Transmission in Sympathetic Ganglia

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IT IS THE PURPOSE of this review to document the classic experiments on the electro- and neurohumoral physiology of transmission in sympathetic ganglia. With this as a background, some of the older experiments on the effects of anesthetics are presented. The literature on this subject has burgeoned in recent years, for not only is this of importance in understanding the circulatory effects of anesthetics, but anesthetic effects on the ganglion, a simple peripherally-accessible model, may provide some clue as to central anesthetic action.

Function of a Ganglion

Vertebrate smooth muscle and glands are controlled by two sets of neurons, one group originating in the brain stem and spinal cord and another which arises from peripheral ganglia. Within the ganglia numerous points of contact occur between the nerve endings of the first, or preganglionic, group of neurons and the cell bodies of the second, or postganglionic, group of neurons. The propagation of impulses from the nervous system to the organs under its control is thus interrupted by this synapse or junction. Any fiber which forms a synapse on a ganglion cell is probably excitatory; after an impulse arrives at the presynaptic terminals of a ganglion cell the tendency for that cell to discharge is increased. There is considerable experimental proof that excitation at the synapse is mediated by a single transmitter substance, acetylcholine. A sympathetic ganglion permits a more economical distribution of those nerves which originate in the spinal cord. Although each visceral motor unit is regulated by specific postganglionic sympathetic nerves, there is a considerable overlapping of the preganglionic nerves at the synapse. Accordingly, preganglionic fibers from different levels of the spinal cord may interact at the ganglion.

Only one transmitter substance is released by the nerve terminals of a particular neuron. Some sympathetic ganglia contain two varieties of postganglionic fibers which, when stimulated, elicit widely differing physiologic effects. Sweat glands and the blood vessels in skeletal muscle, for example, are controlled by sympathetic nerves, yet they are innervated by a group of postganglionic nerve fibers entirely different from those which innervate the blood vessels of the skin or the piloerector muscles. Thus the synaptic "relay" between the nervous system and the organ under its control does provide for dual innervation at the periphery by nerves which release either acetylcholine or norepinephrine.

Impulse Transmission in Nerve Fibers

The initiation and propagation of conducted responses in nerve fibers differ greatly from the excitatory process at the postsynaptic membrane of ganglion cells. The former can be satisfactorily described by physicochemical principles and by analogies to Ohm's law which govern the flow of current in a volume conductor. The ganglion synapse, however, responds not to electric currents but to a transmitter substance released from nerve terminals located nearby. Some nerve fibers propagate impulses at considerable speeds and at frequencies as high as 100 per second. Among the population of nerve fibers in a mixed nerve trunk the conduction velocities may vary by as much as a hundred-fold, depending upon the diameters of the fibers and the amounts of myelin deposited around their exteriors.

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Action Potentials in Nerve

Spikes or action potentials are formed in a nerve fiber through a highly specific alteration in its permeability to sodium ions. The entry of a very small number of these ions produces a transient potential difference across the cell membrane 120 mv. above the resting potential. Excitation of this membrane is a self-regenerating process and largely accounts for its all-or-none response capability. As an area on the nerve cell membrane is initially depolarized by a stimulus, it becomes progressively more permeable to sodium ions until an all-or-none spike is formed. For a spike to be propagated, on the other hand, some fraction of its potential must depolarize an inactive segment of the nerve some distance away. In a myelinated fiber the voltage which spreads from an active to a resting node usually exceeds by five to ten times the minimal stimulus normally required for excitation.

