PHYSIOLOGY AND PHARMACOLOGY OF VOMITING[1]

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INTRODUCTION

The vomiting act is one of the most primitive protective functions with which animals are endowed. The extreme variety of circumstances under which vomiting can occur defies description. It may follow simple overeating or signal approaching death. It often represents one of the chief signs of drug toxicity regardless of the route by which the drug is administered. In spite of its universal appearance and great clinical importance, the nervous mechanism of the vomiting act and the emetic action of many drugs are not well understood.

This review is limited almost exclusively to the results of animal experimentation concerned with the *mechanism* of vomiting. Clinical studies on vomiting are included only insofar as they elucidate physiologic processes.

The article on vomiting written by Hatcher (97) in 1924 represents the

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latest authoritative survey of the subject to be found in the accessible literature. During the last generation, Hatcher and his coworkers were the leading investigators in the field of emetics. In large measure, the interpretations of most experiments on emesis, reported up to 1949, rested on the ideas expounded by this group. In 1948, DuToit and Christensen (64) completed a comprehensive review of the literature on emetics (629 references) for "restricted" use by the U. S. Government. While a great fund of information on emetic substances was collected by these authors, the physiological and pharmacological principles expressed by them are basically the same as those presented by Hatcher (97).

There is no universal agreement on the definitions of the various terms used to describe the component parts of the emetic syndrome. The following definitions are presented at the outset to reduce ambiguity and to establish a reasonable measure of uniformity in the subsequent text. *Vomiting* or *emesis* applies only to the forceful expulsion of the gastrointestinal contents through the mouth. *Retching* is defined as the labored rhythmic activity of the respiratory musculature which usually precedes or accompanies vomiting. Vomiting is neither synonymous with retching nor an invariable consequence of it. *Movements suggestive of vomiting* are not equivalent to retching since retching is not ordinarily accompanied by opening of the mouth. The mouth opens immediately preceding the evacuation of the stomach whether vomiting is projectile or labored. If the mouth is opened widely but no expulsion of vomitus occurs, this act, together with the assumption of a typical posture, is considered suggestive of vomiting. *Nausea* is a psychic experience of human beings which may or may not be associated with vomiting. It is impossible to determine whether nausea is experienced by experimental animals. Nevertheless, the consistent appearance of certain emetic prodromata has prompted the assumption by many investigators that nausea is experienced when such prodromal signs are observed. However, most of these signs are still elicitable after decerebration and, therefore, cannot be considered positive evidence of nausea.

VOMITING CENTER AND EMETIC CHEMORECEPTOR TRIGGER ZONE

Thumas (172) abolished the emetic response to parenteral apomorphine in the dog by destroying a portion of the medulla oblongata from which he initiated vomiting with apomorphine applied locally. He concluded that the vomiting center was located in deeper structures of a midline area, 2 mm. wide and 5 mm. long, which extended through the obex. This work was repeated and somewhat refined by Hatcher and Weiss (100, 101). They confirmed Thumas' results with apomorphine, but they were able to elicit emesis with oral mercuric chloride in dogs which were refractory to apomorphine. On the other hand, Hatcher and Weiss (101) prevented vomiting induced with either apomorphine or mercuric chloride by destroying the ala cinerea, which they considered to be the site of the vomiting center. According to these investigators, Thumas erroneously implicated midline structures as a result of adventitious injury to the closely situated ala cinerea.

Two fundamental inadequacies are evident in the work of the aforementioned investigators. Only acute preparations were used and localization was determined primarily on the basis of drug application. Koppanyi (121) demonstrated, in dogs with *chronic* lesions in the ala cinerea, that the emetic sensitivity to parenteral apomorphine was reduced while irritant emetics remained effective by the oral route. Thus, the hypothesis that the vomiting center is embodied in the ala cinerea was placed in serious doubt.

The contention has been made that there are two centers—one for apomorphine, referred to by some workers as automatic, and another for reflex vomiting (see Hatcher (97)). This is not surprising in view of the exquisite emetic specificity of apomorphine. Most physiologists have agreed only to the *existence* of the vomiting center, and not to its precise *location*, in the medulla oblongata.

Probably no single experiment suffices to demonstrate the existence of a center. The claim for a center must be held in abeyance until the structures in question are demonstrated both physiologically and morphologically to have an integrating function. Most arguments advanced in support of an emetic center, on the basis of ablation or even stimulation experiments, can very well apply to receptor elements. An hypothesis for a neural center can be considered valid only if it encompasses all aspects concerned in the regulation of the given function, and when it has stood the test of time and trial.

Borison and Wang (18, 26) elicited vomiting in the cat by electrical stimulation of the lateral reticular formation in the immediate vicinity of the fasciculus solitarius. No other portion of the lower brain stem yielded such responses. Vomiting was elicited without prior retching, following the short latency required for maximal inspiration, and it was continuous for a period of 5 to 15 seconds of stimulation. The vomiting ceased *immediately* upon the cessation of stimulation. In a study in chronic dogs, Wang and Borison (180, 183) found that superficial medullary lesions with minimal damage to the ala cinerea abolished the emetic response to intravenous apomorphine and certain cardiac glycosides without disturbing the response to oral copper sulfate, whereas deeper lesions which also involved the lateral reticular formation impaired the responsiveness to oral copper sulfate as well as to intravenous apomorphine. These results were interpreted to mean that the vomiting center is situated in the dorsal portion of the lateral reticular formation and that there exists in the medullary surface a specialized chemoreceptor trigger zone which serves as a receptor site for certain central emetic agents. However, the critical experiment to settle the question as to whether the superficially situated chemoreceptor trigger zone is merely a *receptor* area or has integrative functions is one in which the lateral reticular formation is destroyed while leaving periventricular structures intact. This was accomplished with the use of radon seeds inserted through the dorsum of the flexed cervical spinal cord (27, 182, 78). The experiments, performed in chronic dogs, demonstrated that lesions in the lateral reticular formation, with no histologically detectable damage to surface structures, elevated the thresholds to a variety of emetic agents includ-

ing intravenous apomorphine and digitalis and oral copper sulfate. It is unfortunate that neither Thumas (172) nor Hatcher and Weiss (101) had reported histological studies of their experimental lesions. Consequently, there is no way of knowing how deep the destruction extended and, particularly in the work of Hatcher and Weiss (101), it is possible that the lateral reticular formation and fasciculus solitarius were damaged. It has been demonstrated by Borison and Brizzee (19, 20, 31) that the chemoreceptor trigger zone, in the cat at least, is situated in the area postrema and that the ala cinerea is damaged slightly or not at all by lesions which abolish the emetic responsiveness to cardiac glycosides. The morphology of the area postrema has been studied by Wislocki and Putnam (189), King (120), Cammermeyer (35, 36) and more recently by Brizzee and Neal (32). A comparative morphological study of the area postrema may help to shed some light on the emetic inactivity of rodents. However, the *universal* refractoriness of these animals to emesis-provoking stimuli suggests that this trait is more probably associated with some property of the brain stem reticular formation and vomiting center proper than of the area postrema.

CENTRAL NERVOUS INTEGRATION OF EMETIC COMPLEX

Although the literature prior to 1924 was covered adequately by Hatcher (97) the reviewers wish to give special attention here to the work of Thumas (172), reported in 1891. A number of noteworthy conclusions were reached at that time. Thumas placed great emphasis on the caudal tip of the calamus scriptorius as the site of the vomiting center. He showed that the function of vomiting was intact after transection of the brain stem at the acoustic striae. Furthermore, he indicated that the emetic center is located in deep structures. He pointed out the futility of making lesions in only one side of the medulla and specifically mentioned that unilateral destruction of the ala cinerea does not abolish drug-induced emesis; this statement directly conflicts with the later report by Hatcher and Weiss (101) that "certain" destruction of the ala cinerea on one side abolishes the vomiting initiated by various emetic stimuli. Thumas discussed certain physiologic similarities and relationships between the activities of the vomiting and the respiratory centers, but he denied that these centers are identical. His conclusion has been borne out by experiments of Borison and Wang (26), who showed that while the respiratory and vomiting centers are located in close mutual proximity in the reticular formation, they remain separate entities. Grimm (91) and Greve (90) claimed that the respiratory and emetic centers are identical on the basis of experiments which showed that vomiting is impossible during the apnea which results from hyperventilation. However, there is ample proof (180, 182) that vomiting can be abolished, without significant impairment of respiration, as a consequence of properly placed lesions in the medulla. It is not surprising from the morphologic continuity of the two centers that they react similarly to such influences as narcosis and apnea.

Several workers (128, 176) have failed to elicit emesis by electrical stimula-

tion of the dorsal vagal nucleus. Miller and Sherrington (148) elicited swallowing but not emesis on stimulation of the inferior fovea. Borison *et al.* (23, 17) elicited retching movements but not vomiting on stimulation of the descending vestibular root. These latter experiments were performed mostly on cats anesthetized with pentobarbital. Vomiting was elicited only once in a large series of medullary stimulation experiments in anesthetized cats (26). Borison and Wang (26) produced vomiting successfully and consistently with electrical stimulation of the lateral reticular formation of the medulla oblongata in *decerebrate* cats. Most of the responsive points were found to be situated in the reticular formation but a few were localized in the fasciculus solitarius. It is therefore necessary to include this structure and its nucleus as a part of the regulatory mechanism of vomiting.

The localization of the vomiting center in the lateral reticular formation assumes special meaning when this region is viewed in its morphological relationship to neuronal loci regulating important visceral and somatic functions. These loci include (a) the spasmodic respiratory center (17), (b) the inspiratory and expiratory centers (158), (c) the vasomotor center (187), (d) the salivatory nuclei (177), (e) the vestibular nuclei, and (f) the bulbofacilitatory and inhibitory systems (140). The locus for vomiting is strategically situated in the core of these regulatory foci. A consideration of the vomiting act shows that all the represented activities are involved in its motor expression.

Brooks and Luckardt (33) have described the cardiovascular changes in dogs occurring concomitantly with vomiting. Crittenden and Ivy (43) examined the cardiac irregularities associated with nausea and vomiting in dogs and man. Their results indicate that nausea, retching and vomiting induced by the subcutaneous injection of apomorphine in normal unanesthetized dogs may cause cardiac rhythm irregularities such as heart block, cardiac arrest, and ventricular and auricular ectopic beats. They are most likely to occur during retching. The intravenous injection of atropine almost completely inhibits the cardiac irregularities. There are also marked changes in cardiac rate, nausea usually associated with a tachycardia and retching with a bradycardia. Crittenden and Ivy (43) claimed that icterus sensitizes the cardiac vagal nerves so that there is an increased incidence of cardiac irregularities occurring with the nausea, vomiting and pain elicited by distention of the biliary passages. However, this apparent synergism was not quantitated.

