THE INHIBITION OF GASTRIC SECRETION: A REVIEW

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Throughout the following review greatest attention has been directed to studies believed to have contributed most to current concepts concerning the inhibition of gastric secretions. But current concepts change and have personal bias. Investigations omitted now may be important later when new facts will open new vistas or reopen old ones. No escape is therefore offered to the investigator from the recurring task of reviewing source literature. This review will serve its greatest usefulness as a temporary vantage point from which to visualize future profitable lines of investigation.

MODES OF ACTION OF GASTRIC SECRETORY INHIBITORS

Gastric juice is usually produced by the action of secretagogues which are brought to the gastric mucosa via the blood stream or are liberated and act locally within the stomach or in the mucosa. These secretory mechanisms simplify the problem of the mode of action of inhibitors for when they are in operation inhibition of gastric secretion may be produced in two fashions; (1) by depression of the formation of the secretagogues and (2) by depression of the action of the secretagogues. Other modes of action may exist, but these simple mechanisms offer clear and direct approaches to the study of inhibition of gastric secretion.

Depression of Formation of Secretagogues. Reduced formation of secretagogues resulting in lowered output of juice may occur during the gastric and intestinal phases of the response to a meal whenever digestion or propulsion of the food is impaired. Also during the psychic phase of the response to a meal, influences which diminish or block vagal secretory impulses may also depress formation of the secretagogues in the mucosa and so limit the amount of juice produced.

The situation can become more complicated. The application of procaine to a portion of gastric mucosa can suppress its ability to form secretagogues without abolishing its ability to form gastric juice in response to secretagogues brought to it via the blood stream from other unanesthetized portions of mucosa (123).

Depression of Action of Secretagogues. Little is known regarding the depression of action of secretagogues. The site of action is "end organ" in type, the end organs in this instance being the peptic and parietal cells of the mucosa. Conceivably, these cells could be differentially affected by inhibitors; certainly they can be so affected by stimulants. It is possible that substances may depress the action of secretagogues by blocking their access to the cell or by combining in the cell with the substances with which the secretagogues normally unite. If these sites of union could be occupied firmly enough by a substance which itself did not not produce secretion, reaction with the secretagogue could be prevented and secretion inhibited. It is not known, however, whether any of the inhibitors of gastric secretion act through such mechanisms.

General suppression of metabolism of the mucosa by nonspecific procedures, such as reduction of the supply of blood or oxygen or general cellular trauma, may depress the response of the mucosal cells to secretagogues, but in intact animals other tissues are likely to be affected before the gastric mucosa. The

inhibition of specific enzymic reactions by specific compounds offers an avenue of approach which is more likely to lead to reduced production of specific ingredients of gastric juice and to a clearer understanding of the intimate metabolism of the secreting cell. Tests have been made of the effects of inhibitors of enzymes known to be present in gastric mucosa (75, 218). The approach is new and promising. It is limited at present by lack of knowledge of the enzymic mechanisms involved in the production of gastric juice.

Thus, gastric secretion may be inhibited through any of the many avenues by means of which it is stimulated or through any of the cellular mechanisms concerned with its formation. This complex pattern forms the background upon which the action of inhibitors is superimposed. The multiplicity of possible sites of action of inhibitors within this pattern is apparent and needs to be borne in mind especially when selecting methods for their assay.

METHODS OF DETERMINING GASTRIC SECRETORY INHIBITION

The method selected for determining inhibitor action will be the method which is expected to give the most exact and precise answer to the specific question under study. As a rule, the most decisive and interpretable results are obtained when the procedures used fulfill two requirements: (1) that the mechanism of the secretory process used to assess the inhibitor be understood and, if possible, that it be simple, and (2) that the method allows quantitative appraisal of the degree of action of the inhibitor.

In general, suppression of secretion may be assayed by measuring either changes in the threshold of secretion or changes in the amount and composition of secretion. With the first, comparison is made of the degree of stimulation necessary to initiate secretion when the effects of the inhibitor are present and when they are absent. This method has been neglected. It deserves further use, particularly because it represents an aspect of the action of inhibitors concerning which little is known. The strength of inhibitors' influences is most commonly determined by measurement of changes in the amount of secretion. Both procedures require the secretion of gastric juice and for this some form of stimulation is usually necessary.

Secretory Stimulation. In Response to a Meal. The secretory response to a meal has the advantage of being physiologic but the disadvantage of being complex. No investigation of an inhibitor's action is complete, however, without study of its effect on prandial secretion. If observations are to be made on the complete response to a meal, then the food used should contribute secretagogues during the chemical phases of the response. Foods vary considerably in their ability to stimulate this phase of gastric secretion (16, 242, 289). Meat or various preparations of meat were used extensively by Pavlov and his pupils more than fifty years ago for this purpose, and have been satisfactorily employed for it ever since (201, 242). When used to test the activity of an inhibitor, the meat has usually been given as a single meal (185, 231); occasionally it has been given in small, frequently repeated feedings (46). In either instance, an adequate number of concomitant control observations, free of the inhibitor's influences,

are needed. One satisfactory procedure is to bracket the inhibitor test with control feedings done on preceding and succeeding days and to express the inhibition produced as per cent of the mean of the two control observations.

Test of the action of an inhibitor on the separate components of the response to a meal will allow more precise definition of its action and, as in the case of atropine, may aid in the elucidation of secretory mechanisms. To obtain psychic secretion for the elucidation of the mechanism of the inhibition produced by the ingestion of fat, workers in Pavlov's laboratory employed sham feeding of dogs with esophagotomies and gastrostomies (14*a* and *c*, 241*a*). Since then the procedure has been used satisfactorily many times by others (1, 80, 196). Great care must be taken to control the conditions of the tests if quantitative results are to be obtained. Nervous secretion induced by hypoglycemia after the administration of insulin (190–192) has been used for the same purpose (196). The secretory response of dogs to eating dry bread was found by Pavlov (241*b*) and Orbeli (237) to be almost entirely if not entirely due to nervous action. This simple mode of inducing nervous secretion might be very useful in studies of the action of an inhibitor and deserves further testing.

The secretion of vagally denervated pouches of dogs may be used to assess the strength of depressant influences on the humoral mechanisms of the chemical phases of the response to a meal. Secretagogues which may be liberated during psychic or nervous secretion are apparently incapable of stimulating the production of juice from mucosa upon which vagal secretory impulses are not acting (304). The Heidenhain type of pouch provides such mucosa and, when the food is placed in the appropriate organ, the gastric and intestinal phases of the response may be separated.

The humoral agent or agents involved in the gastric secretory response to a meal have not been identified with certainty (126). Gastrin and histamine are implicated (126, 154). Study of the action of inhibitors will be simplified when their exact roles in the secretory process have been identified. If gastrin plays the part in the secretory process assigned to it on the basis of accumulated knowledge, then its preparation in quantities sufficient to allow its widespread use would greatly facilitate the assignment of precise modes of action of inhibitors, as well as aid in many other physiologic and pharmocologic studies. Designation of the exact role of histamine in the secretory process would clarify the interpretation of existing data and make this substance a more precise implement in studies of gastric secretory inhibition.

In Response to Histamine. Of the secretagogues which are readily available and whose chemical composition is known, histamine has proved to be the most useful in studies of both secretion and inhibition. It has been used extensively in investigations on human beings, cats and dogs. Knowledge of its mode of action has been reviewed by Babkin (14*b* and 19*b*), Feldberg and Schilf (96) and Best and McHenry (31). It stimulates secretion from mucosa which has been deprived of its extraneous nerve supply (156, 180). At least a part of its action seems to be directly upon the secretory cells or upon structures or factors intimately associated anatomically with the secretory cells. This extreme peripheral

action enhances its usefulness in studies of inhibition. So far, factors which have inhibited gastric secretion induced by histamine have also been effective or more effective in depressing secretion stimulated by other agents. The reverse has not always been true.

Histamine stimulates the production of a highly acid gastric juice. Its predominant and most clear-cut effect is upon the parietal cells. For practical purposes, it does not stimulate the mucous cells and the extent of its action on the peptic cells seems to depend somewhat upon the conditions of the tests (35, 50, 51, 108, 258, 317). In studies of action of an inhibitor it has been employed most often as a stimulant of acid gastric secretion.

In Response to Alcohol. Stimulation of gastric secretion by alcohol has been used in the assessment of inhibitors of gastric secretion (65, 113, 172, 189, 237). As a rule the alcohol is administered as a test meal. Successive tests result in a sufficiently similar output of juice (39, 182) so that quantitative determinations of inhibitor activity may be made. The mechanism by which alcohol stimulates gastric secretion is not known. It has been suggested that it does so through the liberation of histamine (89). If this proves to be the case, then alcohol will be useful in the search for an inhibitor which will depress the liberation of histamine without affecting its secretory action.

In Response to Vagal Stimulation. The effects of some inhibitory influences have been tested on gastric secretion induced by electrical stimulation of the vagi (23, 80, 241c, 304). The experiments are difficult and as a result vagal stimulation has usually been accomplished indirectly by the administration of parasympathomimetic drugs. Acetylcholine, acetyl-β-methylcholine chloride (methacholine) and pilocarpine have been most frequently employed. The effects of the choline esters on gastric secretion have recently been reviewed by Babkin (19c) and those of pilocarpine by Hollander (148). Their actions are complex and possibly reflect the varied actions of the vagus nerve itself. Pepsin, acid and mucous secretion are separately and sometimes differently affected. Inhibitory as well as stimulatory effects may sometimes occur (114, 233, 295). These factors combine to make the use of parasympathomimetic drugs difficult in tests of an inhibitor's action. When they have to be employed, as for example in the elucidation of the mechanism of action of an inhibitor (127), satisfactory quantitative data can be obtained only if the vagaries of their actions are kept in mind and adequate numbers of control observations are made.

In Response to Spontaneous Secretion. Spontaneous secretion is usually considered to be that secretion which occurs during the interdigestive period and for which there is no evident stimulus. Secretion of this type therefore has been ascribed to the inherent ability of the mucosa to secrete and is looked upon as a physiologic consequence of life in the mucosa! A more provocative viewpoint is that this secretion is produced through mechanisms which need elucidation. Carlson (1919) reported it as the "continuous" secretion of gastric juice occurring in human beings in the absence of food and evident psychic factors (55), and Lim (1924) later called it the "basal" secretion of the stomach in dogs (200). (In review, see Babkin 15 and 19a.) No matter what the cause of spontaneous secre-

tion, it can be used for appraisal of an inhibitor's action if it is constant enough and if control tests are sufficiently reproducible. For practical purposes these requirements are fulfilled only in man and rats. In man night secretion or morning fasting secretion is usually used (177, 178) and in rats the secretion which collects in the stomach after duodenal ligation is regularly employed (100, 102, 286). Since the mechanism of spontaneous secretion is not established, the mode of action of the inhibitor may not be particularly clarified by the demonstration that it depresses the formation of this juice.

Tests of Inhibition During Intermittent and Continuous Secretion. The effects of an inhibitor may be assessed against an intermittent or continuous secretion of gastric juice. Intermittent secretion is usually induced by a single injection of histamine or other secretagogue. In practice, the complete response to each of two separate injections is usually followed; in the case of histamine the double histamine test is used, such as that first studied by Klumpp and Bowie (182). The inhibitor as a rule is given between the responses to histamine and often with the second histamine injection. The same procedure may be followed with other stimulants. The test, however, is particularly attractive with histamine because control responses to two successive injections of histamine are usually so similar (119, 168, 259). When used to appraise action of an inhibitor, however, the procedure has a number of disadvantages. Multiple tests may be necessary if the temporal characteristics of the action of the inhibitor are to be determined. Indeed, if stimulant and inhibitor are given simultaneously and the action of the inhibitor is delayed, it may be missed altogether; or, if the inhibitor is given with the first injection some remnant of its action may be present after the second. Maximal inhibition is likely to occur only if the maximal effect of the inhibitor coincides with the period of greatest stimulation by histamine. Also, during the response to a single injection of histamine the output of juice per minute increases quickly to a peak and then declines rapidly. The inhibitor, whose onset of action may differ from that of histamine, may have different depressant effects on different rates of secretion. These factors may combine to make repeated quantitative determinations difficult. Double and triple histamine tests, however, are simple and quickly performed, and once the temporal characteristics of an inhibitor's action are known, the tests can often be usefully employed.