Synaptic Transmission in Autonomic Ganglia

Ganglion cells normally discharge impulses at much lower frequencies than peripheral nerve, usually no greater than 20 per second.[1] Furthermore, impulses are transmitted through a synapse in one direction only. The response of the ganglion-cell membrane to presynaptic impulses is rather slow and develops in a cumulative manner more or less in proportion to the number of impulses it receives in a given period of time. A postsynaptic spike may not be elicited until several presynaptic volleys have arrived at the synapses of the ganglion cell.[1] Moreover, these impulses may have originated from different levels in the spinal cord. For this reason synaptic transmission should not be represented as a simple transfer or relay of signals from one neuron to another. The regenerative character of the impulses conducted by an axon, when compared with the graded excitatory process at the postsynaptic membrane, does indeed emphasize that synaptic transmission is a more restricted function. This difference may be responsible for the fact that ganglia, as opposed to nerve fibers, are more susceptible not only to interference in their metabolism but to the actions of many pharmacological agents as well.[2, 3, 4]

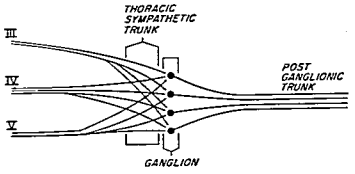

FIG. 1. Synaptic connections within the stellate ganglion. Only a small fraction of the 300,000 ganglion cells in this preparation are shown. Numerous other post-synaptic fibers are distributed from the ganglion to various autonomic effectors by way of different postganglionic trunks.

Ganglion-cell Responses to Presynaptic Nerve Stimulation

Various neural factors initiate and regulate the discharge of ganglion cells. In most of the experiments to be cited, the superior cervical ganglion of the cat or the rabbit has been used routinely. However, the stellate ganglion of the cat is better suited for studies of the functional relation between the presynaptic nerves of a ganglion and its postsynaptic responses.[5] Figure 1 shows the connections within the stellate ganglion of several groups of presynaptic nerves. All presynaptic (or preganglionic) fibers can be seen to distribute many branches to the ganglion cells. In this preparation the white rami, labeled III, IV and V, contain the bulk of the presynaptic innervation. The experimenter, therefore, can select a large or small input to the ganglion cells, depending upon the number of rami which are placed upon stimulating electrodes. The response of the ganglion-cell population to presynaptic stimuli can be measured electrically as a compound spike in a postganglionic trunk (inferior cardiac nerve) (fig. 1).[1, 5]

Temporal Summation

Only a small number of postsynaptic fibers will discharge spikes when a single weak shock is applied to one ramus alone. Although electrical signs of activity may be absent in the postsynaptic fibers themselves, a large number of their cell bodies nevertheless may become more excitable after impulses have arrived at

the junction. This may be seen in their subsequent responses to a succession of volleys, each applied within 0.1 second of the previous one. When the same weak stimulus is applied repeatedly at close intervals, the compound spike progressively increases in magnitude; a larger number of ganglion cells are recruited into the response (temporal summation).[1,5] If stimuli are applied at rates greater than 20 per second, however, the resulting spikes become smaller.

Spatial Summation

The effect of a weak stimulus on the excitability of ganglion cells may also be shown by testing their responses to impulses reaching the synapse by other presynaptic nerves. If another volley is applied concurrently through a different ramus, *i.e.*, to another fraction of the preganglionic input to the ganglion, a larger number of postsynaptic fibers will discharge than would have resulted from stimulation of either ramus alone (spatial summation).[1,5] Shocks applied to several rami simultaneously and in rapid succession not only generate a larger compound spike but also cause the ganglion cells to discharge repetitively after stimulation has stopped (after-discharge).[1,5] Since a large number of presynaptic fibers terminate on each ganglion cell, there is a considerable degree of overlapping innervation. For this reason most of the postsynaptic fibers of a ganglion can be made to discharge by stimulating about half of its presynaptic input. It is this overlap that makes possible the spatial summation of weak stimuli concurrently applied to several rami.

