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GASTRIC ELECTRICAL ACTIVITY:
THE EFFECTS OF VAGAL SECTION AND VAGAL STIMULATION

by

MORTON LAWRENCE DORAN

M.D., University of Toronto, 1964

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in the Department

of

Surgery

We accept this thesis as conforming to the

required standard

The University of British Columbia

April, 1973

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Department of Surgery

The University of British Columbia
Vancouver 8, Canada

Date Apr. 24th, 1973

ABSTRACT

The current enthusiasm for vagotomy as treatment for peptic ulcer disease has been dampened by several problems, the most serious of which is recurrent ulceration. As this is due in most instances to incomplete vagal section, it is clear that the development of a reliable method to assess completeness of vagotomy during the course of surgery is an essential step toward reducing the 10-15% incidence of recurrent ulcer.

The problem has been approached by studying some of the gastric effects of vagal stimulation during operation. These include changes in intragastric pressure, acid secretion, and electrical activity. The investigation as outlined in this thesis was aimed at developing a reliable, reproducible intra-operative method for assessing the completeness of vagotomy. The plan of the experiment was essentially twofold:

(i) to determine whether <u>complete</u> vagotomy would alter the gastric electrical activity in some reproducible manner such as would indicate that <u>all</u> vagal connections had been severed;

(ii) to divide one vagus nerve at the level of the esophageal hiatus, assess the effect on electrical activity of stimulation of its distal or peripheral end, and then stimulate the central end with view to eliciting a response in the electrical activity via reflex pathways through the brainstem, vagal nuclei, and along the remaining intact efferent vagal fibres;

these remaining fibres would then be divided, central stimulation of either vagal trunk repeated, and presumably the previously observed "characteristic" response of the gastric electrical activity would no longer be obtained, indicating complete division of all vagal fibres.

Vago-vagal reflex responses to afferent vagal stimulation have been documented with respect to influence on both gastric tone and secretion. One may reasonably expect to be able to demonstrate the existence of a vago-vagal reflex pathway whereby one might alter gastric electrical activity by central or reflex stimulation of the afferent vagal fibres.

Gastric electrical activity has been recorded, and the effects of vagal section on this electrical activity have been assessed. The reduction in the frequency of the basic electrical rhythm (BER) observed following complete vagotomy, though of significance statistically, was found to be caused as well by other non-related factors, and was in any case of such a low order as to be of limited value in assessing any individual case. It could therefore not be considered indicative of complete vagal section. The disorganization of the BER observed following vagotomy was both temporary and inconsistent, and could not be interpreted as pathognomonic of complete vagotomy.

The observations recorded during electrical stimulation of afferent vagal fibres have demonstrated the existence of a

vago-vagal reflex pathway whereby gastric electrical and motor activity can be modified by afferent vagal stimulation. These effects are presumably conveyed via pathways through the central nervous system and along the intact efferent vagal fibres. The effects on gastric electrical activity are neither consistent nor reproducible, whereas the effects on gastric motor activity appear to be considerably more reliable. In the light of these observations, it would seem more appropriate to study the changes in the contractile force of gastrointestinal smooth muscle subsequent to afferent vagal stimulation in the search for a method to assess completeness of vagotomy during the course of surgery. The development of such a test will be a major factor in preventing this form of treatment from falling into disrepute because of a continued high rate of recurrent ulceration.

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ACKNOWLEDGEMENTS

Many people have shown interest and concern in the preparation and day-to-day work of this project, and their contributions have been both valuable and much appreciated. Dr. R.C. Harrison's enthusiasm and perseverance in the search for a reliable intraoperative method to assess the completeness of vagotomy has been the major stimulus in initiating this investigation. His support and encouragement throughout the course of the study, despite criticism from skeptics, has and will continue to ensure that even though the search for such a test has not concluded, the problem will not be allowed to remain unanswered. My appreciation is also extended to Mr. Jan Van Den Broek and his staff, who have greatly facilitated the experimental work of this project by operating a very efficient, congenial animal research laboratory. In any investigation of this type, there is perhaps one person without whom the project could not function. I am therefore particularly indebted to Mr. Ken Pope for his continued help in solving the many technical problems encountered throughout the study, including the design and maintenance of the stimulating and recording equipment so indispensable to this type of investigation.

