked by atropine (139, 153, 226, 310, 346, 370, 371). In general the reptilian heart is inhibited by acetylcholine and excited by catecholamines (153, 156, 230). The ventricle is believed to be without innervation because it is relatively insensitive to acetylcholine (163, 225) and to adrenaline (260).

The sympathetic nerve in crocodiles arises from the eleventh spinal ganglion, runs separately to the heart, and is accelerator in action (226, 228, 230). The accelerator nerve follows the vertebral artery to the superior vena cava and then

follows this to form a plexus with the vagus on the sinus (226). In turtles, the sympathetic accelerator nerves leave the spinal cord at the level of the tenth spinal nerve, run forward through three ganglia of the sympathetic chain, and then extend toward the heart (230, 370). Adrenaline and noradrenaline cause acceleration of the atrium, which is antagonised by the beta blocker dichloroisoproterenol (153). The transmitter released by the sympathetic nerves is noradrenaline (27), and fluorometric assay of adrenaline and noradrenaline levels in the atrium showed noradrenaline to be the dominant catecholamine (139). The presence of vagal ganglia in the lizard atrium has been demonstrated (153).

G. Birds

The heart consists of two atria and two ventricles, but no sinus venosus. The heart rate is exceptionally high in birds (86, 487). The vagus is inhibitory (cholinergic), the sympathetic excitatory (adrenergic), to the heart (see Sturkie, 490). It is claimed that the ventricle in birds is supplied by cholinergic inhibitory fibres (67, 71), in contrast to the mammals, where few, if any, cholinergic fibres reach the ventricle. The nerve-free chick embryo heart is unresponsive to acetylcholine (142, 172).

Johansen and Reite (297) considered that the resting sympathetic influence on the avian heart is considerably higher than in mammals. Vagotomy causes considerable increase in heart rate of most birds (316, 429, 487, 489), especially in species with large heart size in relation to body size (*e.g.*, pigeons, seagulls, and ducks); tonic vagal activity is considerably less for flightless birds (*e.g.*, chickens) (487). The results of stimulation of the vagus nerve reflect this finding; it produces a strong inhibitory action in some birds (35, 160, 297, 306, 487) and a weaker inhibitory action in others (316, 495).

The right vagus nerve exerts a more pronounced inhibitory action on the heart than the left (297). The same difference between the action of left and right vagi has also been demonstrated in fish, amphibia, reptiles, and mammals (305).

Studies of the time of appearance of catecholamines during the development of the chick heart revealed the surprising result that whereas noradrenaline and adrenaline were both present in small but significant amounts in the 3-day-old heart, their precursors dopa and dopamine did not appear until 4 and 6 days respectively (280). Fluorescent nerve fibres are not visible in the musculature of the heart until the 16-day embryo, but cells with bright yellow fluorescence are present from day 6 (174).

H. Summary (fig. 5)

1) The innervation of the vertebrate heart by inhibitory vagal cholinergic fibres and by excitatory sympathetic adrenergic fibres was established early (in teleost fish) and retained virtually unchanged through evolution to mammals. Cyclostome and elasmobranch fish appear to lack adrenergic cardioaccelerator fibres. It has been suggested that the phylogenetically old nature of the heart of the lamprey is reflected by the observation that acetylcholine action is blocked more efficiently by tubocurarine than by atropine (284).

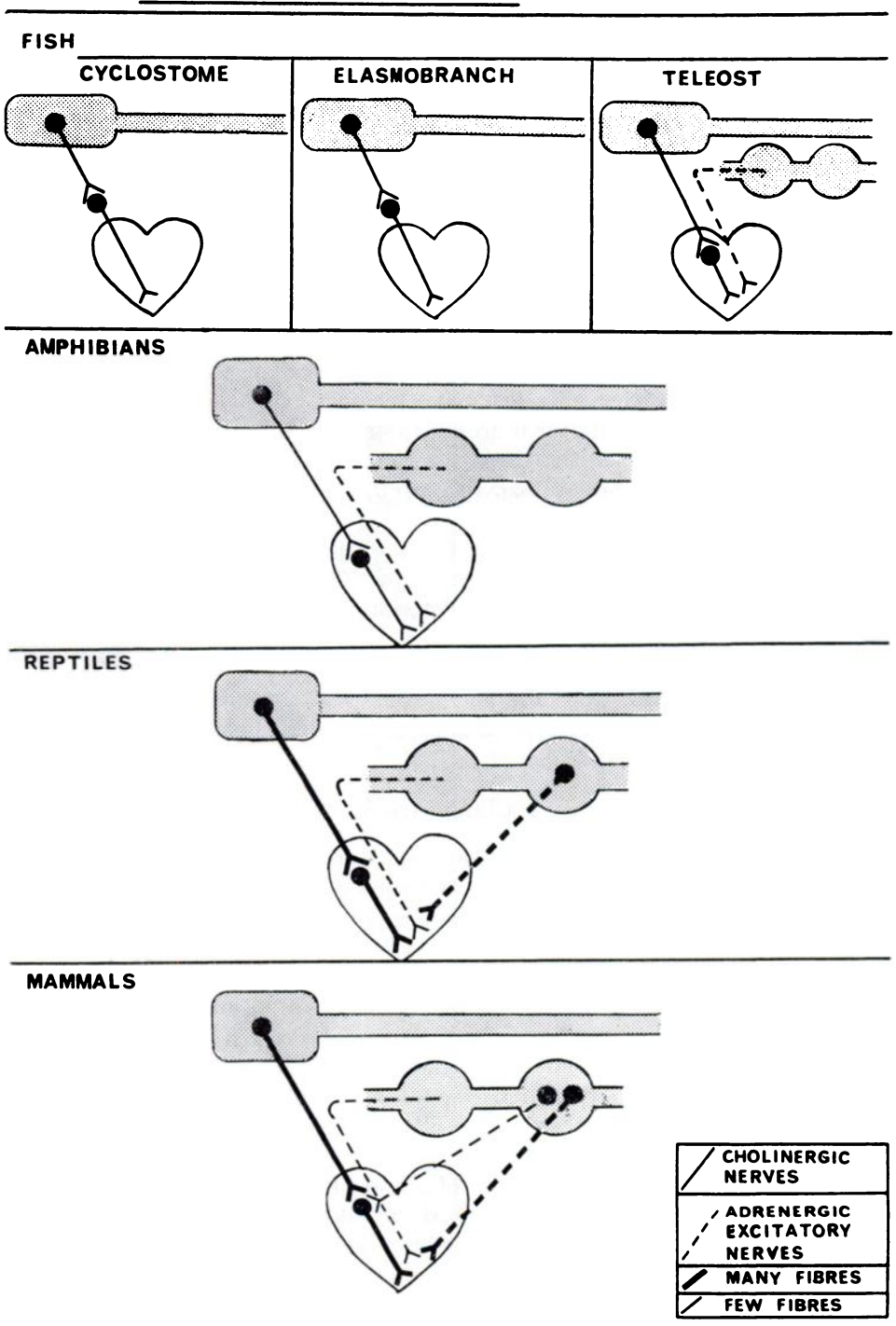

FIG. 5. Diagrammatic representation of the autonomic innervation of the heart. Central nervous system and sympathetic chain are represented by shaded areas. No distinction has been made between the innervation of different regions of the heart. However, vagal inhibitory cholinergic nerves do not extend beyond the auricle into the ventricle, except in birds. In contrast, adrenergic cardioaccelerator nerves supply the ventricle as well as the auricles in most vertebrates from teleost fish to higher vertebrates. Catecholamine-containing cells have been reported in the heart of all vertebrates, but it has not been clearly established yet whether they represent unusual ganglion cells or "chromaffin-type" cells with long processes. Note that adrenergic terminals about cardiac ganglion cells are found for the first time in mammals.