Assay of an inhibitor's action against continuous secretion of gastric juice eliminates many of the objections to the intermittent tests. Gray, Bradley and Ivy (115) introduced the procedure. They gave histamine subcutaneously in fixed doses every ten minutes. In dogs such injections produce a plateau of secretion which is maintained almost constantly for many hours if the injections of histamine are continued (59, 115). When a steady state of secretion is developed the inhibitor is given and the injections are continued. By this method the precise temporal relations of the inhibitor's action may be noted (38, 126). The time of its onset of action and its period of maximal effect are clearly evident, and the time of release of the cells from its depressant influence is obvious if the tests are continued long enough.

Relationship of Rate of Secretion to Amount of Inhibition. With the use of histamine as a secretory stimulant, Gray, Bradley and Ivy (115) noted that the degree of inhibition produced by enterogastrone was dependent, in part at least, upon the rate of secretion at the time of testing. Uniform doses of enterogastrone produced greater inhibition at slower rates of secretion. Other investigators also used histamine as the secretory stimulant and found a similar relationship when determinations were made of the inhibition produced by extracts of gastric mucus (59). The observations indicate that if quantitative determinations of the inhibition produced by these and other preparations with similar actions are to be repeated with similar results, then the rate of secretion per unit of gastric mucosa must be the same or comparable in all tests. Code, Blackburn, Livermore and Ratke (59) have accomplished this, at least in a rough fashion, in a method they have devised for use in dogs with Heidenhain pouches. The maximal rate of secretion of acid possible from each pouch in response to histamine is first determined and then when the potency of the inhibitor is to be assessed, a rate of secretion which represents a definite proportion of the maximal rate is used. In this way similar states of physiologic activity per unit of mucosa are obtained in each dog independent of the animal's size or the size of its pouch. With uniform doses of an inhibitor, much greater depression of secretion occurred at slow rates than at fast rates of secretion. For example, at rates which were 25 per cent of the maximum the inhibition was complete, while at rates which were 50 per cent of the maximum the inhibition was only about 60 per cent complete. Indeed, the amount of inhibition produced remained the same at rates of secretion in excess of about 40 per cent of the maximum.

A relationship between degree of inhibition and rate of secretion has been demonstrated only when histamine is used as the secretory stimulant and when enterogastrone or extracts of gastric mucus are used as inhibiting agents. The action of other depressants may not be so dependent upon the rate of secretion and a different relationship might be found with other stimulants. Study of the relationship is, however, one method of gaining insight into the mechanism of inhibition and for this reason it should be an important consideration in all tests of depressant influences.

Special Features of Different Species Employed in Tests of Inhibition of Gastric Secretion. Most studies on inhibition of gastric secretion have been carried out on human beings, dogs, cats or rats. There are limitations to the results obtained with each. Their seriousness depends somewhat on the objectives of a study. Consideration of the limitations relative to each species may aid in devising experiments which give decisive answers to questions under study.

Human Beings. The major detriments in determinations of the activity of an inhibitor are the errors which may arise as a result of incomplete or contaminated collections of gastric juice from human beings. If the inhibition is calculated upon the basis of output of acid or pepsin, and this is usually the most satisfactory way to express the results, then collections of juice during the tests must be complete. Losses into the duodenum, even if they are constant during the control period, may be increased or decreased by the action of the agent under investiga-

tion and lead to false indications of stimulation or inhibition. Contamination with secretions from above the stomach also may alter values of volume and of acid. Much has been done to overcome these difficulties. Continuous removal of the juice from the stomach by constant suction and careful expectoration by the patient of all secretions collecting in the mouth have enabled investigators to carry out repeatable quantitative assays (177). Double histamine tests, secretion in response to alcohol, continuous secretion and responses to a meal have all been used. In the first three procedures the collections generally represent pure gastric juice but in the fourth the problem arises as to what to do with the samples containing food. If the food is removed the mucosa is being deprived of stimulant. If it is replaced, escape of juice into the duodenum is bound to occur and collections will be incomplete and irregular (182); then the assay must be based on changes in the concentration of pepsin or acid and not on changes in their output. One group of investigators has solved the problem, in part at least, by not starting the tests until one hour after feeding, when much of the meal has passed out of the stomach; the stomach is then emptied and continuous collections of juice are started. A plateau of secretion is obtained which probably represents the later phases of the secretory response to the meal and upon this plateau tests of inhibitor activity can be superimposed (98).

The major advantage of studies on human beings is that the action of inhibitors in this species is usually of greatest practical importance as well as interest.

Dogs. The major advantages in the use of dogs are (1) complete collections of juice are possible and (2) the animals may be studied in the unanesthetized state. Complete collections of juice are made from the entire stomach or from pouches of the stomach draining only to the exterior. The preparation of pouches from different portions of the stomach with complete nerve supply or in various stages of denervation, affords a means of precisely delineating the site of action of an inhibitor. Also, a variety of tests may be done by use of different secretory stimuli. These facts make the dog the most completely satisfactory animal now available for use in the investigation of inhibitor agents.

Cat. Studies on inhibition of gastric secretion in cats have been carried out mainly with the animal under anesthesia. This introduces a complicating factor because the anesthesia may alter the action of the inhibitor, and check determinations are difficult to make on unanesthetized members of this species. Nonetheless, cats seem to be particularly suitable for studies in which gastric secretion is produced by direct stimulation of nerves (23, 304). Anesthetized cats also give reproducible responses to histamine. These reponses may be satisfactorily employed for assay of action of gastric secretory inhibitors (150, 305).

Rat. The "Shay rat" was introduced by Shay, Komarov, Fels, Meranze, Gruenstein and Siplet (286) as a simple preparation in which gastric ulceration quickly occurred and which they believed could be readily adapted for use in assays of antacids and antiulcer agents. Their anticipations were correct for their procedure has been adopted by others and now is widely used in determinations of both antiulcer and antisecretory factors (102, 240, 257, 314). The procedure is based upon the observation that fasted, lightly anesthetized rats

submitted to pyloric ligation have a more or less continuous secretion of gastric juice which persists for many hours (100, 184, 286). Determinations of secretory inhibition are made by comparing the amount of juice obtained from a series of treated animals with that obtained from a control series.

It has been stated that the continuous secretion obtained from the rat under these circumstances is caused by nervous stimulation because it is eliminated by vagus section or atropinization and reduced by deep narcosis (286). The observations are important and need expansion for if they are substantiated the usefulness of the method will be increased further, since some specificity of action could then be ascribed to an effective inhibitor and the procedure employed in studies aimed at the mechanism of inhibition.

Final Comment Regarding Methods for Determining Secretory Inhibition. Methods employing antiulcer effects for measurement of antisecretory activity have not been discussed. Antiulcer effects may be due to factors other than secretory inhibition (267). No matter what method of testing is used, results obtained from one species cannot be applied without qualifications to another species for at present it is not clear to what extent the action of inhibitors may differ from one species to another. Quantitative studies aimed at this question should yield significant information. Likewise, it is exceedingly difficult at present to make integrated interpretations of results obtained by different methods. Quantitative comparisons of the inhibition produced by similar dosages of depressants in the various procedures now available are greatly needed.

CLASSIFICATION OF GASTRIC SECRETORY INHIBITION

The causes of gastric secretory inhibition may be classified as physiologic, pathologic or pharmacologic. They are discussed in this order herein because inhibition by pharmacologic means may involve physiologic and pathologic mechanisms.

PHYSIOLOGIC GASTRIC SECRETORY INHIBITION

Basal Secretion. Basal secretion collected from dogs and human beings has usually been that obtained at night or in the morning, after a meal the preceding noon or afternoon (149, 177, 200, 273). Some of this secretion is therefore likely to be prandial in origin. Studies are needed after more prolonged fasting. No matter what the cause of basal secretion its presence or absence may affect the response to secretagogues. Lim (200) found in dogs that the total acid output after administration of histamine represented the sum of the basal secretion plus that evoked by histamine. Dependence of the secretory response of human beings on basal rate has been observed (202). It was found that persons with low basal rates did not secrete as much or as concentrated hydrochloric acid in response to the injection of a standard dose of histamine. Studies are needed to determine whether or not the presence or absence of basal secretion affects the threshold amount of different stimuli. Is priming of the secretory mechanism advantageous when attempting to obtain maximal responses to single fixed intensities of secretory stimuli? With some drugs it is (233, 262). Conversely,

are there factors related to basal secretion which could be brought into play to reduce the response to stimulation? It has been noted casually by a number of workers with whom the author is associated that a forty-eight-hour fast reduces the responsiveness of Heidenhain pouches in dogs to standard doses of histamine, and it also has been noted that the susceptibility to stimulation varies in different types of gastric pouches. Casual observations in our laboratory, however, have been notoriously misleading in the past! Although considerable work has already been done on the factors controlling basal secretion, additional systematic studies are needed on the relation of basal secretion to the susceptibility of the mucosa to stimulation.

Acid. Pavlov (241*d*) reported that accumulation of acid in the stomach during digestion ultimately prevented the further secretion of gastric juice. His pupil, Sokolov (294), observed that in dogs with gastric and duodenal fistulae, and with Pavlov pouches and stomachs disconnected from the duodenum, inhibition of secretion from the pouch occurred when 0.5 per cent hydrochloric acid solution was introduced into the stomach or when gastric juice was introduced into the duodenum. These early observations have been confirmed and extended. The inhibition is apparently excited by contact of acid with gastric or duodenal mucosa, although in some studies, particularly some of those on human beings, the influence of these two regions could not be separated because acid was often placed in the stomach without prevention or determination of its passage into the duodenum. Also, the objective of studies in which acid was placed in the stomach was often not a search for inhibition of acid secretion but rather its neutralization or dilution. Many of these investigations therefore lack control tests and as a result, from the point of view of inhibition, their results are not decisive. When specific tests have been made of the effects of acid in the duodenum on secretion in the stomach, clear-cut results have been obtained (81, 244, 284). In normal animals and human beings acid in the duodenum is an effective inhibitor of the secretion of acid by the stomach.

Most types of gastric secretion are inhibited by acid. The acid used is not a determining factor since similar results have generally been obtained with hydrochloric, sulfuric, acetic and butyric acids (18, 94, 110, 217, 307, 308). The concentration, however, is important. Little inhibition has been noted in the stomachs of human beings and dogs until strengths of acid of 0.03 (282) and 0.08 (325) normal, respectively, are used or until the pH of the duodenal contents is less than 2.5 (244).

Fasting, continuous or basal secretion in pouches of dogs is unaffected by acid in the duodenum (244) but is somewhat diminished by instillation of acid directly in the pouch (94, 110). In human beings, acid placed in the stomach may reduce fasting secretion (28, 217) particularly if the concentration of the acid is high (282).

Psychic or nervous secretion incited by sham feeding (81) or insulin (244) and the first hour of the secretory response of a Pavlov pouch to feeding (244), which is predominantly nervous in origin, are all definitely inhibited by acid in the duodenum, the inhibition ranging from about 30 to 60 per cent. Acid introduced

into the stomach instead of the duodenum may not be as effective although lack of control tests makes it impossible to express the results quantitatively (323).

The secretory response to the ingestion of a meal in human beings is suppressed by placing acid in the duodenum (125, 284) or in the stomach (8, 217, 307), but since some of the acid may have passed into the duodenum the site of origin of the inhibition in these tests is not known. In dogs the gastric phase of the secretory response to a meal may be reduced by contact of acid with gastric mucosa (110, 325) or by acid in the duodenum (244). The intestinal phase of the response to a meal is decisively and uniformly inhibited by acid in the duodenum (81, 244, 322), but may not be affected by the presence of acid in the stomach (322). Acid in the stomach seems to be effective only in inhibiting prandial secretion when the meal and the acid are in contact with the same mucosa. For example, an acidified meal always produced less acid from a pouch of most of the stomach when the meal was placed in the pouch (322) while acid in a pouch did not much affect the secretion of that pouch when it was being stimulated by a meal in the main stomach (110). The results suggest that acid may inhibit the release of secretagogues in the mucosa.