CHAPTER ONE

INTRODUCTION

The current enthusiasm for vagotomy with an associated drainage procedure as treatment for peptic ulcer disease has been dampened by several problems, the most serious of which is recurrent ulceration. This is due in most instances to incomplete interruption of the parasympathetic innervation to the stomach. When one considers that the results obtained from post-operative assessment of completeness of vagotomy as measured by insulin-induced hypoglycemia or maximum stimulated acid secretion are often equivocal,[70] and that these tests are limited in value by virtue of their being post-operative, it is clear that the development of a reliable, reproducible method for determining the completeness of vagotomy during the course of surgery is an essential step toward reducing the 10-15% incidence of recurrent ulceration.

This problem has been approached by studying some of the gastric responses to vagal stimulation during operation. These include changes in intragastric pressure, acid secretion, and electrical activity.

SECTION I. INTRAGASTRIC PRESSURE

The electrical stimulation test as described by Burge,[23, 24] in which platinum electrodes applied to the esophagus effect vagal stimulation, depends on eliciting an increase in intragastric pressure upon stimulation of intact efferent vagal

motor fibres, and reduction of this pressure when continuity of these fibres has been interrupted. This test depends on the premise that stimulation of efferent vagal motor fibres to the stomach causes an increase in intragastric pressure. Notwithstanding the fact that this method is cumbersome in its application, the premise upon which it is based is at variance with the observations of Harper,[59] who noted a decrease in intragastric pressure subsequent to stimulation of vagal efferents. In both instances, the observations were initially recorded in cats, using similar but not identical electrical stimulation characteristics of voltage, impulse duration, and impulse frequency. The discrepancy in these observations may be accounted for in part by Martinson's series of investigations[66, 81-85] which have demonstrated in cats the existence of both excitatory and inhibitory vagal efferents, differentiated by graded vagal stimulation; "low threshold" excitatory fibres responding to short duration impulses, causing increased tone and contractility, and "high threshold" inhibitory fibres responding to longer duration impulses, causing a decrease in intraluminal pressure and reduction in contractile force predominantly in the corpus and fundus, but not in the antrum. The point to be made here is that the results may differ, depending on the stimulus parameters and at what location intragastric pressure is measured. These factors would tend to lend somewhat less credence to the validity and reliability of the electrical stimulation test as described by Burge.

The determination of the effect of efferent motor nerve stimulation may also be influenced by the fact that most of the vagal fibres at the level of the diaphragm are afferent fibres, and that the relatively few efferent fibres which are stimulated, though having an effect on smooth muscle tonus, may in fact have little or no effect on secretion. Investigation in cats[1] has demonstrated that at the diaphragmatic level, 90% of the 31,000 vagal fibres are small, myelinated afferent fibres, 2-4 u in diameter. The remaining 10% of fibres are larger diameter efferents with their cell bodies in the central nervous system; these efferent fibres synapse directly with neurones of the myenteric plexuses. Hence there is an enormous discrepancy between the number of nerve cells in the myenteric plexuses (20-30 million) and the 3,000 vagal efferent fibres. Similar studies in rabbits[56] reveal a comparably low percentage of vagal fibres at the diaphragmatic level which are efferent motor in function.