2) The existence of a small number of catecholamine-containing cells in the heart has been demonstrated in teleost fish, amphibia, and mammals, but their role has not yet been established.

3) In mammals, but not in lower vertebrates, there are some sympathetic adrenergic terminals about ganglion cells in the heart. This suggests that a sympathetic mechanism for the modulation of vagal control has been introduced.

VIII. BLOOD VESSELS

Cardiovascular function has undergone pronounced changes during vertebrate evolution. Gaseous exchange in fish takes place in gills, which have vascular channels in direct series with the heart and systemic vessels. Progressive elaboration of the heart structure has been associated with parallel changes in the dynamics of the circulatory system. In general, the aquatic medium provides a uniform and stable environment, so that there is little need for the elaborate adaptive mechanisms required to cope with the rapidly changing conditions that are encountered by terrestrial animals.

Studies of the innervation of the vascular system in lower vertebrates has been a particularly neglected field. Several recordings have been made of arterial and venous pressures in anaesthetised animals: elasmobranchs (28, 96, 294, 382, 531); teleosts (313, 378, 441); and amphibians (127, 293, 516). However there have been few studies of isolated vessels: fish, amphibia, and reptiles (106, 312) and birds (68–70, 482).

A. Mammals

Knowledge of the cardiovascular system in lower vertebrates is so limited that it is necessary to turn to the extensive work on mammals as a reference point (209, 210, 521). The large arteries contain a high proportion of elastic tissue, and this converts the pulsatile output from the heart into a smoother flow to the tissues.

Changes in diameter of the resistance vessels (small arteries and arterioles) determine regional flow of the various vascular beds. Fine control of these vessels is brought about largely by competition between centrally directed vasoconstrictor nerves and vasodilator effects of locally produced metabolites. The smooth muscle of the resistance vessels is often spontaneously active, providing a "basal tone." The level of tone can be affected by extrinsic nerves and local environmental factors. The phenomenon of autoregulation of flow (the increased vasodilatation that compensates for a primary decrease in pressure and flow through a circuit and the converse changes) is a product of the inherent myogenic tone of the resistance vessels.

A precapillary sphincter action regulates blood flow through the capillary network. This action is controlled primarily by local factors, but there is also an extrinsic nerve supply.

Changes in the lumen of the capacitance vessels (venules and veins) have a profound effect on venous capacity, with little effect on resistance to flow, and

hence on the filling of the heart and cardiac output. The smooth muscle of the capacitance vessels is controlled by extrinsic vasoconstrictor nerves. Apart from the spontaneous activity of the longitudinal muscle coat found in large veins, venous smooth muscle is generally quiescent.

Thus, in general, those components of the vascular circuit which subserve no local function, namely the large arteries and the capacitance vessels, are controlled exclusively by extrinsic nerves, and show little spontaneous activity. On the other hand, the muscular arteries are under tonic neurogenic control of sympathetic noradrenergic vasoconstrictor fibres, which is governed by discharge from the medullary vasomotor centre. Decreased discharge of these fibres produces a fall in tone of the vessels or vasodilatation without the involvement of specific vasodilator nerve fibres. In the precapillary resistance vessels vasodilatation is effected by release of various vasodilator metabolites. Catecholamine released from the adrenal medulla undoubtedly affects the smooth muscle of most vessels, but is of less general importance than neurogenic or local control of vessel diameter.

Cholinergic vasodilator fibres of several kinds have been demonstrated in mammals. Cholinergic fibres of sympathetic origin supply the arteriolar section of the resistance vessels of skeletal muscle beds (211, 240, 501; but see Viveros *et al.* (506a), who demonstrated adrenergic vasodilators in dog skeletal muscle).

The fibres are activated by corticohypothalamic discharges apparently activated in the "alarm-defence" reaction. Secondly, cholinergic sympathetic fibres produce local vasodilatation of vessels in the skin of the face and neck (209, 257, 273). The third type of cholinergic vasodilator fibre appears to be of sacral parasympathetic origin. These run in the *nervi erigentes* and produce dilatation of the arteries (and constriction of the veins) supplying erectile tissue of the genitalia (486). Cholinergic fibres produce vasodilatation of uterine arteries in late pregnancy (42). Finally, stimulation of parasympathetic nerves to the salivary and sweat glands also produces vasodilatation, but this may be due to a secondary release of bradykinin (342).

Many pharmacological studies on spiral strips of large arteries have been reported, and both alpha (excitatory) and beta (inhibitory) adrenotrophic receptors have been demonstrated (59, 219, 220, 364, 428). However, the beta-receptor-activating properties of noradrenaline on these and other arteries are weak, and vasoconstriction normally predominates.

The nature of the nervous control of the coronary arteries is controversial. There is evidence for control by both noradrenergic vasoconstrictor and cholinergic vasodilator fibres (517). However, it is also generally accepted that adrenaline increases coronary flow, but the effect is secondary, being a reactive hyperaemia (55).

Blood vessels in the head and neck are supplied by sympathetic postganglionic fibres from the superior cervical ganglia, those in the arms and upper part of the body of fibres from the stellate and upper thoracic ganglia, those in the abdominal viscera by fibres from the coeliac and mesenteric ganglia, and those in the lower part of the trunk and legs by fibres from the lumbar ganglia.

B. Fish

In cyclostome fish, the large sinuses or lacunar spaces interposed between the arteries and veins pose a number of problems for the dynamics of circulation. For example, the circulatory system in cyclostomes is characterised by the presence of auxiliary pumping mechanisms such as accessory hearts, inherent peristalsis of blood vessels, and a major role for skeletal musculature in maintaining intravascular pressures. Some very good descriptions of these systems exist (241, 296, 450), and an account of this work would be out of place in this review. The physiological significance of the lacunar circulation in these lower vertebrates and the possible homology with the lymphatic system in higher vertebrates is not known. Very little is known about the nervous control of vessels in the cyclostome fish (see Johansen and Martin, 296). It is known that the inherent rhythmicity of the portal heart is aneural (24), but an adrenergic innervation of some blood vessels has been demonstrated histochemically in cyclostome fish (341).