Although the exact roles and sequence of action in vomiting, of the various elements of the respiratory apparatus, are not completely agreed upon (82, 152, 153, 171), there is no question as to the importance of the respiratory contribution to the vomiting act. Borison and Wang (26) have shown that the emesis elicited by electrical stimulation centrally was projectile in type, and that it was initiated at the peak of a maximal inspiration recorded by both thoracic and abdominal pneumographs. The pneumographic inspiratory response fell slightly but continuously during the ejection of the gastric contents. The vocal accompaniment which occasionally occurred during central stimulation indicated that the thoracic viscera were under positive pressure during the

period of vomiting. No rhythmic hyperactivity of the respiratory musculature was observed prior to, during or following the vomiting episode which terminated on the cessation of stimulation. On the other hand, strong, rhythmic and explosive respiratory activity was elicited by Borison (17) from the descending vestibular root. On this basis, Borison and Wang (26, 179, 182) have made a physiologic distinction between vomiting and retching. These are exemplified clinically by (1) projectile vomiting which is often associated with elevated cerebrospinal fluid pressure and which occurs without preliminary retching, and (2) the fatiguing and unproductive retching referred to as "dry heaves". There is no doubt that the particular form of vomiting is largely related to the amount and the nature of the gastric contents. Furthermore, the influence of the stomach contents must be considered not only from the mechanical viewpoint but also, and perhaps more important, from the viewpoint of the effect on the medulla oblongata of sensory impulses originating in the gastrointestinal wall. It is not improbable that the character of such impulses may determine the relative participation of the spasmodic respiratory center and the vomiting center in the vomiting act.

The characterization by Magoun and his coworkers (140) of a facilitatory and inhibitory system in the brain stem reticular formation casts a new light on the regulation of postural tone. Our only task here is to point out the postural attitude in vomiting and the favorable architecture of the reticular formation for the interaction of the vomiting center with neuronal complexes regulating postural tone. In this regard, it is interesting that apomorphine has been shown by Vernier and Unna (174, 175) to reduce tremor and postural tone through an action on the brain stem reticular formation. This action is independent of its emetic action since apomorphine produces muscular relaxation in dogs which manifest emetic refractoriness as a result of lesions placed in the chemoreceptor trigger zone (178). Hatcher (97) has described muscular relaxation after direct application of apomorphine to the obex, but he apparently attributed the effect to a peripheral muscular action. In contrast, Dordoni (53) has shown in the decerebrate dog that local application of apomorphine to the medullary emetic chemoreceptor trigger zone evokes vomiting without a reduction in decerebrate rigidity, whereas parenteral apomorphine causes depression of the muscular rigidity in addition to vomiting. The fact that apomorphine induced changes in respiration without causing vomiting in dogs with medullary lesions was one of the chief arguments offered by Thumas (172) that the vomiting center is not identical with the respiratory center. Just how apomorphine affects respiration without causing emesis is not known. The central action of apomorphine on postural tone suggests that this drug may influence the respiration by acting directly on a limited region of the brain stem reticular formation.

Hess (108–110, 112, 113) stimulated electrically the diencephalon and other forebrain structures in the unanesthetized cat and observed licking, swallowing, retching and occasionally vomiting. The vomiting act consisted of rhythmic retching movements accompanied by the expulsion of vomitus, and it

generally occurred after some seconds of stimulation or even as long as 2 minutes after a short period of stimulation. This is to be contrasted with the experiments of Borison and Wang (18, 26) in which stimulation of the medulla resulted in immediate projectile vomiting which terminated abruptly on cessation of stimulation. These authors agree with Hess that the medullary emetic center is essential to the vomiting induced by diencephalic stimulation. The critical fact remains that vomiting, with all of its associated activities, occurs without diminution in the decerebrate animal. Therefore, the conclusion is inescapable that the basic integrating mechanism for emesis resides in the medulla oblongata. Nevertheless, the experiments of Hess (110) demonstrate admirably that there are supramedullary neuronal loci which not only initiate vomiting by sending effective barrages of impulses downstream but probably affect the reflex excitability of the medullary emetic center with impulses of subliminal effect. Several workers (14, 107, 118, 143, 165, 185) described various changes in gastrointestinal motility resulting from hypothalamic stimulation, but they have not reported vomiting responses. Kabat (118) observed rhythmic spitting as a result of stimulation of the rostral part of the lateral hypothalamic area in the cat. The cerebral cortex and more particularly the orbital cortex and nearby rhinencephalic structures have received considerable attention (160, 141, 9, 111, 6, 7, 8, 2, 71, 154, 155, 117) as supraregulatory foci which control certain activities related to smelling and eating. Among the responses elicited by electrical stimulation of these regions are sniffing, sneezing, coughing, retching, biting, chewing, licking, lapping, swallowing, salivation, defecation, micturition, and changes in gastrointestinal motility. The representation of these activities in the basal and medial portions of the cerebral cortex has been thoroughly reviewed by Kaada (117). Furthermore, it has been proposed (137) that the rhinencephalon plays an important role in emotional expression. Although retching has been described as an occasional response to electrical stimulation of the cerebral cortex, no report of the *direct* elicitation of frank vomiting by this technic has been encountered by the reviewers. With regard to vomiting produced by psychic stimulation, it is not clear at the present time whether this is mediated directly through corticobulbar connections or whether it is the result of impulses relayed through subcortical structures.

On the basis of experiments in which emetic responses were elicited with pilocarpine and posterior pituitary injected into the lateral ventricles of man, Cushing (44–47) postulated a direct action of these drugs on subependymal hypothalamic nuclei (see page 218). However, in light of the recent demonstration that the chemoreceptor trigger zone constitutes the specific site of action of apomorphine in the medulla, it seems more reasonable to postulate that pilocarpine and posterior pituitary may induce vomiting through stimulation of analogous cerebral ependymal receptors which act in conjunction with certain subcortical neuronal loci. In any event, available data are insufficient to permit the construction of a convincing theory for the action of drugs at the diencephalic level.

Vomiting has been observed in cats as a behavioral disturbance resulting

from exposure to certain conditioning stimuli (65). This is perhaps one way to approach experimentally the factors concerned in the functional vomiting which occurs in certain psychoneurotic humans.

Riddle and Burns (159) have described a conditioned emetic reflex in the pigeon which they obtained after 3 to 8 oral administrations of yohimbine hydrochloride. From the experimental standpoint, this observation is important in the repeated use of the same birds for the assay of digitalis by the pigeon-emesis method. Talmud (170) failed to produce in dogs a conditioned emetic reflex to alcohol sprayed into the mouth after the oral administration of $CuSO_4$. However, conditioned vomiting occasionally occurred following the procedure of washing the stomach prior to the administration of $CuSO_4$. Talmud discussed some poorly rewarded attempts by other workers to obtain conditioned responses with apomorphine as the unconditioned stimulus. On the other hand, Gold *et al.* (85) reported the development of conditioned vomiting in a number of dogs after a few days of successive administration of digitalis glycosides. In a large series of animals, Dresbach (60) noted conditioned emesis in only one cat following the injection of strophanthidin. In the experience of the reviewers with chronic administration of emetics to dogs and cats, there has been observed no instance of frank vomiting as a conditioned response; on the other hand, conditioned salivation occurred in a number of cases.

Defecation often accompanies the vomiting act. This is particularly true for drug-induced vomiting. At the suggestion of Hatcher, Koppanyi (121) studied the central site of action of "evacuant" drugs. He succeeded in producing defecation by the local application of picrotoxin, heroine and codeine to the floor of the fourth ventricle, and he abolished the evacuant effect of these drugs by making lesions in the vicinity of the ala cinerea or by applying morphine to this region. Because of the concomitant refractoriness to emetic agents such as apomorphine, resulting from these procedures, Koppanyi concluded that his experiments established the existence of a defecation center in the vicinity of the vomiting center. Since it is now known that apomorphine acts not on the vomiting center but on a specialized medullary chemoreceptor trigger zone, the question logically arises whether the same elements in this zone subserve both the functions of vomiting and defecation or whether there exist separate receptors for each of these functions. Furthermore, does the vomiting center in the reticular formation have a defecation counterpart elsewhere in the lower brain stem or does the lateral reticular formation integrate both functions? The observation by Wang (178) that apomorphine is capable of eliciting defecation in dogs refractory to the emetic action of this drug as a result of surgical destruction of the chemoreceptor trigger zone clearly establishes a distinction between central receptors for vomiting and for defecation. On the other hand, according to Koppanyi (121), the facts that apomorphine frequently produces defecation and that codeine almost invariably produces nausea before defecation suggests the possibility that the centers for vomiting and defecation are acted upon by essentially the same kind of stimuli, with the ultimate response depending largely upon the state of the peripheral organs. Hess (112, 109, 110)

elicited the defecation act by electrical stimulation of points in the diencephalon in the cat in a manner similar to that by which he obtained vomiting. Kaada (117) evoked defecation by stimulation of the basal cortex of the cerebrum. Retching has also been elicited from this region of the cortex (160). It is possible, therefore, that the frequently associated purging functions are coordinated at a supramedullary level. However, no study of drug-induced defecation in the decerebrate animal has come to the reviewers' attention.

Because of the tremendous economic and military importance of motion sickness, much research has been done on this functional disorder and a comprehensive analysis of the pertinent literature has been made by Tyler and Bard (173). According to these authors, the vomiting induced by motion seems to be entirely like that produced by other stimuli and conditions which evoke emesis. It appears certain that labyrinthine stimulation is the primary factor in the etiology of motion sickness. Either labyrinthectomy or section of the eighth cranial nerves renders animals immune to the emetic effects of motion. Bard *et al.* (11) demonstrated in a chronic decerebrate dog that the essential central nervous mechanism for motion sickness operates independently of the forebrain and the rostral portion of the midbrain. The fact that the best known suprasegmental representation of the vestibular receptors lies in the cerebellum led Bard *et al.* (11, 12) to examine this structure as a participating factor in motion-induced emesis. They prevented vomiting in previously susceptible dogs by removing the cerebellar nodulus, uvula and pyramis. However, the protected animals showed mild salivation and licking in the absence of panting. These symptoms were considered as possibly due to the functional integrity of the lingula and flocculi, whose role in motion sickness remains uncertain. In control experiments Bard and coworkers (11, 12) found that ablation of all parts of the vermis between the primary fissure and pyramis or removal of the pyramis and a few folia of the uvula failed to prevent motion-induced vomiting. These workers concluded that the nodulus and uvula contain neural mechanisms which are prepotently involved in the genesis of motion sickness in dogs. Wang and Chinn (184) recently confirmed this conclusion. It is well known (173, 97) that total decerebellation does not reduce the sensitivity of animals to the emetic action of apomorphine. In contrast, Wang and Chinn (184) have demonstrated that animals rendered refractory to the emetic action of apomorphine by ablation of the medullary emetic chemoreceptor trigger zone are immune to the emetic action of swinging motion. This finding indicates that the chemoreceptor trigger zone is in the direct pathway of the vestibular reflex concerned in motion sickness.