SECTION II. ACID SECRETION

A second approach to this problem entails intraoperative pH mapping of the gastric mucosa, and assessing completeness of vagotomy by demonstrating alkalinity of the entire parietal cell mass. This method has merit in that it can accurately indicate complete denervation of the parietal cells. However, it deals with only one of the two major mechanisms of vagal influence on gastric secretion, specifically the vagal excitation of the

parietal cell mass. It does not indicate vagal denervation of the antrum, and therefore does not rule out the possible delayed release of antral gastrin.[27]

Griffith and his colleagues have clearly demonstrated the concept of segmental innervation of the stomach by combining electrical stimulation and neutral red dye to visualize the extent of gastric secretion.[58, 59] They have demonstrated a progressively decreasing overlap of innervation as one stimulates vagal fibres successively from the level of the esophageal plexus to that of the terminal gastric branches. Griffith has demonstrated that stimulation of one vagal fibre cannot influence the entire gastric mucosa via connections within Meissner's submucosalplexus, but that stimulation of any fibre which innervates the antrum can, by way of antral release of gastrin, cause a delayed, generalized secretion of the parietal cell mucosa. Even though a vagally denervated parietal cell mass would be less responsive to endogenous gastrin, with reduced acid secretion, pH mapping would not necessarily indicate that the antrum had been denervated. Failure to achieve reduction in basal acid output after a selective vagotomy may be due to vagal innervation via the undisturbed hepatic branch of the anterior vagal trunk, with fibres reaching the antrum along the course of the right gastric artery. Alternatively, innervation may occur via parasympathetic fibres emerging with thoracic dorsal spinal roots. Hypersecretion following selective vagotomy may be attributed to this circuitous antral innervation with the subsequent delayed antral release of gastrin; the

delayed effect of this gastrin on the parietal cells may not be detected by intraoperative pH mapping.

There are other factors to be considered in pH mapping of the gastric mucosa. The acid-alkaline junction is not always a precisely defined zone of transition, but may in fact extend across a distance of one centimetre. The antrum may not be uniformly alkaline, rendering it difficult for the pH assay to accurately demarcate the extent of antral mucosa. There is an inverse relationship between the size of the antrum and that of the parietal cell mass; a small antrum is usually to be found in a patient with an uncomplicated duodenal ulcer and high acid production, as compared with a large alkaline area in a patient with either a gastric ulcer or a duodenal ulcer complicated by pyloric obstruction.[27] Incomplete denervation of the antrum (or incomplete removal of antral mucosa during gastrectomy) will therefore result in continued gastrin production, with the risk of recurrent ulceration. This factor will be of greater significance in patients with duodenal ulcer than in those with an uncomplicated gastric ulcer, as the latter have less gastrin production and generally a small, atrophied parietal cell mass.

The concept of segmental innervation may account for the anatomically incomplete but "adequate" vagotomy.[99] A small, delayed response to insulin hypoglycemia, though indicating a technically incomplete vagotomy, may in fact be due to an intact terminal gastric branch to the fundus, with minimal risk

of recurrent ulceration. On the other hand, a pronounced, early response to insulin hypoglycemia would indicate an incomplete vagotomy with inadequate protection against recurrent ulceration.

Notwithstanding the criticism levied against the pH mapping technique in assessing the completeness of vagotomy, this tool can be of significant value in upgrading the surgical treatment of peptic ulcer disease, and much can be said in its defence. Clinical studies suggest there is a high incidence of incomplete antrectomy in patients who develop recurrent ulceration following gastrectomy with or without associated vagotomy.[49] This group of patients shows a persistent elevation of acid secretion which may be due either to an incomplete vagotomy, or to residual antral tissue with continued gastrin production. Drs. R.C. Harrison and J.L. Stoller, in the Department of Surgery at the Vancouver General Hospital, have evaluated the effects on acid secretion (from Heidenhain pouches in dogs) that have resulted from the deliberate performance of an incomplete antrectomy associated with vagotomy. Their results indicate that even a small portion of residual antrum left in situ significantly alters the secretion from such a preparation, and suggest that if antrectomy is to be performed in association with vagotomy, it must be complete. In order to facilitate demarcation of the proximal extent of the antrum, they have devised a method whereby following mild histamine stimulation, the acid-alkaline junction can be identified by means of a