In both elasmobranch and teleost fish there is evidence for sympathetic nervous control of many blood vessels (106, 270, 294, 312). Recent fluorescent histochemical studies have shown adrenergic fibres to be present in the perivascular plexuses about many arteries in teleosts (36, 189, 224, 312, 341, 446, 447), but there have not been comparable studies yet in elasmobranchs. There are, however, reports that catecholamines injected into the circulation cause pressor responses in elasmobranchs (96, 294, 355, 382) and in teleosts (313, 378, 441).

Kirby and Burnstock (312) recorded the responses of isolated spiral strips of the ventral aorta of eel and trout and concluded that most of the excitatory nerve supply was cholinergic, but that a small proportion was adrenergic. This conclusion was supported by histochemical studies (312). A comparative survey of the responses of spiral strips of large arteries from fish, amphibians, and reptiles to catecholamines (see table 6) led Burnstock and Kirby (106) to conclude that there is a progressive increase in the adrenergic nerve component supplying these arteries during the course of vertebrate evolution. These authors also provided evidence that, in contrast to mammals, there are no catecholamine receptors that mediate inhibition in the large arteries of lower vertebrates.

There is no account available yet of the effect of autonomic nerve stimulation on the resistance of any vascular bed in fish, but indirect evidence suggests that sympathetic vasomotor tone may be lacking or rudimentary. For example, adrenergic blocking drugs caused little, if any, change in blood pressure recorded in the aorta of an elasmobranch (96) or of a teleost (441) and no compensatory cardiovascular responses to haemorrhage were detected in elasmobranch fish (525). Randall and Stevens (441) proposed that any generalised control of systems in vascular resistance is likely to be mediated, not by sympathetic nerves, but rather by circulating catecholamines released from diffusely distributed chromaffin cells.

In contrast, there is some indirect evidence that the post-trematic rami of the vagus nerve in teleosts and of both the glossopharyngeal and vagus nerves in elasmobranchs may innervate the branchial vascular bed (270, 461). No vasomotor responses were recorded from the isolated gills of the selachian fish *Squalus acanthias* (424). However, acetylcholine constricts and catecholamines dilate the

TABLE 6

Comparison of the responses of spiral strips of large arteries to catecholamines (concentrations in g/ml) in different vertebrate classes, and the actions of alpha and beta blockers on these responses

	Mammalia	Reptilia	Amphibia	Teleostei
Noradrenaline	+ (10^{-10}–2×10^{-9})	+ (10^{-9})	+ (10^{-8}–10^{-7})	+ (10^{-6}–10^{-4})
Adrenaline	+ (10^{-10}–2×10^{-9})	+ (10^{-9})	+ (10^{-8}–10^{-7})	+ (10^{-6}–10^{-4})
Isoprenaline	− (10^{-6}) (10^{-9}–10^{-8})	+ (10^{-5})	No effect	No effect
Alpha blockers	Block +	Block +	Block +	Block +
Beta blockers	Block −	Block +	Block +	Block +

* The symbols in the table are: + = contraction; − = relaxation; Block + = blockade of contractile response; Block − = blockade of inhibitory response.

Table taken from Burnstock and Kirby (106).

branchial vasculature in teleosts (309, 322, 424) and in lungfish (295). In view of these results, and by analogy with the vasoconstriction mediated by cholinergic vagal nerves, which is well established in the amphibian lung (350), it seems likely that there are vagal cholinergic vasoconstrictor fibres to the gills, at least in teleost fish. It is of interest in this respect that the coronary vessels of mammals, which are derived embryologically from visceral arch (gill) arteries (98, 197, 309), are also dilated by catecholamines.

Stimulation of the posterior spinal nerves in the skate causes vasodilatation in the claspers (218), but the transmitter involved is not known.

There have been several reports of reflex cardiovascular changes synchronised with respiratory changes in elasmobranch fish (353, 460). Bradycardia produced by anoxia was abolished by sectioning the vagi or by atropine, but the vasoconstriction of the gill vessels that also occurs during anoxia appears to be a direct response of the vascular smooth muscle (461). Holeton and Randall (270) suggested that the pressor response recorded in the aorta of the teleost (trout and tench) during hypoxia was due to increase in resistance in the gill and peripheral systemic vessels. Johansen and Martin (296) concluded, in relation to the bradycardia produced in response to anoxia in vertebrates, that the carotid sinus pressure receptors of the mammals are phylogenetically linked with more widespread sensitive areas in teleost fish.

The veins in fish do not have valves and do not appear to be innervated by adrenergic nerves (224, 446–448).

C. Amphibians

Intravenous injections of catecholamines in anaesthetised whole-animal studies in frog and toad (177, 313, 516) have produced pressor responses. The potency ratio, noradrenaline > adrenaline > isoprenaline indicates that the receptors in-

volved are of the alpha type. Indirectly acting sympathomimetics have the same pressor action in the toad as in mammals (313).

Burnstock and Kirby (106) have shown that the sensitivity of isolated spiral strips of the systemic artery of the toad to catecholamines is lower than that of systemic arterial strips of the lizard and that the excitatory response to transmural stimulation is partially blocked by adrenergic blocking agents (312). Since atropine produced some block of the excitatory response to stimulation of the intramural nerves, a small cholinergic excitatory component in nervous control appears to be present.

Sympathetic vasoconstrictor fibres innervating the renal vessels of the toad have been reported (532), and this is also known for mammals (465).

Lung vessels of the frog are under vagal vasoconstrictor influence (350a). It seems likely that these fibres are cholinergic since acetylcholine constricts the vascular bed (81, 510), a system derived from the fish branchial vasculature. Furthermore, the response to stimulation of the vasoconstrictor fibres to the lung is blocked by atropine (115, 350a). Mammalian pulmonary vessels are innervated by sympathetic noradrenergic vasoconstrictor fibres and vagal cholinergic vasodilator fibres (149).

There have been some reports on the innervation and pharmacology of isolated perfused vascular beds in anuran amphibians. It was found that the toad hind leg vessels were innervated by vasoconstrictor fibres which arise from the ninth and tenth sympathetic ganglia and by dorsal root vasodilator fibres (324, 444). Adrenotropic receptors in the frog hind limb vessels have been studied by Erlij *et al.* (177). These workers found that injection of adrenaline and noradrenaline produced vasoconstriction by stimulation of alpha receptors and that isoprenaline injection caused vasodilatation by beta stimulation, as in mammals (4). In perfused preparations of the frog tongue the vessels are constricted by adrenaline and dilated by histamine (311).