NERVOUS PATHWAYS IN VOMITING

Efferent pathways in vomiting will not be considered in detail since these are mainly somatic and their connections are well known. As for the importance of visceral efferents in the execution of emesis, there is no essential difference in the vomiting act performed by normal and gut-denervated animals. The role of the visceral efferent nerves in gastrointestinal motility will be considered

as the need arises. The subject of the extrinsic motor innervation of the gut has been thoroughly reviewed in the literature (42, 194, 5, 133, 134, 135, 138).

Afferent pathways are very difficult to study because vomiting may be initiated from almost any site in the body. Transmission of impulses, originating from the same source, to the vomiting center may occur over more than one pathway. With regard to emetic chemicals, these may induce vomiting by stimulation of receptors in or out of the central nervous system or perhaps by acting simultaneously at a multiplicity of sites. Probably many such receptor sites remain to be discovered.

In this section, emphasis will be placed on nerve pathways without attention to the intricacies in activity of emetic substances. Details of the mechanisms of emetic action of drugs are given below, in the section on pharmacology.

Sutton and King (168) described vomiting in dogs as a result of compression of the coronary vessels. They found that section of the vagi did not abolish pain but it prevented a fall in blood pressure following coronary compression. The effect of vagotomy on induced nausea and vomiting was not reported. Removal of the left stellate ganglion abolished the sensation of pain but salivation continued.

Walton *et al.* (176) studied the pathways in the vomiting of peritonitis resulting from the intraperitoneal injection of *E. coli*. They found that impulses passed to the emetic center by way of afferent fibers in both the vagal and the sympathetic nerves. They maintained that, since neither sympathectomy nor vagotomy alone abolished the vomiting of peritonitis, the afferent emetic impulse transverses either pathway with equal facility. Actually this conclusion with regard to relative transmissibility is not justified since these workers could not quantitate in their experiments the threshold level of irritation necessary to cause vomiting after each of the nerve sections. A somewhat parallel situation was found by Wang and Borison (181) in the vomiting induced by oral copper sulfate. Either the vagi or abdominal sympathetics suffice to transmit emetic impulses to the vomiting center. However, these investigators demonstrated that the vagus is the more important pathway, since no change in the emetic threshold level of copper sulfate occurred after sympathectomy alone, whereas a two-fold increase in threshold occurred after vagotomy alone. Walton *et al.* (176) made the very interesting observation that although the somatic innervation to the parietal peritoneum remained intact, peritonitis did not cause vomiting after abdominal sympathectomy and thoracic vagotomy. From this fact, they arrived at the conclusion that *only* visceral afferent fibers are important in the vomiting act, and that it is irritation of the visceral rather than the parietal peritoneum which causes vomiting in peritonitis. Whether these investigators are justified in their conclusion that somatic afferents are not concerned in vomiting is debatable. In studying the local emetic action of mustard, Miller (146) was unable to demonstrate that the splanchnics transmit sensory impulses from the gastric mucosa. On the other hand, he prevented the vomiting movements induced by intragastric mustard by division of the vagi.

In addition he induced salivation and a modified form of emesis by electrical stimulation of the central ends of the vagal branches of the stomach.

Herrin and Meek (105) reported that continuous distention of intestinal fistulae in dogs resulted in a condition closely simulating acute bowel obstruction. The dogs showed anorexia and vomiting, but no indication of acute pain. Denervation of the mesenteric pedicle prevented these manifestations of intestinal distention. Subsequently the same authors (106) identified the afferent nerves and described their respective roles in the syndrome of intestinal obstruction. Vagotomy did not abolish the vomiting or anorexia. Bilateral abdominal sympathectomy abolished the vomiting but not the anorexia. Combined vagotomy and sympathectomy abolished all symptoms. Hence, the vomiting induced by intestinal distention is entirely of nervous origin, and is transmitted centrally via afferent fibers in the sympathetic nerves. The anorexia, on the other hand, apparently is mediated by both afferent pathways. Pennington *et al.* (156) found in the unanesthetized dog that moderate distention of an isolated jejunal segment may produce a decrease in tonus of cardia without evidence of nausea or other signs of distress.

Schrager and Ivy (164) demonstrated in unanesthetized dogs that distention of the gall bladder and biliary passages produces, in addition to inhibition of respiration in the inspiratory position, symptoms such as nausea, vomiting and distress in proportion to the degree of distention. The effects on blood pressure and heart rate were not uniform. Distention of the biliary ducts caused more striking symptoms than distention of the gall bladder. They observed that nausea, vomiting and some of the respiratory inhibition were abolished by section of the vagi and left splanchnic nerve and that distress and some respiratory inhibition were likewise abolished by section of the right splanchnic nerve. Section of both vagi and splanchnic nerves abolished all reflexes unless the distending pressure was greater than 300 mm. Hg.

Goldberg (86) showed that distention of pyloric pouches with pressures of 30 to 35 mm. Hg invariably induced vomiting. The effective pressure level remained remarkably constant regardless of whether water, dilute acids, alkalis or mustard solution was used for distention. It had been the previous contention that such pouches were denervated when prepared according to the method used by this author. However, Goldberg was able to abolish the vomiting from distention by transthoracic vagotomy. Since removal of appropriate sections of the sympathetic chains had no effect by itself on the emetic response, this worker concludes that the afferent pathway of this reflex arc is entirely through the vagus nerves. He also reported the interesting observation that distention of pouches of the gastric fundus never resulted in emesis.

In studying the absorption of glucose from the colon of the dog, Burget *et al.* (34) found that distention of a chronic closed loop of colon may produce defecation and vomiting. These authors did not investigate the nervous pathway for the response. Whether the vomiting and defecation reflexes thus initiated are mediated through identical pathways remains to be demonstrated.

Franklin and McLachlin (75) showed that ligation of the mesenteric vein,

but not of the splanchnic vein, produced emesis in the anesthetized cat. This occurred even though the venous drainage of the stomach and first few centimeters of the small intestine was entirely unaffected. Nervous pathways were not investigated, but the results are in line with reports (190, 193, 4, 132) that irritation or distention of the small intestine is more effective in causing nausea and vomiting than is similar stimulation of the stomach.

In an intensive study of the vomiting caused by staphylococcus enterotoxin in the cat, Bayliss (13) made the following observations. Celiac ganglionectomy, gastrectomy, spinal cord transection at T-2, or unilateral vagotomy did not influence the emetic response. After double vagotomy, abdominal evisceration, or spinal cord transection at C-7, only mild retching movements and rarely emesis resulted in response to enterotoxin administration. Vomiting could not be induced with enterotoxin after trauma to the floor of the fourth ventricle or by local injection of this substance into the fourth ventricle or after transection of the brain stem at the anterior border of the pons. He concluded that the action of staphylococcus enterotoxin on peripheral sensory structures (presumably innervated by the vagus) is of greater importance in the initiation of emesis than is a direct action of the enterotoxin on the vomiting center. This may be true, but the fact that emesis was invariably abolished by pontile decerebration and not by peripheral denervation requires explanation if a satisfactory hypothesis is to be evolved.

Derbyshire and Ferguson (50) produced vomiting regularly in decerebrate cats and dogs by electrical stimulation of the ventral vagus trunk. Great difficulties in interpretation arise here since, not only are centripetal vagal impulses generated but, secondary effects may be produced centrifugally by motor stimulation of thoracic and abdominal viscera. This latter possibility is strengthened by the fact that a period of summation of approximately 15 seconds was generally required to produce the vomiting response. Derbyshire and Ferguson observed that whenever apneustic breathing appeared vomiting could no longer be elicited. Borison and Fairbanks (24) found in the decerebrate cat that electrical stimulation of the nodose ganglion may elicit vomiting at a time when stimulation of the central end of the vagus is ineffective. In this connection, these workers have demonstrated that the nodose ganglion is the site of emetic action of the veratrum alkaloids (see below).

Vomiting is often associated with bilateral vagotomy and it may be generalized that the higher the vagotomy, the more frequent and persistent is the vomiting. Hwang *et al.* (114) made roentgenographic studies of the esophageal passage of barium sulfate after section of the vagi at various levels in the dog. They found that esophageal stasis and retrograde flow of its contents varied directly with the extent of paralysis of the esophagus produced by vagotomy. This is complicated by an over-all tonic contraction of the denervated esophagus, as a response to distention, which in the presence of a hypertonic cardia causes a regurgitation of the esophageal contents into the pharynx. Hwang *et al.* suggest that the vomiting occurs as a result of "irritation" of the pharynx by food regurgitated from the paralyzed esophagus. Furthermore, they main-

tain that the response to pharyngeal stimulation becomes enhanced and that the sensitivity to apomorphine is increased after vagotomy. In contrast, Wang and Borison (181) found no reduction in the emetic threshold to intravenous apomorphine as a result of vagotomy.

It has long been thought that the early death which follows bilateral cervical vagotomy is due to laryngeal paralysis with consequent asphyxia. However, Samaan (162) has shown that dogs survive in perfect condition after section of the recurrent laryngeal nerves at their vagal origin. This investigator maintains that death is the result of aspiration of food into the denervated trachea, which occurs during the vomiting resulting from vagotomy. Samaan kept vagotomized dogs alive by the combined procedure of glottal obstruction and tracheotomy. On the other hand, Schafer (163) believes that death in vagotomized cats is due only to slow asphyxia resulting from a falling together of the arytenoid cartilages during inspiration. He prepared cats which survived indefinitely after double cervical vagotomy, by the simple procedure of cauterizing the thyroarytenoid ligaments.

NAUSEA, VOMITING AND GASTROINTESTINAL MOTILITY

Alvarez (4) considers it an interesting commentary on the mental processes of physiologists that he was unable to find a word in the literature, up to 1925, about the behavior of the small bowel during vomiting. The reviewers are able to report that there is considerable material on this subject in the literature today. Indeed, a great part of it has been written and discussed by Alvarez. In spite of this, no clear evidence of cause and effect is available concerning the relationship of small bowel activity to nausea and vomiting.

This subject can be conveniently divided into three major considerations. (1) Is a particular type of gastrointestinal activity the *sine qua non* of nausea or is nausea simply the response to stimuli which induce vomiting? (2) Is the character of nausea and of vomiting evoked by stimulation of the small bowel different from emetic effects produced by other means? (3) Does intestinal antiperistalsis normally precede vomiting and what is its physiologic significance in this regard?