wandering pH sensitive electrode introduced perorally into the stomach. Best results are likely to be obtained in duodenal ulcer patients with active parietal cell activity, though the alkaline area in gastric ulcer patients with low acid secretion can be adequately mapped as well. In interpretation of these results, one must recognize that the terms "alkaline area" and "antrum" are not necessarily synonymous. Though "antrum" is intended to designate the gastrin producing area of the stomach, the alkaline area in a patient with significant gastritis may well have extended into an area previously occupied by active parietal cells. This newly established alkaline area presumably does not produce gastrin. Coupled with the observation that the antrum is not necessarily uniformly alkaline, the pH assay may not always indicate precisely how much stomach to resect in order to ensure the complete removal of all antral tissue (and thus remove the source of gastrin), without extending the resection too far proximally. Moreover, the pH assay cannot solve the problem which may arise from gastrin release from more distal sites in the intestinal tract, though the significance of this small amount of gastrin as a cause of persistent hypersecretion is as yet undetermined.

SECTION III. GASTRIC ELECTRICAL ACTIVITY

A third approach to the problem of developing an intraoperative test to assess completeness of vagotomy has been to study the electrical activity of the stomach; more specifically,

to study changes in electrical activity before and after vagotomy, and the effect of both afferent (reflex) and efferent vagal stimulation on this electrical activity.

A. History

Several investigations serve as landmarks of historical interest in the development of this approach. The origin and control of gastric peristalsis has been studied by various techniques, including direct visualization of the stomach, intragastric pressure recording, and visualization by means of contrast media and fluoroscopy. With the development of the concept of the cardiac pacemaker, the stomach was examined for the presence of a similar mechanism. Early investigation suggested that pacemaker-like tissue in the lesser curve ganglia, in neuromuscular tissue at the gastroesophageal junction,[4] or in the well-developed lesser curve myenteric plexus may be responsible for coordinating gastric peristalsis.[110] In 1922, Alvarez[3] described a slow, rhythmic electrical activity occurring in gastric muscle. These "action currents" were recorded constantly in the gastrointestinal tract, even in the absence of obvious contractile activity.[4, 43] Using isolated muscle strips from various areas of the stomach, he demonstrated that the frequency of the rhythmic activity was highest in the proximal stomach, and lowest in the distal stomach. He suggested that a pacemaker was present in the region of the cardia,[4] and that these electrical currents were propagated aborally along the stomach. Alvarez suggested that these spreading currents may

coordinate mechanical and chemical functions of the stomach which had previously been attributed to hormones and neural pathways. On the basis of these observations, Alvarez introduced the "electroenterogram" to the study of gastrointestinal motility and its electrical counterpart. Though he was not able to differentiate between what are now termed the basic electrical rhythm and action potentials, he nevertheless introduced one more parameter of study to this field of investigation.

B. Electrical Recording

The concepts of motility should be based on the measurement of variables which contribute to contractility.[14] Activation of muscle fibres is accompanied by electrical charges across the surface of their membranes and in the surrounding extracellular fluid. These in vivo bioelectrical phenomena, as portrayed in the enterogram, can supplement data obtained from manometry, radiology, and other standard methods of evaluation of motility.[3, 14]

There are three types of bioelectric phenomena which occur in the GI tract. They may be classified according to the method of recording:

(i) transmembrane potentials, which are voltage changes across a single cell membrane of an isolated tissue; this type of potential would be detectable, for example, by inserting a microelectrode into a single smooth muscle cell; potentials from specific muscle layers may be recorded in this fashion;

(ii) transmucosal potentials, indicating voltage change across a mucosal surface;

(iii) surface or extracellular potentials, which consist of voltage changes across tissue surfaces or extracellular fluid as recorded by externally applied electrodes; surface electrodes register the mean of potentials generated by many cells exposed to the recording tip.

The electroenterogram described by Alvarez is an example of surface potential recording, as are the ECG and EEG.

