PHARMACOLOGY OF AUTONOMIC GANGLIA[1,2,3]

By U. Trendelenburg

Department of Pharmacology, Harvard Medical School, Boston, Massachusetts

This report is a review of the work on autonomic ganglion cells carried out during the last three years. Since this is the first volume of a new series of *Annual Reviews*, pertinent older literature will also be mentioned. The reviewer thought it appropriate to include what may be described as "odd results," *i.e.*, observations which have not yet found an explanation or even confirmation. Such findings may turn out to be artifacts rather than genuine drug effects; they may, however, turn out to be the beginning of a new and important development.

The reviewer does not see any necessity to challenge the classical concept that the release of acetylcholine (ACh) is the central event in ganglionic transmission, although there is good possibility that detailed studies with improved methods of the mechanism of synaptic transmission will lead to some modifications of the classical theory. During the last few years, the following suggestions have been made: (*a*) An inhibitory system arising from the central nervous system (CNS) may act on the presynaptic nerve terminals. (*b*) Presynaptic nerve terminals may be an important site for the action of drugs hitherto believed to have an action on postsynaptic structures only. Similar ideas are discussed in connection with motor nerve endings, and postganglionic nerve endings are now recognized as an important site of drug action. (*c*) Ganglion cells may be affected or even stimulated by a variety of substances which differ from ACh and the well-known group of nicotine-like substances. (*d*) Peripheral ganglion cells may serve functions which extend considerably beyond those of a simple relay station; they may, for instance, be acted upon by sensory structures.

For earlier reviews the reader is referred to those of Paton (168, 169), Ambache (4, 5), and Perry (176), which cover part of this field. Attention is also drawn to Konzet & Rothlin's interesting comparison of the effects of various drugs on autonomic ganglion cells, on the adrenal medulla, and on certain sensory structures (117). Such comparisons are good illustrations of the view that seemingly qualitative differences between various tissues may be, in some respects, quantitative rather than qualitative in nature (see below).

[1] The survey of literature pertaining to this review was concluded in June, 1960.

[2] The following abbreviations have been used in this chapter: ACh (acetylcholine); SCG (superior cervical ganglion); TEA (tetraethylammonium); TMA (tetramethylammonium); DFP (di-isopropylfluorophosphate); TEPP (tetraethylpyrophosphate); CNS (central nervous system).

[3] This work was supported in part by U. S. Public Health Service Research Grant B-1713.

The isolated and perfused superior cervical ganglion (SCG) of the cat is the classical preparation for the study of the pharmacology of autonomic ganglia. From a survey of the literature it is evident that the disadvantages and limitations of this preparation are not always realized; they have been discussed by Paton (168) and by Ambache (4), and important modifications have been described or referred to by Perry (175). An additional disadvantage of perfused preparations is their low sensitivity to certain substances; the perfused ganglion is 100 times less sensitive to histamine and 5-hydroxytryptamine than the nonperfused preparation (*222*). For details of method of the nonperfused SCG of the cat see (115, 168, 219, *226*).

Observations on Anatomy and Physiology of Autonomic Ganglia

The toughness of the tissues surrounding ganglion cells precludes the use of certain electrophysiological methods as routine procedures in the analysis of the action of drugs on ganglionic transmission. In comparison with the study of the neuromuscular junction, the pharmacology of autonomic ganglia is, thus, severely handicapped. Because of the many similarities of the two transmission processes, it is customary to apply certain conclusions from one field to the other by analogy. It should, however, be borne in mind that there are many anatomical differences which may imply functional differences. The preganglionic fibers of the SCG, for instance, consist of four different groups possessing different conduction velocities [S_1 to S_4, Eccles (51)]. The fastest (S_1) innervate structures in the orbit, whereas S_2 fibers carry vasomotor impulses. These observations have recently been confirmed by Folkow *et al.* (65), who also identified the very slowly conducting fibers as sympathetic vasodilators. To the reviewer's knowledge no systematic study has yet been made of the stimulating or depressing action of drugs on these functionally differing groups of fibers. In the evaluation of ganglion-blocking substances it is customary to use either the nictitating membrane (i.e., the S_1 fibers) or "the postganglionic action potential" (presumably the S_2 fibers, since these contribute most to the size of the action potential). It is unknown, however, whether the different groups of fibers are equally sensitive to ganglion-blocking agents; occasionally reported "resistent" pathways (see below) may find their explanation in such quantitative differences of sensitivity.

Douglas & Ritchie (49) reported the occurrence of an accessory cervical ganglion in the rabbit, and Boyd (21) discussed the occurrence of intermediate sympathetic ganglia, which may escape sympathectomy. Chronic preganglionic denervation of the SCG increases its sensitivity to ACh by a factor of about three (38) and completely changes the characteristics of its response to hexamethonium and azamethonium [Perry & Reinert (178)]. Perfusion of a normal ganglion with low-potassium perfusate results in similar changes, whereas perfusion of a denervated ganglion with high-potassium perfusate or with glutamate restores it to normal. Further

analysis of the effects of various amino acids and determinations of intracellular potassium concentrations showed that this "effect of denervation" is attributable to changes in the oxidative metabolism of denervated ganglion cells rather than to their decreased intracellular concentration of potassium ions (77, 179).

Homologous reinnervation (i.e., reinnervation of the SCG by cholinergic fibers of the glossopharyngeal, the phrenic, or the vagus nerve) is easily established. Contrary to earlier postulates, heterogeneous reinnervation also seems to be possible: de Castro (37) reported that the ascending sensory fibers of the vagus are able to make functional contact with the ganglion as indicated by a response of the nictitating membrane to stimulation of the afferent fibers of the vagus. Unfortunately, this interesting "synapse" has not been studied pharmacologically. Sensory vagal fibers can be assumed to liberate the sensory transmitter substance; Holton recently confirmed earlier observations that antidromic stimulation of sensory nerves of the rabbit ear causes the appearance of ATP in the perfusate (99). The occurrence and importance of collateral sprouting after partial denervation of the SCG has been studied in great detail by Murray & Thompson (157, 158).

Zakusov & Ul'ianova (245) observed that distension of the bladder or of part of the intestine causes a relaxation of another part of the intestine. This viscero-visceral reflex persists after total destruction of the CNS and after chronic preganglionic denervation; it is abolished by ganglionectomy or by ganglion-blocking substances. The abnormal pathways described by Brown & Pascoe (24), McLennan & Pascoe (153), and Job & Lundberg (104) may be involved. A somewhat similar situation is encountered in the peristaltic reflex which is well known to be independent of the CNS and to be blocked by hexamethonium. Such observations seem to imply that sensory fibers may establish functional contact with peripheral ganglion cells of the autonomic nervous system. Although ACh is able to stimulate sensory organs and nerve endings, and although hexamethonium abolishes these effects, the latter substance is not able to block the response of sensory structures to their physiological stimulus (50, 83). Such evidence suggests that the site of action of hexamethonium in the above mentioned reflexes is probably at some ganglion cells and not in the afferent pathway of the reflexes.

Considerable evidence is accumulating for the view that presynaptic motor nerve terminals are an important site of drug-action [for review see Werner & Kuperman (238)]. Riker & Szreniawski (186) found that ACh and TMA, when injected into the blood supply of the SCG, elicit antidromic preganglionic activity in addition to the well-known postganglionic effects. Intermittent spontaneous antidromic activity in preganglionic fibers has also been demonstrated in the SCG of the rat after infection with pseudorabies virus, the activity being increased by ACh and physostigmine, and inhibited by *d*-tubocurarine [Dempsher *et al.* (44, 45)]. This activity is increased by topical application of cocaine or by section of the pre-

ganglionic fibers, and reduced by gamma-aminobutyric acid, epinephrine, and norepinephrine (46, 47). From such observations it has been postulated that ACh has a presynaptic site of action and that an inhibitory system originates in the CNS and acts on the preganglionic nerve terminals.

Factor I of Florey & McLennan (63) does not affect synaptic transmission through the SCG of the cat, but other ganglia of the cat and of the rabbit are blocked (63, 100). Gamma-aminobutyric acid, gamma-aminobutyrylcholine, β-guanidinopropionic acid, and gamma-guanidinobutyric acid, on the other hand, are ineffective (100, 147, 217).

The role of cholinesterase.—Karczmar & Koppanyi (108) demonstrated the importance of "transport" cholinesterase; an increased response to injected ACh was obtained by reduction of the activity of plasma cholinesterase when there was no concomitant change of the cholinesterase activity of the effector organ.

