Clinical Autonomic Failure

Practical concepts

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Introduction

Medical students, internists, and neurologists too may have only a cursory acquaintance with clinical concepts of autonomic failure and, confronted with such patients, often seek help from books on physiology, pharmacology, or sometimes behavioral medicine. The autonomic nervous system affects functions of all other systems and influences behavior. It is the orchestrator for adaptive responses to stress, be it emotional, environmental, or sociologic. It is not surprising, therefore, that clinical manifestations of any illness are influenced by the autonomic nervous system which also affects interactions of individuals with their surroundings.

Medical students, fresh from basic science 'blocks', often find it difficult to master the transition to the bedside and to acquire clinical experience of autonomic failure which influences symptoms and signs of many disorders, adaptation of patients to their misfortune, response to treatment and recovery.

Because published work in this field is so extensive, the issues are so big and most physicians do not get beyond nebulous concepts of autonomic dysfunctions, this book will serve by emphasizing the size, the expanse, and the clinical relevance of concepts of autonomic physiology, anatomy, and pharmacology and place these into their proper clinical setting. It will help the transition from early student days to clinical clerkships and eventually practice.

The book reviews some scientific background important to concepts of clinical autonomic failure and concentrates on specific aspects often baffling to the uninitiated (who may find the tables helpful) and to those who might not customarily think about autonomic concepts relevant to general disease. Sections spanning many disciplines have been gathered together to give an overview of the influence of autonomic dysfunction in disorders of widely different pathogeneses.

The clinical significance of autonomic failure in disease emerges as a somewhat fuzzy picture without absolute answers. The not surprising message of most chapters, therefore, is that recent work remains inconclusive and equivocal and, for those interested in clinical autonomic failure, the avenues to advance knowledge by new ideas and concepts remain widely open and uncrowded.

Otto Appenzeller, M.D., Ph.D.
December 1985

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CHAPTER 1

Anatomy and histology

Galen (quoted in Opus de Usu Partium Corporis Humani, Paris, 1528) seems to have been the first to refer to a part of the autonomic nervous system when he described a nerve trunk lying along rib heads and recognized its connecting fibers with the spinal cord. He thought that this was a branch of the vagus and believed that through it the viscera received sensitivity from the brain and power to move from the spinal cord. Galen also observed at least three enlargements along the course of the sympathetic chain and described the ganglion at the entrance of the chain into the abdomen, which might have been the semilunar ganglion of the celiac plexus. He suggested, a widely accepted belief thereafter, that there was 'sympathy' or 'consent' between body parts and regarded the peripheral nerves as tubes through which animal spirits were distributed to bring about this 'sympathy'.

Galen's belief that the vagi and sympathetic trunks were a single unit, both functionally and anatomically, was shared by subsequent anatomists until Estienne (1545) recognized the sympathetic trunks as a distinct anatomical structure. Willis (1664) gave the name of 'intercostal nerve' to the sympathetic trunk and believed that the cerebellum was responsible for involuntary movements which he distinguished from voluntary motion.

Although Willis recognized the innervation of the heart by the vagus nerve, the functional significance of this was not discovered until Lower's (1669) description of the effects of vagus section on heart rate.

The suggestion that involuntary movements are initiated by local stimulation due to nerve irritation is attributed to Whytt (1751) and he used this as an explanation for the reaction of the pupil to light. Whytt's importance to neurophysiology is further enhanced by his suggestion that all 'sympathy' or 'consent' must be referred to the central nervous system since it occurs between body parts whose nerves make no connection with each other so that the transmission of 'sympathy' cannot involve the flux of matter and must therefore occur in an area where all nerves have their origin (Whytt, 1765).

Du Petit (1727) pointed out that the sympathetic trunk was not directly connected with the brain and was a separate structure from the vagus, but it was Winslow (1732) who first designated the paravertebral chain as 'the great sympathetic nerve'.

In 1764 Johnstone said that the movements of the heart and intestine are involuntary

because the sympathetic ganglia blocked the actions of the will and prevented them from reaching these structures and that this blockade also accounted for the relative insensitivity of the viscera.

Studies by Bichat in 1802 led to the concept of 'animal life' and 'organic life'. He pointed to the continuous action which was the hallmark of organic life distinct from the intermittent activity of animal life, a concept which is still widely expressed by the terms 'visceral' and 'somatic' respectively. Bichat was aware of the different appearances of gray and white rami communicantes but did not recognize their significance.

The term 'vegetative nervous system' was used by Reil (1857). He thought that the rami communicantes served as connectors between the animal and vegetative nervous systems. An early description of nerve cell bodies in sympathetic ganglia appeared in Ehrenberg's (1833) writing, together with comments on the microscopic structure of nerve fibers. In the 19th century the ciliary, sphenopalatine, otic and submandibular ganglia were thought of as part of the autonomic nervous system but their functional significance was not appreciated.

