DRUG ACTION ON DIGESTIVE SYSTEM[1]

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This review has been limited, for reasons of space, to substances which act on the three cardinal functions of the digestive tract, secretion, absorption, and motility, taking into account the esophagus, stomach, and intestine.

Gastric Secretion and Its Role in the Etiology of Gastric and Duodenal Ulcer

Stimulation.—This problem has been discussed extensively and reviewed up to 1962 (1). More recently, some authors support the idea that experimental gastric and duodenal ulcers have different etiologies. According to Anderson & Soman (2), duodenal ulcers produced by the injection of histamine into guinea pigs, are the result of contact of the duodenum with the acid gastric juice so their incidence may change with the rate of emptying of the stomach (2, 3). On the other hand, production of gastric ulcers would require the devitalization of the gastric mucosa by a high dose of histamine prior to the action of the gastric juice. Even before 1962 some authors (4–7), insisted on different origins of experimental ulcers of the stomach and duodenum. Others (8) elaborated a method which permitted the induction of histamine ulcers only on the duodenum.

Gastrin was isolated in 1964 (9). This hormone, a polypeptide of 17 amino acids, was synthetized by Anderson et al. (10). Two fragments also were effective stimulants of gastric secretion a C-terminal tetrapeptide Try. Met. Asp. Phe.-NH_2 (11), and particularly a pentapeptide, N-*t*-butyl-oxycarbonyl-β-Ala. Try. Met. Asp. Phe.-NH_2 (12). According to Sewing (13), after an injection of histamine, the tetrapeptide stimulates the secretion of pepsin in the cat, whereas histamine mainly stimulates the production of HCl. Since histamine stimulates the secretion of HCl
man (14, 15), the pentapeptide has been used to replace that amine as a diagnostic aid for the investigation of gastric secretion (16). It has been suggested that gastrin action would be mediated through the release of histamine in the gastric mucosa (17, 18). Histamine, as an ulcerogenic agent (19) is still used as an experimental tool. Anderson & Soman (20) have produced gastric ulcers in guinea pigs, by means of rather small parenteral doses of histamine prior to high duodenal ligature, similar to experiments performed by Shay et al. in the rat (21). In this manner, they avoid massive dosage of

[1] The survey of the literature pertaining to this review was concluded in March 1967.

histamine and protection of the animal by means of antihistamines (22), which may modify the picture of ulceration. It is interesting that very high doses of histamine, although provoking ulcers, can inhibit secretion of gastric juice (29). Such reduction of gastric secretion may be due to an angiotoxic effect of histamine. According to Kowalewski (23), the vascular response of the splanchnic area and the following congestion with anoxia of the viscera would be one of the causes of histamine-induced gastric ulceration.

Histamine releasers, such as polymyxin B and compound 48/80, also provoke massive ulcerations and hemorrhages in the rat's stomach. These are attributed more to an effect of histamine on the gastric vascular bed than to an increase of gastric acid (24–27). In fact, histamine releasers diminish the volume of gastric juice and the quantity of free acid (24). Neither antacids nor anticholinergics, in doses which virtually eliminate the free acid of the stomach, are capable of protecting the animals.

Induction of gastric ulcers in rats by high doses of 5-hydroxytryptamine (5-HT) (28, 29) is probably a histamine releasing effect, rather than a direct action on the gastric mucosa (30). On the other hand in dogs, 5-HT inhibits the gastric hypersecretion induced by exogenous histamine, simultaneously increasing mucus secretion (31).

Electrolyte changes in plasma and tissue might be an important factor in the etiology of posthistaminic gastric ulceration (23). In fact, loss of potassium from gastric tissue (presumably due to smooth muscle stimulation), followed by hyperkalemia, as well as an increase of Cl^- (due to stimulation of the secretory mucosa), was observed in guinea pigs after histamine administration. Also, changes in the concentration of extracellular electrolytes modify the secretion of HCl from the frog's isolated stomach (32). Decrease of Na^+ or K^+ in the bath reduces the secretion of HCl and the addition of cardiac glycosides strongly inhibits acid secretion (32, 33). This effect which can be counteracted by increasing K^+ concentration in the bath is probably a result of blocking ATPase, which is activated by Na^+ and K^+ (32).