Extracellular recording entails the use of external electrodes which serve as connectors between a designated region of biological tissue and an amplifying and recording device. To record in a monopolar fashion, one electrode is placed in contact with the tissue under investigation, and a reference electrode is placed in an area of low electrical activity. Though other biological generators may lie in the path of the voltage being measured, and may thus contribute to the potential difference recorded, these unwanted potentials are usually randomly orientated, and tend to cancel each other out. The configuration of the potential recorded is influenced by many physical factors;[14, 20] included among the factors to be considered are the amount of pressure exerted by the electrode, the degree of penetration of the electrode into the tissue, the size of the recording tip, the amount of electrolyte between the electrode and the active tissue, the development of connective tissue

beneath the electrode during the course of long-term recording, the propagation of the potentials, and the sink relations via low-resistance pathways to distant sources.[100]

Surface recordings of electrical potential from the gastrointestinal tract of intact animals have several distinct advantages:[12, 14, 100]

(i) the preparation is physiological;

(ii) multiple tests may be carried out in the same animal under variable conditions, or over a prolonged period;

(iii) many areas of the GI tract can be explored simultaneously in the same preparation;

(iv) activity can be recorded from a localized area;

(v) the recording unit does not obstruct the bowel lumen, and does not act as an abnormal stimulus to mucosal reflexes;

(vi) the electrical event is a more sensitive parameter than is intraluminal pressure for monitoring motor activity.

C. The Basic Electrical Rhythm: Its Origin and Propagation

Research over the years has more accurately defined the electrical activity of the stomach as comprising two types of potential variation.[43] The repetitive "action currents" recorded by Alvarez are now described as a rhythmic, omnipresent electrical depolarization with a characteristic triphasic

(positive, negative, positive) configuration, designated the basic electrical rhythm, or BER. "Basic" indicates the persistent or fundamental property of the event; "electrical" describes the type of phenomenon; "rhythm" denotes periodicity.[14] The BER has two components; a fast initial depolarization, and a slow, plateau-like depolarization which follows. It is a cyclical alteration of resting potential of smooth muscle cells which renders the muscle alternately relatively excitable and absolutely refractory.[63] Synonymous terms for the BER include initial potential, slow wave, pacesetter potential (PP), and electrical control activity.[45]

The BER originates in bundles of longitudinal muscle located at the junction of the proximal and middle thirds of the greater curvature of the stomach,[110] and is propagated caudally along the longitudinal muscle fibres to the antrum and to the lesser curve by fibres which sweep up from the greater curve. The potential is propagated as a continuous sheath along the muscle wall, such that it is at the same phase in any circumferential cross-section of the stomach at any one point in time.[14, 75]

Anatomical studies of the gastric musculature[110] reveal a confluence of longitudinal muscle bundles on both anterior and posterior aspects of the upper third of the greater curve. From this region, the muscle bundles radiate in multiple arcs along the greater curve to the antrum, and across to the lesser curve. In the distal antrum, longitudinal muscle bundles from

the greater curve continue over the lesser curve, and join similar bundles from the opposite side. In the proximal three-fourths of the stomach, the radiating fibres from the greater curve terminate before reaching the superior margin of the lesser curve. An assessment of partial transection of these muscle bundles at various levels has demonstrated that a narrow bridge of muscle along the greater curve (20% of the circumference) is sufficient to maintain normal electrical continuity and entrainment in the segment of the stomach distal to the transection, indicating that the greater curve is considerably more important in gastric conduction than are other areas of the stomach, including the lesser curve. The paucity of longitudinal muscle on the proximal three-fourths of the lesser curve explains the absence of slow wave activity and conduction in this region.

