THE MECHANISM OF DRUG CONTROL OF GASTRIC MOTILITY[1]

FRANK E. HAMILTON, M.D. and GEORGE M. CURTIS, M.D.,
From the Department of Research Surgery
of the Ohio State University

Recent clinical investigation has demonstrated the significance of the motor behavior of the human stomach during certain pathologic states. Hoffmeister, Cannon, and Magnus (30) were among the first investigators to recognize this physiologic principle. Their studies of gastric motility led to investigations of the emptying time of the stomach and the effect of denervation operations on the activity of the stomach. Most of the early studies were conducted on animals and the results obtained lacked uniformity. More recently, members of the Department of Research Surgery of the Ohio State University have had the opportunity to study gastric motility in the human subject.

Barron and Curtis (1) found that following bilateral splanchnic resection there ensues increased motility of the human stomach, while after subdiaphragmatic resection of the left vagus (2) there follows a decreased motility. Veach (36) and Veach, Lauer, and James (37) found that movements of the normal as well as the pathologic human stomach could be controlled by various drugs. Morphine was predominantly motor to the human stomach, while atropine was constantly inhibitory. Prostigmin administered alone was inhibitory to the human stomach, but when administered in conjunction with atropine it became motor.

Recently these investigations in clinical physiology have been put to clinical tests in the management of postoperative gas pains and nausea, the control of the pain of biliary colic, and the relief of certain of the symptoms of obstructive duodenal ulcer. Nevertheless, valuable as is the application of these findings from a clinical standpoint, the factor of fundamental importance is the nature of the mechanism of control of gastric motility.

Under the older theories, visceral motility was thought to be the result of a balance between the activities of the

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sympathetic and parasympathetic divisions of the autonomic nervous system. Accordingly, the motor response of the stomach, following administration of any certain drug, would be the result of stimulating or inhibiting one or the other of the two autonomic divisions, and thus upsetting the balance between these two forces.

However, McCrea (29), McSwiney and Wadge (31), Barry (3), and Harrison and McSwiney (24) have by the use of experiment shown the presence of motor and inhibitory fibres in both the vagus and splanchnic nerves. Gayet, Minz, and Quivy (23) have recently supplied further confirmation of these observations by demonstrating the release of acetylcholine following stimulation of the splanchnic nerve. These investigators have demonstrated that the effect of stimulation of the cut end of either the vagus or the splanchnic may result in either increased activity or inhibition of the stomach; moreover, the result appears to depend largely on the existing degree of gastric *tonus* present at the time of stimulation.

However, it appears to be clear that the vagi are predominantly motor to the stomach while the splanchnics are predominantly inhibitory.

Further evidence of the inadequacy of the older theory postulating the dependence of visceral motor function on a balance between the sympathetic and parasympathetic divisions, is furnished by the recent work of Dale (15, 16, 17, 18, 19, 20), Loewi (26, 27), and Cannon (10, 11, 12, 13). Dale investigated the chemical transmission of the nervous impulse and eventually formulated the adrenergic-cholinergic theory of balance. Since his work, together with the fundamental investigations of Loewi and Cannon, have provided the principal background for the present concept of the control of visceral motility, these studies will be briefly reviewed.

THE CHOLINERGIC DIVISION OF THE AUTONOMIC NERVOUS SYSTEM

Elliott (16) in 1904 observed the similarity between the action of adrenalin and the stimulation of the "true" sympathetic nerves. Dixon (16) in 1906 argued that the parasympathetic nerves similarly release a chemical transmitter of their effects. The same year Howell (16) suggested that inhibition of the heart by vagus impulses is due to mobilization of potassium ions.

In 1921 Otto Loewi (26) stimulated the vagus to an isolated frog heart, removed the saline from the chamber, and something in the fluid inhibited a second frog heart. This proved the liberation of a specific chemical stimulator in the transmission of a peripheral autonomic stimulus. Later, Loewi (16) showed his "Vagusstoff" to be identical with acetylcholine in obtaining certain biological reactions.

Sir Henry Dale in 1933 (15) showed that when the sympathetic nerves of the sweat glands are stimulated, acetylcholine is produced. Therefore, he suggested a reclassification of the autonomic nervous system into adrenergic and cholinergic fibres, which on stimulation will produce adrenine or acetylcholine. Later work (16) has shown that all preganglionic fibres and most postganglionic fibres are cholinergic; the only adrenergic nerves are the postganglionic fibres of the "true" sympathetic nerves. Dale (17) believes that a propagated nervous impulse releases a wave of mobilization of potassium ions along a nerve fibre; this process arrives at the ending of a preganglionic fibre and there immediately liberates a small charge of acetylcholine, which causes the discharge of a new impulse, with perhaps a new wave of potassium mobilization passing along the postganglionic fibre. He believes that the excitatory impulse is actually transmitted across a synapse by the liberation of acetylcholine. Dale suggested in 1914 (18) that this is possible within the reaction time if acetylcholine were circulating in the blood in an inactive state, perhaps as choline, and when made active by its ester, is immediately inactivated by some substance, as cholinesterase. This suggestion was supported in 1936 in the course of further studies by Dale, Feldberg, and Vogt (19).