Luckhardt and Carlson (350a) reviewed the early literature on cardiovascular reflexes in amphibia. Mechanical stimulation of the viscera of both the anurans and urodeles leads to bradycardia and general vasodilatation of the resistance beds. Increasing the pressure in the aortic wall of the frog leads to a reflex fall in blood pressure (327). Tonically active depressor fibres in the glossopharyngeal nerve were demonstrated by Meyer (367), who also suggested that the carotid region of the frog was homologous with the carotid sinus of mammals, since increasing the pressure in the region led to reflex depression. Stretch receptors have been demonstrated in the carotid gland, the common carotid artery, and the pulmocutaneous trunk (396). However, the pressure required to bring about baroreceptor discharge was far higher than the normal blood pressure (282, 283). This suggests that the baroreceptors do not operate under normal conditions, in contrast to the baroreceptors in the mammalian aortic arch and carotid sinus, which show tonic activity in normal conditions (258). The carotid gland area of the frog has also been shown to be sensitive to hypoxia and some substances known to stimulate the mammalian carotid area (282, 283, 479). Cardiovascular reflexes synchronised with the breathing cycle have also been demonstrated (293, 355).

The veins in amphibians do not appear to be supplied by adrenergic nerves. However, cells containing high levels of monoamine are commonly found distributed at intervals along veins in the mesentery, lungs, and bladder (386, 388), and one might speculate that, when released, perhaps by circulatory hormones, these amines exert some control over the veins.

D. Reptiles and birds

When injected into anaesthetised turtles, lizards, and alligators, noradrenaline and adrenaline are pressor and acetylcholine is depressor (probably indirectly by inhibiting the heart beat) (6, 313).

Small arteries and arterioles, but not veins, in the urinary bladder and in the lung of the lizard are surrounded by an adrenergic ground plexus of nerves which contain noradrenaline (387, 389). Some fluorescent nerves were seen about veins in the lizard gut (446, 447). Transmural stimulation of isolated spiral strips of the systemic artery of the sleepy lizard (*Tiliqua rugosa*) elicited excitatory responses which were partially blocked by both alpha- and beta-adrenergic blocking agents. This result together with reports of their high sensitivity to excitation by noradrenaline suggests that a high proportion of the nerves supplying large arteries are adrenergic vasoconstrictors (106, 312). The remainder of the excitatory nerve supply appears to be cholinergic.

The coronary circulation of the tortoise heart has been the object of study (304). Adrenaline produces vasoconstriction, in contrast to the vasodilatation of the mammalian coronary vessels, while acetcylcholine causes vasodilatation. Unlike those in mammals, the coronary arteries are unable to adapt themselves to changes in cardiac metabolism, probably because of the absence of true capillaries in the heart.

Reflex cardiac inhibition upon stimulation of the viscera in turtles is accompanied by a fall in arterial pressure (350a, 371). The existence of stretch receptors has been demonstrated in the lung of the turtle (350a). If both the vagi were sectioned, stimulation of the central end of one produced increased arterial pressure, implying the presence of peripheral vasoconstrictor fibres, comparable to those seen in amphibians. Cardiovascular reflex responses to stimulation of the carotid bifurcation area were comparable to those known for mammals (60, 78, 403, 443). There has been considerable interest in the cardiovascular responses to diving in alligators, turtles, snakes, and lizards (11, 40, 54, 292, 524). Murdaugh and Jackson (380) showed that the bradycardia of the "dive reflex" in water snakes was blocked by atropine and suggested that some arterial vasoconstriction occurs on the basis of increased lactic acid levels in the blood during diving. Johansen and Martin (296) have pointed out that the "dive reflex" of mammals and reptiles is similar to the response to anoxia in elasmobranchs and teleost fish.

It is interesting to note that although the heart rate decreases during winter in both the lizard and toad, the mean arterial pressure is maintained in the lizard, but falls in the toad. In the toad, the seasonal fall in mean arterial pressure may be due to a reduction of sympathetic influence on the cardiovascular system; decreased concentrations of circulating catecholamines have been reported in the winter months (467). Another reason for reduced arterial pressure in toads may be

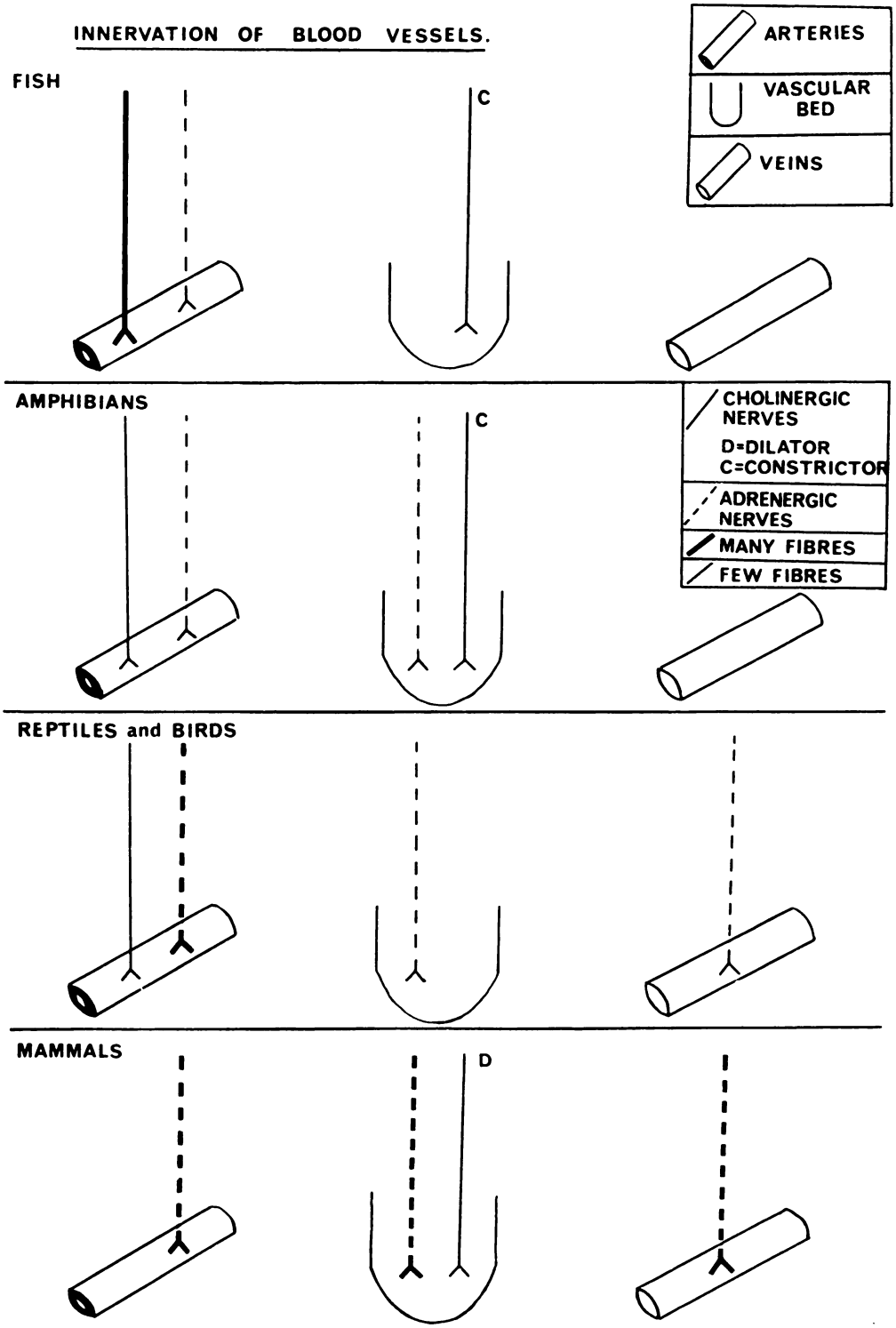
INNERVATION OF BLOOD VESSELS.
ARTERIES
VASCULAR BED
VEINS
FISH
C
AMPHIBIANS
C
CHOLINERGIC NERVES
D=DILATOR
C=CONSTRICTOR
ADRENERGIC NERVES
MANY FIBRES
FEW FIBRES
REPTILES and BIRDS
MAMMALS
D