Meissner's (1857) mention of the submucous plexus and the description of the myenteric plexus by Auerbach (1864) in the second half of the 19th century concluded the anatomic studies which paved the way for the physiologic work on vasomotor function by Bernard (1878). His studies led to the concept of sympathetic vasoconstrictor action but not until some time later was he able to demonstrate vasodilator nerves in arteries supplying the submandibular gland after stimulation of the chorda tympani. Bernard thought that the sympathetic reflexes were mediated by the spinal cord and that on stimulation of some areas of the brain impulses were discharged through the sympathetic fibers.

Gaskell (1886) gave a detailed description of the anatomy of the rami communicantes and recognized that the efferent fibers within these nerves arise in the spinal cord and that corresponding fibers can be found in some cranial nerves. He also recognized the connection with the central nervous system of the peripherally located ganglion masses through medullated fibers and divided these fibers into bulbar, thoracolumbar and sacral groups. Langley and Dickinson (1889) used the action of nicotine on ganglia to study the relation of the nerve fibers to the peripheral ganglion cells and proposed the name 'autonomic nervous system'. When this term was coined the different distribution and functional effects of the thoracolumbar and craniosacral outflows were known and Langley separated the former from the rest of the autonomic nervous system. After the discovery of substances which either produced actions similar to those obtained by stimulation of the thoracolumbar or of the craniosacral outflows he coined the term 'parasympathetic' for the latter (Langley, 1901).

ANATOMY OF THE AUTONOMIC NERVOUS SYSTEM

Body functions, which can proceed independently of volitional activity, are regulated at least in part by reflex mechanisms served by afferents, efferents and central integrating structures which are included in the autonomic or vegetative nervous system. Although the activity of this system is essentially autonomous, it is not entirely free from voluntary control. The vegetative nervous system is made up of all neurones which lie outside the central nervous system and is concerned with visceral innervation. The only exceptions are those that are part of the afferent system of the cerebrospinal nerves and are located in the posterior root ganglia or some sensory cranial nerve ganglia. The neurones in the brain, brainstem and spinal cord,

through which these autonomic neurones are functionally connected, are also included in the vegetative nervous system.

There are two divisions of this system, the sympathetic and parasympathetic, each usually made up of preganglionic and postganglionic neurones. The cell bodies of the preganglionic neurones lie in the brain or spinal cord and those of the postganglionic neurones in the autonomic ganglia. The preganglionic sympathetic neurones are in the thoracic and upper lumbar cord and this part of the vegetative nervous system is also called the thoracolumbar division (Fig. 1). Preganglionic neurones of the parasympathetic nervous system are in the brainstem and sacral cord and this is also termed the craniosacral division (Figs. 2 and 3). The viscera are mostly innervated by both sympathetic and parasympathetic fibers. Many structures supplied by the vegetative nervous system have, however, a single innervation only, such as some blood vessels and sweat glands.

The preganglionic fibers of the sympathetic nervous system arise in the intermediolateral and intermediomedial cell columns of the spinal cord and join the ventral roots of T1 to L2.