The blockade of the enzymes involved in the catabolism of histamine may increase gastric secretion induced by this amine (34, 35). Some of the blocking agents which have been used are: aminoguanidine for diaminoxydase (DAO); iproniazid for monoamineoxidase (MAO); chlorpromazine and bromolysergic acid diethylamide for imidazol-N-methyl-transferase (36).

Reserpine is another drug capable of producing hypersecretion, gastric ulceration or both (37–40). Inasmuch as the response to reserpine is abolished by prior administration of the same drug (40), which depletes the stores of 5-HT and catecholamines, it is possible that these amines might be involved in this phenomenon. Based on studies with DOPA and inhibitors of MAO and catechol orthomethyl transferase (COMT), other authors (41) concluded that the cause of reserpine ulcers is not a reduced level of 5-HT but a reduction of catecholamines. Here, we may recall that epinephrine, norepinephrine and isoproterenol inhibit or depress gastric secretion (42)

which may be related to the β-receptors and independent of an action on the vascular bed of the gastric mucosa (43). Epinephrine is effective in the prevention of gastric ulcer induced by polymyxin B (27). However, various authors (44–48) reported inhibition of gastric secretion, ulcerogenesis or both after adrenalectomy, referring this effect to the lack of adreno-cortical or medullar function (water and electrolyte metabolism, reduction of catecholamines). For some workers (48, 49), the increase of gastric secretion and ulcerations caused by reserpine is explainable by an increase of parasympathetic tonus. Others (50) report that reserpine releases gastrin from the cat's antrum. Recalling that gastrin, in its turn, releases histamine (18), we find another possible explanation for the hypersecretion and ulcerogenesis attributable to reserpine.

The induction of gastric ulcerations by corticosteroids has been studied experimentally (51). Whereas clinical ulcers induced by steroids are more of the gastric than the duodenal type (51), the ulcerogenic effect of cortisone in the rat is limited to the pyloric portion of the stomach; at the proximal portion, the drug produces an antiulcerogenic effect (5–7). An increase of volume and acidity of the gastric juice or a reduction of the mucus secretion, claimed as causes of the ulcerogenic activity of the corticosteroids (51), could not be demonstrated (7). According to Hadnagy et al. (7), protein catabolism and inhibition of mitosis induced by corticosteroids may be involved in the production of pyloric ulcerations in the rat. Contrary to this, however, proximal gastric ulcer may be due to inflammatory phenomena which could be counteracted by cortisone.

Both clinical (52–58) and experimental papers (59–63) have agreed on the induction of gastric ulcerations by analgesics, especially aspirin. In laboratory animals, an oral dose of aspirin provokes erosions and hemorrhages of the gastric mucosa. Anderson (62) attributes these lesions to an irritative gastritis with superficial epithelial desquamation, which by deepening would lead to hemorrhages from disrupted subepithelial capillaries. Gastric acidity does not appear to be involved in the genesis of the lesion since aspirin inhibits the basal secretion of gastric acid in guinea pigs (59, 60). Furthermore, the addition of normal doses of antacids does not reduce the incidence of gastric lesions (61). In addition, stress produced by fasting and restraint increases the sensitivity of the gastric mucosa to aspirin (6). However, the interruption of nerve impulses in the vago-vagal reflex arc (64, 65) by anticholinergics, ganglionic blockers, interneuronal blockers (meprobamate), or by vagotomy, reduces gastric lesions caused by aspirin (62), suggesting that some proteolytic and motor activity is necessary to produce erosion.