Each initial potential extends over a specific segment of stomach wall, and may be described as having a wave or cycle length. The segment of stomach (or bowel) beneath each cycle of this potential represents a physiological motor segment.[34, 71] The BER or pacesetter potential determines the dimensions of this segment, and controls its motor activity. Rate of propagation of the BER increases as the antrum is approached, with rates ranging from 0.1 cm. per second in the corpus to 2-4 cm. per second in the terminal antrum.[43, 93] Cycle length is equal to velocity/frequency; therefore, as the velocity of propagation increases, the cycle length increases proportionately, and hence

the length of the underlying motor segment is also increased. This rapid spread of depolarization over the entire antrum is responsible for its behaviour as a motor unit. The BER has a rate or frequency which is constant and species specific (4-5 cycles per minute in dogs, 3 cycles per minute in man). The triphasic complex occupies 1.5-2.5 seconds, and is followed by a refractory period of just less than three seconds.[43]

Propagation is facilitated by nexal connections,[45, 46, 50, 51] which are areas of fusion of adjacent cell membranes. The nexus provides a direct electrical connection between cell interiors without intervening extracellular space, while maintaining cellular integrity. Contiguous cells provide simultaneous current sources and current sinks, allowing electrotonic spread from one cell membrane to another.[20, 21] The smooth muscle cells behave electrically as though their interiors were connected, and electrotonic spread of current occurs between cells much as current is propagated along an axon. The cell membranes at sites of nexal connections are exposed to high potassium and low calcium concentrations, are depolarized, and thus provide low resistance pathways for current flow.

Controversy has surrounded the origin of the BER. Most evidence favours a myogenic rather than a neurogenic origin.[14] Factors which support this concept include:

(i) the inability of neurotropic drugs to alter the BER;

(ii) a theoretical inability of the small mass of neurogenic elements of the gastrointestinal tract to generate a potential of the magnitude of the BER;

(iii) the absence of the BER in hypomuscular areas of the GI tract, for example, the gastroduodenal junction;

(iv) cyclical electrical phenomena are generated in the longitudinal but not the circular muscle layers of the GI tract.

D. Action Potentials

The BER has been designated the "electrical control activity" as it controls the appearance of the "response activity", contraction. This is represented electrically as a second depolarization following the initial or pacesetter potential (PP), and is characterized by a more prolonged (4-8 seconds) negative deflection, upon which may be superimposed a series of faster "spikes".[43, 45] This "second potential" immediately precedes contractile activity (usually by 0.5 seconds) as observed visually or measured either kymographically or with strain gauges. Each BER cycle or motor segment has associated with it only one burst of "second" or "action potentials", and thus only one band of contracting fibres. The BER fixes the maximum frequency of contraction, and its caudal migration synchronizes and coordinates the contraction, determining the velocity of its propagation and the width of the contracting band. The frequency of contraction can therefore not exceed the frequency of the BER. During the fasting state, action potentials (AP's) occur in association with approximately 25% of BER cycles.[14, 71] This percentage is markedly increased during feeding, and during

the administration of various drugs.[35, 37, 43, 91] The action or "spike" potential, unlike the BER, is not propagated more than a few millimetres in either direction.[43]

Action potentials have been directly correlated with contractile activity as measured by increase in intraluminal pressure. However, a measurement of intraluminal pressure records a change due to the mean effect of all muscle layers, and does not indicate within which layer the contractile activity originates. By means of strain gauges orientated so as to record simultaneously the contractile activity of both longitudinal and circular muscle, it has been demonstrated that the action potentials are associated with circular muscle contraction.[14] The number and amplitude of AP's are directly proportional to either the change in intraluminal pressure or the contractile force as measured with strain gauges; this would tend to confirm that action potentials are myogenic in origin. Further evidence in support of the myogenic origin of these potentials is found in the rhythmic contraction which occurs in muscle cells of the chick amnion, which is devoid of nerve fibres.[88] This observation would indicate that spontaneous contraction need not be neurogenic in origin.

E. Coordination of Gastric Peristalsis

Coordinated gastric peristalsis depends on the pacesetter potential sweeping in a rhythmic pattern from its origin to the pylorus. It synchronizes the gastric musculature by providing a suitable electrical framework through which gastric stimuli

may act to alter motor activity,[71] and regulates the maximum frequency of contraction.