Fig. 6.

that respiration becomes completely cutaneous during the winter instead of a mixture of pulmonary and cutaneous as it is in the summer. Any cutaneous vasoconstriction that might occur during the winter as a method of maintaining arterial pressure would probably interfere with the cutaneous respiration process.

Early reports have always assumed that birds are similar to mammals in the regulation of their circulation (see review by Sturkie, 490). However, differences between avian and mammalian systems have been claimed in relation to the nature of the carotid sinus reflexes (134, 258). A marked increase in systemic arterial blood pressure was recorded in birds after bilateral vagotomy (487). More recently Johansen and Reite (297) found that cutting the right vagus gave a fall in blood pressure, whereas cutting the left vagus gave a marked rise in blood pressure, and suggested that this indicated that the right vagus in birds normally mediates a pressure tonus.

Bennett (46) has demonstrated a dense adrenergic and cholinergic perivascular plexus about the coeliac artery in the chick and pigeon, as well as a sparse adrenergic nerve supply to the mesenteric veins. Both *alpha*- and *beta*-adrenoreceptors were demonstrated in helical strips of fowl aorta and visceral veins (70). Thus the reactions of the bird aorta are like those known for mammalian aortic strips, except that dopamine produced a greater maximal contraction than noradrenaline (70).

E. Summary (see fig. 6).

1) Many arteries are supplied by both constrictor adrenergic and constrictor cholinergic nerves in fish. During evolution there has been a progressive increase in the adrenergic compared to the cholinergic component, until in mammals many arteries have only adrenergic excitatory control. Cholinergic vasoconstrictor nerves in fish appear to be of both sympathetic and parasympathetic origin. In some vessels (*e.g.*, small arteries in the skin of the neck and cheek, arterioles in muscle pulmonary microcirculation, and uterine arteries) cholinergic nerves have taken up an inhibitory (*i.e.*, vasodilator) action in mammals.

2) Few, if any, veins have an adrenergic nerve supply in fish, amphibia, and reptiles, but some veins in birds and many in mammals have an adrenergic innervation.

3) There are no catecholamine receptors that mediate inhibition in large arteries (*e.g.*, aorta or systemic artery) of lower vertebrates (fish, amphibia, reptiles), all the receptors being of the *alpha* type. Thus it appears that the presence of

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FIG. 6. Diagrammatic representation of the autonomic innervation of arteries, vascular beds, and veins. Central nervous system and sympathetic chain are represented by shaded areas. The vascular bed depicted in lower vertebrates is limited to the branchial vascular bed of teleost fish and to the pulmonary vascular bed of amphibians. It is likely that control of vascular resistance in fish is maintained by catecholamines released from locally distributed chromaffin cells. The vascular beds depicted for mammals are the skeletal muscle and pulmonary circulation, both of which include cholinergic vasodilator fibres. Note the gradual transition from predominantly cholinergic innervation of arteries in fish to adrenergic innervation in mammals and that adrenergic innervation of the veins is lacking in lower vertebrates. There is a paucity of information in this field, so that the models proposed must be regarded as tentative and oversimplified.

alpha- and *beta*-adrenotrophic receptors to differentiate excitatory or inhibitory actions of catecholamines, at least on large arteries, are a late evolutionary development in birds and mammals.

4) The presence of chemo- and mechanoreceptors in the carotid region involved in cardiovascular reflex responses first appears in amphibians and is retained in reptiles and mammals.

5) Control of the branchial vasculature in teleost fish and the lung vessels in amphibia and reptiles is largely by cholinergic vasoconstrictors of parasympathetic (vagal) origin. In mammals control of lung vessels is by a mixture of sympathetic noradrenergic vasoconstrictor nerves and cholinergic vasodilators.

IX. EVOLUTIONARY SPECULATIONS

The view put forward by J. Z. Young (542), that antagonistic excitatory and inhibitory autonomic nervous control of the viscera is lacking in lower vertebrates, has been challenged by the discovery that the vagus nerve consists primitively of noncholinergic inhibitory nerves to the stomach and lungs (see Campbell and Burnstock, 120; Burnstock and Wood, 111). In fish and amphibians these inhibitory parasympathetic nerves are opposed by cholinergic excitatory nerves of sympathetic origin. Furthermore, contrary to earlier reports, sympathetic adrenergic excitatory fibres to the heart of teleost fish have recently been clearly demonstrated (224); these provide an antagonistic pathway to vagal inhibition. Inhibitory adrenergic pathways probably first appeared in the sympathetic nerves supplying the intestine, since the vagal inhibitory fibres do not extend much beyond the stomach in fish. At the amphibian level of evolution, a separate excitatory cholinergic sacral parasympathetic system was introduced, probably in connection with the formation of a cloacal bladder, and this may be associated with the gradual increase in proportion of inhibitory adrenergic, relative to excitatory cholinergic, fibres in the sympathetic nerves opposing them in higher classes.

The proposal of von Euler and Fänge (186), that in primitive verebrates adrenergic innervation of visceral and cardiovascular systems is poorly developed, receives some support from more recent experiments. Many of the sympathetic fibres supplying visceral organs are cholinergic, and adrenergic innervation of the heart and many blood vessels is rudimentary in fish. However, some organs in fish are heavily innervated by adrenergic nerves. For example, the circular muscle coat of the eel gut is more extensively innervated by adrenergic nerves than the gut of any other vertebrate so far examined (448). The swim bladder has an elaborate system of nervous control by extensive adrenergic plexuses, including peripheral control of the ganglion cells by pericellular adrenergic networks, a sophistication not seen extensively until birds and mammals.