Stimulation of gastric secretion by alcohol is inhibited in human beings by acid placed in the stomach (217) or in the duodenum (125). When the stimulus is histamine, in the dog at least, acid in the stomach (324) or in the duodenum (244) has no effect on the response. Since alcohol may cause gastric secretion by liberating histamine, there is again the implication that acid may produce some of its inhibiting effect by diminishing the formation of secretagogue in the mucosa. Some intermediate mechanism must be in action when acid in the duodenum is suppressing secretion in the stomach. Search for an inhibitor in the juices secreted as the inhibition develops is indicated. Only the circumstances under which inhibition by acid occurs have really been determined; little is known of the intimate mechanisms involved.

Nervous Inhibition of Gastric Secretion. Two means of producing gastric secretory inhibition through nervous channels are theoretically possible: 1. Inhibition could be produced by increasing the number of impulses passing peripherally to terminations whose stimulation would lead to reduced secretory output by the gastric mucosa. This would be an active process of peripheral inhibition produced by stimulation of inhibitory nerves or their terminations. 2. Inhibition could be produced by reducing the number of impulses reaching terminations of nerves whose stimulation leads to the production of gastric juice. Secretion excited through nervous channels would then be reduced and possibly the secretory reactivity of the mucosa depressed. This would be a process of inhibition produced by suppression or the blocking of secretory impulses. It could conceivably arise anywhere in a reflex arc producing gastric secretion, in the end organ of the afferent nerve or the afferent nerve itself, or centrally or peripherally in the efferent nerve or its terminations.

Stimulation of Vagus Nerve. Due to the long latent period of fifteen to sixty minutes or more preceding the secretion of gastric juice which occurred when

he stimulated the vagus nerve directly, Pavlov thought there were inhibitory as well as secretory fibers in the nerve (241*e*). This latent period has been shortened to seven to forty-two minutes (312), three to five minutes (141) and fifteen to twenty minutes (44) by modifications in the method of stimulation and control of the loss of carbon dioxide which apparently occurred in Pavlov's dogs as a result of forced artificial respiration used in his laboratory (18). While these latent periods may still be rather long, they certainly cannot be taken as indicative of secretory-inhibitory fibers in the vagus. They simply keep the question open and suggest that the problem might be attacked in another fashion. For example, weak electrical stimulation of the vagus nerves has been observed to stimulate mucous secretion (23, 312), stronger stimulation being necessary to produce acid. A search, with various types of stimuli, might reveal inhibitory effects such as a raised threshold of the acid secreting cells of the mucosa while mucous secretion was being stimulated.

Stimulation of Sympathetic Nerves. From a review of the literature and a presentation of some of his own experiments Bickel, in 1925 (33), concluded that the sympathetic nervous system provides both secretory and inhibitory fibers to the gastric mucosa. The sympathetic secretory fibers, he stated, were concerned with the secretion of the solids in the juice. It is established now that electrical stimulation of the sympathetic nerves supplying the stomach causes a secretion of a mucoid juice, particularly from the antrum, which is low in enzyme activity (23, 141). Whether or not sympathetic nerves carry gastric secretory-inhibitory fibers was not decisively settled by the evidence presented by Bickel in 1925 (33) nor has it been settled since. For example, basal gastric secretion may be reduced in volume (141) and its acidity raised (141) or lowered (23) and the secretory response to histamine may be reduced or unaffected (24) by electrical stimulation of the splanchnic nerves. The bulk of the evidence indicates that increased mucous secretion occurs during stimulation of the splanchnic nerves. The changes observed, however, have always been small and the experiments often complicated by anesthesia, acute operative procedures, degenerating nerves (315) and inductional methods of nerve stimulation. The problem needs re-exploration in healthy unanesthetized dogs with the more subtle methods of stimulation of nerves now available.

Extirpation of Nerves. 1. Vagotomy. Pavlov decisively demonstrated that bilateral vagotomy abolishes the secretory response of the stomach to sham feeding (241*f*), and that avoidance of psychic, oral and esophageal stimulation when food is placed directly in the stomach results in a delayed and reduced output of juice (241*g*). These observations were extended in his own laboratory (237) and have been amply confirmed by subsequent investigators (5, 6). Today it is agreed that vagotomy abolishes gastric secretion caused by stimulation of the vagus nerve. Does resection of the vagi do more? The gastric secretory responses of patients with peptic ulcer and of dogs with innervated pouches of the entire stomach to injections of standard doses of histamine are reduced by vagotomy (65, 236, 297). The patients also show a reduced gastric secretory response to alcohol test meals and a reduction in continuous night secretion after vagotomy

(58, 236, 297). The twenty-four-hour output of gastric juice by dogs with pouches of the entire stomach is also suppressed by section of the vagi (327, 328). These tests, however, are superimposed on somewhat abnormal conditions. Patients with peptic ulcer may be unusually resistant to the inhibitory effects of acid in the duodenum (284). Dogs with pouches of the entire stomach are denied this mechanism for the suppression of their gastric secretion, a fact which may contribute to their high twenty-four-hour output. Possibly under these conditions the mucosa may be more easily stimulated than normally. The results already cited definitely demonstrate that vagotomy reduces the responsiveness of such mucosa to histamine. But does the operation do more under these circumstances than simply restore mucosal excitability to normal? In dogs with pouches of the entire stomach it may not, for the threshold dose of histamine, when pouches of the entire stomach are vagally denervated, has been found to be the same as in intact animals (131). Decisive tests of excitability before and after vagotomy under uncomplicated conditions, for example, in dogs with the newer types of innervated gastric pouches (124, 148a, 162, 301), have apparently not been made. Orbeli (237), as long ago as 1906, felt that his tests indicated a reduced excitability of the mucosa after vagotomy. His vagotomy, however, included separation of the pouch from the stomach, and interruption of enteric continuity may have affected his results. This factor, common to studies in Heidenhain pouches, and that of lack of acid in the duodenum, common to studies of pouches of the entire stomach, would be avoided by use of the Jemerin-Hollander type of innervated pouch (124, 163, 301). The results would be more certainly quantitative than those obtained in dogs with gastric fistulas, in which the animals' gastric secretory responses have already been found to be reduced by vagotomy (7).

2. Sympathectomy. There is no doubt that anesthetization or removal of the splanchnic nerves produces little or no lasting change in the secretion of gastric juice of human beings or animals (24, 141–143, 152, 226, 290). Temporarily, spontaneous secretion of mucus may be increased and the response to sham feeding reduced. The acidity of the juice secreted in response to a meal may be increased (142, 143, 226), but the changes reported are small and the vagaries of the tests used are great. It seems safe therefore to conclude that preganglionic sympathectomy does not have significant lasting effect on gastric secretion. Quite different results might be obtained if the effects of postganglionic sympathectomy were tested. This suggestion is based on the observation, first reported in 1903 (247) and later amply substantiated (106, 198, 204, 302), that removal of the celiac and superior mesenteric ganglia in dogs is followed by a severe watery, bloody diarrhea and in some of the animals by the development of typical peptic ulcers in the stomach and duodenum. Failure to induce these findings may be due to incomplete removal of ganglia and postganglionic fibers, for in the most recent studies (198, 204), when the celiac, superior and inferior mesenteric ganglia and the nerve fibers extending along associated vessels were removed, the results were consistent. Reports have not been found of the effect of this procedure on gastric secretion in otherwsie innervated pouches. The re-

sults might show whether or not there are fibers in the sympathetic nerves supplying the stomach which can inhibit secretion or change mucosal excitability.

Central Inhibition. Bickel and Sasaki (34) observed a decisive diminution in psychic secretion induced in a dog by sham feeding when a cat was brought into the presence of the dog. The dog was enraged and frustrated and in the two experiments reported the response to sham feeding was reduced 86 and 89 per cent. Others have induced emotional upsets in human beings under hypnosis and have observed prompt inhibition of psychic secretion (146) and the secretory response to a meal (27). The dimensions of the problem have not been thoroughly charted. For example, does inhibition which involves a central nervous mechanism produce its effect only by reducing the number of impulses passing down secretory fibers of the vagus nerve or can it also alter the secretory response of the mucosa to other stimuli?

Continuity of the Enteric Plexus. Hou and Lim (149) found consistently higher basal secretory rates in pouches with intact or partially intact enteric connections to the main stomach than in pouches which had been completely separated from the stomach. Isolation of pouches from the stomach, which interrupts continuity of the enteric plexus, is a factor often lost from sight in studies of gastric secretory function. It is generally agreed that motor impulses spread along the gut through the enteric plexuses. It is not known whether the presence of food in one portion of the stomach can incite secretion in another portion simply by spread of impulses along enteric nerve plexuses in the wall of the stomach. The factor needs study in relation to the responses of different types of pouches. For example, when a pouch is separated from the stomach, continuity of the enteric plexuses as well as central vagal connections are lost. The part which the loss of enteric continuity may play in the altered responses of such a pouch has not been assessed.

Exercise. The secretory response of a Pavlov type of pouch in a dog to feeding is reduced by moderate or strenuous muscular work (42, 64, 250). Psychic secretion induced by sham feeding is also suppressed (250). Similar effects have been observed in human beings (135, 136, 276). The inhibition is accompanied by a reduction in gastric motility (134, 137) and the suppression of gastric secretion in the studies enumerated could therefore be caused by reduced vagal secretory stimulation combined with reduced liberation of secretagogues caused by the interruption of motility and digestion. Additional factors, however, may be involved. Secretion stimulated by alcohol is depressed by exercise (138); that induced by histamine has been found to be reduced (197, 276) or to be unchanged (138). A suppression of responsiveness of the mucosa itself may be involved. Thus although the origin of the inhibition is admittedly central, whether or not the efferent channel is solely vagal and its mode of action entirely one of suppression of secretory impulses is not settled. Tests in vagotomized animals seem indicated.

Fat and Enterogastrone. Complete and excellent reviews of the physiologic aspects of the inhibition of gastric secretion by fat and enterogastrone are avail-

able (126, 157, 251). Only some basic facts and considerations which might be helpful from a pharmacologic point of view need be summarized here.

Fat. Ewald and Boas (93) in 1886 were the first to show that the ingestion of fat inhibits gastric secretion. They added olive oil to a test meal and observed suppressed secretion of acid and delay in passage of the meal from the stomach. Pavlov and his pupils some years later decisively demonstrated the inhibitory action of fat by quantitative studies in dogs with pouches and various fistulae (14*a* and *c*, 241*a*).

Site of Action. The main inhibitory effect of fat on gastric secretion originates in the duodenum (241*a*). Fat confined to the stomach has little or no inhibitory action as compared to fat placed in the upper portion of the intestine (201, 211, 293). This is also true of the inhibitory effect of fat on gastric motility (254, 316)

Types of Secretion Inhibited. Nervous secretion in response to sham feeding or injection of insulin is reduced or abolished by fat in the duodenum and nervous secretion in response to a meal is delayed, suppressed and often prolonged (196, 241*a*, 283). Basal and prandial secretion is inhibited in dogs with vagotomized pouches of the entire stomach (159). Tests on secretion induced by histamine have given more variable results (2, 3, 261, 283). There is some suggestion that the variability may depend on the size of the dose of histamine in relation to the amount of fat placed in the duodenum and the period between the instillation of the fat and the administration of the histamine. Strong stimulation by histamine and pilocarpine may, after an initial delay, break through the inhibitory influence of the fat (2).

The volume of the juice, the output of acid and the concentration of pepsin in the juice are all decisively reduced by the ingestion of fat. The fall in concentration of pepsin is often striking (2, 3, 241*a*, 283).

Mechanism of Inhibition. Pavlov and his co-workers held the view that the inhibition involved a nervous mechanism, the interposition of a nervous reflex between the duodenum and the stomach (14*a*, 241*a*, 293) with the vagus nerve playing a decisive role (237). Their tests, however, did not settle the problem. Evidence accumulated during the years from 1920 to 1929 showed that a humoral factor or factors must be involved.