The majority of Dale's investigations have been confirmed and accepted by other students. Lehnartz (25) in 1936 found a similar mobilization of potassium ions could be produced by stimulation of the vagus with acetylcholine. Bureau (9) reports a detectable increase of potassium ions following electrical stimulation of frog muscle immersed in Ringer's solution.

If the nervous impulse is transmitted by acetylcholine, the origin of this substance is of importance. Recently considerable evidence has pointed to the presence of a precursor of acetylcholine in certain tissues. Dikshit (21) finds that

in the presence of eserine, acetylcholine is formed by thin slices of the brain of the dog and rabbit. Corteggiani (14) finds that the brain, spinal cord, nerves of many vertebrates, the vagus of the dog, and intestine of the hedgehog contain quantities of acetylcholine which can be liberated on heating. Pinotti (34) noted that the fibres of the vagus contain acetylcholine in the inactive state. These findings add weight to the conclusions of Brown and Feldberg (6) who believe acetylcholine is mobilized from a preformed store by immediate synthesis upon the arrival of the nervous impulse.

The theory of the production of acetylcholine as the substance of transmission of nervous impulses in muscle contraction also implies its extremely rapid disintegration. This extraordinary evanescence of action of acetylcholine was noted by Dale in 1914 (18) and he suggested at that time that it was probably hydrolyzed with great rapidity by an esterase in the blood. This has been confirmed by Marnay and Nachmansohn (28) who noted that the concentration of cholinesterase at the nerve end plates in the frog sartorius is many times that found in nerveless muscle tissue. This enables the muscle to split the acetylcholine liberated by nerve impulses during the refractory period. The chemical changes can occur with the rapidity necessary for the assumption of a chemical transmission of nerve impulses in such quickly reacting cells as fibres of voluntary muscle. However, owing to technical difficulties, it has not been possible to isolate cholinesterase, or to assay its activity at parasympathetic endings.

Clinicians who have used acetylcholine are struck by the uncertain and variable results following subcutaneous or intravenous injection of the substance. This is interpreted as due to the remarkable evanescence of acetylcholine, because of its rapid hydrolysis by the cholinesterase present in the blood and tissues. Fraser (22) found that subcutaneous injection of acetylcholine in man is usually without apparent effects, and even when introduced intravenously no effect is obtained if the blood is allowed to flow back into the syringe. It is therefore probable that following the arrival of the impulse at the nerve endings, acetylcholine is produced, transmits the effect of the impulse, and is almost immediately destroyed by the cholinesterase present locally in the tissue.

THE ADRENERGIC DIVISION OF THE AUTONOMIC NERVOUS SYSTEM

Cannon and Bacq (11) in 1931 elaborated Elliott's original finding and proved that any smooth muscle when affected by sympathetic impulses gives off a hormone, which when reinjected into the blood stream, will increase the blood pressure and heart rate. This hormone was named "Sympathin" and at first was thought to be identical with adrenalin.

However, Cannon and Rosenblueth (12), investigating this sympathetic substance in 1933, concluded that sympathin was not identical with adrenalin. Further they postulated the formation of two forms of sympathin. Sympathin E, which is formed when the action is excitatory, and Sympathin I, which is formed when the action is inhibitory. In addition they postulated a mediator M; thus the local effect is produced by the combination of M with E or I to form ME or MI.

It appears to be established that by whatever means the nervous impulse is transmitted, acetylcholine is produced at or near the end plate of the cholinergic nerve. The effect is then transmitted to the smooth muscle cell, and the acetylcholine is almost immediately hydrolyzed by cholinesterase. Sympathin is likewise produced at or near the end plate of the adrenergic nerves. Thus the activity of the organ involved by autonomic stimulation is the result of an interaction between acetylcholine, cholinesterase and sympathin. (Chart 1.)

Myerson (32) summarizes the opinion of many investigators when he calls attention to the inadequacy of even this concept of balance to explain all autonomic functions. However, investigators at present agree that visceral activity depends on a chemical balance. Therefore, the present concept of the activity of drugs on smooth muscle will be reviewed. (Chart 2.)

Acetylcholine, mecholyl (acetyl-beta-methylcholine-chloride), adrenalin, and benzedrine sulphate are believed to act directly on the smooth muscle fibre. Dale (17) noted a two phase reaction of acetylcholine following injection of the substance into smooth muscle. Brown and Harvey (7) repeated the arterial injection of acetylcholine into avian muscle. Raventos (35) injected acetylcholine into the tibialis artery of frogs. All these observers agreed that the action of acetylcholine was first at the end plate, and second on the muscle itself. Buchthal and Lindhard (8) noted that the thoracic muscle of the lizard

will contract when acetylcholine is applied directly to the muscle.