Inhibition.—There is still some controversy over the inhibition of gastric secretion in ulcer patients by usual doses of anticholinergic drugs (66, 67). However, it has been reported that larger doses (68), inhibit the basal secretion as well as that induced by a standard meal (69, 70), histamine, or insulin (71, 72). Even after stimulation by high doses of histamine [Kay method (73)], a reduction of the acid secretion with antimuscarinic drugs

has been obtained (74). In the cat, atropine does not affect gastric secretion stimulated by histamine (13). In the dog, secretion is partially inhibited and basal secretion depressed by strong doses of atropine (66). In the Shay rat, the anticholinergics inhibit the volume and acidity of gastric secretion, as well as the production of ulcers (75–78, 48). In the case of polymyxin B, which reduces the volume and acidity of the secretion, atropine suppressed this effect entirely, without preventing the ulceration caused by the antibiotic (27). Anderson & Soman reported that in guinea pigs, atropine reduces ulceration provoked by histamine in the duodenum, but not in the stomach (2). Finally, certain anticholinergics, such as methscopolamine, reduce the secretion of acid and mucus in the stomach of fasting or restrained rats, but permit the deposition of a layer of dense mucus, rich in hexosamine, over the mucosa, protecting it against the development of ulcers (79, 80).

Antihistamines are poor inhibitors of gastric hypersecretion and ulcerogenesis induced by histamine (81). However, recent investigations showed that gastric ulcers provoked by moderate doses of histamine, may be counteracted by adequate doses of mepyramine. This drug, however, is unable to protect animals against histamine ulcers in the duodenum. For this reason, different pathogenic mechanisms have been invoked for the two types of lesions (82, 83). Antihistamines have also been found effective in the prevention of hemorrhagic ulcers provoked by polymyxin B (27).

Experimental ulcers have been induced by means of physical or psychic stress, such as restraint,[2]
ble emotional genesis of peptic and especially duodenal ulcers (88–90). Drugs have also been utilized in the search for a possible central mechanism of ulcerogenesis. Chlorpromazine, before potentiating the secretory response to histamine by blocking the imidazol-N-methyl-transferase (36), produces a temporary inhibition of acid secretion in rats (91). This effect, which is analogous to the inhibition of gastric secretion observed in healthy persons (92), as well as ulcerous patients (93) and dogs (94), is considered a phenomenon of central origin, mediate by the vagus (94). Likewise, the experimental antiulcer activity of chlordiazepoxide (95), chlorbenzoxamine (96), some *l*-alkylbenzimidazoles (97), and reserpine (98) has been explained by an inhibitory action on a supposed central mechanism, connected with ulcer formation. These drugs act, perhaps, in the hypothalamic region (97), reducing the vulnerability of the organism to stress (95). The existence of a hypothalamic control center for gastric secretion has been claimed (99), and the antiulcer activity of chlorbenzoxamine is eliminated by hypophysectomy (96). With regard to reserpine, its antiulcer activity, of central origin, appears at the beginning of the third day of treatment, whereas ulcerogenic action (peripheral) develops mainly during the first two days (98). In the last few years, some anti-

[2] It is interesting that ulcers caused by restraint are principally located at the glandular portion of the stomach (46).

ulcer drugs without anticholinergic properties have been developed, such as 3-methylamine-2,1-benzisothiazole (100) and 2,2′-bipyridine (101). They presumably act on a histaminergic, adrenergic, or serotonergic system of the gastric mucosa. Other compounds, like geranyl pharnesylacetate, have not as yet been studied with respect to their mechanism (102, 103).

Only a few studies of pharmacological significance have been made recently on antacids and demulcents. However, the finding that mucoitin and chondroitin sulfuric acids of the gastric mucus reduce peptic activity without diminishing free acidity (104) suggests that in ulcerogenesis, free acidity itself is a less important factor than the presence of proteases or the continuity of gastric juice production (105, 106). This has led to studies on the protective action of sulfated polysaccharides, especially carrageenan and heparin Carrageenan is bound with the mucine layer and the cell protein of the ulcer crater, and does not permit penetration of pepsin into the injured area (107). It has also been suggested that by a mechanism not yet totally understood, carrageenan counteracts the histamine-induced hyperplasia of the parietal cells (108). In guinea pigs, carrageenan reduces the volume and acidity of the gastric juice formed by histamine stimulation by 50 per cent (109). Heparin, like carrageenan, clearly inhibits the response of gastric secretion to histamine. However, the stomach still responds well to an analogue of histamine, ametazole, indicating that like carrageenan, heparin does not block the acid secretion mechanism (109*a*).