Lim, Ivy and McCarthy (201) demonstrated that mechanically induced gastric secretion in vagotomized stomachs which were separated from the esophagus and intestines was inhibited by fat in the duodenum. The vagus nerves did not participate in this inhibition. The participation of a humoral mechanism in the suppression of gastric secretion and gastric motility was proved by Feng, Hou and Lim (97) and Farrell and Ivy (95) when they showed that the ingestion of fat inhibited the secretion (97) and the motility (95) in a totally denervated autotransplanted pouch. The autotransplanted pouch was stimulated to secrete by the ingestion of a meal and its inhibition might have been due, in part at least, to reduced formation of secretagogues in the remaining gastro-intestinal tract. Also, in such preparations the nerve connections between the duodenum and the main stomach are usually intact and an inhibitory hormone could con-

ceivably have been liberated from this portion of the stomach by a reflex operating between it and the duodenum. That such mechanism is not necessary for the inhibition of gastric motility by fat was settled when Quigley, Zettelman and Ivy (254) found that fat introduced into the duodenum inhibits gastric motility in vagotomized pouches of the entire stomach and other more completely denervated stomach pouches, the only significant difference from intact animals being that the onset of inhibition was somewhat delayed in the denervated preparations. Separation of vagal influence from the secretory inhibitory effects of fat has not been as complete. For example, inhibition of the secretion of pepsin by fat does not occur if the vagi are severed (128). Whether or not an inhibitory reflex between the duodenum and innervated portions of the stomach is ever involved in the inhibition of the secretion of acid by fat is not settled, but the fact that the formation of gastric juice in a completely denervated pouch in response to direct mechanical stimulation is suppressed by fat establishes beyond any doubt the participation of an inhibitory agent which circulates in the blood. This agent may be enterogastrone.

Enterogastrone. Once participation of a humoral mechanism in the inhibition by fat was recognized, extracts of the bowel were soon tested and found to possess inhibitory effects (185, 186, 188). In 1930, the name "enterogastrone" was appropriately suggested by Kosaka and Lim for the active principle in these extracts (185).

Action. The effects of purified preparations of enterogastrone may be summarized as follows. In dogs, the volume, the acid output and usually the acid concentration of all of the types of secretion so far tested, from pouches of portions or all of the stomach, with nerve supply intact or in various stages of denervation, are decreased by the intravenous injection of extracts of enterogastrone. Cephalic secretion in response to sham feeding or insulin, the response to a meal and that to histamine or pilocarpine are all inhibited in dogs (115, 128, 188, 196). Continuous secretion is diminished in the rat (102, 314). Extremely large doses are apparently required to reduce secretion in human beings (98, 177, 178, 194, 246), and conflicting results have been obtained when preparations of enterogastrone have been given to anesthetized cats in which gastric juice was secreted in response to histamine (150, 305).

Differences between the effect of extracts of enterogastrone and the action of fat in the duodenum have been demonstrated. For example, preparations of enterogastrone are much more potent inhibitors of secretion induced by histamine (115) and have much less effect than fat on the secretion of pepsin. In fact, the concentration and output of pepsin are sometimes increased after injections of enterogastrone (128). Fat in the upper protion of the intestine inhibits motility in the denervated stomach (254) while enterogastrone does not inhibit the motility in a stomach with all nerve connections severed (187) or in one with its vagal nerve supply sectioned (132). Extremely large doses of enterogastrone are needed to inhibit gastric secretion of human beings (178); on the other hand fat in the duodenum is very effective (283). Enterogastrone has been given intramuscularly to human beings, and this may account for its

comparative ineffectiveness. Ultimately these differences may not be important, but they require resolution before the conclusion can be drawn that the activity found in intestinal extracts is the hormone, enterogastrone, whose existence is supported by such strong physiologic evidence. The problem seems to rest largely with the chemical purification of the active ingredient and this has proved to be a most difficult task.

Carbohydrate in the Duodenum. The stimulating prospect pharmacologically lies in the answer to the question, Can pharmacologic agents be found which will specifically excite the liberation of enterogastrone or excite an enterogastric inhibitory reflex? Drugs with this specific action have not been reported. Yet, other substances have effects similar to those of fat. As reviewed earlier, acid in the duodenum inhibits gastric secretion. The ingestion of concentrated solutions of glucose or large amounts of other carbohydrates depress the secretion and delay evacuation of the contents of the stomach of human beings (225) and dogs (80, 99, 219, 252). The effects are due to the presence of sugar in the duodenum and not to an elevated concentration of blood sugar or to the presence of sugar in the stomach (253, 285). In the dog the inhibition of motility by carbohydrate, like that by fat, is independent of the nerve supply of the stomach (285). Gastric secretion stimulated by nervous means, for example by sham feeding and by administration of insulin and pilocarpine, is decisively inhibited (80, 99, 219), while gastric secretion after the administration of histamine is less effected (80).Thus other agents besides fat can excite an enterogastric inhibitory mechanism. A pharmacologic agent with this specific action is needed.

Pregnancy and Urogastrone. Towards the end of 1939 three groups of investigators became interested simultaneously in the gastric secretory inhibitory activity of urine. Sandweiss and his co-workers became interested through their discovery that extracts of urine from pregnant women had a beneficial effect on ulcers produced in dogs by the Mann-Williamson operation (43, 270); Gray, Wieczorowski and Ivy, through their intense interest in enterogastrone and the prospect that the active ingredient in the urine might represent excreted enterogastrone (117); and Necheles and his collaborators through the possibility that hormones of the gastro-intestinal tract, like those from some other sources, might be excreted in an active form in the urine (231). From this trilogy has sprung our present knowledge of substances in urine which affect the gastro-intestinal tract.

The prevention of ulcers in Mann-Williamson dogs by urinary extracts was pursued particularly by Sandweiss and his co-workers. Such prevention was soon found to occur with administration of extracts from nonpregnant women (266, 271) and to be due, not to the inhibition of gastric secretion, since with the doses used depression was not observed (26, 269, 271) but to another factor believed responsible for the prevention and healing of the ulcers which Sandweiss has named "anthelone" (266). Gray and Ivy and their collaborators pursued particularly the factor in urine which inhibits gastric secretion. This they soon named "urogastrone" (121), and the source, action and pharmacologic possibilities of this factor are particularly pertinent to this review.

Urogastrone. Urogastrone has been found in extracts of urine from normal human beings and dogs and in the urine of pregnant women (103, 104, 117, 118, 231). It is demonstrable in the urine of patients with peptic ulcer (103), gastric cancer and pernicious anemia (101), although the amount in the urine of patients with peptic ulcer may be less than that found in the urine of normal persons (120). Purified preparations of urogastrone are the most potent inhibitors of gastric secretion so far tested. Doses of less than 1 mg. reduce the secretory response of dogs to histamine (122). Cephalic and prandial secretions are also suppressed (101). Biliary and pancreatic secretion are unaffected and no immediate changes are produced in salivary secretion (122). Gastric secretion stimulated by histamine in cats (150), guinea pigs and pigeons (101) and that which occurs after duodenal ligation in rats (102, 151) has been reported to be reduced. In man, basal secretion and that induced by histamine are suppressed by subcutaneous injections of urogastrone (320). One preparation of urogastrone given intravenously to two patients caused reactions in both and reduced the free acidity of the gastric juice in one (268). The intimate mechanism by means of which urogastrone suppresses the formation of juice in the gastric mucosa is not known. It seems to act directly and with some specificity on gastric mucosa. Once its chemical constitution is known, other related compounds will certainly be tried and it is hoped a more easily prepared substitute will be found.

The Relationship Between Urogastrone and Enterogastrone. Although the attractive prospect that urogastrone represents excreted enterogastrone was at first entertained (117), and some preliminary evidence in support of the possibility was uncovered (70), it later had to be abandoned, in part at least (120). The question of whether or not any of the gastric secretory depressant action of urinary extracts is due to excreted enterogastrone is still unsettled. It is present in the urine of dogs after gastrectomy and duodenectomy (101, 104), and although the amount in the urine is apparently reduced by enterectomy, some is still present (120). One limited conclusion at least is warranted from these results; if the small bowel is at all a source of the gastric secretory depressant activity in urine, it is not the only one (120). Lack of quantitative methods of extraction of urogastrone have hindered these investigations (120) and, as emphasized currently by Grossman (126), further clarification of this relationship awaits their development.

Urogastrone and the Endocrine Glands. Oophorectomy in dogs may reduce the amount of urogastrone in the urine (168, 169) while thyroidectomy is without effect (169). Kaulbersz, Patterson, Sandweiss and Saltzstein have made two studies of the effect of hypophysectomy on the urogastrone content of the urine. In the first (167, 168), the urine of two hypophysectomized dogs was found to contain little or no inhibitory action on gastric secretion when determined by their assay procedure. They used a double histamine test in dogs with Heidenhain pouches or gastric fistulas but they usually gave the urinary extracts with the first injection of histamine. The control, and in this case the second injection of histamine, was given three hours after the first test was completed or about four and a half hours after the injection of urogastrone (167, 168). In the sec-

ond study, they gave the urinary extracts before or after the first injection of histamine and then found a slowly developing and long acting inhibitor of gastric secretion in the extracts of urine from hypophysectomized dogs (239, 272). The relationship between urogastrone and the pituitary gland thus has again become obscured. The experience illustrates the inadequacy of the double histamine test in appraising the temporal characteristics of an inhibitor's action and suggests that it should not be used unless the time of onset and the duration of action of the inhibitor are known. Other urogastrone preparations inhibit gastric secretion for many hours. For example, in a limited series of tests Ratke and the reviewer (unpublished data) have found that the inhibitory action of urogastrone extracts of urine from pregnant women may persist for five hours or more. Use of a continuous gastric secretion enables such prolonged effects to be promptly detected. Febrile reactions were common with this particular extract. They must have occurred often in assays of other impure preparations. The problem would be tremendously abetted by the development of precise quantitative methods for the extraction of a reaction-free product.

Urogastrone and Pregnancy. The prospect of a relationship between pregnancy and the occurrence of a gastric secretory depressant in urine was one of the origins from which knowledge of urogastrone has sprung. Recently its study has been neglected, although there are ample data to more than justify its further exploration. For example, as long ago as the late twenties and early thirties it was shown that the concentrations of acid and pepsin of women were usually low during pregnancy and nearly always rose after delivery (9, 298). Administration of emmenin, which was originally an extract of human placenta, was found in 1937 to produce a slight reduction in the volume of juice obtained in response to histamine from two patients with duodenal ulcer (12). Anterior pituitary-like hormone, prepared from pregnancy urine (antuitrin-S and follutein), was given subcutaneously or intramuscularly in doses of 1000 to 5000 units to five female dogs with Pavlov pouches for five consecutive days. They produced a reduction of the volume and of the free and total acid of the juice secreted in response to test meals in four of the dogs (68, 69). Other tests, however, in which "antuitrin-S" has been given in single daily subcutaneous or intramuscular injections have given negative results in dogs and human beings (271). The inhibitory action of three proprietary gonadotropic hormone preparations on gastric secretion has recently been tested in our laboratory in dogs with Heidenhain pouches secreting at rates of more than 40 per cent of the maximum in response to repeated doses of histamine (unpublished data). When given intravenously two of the preparations showed inhibitory activity. Reports of quantitative comparisons of the twenty-four-hour output of urogastrone in the urine of pregnant and nonpregnant women have not been found in the literature. It would be interesting to know if pregnancy alters the amount. Again, lack of a quantitative procedure has no doubt blocked such studies. Despite this lack all evidence so far accumulated indicates a close association between urogastrone and the chorionic gonadotrophic hormone excreted during pregnancy. Similar methods have always been used for their extraction (70, 101, 121). That they

are not identical chemically was clearly demonstrated by early work (122), but that they are closely related chemically is decisively supported by the recent studies of Huff, Risley and Barnes (151). There is a definite possibility that the tie between these active substances stems from membership in the same family of chemical substances (151). Crude concentrates of urogastrone appear to be mucoprotein in character (122). Highly purified preparations contain carbohydrate (151). A mucopolysaccharide with protein or polypeptides attached to make a big molecule, as indicated by the work of Huff, Risley and Barnes (151), or with few or no such attachments, to make the smaller molecule indicated by the detailed study of Gray, Wieczorowski, Wells and Harris (122), would bring the purified urogastrone products isolated by these two groups of workers into the same family of compounds, that is, the mucoproteins or glycoproteins, and would orient urogastrone with the mucoproteins of chorionic origin (151, 223). But enough of such schemes. The evidence for such chemical relationship is decidedly sketchy and consideration of their prospect is justified only if it leads to extensions of knowledge in this perplexing field. A mucopolysaccharide has not been identified in urogastrone and until it has no conclusions can be drawn.