Prolonged Facilitation

There is a striking increase in the response of the ganglion cells to single volleys after the presynaptic elements have undergone prolonged repetitive stimulation (conditioning).[6] Transmission through the ganglion may be facilitated for several minutes depending upon the stimulus rate and the duration of the conditioning. Proportionately more ganglion cells are recruited into the response to the test stimulus when the number of presynaptic fibers undergoing stimulation is small. If the conditioning trains enter the ganglion antidromically, transmission by way of the presynaptic fibers is not enhanced subsequently.[6] The persistent elevation in ganglion-cell excitability produced by the conditioning probably arises from a change in the properties of the presynaptic elements themselves. This has been suggested because repetitive stimulation of one ramus fails to facilitate transmission through the same ganglion when the test stimulus is applied to another ramus.[6]

Whether transmission is similarly facilitated by the type of repetitive activity encountered under physiologic conditions is difficult to answer. In the animal the maximal discharge rate of the fibers to the ganglion may be much less than the rate at which stimuli are applied experimentally.

Many proposals have sought to explain the phenomenon of prolonged facilitation in sympathetic ganglia, perhaps in the conviction that the underlying principle may apply to posttetanic potentiation in the spinal cord also. For example, conditioning of the presynaptic nerves by trains of stimuli may promote the release of transmitter substance from the nerve endings.[7] Most nerve fibers become hyperpolarized (positive after-potential) following brief periods of repetitive stimulation. An action potential or spike generated subsequently under these conditions would be larger in magnitude and presumably would be a more effective stimulus to discharge a transmitter substance. Another explanation holds that the intracellular accumulation of sodium ions which occurs during activity would promote a greater transmitter release by displacing Ca^{++} from the membrane of the nerve terminal.[8]

Synaptic Potentials

Presynaptic volleys elicit graded electrical responses from the postsynaptic membrane of single ganglion cells.[9] In the superior cervical ganglion isolated from the rabbit these "synaptic potentials" have been measured intracellularly by means of capillary microelectrodes. Resting potentials of ca. −70 mv. which have been recorded in this preparation are similar to those found in mammalian motoneurons of the spinal cord. When a ganglion cell receives impulses by way of its presynaptic terminals, the postsynaptic membrane un-

dergoes varying degrees of depolarization of around 30 mv.; its normal resting potential slowly diminishes (becoming less negative) in proportion to the rate of the presynaptic discharge. Accordingly, an all-or-none spike is generated by a ganglion cell when it is depolarized to around −40 mv. The spike itself is only slightly greater in magnitude than the resting potential of the cell and is of much shorter duration than the synaptic potential. It should be emphasized that spikes are produced by the axon, at some distance from the presynaptic terminals and the postsynaptic membrane. Their properties are altogether different from the synaptic potentials which undergo summation until a threshold depolarization is attained. This excitatory process at the postsynaptic membrane, as revealed by the membrane potential, becomes obscured as soon as the spike is formed. The full time course of the synaptic potential, which may be seen only after synaptic transmission is blocked, may persist for as long as 100 msec.[9]

Transmembrane potential measurements in ganglia are made only with great difficulty. It is far more convenient to measure the electrical response of the entire ganglion-cell population by means of surface electrodes.[10] In this case, the potential changes between electrodes placed on the ganglion itself and on the postganglionic trunk are quite similar to the recordings obtained from single cells.

Postsynaptic Potentials in Ganglia Following Blockade

Transmission in a sympathetic ganglion can be specifically prevented by hexamethonium, high doses of curare, or dihydro-β-erythroidin. These compounds probably occupy the site on the postsynaptic membrane which normally responds to ACh. Thereafter, however, the stimulated ganglion continues to display a number of slow potentials, each of different polarity.[10] Three specific electrical responses are believed to result from the action of chemical transmitters upon separate and distinct sites of the postsynaptic membrane. Accordingly, after transmission is blocked in the superior cervical ganglion of the rabbit, postsynaptic stimuli elicit: (1) An initial N(egative) wave which is the primary synaptic potential

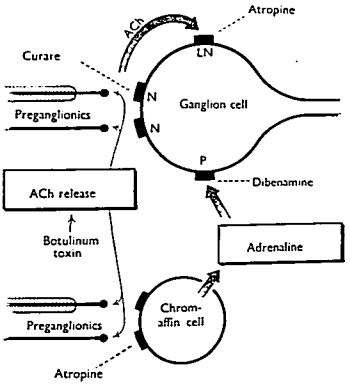

FIG. 2. Diagrammatic representation of a single ganglion cell to illustrate the synaptic origins and the blockade mechanism of the N, P and LN responses. The receptor site for each of the foregoing responses is shown by a small block. There is no particular significance to their location on the ganglion cell, which was chosen for convenience in illustration. From Eccles and Libet, reprinted by permission of *J. Physiology* and Rosamond Eccles.