Finally, we would like to mention the experiences of Sanyal et al. (110–113) with the antiulcer properties of the green banana, which are attributed mainly to the presence of 5-HT (114–116) and the antisecretory action of this amine.

Absorption

There are several reviews on the action of drugs on gastric and intestinal absorption and the active transport of water, electrolytes, and nutrients which emphasize the determining factors of the phenomena of absorption, such as diffusion, lipid solubility, lipid-to-water partition ratios, dissociation and association constants, gradients of pH, active transport, etc (117–121). Recently, several papers were published on the inhibition of absorption by some laxatives. Diacetoxy-diphenyl-pyridyl-methane and dihydroxydiphenylisatin reduce, *in vitro* and *in vivo*, the active transport of sodium and water in the small intestine of the rat by inhibition of the "sodium pump" (122). Inhibition is even more intense in the colon contributing essentially to the laxative properties of these compounds (123–125). A certain independence exists between the absorption of sodium and water, with evidence of a greater retention of sodium, possibly related to water elimination into the lumen of the colon. In addition, some K^+ is excreted (126, 127).

The free bile acids, especially desoxycholic acid, also inhibit active transport in the intestine, and they are considered to play a physiological role in

the maintenance of the softness of stools (122, 125, 128). Several laxatives, and free bile acids, limit the absorption of glucose by blocking its transport mechanism (122, 128, 129). The fact that some of these substances also block the absorption of amino acids by the isolated ileum (130) suggests a general activity of such drugs on the active transport of water, electrolytes, and nutrients.

The blockade of active absorption of nutritive substances by certain drugs may suggest the characteristics of the carriers involved in such processes. The inhibitory effect of phlorizin on the absorption of glucose and butyrate (117, 131), that of thevitin on the absorption of glucose (132), and that of cetrimide (hexadecyltrimethylammonium) on the absorption of glucose, butyrate, and methionine (133) are well known. It has been shown that these drugs, as well as laurylsulfate and chloroquine, in small doses, stimulate the absorption of glucose, and in high doses, prevent it (120). If five drugs, so different in chemical composition, produce the same effect on active absorption, the combination drug-receptor in the corresponding carrier is probably not too specific. In view of this and the fact already mentioned that one drug can block the absorption of various types of nutrients, it has been suggested (120) that instead of one specific protein carrier for each nutrient, a spectrum of intracellular proteins with different affinities may exist. However, cetrimide, more specifically, in doses which still permit the absorption of butyrate, produces a striking reversal of the flow of glucose, which leaks back into the intestinal lumen. This may indicate that the drug blocks an "antileakage mechanism" for glucose, and combines with a receptor site of the carrier in charge of the active transport of this sugar in the interior of the cell. This receptor site should be different from the common receptor for glucose and butyrate which is sensitive to phlorizin. Accordingly, Nissim (120) proposed a mechanism of active transport of glucose for the mucosal cell of the intestine based on a carrier system of two receptors: the first one, fixed in the inner side of the membrane, sensitive to phlorizin and receiving the molecule at its entrance into the cell; the second, mobile and sensitive to cetrimide. The latter would move between the mucosal and serosal poles of the cell, carrying the molecule to be transported and releasing it on the serosal pole. To achieve this, the carrier must be equipped with a greater association constant on the mucosal pole of the cell and a greater dissociation constant on the serosal pole. The major or minor affinity, existing between the intracellular proteins and the substances actively transported, should depend on different metabolic activities developed on the two opposite ends of the cell. Such metabolic activities would maintain an intracellular gradient in pH, redox, and electric potential, or a combination of the three, requiring an expenditure of energy. This theory does not exclude the existence of carriers of greater specificity, necessary for the absorption of certain substances, such as cystine (134) and tyrosine (135).

Some drugs, such as 5-HT, norepinephrine, or vasopressin, reduce the absorption of water labeled with tritium (136–139) by vasoconstriction. Such

delay in the absorption of water is observed in the small intestine (136), and colon (137) of the rat. This could be a cause of aqueous diarrheas occurring in carcinoid patients. It has also been reported that vasoconstriction caused by 5-HT and norepinephrine provokes some decrease of excretion of labeled water into the intestinal lumen (139).