Mucus and Gastric Secretory Inhibition. Brunschwig and his co-workers, in a series of papers published during the years 1939 to 1943, reported finding a gastric secretory depressant in gastric juice of human beings and dogs (45–49, 280). The juice from patients to be tested for secretory depressant activity was secreted in response to histamine and that from dogs was obtained after feeding. Assays of action of the inhibitor were made on dogs with subtotal, wedge or Heidenhain types of gastric pouches. The pouches were stimulated every ten to forty minutes by small feedings of meat. In the first group of reports the juice to be tested was simply neutralized and then injected intravenously (45, 46, 48). Later, acid extracts were made of normal and cancerous gastric mucosa from human beings. These were neutralized, suspended and injected intravenously (45, 47). In the final studies of the series, precipitates of gastric juice were prepared by the addition of sufficient ethanol to bring the concentration to 80 per cent. The precipitates were collected, mixed with water or saline solution and, after suspending any undissolved material, were injected into the test animals (45, 49, 280).

In the earlier studies when the neutralized juice only was used, definite inhibition of secretion was produced most frequently by the injection of achlorhydric juice from patients with pernicious anemia or cancer of the stomach (45, 46, 48). About 70 to 90 per cent of these tests showed activity of an inhibitor. Results of only about 17 to 20 per cent of the tests were positive when acid gastric juice was used. When achlorhydric juice from patients without pernicious anemia or cancer of the stomach was used, 28 per cent of the tests had positive results (46). Juice from normal dogs showed no activity (48). When the alcoholic procedure was used, however, gastric secretory inhibitory activity was found much oftener in gastric pouch juice of dogs, human acid gastric juice and achlorhydric juice of patients without pernicious anemia or cancer (49). Alcoholic precipitation allowed concentration of the material and the doses of juice and pre-

cipitate used routinely favored the precipitate (1 cc. untreated juice per kilogram of body weight compared to precipitate from 10 to 30 cc. of juice given to dogs weighing 6 to 10 kg.). Yet, the finding of activity in precipitates from types of juice in which it had not been noted when untreated samples were used suggests that the alcoholic procedure may have enhanced the activity.

The qualitative methods employed in the assessment of the activity and the lack of quantitative procedures throughout the studies make comparisons difficult and possibly misleading. For the same reasons, the actual amount or concentration of the activity in the different types of juices cannot be stated. It appeared, however, to the investigators, and their data certainly support such a contention, that the inhibitory factor was present in highest concentration in the achlorhydric gastric juice of patients with pernicious anemia and carcinoma of the stomach (280). Their position in this regard was strengthened somewhat by the results of their tests for activity in their extracts of gastric mucosa and gastric cancer. About half of the extracts of the cancers or the mucosa from achlorhydric stomachs showed activity of an inhibitor while the incidence with extracts from normal mucosa was about 19 per cent. Their results definitely indicate that a gastric secretory depressant may be present at times in acid gastric juice of human beings and dogs more frequently and possibly in greater concentration in achlorhydric juice of patients with pernicious anemia or carcinoma of the stomach. Its concentration, however, is not related to the hydrogen-ion concentration of the juice (179). Caution in interpretation is necessary. Besides the lack of quantitation in the assay procedure, reactions seem to have occurred rather frequently after injections of the juice, the extracts and the precipitates. The data presented do not include precise statements of their severity or incidence. When they occurred it is highly probable that they contributed to the secretory inhibition. Nonetheless, the studies are interesting. They have opened a new approach to a difficult problem and judgment of their validity must await accumulation of more data.

Recently, a group of workers stimulated by the results obtained by Brunschwig and his collaborators reopened the search for a gastric secretory depressant in gastric juice. They first attempted to develop a more accurate method for the quantitative determination of the action of a gastric secretory inhibitor. This has been accomplished (59). Continuous secretion of gastric juice at known rates from Heidenhain pouches in response to histamine forms the background against which the strength of the inhibitor is assessed. By means of this method Blackburn and collaborators (37) determined the inhibitory activity of alcoholic precipitates of achlorhydric gastric juice from patients with pernicious anemia, of achlorhydric juice from otherwise normal individuals and of acid gastric juice from normal persons. All of the assays were done at secretory rates in excess of 40 per cent of the maximum. Doses of 10 mg. of precipitates from the achlorhydric juice of the patients with pernicious anemia produced, on the average, 71 per cent inhibition; doses of 25 mg. of the precipitates from the achlorhydric juice from otherwise normal persons were required to produce the same degree of suppression while doses of 100 mg. of precipitates from acid gastric juice

showed either less inhibitory activity or none at all. The results confirm the general findings of Brunschwig and his co-workers and, in addition, show that the active factor is capable of inhibiting secretion induced by histamine.

In a search for the source of inhibitory activity in the alcohol precipitates, commercially available gastric mucin and pepsin of hogs were tested (36). None of the preparations of pepsin so far employed have shown any inhibitory activity. A similar result was obtained by Atkinson and Ivy (12) when they gave pepsin subcutaneously. Most of the preparations of hog gastric mucin so far tested have been active. The inhibition obtained is proportional to the dose administered (265) and is present even if only the soluble material extractable from the mucin is given. Because of the rather drastic acid treatment used in the preparation of hog gastric mucin for commercial purposes, tests were carried out with fresh gastric mucus obtained immediately after killing hogs. Simple saline solutions of this material produced definite secretory inhibition and the activity was completely precipitated by 80 per cent ethanol (61). The results have prompted a search for inhibitor activity in other mucigenous secretions, particularly saliva, since some of the mucus in the stomach is no doubt derived from this source. Brunschwig and co-workers gave human saliva to dogs intravenously (45) and in some instances observed secretory suppression. Redissolved alcoholic precipitates of saliva produced some inhibition though less than that obtained with comparable amounts of fresh gastric mucus of hogs (61). Alcoholic precipitates of canine gastric juice also have been found to contain activity (205). A search has been initiated for a possible stimulant of inhibitor secretion from the gastric mucosa (60). Methacholine was tested because of its auto-inhibiting and mucous stimulating action when given repeatedly (114, 295). Juice obtained after its injection had a higher content of inhibitor activity than juice secreted in response to histamine (205).

A close association was indicated between the gastric secretory inhibitor activity and mucus, particularly in cases in which fresh mucus was scraped from the surface of the hog's stomach, diluted and the soluble portion promptly given to a dog used for assay. Treatment with alcohol precipitates the mucus and the activity accompanies the precipitate. As in the case of urogastrone, a search for a mucopolysaccharide, a mucoprotein or a closely related family of such compounds with similar activity is indicated.

But again a note of caution must be sounded. In six of the last seven reports just cited, mention is made of reactions which may accompany the intravenous injection of preparations of mucigenous materials. While the reactions do not always occur they are noted sufficiently frequently to force investigators to await clarification of the mechanism of the inhibition and the role which the reactions may play in its production before assigning even a tentative function to this type of gastric secretory inhibition. Search for the active factor may lead only to the door of the culprit producing the reactions!

Changes in Circulation. The multiple sources from which the stomach receives its supply of blood have made determinations of flow of blood to the organ difficult and have retarded the accumulation of knowledge regarding the relation of

flow of blood to gastric secretion and inhibition. Excellent studies on the isolated perfused stomach have been made and these have shown that, within wide limits, gastric secretion occurs independently of flow of blood (202*a*). For example, in these studies the pronounced vasodilatation and increased flow of blood caused by sodium nitrate was unaccompanied by stimulation of secretion and even when the blood flow was steadily diminishing the secretory response to histamine continued (202*a*). While it seems likely that pronounced vasoconstriction and diminished flow of blood may affect gastric secretion the precise contribution which they may make to the development of inhibition has not been assessed in intact unanesthetized animals. (For further data see sections on epinephrine and posterior pituitary extracts.)

PATHOLOGIC GASTRIC SECRETORY INHIBITION

During the course of pharmacologic or physiologic studies of the inhibition of gastric secretions, the injection of crude extracts or even pure compounds may produce reactions of an abnormal nature and these may cause inhibition of gastric secretion. Should their occurrence be missed, the inhibition they produce may be falsely assigned. Their importance, therefore, to investigations of gastric secretory inhibition cannot be overestimated.

Nausea. Pavlov recognized that cephalic secretion or that related to appetite was reduced in distracted or distraught dogs, and since his time it has been generally appreciated that "unappetizing" experiences may diminish psychic secretion. But few experimental studies of factors having an emotional association or content have been made (see discussion of Central Inhibition), and it has not been generally recognized that other types of gastric secretion also may be affected. The two best reports dealing specifically with the effects of nausea and vomiting on gastric secretion are those by Atkinson and Ivy (11) and Grossman, Woolley, Dutton and Ivy (129). In the first, emetic drugs were used. Their effects were tested on dogs with Pavlov pouches and patients with duodenal ulcer. Fixed doses of histamine were used as the secretory stimulus. The subcutaneous injection of 6 mg. apomorphine hydrochloride combined with 36 mg. codeine sulfate produced vomiting accompanied by a reduction in the response to histamine of about 50 per cent in volume and 30 per cent in acid output. Intravenous administration of 120 mg. of emetine hydrochloride produced vomiting and diarrhea and stopped secretion entirely; 65 mg. decreased secretion of acid by 30 per cent. It is not stated whether or not this dose induced vomiting. A combination of 15 mg. of morphine sulfate and 6 mg. of apomorphine were given by subcutaneous injection to the human beings. Although the maximal concentration of acid secreted in response to histamine was the same as in control tests, the secretion declined more rapidly and the total output was less. The complete suppression of secretion by the larger dose of emetine deserves consideration by all those testing drugs or extracts of biologic material.

In the study by Grossman and co-workers (129) nausea was induced in six dogs with vagotomized pouches of the entire stomach and two with subcutaneously translated pouches of the fundus and vagotomized pouches of the re-

mainder of their stomachs. After preliminary tests in these animals a preganglionic sympathectomy was performed, thus depriving their pouches of all ordinary connections with the central nervous system. Nausea, salivation and retching were induced by drawing a balloon over the esophageal duodenal anastomosis a number of times while the pouches were secreting continously in response to repeated injections of histamine. The procedure inhibited secretion of all of the pouches. The results indicate that a humoral agent is involved in the production of the inhibition. The humoral factor might have arisen at the site of irritation by the balloon or from some other area not included in the denervation which was excited through an esophageal reflex originating above the esophageal-duodenal anastomosis. The inhibition produced was decisive. The inhibitory potency of factors which produce nausea, vomiting and retching is impressively displayed. The potential danger of masking the visible signs of nausea, salivation, vomiting and retching by anesthesia should always be considered if assays of an inhibitor's activity are to be made in its presence.

Fever. The first thorough tests of the effect of fever on gastric secretion were made by Meyer, Cohen and Carlson in 1918 (222). Dogs with Pavlov pouches which had been fed a test meal of meat were used in all of their experiments. In some cases forced feeding was necessary. Two sets of experiments were performed. In the first, fever was induced by the intravenous injection of killed cultures of *Bacillus prodigiosus* or 10 per cent solutions of sodium nucleate. Most of the dogs had diarrhea, mucous and bloody stools and some had severe chills and prostration after the injections. Body temperatures rose from control values of 101 to 102° F. to temperatures of 103.7 to 106.1° F., and an inhibition of secretion of about 60 to 90 per cent occurred. In the second set of tests a rise in body temperature was induced by use of a fever cabinet. The body temperature was elevated from maximal control levels which were less than 102° to values ranging from about 103° to 108° F. The volume and total and free acidity of the juice were greatly reduced or secretion was abolished. Factors other than just the fever often seem to have been involved. The injection of foreign materials usually produced toxic effects besides raising the body temperature, and the animal's sojourn in the fever box may sometimes have been a distressing experience capable of inducing some central inhibitory influences. No experiments were reported in which the dogs were put in the box without inducing fever.