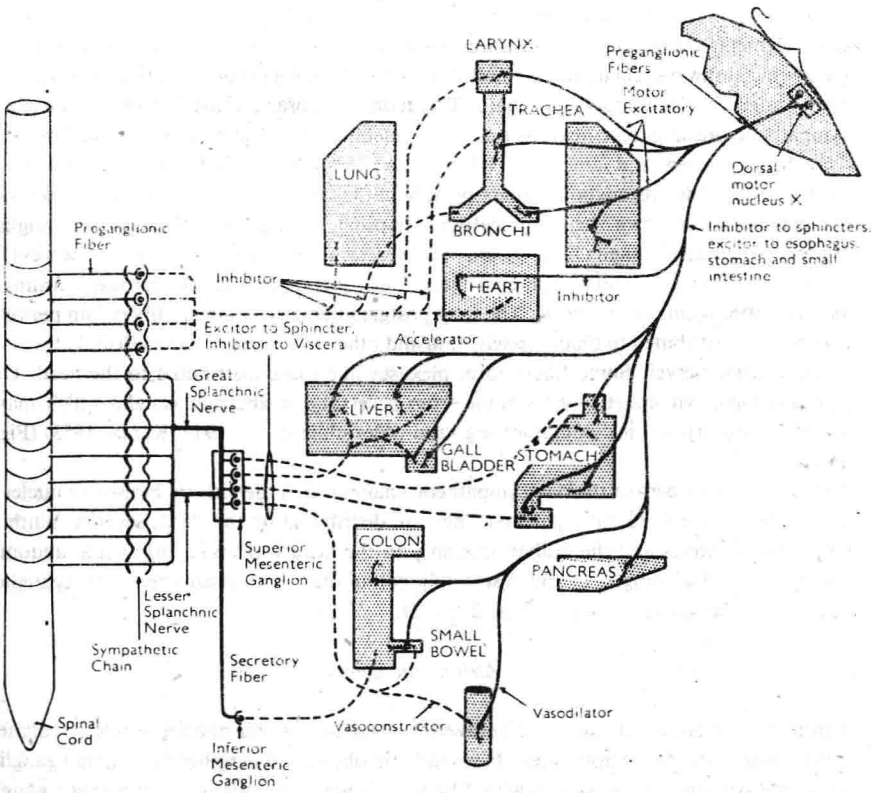


Fig. 1. Diagram to show the pre- and postganglionic fibers of the autonomic innervation of the thoracic and abdominal viscera. Dotted lines: postganglionic fibers of the thoracolumbar division. Short solid lines on viscera: postganglionic fibers of craniosacral division. Drawn by M. Norviel.

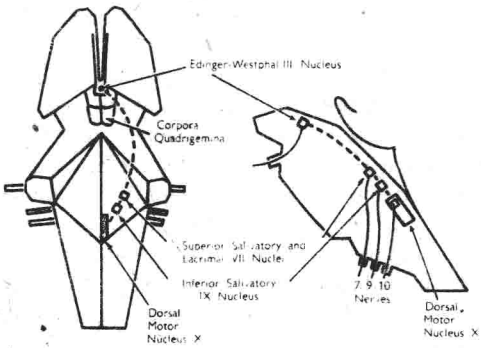


Fig. 2. Diagram to show the brainstem nuclear masses which form part of the craniosacral division of the autonomic nervous system. Left: dorsal aspect; right: lateral aspect. Drawn by M. Norviel.

Variations of this occur and preganglionic fibers from C7 (Harman, 1900) and as low as L4 cord segments have been demonstrated (Randall et al., 1955; Monro, 1959). Some preganglionic pathways remain intraspinally for up to 12 segments before exiting through ventral roots to reach the sympathetic chain. The axons to thoracic glanglia arise from ipsilateral sympathetic preganglionic neurons but those reaching lumbar ganglia are of bilateral origin. Therefore, crossed and uncrossed intraspinal preganglionic pathways exist (Faden and Petras, 1978). The preganglionic fibers synapse in the sympathetic chain or traverse several of the ganglia up or down the chain before synapsing, or may pass through the ganglia to synapse in collateral ganglia near viscera. These latter fibers form the splanchnic nerves (Figs. 1, 4 and 5). They also contain some postganglionic fibers, particularly near their termination (Kuntz, 1956; Kuntz et al., 1957). The long postganglionic sympathetic fibers join peripheral nerves to be distributed to blood vessels, skin and other structures or form visceral nerves such as the cardiac nerves. Some fibers form plexuses like those distributed to the head. Other postganglionic sympathetic fibers come from accessory or aberrant ganglia which may be found in neve trunks or communicating rami (Alexander et al., 1949; Kuntz, 1953) (Figs. 4 and 6).

Preganglionic fibers of the parasympathetic chain arise in the visceral brainstem nuclei and the second to fourth sacral segments. They are distributed by the third, seventh, ninth and tenth cranial nerves and the bulbar accessory to the head and neck, thorax and abdominal viscera. The distal ganglia of the descending colon and pelvic organs receive preganglionic fibers from the sacral segments (Figs. 2 and 3).

Autonomic ganglia

Autonomic ganglia are divided into paravertebral (chain) ganglia and prevertebral (collateral) ganglia which are the synaptic sites of sympathetic fibers, and peripheral (terminal) ganglia in which the synapses of parasympathetic fibers are found. The origin of sympathetic ganglion neurones remains in doubt. Experimentally it can be shown that they arise either entirely from the neural crest (Hammond, 1946; Yntema and Hammond, 1947, 1955) or the basal plate of the neural tube (Brizzee, 1949; Brizzee and Kuntz, 1950), or from both sites (Triplett, 1958). It