Earlier observations by Kamijo & Koelle (107) that inhibition of acetylcholinesterase [by di-isopropylfluorophosphate (DFP)] causes facilitation of ganglionic transmission have been confirmed by Fehér & Bokri (62), who used tetraethylpyrophosphate (TEPP) as an inhibitor. The depressant effects of very large amounts of DFP (107) are, presumably, a direct effect of this substance on postsynaptic structures and unrelated to the inhibition of cholinesterase, since TEPP failed to block ganglionic transmission (62).

In recent years cholinesterase inhibitors that do not penetrate into ganglion cells have become available (111), and with their help it has been possible to demonstrate histochemically that part of the enzyme is located intracellularly ("internal") and part of it extracellularly ("external acetylcholinesterase"). McIsaac & Koelle (151) analyzed the physiological and pharmacological importance of internal and external acetylcholinesterase by using an inhibitor which blocks both enzymes, and another one which blocks only external acetylcholinesterase. Comparison of the effects of such a pair of inhibitors on ganglionic transmission, on total enzyme activity, and (by histochemical methods) on external and internal acetylcholinesterase suggests that only external ("functional") acetylcholinesterase is involved in the hydrolysis of endogenously liberated ACh; internal ("reserve") acetylcholinesterase may serve as a source of replacement of the former. A study of normal and of chronically denervated sympathetic ganglia showed that essentially all the functional cholinesterase is presynaptic, whereas in the ciliary ganglion it is both pre- and postsynaptic. Koelle & Koelle (112) concluded from these and other observations that the primary physiological role of ganglionic functional acetylcholinesterase is the prevention of postsynaptic activation by ACh liberated during rest; a secondary role may be the protection of presynaptic nerve terminals against initiation of antidromic firing by ACh.

Preganglionic (cholinergic) fibers of sympathetic ganglia have a high acetylcholinesterase activity, as demonstrated by histochemical methods, whereas postganglionic (adrenergic) fibers have a low activity (78, 112).

Holmstedt & Sjöqvist (97) found that only a small number of ganglion cells of various sympathetic ganglia was stained, the proportion of stained cells being greater in the SCG and stellate ganglion than in the abdominal ganglia. These observations may be related to the fact that some sympathetic ganglion cells have cholinergic axons (vasodilator fibers, etc.); but whatever explanation may be found, the findings illustrate the inhomogeneity of the cells of sympathetic ganglia.

Ganglion-Stimulating Substances

Nicotine-like substances.—These may be defined as ganglion-stimulating substances, the action of which is *(a)* abolished by depolarization of the ganglion cells as well as by the "competitive" ganglion-blocking substances (hexamethonium, TEA), and *(b)* resistant to atropine administered in amounts sufficient to block "muscarinic" effects of ACh. Schneider & Timms (196) studied the nicotinic, muscarinic, and atropine-like potency of a homologous series of choline esters of fatty acids; muscarinic potency declines beyond ACh, nicotinic potency increases with chain length and declines beyond butyrylcholine, and atropine-like activity is strongest with tetradecanoylcholine. Maleylcholine and succinylcholine cause a rise of blood pressure without prior atropinization, lactylcholine and pyruvylcholine only after atropine; lactylcholine causes a pressor response mainly through an action on the adrenal medulla, pyruvylcholine mainly through stimulation of sympathetic ganglia (54). N-methyl- and N,N-dimethylcarbachol are much weaker muscarine-like agents than carbachol, but their nicotine-like potency is four times greater (8). The absence of any stimulant action of acetyl-β-methylcholine on the adrenal medulla has been confirmed (34), but butyryl-β-methylcholine and benzoyl-β-methylcholine stimulate the superior cervical ganglion (41). Other nicotine-like choline esters are benzoylcholine and certain derivatives (164), nicotinylcholine (but the corresponding bis-quaternary compound is a pure ganglion-blocker) (96), pyridylacetylcholine (191), and a series of thiocholine esters (244).

Murexine [β-(4-imidazole) acrylcholine] like other β-substituted acrylcholines has hardly any muscarinic effects but stimulates ganglion cells (56, 98). In a series of 19 derivatives of murexine, dihydromurexine was the most potent (57). Its ganglionic effects, as well as those of murexine and of imidazoleacetylcholine, have been confirmed and the study extended by other workers (216, 243).

p-Bromo-benzyltrimethylammonium bromide has nicotine-like actions and resembles tetramethylammonium (TMA), whereas the corresponding unsubstituted or *m*-bromo- and *o*-bromo-compounds have only muscarine-like actions (42). A naturally occurring substance, (m-hydroxyphenethyl) trimethylammonium picrate (leptodactyline) is nicotine-like with apparently no muscarinic activity (58). The ganglionic actions of dimethylphenylpiperazine have recently been examined in detail by Ling (133); further studies of the cardiovascular actions of this substance showed that dimethyl-

phenylpiperazine, in addition to its ganglionic actions, elicits reflexes and acts directly on vascular and cardiac muscle (203, 241, 242).

Nonnicotinic ganglion-stimulating substances.—In recent years a study has been made of a group of ganglion-stimulating substances which differ in some respects from nicotine-like agents. Although their effects on ganglia are blocked by "depolarizing" ganglion-blocking substances, they are not antagonized by amounts of "competitive" blocking substances which abolish the effects of nicotine-like substances. Their mode of action has recently been discussed (226), and only a few points will be summarized here.

(a) Histamine.—Small doses facilitate submaximal ganglionic transmission and increase the response of the ganglion to ACh and similar substances (55, 114, 133, 219, 220, 222, 223); moderate doses stimulate the nonperfused SCG, and this effect is antagonized by "depolarizing" ganglion-blocking substances, by cocaine, and by morphine (219, 224, 225) but not by hexamethonium (219). The stimulation of the adrenal medulla by histamine is also not antagonized by hexamethonium or tetraethylammonium (TEA) (87, 219). Large amounts of histamine apparently block the transmission of supramaximal preganglionic impulses through the SCG (75), an observation that does not contradict earlier findings.

The pressor response of the spinal cat to histamine is mainly caused by stimulation of the adrenal medulla (12, 29, 201, 220), but there is also some stimulation of sympathetic ganglia (220). This has been confirmed by the observation that pretreatment with reserpine prevents the pressor response to histamine, whereas 2,6-xylyl ether of choline (which does not influence the release of catecholamines from the adrenal medulla) does not affect it; in adrenalectomized preparations, however, 2,6-xylyl ether of choline (which prevents the liberation of norepinephrine from postganglionic nerve endings) abolishes the pressor response to histamine (227). In rabbits the pressor response to histamine is not mediated through the release of an epinephrine-like substance (162). Neither is the stimulant effect of histamine on isolated atria of various species mediated through the release of an epinephrine-like substance (32, 228), although such a mechanism has been postulated by Went *et al.* (236, 237). Histamine has some actions on the neuromuscular junction (138, 194), and methylated histamine derivatives seem to have more pronounced ganglionic actions (231).

(b) Pilocarpine.—The ganglionic actions of this substance are very similar to those of histamine (199, 219, 220, 222, 223, 226), but, in addition, both its direct actions on smooth muscle and its ganglionic effects are antagonized by very small amounts of atropine (3, 120, 143, 199, 219). Like histamine it causes a pressor response in the spinal cat (and dog); this response is mainly caused by stimulation of sympathetic ganglia, the effect of pilocarpine on the adrenal medulla being rather weak (189, 199, 219). This has been confirmed by the observation that 2,6-xylyl ether of choline and pretreatment with reserpine abolish the pressor response (227).

(c) 5-Hydroxytryptamine.—Stimulating both the superior cervical gan-

glion and the adrenal medulla of the cat, 5-hydroxytryptamine's mode of action resembles that of histamine (55, 187, 221, 222, 223, 235); it seems to block transmission through the ciliary ganglion of the dog (165).

No 5-hydroxytryptamine has been found in ganglia or in the adrenal medulla (68, 72), although the ganglion is rich in 5-hydroxytryptophane-decarboxylase (66). None has been detected in the effluent of the perfused SCG whether resting or preganglionically stimulated. Some 5-hydroxytryptamine appears in the effluent after the addition of amine oxidase inhibitors to the perfusate, but its appearance is not related to preganglionic stimulation (76).