By means of intact, vagotomized or splanchnicectomized dogs in which gastric analysis was carried out by oral intubation, Vanzant and Snell (310) found that the intravenous injection of killed cultures of *Bacillus prodigiosus* usually produced a rise in body temperature of 4° F. or more and a marked reduction in the secretory response to histamine. These results have been extended recently in a quantitative study of the effect of purified pyrogens on gastric secretion in dogs with pouches of the entire stomach (38). The pyrogens were given while the pouches were secreting continuously in response to repeated injections of histamine. The pyrogens used were pyromen, prepared from cultures of *Pseudomonas aeruginosa*, and pyrexin, prepared from sterile exudates induced by turpentine in the pleural cavity of dogs. Both preparations produced definite gastric

secretory inhibition only when a rise in body temperature occurred. There was some association between increase of temperature and the amount of secretory inhibition, but as much inhibition was sometimes produced by increases of 1° as occurred with elevations of 3° to 4°. It is possible that the pyrogenic preparations contained mucoproteins and that some fundamental chemical reason exists for the simultaneous presence of pyrogenic activity and secretory inhibitory activity in these extracts. The mechanism of the secretory inhibition produced by pyrogens is not known. Would it affect isolated perfused gastric mucosa, the temperature of which could be kept within normal limits? In this regard, the experiments of Necheles and co-workers are pertinent. They found that subpyrogenic doses of pyrogens can cause inhibition of gastric motility in dogs (234) and may also affect secretion (228). The co-existence of secretory depressant and pyrogenic activity in the same compound or in a group of closely related compounds is worth setting up as a temporary hypothesis to be tested by further experimentation.

The most careful study of the effect of fever on gastric secretion in human beings is that of Bandes, Hollander and Bierman (22) which also includes a review of the earlier clinical literature. They tested the effect of elevations of body temperature to peaks of 102° to 106.1° F. produced by use of a fever cabinet. Whenever a high fever was induced and continued for more than three and a half hours a transitory anacidity occurred during which stimulation by alcohol was ineffective. The authors could not find a satisfactory explanation for the temporary anacidity. No matter what the mechanism involved may be, it is clear that gastric secretory inhibition often will accompany fever and this alone dictates the necessity of frequent checks of body temperature during all tests of inhibitory activity.

Anoxia. It was shown many years ago that gastric secretion was diminished in dogs when they were transported to high altitudes (25, 82). The problem has been carefully studied in dogs with Pavlov and Heidenhain pouches by Van Liere and collaborators. They have found that the volume, total acidity and pH of the juice secreted in response to a test meal of meat are reduced by exposure of the animals to partial pressures of oxygen ranging from 94 to 63 mm. of mercury (243). Dramatic changes were produced by partial pressure of 63 mm. of mercury only, which corresponds to an altitude of 28,000 feet. The basal secretion obtained fifteen to nineteen hours postprandial from Pavlov pouches was affected little by oxygen want within ranges compatible with consciousness in unacclimatized dogs (311). The results obtained for human beings have been somewhat conflicting. One group of observers has noted that degrees of anoxemia which markedly suppressed activity of the cerebral cortex and came close to paralyzing vital centers caused little or no inhibition of gastric secretion (139). Other workers have observed diminution in the volume and acidity of juice at a simulated altitude of 5000 meters which ordinarily would produce some signs of cerebral anoxia (165). The possibility of psychically induced inhibition must be borne in mind when interpreting the results of all these studies. It is clear from them, however, that anoxia must be severe before dramatic re-

ductions in gastric secretion occur, and that the gastric mucosa can secrete acid even when the amount of oxygen contained in the blood is greatly reduced.

Metabolic Disturbances. Hypercalcemia. Elevation of the concentration of calcium in the blood depresses gastric secretion. This was decisively demonstrated by Babkin, Komarov and Komarov (21) in 1940. Subsequent reports by Babkin and his pupils have extended the original findings (17, 111, 278). Hypercalcemia induced by the intravenous injection of calcium lactate, the administration of parathyroid hormone or activated ergosterol inhibits the gastric secretory response of dogs to feeding. The nervous phase is particularly affected, responses to bread, sham feeding and injections of insulin being seriously reduced (17, 21). Secretion induced by histamine may be unaffected (21) or slightly reduced (17) by parathyroid hormone and more definitely affected by injections of calcium (111). The main effect of a high concentration of calcium, however, is a depression of the nervous mechanisms of gastric secretion, possibly both centrally in the nervous system and peripherally in the nervous tissue of the stomach.

Hyperglycemia. Prolonged hyperglycemia of patients with diabetes may be accompanied by a reduction of the acidity and volume of the gastric juice. (For a concise review of the clinical literature, see references 80 and 285.) Experimentally, the intravenous injection of large quantities of glucose has been found to suppress gastric secretion in cats and dogs (80, 99, 196, 219, 235) and human beings (285). If sufficient amounts of glucose are given, all types of secretion so far tested can be affected. If 4 to 5 gm. per kilogram of body weight is injected intravenously into dogs (196), or 8 to 9 gm. per kilogram of body weight into cats (235), gastric secretion in response to histamine is reduced while lesser quantities of sugar may fail to counteract its action (80, 99). Nervous secretion provoked by sham feeding is very susceptible (80). In human beings, the intravenous injection of 10 per cent solutions of glucose can produce some inhibition of gastric secretion in response to feeding (285).

The mechanism of the inhibition has not been clarified. Hypertonicity of the solutions given may be an initiating factor, but regardless of whether or not it is the sugar or the hypertonicity of its solution which initiates the response, the inhibition itself may originate centrally in the nervous system or peripherally in the mucosa. Some preliminary experiments indicate that section of the vagus nerves may diminish the inhibition (99). These deserve extension.

Deficiency of Vitamin B Complex. Deficiency of vitamin B complex produces another situation in which carbohydrate metabolism may be disturbed and gastric secretion inhibited. As high as 50 per cent of patients with pellagra may have achlorhydria, and it may also occur in some cases of beriberi (164, 321). Webster and Armour gave a vitamin-free diet to dogs and observed first a marked diminution and later a disappearance of the secretion of gastric juice in response to sham feeding, alcohol placed in the intestine or histamine injected subcutaneously (318). The normal secretory responses of the animals to these stimuli were restored by feeding powdered yeast (318) but not by giving cod-liver oil (319). Cowgill and Gilman (63) produced a marked diminution in the response to histamine from Pavlov pouches in each of three dogs fed a diet deficient in

vitamin B complex and mainly in vitamin B_1. In one dog, a true achlorhydria developed. There was no change, however, in the secretory response of a Heidenhain pouch in a fourth dog given the same diet. Dogs with Heidenhain and Pavlov pouches which were fed another diet (Goldberger's diet number 195) known to produce black tongue failed to produce any change in the secretory response to histamine. A difference between deficiency of thiamine and niacin is indicated. It should be pointed out that these experimental studies were carried out before the components of the B complex had been decisively separated. More specific deficiencies could now be produced and these might yield interesting results. A recent study in the mouse supports this possibility. Davenport and Jones (79) have found that the excised stomachs of thiamine-deficient mice show a reduced ability to utilize pyruvate and to secrete inorganic acid.

Besides offering new approaches to the problem of gastric secretory inhibition these investigations serve to alert those studying secretory inhibition to the necessity of maintaining a high and uniform nutritional status in all animals used for assay purposes.

Miscellaneous Factors. Increased Intragastric Pressure. It has recently been shown in anesthetized dogs that when the intragastric pressure is elevated to 35 or 40 cm. of water the secretion of hydrochloric acid in response to histamine ceases (260).

Acidosis. The intravenous injection of hydrochloric or lactic acid in dogs in amounts sufficient to reduce the carbon dioxide combining power of the plasma to less than 30 volumes per 100 cc. will reduce the secretory response of the gastric mucosa to electric stimulation of vagus nerves (44). Even greater reductions in the carbon dioxide apparently must be present before secretion induced by histamine is affected (44).

Mucosal Irritation. It was demonstrated in Pavlov's laboratory that the instillation of a 95 per cent solution of alcohol into the gastric pouch of a dog results in the secretion of alkaline mucus with extremely low digestive power, accompanied by a diminution of normal secretory activity (277). It is now well known that strong irritants applied to the mucosa lead to the secretion of mucus (94, 292), but the effect which this has upon the gastric secretory response to physiologic stimulants has not often been studied. Necheles and Meyer have shown that the instillation of oil of peppermint in Heidenhain or Pavlov pouches suppresses their response to small or moderate doses of histamine but usually has little effect on their response to large doses (229). Atkinson and Ivy (12) found that frequent gastric lavages with irritating solutions of silver nitrate or sodium selenite for a month or more increased the amount of mucus secreted and reduced the secretory response of the mucosa to a meal and to histamine (12). Once again there is an association between mucus, mucoprotein and gastric secretory inhibition. Tests for an inhibitor of gastric secretion in the mucus secreted in response to irritation might aid in the elucidation of the mechanism of this interesting phenomenon.

Ionizing Radiations. It has been demonstrated repeatedly in dogs that exposure of the gastric mucosa to roentgen rays or gamma rays of radium pro-

duces a variable and temporary reduction in gastric secretion (57, 160, 163, 224, 249, 291). Careful study has established that an adequate dose of roentgen radiation always depresses the gastric secretion of human beings, frequently to the point of achlorhydria, but the effects are variable, temporary and unpredictable (238). In a recent study Simon (287) found that exposure of the mucosa of Heidenhain pouches in dogs to the radioactive isotope of phosphorus was followed, in a few days, by a decrease in the concentration of hydrochloric acid and the volume of the juice secreted by the pouches in response to histamine. All five animals which he studied eventually showed 90 per cent inhibition or more. An ulcer developed in the irradiated pouch of one animal. Simon's study indicates that the beta particles of P^{32} offer a new and potentially useful means of altering the activity of the cells of the gastric mucosa.

PHARMACOLOGIC GASTRIC SECRETORY INHIBITION

There are comparatively few papers in the literature which deal specifically with the effects of pharmacologic agents on gastric secretion. A tremendous number of tests of drug action, however, have been made. These, for the most part, have been secondary to the study of some other aspect of the secretory mechanism. Many papers containing such data have been missed. These omissions coupled with those made from ignorance make the presentation which follows a survey rather than a review.

One of the reasons for the shortage of specific pharmacologic data is lack of knowledge of the intimate details of the secretory process in the cells of the mucosa. This prevents the pharmacologist and his colleagues in the field of chemistry from selecting and then attacking a potentially vulnerable site in the chain of chemical reactions leading to the production of juice. To this restraining factor may be added the confusing array of preparations on which the action of drugs may be tested. For example, there are pouches of the entire stomach or portions of it in varying degrees of myenteric separation from the parent organ and with nerve supply intact or in different stages of central separation and peripheral degeneration. Each, therefore, presents a different possibility of altered pharmacologic sensitivity. These factors, too, make summarization of existing data difficult and generalizations from them distinctly tentative.

Cholinergic Blocking Agents. Atropine. Careful study of the action of atropine on gastric secretion commenced nearly seventy years ago and continues currently. The results of some of the investigations which have been made may be summarized as follows.

1. Basal, Continuous Fasting or Interdigestive Secretion. When loosely used these terms are synonymous. In most experiments the juice they designate is that collected after an overnight fast. Atropine greatly diminishes or abolishes this secretion in normal human beings (53, 147, 175, 220), in some patients with duodenal ulcer (161, 297) and in rats with duodenal ligation (286). When abnormal amounts of basal secretion are produced by transplanted gastric pouches in dogs (181) or by Pavlov pouches in Mann-Williamson dogs (155), atropine does not produce its usual decisive effect. The secretion of acid may be reduced

somewhat but it is not abolished (155, 181). The divergence from normal has been sufficient to prompt the suggestion that under these circumstances an abnormal mechanism may be operating.