Elliott (16) in 1904 noted that after the sympathetic fibres had been cut and had degenerated, the structures previously innervated by them responded in a characteristic manner to adrenine. Nachmansohn (33) believes the action of adrenalin is on the muscle itself, independently of the nervous system, since adrenalin accelerated glycolysis in chopped muscle.

Finally, Cannon and Rosenblueth (13) showed that smooth muscle cells, completely deprived of their autonomic innervation, will react in the usual manner to adrenalin.

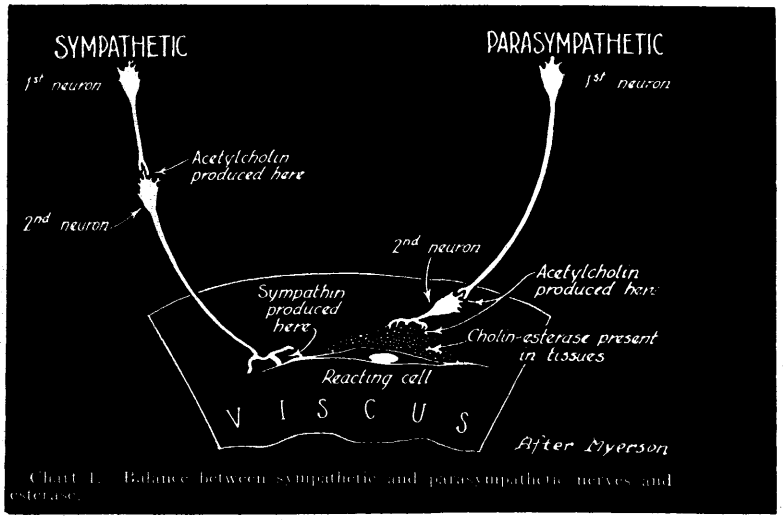

Chart 1. Balance between sympathetic and parasympathetic nerves and esterase.

Bozler (4) draws attention to the protoplasmic connections existing between certain smooth muscle cells and states that after stimulation, an isolated strip of visceral smooth muscle acts as a single cell, following the "all or none" law. He believes that adrenalin decreases the excitability of the muscle; thus there is a resultant action of the muscle which appears to be due to the drug.

From these somewhat conflicting views, Myerson (32) has summarized the present concept of the action of drugs on smooth muscle. (Chart 2.) Atropine sulphate, physostigmine, and the commercial preparation of similar properties, Prostigmin, are believed to act in the region of the parasympathetic

end plates. Atropine in some unknown fashion blocks the action of acetylcholine. This it does, probably not by paralyzing the vagus, but by inhibiting the effect of acetylcholine on the cell of the effector organ either by a direct chemical block of acetylcholine or by enhancing the action of cholinesterase in such a fashion that acetylcholine is hydrolyzed more rapidly. In any case, by neutralizing or removing the cholinergic factor, atropine acts as a synergist to the adrenergic factor.

Prostigmin enhances the action of acetylcholine at the parasympathetic end plate. This is accomplished either by

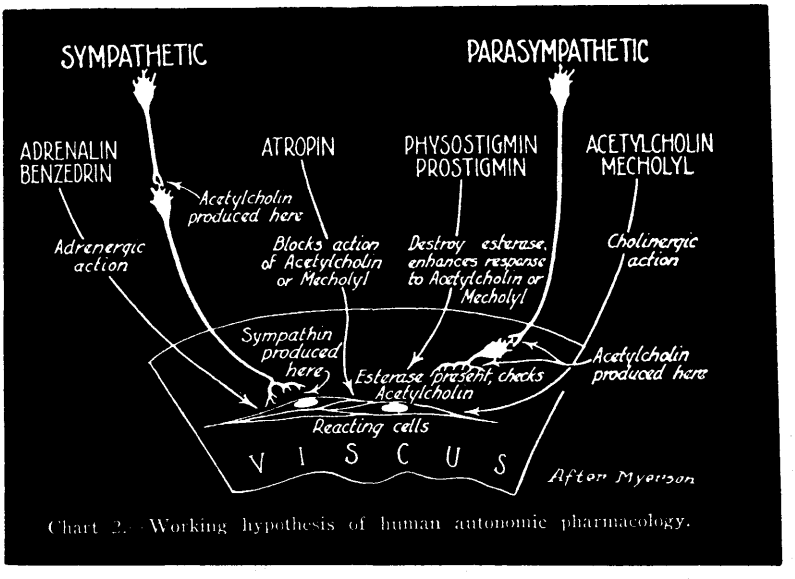

Chart 2. Working hypothesis of human autonomic pharmacology.