5-Hydroxytryptamine has a stimulant effect on cholinergic nervous structures of the isolated guinea-pig ileum (67, 69, 188) and may also stimulate adrenergic nervous structures of the gut (215). Its stimulant effect on isolated rabbit atria seems to be mediated through the release of an epinephrine-like substance, but it stimulates isolated cat atria by a different mechanism of action (228).

The evidence obtained with these nonnicotinic ganglion-stimulating substances is compatible with the view that their site of action differs from that of "nicotine-like" substances, *i.e.*, that they combine with receptors different from the ACh receptors (226).

Muscarine.—According to classical concepts this substance would not be expected to act on ganglion cells, but, in fact, highly purified preparations (6) and even crystalline muscarine (119) stimulate the perfused SCG of the cat; this effect seems to be abolished by small amounts of atropine (6). In experiments with intravenous injections of muscarine into nonatropinized, or with intra-arterial injections into atropinized preparations, no ganglion-stimulating effects of muscarine have been observed (86, 88, 234), whereas various muscarones had ganglion-stimulating properties under these conditions (88, 234). It seems likely that the very pronounced direct effects of muscarine on smooth muscle mask its ganglion-stimulating properties in the intact animal and that its ganglionic effects (like those of pilocarpine and unlike those of nicotine) are abolished by atropine.

Sympathomimetic amines.—Epinephrine and closely related substances do not stimulate ganglia. There is general agreement that large amounts of epinephrine and norepinephrine inhibit ganglionic transmission. This effect results from a reduction of the release of ACh and from a decreased sensitivity of the ganglion cell (171). Facilitation by small amounts of epinephrine of ganglionic transmission and of the response of the ganglion to stimulation by nicotine-like substances has been reported by some authors (26, 110, 113, 140, 222) but not by others (136, 144, 145, 146, 213). The discrepancy is probably a result of the methods employed, since most of the positive findings were obtained with perfused or fatigued preparations, whereas intravenous injections into intact animals only caused depression of transmission. Recent observations on the neuromuscular junction sup-

port the view that epinephrine has two different effects: by an action on presynaptic nerve terminals it seems to restore fatigued transmission, whereas it causes neuromuscular block by an action on postsynaptic structures (126). Reserpine depletes the stores of catecholamines present in sympathetic ganglia (160) but does not influence ganglionic transmission (230).

Amphetamine and related substances have a nicotine-like action on the perfused SCG of the cat (110, 185), and depolarization of this ganglion by amphetamine, hordenine, and mescaline has been demonstrated (82). On the isolated heart, however, amphetamine does not seem to have a nicotine-like action, since its effect is not abolished by bretylium, 2,6-xylyl ether of choline (102), or hexamethonium (13).

Ephedrine has been claimed to stimulate isolated atria of the guinea pig by a nicotine-like action (173), but Trendelenburg (229) observed no antagonistic effect of hexamethonium applied in a concentration 100 times higher than that required for abolition of the positive chronotropic response to nicotine.

Miscellaneous substances.—Cardiac glycosides increase the response of the SCG to submaximal preganglionic stimulation and to injections of ACh; larger doses depress ganglionic transmission (115, 116, 177). Stimulation of the ganglion by cardiac glycosides is not abolished by hexamethonium (115). Scillaren A also increases the effect of ACh on the chemoreceptors of the carotid body (36). Veratrum ester alkaloids have similar actions in the perfused SCG of the cat (118). Veratramine has a pure depressing effect on the SCG of the rat, but in this preparation even nicotine, TMA, and ACh fail to elicit stimulation (105, 106).

Intra-arterial injections of small amounts of Substance P facilitate ganglionic transmission as well as the response of the ganglion to injections of ACh; the response to postganglionic stimulation remains unaffected. Larger amounts of Substance P depress ganglionic transmission (14). No stimulation of the quiescent ganglion is observed.

An analysis of the action of "Darmstoff" on the isolated guinea-pig ileum provided evidence for an action of this substance on some nervous mechanism sensitive to morphine and to atropine (233).

Peripheral Ganglion Cells

As already pointed out, many ganglion-stimulating substances are also able to stimulate certain sensory structures. Moreover, it has been shown that chromaffin cells occur in peripheral tissues believed to be innervated only by postganglionic adrenergic nerve endings (30). Under these conditions it is difficult to decide whether a "sympathomimetic" response of an isolated organ to a ganglion-stimulating substance is attributable to a direct effect of this substance on smooth muscle or is mediated through an axon reflex, stimulation of chromaffin cells, or stimulation of intramural ganglion cells. Lack of space does not permit more than a brief reference

to part of the relevant bibliography: isolated bronchial muscle (92), isolated hearts or atria (32, 81, 124, 129, 130, 131, 184, 203, 228), aortic strips (31, 33, 154, 197), perfused rabbit ears (30, 31, 32, 81, 125), isolated nictitating membrane (30, 218). The study of the peristaltic reflex involves mainly cholinergic mechanisms together with sensory structures with multiple possible sites of drug action (15, 16, 17, 27, 28, 122, 132).

Ganglion-Blocking Substances

Hexamethonium and tetraethylammonium.—In most experimental studies as well as in studies of structure-action relationships, hexamethonium or TEA, or both, are used as reference substances. Paton & Perry (170) showed that both agents block ganglionic transmission without causing depolarization and suggested their classification as "competitive" ganglion-blocking substances. These substances are usually assumed to have the same mode of action, but certain differences should be noted: after chronic denervation of the SCG of the cat, hexamethonium fails to block the response to ACh and is itself a stimulant agent; the same phenomenon is produced by the perfusion of normal ganglia with low-potassium solutions; the action of TEA is not changed by these procedures (178). Although hexamethonium and TEA have pure additive effects on the SCG (91), they differ in their effects on the late stages of transmission (stage IV of Rosenblueth) (39). Gill's study of various bis-quaternary compounds (80) showed that the blocking action of methonium compounds (hexamethonium, etc.) depends on the length of the chain; this is not true for the potency of ethonium compounds. Gill concludes that methonium compounds combine with the ACh receptor and an anchoring site, the second attachment preventing the depolarization normally resulting from the combination of the ACh receptor with a trimethylammonium group. Triethylammonium groups, on the other hand, are unable to cause depolarization because of the large substituents; these substances combine less intimately with the receptor (and not with an additional site) and, thereby, prevent the access of ACh to the receptor.

In addition to its ganglionic actions, TEA affects the neuromuscular junction; unlike hexamethonium its effects are not curare-like but resemble those of calcium ions [Stovner (207 to 211)]. An effect of TEA on smooth muscle has also been described (35).

The SCG of the rat (*in situ*) is usually not stimulated by nicotine or ACh (106), but these substances cause stimulation when applied some time after the administration of a moderate amount of hexamethonium. No explanation is yet available for this peculiar phenomenon.

Quaternary ammonium compounds.—The structure-action relationship of ganglion-blocking substances has been discussed by Barlow (10) and by Ing (103). Three series of substances were studied by Fakstorp *et al.* (59, 60, 61), and two others by Hidalgo *et al.* (95) and Horovitz *et al.* (101). Conversion of hexamethonium into the corresponding bis-sulfonium com-

pound results in a loss of potency (11), but substitution of only one of the two quaternary nitrogens by a tertiary sulfonium group leads to compounds with up to 3.3 times the potency of hexamethonium (22). A new group of ganglion-blocking substances has been developed from benzhydryl compounds, some of which have been tried clinically [e.g., N^1-(5-cyano-5-5-diphenylpentyl)-N^1,N^1,N^2-trimethylene-1-ammonium-2-morpholinium bis-methylsulfate, pentacynium bis-methylsulfate] (2, 19, 84, 134, 152).

From several species of magnoliaceae and menispermaceae four alkaloids with curare-like and ganglion-blocking effects have been isolated: menisperine, laurifoline, magnocurarine, magnoflorine (200).

Secondary and tertiary amines.—Mecamylamine (3-methylaminoisocamphane) was the first substance of this group to be studied in detail and to be used clinically (202, 206). Its outstanding property is that it is readily absorbed from the intestine. Its excretion into the urine is inversely related to the pH (155) as is its secretion into the stomach (246); the secretion of mecamylamine into the stomach may be partly responsible for its prolonged action. Inhalation of carbon dioxide (i.e., lowering of the extracellular pH) increases the plasma level of mecamylamine and its hypotensive effect (172). Mecamylamine readily penetrates into the CNS and may cause neurological disturbances (43, 174, 195). When its mode of action was studied in more detail, it was found to differ from that of hexamethonium, and Bennet *et al.* (18) concluded that it does not compete with ACh. Other evidence for a noncompetitive mode of action of mecamylamine was obtained with the frog rectus as test organ (190). The findings of Bennet *et al.* have been confirmed by some (205) and contradicted by others (40).