The pacesetter potentials originate in the longitudinal muscle layer, and are propagated electronically into the circular muscle layer.[44] The physiological conducting units consist of bundles of 100-300 muscle fibres (and associated connective tissue) in parallel which connect the two layers.[76, 100] The band of depolarization that spreads to the circular layer then interacts with such local factors as acetylcholine, the intramural nerve plexuses and perhaps other excitatory transmitters to initiate contractile activity.

Whether the action potentials actually initiate contraction or are electrical depolarizations which simply parallel contraction is undecided. The pacesetter potential may act solely by triggering the release of acetylcholine (Ach), or it may sensitize the gastric musculature to the effects of Ach. The released Ach may initiate the second depolarization or action potential, which in turn results in calcium release and subsequent contraction.[43] Whether or not a contraction follows the BER complex will depend upon the state of stretch of the muscle, local hormone and transmitter activity, and nerve impulses mediated via both intrinsic and extrinsic networks.

The fact that the longitudinal and circular muscle layers contract simultaneously, and are able to do so in the absence of Meissner's plexus, suggests that peristaltic activity is controlled primarily by a myogenic phenomenon.[22] Neural control

is not a prerequisite for peristalsis, and is more modulating rather than commanding in its role. Peristalsis can also occur in the presence of tetrodotoxin,[43] which eliminates all neural activity. It is likely that neural activity modulates the response to slow wave depolarization by increasing or decreasing the probability of spiking during the depolarized phase of the BER complex.

F. Pacemaker Dominance

Experimental transection of the stomach in various planes and at various levels has demonstrated not only the location of the gastric pacemaker, but has supported the concept of dominance of higher order pacemakers.[73, 106, 108, 110] If one transects the stomach distal to the dominant pacemaker, the normal PP is not propagated across the site of transection, and a pacemaker with an inherently slower rate in the distal segment of the stomach will assume pacemaking activity. The new, distal BER will have a slower frequency, and may show both caudad and retrograde propagation and occasional irregularity due to interposed potentials from ectopic foci of impulse generation. Similarly, longitudinal gastric bisection separating the greater from the lesser curvature causes the lesser curve segment to be no longer driven by the dominant gastric pacemaker. This procedure also results in the development of a reduced BER frequency and an irregularity in the BER due to the appearance of multiple ectopic foci of pacemaking activity.[73] This uncoupling of electrical activity

between the two segments is only temporary, with recovery occurring by two weeks. The re-establishment of coupling has not been observed following horizontal transection studies,[104, 106] but the models in each instance are not comparable inasmuch as the longitudinal muscle bundles in the horizontal transection studies have been divided, whereas this has not been done in the bisection study. Following horizontal transection, the "permanently" lower BER frequency is in keeping with the concept of a gradient in the rate of generation of the natural or intrinsic pacesetter potential in smooth muscle cells of the gastrointestinal tract.[73]

The normal pacemaker on the proximal third of the greater curve, having the fastest intrinsic frequency, entrains the lesser curve and distal stomach.[73, 110] The more distal stomach has a lower intrinsic PP frequency, but can accept and be driven by the faster orad pacemaker. The direction of propagation of the PP is determined by the site of the group of cells having the fastest frequency; propagation occurs from this region to those with slower inherent frequencies.

The smooth muscle cells of the fundus and proximal corpus possess electrical properties different from those of the remainder of the stomach, as they neither accept nor propagate the corporal PP.[73] Lack of measurable rhythmic electrical activity in these areas supports this observation.[110]

G. Relaxation Oscillators

In order to elaborate on the mechanism of entrainment, it

is relevant to discuss the concept of relaxation oscillators and their role in the electrical control of gastrointestinal motility.[43, 102] GI smooth muscle acts like a matrix of loosely coupled relaxation oscillators in which potential pacemaking foci oscillate with frequencies inherent to their specific locale in the GI tract.[75] Individual longitudinal muscle cells are capable of spontaneous slow wave generation. Individual oscillating units may be as small as one cell, or, more likely, comprise a collection of cells oscillating in phase. Coupling occurs via nexal contact or current flow in the surrounding extracellular fluid. Thus each cell or cell group can simultaneously contain both a source and sink of current.