2. Response to Meal. It has been known for many years that in dogs atropine reduces the secretory response of a Pavlov pouch to the ingestion of a meal (256). The result has been confirmed repeatedly (11, 173, 181). The output of acid is often reduced by 60 to 70 per cent and sometimes it is abolished. When the effect of atropine on the secretory response of the intact stomach to a meal is tested, as it is often in studies on human beings, complications arise, for the drug not only affects secretion but it also reduces motility. When the drug is given, the contents of the stomach may be greater and the acidity higher at various times during the course of the response to the meal, even though the output of acid by the mucosa may have been less. This plus the mixing of food with the juice and the lack of quantitative estimates of how much material passed from stomach to duodenum makes interpretations of studies on human beings in which ordinary test meals are used exceedingly difficult. As a consequence divergent results have been reported. Atropine has been found to increase (66), to inhibit moderately (206, 256, 265), or to have no effect on the secretory response of human beings to the ingestion of food. (For review, see articles cited and Altshuler [4] and Atkinson and Ivy [11].)

3. Cephalic Secretion. Workers in Pavlov's laboratory demonstrated before the turn of the century that atropine abolishes the gastric secretory response of dogs to sham feeding and to electric stimulation of the vagi (303). In dogs cephalic secretion induced by insulin is also abolished by atropine (191). In the cat atropine eliminates the secretion induced by hypoglycemic central stimulation (299) and that which follows electrical stimulation of the vagus nerve trunks or injections of eserine (306).

4. Gastric Phase. If food is placed directly in the stomach of a dog and at the same time any psychic stimulation is avoided the gastric phase of the secretory response to a meal will be induced. Sanozki (275) showed that atropine inhibited this type of secretion. Atropine will also suppress the response if the food is placed in an antral pouch of the stomach (330, 331). A Heidenhain pouch, because it is separated from the main stomach, has little or no vagal nerve supply, and the first portion of its response to the ingestion of a meal presumably is largely due to influences of secretagogues liberated in the stomach during the gastric phase and brought to the pouch by the blood stream. If enough atropine is given before a meal is eaten the response of the Heidenhain pouch is abolished; if it is given after secretion has commenced the output of acid is reduced but not completely suppressed (181). In transplanted gastric pouches which are completely denervated the response to the ingestion of a meal is also inhibited by atropine (181). Three stimulating factors, however, are involved in the secretory response of the stomach to the presence of the meal: (1) mechanical or physical contact between meal and mucosa, (2) secretagogues liberated from the food, and (3) secretagogues liberated by the mucosa (153, 154). The use of dogs with

Heidenhain pouches in tests of the effect of atropine on the gastric response to feeding does not separate the three factors.

5. Mechanical Stimulation. Lim, Ivy and McCarthy (201) have shown that atropine abolishes the secretory response of the mucosa to mechanical stimulation.

6. Secretagogues in Food. It has been known for years that extracts of meat will stimulate gastric secretion if they are given subcutaneously or intravenously (227, 331). All such crude extracts must contain histamine since it is a normal constituent of muscle, liver and lung. Kim and Ivy have been the only investigators to employ extracts free of this constituent (174). The action of their vasodepressor-free extracts, containing little or no histamine or histamine-like substances, was completely suppressed by atropine. The secretory action of those containing vasodepressor activity, owing no doubt to the presence of histamine or similar substances, was not so affected. The action of the secretagogue in extracts of meat therefore is most probably due to histamine or histamine-like compounds whose effects are resistant to atropine and another group whose action is seriously impaired by atropine. The latter group of substances may act directly on the cells of the mucosa or may act by liberating a secretagogue from the mucosa itself. Such a secretagogue might be gastrin or histamine.

"Gastrin" is the name given by Edkins to the secretagogue or secretagogues in extracts he made of pyloric mucosa (91). The original extracts undoubtedly contained histamine and this is also true of many of those used in later studies. Whether gastrin and histamine are the same or different substances is still controversial, although recent evidence substantiates the claim for their separate identity. (For a review of present status of subject, see Grossman [126].) Tests of the effect of atropine on the secretion evoked by the extracts has not aided their separation. Atropine has consistently failed to abolish the acid secretory response to crude extracts (91), partially purified extracts (173), or highly purified extracts (183). At best it only partially inhibits the secretion evoked by the extracts. Yet atropine can completely suppress the response to a meal. Thus, if gastrin participates in the response to a meal, atropine must inhibit prandial secretion by preventing the liberation of gastrin (112, 154, 181). By the same reasoning, if histamine participates in the secretory response to a meal, atropine must also prevent its liberation.

7. Intestinal Phase. When a dog with an esophageal-duodenal anastomosis and a pouch of the entire stomach is fed by mouth, secretion from the pouch represents pure intestinal phase juice. This secretion is completely abolished by adequate doses of atropine (112, 159). Again, if histamine is the humoral agent responsible for the secretion of the pouch, atropine must act by preventing its liberation.

8. Histamine. In general, atropine is not an effective inhibitor of gastric secretion induced by histamine. A relationship does exist between the size of the dose and the result, however, for larger amounts of atropine produce greater reductions of secretion with smaller doses of histamine, but atropine never seems

to erase the effects of histamine. This is particularly so in human beings. The output of acid apparently may be reduced, but the changes are small (245). Sometimes none is noted (202). Toxic effects may be present before significant inhibition occurs (11). The volume of the juice secreted by patients with duodenal ulcer may be reduced without the pH being affected (176). (For a discussion of reasons for inconsistencies in the observations on human beings, see Gray [112].)

In dogs, accumulated evidence clearly indicates that atropine does have an effect on gastric secretion stimulated by histamine. For example, the secretory response of Pavlov pouches to histamine is always reduced by atropine, the degree of inhibition ranging from insignificant to as high as 72 per cent depending upon the doses used (11, 155, 173, 200). In pouches of the entire stomach, atropine is about as effective in diminishing the response to histamine when the vagi are intact as when they are sectioned (236). Gray has made a most accurate study on the effect of varying doses of atropine in dogs with vagotomized pouches of the entire stomach (112). When the output of hydrochloric acid of the pouches was held at 5 mg. per minute by repeated injections of histamine, 0.5 mg. atropine produced 24 per cent inhibition, 1.0 mg. 37 per cent and 2.0 mg. 43 per cent. In our laboratory atropine has been found to reduce the output of hydrochloric acid of Heidenhain pouches, secreting continuously in response to histamine, by about 25 per cent (unpublished data).

The mechanism involved in the inhibiting effect of atropine on secretion induced by histamine poses two interesting questions: (1) Is some portion of the secretory response to histamine of nervous origin? (2) Is atropine, by acting directly on the secretory cells, capable of blocking some of the stimulating effects of histamine?

9. Alcohol. Doses of atropine in the customary therapeutic range will reduce but not abolish the secretory response to alcohol (113, 172). Large doses, however, may abolish the response (189, 237).

10. Thermal Trauma. Necheles, Prescott and Olson (232) have found that atropine does not affect the increased gastric secretion which follows burns.

11. Topical Application. Atropine applied directly to the mucosa may reduce its response to contact with food (83) without affecting its response to subcutaneous injections of histamine (202).

Substitutes for Atropine. In a study in which the effects of atropine, bellafoline, novatropine and methatropine in patients with duodenal ulcer were compared, Atkinson and Ivy (11) found that atropine was as effective as any of these substances in reducing the volume of juice and the output of hydrochloric acid secreted in response to histamine. In order to cause a depression of secretion, all drugs had to be given in amounts sufficient to produce dryness of the mouth, blurring of vision or fullness in the head.

Methylscopolamine has been found to be somewhat more effective than atropine in reducing the gastric secretory response of dogs to hypoglycemia (299). Popielski noticed many years ago that scopolamine hydrochloride had little or

no effect on gastric secretion induced by the subcutaneous injection of histamine (248).

Dibutyl urethane of dimethyl ethyl-β-hydroxyethyl ammonium sulfate (dibutoline or dibuline) has been found to reduce the secretory response of pouches of the entire stomach to injections of histamine and to produce a prompt but transitory suppression of the basal secretion in patients with duodenal ulcer (220). Further tests have indicated that the action of the drug on the interdigestive secretion of patients with duodenal ulcer is variable, transitory and unpredictable (195).

Quaternary Ammonium Salts. The intravenous injection of 400 to 600 mg. of tetra-ethyl-ammonium chloride has been found to reduce basal secretion of human beings by about 88 per cent and the secretory response to a continuous infusion of histamine by about 70 per cent (336). Ethyl dimethyl beta (9-xanthene carboxylate) ethyl ammonium chloride (banthine) is the first derivative of this family of compounds to have practical therapeutic possibilities for the control of gastric secretion of patients with ulcer (210). Oral and intravenous administrations of the drug result in a pronounced reduction in the continuous gastric secretion of human beings. The margin of safety between inhibitory effects and toxic manifestations seems sufficiently large to justify more thorough laboratory and clinical trial.

Hexamethonium Iodide (C6). Kay and Smith have investigated the action of this compound on gastric secretion (170). The spontaneous morning and night secretions of patients with duodenal ulcer were reduced by the intramuscular injection of 100 mg. of this drug and a similar dose inhibited the secretion induced by hypoglycemia. Secretion provoked by histamine was unaffected. Prolonged inhibition of gastric motor activity followed its administration. The pain of ulcer and hunger were relieved. Some mild side effects occurred. Further testing with this compound will be necessary before its clinical usefulness can be assessed, but the results of this preliminary investigation certainly justify its further study.

Parasympathomimetic Drugs. Gray and Ivy (114) have shown that subcutaneous injections of acetyl-β-methylcholine chloride (methacholine chloride) every ten minutes in dogs produces a pronounced stimulation of gastric secretion which reaches a peak in about one to two hours and thereafter declines, often to extremely low levels. The decline can be hastened by giving larger doses from the outset or by administration of a large dose at the peak of the response (114, 295). Similar results have been obtained with acetylcholine (114). The effect may be described as "auto-inhibition". If the parasympathomimetic drugs are given in stimulating doses during a secretory response to histamine or if histamine is given while they are stimulating secretion, an augmentation of secretion is observed (114, 233, 262, 295). If, on the other hand, histamine is given during the period of auto-inhibition produced by the parasympathomimetic drug, its effects are greatly reduced (114). Likewise, large doses of methacholine chloride will inhibit the continuous secretion of gastric juice produced by repeated in-

jections of histamine (114). Atropine abolishes both the excitatory and the inhibitory actions of methacholine (114).

The means by which the auto-inhibitory state is produced is not known. Does it mean that there are inhibitory influences which may be excited through the peripheral cholinergic mechanism? In anesthetized cats, acetylcholine has not been found to produce secretion of hydrochloric acid but only a scanty flow of mucus (306). Injection of the compound into the arteries supplying the stomachs of dogs often will produce mucous secretion and little or no acid (296, 313). The effect is similar to that produced by weak electrical stimulation of the vagus nerves, which has been observed to stimulate mucous secretion (23, 312). There is again the interesting possibility of the simultaneous occurrence of mucous secretion with acid inhibition. An inhibitory state may also occur in the mucosa after injections of histamine. Alley (1) found that in dogs the response to sham feeding was reduced when such feeding was carried out immediately after cessation of secretion provoked by histamine. Tests have not been made to determine whether other forms of secretion induced by nervous mechanisms are affected by a previous response of the mucosa to histamine.

Comment. Complete atropinization is sometimes considered the equivalent of vagotomy. More, however, is accomplished than when the nerves are sectioned. After vagotomy, peripheral cholinergic nervous elements remain in the wall of the stomach and atropine can block whatever effects they are capable of producing. Also, it is possible that atropine, particularly in large doses, may directly depress the secretory activity of the mucosal cells. The decisive and well-established action of atropine is, however, to block cholinergic influences at the mucosal cells, so that impulses reaching the peripheral cholinergic system via parasympathetic nerve trunks and any which may arise locally in the wall of the stomach are prevented from having their effect on the secretory cells.