and is analogous to the end-plate potential as already mentioned. This is followed by (2) a P(ositive) wave which arises from the action of epinephrine at the postsynaptic membrane. The source of this mediator is a group of chromaffin cells near the ganglion which are activated to discharge by acetylcholine released from the preganglionic terminals. (3) The L(ate) N(egative) wave is also generated by the ganglion cells and is produced by the action of the transmitter on areas of the postsynaptic membrane quite apart from the synapse itself.[10]

The N, P and LN potentials are truly indicative of electrical events at the synapse. Unlike the negative and positive afterpotentials, they are not dependent upon the discharge of spikes from the postsynaptic elements of the ganglion. The well-known action of veratrine which enhances the negative afterpotential of a nerve trunk is without effect on the N, P or LN responses of a ganglion. All three potentials, however, are abolished by botulinus toxin, which has no significant effect

on conducted responses in nerve trunks. The conclusion of Eccles and Libet,[10] that these responses are true reflections of the electrical events at the synapse seems warranted. A summary of their findings, obtained from ganglia treated with dihydro-β-erythroidin as a blocking agent, appears in figure 2. It should be noted that the P wave generated by epinephrine is specifically blocked by dibenamine or by atropine, whereas the LN response is blocked by atropine only.

Comparison of Endplate and Postsynaptic Membrane

The area of the postsynaptic membrane beneath a single preganglionic nerve ending (bouton termineau) is smaller than a somatic muscle endplate, but the surface of the ganglion cell is many times larger, being nearly completely covered with boutons. The release of chemical mediator from the nerve terminals of both structures and the subsequent postsynaptic action of the transmitter must be very similar. Acetylcholine release by the motor nerve terminals in somatic muscle and the presynaptic nerve endings in the ganglion is diminished or abolished when they are deprived of calcium ions. Transmission at both junctions is also blocked by hemicholinium #3, an inhibitor of choline transport into nerve endings.[11] Blockade of both ganglia and neuromuscular junctions occurs in animals poisoned by botulinus toxin, a substance which interferes specifically with transmitter release in cholinergic nerves.

At the skeletal muscle endplate the transmitter reduces the resting potential (depolarization) by producing a transient increase in the permeability of this region of the muscle fiber to Na^+, K^+ and Cl^- alike. These endplate potentials elicited by *single* nerve terminals last only 5 msec and do not normally summate.[12, 13] In contrast, the primary synaptic potential in a ganglion persists for as long as 100 msec[14] and is produced by a transmitter released from *numerous* presynaptic terminals. This slow decay of the synaptic potential at the ganglion synapse may be due to the residual action of the transmitter.[15] Despite the differences between the time course of the excitatory process at the two junctions, they are both undoubtedly generated by a transient depolarization and caused by the same migration of ions such as occurs at the endplate.