The reviewers have attempted to limit the following discussion to those experimental investigations in which participation of psychic factors has been reduced to a minimum, if this is at all possible in the study of nausea. It should be added that salivation associated with swallowing and frequent rhythmic forward licking in cats and dogs have long been considered manifestations of nausea which, according to some investigators, can be graded in intensity from mild to severe. An additional but less frequent sign which almost invariably heralds vomiting in the cat is a peculiar deep-throated vocalization which is not unlike its mating call. Of interest is the fact that all these signs of "nausea", except for the cry of distress, can be observed in the *decerebrate* cat in response to electrical stimulation of the medulla or to drug administration.

Several workers (92, 93, 167, 150, 87, 88, 144) have reported the effect of parenterally administered apomorphine on the movements of the small in-

testine in dogs. While there is no close agreement in the various experimental findings, it is the general consensus that the first signs of nausea are accompanied by an inhibition of intestinal tone. This may be followed by variable changes in tone and motility (93). Gregory (87) concluded that the response of the small intestine following parenteral apomorphine in the dog is of nervous reflex origin since in his experiments such responses were abolished by denervation of the mesenteric pedicle to an intestinal loop. He showed furthermore that the vagus nerves constitute the efferent pathway for this reflex as well as for the increased intestinal secretion in response to apomorphine; the splanchnic nerves do not contain fibers which are concerned in the intestinal responses described (88). This finding, coupled with the fact that apomorphine still induces "nausea" and "vomiting" after gut denervation and even abdominal evisceration (97), demonstrates unequivocally that neither a specific form of activity in the small intestine nor even the presence of that structure is necessary for the manifestation of the premonitory signs of vomiting. In a study in man, Ingelfinger and Moss (116) showed that nausea, whether caused by excitation of the semicircular canals or by the administration of morphine, is frequently accompanied by a generalized contraction of the descending duodenum. They stated that the hypothesis of nausea resulting from duodenal contraction, though possible, is unlikely since narrowing of the duodenal lumen does not always accompany nausea. This opinion has recently been reiterated by Abbot *et al.* (1). Lebensohn (130) stated that the labyrinthine-intestinal reflex is independent of the cerebral cortex, since it persists after transection of the mid-brain; it is also not affected by section of the splanchnic nerves. Barclay (10) described in humans a reduction in gastric tone which occurs with the onset of nausea. Wolf (190), using a combination of neostigmine and atropine, was able to prevent both the gastric inhibition and the nausea evoked by vestibular stimulation in man. From this fact he claimed that *gastric* relaxation and hypomotility are essential to the occurrence of nausea. However, the disturbing possibility remains that other effects of neostigmine and atropine, particularly on the central nervous system, might result in the inhibition of nausea. Wolf stated that changes in gastric motility which occurred in his experiments did not result from nausea since they antedated the onset of the sensation and occurred following stimuli of insufficient intensity to cause nausea. This is a moot statement since, if nausea represents the conscious awareness of certain subcortical autonomic processes prodromal to emesis, then it can be argued that such processes, which also occur in the decerebrate animal (11, 18, 26), may be active in advance of cortical excitation particularly in situations of slow induction of nausea. This view is strengthened by the fact that in motion sickness the symptoms of drowsiness, pallor, cold sweating, and salivation with swallowing regularly precede the sensation of nausea (173). Indeed, Doig, Wolf and Wolff (52) reported characteristic symptoms of motion sickness, including facial pallor, tachycardia, weak pulse and finally retching and vomiting, in a "decorticate" man subjected to the stimulation of a rough plane journey. In this man, irrigation of the external auditory canals

with ice water produced no inhibition of gastric contractions although nystagmus, lasting several minutes, resulted. Fuglsang-Frederikson and Horstmann (76) confirmed the view of Wolf that nausea is associated with inhibition of gastric contraction, which inhibition starts before and ends later than the nausea. On the other hand, they did not believe that the inhibition of motility is the cause of nausea. They stated that no apparent correlation exists between the effects of various drugs on nausea and on gastric motility. They concluded that the motor function of the stomach cannot be used as a test of the effect of drugs on nausea.

The history of experimental investigation on the representation of gastrointestinal activity of the cerebral cortex has been summarized by Kaada (117). Early workers confined their studies to the lateral surface of the cerebral hemisphere. There was no good agreement by these investigators on the effects of cortical stimulation on gastric motility. More recently, the medial and basal areas of the cerebrum have been stimulated for the purpose of evoking gastrointestinal responses (117, 9, 6–8, 71). The general finding was inhibition of pyloric antral contractions and tonus. Penfield and Rasmussen (155) described responses of salivation and nausea resulting from stimulation of the pre- and postcentral cortex in the vicinity of the sylvian fissure in conscious human beings. Abdominal sensations were especially elicited from the anterior portion of the island of Reil and one patient vomited a few minutes after the insular cortex had been stimulated. Penfield and Erickson (154) cited a number of cases in which vomiting occurred always *after* stimulation of the cerebral cortex. Furthermore, these emetic responses were not necessarily associated with nausea and they resulted from cortical stimulation at widely separated points. The investigators found no examples of intussusception and no production of diarrhea or defecation in response to stimulation of the cortex. Penfield and Erickson (154) also described salivation, nausea and vomiting which resulted from stimulation of the large veins that cross the subdural space to the dural sinuses or from the sinuses themselves. They suggested that these responses are mediated via a *vascular reflex pathway* which follows an extracerebral course to reach the brain stem.

It has been well established that the intestine is a very important source of emetic impulses, and that vomiting regularly follows excessive intestinal distention or irritation (4). Indeed, it has been demonstrated (193, 119, 132) that the duodenum is much more sensitive than the stomach to emetic stimuli. Although vomiting may be readily initiated by stimulation of the duodenum and the small intestine generally, there is no reason to believe that the character of the vomiting is different from that produced by effective emetic stimuli acting elsewhere in the body.

Alvarez (3, 4) has devoted much attention to the question of reverse peristalsis in the small intestine. The syndrome of reverse peristalsis, introduced by him in 1917, is given such comprehensive treatment in his textbook that detailed discussion of it is unwarranted in this review. Alvarez (4) states: "Among the symptoms that make one think of the possible presence of mild reverse peristalsis

are vomiting, regurgitation, rumination, some types of heart burn, belching, gurgles running up the esophagus, nausea, perhaps some type of biliousness, coated tongue, some types of bad breath, a feeling of fullness immediately after beginning to eat, some forms of hiccup and some of the strangling sensations felt about the cardia." Despite the apparent certainty of Alvarez concerning the existence of reverse peristalsis and its consequences, the status of this phenomenon is far from settled, as exemplified by the few selected quotations from the literature. Bolton and Salmond (16) state: "Antiperistalsis is a normal movement of the duodenum. Its effects are to delay the food in the duodenum, to ensure its admixture with the digestive juices, and to produce conditions favourable to regurgitation into the stomach." Mecray (145) states: "Despite the production of emesis containing small intestinal contents no antiperistalsis was observed." Oppenheimer and Mann (150) state: "These findings coupled with the appearance of bile in late bouts of vomiting in any series suggest that the activity that we observe is antiperistalsis although we realize that this is not proved." Mathur *et al.* (144) state: "In our experiments we have observed that after a previous period of inactivity a few minutes after an injection of apomorphine hydrochloride, rapidly increasing contractions appear, first in the jejunum and then in the distal and proximal parts of the duodenum. As these contractions end in vomiting, and seem to travel aborally (*sic*), they are suggestive of antiperistalsis." Ingelfinger and Moss (116) state: "Our records indicate that during nausea balloons in the descending duodenum are pushed backwards into the stomach even though the peristaltic waves continue to travel aborally."

The role of the small intestine in nausea and vomiting can be summarized as follows. The intestine is sensitive to emetic stimuli, and impulses arising from it may initiate nausea and vomiting, depending on the intensity of stimulation, by way of established reflex pathways. Intestinal contents are frequently found in the vomitus, particularly following repeated bouts of retching. Although reverse peristalsis has been reported, the mechanism by which the intestinal contents are regurgitated into the stomach is not settled. Neither the innervation to nor even the presence of the small intestine is necessary for the production of nausea and vomiting by a wide variety of means.

PHARMACOLOGY OF VOMITING

Introduction

The mechanism of action of emetic drugs has been one of the most perplexing and unrewarding problems in pharmacology. The subject has been utterly confounded by the attempts of investigators to draw conclusions from anti-emetic effects of substances which are emetic agents in their own right, coupled with the fact that the pharmacologic actions of these drugs are only incompletely understood. Furthermore, the field has been permeated with unjustified conclusions, *e.g.*, that an emetic acts centrally if it causes vomiting movements after surgical removal of the gastrointestinal tract. This type of reasoning has

been adopted by some workers to the extent that vomiting after parenteral administration of a drug is taken as proof of its central emetic action.

With the demonstration by Wang and Borison (180, 183, 28) of a specialized chemoreceptor trigger zone in the medulla, distinct from the vomiting center, the concept of a direct action of "central emetics" on the vomiting center is no longer tenable. Indeed, there is, at present, no good evidence that any substance which causes emesis, as its chief or side effect, does so by direct stimulation of the vomiting center.

In 1923, Hatcher and Weiss (101) published their extensive studies on the location of the vomiting center, the receptor sites for certain emetic agents, and the interaction of various drugs on the vomiting reflex. This article has been the source of authoritative information on emesis for many years. On the basis of their experiments on the emetic and anti-emetic actions of drugs, Hatcher and Weiss constructed a system of *autonomic afferent pathways* to account for the postulated peripheral effects of a variety of emetic agents and antagonists. For example, visceral afferent fibers have been divided into sympathetic and parasympathetic types. However, no restriction was placed on anatomic pathways with the result that both types could traverse the established sympathetic and parasympathetic autonomic nerves. Even more remarkable was the suggestion that *normal* afferent emetic impulses pass up the sympathetic afferents only, whereas *abnormal* emetic impulses, induced by poisons, may traverse either path. Ergotoxine according to Hatcher and Weiss, paralyzes the sympathetic type of afferent fiber; hence it blocks normal emetic impulses. In spite of the glaring lack of physiological evidence for such a system, a number of later investigators analyzed their results after the scheme proposed by Hatcher and Weiss. As a consequence, endless confusion has arisen from the perpetuation of the unfounded and totally erroneous conception that autonomic blocking drugs selectively interrupt afferent as well as efferent transmission in the autonomic nervous system. According to modern concepts, somatic and visceral afferent nerve fibers are indistinguishable morphologically and pharmacologically.