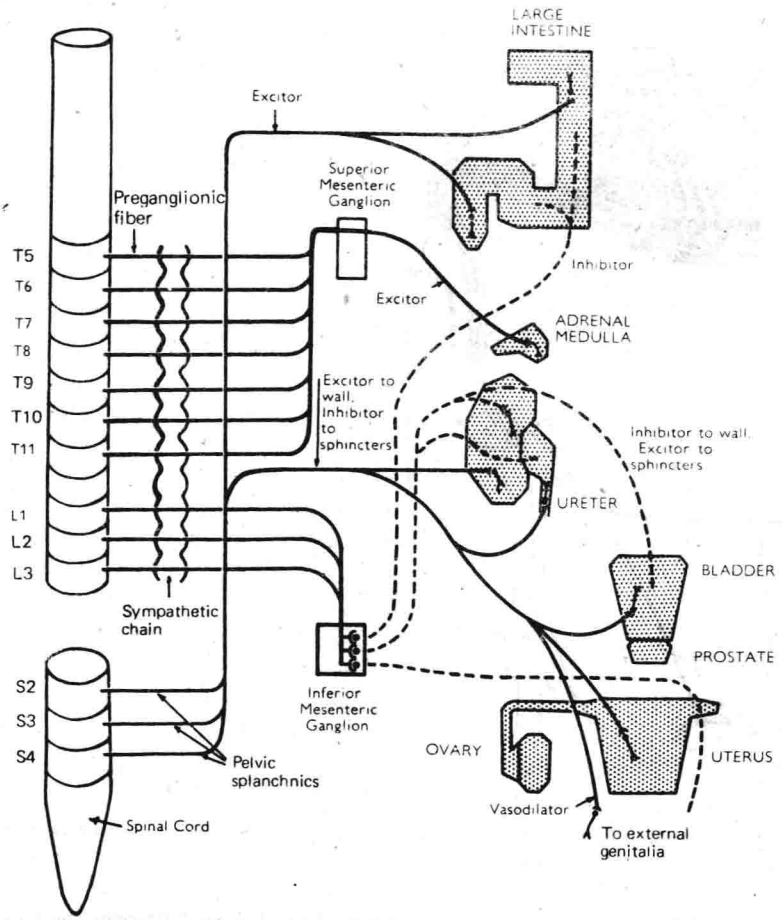


Fig. 3. Diagram to show the pre- and postganglionic fibers of the autonomic innervation of the abdominal and pelvic viscera. Dotted lines: postganglionic fibers of the thoracolumbar division. Short solid lines on viscera: postganglionic fibers of craniosacral division. Drawn by M. Norviel.

may be that their origin varies with the species studied. Studies on the source of myenteric and submucosal plexuses remain inconclusive. Some believe that they come from the neural crest and migrate to the thorax and upper abdomen and that the sacral cord levels of the neural crest contribute neurones that eventually lie in the lower intestine (Yntema and Hammond, 1953). Others believe that these neurones take their origin from the neural tube (Jones, 1942). The neurones of the parasympathetic ganglia of the head and neck also arise from the neural crest (Hammond and Yntema, 1958).

The paravertebral sympathetic ganglia lie on both sides of the vertebral bodies. The ganglia are attached to the ventral roots of the thoracic and lumbar segments by myelinated axons of the preganglionic neurones which reach them through the ventral roots. There is a whitish

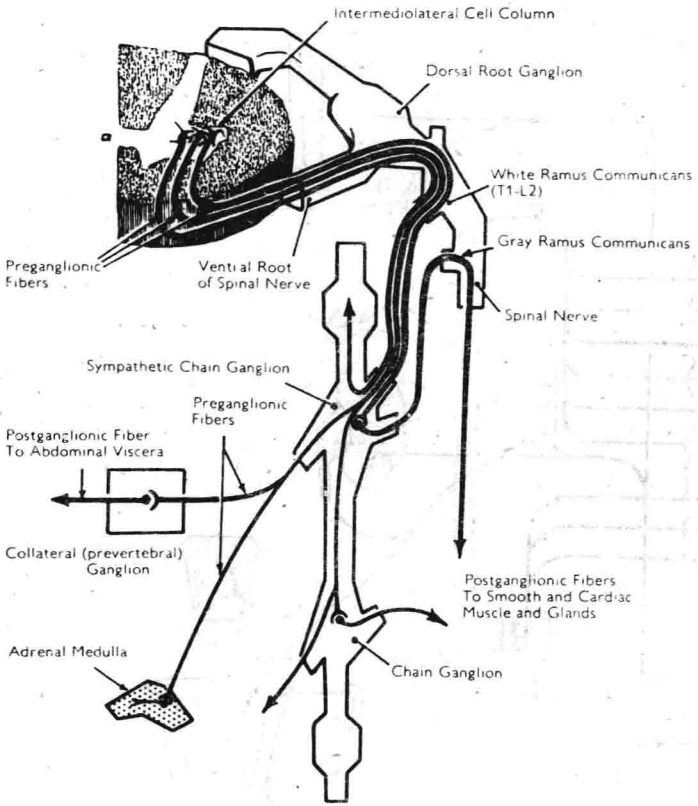
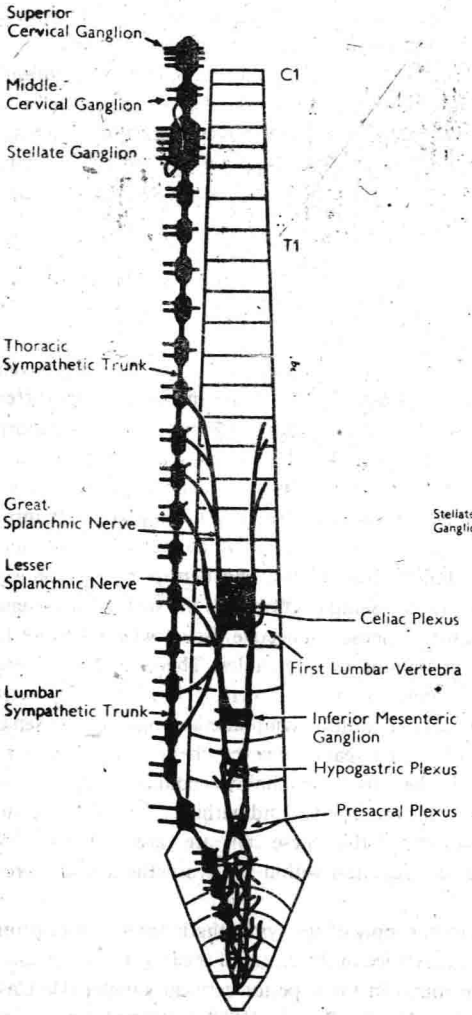