A striking feature of the phylogeny of the autonomic nervous system is that there has been an exchange of cholinergic function from the sympathetic to the cranial parasympathetic outflow at some evolutionary stage between the amphibians and reptiles. Exchange of nervous control of the stomach during evolution was pointed out by Burnstock (100), who found that, in contrast to reptiles and

mammals, the vagal fibres to the stomach of the trout were noncholinergic, while the sympathetic nerves to the stomach were cholinergic and excitatory. A similar exchange has been shown between the nervous control of the lung of amphibians and reptiles (111). A possible explanation for this evolutionary change in nervous control of the lung might be found in relation to changes in the respiratory ventilating mechanism between the amphibians and the reptiles (see Hughes, 277). In the air-breathing amphibians, pumping movements of the buccal floor, while the external nares are closed, forces air from the buccopharyngeal cavity into the lungs (130). Carlson and Luckhardt (125, 350) showed that centrally controlled relaxation of the lungs, which they termed a "receptive relaxation," occurs during inspiratory movements. The inhibition is caused by increased activity in the lung inspiratory centre in the medulla and is mediated by the inhibitory vagal fibres. The value of such inhibition during a positive "pumping" pressure inspiration of this type would be to decrease the amount of pressure in the buccopharynx necessary to overcome pulmonary resistance. The lung inspiratory centre is usually in a state of tonic activity, so that cutting the vagi or destroying the medulla removes the inhibitory control that it exerts on the lungs, permitting the lungs to enter into a permanently contracted state (125, 348, 350).

In reptiles, during inspiration, there is an expansion of the body wall enclosing the lungs, so drawing air into the lungs. In some reptiles, the swallowing mechanism characteristic of amphibian respiration persists, and is sometimes used in emergency (323). The respiratory cycle consists of a rapid expiration and inspiration, most often followed by an inspiratory pause of variable length (383, 512). According to Carlson and Luckhardt (126), the external respiratory act inhibits the lung tonus by inhibiting the lung motor centre in the medulla. During the inspiratory pause there is a strong contraction of the lung musculature caused by increased activity of the lung motor centre. The physiological value of the contraction is not obvious. In reptiles, lung tonus depends primarily on motor impulses reaching the lung *via* the vagus nerve, so that after destruction of the brain or section of the vagi, the lungs become essentially atonic and quiescent (126).

In mammals, inspiration is by active suction, as is the normal method in reptiles. Unlike reptiles, however, there is a regular alternation of inspiration and expiration, with no prolonged pauses. It has been suggested that the smooth muscle of the mammalian lungs may be actively involved in the respiratory movements, relaxing during inspiration and contracting during expiration (356). There is evidence that the musculature of mammalian lungs is normally under some degree of tonic excitatory influence from the central nervous system *via* the vagus, since on administration of atropine or after cutting the vagi there is usually a permanent relaxation of the bronchial musculature (159, 356). However, there have been a number of reports of bronchodilator responses to stimulation of the vagi in mammals (see Widdicombe, 522).

The results discussed above show that in some respects there is a close correlation between central and peripheral mechanisms of respiratory control. Thus, in amphibians, in which tonic inhibitory central control occurs, the vagal fibres are mainly inhibitory. In reptiles and mammals, on the other hand, the lungs are

under tonic excitatory central control, and the vagal fibres are excitatory. Therefore, it would appear that, in the case of the lung innervation, the nature of the peripheral system is determined by the evolutionary state of the central respiratory control mechanism. It would be interesting to determine the location of the cell bodies of the preganglionic neurones of the cholinergic sympathetic outflow in both teleost fish and amphibia.

As the sympathetic system evolved, the segmental ganglia became connected by chains, while the more numerous segmental nerves were replaced by a few splanchnic nerves. The sympathetic system has continued to show a progressive elaboration and specialisation during evolution in several ways, all of which lead to more effective nervous control of the viscera. Adrenergic terminal networks about nonadrenergic ganglion cells in various visceral organs first appeared in reptiles (*e.g.*, gut, bladder) and are numerous in mammalian systems, including the heart. Displacement of adrenergic ganglion cells into visceral organs has been developed independently several times in different groups (*e.g.*, in the frog bladder; in the toad lung; in the lizard intestine) but does not appear to have become well enough established to be regarded as an evolutionary trend. The structure of sympathetic ganglion cells throughout the vertebrates shows considerable uniformity, and this lack of change suggests that elaboration of the sympathetic nervous system has taken place largely by development of more sophisticated pathways and by alteration in relationships at neuroeffector and possibly peripheral ganglion sites, rather than by specialisation of cell structure (see Nicol, 401). Fluorescent histochemical (46, 386–388, 446–448) and electronmicroscopic (50, 51, 456, 457, 492, 494, 533) studies of the innervation of various tissues in lower vertebrates have shown that the complex nature of neuroeffector relationships is established early in vertebrate evolution, *i.e.*, the peripheral extensions of sympathetic nerves are varicose with high levels of catecholamines located within the varicosities, suggesting "en passage" release of transmitter during transmission, as in mammals (411).

The question has been raised (537) whether the dorsal and ventral root outflows of mammals are the remains of a previous metameric arrangement in which there was a complete double series of visceromotor fibres, leaving in the dorsal and ventral roots of every segment throughout the body. Young came to the conclusion that it was likely that the ventral root system arose rather late in phylogeny (see also Goodrich, 237), after the specialisation of the cranial region, and that it only secondarily grew forwards into the head. This is supported by the fact that the ventral root system occurs only in the trunk region of selachian fish and the sturgeons and does not extend into the head, while there are visceral motor fibres in almost every segment from the front of the head to the anus running through the dorsal roots (540). The primitive condition, then, may have resembled that found in *Amphioxus* (215, 255), where the ventral roots innervate only the myotomes and all the visceromotor fibres leave by the dorsal roots. The motor cells may have migrated out along the dorsal roots and become aggregated into separate sympathetic ganglia which secondarily became connected with the ventral roots. Some support for this theory comes from studies of the ontogeny of the

sympathetic nervous system, *i.e.*, neurone cell bodies pass down dorsal as well as ventral roots during early development (122, 534).