The reviewers have found it necessary to refer often to the work of Hatcher and Weiss and a thorough point-by-point analysis of their contributions in the light of more recent investigations is highly desirable. However, such an undertaking is inappropriate here. Instead, the experiments of Hatcher and Weiss will be considered in separate parts in connection with the discussions of pertinent drugs.

Apomorphine and Morphine

Thumas (172) and later Hatcher and Weiss (101) believed that the vomiting center had been localized by the elicitation of emesis with topical application of apomorphine to the medulla oblongata. This observation combined with the finding of Eggleston and Hatcher (68) that vomiting movements are elicitable with apomorphine after removal of the gastrointestinal tract, appeared to

constitute irrefutable evidence that apomorphine acts directly on the vomiting center. However, two problems were unresolved. First, the experiments did not exclude the possibility of additional sites of action of apomorphine; second, it remained possible that apomorphine acts on *receptors* located in the central nervous system and not on the vomiting center itself. Proof that apomorphine does not act directly on the vomiting center but on the closely situated chemoreceptor trigger zone has already been presented (page 195). That apomorphine acts *solely* on the medullary emetic trigger zone was only recently demonstrated by Wang and Borison (183) by experiments in which vomiting in response to apomorphine, given orally as well as intravenously, was prevented by chronic ablation of the chemoreceptor trigger zone. The emetic responsiveness to oral copper sulfate, on the other hand, was not altered by destruction of this zone.

Hatcher and Weiss (101) found that ergotoxine abolishes the emetic action of apomorphine. They believed that ergotoxine acts peripherally only and on sympathetic-type afferent endings. Hence the concept of a direct action of apomorphine on the vomiting center had to be modified. This they accomplished by making the assumption that apomorphine has a strychnine-like action which results in hyperexcitability of the vomiting center to normal afferent impulses. The inhibitory action of ergotoxine is then easily explained by assuming that the drug reduces the normal influx of impulses to the vomiting center with consequent inactivation of the emetic reflex. Koppanyi and Evans (123) challenged this view with the argument that the central action of ergotoxine as an emetic agent is not consistent with the claim of peripheral inhibition of afferent impulses in preventing the emesis induced by apomorphine. The demonstration of a specialized receptor apparatus for certain central emetics, including apomorphine, makes the claim for a strychnine-like action of apomorphine obsolete, but the mechanism of antagonistic action of ergotoxine remains to be elucidated. Effects of the ergot alkaloids on the central nervous system have been reviewed by Nickerson (149). It is probable that the anti-emetic action of these drugs is effected through direct brainstem depression.

It is well known (see Hatcher (97)) that large doses of apomorphine, and morphine, are capable of inhibiting the vomiting induced by apomorphine. This effect is not the result of fatigue of the chemoreceptor trigger zone since small doses of apomorphine continue to elicit vomiting for five or six times in succession without diminution in emetic responsivity (Eggleston and Hatcher (68)). Koppanyi (121) was able to prevent apomorphine-induced vomiting with morphine administered either intravenously or by local application to the medulla oblongata; the emetic response to oral mercuric chloride or zinc sulfate persisted concomitantly. De Busscher (48) maintained that morphine abolishes the emetic effect not only of apomorphine but also of arsenious oxide or copper sulfate. This suggests the possibility of two separate mechanisms for the anti-emetic effects of morphine. Indeed, Dordoni (54) differentially inhibited with parenteral morphine the emetic actions of subcutaneous apomorphine and oral copper sulfate. Leake (129) demonstrated that although subcutaneous morphine induces vomiting within approximately ten minutes, prevention of vomiting to

emetine or apomorphine does not occur for about an hour and lasts for a number of hours. Leake has shown, furthermore, that morphine can inhibit apomorphine-induced emesis without causing vomiting by itself. Gold *et al.* (83) demonstrated that morphine prevents the vomiting in response to oral digitoxin in the cat. It appears that the anti-emetic effect of certain doses of apomorphine and of morphine is the result of a direct action on the reticular formation. The facts that apomorphine reduces postural tone (174, 175) and that morphine depresses respiration support such a suggestion. This view is consistent with the localization of the vomiting center in the lateral reticular formation by Borison and Wang (26, 180, 183). However, definitive experiments have not yet been performed which conclusively demonstrate the locus or loci of anti-emetic action of morphine and apomorphine upon drug-induced vomiting.

Dose-effect data for both apomorphine and morphine are given for a wide variety of animals in the monumental review of Krueger, Eddy and Sumwalt (125). More detailed consideration of the historical development of the subject of apomorphine-induced vomiting may be found in the review by du Toit and Christensen (64). The present reviewers have limited this discussion to phases of the subject which require reconsideration in the light of recent investigations.

The mechanism of the emetic action of morphine has not been as thoroughly investigated as has that of apomorphine. Nevertheless it is the general opinion among pharmacologists that these agents are identical in their emetic action except for their difference in potency. On the other hand, Hatcher and Weiss (101) showed that, whereas apomorphine, morphine and heroine produce vomiting on direct application to the dog medulla, codeine exerts no perceptible effect when similarly applied. Wang and Glaviano (186) have recently demonstrated that normally effective doses of oral and intravenous morphine fail to evoke emesis in chronic dogs with chemoreceptor trigger zone ablation. The mechanism(s) of emetic action of other opium alkaloids is incompletely elucidated.

Bernheim and Bernheim (15) and Kuhn and Surles (126) demonstrated high anti-cholinesterase activities for apomorphine and morphine. They suggested that a cholinergic mechanism might provide the basis of action of central emetics. However, Eggleston (67) showed that intravenous atropine was ineffective in preventing vomiting due to subcutaneous apomorphine or morphine in the dog. Furthermore, Cheymol and Quinquaud (39) were unable to prevent the emetic response to intravenous apomorphine in the dog by applying atropine to the floor of the fourth ventricle. Similarly, Hatcher and Weiss (102, 103) failed to prevent the emetic action of apomorphine with nicotine.

Hatcher and Weiss (101) demonstrated that the emetic action of apomorphine is synergistic with that of ouabain, but that more than 50 per cent of the emetic dose of each is required to produce vomiting in combination. Gold *et al.* (85) produced tolerance to the emetic action of cardiac glycosides and demonstrated a simultaneous cross-tolerance to apomorphine. Previously, Gold (79) showed that morphine habituation results in tolerance to the emetic action of small

doses of intramuscular apomorphine. Co Tui (41) found it necessary to administer large subcutaneous doses of apomorphine daily in dogs in order to produce tolerance to the emetic action of minimal intravenous doses. Minimal subcutaneous doses of morphine also became ineffective for vomiting during the period of apomorphine habituation. Conversely, tolerance to the emetic action of intravenous apomorphine developed in morphine-habituated dogs. This result stands in contrast to the finding of Downs and Eddy (55) that dogs habituated to large doses of morphine vomited in response to doses of apomorphine which were ineffective in *non-habituated* dogs given small doses of morphine. Co Tui showed further that both morphine- and apomorphine-habituated dogs were not tolerant to the emetic action of intravenous pilocarpine.

Cardiac Glycosides

From the facts that digitalis bodies were more effective by vein than by mouth, and that emesis promptly followed their intravenous injection in dogs after surgical removal of the gastrointestinal tract, Hatcher and Eggleston (98) concluded "irresistibly" that the emetic action of the digitalis bodies is exerted upon the vomiting center. A statement from the same article actually represents the only reasonable conclusion which could be derived from these experimental facts: "Our experiments on eviscerated dogs proved conclusively that those digitalis bodies which we employed in this way are capable of inducing emesis, or nausea and vomiting movements, in dogs *without the participation of the action on the gastrointestinal tract.*" (Italics are those of the reviewers.) Nevertheless, in 1927, Hatcher and Weiss (102) in referring to the above mentioned work enlarged on the significance of the results, as follows: "Hatcher and Eggleston . . . showed that the emetic action of the digitalis bodies is not exerted on the gastrointestinal tract regardless of the mode of administration . . . ."

Obviously, the only way to exclude the possibility of an emetic action on the gastrointestinal tract is to eliminate the emetic response to digitalis by denervating some structure or structures *other than the gastrointestinal tract*, without diminishing the excitability of the vomiting center or interfering with its motor expression. This has not yet been accomplished.

To return to the question of a central emetic action of digitalis, this concept was further entrenched by Eggleston and Hatcher (69). Indeed, from results obtained with evisceration experiments, they concluded that practically all emetic agents in common use act directly upon the vomiting center. Hatcher and Weiss (100) reversed this position, for digitalis at least, and they claimed that the digitalis bodies cause *reflex* nausea and vomiting through stimulation of afferent fibers in the heart. Their conclusion was based on two main facts. (1) The application of digitalis bodies to the medulla was without effect whereas apomorphine induced vomiting when administered in this way. (2) The acute interruption of nervous connections between the heart and the medulla always prevented nausea and vomiting after the injection of *moderate* doses of digitalis bodies.

Failure to elicit vomiting by topical application to the medulla, although

provocative, is an example of negative evidence and does not constitute proof for a number of reasons. For example, digitalis may undergo a metabolic alteration after systemic administration which renders it active centrally or the chemical properties of digitalis may prevent its access into the receptor site after local application. The second argument cited above for a cardiac site of emetic action is weakened by the fact that the heart is but one structure among many which are denervated by vagotomy and cord section. The heart appeared to be the logical receptor site for the digitalis bodies owing to the cardiac activity and toxicity of these drugs. Eggleston and Wyckoff (70) accepted the conclusions of Hatcher and Weiss, and Eggleston's original view of a central action of digitalis was discarded in favor of the cardiac reflex mechanism. They believed that this action was demonstrated by the fact that cardiac toxicity invariably preceded the production of emesis in their patients.

Eggleston (67) and Hatcher and Weiss (101) were unable to inhibit the emetic action of the cardiac glycoside with atropine. However, Hatcher and Weiss (101) supported the idea of a cardiac site of emetic action with the fact that ergotoxine almost invariably prevented digitalis-induced vomiting. According to these workers, the concept of a cardiac reflex mechanism followed logically from their claim that ergotoxine acts only peripherally, and that its anti-emetic action is accomplished through a selective paralysis of *sympathetic-type afferent endings*.