Fig. 4. Diagram to show the relation of pre- and postganglionic fibers in chain and collateral ganglia. Drawn by M. Norviel.

appearance to the fiber bundles which also contain myelinated visceral afferents and they are called white communicating rami. The postganglionic fibers from these ganglia also connect the chain to the ventral nerve roots, since they are distributed through the nerves to the periphery. These fibers are not myelinated, or only thinly myelinated, and look grayish in the fresh specimen. They are called gray communicating rami. There may be more than one gray communicating ramus to a spinal nerve (Mitchell, 1953).

The superior cervical ganglion is usually related to the upper four cervical levels. The middle cervical ganglion is inconstant but if present is related to the fifth and sixth cervical segments (Jamieson et al., 1952; Kuntz, 1953; Becker and Grunt, 1957). The inferior cervical ganglion is related to the seventh and eighth cervical segments and in eighty-two percent of cases examined it is fused with the first thoracic ganglion into a large mass of neurones, the so-called 'stellate ganglion'. When the first thoracic ganglion remains separate it is also called the stellate ganglion (Hoffman, 1957). There are up to eleven but often fewer ganglia on each side in the thoracic region. The number in the lumbar and in the sacral region is four each but varies considerably (Kuntz, 1953). The chain ganglia in the coccygeal region are fused into the coccygeal ganglion or ganglion impar.



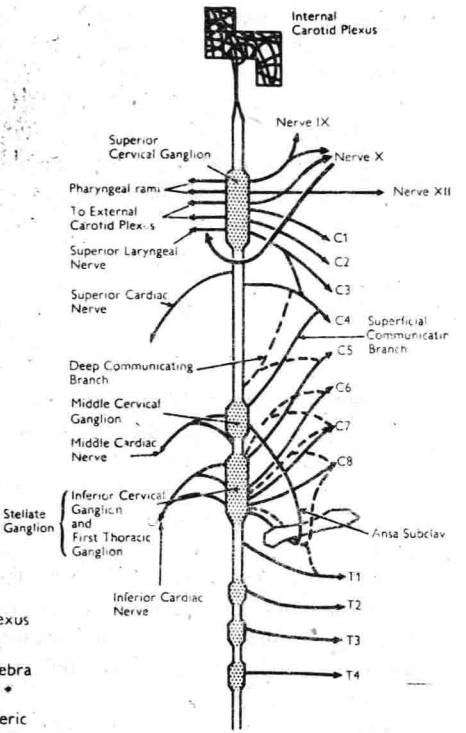


Fig. 5. Diagram to show the paravertebral sympathetic ganglia and splanchnic nerves in man. Drawn by M. Norviel.

Fig. 6. Diagram of cervical sympathetic ganglia to show the formation of visceral nerves. Drawn by M. Norviel.

Preganglionic sympathetic fibers destined to the abdominal and pelvic organs pass through the chain ganglia without synapsing and form the splanchnic nerves which end in collateral ganglia usually situated around branches of the abdominal aorta. The postganglionic fibers originating in these collateral ganglia pass along branches of the aorta to supply the viscera.