Since the discovery of mecamylamine, many new secondary and tertiary amines have been studied. The importance of the position of the methyl groups was investigated in a series of six methyl substituted 3-aminonorcamphanes (192). Simplification of the molecule led to a series of polymethylcyclohexylamines (182) and to substituted tertiary hexylamines; as a result of this study "penbutamine" [N,N,2,2,3-pentamethylbutylamine (3)] was found to be equipotent with, and less toxic than mecamylamine (232). Another series of even simpler compounds (hexamethylene-1,6-bis-t-amines) had already been described in 1955 but were found to be less effective than hexamethonium (181).

In contrast to piperidine and propylpiperidine, which are nicotine-like in their action, 2,3- and 2,4-dimethylpiperidine cause ganglion block without initial stimulation (121). Another ganglion-blocking derivative is 1-methyl-3(delta-dimethylaminobutyl)piperidine (163). In 1958 two independent groups of investigators developed and tested 1,2,2,6,6-pentamethylpiperidine (pempidine) (128, 204). Its pharmacology is very similar to that of mecamylamine (40, 90, 156, 205).

Quaternary derivatives of parasympatholytics.—Most of the quaternary derivatives of atropine-like substances are known to have ganglion-blocking properties. Several of these compounds were tested on the SCG of the cat

and compared with hexamethonium and TEA (9). They were found to be potent but the ganglionic block was of short duration; the ratio of their potencies as atropine-like and as ganglion-blocking substances was about 1000:1. Thus, the ganglion-blocking action of quaternary atropine-like substance does not seem to be of therapeutic importance. A different conclusion was reached when some quaternary parasympatholytics were compared with their teritiary parent compounds: quaternization reduced the atropine-like potency by a factor of 10 and somewhat increased the ganglion-blocking potency; the ganglion-blocking action is claimed to be of therapeutic importance (93). 4-Diphenyl-methyl-dl-tropeyl-tropinium bromide has twice the ganglion-blocking potency of hexamethonium and one-fourth of the antimuscarinic activity of atropine; it is claimed to combine both properties when used clinically (161). A study of various phenothiazine, xanthene, and aniline derivatives showed that changes in the molecule close to the ester linkage cause changes in atropine-like activity, whereas changes in the cationic head result in changes in ganglion-blocking activity (193).

Gyermek (85) developed a method which distinguishes between atropine-like and ganglion-blocking agents: pretreatment of mice with carbachol does not interfere with the mydriasis produced by atropine but prevents that produced by ganglion-blocking substances. Quantitative determination of ganglion block caused by quaternary parasympatholytics is impossible, but an indication of the predominance of peripheral or ganglionic action may be obtained.

Miscellaneous substances.—Paraldehyde, methylpentynol, and methylpentynol carbamate block ganglionic transmission, the latter two by depressing the output of ACh as well as by reducing the sensitivity of the ganglion cells (142, 183). Chlorpromazine and other phenothiazine derivatives depress synaptic transmission when injected into the perfused SCG or applied topically; after intravenous injections of these substances into whole animals, their adrenolytic effects are usually so strong that any ganglion-blocking action is masked (25, 109, 198, 239). On the neuromuscular junction chlorpromazine is curare-like in some respects, but it also reduces the liberation of ACh (212).

Compound 48/40, injected into the perfused SCG, blocks ganglionic transmission without interfering with the release of ACh (73). Monoamine oxidase inhibitors of different chemistry (iproniazide, harmine, and *p*-tolyl ether of choline) cause a very slowly developing block of ganglionic transmission (74).

A new group of antinicotine substances has been described by Surber (214); they antagonize the effects of nicotine without depressing ganglionic transmission or the response to other "nicotine-like" substances, such as dimethylphenylpiperazine. Their mode of action is not yet known.

Release of acetylcholine from preganglionic nerve endings.—Ganglionic block is usually defined as failure of synaptic transmission. Reduction or abolition of the output of ACh in response to preganglionic nerve stimula-

tion is one of the situations resulting in block of synaptic transmission. This is experimentally verifiable, but it should be remembered that the experimental demonstration of an abolition of the release of ACh gives only little indication of the mechanisms involved. Impairment of conduction of the nerve impulse, interference with the synthesis, with the storage, or with the release mechanism of ACh may all result in a decreased liberation of this substance. Detailed studies of these mechanisms are rare, and the problem is further complicated by the fact that many substances that are able to affect the release of ACh also have some effect on postsynaptic structures (sympathomimetics, local anesthetics, anesthetics, etc.).

Hemicholinium has a weak ganglion-blocking action, when tested on the SCG of the cat (240). Experiments on motor nerves and skeletal muscle indicate that its site of action is probably the presynaptic nerve ending (135). When perfused through the SCG, hemicholinium reduces the synthesis of ACh, an action which is antagonized by the addition of choline to the perfusate (137). Studies with various brain tissues indicate that hemicholinium does not affect the cholineacetylase system but interferes with the transport of choline into the cell and into mitochondria (71, 137). For a discussion of the importance of choline for the replenishment of the ACh stores see (53, 175).

Various ions are known to affect the release of acetylcholine in response to preganglionic stimulation; this aspect has been reviewed by Birks & MacIntosh (20). The effect of lead ion resembles that of magnesium ion: the liberation of ACh is reduced, the response of the ganglion to injected ACh remains normal, and an increase in the calcium ion concentration restores ganglionic transmission (123).

Some mechanisms involved in ganglionic blockade.—The problem whether central effects of ganglion-blocking substances contribute to their hypotensive action is the subject of contradictory evidence. Several groups of workers injected ganglion-blocking substances into the blood supply of the head which was perfused from a donor dog; Heymans *et al.* (94) and Murray *et al.* (159) observed no fall in systemic blood pressure of the recipient dog, whereas Lape & Hoppe (127) reported positive results. Under these conditions, negative results are of greater weight, since a leak from the circulation of the head to the systemic circulation would result in positive findings. Hence supra-spinal centers do not seem to be involved in the hypotensive response to ganglion-blocking substances, but these experiments do not exclude the spinal cord as a possible site of action. The electrical recording of preganglionic activity provides another approach to this problem; the results are equally controversial: Dontas & Nickerson (48) observed a pronounced reduction of activity after hexamethonium and TEA, whereas McCubbin & Page (150) found the activity to be increased after hypotensive doses of TEA or mecamylamine. The latter also observed an unchanged preganglionic response to occlusion of the carotid arteries, while postganglionic fibers were silent.

Gallagher (70) demonstrated that the systemic injection of hexamethonium completely abolishes the sympathetic tone of a perfused hindleg with intact nervous connections. But there have been a number of reports of autonomic pathways resistent to ganglionic blockade. Large doses of ganglion-blocking substances fail to prevent pressor responses to supramaximal stimulation of the splanchnic nerve (149). In both rats and dogs the expected hypotensive response to TEA and to clorisondamine is obtained only under anesthesia and not in unanesthetized animals (148, 166); it has been postulated that anesthesia may interfere with compensatory mechanisms which are not blocked by ganglion-blocking substances. These hypothetical compensatory mechanisms seem to be species dependent, since unanesthetized monkeys and rabbits respond to chlorisondamine (148). The existence of pathways that are not affected by ganglionic blockade may be involved in the phenomenon described by Giertz *et al.* (79): the pressor response to certain analeptic substances (pentylenetetrazol, nikethamide) is believed to be of central origin and is antagonized by azamethonium, but there is a mutual antagonism, i.e., larger amounts of the analeptics can overcome the effect of the ganglion blocker. The characteristics of this mutual antagonism vary with species and with the type of anesthesia employed. An alternative explanation for this phenomenon would be the assumption that the analeptics have, in addition to their central effects, a direct action on ganglion cells.