Dresbach and Waddell (61–63) very soon challenged the theory of the cardiac emetic reflex. They showed that strophanthidin induced vomiting in cats after thorough denervation of the heart, provided that sufficient time was allowed for recovery from the immediate effects of the operation. This last qualification is the critical difference between Dresbach's experiments and those of Hatcher (97). Hatcher and Weiss (102, 103) questioned the completeness of the cardiac denervations performed by Dresbach and Waddell. This is surprising since Hatcher and Weiss (101) originally attributed great importance to stellate ganglionectomy alone as a means of sympathetic cardiac denervation whereas Dresbach and Waddell more accurately denoted the upper thoracic sympathetic chains as pathways for cardiac innervation (37). The consistent emetic response to digitalis obtained by Dresbach and Waddell (62) after *chronic* cardiac denervation clearly demonstrated that the cardiac innervation is not essential to digitalis-induced vomiting. Hatcher *et al.* (102, 103, 99) placed great importance on the fact that Dresbach used the intraperitoneal route of administration for strophanthidin, and that nicotine prevented the emesis elicited by intravenous and intramuscular strophanthidin but not that which followed intraperitoneal administration (66). The inhibitory effect of nicotine was attributed to a selective paralysis of afferent endings in the heart, presumably of the sympathetic type, upon which the cardiac glycosides were supposed to act to induce vomiting. They claimed that strophanthidin, given intraperitoneally, induces vomiting by local irritation and hence cannot be blocked by nicotine. In support of this idea Hatcher and French (99) demonstrated that strophanthidin combined with procaine or cocaine, given in-

traperitoneally, was less effective in eliciting emesis after nicotine than strophanthidin given alone. The rationale for this procedure was that the local anesthetic prevented peritoneal irritation and the nicotine prevented the emetic action, at the heart, of the absorbed strophanthidin. However, these authors did not report control studies with strophanthidin in combination with procaine or cocaine, but without the prior administration of nicotine. In any event, Dresbach has shown that emesis may be elicited with digitalis glycosides through various routes of administration after chronic cardiac denervation. Davis *et al.* (49), in pursuing the cardiac reflex theory, attempted to localize in the spinal cord the pathway of afferent cardiac impulses initiated by digitalis glycosides. They concluded that impulses from the heart are transmitted via the anterior columns since *acute* section of these columns, after vagotomy, prevented emesis. This claim has been countered by Dresbach (60) who showed that *chronic* cord section combined with vagotomy does not prevent digitalis-induced vomiting.

That cardiac denervation does not suffice for the abolition of digitalis-induced emesis has been quite adequately confirmed by a number of workers (96, 94, 183). A recent report by Fukuda and Kushizaki (77) once more claims that the cardiac innervation is the essential emetic pathway for digitalis, but this work was performed in the acute animal preparation, to which all the above mentioned criticisms apply. The inhibition of digitalis-induced vomiting after *acute* denervation of the heart may be explained on the basis of temporary reduction in the central excitatory state of the medullary reticular formation as a consequence of interruption of pathways from sources generating tonic excitatory impulses. For example, section of the vagus causes a slowing of respiration, but in time the respiratory rhythm returns to its original rate. Similarly, it is probable that compensatory phenomena, in the chronic denervated-heart animal, result in a restoration of the central excitatory state of the emetic center to its preoperative level. Nonetheless, Wang and Borison (183) point out that not until *all* the receptor sites for the emetic action of digitalis are enumerated can the heart be excluded as one of the possible sites of emetic action. This remains to be done.

Dock *et al.* (51) showed that more digitalis accumulates in the liver than in the heart of the pigeon. Hanzlik and Wood (96) extended this work and claimed that the emetic action of digitalis in the pigeon consists predominantly of a vagus reflex which arises from a local irritant action of digitalis concentrated in the liver, but also secondarily from other abdominal viscera, because vomiting was still elicitable after hepatectomy. Dresbach (56), in experiments on cats confirmed the finding that digitalis continues to induce emesis after hepatic denervation or hepatectomy. Hanzlik and Wood (96) found that nicotine, but neither atropine nor ergotoxine, was effective in preventing digitalis emesis in the pigeon.

Dresbach (56–60) found that no matter how extensive the denervation of thoracic and abdominal organs, cardiac glycosides could excite the vomiting reflex provided good recovery had occurred from the surgical procedures. On this basis, he assumed that digitalis elicits vomiting through a central action,

although he realized this was not proved. The disturbing fact remained that digitalis substances did not induce vomiting after direct application to the medulla oblongata (60, 101). However, Hatcher and Weiss (101) showed that large doses of digitalis directly applied to the region of the ala cinerea, prevented vomiting in response to subsequent intramuscular or intravenous injection of digitalis. Koppanyi (121) reported, as an incidental observation, that digitalis did not elicit vomiting following chronic damage to the ala cinerea. Borison and Wang (28) found that the prompt vomiting response to intravenous glycoside was invariably abolished in dogs which were refractory to apomorphine following chronic destruction of the chemoreceptor trigger zone. This finding demonstrated the existence of the long-debated central emetic action of digitalis. Nevertheless, these workers observed that a late emetic response (1–8 hours) could still be elicited infrequently after near-lethal intravenous doses. Borison (21) substantiated the central action of digitalis, in the cat, and showed furthermore that the emetic response following oral digitalis could still be elicited but with diminished sensitivity after trigger zone ablation. He suggested that the late response to intravenous glycoside is probably mediated through the same peripheral receptors which are stimulated by the oral glycoside.

Pinschmidt (157) found that vomiting initiated by digitoxin is not abolished by removal of the carotid bodies and sinuses and by denervation of the comparable aortic structures in the dog. He suggested the possibility that impulses may arise from any one of several structures all of which would have to be denervated in the same animals to abolish the emetic response to digitalis. Borison and Brizzee (19), in one cat, confirmed the finding of Pinschmidt that section of the carotid and aortic nerves does not prevent digitalis-induced vomiting. In addition, they showed that a subsequent lesion in the chemoreceptor trigger zone was effective in preventing the emetic response. The possibility of a local gastrointestinal irritant action in the elicitation of emesis, with moderate doses of oral cardiac glycosides, had already been discounted by Eggleston and Hatcher (68) in 1912. Nonetheless, it is generally accepted that massive doses of these substances are capable of inducing emesis by such an action (68). The question of a local emetic action with moderate oral doses of the cardiac glycosides has been reopened by the investigations of Gold, *et al.* (83, 80). These workers demonstrated in the cat (80), by bioassay methods, that insufficient glycoside to induce emesis by the intravenous route had been absorbed from the gastrointestinal tract at the time that vomiting resulted from the oral administration of the substances. They claimed that the local irritant effect of certain glycosides (scilliroside, lanatoside C, ouabain, scillaren A) was the chief if not the sole mode of emetic action of these drugs when given by the oral route, and that this action is responsible for vomiting which may occur as long as eight hours after administration. This group of investigators (89, 81) more recently reported observations on the postulated local emetic action of digitalis glycosides in man. Borison (21) demonstrated in the cat that the emetic responsiveness to oral lanatoside C and scillaren A was unaffected by chronic gut denervation which resulted in marked emetic refractoriness to oral

copper sulfate. Wang and Borison (183) substantiated these results in the dog. While these findings do not exclude an irritant action on the gut, they essentially contradict the claim of Gold *et al.* (80) that local irritation is the chief mechanism by which oral glycoside causes emesis. If the postulated local enteric action actually occurs, gut denervation should result in a marked reduction in sensitivity or even abolition of the emetic response. This was not the case, since no diminution in emetic sensitivity could be detected. White and Gisvold (188) administered larger doses of lanatoside C than were reported by Gold *et al.* (80) yet they did not obtain vomiting in cats after the expected latency period. This was used as an argument, but without justification, against a local action in the gastrointestinal tract. It is apparent that White and Gisvold were not acquainted with the long-established fact that vomiting is inhibited when animals are restrained in the supine position (97). Borison (21) reported data on dosage and emetic latency in the normal cat which were in close agreement with those of Gold *et al.* (80).

Östling (151) reported the effects of large digitalis doses on the empty stomach of man. He found that only 2 out of 50 patients in congestive heart failure vomited after taking 1.0 gram of digitalis at 6:00 A.M. He concluded that local irritation rarely follows oral administration of digitalis.

It appears from the work of Hanzlik, and Wood (96) that the pigeon has a poorly developed central receptor apparatus for emesis. By comparing the action of digitalis with that of other emetic agents in the pigeon, they argued that the central emetic mechanism is insusceptible to direct stimulation; hence the seat of emetic action of digitalis in the pigeon must be peripheral. A study of medullary morphology in the pigeon in comparison with those of apomorphine-susceptible animals is greatly to be desired.

Gold *et al.* (84, 85) reported the very interesting observation that frequently repeated doses of the digitalis glycosides may depress the vomiting reflex while simultaneously increasing the intensity of the cardiac poisoning; after an initial period of vomiting, the continued administration may fail to produce emesis and may even cause death without further vomiting. Of great significance is the fact that, during experiments with digitalis, it was found that tolerance had developed to apomorphine. Gold *et al.* (84, 85) claimed no direct evidence for the exact seat of this inhibition of the vomiting reflex; but they suggested, from the then prevalent idea of the cardiac reflex emetic action of digitalis, that the suppression of vomiting was probably also due to a peripheral action. However, in view of the demonstration of a central action of digitalis, it appears more likely that the inhibitory effect occurs either at the medullary emetic chemoreceptor trigger zone or at the vomiting center proper.

In conclusion, the digitalis glycosides elicit emesis by acting at more than one receptor site. The central site of emetic action is the medullary chemoreceptor trigger zone. A local irritant action on the gastrointestinal tract is probably insignificant under most circumstances. While the cardiac innervation is not essential to the emetic reflex, its participation has not been excluded. The peripheral site(s) of emetic action remain to be discovered.

Copper Sulfate

Copper sulfate may be considered the prototype of peripherally-acting emetics such as mercuric chloride and zinc sulfate. The action of minimal effective oral doses is probably a pure expression of gastrointestinal irritation mediated via visceral afferents in both the vagus and sympathetic nerves (see page 202). However, Wang and Borison (181) have demonstrated in gut-denervated dogs that large doses of oral copper sulfate are capable of inducing vomiting, after absorption, by a direct action on the medullary chemoreceptor trigger zone. Dogs which were subjected to trigger zone ablation in addition to gut denervation did not vomit in response to even lethal doses of oral copper sulfate.

Koppanyi (122) showed that an effective emetic dose of copper sulfate injected into a duodenal loop of a dog was ineffective if repeated 3 hours later. He attributed the failure of the second dose to the astringent action of the drug. Koppanyi (122) also found that the injection of atropine into the duodenal fistulas prevented retching and vomiting to copper sulfate instilled into the intestinal loop, whereas intravenous atropine failed to do so. This phenomenon can probably be explained on the basis of the local anesthetic action of atropine. On the other hand, ergotamine tartrate locally administered did not prevent vomiting to copper sulfate placed in a jejunal loop.