Above the diaphragm all sympathetic preganglionic fibers synapse in the chain ganglia and postganglionic fibers are distributed to viscera. Those supplying structures in the head take their origin in the superior cervical ganglia and are distributed along blood vessels.

Terminal or peripheral ganglia are small collections of autonomic neurones on or within the walls of various organs. They are mainly synaptic sites for preganglionic parasympathetic fibers and are often called parasympathetic ganglia. They comprise cranial ganglia such as the ciliary, sphenopalatine, otic, submandibular and Langley's ganglion and the cervical ganglia of the uterus. In the gastrointestinal tract these neurones form plexuses known as myenteric (Auerbach's) and submucosal (Meissner's) plexuses.

THE NORMAL HISTOLOGY OF GANGLIA

Descriptions of the normal histology of human sympathetic ganglion cells have been given by many authors (Stöhr, 1928, 1943a,b, 1948; De Castro, 1932). The ganglion cells are different in various sites. Thus the superior cervical ganglion contains a large number of polymorphic cells, whereas the celiac ganglion is composed predominantly of large stellate cells. All ganglia are surrounded by a connective tissue capsule which extends into the depth of the tissue and separates the cells by septa into small compartments (Martin, 1937). Numerous attempts to establish a pathologically significant increase in the amount of connective tissue and to correlate this with certain diseases have failed. The amount and density of the connective tissue in sections varies with the plane of the cut. Samples from near the surface or the end of the ganglion usually contain large amounts of dense connective tissue, whereas those from near the center show thick septa, often containing nerve bundles. These septa also contain numerous arterioles and venules. In children and fetuses there is little connective tissue (Spiegel and Adolf, 1920). The thin trabeculae in infantile sympathetic ganglia hardly separate the densely packed ganglion cells. Wth advancing years, however, there is an increase in the connective tissue which penetrates between the cells and probably accounts for the growth of the sympathetic ganglia. Numerous mast cells are often found within the capsule and in the trabeculae. Herzog and Sepúlveda (1940) stated that these cells are rarely, if ever, found among the neurones. Their significance and function within the sympathetic chain are not known.

There is little information about the blood supply of the sympathetic ganglia. Occasionally sizable venous channels and arterioles are described in the centre of the larger ones. In animals a rich capillary and venular bed can be found in the superior cervical ganglia (De Castro, 1932). Based on observation with india ink injections, Ranvier (1888) described venous sinuses within the sympathetic ganglia. There are lymphatics in the sympathetic chain and they are occasionally invaded by carcinoma, which then makes these channels visible (Von Doring et al., 1955). A rich lymphatic network surrounds the cervical sympathetic ganglia and it is claimed that this is proof of their high metabolic activity. These lymph vessels drain into the cervical lymph nodes (Rouvière, 1929). Each sympathetic ganglion cell is embedded in a fine fibrillary meshwork which forms various sized holes into which the cells fit snugly. The nuclei of the supporting cells can be seen among this fine network. The cytoplasm of these supporting cells cannot be recognized with ordinary histological methods and requires silver carbonate stains for visualization. These cells have been called capsular cells, satellite cells (Cajal, 1911) or amphicytes (Stöhr, 1928). They surround the ganglion cells and their processes, and appear

analogous to the oligodendrocytes of the central nervous system (Von Doring et al., 1955). They were first clearly defined by Del Hortega Rio and Prado (1942) who named them gliocytes. The function of gliocytes is obscure. It is believed by some that they have endocrine function (Nageotte, 1910). De Castro (1932) suggested that they are the site of acetylcholine formation and Sulkin and Kuntz (1948) showed that ascorbic acid is present in the gliocytes and it is markedly reduced in hypertensive patients. They also observed hyperplasia of the gliocytes in animals given diphtheria toxin and in patients with tuberculosis and pneumonia, and ascribed this to 'toxic irritation'. Conflicting statements and claims are made about specific function and activities of gliocytes and this suggests that their true role in the sympathetic ganglion chain remains to be determined.