General Anesthetic Agents and Ganglionic Transmission

The axons in peripheral nerves are not particularly sensitive to general anesthetics. Conduction in mammalian myelinated fibers of small diameter is more likely to be blocked by a given amount of an anesthetic than that in the large-diameter fibers; yet the absence of myelin, as is the case with postganglionic fibers does not seem to predispose them to the effects of the anesthetic.[3] In artificially-perfused ganglion preparations transmission is blocked by a variety of anesthetic or depressant agents.[2] Some are effective in amounts comparable to those in plasma of anesthetized patients.[16] The postsynaptic responses of the superior cervical ganglion in a cat with intact circulation are blocked more extensively by diethyl ether or by chloroform as the animals are more deeply anesthetized. Postsynaptic spikes, when elicited by weak stimuli, *i.e.*, by a restricted number of presynaptic fibers, are more susceptible to ether, chloroform or thiopental than the spikes produced during stimulation of the entire presynaptic input to the ganglion.[16] Those ganglion cells subserving pupillary dilatation and the nictitating membrane appear to be more sensitive to the anesthetics than the ganglion cells which control vasoconstriction and the pilomotor muscles. A more pronounced depressant effect of an anesthetic on transmission is manifested when the stimulus rate is increased.[2] This finding might suggest that the recovery processes of the ganglion which depend upon metabolism are impaired by anesthetizing substances. A variety of anesthetics which have been examined in this connection do not specifically interfere with the same metabolic pathways of either the ganglion cells or the presynaptic nerves under resting conditions. Yet when a stimulated ganglion is exposed to increasing amounts of an anesthetic, the increased oxidative metabolism resulting from its greater activity declines in direct proportion to the depression of the postsynaptic response.[2]

Cholinoceptive Sites on Ganglion Cells

There appear to be several areas or sites on the postsynaptic membrane where ACh can elicit excitatory responses.[7, 10] The properties of these sites differ markedly; those associated geometrically with the presynaptic terminals require greater amounts of ACh in a perfusate for activation than those somewhat remote from the synaptic region.[7] Moreover, the former, *i.e.*, the subsynaptic regions, are unaffected by atropine, whereas the latter are blocked by this drug.[17, 18] The excitatory postsynaptic responses to endogenous ACh released from presynaptic terminals are blocked by hexamethonium, tetraethylammonium, and curare. Thus, ganglionic transmission is blocked by these agents but not by atropine. A physiologically significant effect of ACh on the postganglionic cell body can be demonstrated, nevertheless, in ganglia treated with hexamethonium or curare. For example, the repetitive firing of a ganglion treated with DFP, an anticholinesterase, is not altered by hexamethonium.[18] After other anticholinesterases such as eserine or neostigmine have been administered, a prolonged or "delayed" repetitive discharge of the ganglion cells is produced by ACh. This "late" component of the response to ACh and the spontaneous firing caused by DFP are readily blocked by atropine but not by the other conventional ganglionic-blocking agents. Anticholinesterase agents are believed to unmask a cholinoceptive area on the postsynaptic membrane which is atropine-sensitive. Repetitive stimulation of the presynaptic nerves similarly conditions the ganglion cells to elicit a prolonged discharge following ACh administration. Other cholinomimetic agents, pilocarpine and muscarine, also stimulate ganglion cells to discharge; these effects similarly are abolished by atropine.[7]

In summary, endogenous ACh from nerve terminals reacts in high concentrations upon subsynaptic areas and may condition extrasynaptic areas to low concentrations of ACh. Mediator added to the ganglion perfusate is not effective at the latter sites unless the preparation is pretreated with an anticholinesterase. At the neuromuscular junction similarly treated with anticholinesterase, the endplate responds to directly-applied ACh as well as to ACh liberated from nerve endings. Both effects are prevented by any of the conventional blocking agents, such as curare, succinylcholine or decamethonium.

The Transmitter Substance in Ganglia

Knowledge of the chemical processes associated with transmission at the ganglionic synapse is quite extensive and the role of chemical transmitters in interneuronal transmission has been supported largely on the basis of studies on ganglia. Several lines of evidence point to a dependent relation between ACh release by presynaptic terminals and the development of an excitatory process in the postsynaptic membrane. It is well known that ACh is localized in the presynaptic terminals of a sympathetic ganglion and its rate of release into a perfusion medium varies in direct proportion to the frequency at which these nerves are stimulated.[11] Moreover, the postganglionic elements can be made to discharge spikes repetitively by adding ACh to the perfusion medium; within limits, the rate of discharge of a single ganglion cell is proportional to the ACh concentration. And the response of the postsynaptic elements to preganglionic stimulation is potentiated by the addition of ACh to the perfusion fluid.[1]

Fairly large amounts of ACh must be added to a perfusion fluid to elicit excitation of ganglion cells, compared with the amount released into the perfusion fluid when the preganglionic nerves are undergoing repetitive stimulation.[1] The difference between the threshold ACh concentration in a perfusion medium and the amount recovered during stimulation almost surely reflects the extent to which the released transmitter is diluted by the surrounding fluid.