Quinine and Quinidine

Eggleston and Hatcher (69) believed that quinine acts directly on the vomiting center because the vomiting response to this agent persisted after surgical removal of the gastrointestinal tract. However, Hatcher and Weiss (101) failed to induce vomiting by the direct application of quinine to the medulla oblongata in the dog. Ernstene and Lowis (72) demonstrated that chronic cardiac denervation does not prevent quinidine emesis. They showed further (73) that quinidine was ineffective on direct application to the medulla of the cat, that nicotine prevented quinidine vomiting, that atropine failed to prevent the vomiting, and that ergotoxine largely prevented the vomiting; in short, the emetic action of quinidine resembles that of digitalis in its susceptibility to pharmacologic agents. Ernstene and Lowis (72) found that bilateral vagotomy and evisceration failed to prevent the emetic response to quinidine, but high spinal cord section prevented vomiting in most cases.

Veratrum Alkaloids

Eggleston and Hatcher (69) concluded that veratrine acts directly on the vomiting center because it could still evoke emesis after surgical removal of the gastrointestinal tract in dogs; however, they did not deny the possibility of a reflex emetic action from the alimentary mucosa. Hatcher and Weiss (101) failed to evoke vomiting in dogs by local application of veratrine sulfate to the dog medulla. Christiansen and McLean (40) and Marsh (142) and Swiss (169) expressed the belief that veratrum derivatives elicit emesis through a central action. Borison and Fairbanks (25) found that veratrum alkaloids elicit emesis after chronic ablation of the chemoreceptor trigger zone and after more com-

plete destruction of the area postrema. These workers (74, 25) subjected decerebrate cats to a series of neurological procedures designed to eliminate structures nonessential to the vomiting reflex initiated by the veratrum alkaloids. Of all the procedures utilized, which compositely were tantamount to total deafferentation of the lower brain stem, interruption of the vagus above the nodose ganglion was the essential maneuver for abolishing veratrum-induced emesis. In chronic experiments on cats, neither vagal section below the nodose ganglion nor decapsulation of the ganglion interfered with the elicitation of emesis, but interruption of the vagus above the nodose ganglion invariably prevented the emetic response to veratrum alkaloids. Borison and Fairbanks (25) concluded that the site of emetic action of these alkaloids is intimately associated with the nodose ganglion and is not located in the central nervous system. Swiss (169) and Borison and Fairbanks (25) showed for the dog and cat, respectively, that gut denervation does not prevent the emetic response to oral veratrum. Veratrine and veratrum album do not produce vomiting in pigeon, after intravenous injection, but violent emesis occurs after intraperitoneal administration of veratrine, presumably as a result of local irritation (51, 96).

Pilocarpine, Pituitrin, Posterior Pituitary, Acetylcholine and Physostigmine

These drugs are considered as a class because all fail to produce vomiting by topical application to the medulla oblongata (vomiting center of Thumas); but, surprisingly, each elicits vomiting and/or nausea when injected into the lateral ventricle. Moreover, the emetic response to these agents is completely prevented or inhibited by atropine injected by any of the parenteral routes or by direct administration into the lateral cerebral ventricle.

Hatcher and Weiss (101) were unable to evoke vomiting in dogs by direct application of pilocarpine to the medulla oblongata, but they elicited hiccough instead. They found that ergotoxine prevented pilocarpine vomiting in the cat, but mercuric chloride remained effective in causing emesis. Furthermore, they showed that atropine and ergotoxine both inhibited the emetic action of pilocarpine but vagotomy did not. These investigators (101) concluded, on the basis of their scheme for autonomic afferent transmission and the effects of drugs thereon, that the emetic action of pilocarpine is exerted on afferent endings limited to the sympathetic system. This claim was subsequently reiterated by Hatcher and Weiss (103) at which time they pointed out an apparent paradox in that pilocarpine is a typical stimulant of "parasympathetic efferent nerves." The lack of knowledge of the physiology of neurohumoral transmission at that time multiplied the pitfalls of such interpretations. Koppanyi (121) failed to cause vomiting with pilocarpine in dogs with chronic lesions in the medulla, although oral mercuric chloride remained an effective emetic. Local application of morphine to the Thumas area likewise prevented pilocarpine vomiting. These facts stand in contrast to the earlier findings of Hatcher and Weiss (101) that local application of pilocarpine to this region failed to evoke vomiting. Cushing (44–47) obtained prompt vomiting in man by injection of pilocarpine into the lateral ventricle of the brain. Prior injection of atropine by the same route

or by subcutaneous administration prevented this response. Henderson and Wilson (104) elicited vomiting in an unanesthetized infant with intraventricular but not with subcutaneous pilocarpine. Light and Bysshe (131) induced vomiting in the monkey with intraventricular pilocarpine. Cheymol and Quinquaud (39) prevented the emetic action of intravenous pilocarpine in the dog by applying atropine to the floor of the fourth ventricle.

Pilocarpine-induced vomiting may be explained on the basis of three possible mechanisms. According to Hatcher and Weiss (100, 101) and Kwit and Hatcher (127) pilocarpine acts on the *heart* to produce vomiting reflexly. However, Koppanyi and Evans (123) obtained vomiting with pilocarpine administered intravenously after bilateral vagotomy and transection of the spinal cord at T-2. Koppanyi (121) abolished the emetic response to pilocarpine by inactivating either surgically or with morphine the region later shown to be the *chemoreceptor trigger zone* (28). Cheymol and Quinquaud (39) did likewise with atropine applied locally to the medulla oblongata. Koppanyi (122) found also that nicotine administered by local application to the medulla reduced the incidence of pilocarpine-induced vomiting in cats. On the other hand, numerous workers have induced vomiting with intraventricular pilocarpine which, presumably, produced this effect by stimulation of *subependymal hypothalmic nuclei.* Atropine inhibited the emetic response elicited by the intraventricular as well as the intravenous injection of pilocarpine.

It seems safe to discount the heart as the site of action for pilocarpine. It is unlikely that injection of pilocarpine into the lateral ventricle should result in vomiting by diffusion of this substance to the chemoreceptor trigger zone in the medulla since direct application to the latter region fails to elicit vomiting. On this basis one might predict that decerebration would abolish the emetic response to pilocarpine.

Cushing (47) obtained prompt retching and vomiting with the intraventricular injection of posterior pituitary in man, whereas intravenous administration elicited no such response. The prior injection of atropine either into the lateral cerebral ventricle or subcutaneously completely prevented the emetic response to posterior pituitary. Light and Bysshe (131) failed to obtain vomiting with intraventricular posterior pituitary in unanesthetized monkeys although they elicited vomiting in one out of four animals with pilocarpine administered in this manner. The failure with posterior pituitary is not surprising in view of the species insensitivity of monkeys to emetics in general. Hatcher and Weiss (101) failed to evoke vomiting by local application of posterior pituitary to the dog medulla. The same arguments presented above for the mechanism of pilocarpine vomiting may be applied equally well for posterior pituitary. The finding of Cushing (47) that tribromoethanol prevents the emetic response to intracerebral posterior pituitary and pilocarpine is not convincing as evidence for a direct action of these agents on the hypothalamus.

Silver and Morton (166) obtained signs of nausea by injecting acetylcholine into the lateral ventricle of the unanesthetized cat. Henderson and Wilson (104), on the other hand, regularly elicited vomiting to acetylcholine injected

into the lateral ventricle of unanesthetized man, sometimes as early as 30 seconds after administration. This response, while in progress, was abolished by intraventricular or subcutaneous atropine. These investigators likewise obtained vomiting with intraventricular physostigmine although the response was delayed for a period of approximately 10 minutes. They demonstrated a synergistic action of substimulant doses of physostigmine and intraventricular acetylcholine. Hatcher and Weiss (101) had previously claimed that physostigmine has no perceptible effect on the vomiting center. Miller (147) obtained repeated deglutition by applying acetylcholine to the medullary obex but did not report vomiting. The deglutition in response to acetylcholine was augmented by physostigmine and abolished or prevented by atropine. Light and Bysshe (131) failed to obtain vomiting with intraventricular acetylcholine in the unanesthetized monkey. However, the species insensitivity of the monkey to emetics minimizes the importance of this finding. Methacholine caused vomiting by intraventricular injection, whereas subcutaneous administration of an equivalent dose failed to evoke emesis (104). Kremer (124) elicited vomiting with large doses of neostigmine administered intrathecally by lumbar puncture in unanesthetized human beings. Since this response could not be elicited in cases of spinal block, the author placed the emetic action of neostigmine at a supraspinal level. He found that intrathecal acetylcholine alone had no effect. However, small amounts of acetylcholine and neostigmine in combination produced effects similar to large doses of neostigmine. The ubiquitous action of atropine in antagonizing the emetic effects of the above mentioned cholinergic agents suggests that this substance acts to block transmission from the hypothalamus to the vomiting center, perhaps at a number of interneural synapses. Such a view is compatible with recent hypotheses of the role of atropine in modifying central nervous function.

Tartar Emetic

Thumas (172) and Hatcher and Weiss (101) failed to induce vomiting in the dog by direct application of tartar emetic to the medulla oblongata. Hatcher and Weiss claimed that tartar emetic induces vomiting by initiating impulses in the heart which then pass upward, mainly by way of the vagus. They were unable to explain their finding that impulses induced by digitalis travel mainly by way of sympathetic nerves. According to these workers tartar emetic also induces vomiting by a local action in the gut. After vagotomy small doses of tartar emetic are no longer effective, regardless of the route of administration. Furthermore, atropine is apparently effective in preventing vomiting to tartar emetic given by any route of administration. However, neither vagotomy nor atropine in any dose is capable of preventing vomiting following the introduction of large doses of tartar emetic into a loop of the duodenum. Ergotoxine does not significantly affect the emetic action of oral tartar emetic. Koppanyi (122) showed that intravenous tartar emetic became ineffective following chronic lesions in the medulla although zinc sulfate and copper sulfate orally elicited

emesis. On the other hand, oral tartar emetic was effective when apomorphine failed to elicit vomiting in a dog with a medullary lesion.

Tartar emetic apparently represents the type of emetic agent, such as digitalis and pilocarpine, which does not produce vomiting by direct application to the medulla but which fails to cause vomiting by systemic administration in animals with chronic lesions in the chemoreceptor trigger zone. As in the case of pilocarpine, it has not yet been established whether decerebration abolishes the response to tartar emetic. Digitalis, on the other hand, continues to elicit vomiting in the decerebrate but otherwise intact cat. Tartar emetic resembles pilocarpine in that both are antagonized by atropine; on the other hand, digitalis-induced vomiting is unaffected by atropine. In contrast, ergotoxine prevents the vomiting to both digitalis and pilocarpine; the effect of ergotoxine on subsequent parenteral administration of tartar emetic has not been reported.