Motility

The literature up to the beginning of 1965 has been reviewed by Burnstock & Holman (140); therefore, this section refers mostly to papers written since that time.

Action of agonist and antagonist on receptors.—Several years ago, it was established (141–145) that potent muscarinic drugs are highly complementary to their receptors and that slight changes in structure provoke loss of affinity. It is also well-known that great differences in potency exist among several optical isomers of atropine-like drugs (146, 147). In 1965, it was observed (147a) that among enantiomorphic esters of β-methylcholine, the potent parasympathomimetics have identical configuration to muscarine. This suggests a close affinity with the receptor. By increasing the size of the acid moiety, a gradual change from agonistic to antagonistic activity is produced. The configuration of the choline component is of secondary importance for atropine-like potency. The authors concluded that atropine-like compounds, although competing with parasympathomimetics for the same receptor, interact only partially with the receptor area (147a).

Differences between muscarinic and nicotinic receptors were studied quantitatively by Leach (148), who corroborated the findings of Paton (149, 150) on the nicotinic character of the emptying phase of the peristaltic reflex (151). The preparatory phase, which consists of contraction of the longitudinal muscle, has been interpreted either as a direct muscular response (152, 153) or as a result of a postganglionic cholinergic mechanism (150, 153), or possibly as a ganglionic phenomenon of serotonergic character (154). Recent studies (155) suggest that the longitudinal muscle contraction is subdivided into: (*a*) a rhythmic sequence of contraction and relaxation controlled by cholinergic ganglia sensitive to hexametonium (C_6); (*b*) a component resistant to this drug. The action of nicotine is variable; in general, it produces contraction (156). In the rabbit's duodenum, a three-phase effect has been described: a first contraction phase, probably of cholinergic character; a second relaxation phase of adrenergic type; and a third phase, characterized by cholinergic and adrenergic blockade (157, 158). Small doses of nicotine, or the prior administration of atropine, produce a relaxation in the rabbit's colon. This would be due to the presence of sympathetic structures and the release of catecholamines (159). Following the use of nicotine, relaxation was also observed in the small intestine of rabbits, treated with botulinus toxin (160) and atropine (161); in the ileo-colic sphincter of the rabbit (162); in the small intestine of the rat (161); and in the human colon (163, 164). In the circular muscle of the human colon and ileum, the relax-

ation provoked by nicotine is antagonized by β-adrenergic blockers (165), considered to be a result of a release of catecholamines by action on ganglionic cells located in the myenteric plexus. It has been suggested that the ganglionic cells of the human colon and ileum are of the sympathetic type, and that the nature of the myenteric plexus varies in the different segments of digestive tract (165). Dimethylphenyl-piperazine (DMPP) abolishes the inhibition of the small intestine of rabbits and guinea pigs induced by stimulation of the periarterial sympathetic nerve (166, 167), even though the catecholamines maintain their relaxing activity. C_6 does not prevent the action of DMPP. This may be due to an adrenergic blockade at postganglionic level, similar to bretylium or guanethidine (168). The action of DMPP as well as that of bretylium and guanethidine is rapidly reversed by DOPAmine and dexamphetamine (168).

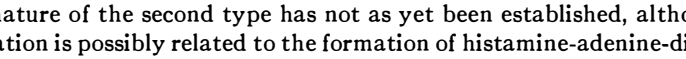
Adrenergic drugs induce intestinal relaxation by stimulation of α- and β-receptors (169–171). Recently, several authors have tried to separate these two types of receptors. Through the use of cold storage, Lum et al. (172) succeeded in damaging selectively α-receptors of the rabbit's jejunum, reducing or abolishing the activity of the α-adrenergic drugs. Van Rossum (173) distinguishes between norepinephrine and DOPAmine receptors. Those of the rabbit's intestine were found to be specific for norepinephrine (173). Some imidazolines can be norepinephrine agonists and DOPAmine antagonists simultaneously (174). In the isolated jejunum of the rabbit (175), the α-sympathomimetics (α-SM) (having direct action on the membrane) induce peristaltic inhibition of a fast onset and a steep dose-response curve; the β-SM (of intracellular action) produce inhibition of slow onset and a flatter dose-response curve. Sympathomimetics of indirect action do not relax the preparation but rather antagonize the α-SM. The indirect sympathomimetics such as tyramine, apparently do not release catecholamines in the rabbit's intestine. It appears that in the esophagus muscles, α-adrenergic receptors provoke stimulation and β-receptors, inhibition (176).