Prostigmin entering into direct chemical union with acetylcholine so as to stabilize it, or by destroying esterase, thus delaying the hydrolyzation of acetylcholine.

This explanation of drug action, although it is accepted at present by many physiologists, does not adequately explain some of the clinical effects we have observed during investigation of the motor activity of the human stomach. In our investigations (37), Prostigmin administered alone inhibits the motility of the human stomach, but when administered in conjunction with atropine a motor effect is observed.

Recent work (5) indicates that drugs may have a more intricate action than is generally believed. The drugs whose

action is dependent upon the production of acetylcholine are believed to act simultaneously wherever acetylcholine is produced. Thus Prostigmin stabilizes the production of acetylcholine at the cholinergic end plate. However, it also stabilizes the production of acetylcholine at the sympathetic ganglion, when acetylcholine is produced to transmit the nerve impulse from the preganglionic to the postganglionic sympathetic fibre. Stabilization of the production of acetylcholine at the sympathetic ganglion would result in stimulation of the postganglionic sympathetic fibre, which would result in the production of a larger amount of sympathin at the adrenergic end plate. If this latter effect should overbalance the effect of stabilization of acetylcholine at the cholinergic end plate, the clinical effect on the stomach would be inhibition of motility following administration of Prostigmin.

In a similar fashion, atropine blocks the action of acetylcholine at the cholinergic end plate, but it also blocks the production of acetylcholine at the sympathetic ganglion. This would presumably prevent the transmission of the sympathetic impulse, so that a motor reaction could follow the administration of atropine. This is believed to explain the Prostigmin-atropine effect. Following administration of either Prostigmin or atropine, the motility of the human stomach is inhibited by enhancement of the adrenergic factor, but when both drugs are administered the chemical balance swings to the cholinergic side, so that clinically a motor effect is observed.

Recent investigations of the action of ephedrine cast some doubt on the similarity of its action with adrenalin and benzedrine. It may later be proved that ephedrine stabilizes the production of sympathin at the adrenergic end plate in the same manner that physostigmine stabilizes the production of acetylcholine at the cholinergic end plate (5). Further investigation on this subject is contemplated.

The action of morphine is not yet clear. Since this drug has several simultaneous sites of action, it is difficult to determine its autonomic pharmacology. An abundance of literature is to be found on the action of morphine, nevertheless, further investigation appears to be necessary. Clinically, Veach (36) has shown morphine to be predominantly motor to the human stomach. Weiss (38) reports that a number of investigators, Plant and Miller, Gruber and Robinson, Orr, Carlson and

others, have shown that morphine in ordinary doses increases the tone, amplitude and frequency of stomach contractions. Large doses stop peristalsis and decrease the tone, but increase the segmentary movements. In our investigations administration of morphine was followed by hypermotility of the stomach which increased the distress of postoperative "gas pains," late postoperative nausea, biliary colic, and pylorospasm due to obstructive duodenal ulcer. It seems probable that in respect to the stomach, morphine acts either as a synergist to acetylcholine, or inhibits the action of the esterases.

It is obvious that these theories do not explain all the details of autonomic pharmacology. Further investigation is necessary on the mechanism of the action of drugs on smooth muscle. It may be that after sympathin and cholinesterase are isolated, further light will be shed on this perplexing problem.

SUMMARY

According to the humoral theory, the activity of any organ involved by autonomic stimulation is the result of an interaction between acetylcholine, sympathin and the esterases. This concept of balance does not explain all autonomic functions. However, according to the present concept of the activity of drugs, acetylcholine acts on the smooth muscle cell, and is hydrolyzed by cholinesterase. Prostigmin enhances the action of acetylcholine, either by entering into direct chemical union with acetylcholine so as to stabilize it, or by destroying esterase, thus delaying hydrolyzation of acetylcholine. Atropine, in some fashion, blocks the action of acetylcholine. This it does, probably not by paralyzing the vagus, but by inhibiting the effect of acetylcholine on the cell of the effector organ. Loewi and Navratil (27) showed that although atropine inhibits the effects of vagal stimulation to the frog heart, it does not prevent the production of acetylcholine at the nerve endings. In any case, by neutralizing or removing the cholinergic factor, atropine acts as a synergist to the adrenergic factor. Benzedrine appears to act as adrenalin, directly on the smooth muscle cell.

Most drugs that affect the autonomic system simulate the effect of stimulation of the cholinergic or adrenergic nerves, although the mechanism of action in many cases is quite different. It is generally believed that the primary seat of action of certain drugs, such as adrenalin and acetylcholine, may be in the region of the end plate, directly on the smooth

muscle cell. In such a case, the action of the drug is independent of the nerve supply. Other drugs, such as atropine and physostigmine, are concerned with the nervous innervation of the muscle, and the customary action would appear to be dependent upon an intact nerve supply.

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