Ipecac (Emetine and Cephaline)

According to Eggleston and Hatcher (69) the alkaloids of ipecac probably have a dual action, such that an emetic response may be elicited through a central action as well as through a reflex action from the alimentary mucosa. Presumably, these two mechanisms are capable of synergism. Eggleston (67) demonstrated that atropine did not prevent vomiting to intravenous emetine. Leake (129) showed that morphine prevents the vomiting to subcutaneous emetine in the dog. Hatcher and Weiss (101) induced vomiting by direct application of emetine to the dog medulla. They later concluded that emetine acts both on the vomiting center and peripherally in the gastrointestinal tract to cause emesis. Koppanyi (122) found that atropine introduced locally into a duodenal loop prevented the vomiting to cephaeline given by the same route although this response was not prevented by intravenous atropine. Cheymol and Quinquaud (39) were able to prevent the emetic action of emetine, administered either intravenously or by local application to the medulla, by the prior direct application of atropine to the floor of the fourth ventricle. In addition, they concluded that oral ipecac induces vomiting only by means of the absorbed emetine. Although atropine, directly applied to the medulla, inhibits the emetic action of emetine but not that of apomorphine, emetine and apomorphine act similarly in the following respects: (a) intravenous atropine fails to inhibit vomiting; (b) emesis is elicited by local application to the medulla; (c) morphine inhibits vomiting.

Nicotine

From results with animals subjected to surgical removal of the gastrointestinal tract, Eggleston and Hatcher (69) concluded that nicotine acts directly on the vomiting center. In 1916, Eggleston (67) showed that intravenous atropine reduced the incidence of vomiting to intravenous nicotine. Hatcher and Weiss (101) elicited vomiting by the direct application of nicotine to the dog medulla. They were unable to inhibit this action with atropine. This stands in contrast

to the finding of Cheymol and Quinquaud (39) that atropine applied to the floor of the fourth ventricle prevented the emetic action of intravenous nicotine. Nicotine abolishes the emetic action of intravenous but not intraperitoneal strophanthidin (103). Hatcher and Weiss (103) concluded that the action of nicotine is on afferent endings in the heart because it blocked the vomiting to intravenous digitalis without affecting the emetic action of intraperitoneal mercuric chloride. Dresbach (60) suggested, on the basis that nicotine produces vomiting and yet does not block its own action, that the impulses for emesis initiated by nicotine and the cardiac glycosides arise at different points. Hatcher and Weiss (103) reported that nicotine had but little influence on the emetic action of digitalis bodies in the *dog*. It is therefore quite surprising that these workers used the fact that nicotine inhibited digitalis-induced emesis in the *cat* as an argument for the cardiac site of emetic action of digitalis, especially since the cat and the dog respond quite similarly to the digitalis glycosides. Because of the similar pharmacological activity of lobeline and nicotine, it is often presumed that the emetic actions of these substances are identical although experimental evidence for such a similarity is lacking.

Ergot Alkaloids

Eggleston and Hatcher (69) believed that ergot acts directly on the vomiting center because the emetic response to this agent was not prevented by surgical removal of the gastrointestinal tract. Hatcher and Weiss (101), on the other hand, claimed that ergotoxine has no perceptible effect on the vomiting center directly, and that any inhibitory effect it exerted on emetic responses to other substances is due to the depression of afferent nerve endings. Koppanyi and Evans (123) failed to produce vomiting in the dog by direct application of ergotamine to the medulla, but they found that the minimal emetic intracarotid dose is smaller than the minimal effective intravenous dose. Furthermore, application of large doses of ergotamine to the medulla suppressed the vomiting responses to intravenous ergotamine as well as apomorphine and digitalis, but oral copper sulfate continued to elicit emesis. Like morphine, small but not large doses of ergotamine tartrate produced vomiting in dogs and cats. In addition, morphine prevented the vomiting response to subsequently administered ergotamine. Ergotamine was able to evoke emesis after bilateral vagotomy and spinal cord section at T-2. Cheymol and Quinquaud (38) demonstrated that ergotamine instilled into the fourth ventricle prevented the emetic responses to intravenously administered drugs but did not interfere with the emetic action of electrolytes given orally. It appears that ergotamine depressed the chemoreceptor trigger zone since a positive response to oral copper sulfate indicated that the vomiting center was active at the time that apomorphine failed to cause emesis. The depression by morphine of ergotamine-induced vomiting cannot be considered evidence for the site of emetic action of ergotamine since morphine probably depresses the medullary reticular formation which includes the vomiting center. However, it has been demonstrated recently by Wang and Glaviano (186) that intravenous Hydergine, a mixture of dihy-

drogenated ergot alkaloids, fails to cause vomiting in dogs with chronic ablation of the medullary emetic chemoreceptor trigger zone.

Atropine

Hatcher and Weiss (101) failed to induce vomiting in dogs by the direct application of atropine to the medulla although toxic doses elicited emesis in the intact animal. They claimed, furthermore, that atropine in moderate amounts has no effect on the vomiting center. Cheymol and Quinquaud (39) found that atropine applied to the medulla of the dog antagonized the emetic action of pilocarpine, emetine, nicotine and methylene blue administered intravenously, as well as that of emetine locally applied to the medulla; but it did not prevent the vomiting in response to intravenous apomorphine or to electrolytes administered orally.

Aconitine

From results with evisceration experiments, Eggleston and Hatcher (69) concluded that aconitine acts directly on the vomiting center. This belief was confirmed by Hatcher and Weiss who induced vomiting in dogs by the direct application of aconitine to the medulla. Nevertheless, these investigators believed that aconitine also acts on the heart because stellate ganglionectomy reduced its emetic effectiveness. Eggleston (67) failed to antagonize vomiting to intravenous aconitine by the prior administration of atropine. Hatcher and Weiss (101) prevented aconitine-induced emesis with ergotoxine. They considered this confirmatory evidence for a peripheral action of aconitine. On the other hand, Hatcher and Weiss (103) attributed the inhibition of aconitine-induced vomiting with nicotine to a slight depression of the vomiting center caused by the nicotine. A comparison of aconitine with apomorphine reveals a number of similarities with regard to the ability to induce vomiting as well as to pharmacological antagonisms. It would appear, therefore, that these agents have a similar mechanism of action; however, this remains to be demonstrated. Certainly, a peripheral factor in aconitine-induced emesis is far from proved.

Staphylococcus Enterotoxin

The sole definitive work on the mechanism of vomiting in response to staphylococcus enterotoxin is that of Bayliss (13). He showed that morphine prevented the vomiting and that ergotoxine severely inhibited or delayed the emetic response. On the other hand, atropine failed to antagonize the response. The direct application of enterotoxin to the medulla failed to induce vomiting, whereas the intraperitoneal injection of enterotoxin in the same animal elicited vomiting. Spinal cord section did not prevent the response but emesis rarely occurred following vagotomy. None of seven cats vomited in response to enterotoxin after decerebration. Transection of the brain stem at the level of the posterior hypothalamus abolished the enterotoxin-induced emesis while it was in progress. Extensive destruction of the obex including the nucleus solitarius invariably prevented vomiting in response to enterotoxin. The only support for

the contention of a peripheral receptor site for staphylococcus enterotoxin was the marked reduction in vomiting after vagotomy. However, these experiments were performed in acute preparations, to which the same objections apply as outlined in the section on digitalis. Although similar objections may be raised with regard to decerebration, it is noteworthy that not a single instance of vomiting to enterotoxin was reported following decerebration whereas the emetic response was not invariably prevented by vagotomy. It is possible, therefore, that the site of emetic action of enterotoxin is situated in the forebrain.

Miscellaneous Emesis-Provoking Drugs

Under this heading are considered those drugs about which only fragmentary information is available to give some hints concerning their mechanisms of emetic action. Hatcher and Weiss (101) evoked emesis in unanesthetized dogs or cats by the local application to the medulla of the following substances: brucine, picrotoxine, sodium salicylate, choline, epinephrine and histamine. These workers evoked "nausea" but not vomiting by the application of cocaine and strychnine to the medulla. However, Magnini and Bartolomei (139) were successful in evoking vomiting with strychnine by this technic. Light and Bysshe (131) obtained vomiting in one monkey with cerebral intraventricular histamine, following a considerable delay (one hour). The long latent period suggests that the histamine acted at the medullary level after diffusion through the cerebrospinal fluid. Hatcher and Weiss (101) failed to evoke vomiting in the dog with the local medullary application of the following agents: caffeine, creatine, guanidine, and thyroxine. Sadusk *et al.* (161) failed to evoke vomiting in the dog with sulfapyridine administered by this technic. Hatcher and French (99) reported that atropine antagonizes, to a variable extent, the emetic actions of intramuscular magnesium chloride, intravenous but not oral potassium arsenite, and oral hypertonic sodium chloride. They also found that nicotine interferes with the emetic action of intramuscular magnesium chloride, and is distinctly more active than atropine in antagonizing the emetic action of oral hypertonic sodium chloride. Preliminary studies by Brand *et al.* (30) on nitrogen mustard, methyl bis (β-chlorethyl) amine, have revealed that certain forebrain structures are essential to the emetic action of this drug. Intravenous nitrogen mustard failed to cause vomiting in chronic decorticate cats and furthermore, vomiting was evoked in cats by local application of nitrogen mustard to the cerebral cortex. Unlike pilocarpine-induced emesis which probably is also mediated by cerebral structures, the vomiting response to nitrogen mustard is not prevented by atropine.

CONCLUDING REMARKS

The authors of this review have attempted to reorient the conceptual meaning of the nervous mechanism of vomiting. The proposed new concept is based on the following considerations: The emetic action of a drug cannot be considered a "central" action unless the specific site of emetic stimulation is unequivocally localized within the central nervous system. There is at present no good evidence

that any drug evokes vomiting by a direct action on the vomiting center. All emetic responses, as far as is known, are mediated via reflex arcs which pass through the vomiting center regardless of whether these responses are initiated at peripheral or central receptor sites. The vomiting center is located in the reticular formation of the medulla oblongata in close functional association with neuronal loci which regulate somatic and visceral functions involved in the emetic syndrome. The vomiting center is influenced like other brain stem regulatory mechanisms by tonic excitatory and inhibitory nervous and metabolic influences.

Certain aspects of vomiting have been omitted from this review. These include such important topics as vomiting in pregnancy, radiation sickness, and therapy of vomiting. All too little is known about the processes concerned in the vomiting wich chharacterizes many clinical syndromes. Since it has become apparent that the central vomiting mechanism cannot be depressed without concurrent depression of closely associated vital functions, the most intelligent therapeutic approach to clinical vomiting is elimination of the specific cause rather than the general effect.

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