Evidence has been obtained for some interaction of adrenergic receptors with other receptors, drugs, or both. Some sympathomimetics (177, 178), exhibit a certain "specificity," in the ileum of the guinea pig antagonizing more intensively the contractions induced by histamine than those induced by acetylcholine or methacholine. On the other hand, the stimulation of the periarterial nerve of the guinea pig's caecum, which normally relaxes the muscle, provokes contractions if the preparation has previously been treated with antiadrenergics and physostigmine (179). Such contractions are blocked by hyoscine, which confirms its cholinergic character. Based on similar experiments with guanethidine, Day & Rand (180) suggest the existence of a cholinergic link in the sympathetic mechanism, as claimed by Burn & Rand (181).

Discussion continues on the direct, indirect, and dual action of 5-hydroxytryptamine [receptors "D" and "M" (182)]. A direct action was found in fundal strips of the stomach of the guinea pig, the cat, and the rat (183, 184),

and more recently in the human stomach, jejunum, ileum, and sigmoid (185–189). The indirect activity of 5-HT (185*a*–187*a*) was shown again (188*a*), confirming that the amine acts on nerve receptors which are different from those of nicotine and DMPP (189*a*). The contraction should be produced by the action of 5-HT on the M receptors and the consecutive release of acetylcholine in the myoneural junction (188*a*, 190). Evidence of release of acetylcholine was recently confirmed (191). According to others, the main site of action of 5-HT is the ganglionic cell, and secondarily the smooth muscle of the gut of the rat and the guinea pig (154, 192–194). Woolley & Gommi (195) apparently have achieved the selective extraction of the serotonin receptors from the isolated stomach and uterus of rats, thus destroying the sensitivity of these organs to 5-HT. Subsequently, they reestablished the sensitivity by addition of gangliosides (196). The self-inhibiting effect of 5-HT was studied in isolated organs, and this property was attributed to an interaction of the amine with α-SM receptors (197). The close chemical relationship between 5-HT and catecholamines increases the likelihood of this hypothesis.

In the isolated ileum of guinea pigs, a competition between H^+ and histamine has been claimed (198–200), suggesting that the changes of activity which occur with the changes of pH are due to the degree of dissociation of the anionic site of the histamine receptor. The existence of at least two types of histamine receptors (201, 202) has recently been confirmed (203): one (H_1), located in the ileum and bronchi of the guinea pig, is easily blocked by low concentrations of antihistamines; the second is located in other tissues, such as the rat's stomach and uterus, and no specific antagonist has yet been found. Histamine-like compounds would present an affinity to the receptor H_1, if they obey the following chemical structure:



The nature of the second type has not as yet been established, although its activation is possibly related to the formation of histamine-adenine-dinucleotide (HAD) from nicotinamide-adenine-dinucleoside (NAD) (203).

Among the polypeptides, the "kinins" produce contraction *in vitro* and *in vivo* in the digestive tract of the guinea pig, rabbit, cat and rat. However, in the small intestine of the rabbit, bradykinin and kallidin frequently provoke a relaxing phase before the contraction (204–210). Both peptides produce relaxation only in the duodenum of the rat and in the caecum of the chicken (206, 207, 211, 212). In the ileum of the dog *in situ*, bradykinin inhibits contractions (213). The inhibiting phase *in situ* has been explained as a reflex mechanism (209, 214). Other authors (207) consider the relaxation a result of the release of catecholamines, because it does not exist in reserpine treated animals. In isolated preparations, a special neurotropic mechanism has been claimed, in a site as yet unknown, which is blocked by morphine, methadone, and pethidine (215). Bradykinin has been classified among the non-nicotinic ganglionic stimulants (216). On the other hand, the problem of the antago-

nists of the kinins is still under discussion (217, 218). The contraction phase, produced by the polypeptides described above, appears to be due to a direct action on the smooth muscle (219), even though some authors suggest the existence of a neurogenic component (220), with release of acetylcholine induced by the peptide. A dual action, direct and indirect, on the gastrointestinal muscle, has been suggested for angiotensin II (216, 219, 221–224).