The phenomenon of tolerance has also been connected with the existence of pathways not blocked by otherwise fully effective doses of ganglion-blocking substances. Postganglionic electrical recording of the activity of renal sympathetic nerves revealed activity persisting after ganglion block; the reflex increase of activity during occlusion of the carotid arteries also persisted (167). Various other mechanisms may contribute to tolerance to ganglion-blocking substances. The "potentiation" of the pressor response to various substances during ganglionic blockade is a well-known phenomenon. Blockade of the compensatory reflexes alone does not seem to be the only factor involved. About equieffective doses of eight different pressor substances were injected before and after pentolinium; the degree of "potentiation" varied from 5 to 240 per cent (89). A much more uniform increase of the response should be expected, if pressoreceptors were of major importance. The authors, therefore, suggest an effect of pentolinium on intrinsically liberated ACh [see (7)]. Furthermore, bilateral removal of the carotid sinus region, together with bilateral vagotomy, does not prevent the increase of pressor responses by ganglion-blocking substances (139). During infusions of ganglion-blocking substances, it has been found that the carotid occlusion reflex is abolished before maximal "potentiation" develops, and during prolonged infusions the response to occlusion of the carotid arteries appears again, although the "potentiation" of pressor responses persists or even increases (167).

There is thus growing evidence for the view that blockade of com-

pensatory mechanism alone cannot explain the phenomenon of "potentiation" of pressor responses by ganglion-blocking substances. An increased responsiveness of smooth muscle during ganglionic blockade has been demonstrated by Mantegazza *et al.* (141): the response of the nicitating membrane to postganglionic stimulation as well as to injections of norepinephrine is increased by hexamethonium and pentolinium. Administration of chlorisondamine for three weeks causes pronounced supersensitivity of the salivary glands and of the nictitating membrane of the cat (52). This latter type of supersensitivity may be quite different from that observed experiments; it may be a result of prolonged "inactivity" of the tissues involved rather than to an action on them of the ganglion-blocking substances.

Parasympathetic ganglion cells do not seem to differ from sympathetic ones in their reaction to ganglion-blocking agents. Comparisons have been made either by simultaneous recording of action potentials from postganglionic fibers of the SCG and of the ciliary ganglion of the cat (64) or by recording the response of the heart to alternating stimulation of the vagus and of the pre- and postganglionic sympathetic fibers (180).

Paton & Perry (170) classified those ganglion-blocking substances that do not interfere with the release of ACh from presynaptic nerve endings as "depolarizing" or as "competitive" agents according to their ability or inability to depolarize ganglion cells. The depolarizing action of some of the former agents (TMA) fully accounts for their ganglion-blocking action, whereas the blocking action of nicotine is of considerably longer duration than its depolarizing effect; in analogy to similar phenomena observed at the neuromuscular junction, the second phase of the blocking action of nicotine is thought to be due to "competitive" blockade. This hypothesis is in agreement with the observation that ganglion cells do not respond to potassium ion during the first phase of the nicotine block, but are excitable by potassium ion during the second (225), just as they respond to this ion during blockade by typical "competitive" blocking substances such as TEA (1) or "curarine" (23). The classification as "depolarizing" and "competitive" blocking agents may need some modification, since chlorisondamine and mecamylamine, which do not cause initial stimulation of ganglion cells (and, therefore, presumably do not cause depolarization), have been found to be noncompetitive (or unsurmountable) antagonists of ACh when tested on the frog rectus (190).

LITERATURE CITED

1. Acheson, G. H., and Pereira, S. A., *J. Pharmacol. Exptl. Therap.*, **87,** 273–80 (1946)
2. Adamson, D. W., Billinghurst, J. W., Green, A. F., and Locket S., *Nature,* **177,** 523–24 (1956)
3. Ambache, N., *J. Physiol (London),* **110,** 164–72 (1949)
4. Ambache, N., *Arch. intern. pharmacodynamie,* **97,** 427–46 (1954)
5. Ambache, N., *Pharmacol. Revs.,* **7,** 467–94 (1955)
6. Ambache, N., Perry, W. L. M., and Robertson, P. A., *Brit. J. Pharma-*

col., **11**, 442–48 (1956)
7. Armin, J., Grant, R. T., Thompson, R. H. S., and Tickner, A., *J. Physiol. (London)*, **121**, 603–22 (1953)
8. Augustinsson, K. B., Fredriksson, T., Sundwall, A., and Jonsson, G., *Biochem. Pharmacol.*, **3**, 68–76 (1959)
9. Bainbridge, J. G., and Brown, D. M., *Brit. J. Pharmacol.*, **15**, 147–51 (1960)
10. Barlow, R. B., *Introduction to Chemical Pharmacology*, 170–79 (Methuen & Co., Ltd., London, England, 343 pp., 1955)
11. Barlow, R. B., and Vane, J. R., *Brit. J. Pharmacol.*, **11**, 198–201 (1956)
12. Bein, H. J., and Meier, R., *Arch. exptl. Pathol. u. Pharmakol.*, **219**, 273–83 (1953)
13. Bejrablaya, D., Burn, J. H., and Walker, J. M., *Brit. J. Pharmacol.*, **13**, 461–66 (1958)
14. Beleslin, D., Radmanović, B., and Varagić, V., *Brit. J. Pharmacol.*, **15**, 10–13 (1960)
15. Beleslin, D., and Varagić, V., *Brit. J. Pharmacol.*, **13**, 321–25 (1958)
16. Beleslin, D., and Varagić, V., *J. Pharm. and Pharmacol.*, **11**, 99–103 (1959)
17. Beleslin, D., and Varagić, V., *Experientia*, **15**, 186–88 (1959)
18. Bennet, G., Tyler, C., and Zaimis, E., *Lancet*, **2**, 218–22 (1957)
19. Billinghurst, J. W., *Hypotensive Drugs*, 35–39 (Pergamon Press, London, England, 222 pp., 1956)
20. Birks, R. S., and MacIntosh, F. C., *Brit. Med. Bull.*, **13**, 157–61 (1957)
21. Boyd, J. D., *Brit. Med. Bull.*, **13**, 207–12 (1957)
22. Brown, D. M., and Turner, D. H., *J. Pharm. and Pharmacol.*, **11**, 95–102T (1959)
23. Brown, G. L., and Feldberg, W., *J. Physiol (London)*, **86**, 10–11P (1936)
24. Brown, G. L., and Pascoe, J. E., *J. Physiol. (London)*, **118**, 113–23 (1952)
25. Budde, H., and Witzleb, E., *Arch. intern. pharmacodynamie*, **102**, 126–38 (1955)
26. Bülbring, E., *J. Physiol. (London)*, **103**, 55–67 (1944)
27. Bülbring, E., and Crema, A., *Brit. J. Pharmacol.*, **13**, 444–57 (1958)
28. Bülbring, E., and Crema, A., *J. Physiol. (London)*, **146**, 29–53 (1959)
29. Burn, J. H., and Dale, H. H., *J. Physiol. (London)*, **61**, 185–214 (1926)
30. Burn, J. H., Leach, E. H., Rand, M. J., and Thompson, J. W., *J. Physiol. (London)*, **148**, 332–52 (1959)
31. Burn, J. H., and Rand, M. J., *Lancet*, **2**, 1097 (1957)
32. Burn, J. H., and Rand, M. J., *Brit. Med. J.*, **I**, 137–39 (1958)
33. Burn, J. H., and Rand, M. J., *Brit. Med. J.*, **I**, 903–8 (1958)
34. Butterworth, K. R., and Mann, M., *J. Pharm. and Pharmacol.*, **10**, 295–301 (1958)
35. Čapek, R., and Knesslová, V., *Arch. exptl. Pathol. u. Pharmakol.*, **236**, 161–62 (1959)
36. Carpi, A., Konzett, H., and Cerletti, A., *Arch. intern. pharmacodynamie*, **109**, 369–76 (1957)
37. Castro, F. de; *Arch. intern. physiol.*, **59**, 479–513 (1951)
38. Chien, S., *Federation Proc.*, **17**, 25 (1958)
39. Clark, W. G., and Harvey, S. C., *Federation Proc.*, **18**, 377 (1959)
40. Corne, S. J., and Edge, N. D., *Brit. J. Pharmacol.*, **13**, 339–49 (1958)
41. Cowan, F. F., *Federation Proc.*, **19**, 285 (1960)
42. Credner, K., *Arch. exptl. Pathol. u. Pharmakol.*, **234**, 303–10 (1958)
43. Deming, Q. B., Hodes, M. E., Edreira, J. G., and Baltazar, A., *New Engl. J. Med.*, **256**, 739–42 (1957)
44. Dempsher, J., Larrabee, M. G., Bang, F. G., and Bodian, D., *Am. J. Physiol.*, **182**, 203–16 (1955)
45. Dempsher, J., and Riker, W. K., *J. Physiol. (London)*, **139**, 145–56 (1957)
46. Dempsher, J., Tokumaru, T., and Zabara, J., *J. Physiol. (London)*, **146**, 428–37 (1959)
47. Dempsher, J., and Zabara, J., *J. Physiol. (London)*, **151**, 217–24 (1960)
48. Dontas, A. S., and Nickerson, M., *J. Pharmacol. Exptl. Therap.*, **120**, 147–59 (1957)
49. Douglas, W. W., and Ritchie, M., *J. Physiol. (London)*, **133**, 220–31 (1956)
50. Douglas, W. W., and Ritchie, J. M., *Federation Proc.*, **18**, 385 (1959)