Acetylcholine Release by Presynaptic Terminals

At rest small amounts of transmitter are released spontaneously from presynaptic nerve endings.[11] Sub-threshold N-responses are generated at the postsynaptic membrane by the transmitter analogous to the miniature endplate potentials. The uniform amplitude of

these randomly-occurring spikes at the end-plate has led to the proposal that ACh escapes from the terminals in quanta or packets each containing the same amount of mediator.[12] A quantum is believed to represent the minimum releasable amount of mediator and may be equivalent to individual storage granules in the nerve endings themselves.[20] Probably a fixed number of granules is discharged when an impulse is propagated into the nerve terminal. During brief periods of stimulation the amount of transmitter released by the nerve endings during activity is independent of the stimulation rate. In ganglia perfused with plasma the amount of mediator released per impulse is constant, at least in the physiologic range of from 1 to 20 per sec.[11] However, during continuous stimulation the initial release is somewhat greater than "steady-state" release established 30 minutes later. Apparently the preganglionic terminals themselves can sustain responses in about the same frequency range as the neuromuscular junction for short periods. Therefore, the transmission failure which occurs during high rates of stimulation may not necessarily be attributable to inadequate release of transmitter substance but might be caused by an excess accumulation of this substance at the postsynaptic membrane. In high concentrations ACh, like nicotine [9] can block transmitted responses in ganglia by combining with the receptors on the postsynaptic membrane.[9] Under these conditions the ganglion cells are depolarized.[12, 15]

Acetylcholine Content of Ganglia

Nearly as much acetylcholine can be recovered from the cat superior cervical ganglion as from an equal weight of central gray matter. During 60 minutes of repetitive stimulation an eserinized ganglion perfused with plasma may discharge into the perfusate up to six times as much mediator as it contains.[11] Under these conditions the ACh content of a ganglion perfused with plasma or one with an intact circulation is not depleted; the acetylation of choline within the nerve terminals is sufficiently rapid to replenish that which is released. It should be mentioned, however, that the stimulated ACh release by an artificially-perfused ganglion is not well maintained for extended periods and nearly half of the ACh stored in the nerve terminals is lost after 60 minutes.[11] Some of this deficiency can be corrected upon the addition of choline to the medium but some unidentified factor in plasma probably is required for optimal synthesis physiologically. The amounts of ACh released initially by plasma-perfused and artificially-perfused ganglia are the same; the output of the latter, however, diminishes by 75 per cent in one hour.

In the intact ganglion there is a rapid synthesis of transmitter. Normally, the plasma supplies sufficient choline to the presynaptic fibers to support maximal ACh release. In the nerve terminals themselves the acetylation of this substrate by acetyl coenzyme A may be governed by the transmitter concentration. It has been estimated that ACh is stored at a concentration of 0.1 molar in the synaptic vesicles.[11] Synaptic and neuromuscular transmission alike are blocked by HC-3, an agent which interferes with ACh synthesis by limiting the availability of choline within the nerve terminals.[11] After this inhibitor is added to the perfusate, the stores of ACh present in the vesicles can sustain transmission during optimal rates of stimulation for as long as five minutes before signs of failure appear. Even when ACh synthesis is abolished by hemicholinium, the stores of transmitter are not totally depleted; 15 per cent of the original ACh remains when blockade is complete. This small "stationary" or nonreleasable fraction is stored in some part of the presynaptic nerve that may be some distance from the synaptic terminal itself.[11]