Movement of ions.—In a K-free bath, the ileum of the guinea pig still contracts and relaxes with high doses of acetylcholine or histamine, provided that the medium contains Ca^{++} (225). This reduces the importance attributed to K^+ in the muscle stimulation, considering (226) that the stimulation caused by ACh may be due mainly to the increase in permeability to Na^+. The abolition of spike activity and the hyperpolarization caused by epinephrine have been related to ionic changes (227). Even though epinephrine increases the permeability of the membrane to K^+, the hyperpolarization reduces the outflow of this ion. Therefore, part of the hyperpolarization would be caused by other actions of epinephrine, such as the fixation of calcium in the membrane, and possibly an active electrogenic expulsion of sodium, in accordance with the hypothesis of Burnstock (228). Arbona (229) has recently suggested a common component in the mechanism of the hyperpolarizative effects of the norepinephrine and depolarization induced by K^+ and cold. It has been suggested also that movement of ions would be involved in the angiotensin action, and that Ca^{++}, as an excitation-contraction link, could affect the cell excitability (230).

The mechanism of some papaverine-like drugs has been studied, in light of the present ideas on the function of Ca^{++} as an intracellular mediator or "coupling factor" between membrane phenomena and the contracting process (231–236). It has been suggested that the basis of their spasmolytic activity may be a dissociation between membrane phenomena and contraction of smooth muscle by an interference at the level of Ca^{++} function (237, 238). In addition, an inhibition of energy-producing processes, particularly that of oxidative phosphorylation (239), should take place.

Action of drugs on release of chemical transmitters.—Takagi et al. (240, 241), studying the release of acetylcholine, claimed two types of stores: one depleted by 5-HT or picric acid and antagonized by morphine and strychnine; the other depleted by phenylacetate but not affected by morphine and strychnine.

With respect to the site of the inhibiting action of morphine on acetylcholine release, some authors (242, 243) place it on the postganglionic cholinergic nerves of the intestine, whereas others (244) locate it on the enteric ganglionic "regulator" and "acceptor" cells involved in the peristaltic reflex. The inhibiting action of morphine on the release of acetylcholine may be antagonized by small doses of nalorphine or levallorphan (245). The ability, attributed to morphine, to inhibit the release of catecholamines may also be recalled (246, 247).

It has been suggested that tyramine and its analogues can release acetyl-

choline, stimulating the small intestine treated with reserpine. This effect is potentiated by eserine and blocked by atropine (248). Similar actions in other organs (249–251) have been interpreted as a direct muscular effect, not mediated through the release of norepinephrine. On the other hand, the stimulating effect of tyramine on the ileum of guinea pigs and rabbits has been attributed to the action on serotonergic receptors (252). Others (253) concluded that tyramine may release norepinephrine in the rat, histamine in the guinea pig, and 5-hydroxytryptamine in the rabbit. In the cardia of the rabbit, it has been shown that spasms provoked by cutting the vagal adrenergic fibers can be counteracted by administration of norepinephrine, but not by tyramine. This indicates that the transmitter stores are not available to the releasing action of tyramine (254). However, the intravenous infusion of norepinephrine makes the subsequent administration of tyramine effective. This effect, according to Muscholl (255), proves that at least a part of the injected norepinephrine can combine to make the transmitter stores within the cardia tissues more available to tyramine.

It has been suggested (256) that nicotine and DMPP release catecholamines from the intestinal stores. Similar suggestions have been previously made (157, 159, 161, 162, 257–259). Hemicholinium and triethylcholine, which impair acetylcholine synthesis (260, 261), block the response of the guinea pig's colon to the stimulation of the sympathetic nerve. This supports the hypothesis of a cholinergic link in the release of catecholamines (181). However, it has also been considered that the inhibition of the guinea pig's caecum, caused by nicotine or acetylcholine, might be due to the stimulation of non-adrenergic inhibitory nerves (262, 263).

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