The size of the ganglion cells varies. Nevertheless, three subdivisions have been described. Large cells with a diameter of 35–155 μm, medium-sized cells with a diameter of 25–32 μm, and small cells with a diameter of 15–22 μm (De Castro, 1932). 50 to 70% of all ganglion cells are of medium size. All cells have a large, somewhat transparent nucleus which contains a clearly delineated nucleolus. Cells with two or more nuclei can be found particularly in fetuses and in children (Herzog, 1931; De Castro, 1932) but are not common in adults. The neurones are filled with a fine neurofibrillary network which leaves only the nuclear zone free. Occassionally the neural processes appear empty but this may also be the result of pathological swelling of the cells (Von Doring et al., 1955). The sympathetic ganglion cells can be further subdivided according to the length of their cell processes (De Castro, 1932). It has been emphasized, however, that the distinction between dendrites and axons can be difficult, although the existence of latter seems to have been proven by Cajal and Stohr. Cells with long neural processes are particularly common in the alimentary canal. Ganglion cells with short and accessory processes are also found. These often branch and twist within the capsule of gliocytes which surround the cell. Sometimes they enclose small spaces that could easily be mistaken for vacuoles. Numerous morphologic types of synapses within the sympathetic chain are described. These include club-like or pear-shaped endings and dendritic skeins (Cajal, 1911). Their distribution is quite haphazard but the large ganglion cells have numerous synaptic endings (Herzog, 1931).

During development, a complex, as yet poorly understood process takes place which must address two problems:

1. How are synapses established between appropriate neurones?
2. How are the number of cells and the number of synaptic contacts between them regulated?

The problem of qualitative accuracy, that is, the way in which synaptic contacts between appropriate partners are achieved, remains largely unsolved. However, there is somewhat more agreement about how quantitative regulation, that is, the relationship between pre- and postsynaptic neuronal populations and synaptic contacts between them, is established. It has, for example, been shown that the innervating population of neurones is well matched to the capacity of target structures. Neurones are overproduced during development and compete for survival in early embryonic life. Presynaptic neurones are dependent on some activity of their targets. If, for example, an increase in target size is achieved experimentally, the survival and size of the innervating neurones is increased, and conversely, artificially decreasing the target size increases neuronal death. Evidence has also been found that a trophic factor is produced by the target for which innervating neurones compete during development. Thus, it is clear that there is no preordained neuronal pool that innervates a target population, but that the number

of neurones is adjusted and depends upon feedback mechanisms. In addition, there are also quantitative adjustments of neuronal contacts by a normally occurring elimination of synaptic cells. These features have experimentally been demonstrated during development of muscle, but synapse elimination occurs also in autonomic ganglia in which synaptic contact is between pre- and postganglionic neurones. Thus, in the mature rat submandibular parasympathetic ganglion about 80% of neurones are innervated by single preganglionic axons. But at birth these neurones receive an average of five different axons. Only after the first few weeks of life is the adult one-to-one pattern established. In developing sympathetic ganglia, which are innervated by a larger number of axons during adulthood, the findings are comparable. In the superior cervical ganglia, normally innervated by about 6 axons in the adult, up to a dozen different axons are found during development. Thus, initial connections are eliminated during the first postnatal weeks even in those neurones which continue to receive more than one presynaptic axon. (Purves and Lichtman, 1980).

At three months gestation the normal human sympathetic chain consists of aggregates of darkly staining, somewhat oval nuclei measuring 6–9 μm in diameter. The cytoplasm of these cells cannot be made out. They contain from three to six chromophilic nucleoli. These nuclei are often arranged in rosettes and accumulate in groups but also extend along the course of the nerve fibers from ganglion to ganglion. No pigment can be seen. Neural processes cannot be identified with silver stains. The rami communicantes and connecting interganglionic fibers do not take myelin stains. The cells described resemble neuroblasts. Numerous lymphocytes are diffusely scattered throughout the ganglia but mast cells are not found. No gliocytes can be seen but elongated cells arranged in rows, presumably fibroblasts, are related to small capillaries. Large vessels are not visible (Figs. 7 and 8).