51. Eccles, J. C., *J. Physiol (London)*, **85,** 179-206 (1935)
52. Emmelin, N., *Brit. J. Pharmacol.*, **14,** 229–33 (1959)
53. Emmelin, N., and MacIntosh, F. C., *J. Physiol. (London)*, **131,** 477–96 (1956)
54. Engelhardt, A., Greeff, K., Richter, W., and Schümann, H. J., *Arch. exptl. Pathol. u. Pharmakol.*, **225,** 541–50 (1955)
55. Engelhardt, G., and Roser, F., *Arch. exptl. Pathol. u. Pharmakol.*, **230,** 90–106 (1957)
56. Erspamer, V., and Glässer, A., *Brit. J. Pharmacol.*, **12,** 176–84 (1957)
57. Erspamer, V., and Glässer, A., *Brit. J. Pharmacol.*, **13,** 378–84 (1958)
58. Erspamer, V., and Glässer, A., *Brit. J. Pharmacol.*, **15,** 14–22 (1960)
59. Fakstorp, J., and Pedersen, J. G. A., *Acta Pharmacol. Toxicol.*, **13,** 359–67 (1957)
60. Fakstorp, J., and Pederson, J. G. A., *Acta Pharmacol. Toxicol.*, **14,** 148–52 (1958)
61. Fakstorp, J., Pedersen, J. G. A., Poulsen, E., and Schilling, M., *Acta Pharmacol. Toxicol.*, **13,** 52–58 (1957)
62. Fehér, O., and Bokri, E., *Arch. ges. Physiol., Pflüger's,* **269,** 55–67 (1959)
63. Florey, E., and McLennan, H., *J. Physiol. (London)*, **129,** 384–92 (1955)
64. Florida, F. A. de, Cato, J., Ramirez, L., and Pardo, E. G., *J. Pharmacol. Exptl. Therap.*, **129,** 433–37 (1960)
65. Folkow, B., Johansson, B., and Öberg, B., *Acta Physiol. Scand.*, **44,** 146–56 (1958)
66. Gaddum, J. H., and Giarman, N. J., *Brit. J. Pharmacol.*, **11,** 88–92 (1956)
67. Gaddum, J. H., and Hameed, K. A., *Brit. J. Pharmacol.*, **9,** 240–48 (1954)
68. Gaddum, J. H., and Paasonen, M. K., *Brit. J. Pharmacol.*, **10,** 474–83 (1955)
69. Gaddum, J. H., and Picarelli, Z. P., *Brit. J. Pharmacol.*, **12,** 323–28 (1957)
70. Gallagher, D. J. A., *Brit. J. Pharmacol.*, **9,** 129–30 (1954)
71. Gardiner, J. E., *J. Physiol. (London)*, **138,** 13–14P (1957)
72. Garven, J. D., *Brit. J. Pharmacol.*, **11,** 66–70 (1956)
73. Gertner, S. B., *Brit. J. Pharmacol.*, **10,** 103–9 (1955)
74. Gertner, S. B., *Nature,* **183,** 750–51 (1959)
75. Gertner, S. B., and Kohn, R., *Brit. J. Pharmacol.*, **14,** 179–82 (1959)
76. Gertner, S. B., Paasonen, M. K., and Giarman, N. J., *J. Pharmacol. Exptl. Therap.*, **127,** 268–75 (1959)
77. Gertner, S. B., and Reinert, H., *Arch. exptl. Pathol. u. Pharmakol.*, **230,** 347–57 (1957)
78. Giacobini, E., *Acta Physiol. Scand.*, **36,** 276–90 (1956)
79. Giertz, H., Hahn, F., and Rummel, W., *Arch. exptl. Pathol. u. Pharmakol.*, **226,** 460–66 (1955)
80. Gill, E. W., *Proc. Roy. Soc. (London), B,* **150,** 381–402 (1959)
81. Ginzel, K. H., and Kottegoda, S. R., *Arch. exptl. Pathol. u. Pharmakol.*, **222,** 178–80 (1954)
82. Gold, D., and Reinert, H., *J. Physiol. (London)*, **151,** 3–4P (1960)
83. Gray, J. A. B., and Diamond, J., *Brit. Med. Bull.*, **13,** 185–88 (1957)
84. Green, A. F., *Hypotensive Drugs,* 95–99 (Pergamon Press, London, England, 222 pp., 1956)
85. Gyermek, L., *J. Pharmacol. Exptl. Therap.*, **127,** 313–17 (1959)
86. Gyermek, L., and Herr, F., *Federation Proc.*, **18,** 399 (1959)
87. Gyermek, L., and Sztanyik, L., *Kisérletes Orvostudomány,* **4,** 1–8 (1952)
88. Gyermek, L., and Unna, K. R., *Proc. Soc. Exptl. Biol. Med.*, **98,** 882–85 (1958)
89. Haas, E., and Goldblatt, H., *Am. J. Physiol.*, **196,** 763–68 (1959)
90. Harington, M., Kincaid-Smith, P., and Milne, M. D., *Lancet,* **2,** 6–11 (1958)
91. Harvey, S. C., *Arch. intern. pharmacodynamie,* **114,** 232–42 (1958)
92. Hawkins, D. F., and Paton, W. D. M., *J. Physiol. (London)*, **144,** 193–219 (1958)
93. Herman, L., Shaw, F. H., and Rosenblum, E. I., *J. Pharm. and Pharmacol.*, **10,** 348–55 (1958)
94. Heymans, C., Delaunois, A. L., and Martini, L., *Arch. intern. pharmacodynamie,* **97,** 313–16 (1954)
95. Hidalgo, J., Wilken, W., Seeberg, V. P., Grigsby, I., and Guldenzopf, J., *Arch. intern. pharmacodynamie,* **118,** 210–30 (1959)