Sympathomimetic Drugs. Epinephrine. The overwhelming impression derived from a review of literature dealing with the effect of epinephrine on gastric secretion is that it does not have an important action on the secretory process. In some tests it increased gastric secretion, in others it decreased secretion and in still others it had no effect (references to work on human beings: 140, 207, 226, 265, 279, 300, 329; dogs: 145, 158, 263, 288; cats: 23, 24, 199). Most changes reported have been small. A systematic search has not been made of its effect on the excitability of the mucosa to other stimuli but such changes as have been observed when it has been given with other stimuli have been small and variable.

Adrenergic Blocking Agents. Ergotamine. As might be expected from the results obtained with epinephrine, ergotamine has not been found to have much effect on gastric secretion. Most of the tests have been carried out on human beings (11, 62, 144, 166). The drug has been given subcutaneously (11, 62, 144) and intravenously (166) and its effects tested on secretion induced by test meals (11, 62, 144) or by injections of histamine (11). The results have been conflicting. At times the experiments have been complicated by the patient's nausea, and this plus the inaccuracies inherent in fractional gastric analysis of human

beings leaves doubt as to whether ergotamine has any action on the types of secretion tested in these experiments. In experiments in animals it has been found to reduce the secretion of mucus produced in the stomach by the stimulation of partially degenerated splanchnic nerves (23). On theoretical grounds ergotamine would not be expected to have much effect on the normal secretory process in which a minor role has certainly been assigned to the sympathetic nerves. Under conditions in which the effects of sympathetic nerves were prominent or unopposed in the stomach this family of drugs might have some action.

Mucosal Anesthesia. Zeljony and Savich (330) demonstrated that the secretion produced in the stomach by mechanical or chemical stimulation of a pouch of the antral region is abolished by anesthetization of the pyloric mucosa with a solution of cocaine. Others have tested the effect of solutions of procaine hydrochloride on mechanical stimulation of gastric secretion (201). Gregory and Ivy (123) have expanded the findings, with the use of mucosal anesthesia as a means of elucidating the mechanism of local mechanical and chemical stimulation of gastric secretion. They used dogs with transplanted fundic pouches and pouches of the remaining main portion of the stomach. Anesthetization of the main pouch by perfusion with procaine solutions suppressed completely its secretory response to mechanical stimulation and to chemical stimulation by secretagogues of liver. If the secretagogues were placed in the unanesthetized stomach or intestine, the anesthetized transplanted pouch responded by secreting gastric juice. It seems most probable that the secretagogues of liver act by liberating an agent in the mucosa which may stimulate secretion locally and certainly can stimulate secretion when carried via the blood to other portions of gastric mucosa. Anesthetization of the mucosa abolishes its release.

Uvnäs (304) has found that in cats a secretagogue is liberated from the pyloric region into the blood during electrical stimulation of the vagus nerves and that its liberation is prevented by local cocainization of the pyloric mucosa.

It may be concluded that local anesthetization of the gastric mucosa by cocaine or procaine hydrochloride prevents the mucosa from liberating its secretagogue or secretagogues during mechanical, chemical (meat secretagogues) or nervous stimulation. The drugs are therefore important and effective inhibitors of a specific step in the secretory process.

Antihistaminic Agents. Considerable evidence has accumulated indicating that histamine participates normally in the mechanism of stimulation of gastric secretion. (For review, see 126.) Agents which destroy histamine or block its action offer, therefore, a potential means of inhibiting gastric secretion.

Enzymic Agents. Diamine Oxidase (Histaminase). In 1929 and 1930 Best and McHenry (29, 30) demonstrated the presence of an enzyme in various tissues which inactivates histamine. Zeller and associates have extended their findings and have shown that the enzyme deaminates a whole series of diamines by oxidation and have hence suggested the name "diamine oxidase" (92, 332, 333, 335). Soon after the enzyme was discovered its effect on gastric secretion was tested. The original preparations reacted slowly with histamine so that destruction of significant amounts of histamine often required some hours (30). The

parenteral administration of these products was found to be without effect on secretion stimulated by injections of histamine (10, 13, 230) or the ingestion of a meal of meat (230). Some preparations of diamine oxidase have produced toxic symptoms when injected intravenously into dogs, and these inhibited gastric secretion even when the enzyme had been inactivated (264). Recently, purified preparations have shown inhibitory action when assessed against secretion induced by feeding or by injections of histamine, methacholine chloride or the urethane of beta-methylcholine chloride (urecholine) (127). No general toxic symptoms were produced by their injection although some of the preparations contained a potent vasopressor substance. It is not known whether or not the inhibition of gastric secretion produced by these preparations was due to diamine oxidase or some other constituent.

It should be emphasized that from a physiologic point of view none of these preparations would be expected to be effective if given by mouth. Best and McHenry (32) and Zeller and Schär (333, 334) have pointed out on a number of occasions that if the enzyme is taken by mouth it would be destroyed by the acid pH of normal gastric juice and that, if it escaped the acidity of the gastric contents, its emzymic properties would be abolished promptly by both pepsin and trypsin. Some of the enzyme might escape these digestive factors but under ordinary circumstances this would be a small proportion indeed of the total ingested.

Histamine Blocking Agents (Synthetic Antihistaminics). Soon after the antihistaminic action of some of the Fourneau series of compounds had been discovered by Bovet and Staub (41), Loew and Chickering (209) demonstrated that Fourneau 929 did not inhibit gastric secretion induced in dogs by the injection of histamine. The observation was soon extended to Fourneau 1571, the other active member of this series, and to tests with other types of secretory stimulants (40, 52, 130). In the main the compounds did not show specific antihistaminic effects on gastric secretion. Results with more recent members have been just as disappointing (105, 133, 150, 171, 274, 281). In fact in some instances the presence of the antihistaminic agent has resulted in an increase in secretion (209, 326). When reduction of secretion has occurred (130, 193, 214–216), it may possibly have resulted from the feeble atropine-like action known to be associated with many antihistaminic compounds (208). It may be concluded that the synthetic antihistaminic compounds so far tested do not block the action of histamine on the cells of the gastric mucosa. Study of the pharmacologic problem involved presents interesting possibilities for advancement of knowledge regarding the action of histamine. What is the nature of the difference between histamine's combination with a smooth muscle cell and a parietal cell?

Posterior Pituitary Extracts. It was first reported, on the basis of rather sketchy tests, that the subcutaneous injection of posterior pituitary preparations reduced the gastric secretion of patients with various disorders (56, 90, 107). Dodds and his co-workers have made a detailed study of the effects of large doses of posterior pituitary preparations on gastric mucosa and gastric secretion in animals. They have found that a single large subcutaneous injection of posterior pituitary

extract produces temporary collapse, bloody diarrhea and loss of appetite in rabbits. If the animals are examined in the early stages of the reaction, acute gastritis, confined to the acid-secreting area of the mucosa, is found (85, 87). Repeated oral or subcutaneous administration of the extracts was found to lead to production of single punched-out ulcers in the acid-bearing area of the stomach (86) which could be prevented by the continuous administration of sodium bicarbonate (84). The gastrotoxic factor was found to be associated with the pressor and not the oxytoxic fractions of the extracts (85). When the effects of the extracts on gastric secretion were tested, pronounced inhibition was observed (71). The tests were made in anesthetized rabbits and cats secreting in response to histamine and in unanesthetized cats stimulated by injections of pilocarpine or insulin or by sham feeding. Pancreatic secretion was affected almost as dramatically as gastric secretion.

In an earlier study on dogs, Atkinson and Ivy (12) did not observe changes in the gastric secretory response of two dogs with Pavlov pouches to a meal by daily subcutaneous injections of 1 cc. of pituitrin or pitressin. Much larger doses have been used by Dodds and his co-workers to produce acute lesions in rabbits (87). Gray, Harris and Wieczorowski (116) have confirmed the finding that intravenous injection of posterior pituitary extract inhibits gastric secretion. They used a double histamine test in dogs with pouches of the entire stomach and found that 4 units of pituitrin produced about as much inhibition as 3 mg. of urogastrone (50 to 60 per cent).

The mechanism of the inhibition has not been determined although experiments by Dodds and his co-workers indicate that it may be related to reduced flow of blood through the stomach produced by the extracts (72). Further study of the secretory inhibition produced by posterior pituitary extracts is needed.

Antimalarial Drugs. Quinine and Quinacrine. Babkin and Karp (20) have found that 0.2 to 0.3 gm. of quinine or 0.05 to 0.1 gm. of quinacrine given intravenously to dogs weighing 8 to 15 kg. inhibits the secretion of gastric juice induced by electrical stimulation of the vagi, while secretion in response to histamine is unaffected. The doses of the drugs used were large and presumably had to be to produce their effect on secretion.

Biguanide Compounds. Burn and Vane (54) have tested the effect of paludrine (N_1-p-chlorophenyl-N_5-isopropyl-biguanide acetate) and a related series of compounds on gastric secretion induced by injections of histamine in anesthetized cats. Paludrine and a similar compound, in which the isopropyl group of paludrine is replaced by a methyl group, were found to have definite inhibitory action on gastric secretion. Subsequent study on human beings has shown that 0.9 to 1.0 gm. of paludrine by mouth will reduce significantly the concentration of acid in juice secreted in response to a test meal of gruel (88, 309). When given intravenously the drug has had no effect on secretion induced by histamine (88). Further work will be necessary to determine the mode of action of paludrine and other antimalarial drugs. The preliminary results indicate that these drugs may be useful in controlling certain types of secretion.

Antienzymic Agents. Urease Inhibitors. Urease is present in gastric mucosa

(212, 213) and in gastric juice (221). The activity of urease in the gastric mucosa of human beings is roughly proportional to its ability to secrete acid (109), and in dogs and human beings its maximum concentration occurs in the region of the parietal cells (109, 203). Mann and Mann (218) have made a systematic study of the effect of inhibitors of urease on gastric secretion provoked by histamine in dogs (218). Solutions of the inhibitors were applied directly to the mucosa, allowed to remain there for a few minutes only and then histamine was given. The heavy metals known to inhibit the enzyme reduced the secretion of acid; those which did not have an effect on the enzyme likewise did not have an effect on secretion. Hydrogen peroxide, quinone, brilliant green and crystal violet, all of which inhibit the enzyme, also lowered the acidity of the juice. The result with hydrogen peroxide confirms earlier observations of Culmer, Atkinson and Ivy (67) who found that lavage of gastric mucosa with 0.5 to 3 per cent solutions of hydrogen peroxide in dogs consistently reduced the acidity of the juice secreted in response to histamine. Less consistent inhibition was obtained when gastric secretion was induced by feeding. The results for human beings also were variable. The secretion of mucus was usually greatly increased and irritation of the mucosa with the strong solutions may have played a part in the inhibition. Mann and Mann, however, used weaker solutions and observed some inhibition. They have pointed out that although their results may be explained on the basis of a temporary inactivation of urease, other enzymes in the gastric mucosa may have been affected.

Carbonic Anhydrase Inhibitors. The enzyme, carbonic anhydrase, has been demonstrated in the gastric mucosa of rats, cats and dogs (73, 74, 78). The possible role of this enzyme in the production of gastric juice has been discussed recently by Davenport (77). He has demonstrated that the oral administration of sodium thiocyanate to dogs results in a diminution in the rate of secretion and the concentration of acid in juice secreted in response to histamine (75). Intravenous injection of thiocyanate has been found to produce even more pronounced inhibition of gastric secretion in anesthetized dogs (255). Sulfanilamide, which is another inhibitor of carbonic anhydrase, has also been tested and has been found to reduce gastric secretion in dogs (76).

Whether or not the substances tested in these studies produced their effects by inhibiting the enzyme against which they were theoretically directed is not settled. In the end it may be unimportant, for through them a new and provocative approach to the investigation of gastric secretory inhibition has been opened.

CONCLUSIONS

An entirely satisfactory inhibitor of gastric secretion is not available today. However, a number of promising possibilities are being studied by different workers and new avenues of approach to this old problem have been opened recently. If opportunity to challenge these potentialities continues uninterrupted, a specific inhibitor suitable for investigative and therapeutic use should be found.

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