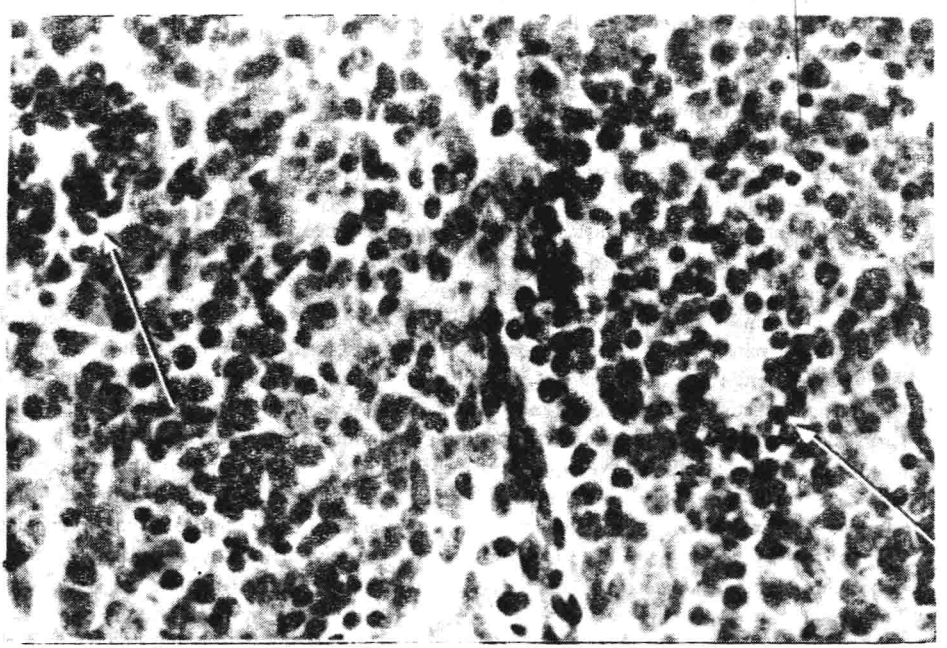


Fig. 7. Sympathetic chain from fetus of 3 months gestation. The arrangement of nuclei in rosettes is seen (cresyl violet). (From Appenzeller, 1966).

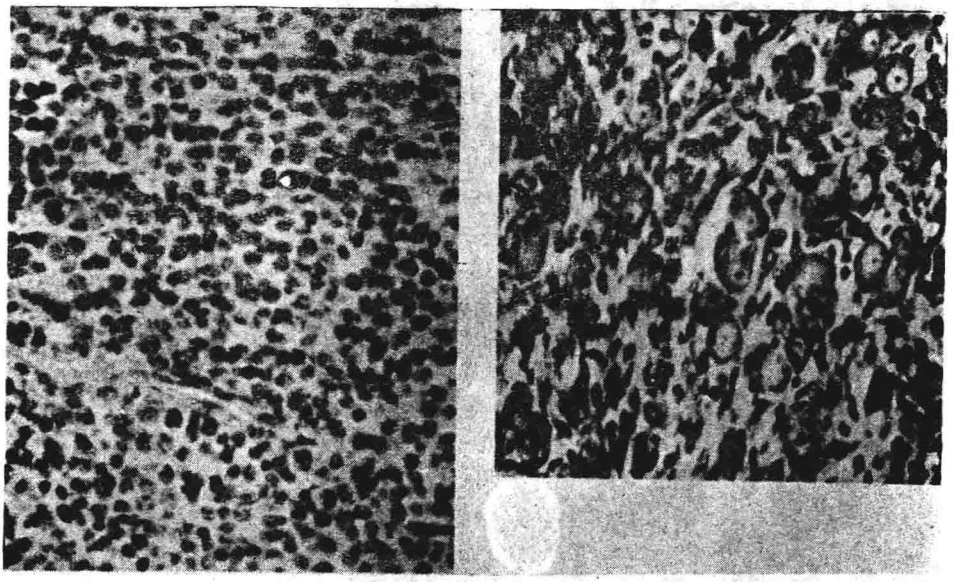


Fig. 8. Sympathetic chain from fetus of 3 months gestation. No neurofibrils or neural processes are seen (Bodian protargol). (From Appenzeller, 1966).

Fig. 9. Sympathetic ganglion at birth. The clear nucleus almost fills the cells (cresyl violet). (From Appenzeller, 1966.)

At birth definite autonomic neurones are found. The cytoplasm is clear and contains Nissl substance. No neural fibrils can be identified with silver stains, although delicate neural processes are seen to emerge from many cells. The nucleus is large and pale, and the nucleolus chromophilic. Cells congregate in ganglia but many neurones are found between ganglia, within the nerves connecting them, and some extend out for a short distance in the rami communicantes. Neurones with two nuclei are frequently found (Figs. 9 and 10). Pigment is occasionally seen in some neurones with silver staining. Gliocytes can be seen closely applied to the neurone. Numerous fibroblasts are visible in the vicinity of capillaries. Myelinated fibers are present and are found in small numbers mainly in the rami communicantes. This appearance remains unaltered except that by the age of two years the axons within the nerves connecting the ganglia show irregular elongated thickenings which become more prominent with advancing years (Fig. 11). The normal sympathetic ch in remains then essentially unchanged throughout life, except for the accumulation of increasing amounts of pigment in the ganglion cells and prominent hyaline thickening of small vessel walls in old subjects (Figs. 12 and 13). Mast cells are abundant, particularly in the perineurium of old patients. A striking increase in silver impregnation of neural processes and fibrils occurs in neurones of old subjects. The increased uptake of silver stains does not appear to be a pathological change as it is found in a variety of unrelated diseases and in subjects dying after accidents (Fig. 14). Fibroblasts are numerous and generally accompany vessels but it is impossible to grade the amount of fibrous