Although the nature of the autonomic innervation of systems other than visceral or cardiovascular have not been covered in the present review, the conclusions reached by other reviewers on the innervation of these structures are pertinent to our present considerations, since comparable evolutionary trends are illustrated. The pattern of evolution of innervation of the iris is summarised in figure 7. A sympathetic innervation of the iris occurs in teleosts, but has never been observed in elasmobranchs. Fibres run anteriorly from the anterior spinal nerves up the sympathetic chain to form synapses in the sympathetic ganglion on the trigeminal nerve (536). Constriction of the pupil in response to stimulation of the sympathetic chain is blocked by atropine, and this indicates that, like many other sympathetic nerves in teleost fish, they are cholinergic (536, 539). Stimulation of the oculomotor nerves (cranial parasympathetic outflow) causes pupillary dilatation in teleosts (536) and has also been reported in one elasmobranch (538). This response is in marked contrast to the pupillary constriction produced by oculomotor nerve stimulation in mammals. The effects of blocking drugs on the response to oculomotor nerve stimulation have not been examined, but it seems likely that acetylcholine is the transmitter. Thus it would appear that both the oculomotor nerve (to the dilator muscle) and the sympathetic fibres to the constrictor pupillae are cholinergic in teleost fish. Sympathetic nerves also appear to supply the striated extra-ocular muscles in teleosts. These fibres are probably excitatory since sympathetic section causes abnormal protrusion of the eyeball (536). Sympathetic adrenergic fibres can cause contraction of the superior rectus muscle in mammals (165). In selachians, the sphincter (constrictor) muscle of the iris contracts in direct response to illumination. The radial (dilator) muscle on the other hand, is innervated by motor fibres from the ciliary and probably also the oculomotor nerve (401, 513, 539). Early investigations of the innervation of the amphibian iris assumed that both pupillary sphincter and dilator muscles were present, and most workers concluded that the sympathetic system provided motor fibres causing dilatation of the pupil while constriction was mediated by excitatory cholinergic fibres in the oculomotor and ciliary nerves (19, 197, 226, 227, 321, 334, 488, 513). However, a recent study of the iris has shown that there is no dilator pupillae (21). The constrictor pupillae is controlled by opposing excitatory cholinergic parasympathetic nerves and inhibitory adrenergic sympathetic nerves. The evolution from sympathetic and parasympathetic excitatory control of separate constrictor and dilator muscles respectively in teleost fish, to antagonistic excitatory and inhibitory control of the sphincter muscle in amphibians, would appear to be a necessary consequence of moving pupillary control from two antagonistic muscles to one muscle. Once dual control became established in evolution, it would seem that it was retained even after two-muscle pupil control reappeared in the reptiles and mammals. Information on the innervation of the iris in reptiles and birds is limited, but, apart from complications resulting from involvement of striated muscle, it appears that the pattern is very close to that seen in mammals (20), *i.e.*, cholinergic excitatory oculomotor nerves possibly

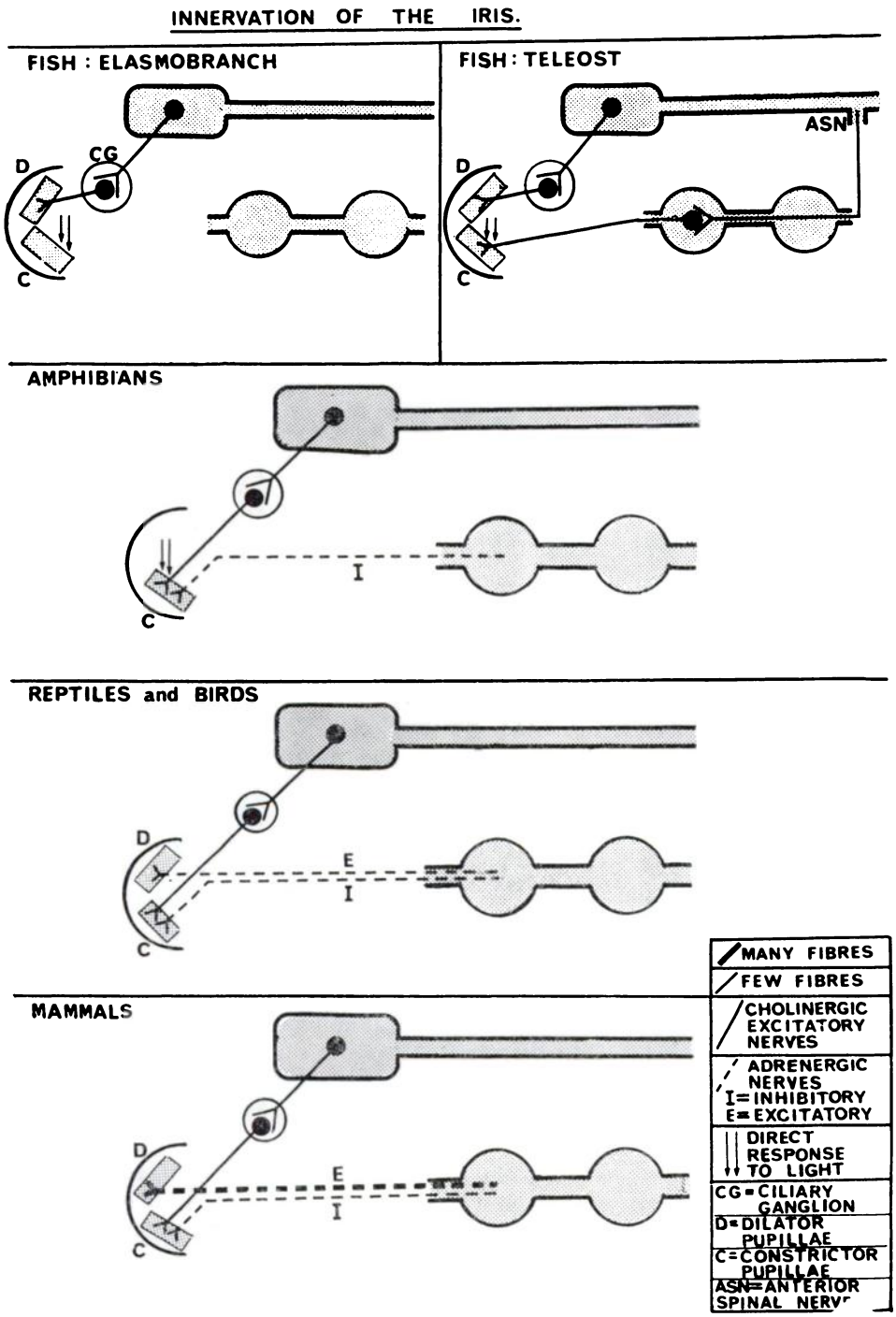

FIG. 7. Diagrammatic representation of the autonomic innervation of the iris musculature. Central nervous system and sympathetic chain are represented by shaded areas. The diagram representing the reptile and bird condition is largely conjectural. Note in particular that adrenergic nervous control of the iris muscles is lacking in fish. In fish the dilator pupillae is innervated by cholinergic parasympathetic nerves; in higher vertebrates these nerves control the constrictor pupillae. Inhibitory adrenergic control of the constrictor muscle first appeared at the amphibian level, whereas adrenergic excitatory control of the dilator muscle is strongly represented in mammals.

together with some adrenergic inhibitory nerves pass to the constrictor muscle while adrenergic excitatory sympathetic fibres supply the dilator muscles. Thus, this system again illustrates a phylogenetic switch from cholinergic sympathetic nervous control in fish to increasingly elaborate adrenergic sympathetic innervation in higher vertebrates. It should be pointed out that pupillary constriction in the amphibian and fish can result from direct stimulation of the sphincter muscle fibres by light as well as from nervous control. In contrast, in higher vertebrates, changes in pupil size are under nervous control only, involving retinal receptors and reflexes mediated by the central nervous system. A double innervation of the mammalian sphincter pupillae has been postulated in many mammals, such that sympathetic stimulation would lead to inhibition of the sphincter in association with contraction of the dilator muscle. Some support for this idea comes from the evolutionary studies, if one imagines dual innervation of the sphincter in mammals as a feature retained from the amphibia. However, Loewenfeld (345), in an extensive review, pointed out that many of the results reported in this field are questionable, because of the technical difficulties in resolving such systems.