96. Holmstedt, B., Larsson, L., and Sundwall, A., *Biochem. Pharmacol.*, **3**, 155–62 (1960)
97. Holmstedt, B., and Sjöqvist, F., *Acta. Physiol. Scand.*, **47**, 284–96 (1959)
98. Holmstedt, B., and Whittaker, V. P., *Brit. J. Pharmacol.*, **13**, 308–14 (1958)
99. Holton, P., *J. Physiol. (London)*, **145**, 494–504 (1959)
100. Honour, A. J., and McLennan, H., *J. Physiol. (London)*, **150**, 306-18 (1960)
101. Horovitz, Z. P., Reif, E. C., and Buckley, J. P., *J. Am. Pharm. Assoc.*, **47**, 718-21 (1958)
102. Huković, S., *Brit. J. Pharmacol.*, **15**, 117–21 (1960)
103. Ing, H. R., *Hypotensive Drugs*, 7–22 (Pergamon Press, London, England, 222 pp., 1956)
104. Job, C., and Lundberg, A., *Acta Physiol. Scand.*, **26**, 366–82 (1952)
105. Kaller, H., *Arch. intern. pharmacodynamie*, **105**, 337–48 (1956)
106. Kaller, H., *Arch. exptl. Pathol. u. Pharmakol.*, **228**, 361–66 (1956)
107. Kamijo, K., and Koelle, G. B., *J. Pharmacol. Exptl. Therap.*, **105**, 349–57 (1952)
108. Karczmar, A. G., and Koppanyi, T., *J. Pharmacol. Exptl. Therap.*, **116**, 245–53 (1956)
109. Kewitz, H., *Arch. exptl. Pathol. u. Pharmakol.*, **222**, 323–29 (1954)
110. Kewitz, H., and Reinert, H., *Arch. exptl. Pathol. u. Pharmakol.*, **222**, 311–14 (1954)
111. Koelle, G. B., *J. Pharmacol. Exptl. Therap.*, **120**, 488–503 (1957)
112. Koelle, W. A., and Koelle, G. B., *J. Pharmacol. Exptl. Therap.*, **126**, 1–8 (1959)
113. Konzett, H., *Helv. Physiol. et Pharmacol. Acta.*, **8**, 245–58 (1950)
114. Konzett, H., *J. Mt. Sinai Hosp. N.Y.*, **19**, 149–53 (1952)
115. Konzett, H., and Carpi, A., *Helv. Physiol. et Pharmacol. Acta.*, **14**, 235–50 (1956)
116. Konzett, H., and Rothlin, E., *Arch. intern. pharmacodynamie*, **89**, 343–52 (1952)
117. Konzett, H., and Rothlin, E., *Experientia*, **9**, 405 (1953)
118. Konzett, H., and Rothlin, E., *Arch. exptl. Pathol. u. Pharmakol.*, **225**, 101–4 (1955)
119. Konzett, H., and Waser, P. G., *Helv. Physiol. et Pharmacol. Acta*, **14**, 202–6 (1956)
120. Koppanyi, T., *J. Pharmacol. Exptl. Therap.*, **46**, 395–405 (1932)
121. Koppanyi, T., and Vivino, E., *Federation Proc.*, **5**, 186–87 (1946)
122. Kosterlitz, H. W., and Robinson, J. A., *J. Physiol. (London)*, **146**, 369–79 (1959)
123. Kostial, K., and Vouk, V. B., *Brit. J. Pharmacol.*, **12**, 219–22 (1957)
124. Kottegoda, S. R., *Brit. J. Pharmacol.*, **8**, 83–86 (1953)
125. Kottegoda, S. R., *Brit. J. Pharmacol.*, **8**, 156–61 (1953)
126. Krnjević, K., and Miledi, R., *J. Physiol. (London)*, **141**, 291–304 (1958)
127. Lape, H. E., and Hoppe, J. O., *J. Pharmacol. Exptl. Therap.*, **116**, 453–61 (1956)
128. Lee, G. E., Wragg, W. R., Corne, S. J., Edge, N. D., and Reading, H. W., *Nature*, **181**, 1717–18 (1958)
129. Lee, W. C., and Shideman, F. E., *Circulation Research*, **6**, 66–71 (1958)
130. Lee, W. C., and Shideman, F. E., *J. Pharmacol. Exptl. Therap.*, **126**, 239–49 (1959)
131. Lee, W. C., and Shideman, F. E., *J. Pharmacol. Exptl. Therap.*, **127**, 219–28 (1959)
132. Lembeck, F., *Arch. ges. Physiol., Pflüger's*, **265**, 567–74 (1958)
133. Ling, H. W., *Brit. J. Pharmacol.*, **14**, 505–11 (1959)
134. Locket, S., *Brit. Med. J.*, **2**, 74–78 (1958)
135. Longo, V. G., *Arch. intern. pharmacodynamie*, **119**, 1–9 (1959)
136. Lundberg, A., *Acta Physiol. Scand.*, **26**, 252–63 (1952)
137. MacIntosh, F. C., Birks, R. I., and Sastry, P. B., *Nature*, **178**, 1181 (1956)
138. MacMillan, W. H., *Arch. intern. pharmacodynamie*, **108**, 19–26 (1956)
139. Maengwyn-Davies, G. D. Walz, D. T., and Koppanyi, T., *Arch. intern. pharmacodynamie*, **113**, 427–31 (1957)
140. Malméjac, J., *J. Physiol. (London)*, **130**, 497–512 (1955)
141. Mantegazza, P., Tyler, C., and Zaimis, E., *Brit. J. Pharmacol.*, **13**, 480–84 (1958)
142. Marley, E., and Paton, W. D. M., *Brit. J. Pharmacol.*, **14**, 303–6 (1959)

143. Marrazzi, A. S., *J. Pharmacol. Exptl. Therap.*, **65,** 18–35 (1939)
144. Marrazzi, A. S., *J. Pharmacol. Explt. Therap.*, **65,** 395–404 (1939)
145. Marrazzi, A. S., and Marrazzi, R. N., *J. Neurophysiol.*, **10,** 165–78 (1947)
146. Matthews, R. J., *J. Pharmacol. Exptl. Therap.*, **116,** 433–43 (1956)
147. Matthews, R. J., and Roberts, B. J., *The Pharmacologist,* **1,** 57 (1959)
148. Maxwell, R. A., Plummer, A. J., Ross, S. D., Daniel, A. I., and Schneider, F., *J. Pharmacol., Exptl. Therap.*, **123,** 238–46 (1958)
149. Maxwell, R. A., Plummer, A. J., Ross, S. D., and Osborne, M. W., *Proc. Soc. Exptl. Biol. Med.*, **92,** 225–27 (1956)
150. McCubbin, J. W., and Page, I. H., *Circulation Research,* **6,** 816–24 (1958)
151. McIssac, R. C., and Koelle, G. B., *J. Pharmacol. Exptl. Therap.*, **126,** 9–20 (1959)
152. McKendrick, C. S., and Jones, P. O., *Lancet,* **1,** 340–43 (1958)
153. McLennan, H., and Pascoe, J. E., *J. Physiol. (London),* **124,** 145–56 (1954)
154. Millson, D. R., *Brit. J. Pharmacol.*, **14,** 239–42 (1959)
155. Milne, M. D., Rowe, G. G., Somers, K., Muehrcke, R. C., and Crawford, M. A., *Clin. Sci.*, **16,** 599–614 (1957)
156. Muggleton, D. F., and Reading, H. W., *Brit. J. Pharmacol.*, **14,** 202–8 (1959)
157. Murray, J. G., and Thompson, J. W., *J. Physiol. (London),* **135,** 133–62 (1957)
158. Murray, J. G., and Thompson, J. W., *Brit. Med. Bull.*, **13,** 213–19 (1957)
159. Murray, R., Beck, L., Rondell, P. A., and Bohr, D. F., *J. Pharmacol. Exptl. Therap.*, **127,** 157–63 (1959)
160. Muscholl, E., and Vogt, M., *J. Physiol. (London),* **141,** 132–55 (1958)
161. Nador, K., and Gyermek, L., *Arzneimittel-Forsch.*, **8,** 336–40 (1958)
162. Naranjo, P., and Naranjo, E. B. de, *J. Pharmacol. Exptl. Therap.*, **123,** 16–21 (1958)
163. Norton, S., and Phillips, A. P., *Nature,* **172,** 867 (1953)
164. Ormerod, W. E., *Brit. J. Pharmacol.*, **11,** 267–72 (1956)
165. Page, I. H., and McCubbin, J. W., *Circulation Research,* **1,** 354–62 (1953)
166. Page, I. H., and McCubbin, J. W., *Am. J. Physiol.*, **194,** 597–600 (1958)
167. Page, I. H., and McCubbin, J. W., *Am. J. Physiol.*, **197,** 217–22 (1959)
168. Paton, W. D. M., *Arch. intern pharmacodynamie,* **97,** 267–81 (1954)
169. Paton, W. D. M., *Ann. Rev. Physiol.*, **20,** 431–70 (1958)
170. Paton, W. D. M., and Perry, W. L. M., *J. Physiol. (London),* **119,** 43–57 (1953)
171. Paton, W. D. M., and Thompson, J. W., *Intern. Congr. Physiol., 19th Congr.*, **664** (Montreal, 1953)
172. Payne, J. P., and Rowe, G. G., *Brit. J. Pharmacol.*, **12,** 457–60 (1957)
173. Pepeu, G., Masi, R., and Giotti, A., *Arch. intern. pharmacodynamie,* **119,** 334–44 (1959)
174. Perry, H. M., and Schroeder, H. A., *J. Am. Med. Assoc.*, **164,** 1455–58 (1957)
175. Perry, W. L. M., *J. Physiol. (London),* **119,** 439–54 (1953)
176. Perry, W. L. M., *Brit. Med. Bull.*, **13,** 220–26 (1957)
177. Perry, W. L. M., and Reinert, H., *Brit. J. Pharmacol.*, **9,** 324–28 (1954)
178. Perry, W. L. M., and Reinert, H., *J. Physiol. (London),* **126,** 101–15 (1954)
179. Perry, W. L. M., and Reinert, H., *J. Physiol. (London),* **130,** 156–66 (1955)
180. Perry, W. L. M., and Wilson, C. W. M., *Brit. J. Pharmacol.*, **11,** 81–87 (1956)
181. Phillips, A. P., *J. Am. Chem. Soc.*, **77,** 1693–95 (1955)
182. Protiva, M., Rajšner, M., Trčka, V., Vaněček, M., and Vejdělek, Z. J., *Experientia,* **15,** 54–55 (1959)
183. Quilliam, J. P., *Brit. J. Pharmacol.*, **14,** 277–83 (1959)
184. Reinert, H., *Arch. exptl. Pathol. u. Pharmakol.*, **236,** 134–35 (1959)
185. Reinert, H., *Neuropsychopharmacology,* 399–404 (Elsevier Publishing Co., Amsterdam, The Netherlands, 727 pp., 1959)
186. Riker, W. K., and Szreniawski, Z., *J. Pharmacol. Exptl. Therap.*, **126,** 233–38 (1959)
187. Robertson, P. A., *J. Physiol. (London),* **125,** 37–38P (1954)
188. Rocha e Silva, M., Valle, J. R., and