Function of Acetylcholinesterase

After acetylcholine is released by the presynaptic nerve endings it undergoes rapid hydrolysis by acetylcholinesterase. In fact, before the mediator can be recovered from the solutions bathing a ganglion, the preparation must first be treated with an inhibitor of AChE, usually physostigmine. In the presence of such drugs the response of ganglion cells to presynaptic volleys is prolonged and repetitive spikes may be elicited by single stimuli. The presence of AChE at the ganglion synapse must limit the duration of the

transmitter action by ACh as well as its spatial influence on postsynaptic sites. At the neuromuscular junction this enzyme is localized mainly at the endplate. In a ganglion, on the other hand, AChE is confined chiefly to presynaptic regions.[21] In small amounts, ACh or carbachol exerts a direct action on presynaptic fibers, causing endogenous ACh to be released from the nerve terminals. It would appear that the primary role of AChE in a ganglion may be to protect presynaptic nerves from re-excitation by ACh; its spatial or geometric effect on the abundant presynaptic innervation of ganglion cells is thereby limited.

It should be noted that few, if any, physiologic effects of the anticholinesterases in man can be attributed to the persistence of ACh at ganglionic junctions; the actions of eserine or prostigmine as seen clinically are most prominent on the neuromuscular junction of skeletal muscle, certain smooth muscles such as the bladder and the iris, and the gastrointestinal tract.

Adrenergic Influences at the Ganglion Synapse

Perhaps not all the presynaptic fibers *within* a ganglion are cholinergic; indeed, there is some histologic evidence to support this.[22] Moreover, it has been demonstrated repeatedly that ganglionic transmission can be depressed by epinephrine, particularly norepinephrine.[19, 23] This inhibitory action of the catecholamines, as well as the hyperpolarization of the ganglion cells,[10] is prevented by α-receptor blocking agents.[19] β-adrenergic receptors which enhance transmission and induce ganglionic depolarization have also been identified.[19] It remains to be established, however, that an adrenergic mediator is responsible for a *physiologically* active inhibitory or excitatory mechanism in autonomic ganglia.

Conclusions

An author usually may be allowed some latitude to present conclusions of his own which may or may not have any basis in fact. Accordingly, let me reveal my interest in the autonomic ganglion as providing a means of understanding the actions of general anesthetic agents. The most likely site of action of centrally-acting depressant drugs is the diffuse multisynaptic pathways of the brain-stem reticular formation.[24] To study this problem in conscious animals is, of course, sufficiently difficult to warrant a search for a more accessible but equally relevant preparation. Surely the excitatory processes associated with transmission in the reticular formation and the more peripherally located neuronal junctions are similar. Information which may be applicable to the "anesthetic state" at the synapse already has been provided by experiments on the neuromuscular junction; it was shown that diethyl ether and halothane prevent transmission by a postjunctional means.[25, 26] To continue this line of thought, one might examine in a perfused ganglion the functional alteration, caused by anesthetics, of:

(1) The release of acetylcholine from the presynaptic terminals after a fixed train of electric stimuli are applied;

(2) The response of the postsynaptic membrane of the ganglion cells to different amounts of acetylcholine; and

(3) The stores of acetylcholine of the ganglion following prolonged repetitive stimulation.

If an autonomic ganglion preparation indeed can be considered a miniaturized nervous system *in vitro*, it may be hoped that such endeavor will further illuminate this area which is so fundamental to the discipline of anesthesiology.

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Anesthesia

LOCAL ANESTHETICS The effects of carbonic acid salts of lidocaine and prilocaine were compared with those of standard hydrochloride salts of these drugs in two groups of patients. A total of 853 patients received various types of peripheral nerve blocks, epidural blocks for general surgical procedures, and epidural blocks for abdominal and vaginal obstetrical procedures. Carbonated compounds shortened induction time by 33 per cent, increased intensity of analgesia by 33 per cent, and slightly prolonged duration of block. Dose requirements were smaller than when hydrochloride compounds were used. (*Bromage, P. R.: Improved Conduction Blockade in Surgery and Obstetrics: Carbonated Local Anesthetics, Canad. Med. Ass. J. 97: 1377 (Dec.) 1967.*)