The main conclusion concerning the nervous control of dermal chromatophores in fish is that the melanophores in most teleosts are under the control of sympathetic adrenergic nerve fibres, stimulation of which causes concentration of the melanophore pigment (206, 427, 541). Sympathetic adrenergic innervation of dermal photophores in teleosts has also been postulated (402). The existence of cholinergic sympathetic fibres that mediate pigment dispersal in melanophores has also been proposed (206); they provide a further example of antagonistic autonomic nervous control in a lower vertebrate. The control of chromatophore functions by the sympathetic nervous system in fish was probably derived from the peripheral extension of nerve fibres destined for blood vessels. This represents an independent specialisation not repeated again until the reptiles (459). Control of melanophores in many elasmobranch fish and amphibians is apparently aneural (265–267, 426, 478, 540, 541). Innervation of the chromatophore system in teleost fish once again illustrates the error of assuming that all systems fit into a general evolutionary trend, *i.e.*, although adrenergic nerves are rudimentary in many organs in fish, they are highly developed in others.

Many features of the mammalian autonomic nervous system which have been regarded as deviations from the classical picture (see Campbell, 116) can now be considered as relics of the primitive autonomic organisation. For example, the cholinergic sympathetic postganglionic neurones, which have been shown to supply a number of visceral organs (see Burn and Rand, 99), are represented in much greater numbers in lower vertebrates. The recent discovery of nonadrenergic inhibitory fibres in the mammalian gut (45, 104, 105, 108), many of which are under the control of preganglionic vagal nerve fibres (92, 113, 332, 361), appears to be another example of a component of the autonomic nervous system strongly represented in primitive vertebrates (see Campbell and Burnstock, 120). The presence of a small number of adrenergic fibres in the vagus nerve in mammals (140, 148, 239, 338, 369, 375) has caused some confusion, but, in view of the substantial component of sympathetic nerves that join the vagal trunk in lower

vertebrates, this also appears to be a declining relic of the primitive state. On the other hand, the presence of adrenergic terminal networks about ganglion cells in the bladder, heart, and gut in mammals appears to represent the emergence of a new evolutionary trend, although it is found in rudimentary form in reptiles. The presence of cholinergic vasodilator fibres to resistance vessels in skeletal muscle beds appears to be a new evolutionary development unique to mammals.

It must by now be apparent that great care should be taken in making speculations in this field. Despite the general evolutionary trends outlined above, there is often a surprisingly high degree of variation in autonomic innervation of a particular organ even between closely related species (*e.g.*, nervous control of toad and frog bladder). When these variations occur, they may be the result of specific differences in ecological or behavioural conditions. In other cases the difference may represent divergent evolutionary trends in which there is little selective advantage or disadvantage between adrenergic and cholinergic excitatory control. Furthermore, the existence of evolutionary trends in the innervation of one particular organ does not imply the presence of parallel trends in the innervation of another organ, even when both organs are innervated by branches of the same nerve. It is necessary to correlate any evolutionary changes in the innervation of a particular organ with concurrent changes in the central nervous control of the organ and in the activities of other organs functionally linked to it. It is also important to take into account the degree of control of the organ exerted by circulating hormones.

X. GENERAL SUMMARY

1) The anatomy of the autonomic nervous system in teleost fish, amphibia, reptiles, and birds is essentially similar to that seen in mammals. However, a sacral parasympathetic system is not present in teleost fish and urodele amphibians and is only rudimentary in anurans. In cyclostome fish there are no sympathetic chains or segmental sympathetic ganglia and in elasmobranchs there are series of paravertebral ganglia linked by a loose plexus of nerve bundles rather than a compact sympathetic chain, and grey rami are absent.

2) The vagal supply to visceral muscles such as the stomach and lung is primitively nonadrenergic and inhibitory. At some evolutionary stage higher than the Amphibia, the cholinergic excitatory function classically attributed to the vagus has been transferred from the sympathetic to the parasympathetic outflow. This may also be correlated with the switch from primitive sympathetic cholinergic excitatory supply of the viscera to predominantly adrenergic inhibitory control.

3) The primitive parasympathetic innervation of the heart is cholinergic and inhibitory and this has been consistently retained throughout vertebrate evolution. Similarly adrenergic cardioaccelerator fibres appear early in evolution and are retained throughout. Primitively they run together with vagal fibres in the vagosympathetic trunks and only at the reptile level reach the heart by separate nerve trunks, although the presence of a few adrenergic fibres of sympathetic origin still remain in the vagal trunks even in mammals. The presence of special catecholamine-containing cells appears to be a consistent feature of the vertebrate heart.

4) Nerve trunks of the morphologically defined sympathetic nervous system in fish and amphibia consist of predominantly excitatory cholinergic fibres. There are various proportions of adrenergic and cholinergic fibres in sympathetic trunks in reptiles and birds, while in mammals, most, and sometimes all, of the fibres in sympathetic trunks are adrenergic. Thus, there has been an overall trend from cholinergic to adrenergic sympathetic control of visceral and vascular systems.

5) The development of preganglionic adrenergic fibres modulating the activity of nonadrenergic intramural ganglion cells in such organs as gut and bladder is not established until the mammals, although there is some rudimentary development of this kind in reptiles and birds.

6) The presence of intramural adrenergic nerve cells in various organs appears to be an evolutionary development that has taken place independently in many groups (*e.g.*, lizard gut, toad lung, frog bladder). However it has not become established as a major feature of later evolution in mammals; no adrenergic cell bodies have been found in the gut and few in the heart and bladder.

7) The influence of circulating catecholamines released from diffusely distributed chromaffin cells appears to play a much more significant role in lower, than in higher vertebrates, in which direct nervous control has been developed to a more sophisticated degree. Chromaffin tissue is widespread in cyclostomes and is closely associated with the segmentally arranged sympathetic ganglia in elasmobranchs and to a large extent in teleosts and amphibians.

8) Models have been put forward in this review of the pattern of evolution of the autonomic innervation of various visceral and cardiovascular systems. However it should be emphasised that these models are largely speculative and it is hoped that they will provoke further experimentation in the field which will lead to modification, refutation, and, one hopes, even support of some of the ideas proposed.

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