Picarelli, Z. P., *Brit. J. Pharmacol.* **8,** 378–88 (1953)
189. Root, M. A., *J. Pharmacol. Exptl. Therap.,* **101,** 125–31 (1951)
190. Rossum, J. H. van, and Ariëns, E. J., *Arch. intern. pharmacodynamie,* **118,** 447–66 (1959)
191. Rubin, A. A., Mershon, J., Tabachnik, I. I. A., and Govier, W. M., *J. Pharmacol. Exptl. Therap.,* **123,** 104–7 (1958)
192. Rubinstein, K., Pedersen, J. G. A., Fakstorp., J., and Ronnov-Jessen, V., *Experientia,* **14,** 222–23 (1958)
193. Schaeppi, U., and Waser, P., *Arzneimittel Forsch.,* **8,** 107–13 (1958)
194. Schenk, E. A., and Anderson, E. G., *J. Pharmacol. Exptl. Therap.,* **122,** 234–38 (1958)
195. Schneckloth, R. E., Corcoran, A. C., Dustan, H. P., and Page, I. H., *J. Am. Med. Assoc.,* **162,** 868–75 (1956)
196. Schneider, R., and Timms, A. R., *Brit. J. Pharmacol.,* **12,** 30–38 (1957)
197. Setnikar, I., and Ravasi, M., *Nature,* **183,** 898–99 (1959)
198. Sherif, M. A. F., Chata, M. K., and Madkour, M. K., *Arch. intern. pharmacodynamie,* **115,** 269–77 (1958)
199. Shimamoto, K., and Inoue, K., *Japan. J. Pharmacol.,* **7,** 94–103 (1958)
200. Shimamoto, K., Inoue, K., and Ogiu, K., *Japan. J. Pharmacol.,* **7,** 135–56 (1958)
201. Slater, I. H., and Dresel, P. E., *J. Pharmacol. Exptl. Therap.,* **105,** 101–7 (1952)
202. Smirk, F. H., and McQueen, E. G., *Brit. Med. J.,* **1,** 422 (1957)
203. Soncin, E., and Maffii, G., *Arch. intern. pharmacodynamie,* **123,** 148–67 (1959)
204. Spinks, A., and Young, E. H. P., *Nature,* **181,** 1397–98 (1958)
205. Spinks, A., Young, E. H. P., Farrington, J. A., and Dunlop, D., *Brit. J. Pharmacol.,* **13,** 501–20 (1958)
206. Stone, C. A., Torchiana, M. L., Navarro, A., and Beyer, K. H., *J. Pharmacol. Exptl. Therap.,* **117,** 169–83 (1956)
207. Stovner, J., *Acta Physiol. Scand.,* **40,** 275–84 (1957)
208. Stovner, J., *Acta Physiol. Scand.,* **40,** 285–96 (1957)
209. Stovner, J., *Acta Physiol. Scand.,* **41,** 370–83 (1957)
210. Stovner, J., *Acta Pharmacol. Toxicol.,* **14,** 317–32 (1958)
211. Stovner, J., *Acta Pharmacol. Toxicol.,* **15,** 55–69 (1958)
212. Su, C., and Lee, C. Y., *Brit. J. Pharmacol.,* **15,** 88–94 (1960)
213. Suden, C. tum, and Marrazzi, A. S., *Federation Proc.,* **10,** 138 (1951)
214. Surber, W., *Helv. Physiol. Acta,* **16,** 277–86 (1958)
215. Szerb, J. C., *Federation Proc.,* **17,** 633 (1958)
216. Tabachnik, I. I. A., Roth, F. E., Mershon, J., Rubin, A. A., Eckhardt, E. T., and Govier, W. M., *J. Pharmacol. Exptl. Therap.,* **123,** 98–103 (1958)
217. Takahashi, H., Tiba, M., Yamazaki, T., and Noguchi, F., *Japan. J. Pharmacol.,* **8,** 378–90 (1958)
218. Thompson, J. W., *J. Physiol. (London),* **141,** 46–72 (1958)
219. Trendelenburg, U., *Brit. J. Pharmacol.,* **9,** 481–87 (1954)
220. Trendelenburg, U., *J. Physiol. (London),* **129,** 337–51 (1955)
221. Trendelenburg, U., *Brit. J. Pharmacol.,* **11,** 74–80 (1956)
222. Trendelenburg, U., *J. Physiol. (London),* **135,** 66–72 (1957)
223. Trendelenburg, U., *J. Physiol. (London),* **135,** 66–72 (1957)
224. Trendelenburg, U., *Brit. J. Pharmacol.,* **12,** 79–85 (1957)
225. Trendelenburg, U., *Arch. exptl. Pathol. u. Pharmakol.,* **230,** 448–56 (1957)
226. Trendelenburg, U., *Federation Proc.,* **18,** 1001–5 (1959)
227. Trendelenburg, U., *J. Pharmacol. Exptl. Therap.* (In press)
228. Trendelenburg, U., *J. Pharmacol. Exptl. Therap.* (In press)
229. Trendelenburg, U. (Unpublished data)
230. Trendelenburg, U., and Gravenstein, J. S., *Science,* **128,** 901–3 (1958)
231. Vartiainen, A., *J. Pharmacol. Exptl. Therap.,* **54,** 265–82 (1935)
232. Vejdělek, Z. J., and Trčka, V., *Experientia,* **15,** 215–16 (1959)
233. Vogt, W., *Arch. exptl. Pathol. u. Pharmakol.,* **235,** 550–58 (1959)
234. Waser, P. G., *Experientia,* **14,** 356–58 (1958)
235. Weidmann, H., and Cerletti, A., *Arch. intern. pharmacodynamie,* **111,** 98–107 (1957)
236. Went, I., Varga, E., Szücs, E., and Fehér, O., *Acta Physiol. Acad. Sci. Hung.,* **5,** 121–30 (1954)

237. Went, S., Varga, E., Szücs, E., and Fehér, O., *Arch. exptl. Pathol. u. Pharmakol.*, **215**, 129–32 (1952)
238. Werner, G., and Kuperman, A., *Heffter's Handbuch exptl. Pharmakol.*, **15** (In preparation) (in English)
239. Wiedling, S., *Acta Pharmacol. Toxicol.*, **14**, 112–29 (1958)
240. Wilson, H., and Long, J. P., *Arch. intern. pharmacodynamie*, **120**, 343–52 (1959)
241. Winbury, M. M., *J. Pharmacol. Exptl. Therap.*, **124**, 25–34 (1958)
242. Winbury, M. M., *J. Physiol. (London)*, **147**, 1–13 (1959)
243. Winbury, M. M., Wolf, J. K., and Tabachnik, I. I. A., *J. Pharmacol. Exptl. Therap.*, **122**, 207–14 (1958)
244. Wurzel, M., *Arch. intern. pharmacodynamie*, **124**, 330–35 (1960)
245. Zakusov, V. V., and Ul'ianova, O. V., *Pharmacol. Toxicol. (U.S.S.R.)*, **21**, 105–9 (1958)
246. Zawoiski, E. J., Baer, J. E., Braunschweig, L. W., Paulson, S. F., Shermer, A., and Beyer, K. H., *J. Pharmacol., Exptl. Therap.*, **122**, 442–48 (1958)

CONTENTS