An oscillator with a higher natural frequency can dominate, "pull in", or entrain lower frequency oscillators such that the latter tend to accept the frequency of the faster oscillator. The relaxation properties of the lower frequency oscillators allow this modulation to occur.[102] This concept may be best illustrated by reference to the conducting system of the heart.[43] The SA and AV nodes behave as coupled relaxation oscillators, with the SA node dominant, and the AV node tending to "pull in" towards the rate of the dominant node. The less stable, lower frequency oscillator adopts a rate equal to or some harmonic of the rate of the dominant oscillator. One can see how this concept may be applied to the stomach and intestine, in which each area has its own inherent rate of pacemaking activity

with a gradient of frequency decreasing from proximal to distal stomach, and from proximal to distal small bowel. Proximal pacemakers in each of these regions of the GI tract "pull in" or entrain the more distal segments by coupling of serial oscillating pacemakers.

The transection and re-anastomosis experiments described in the previous section[104, 106] have demonstrated in both stomach and small intestine a slower BER frequency in the post-anastomotic segments, with evidence of abnormal propagation secondary to the emergence of ectopic pacemakers no longer under the control of the faster, dominant proximal pacemaker. This is, in effect, an uncoupling of the pacemakers. Similar effects are observed following local trauma, local cooling, or local anaesthesia applied to a cross-sectional zone of stomach or bowel. These effects are temporary, remaining for periods up to two weeks.[71] It has been suggested that coupling of the pacemakers occurs such that the original BER frequency is restored in the post-anastomotic segment. An analogous situation is observed in the heart; an atrial pacemaker generates the highest frequency of activity, but the ventricle is capable of its own intrinsic rhythmic frequency in the event of an AV conduction block. This situation may also be interpreted as an uncoupling of oscillators, and may be temporary or permanent. Correction of the AV block will allow recoupling of the oscillators, and the dominant atrial pacemaker will assume electrical control of the cardiac muscle.

This concept is important in consideration of disorganized motility and delayed gastric emptying which so often follows vagotomy or gastric resection. The proximal gastric pacemaker has the highest intrinsic frequency of oscillation; uncoupling of the distal stomach from the electrical dominance of this proximal pacemaker by gastric resection and/or vagotomy may be a significant factor in the motility disturbances encountered after these procedures.[110] As a corollary to this premise, it may be possible to utilize this model and apply external oscillators to the stomach to override the undesirable, altered electrical rhythm disturbances which occur following ulcer surgery, much in the same manner in which cardiac pacing overrides the undesirable arrythmias and conduction disorders following myocardial damage.

Kelly and his co-workers[74] have applied this principle to pacing the canine stomach electrically. Using currents of 1-8 ma, and impulses of 0.1-2.0 seconds' duration applied at 2-12 impulses per minute, he has demonstrated coupling between the stimulus and the excitable tissues in the gastric wall such that the frequency of the PP corresponded exactly to the frequency of applied stimulation, with subsequent suppression of the natural gastric PP. The artificially generated PP was propagated bidirectionally, but was not observed in the fundus. The velocity of propagation was identical in both directions, and was of the same magnitude as that of the natural PP. The natural PP in this study had a mean frequency of 5.0 cycles per

minute; this could be increased to 8.0 cycles per minute, or decreased to 4.2 cycles per minute by varying the frequency of applied stimulation. Beyond these limits, the natural PP reappeared.

Previous attempts to generate PP's and consequently control gastrointestinal activity have generally met with little success and have contributed little in the way of concrete results. Varied studies have demonstrated increased gastric contractile activity and associated AP's following externally applied electrical stimulation to the stomach, but have not resulted in any particular success in altering post-operative gastrointestinal motility.[76, 92, 101] By delivering electrical stimuli at a frequency and with a rhythm not unlike that of the natural gastric pacemaker, Kelly has been able to override the natural pacemaker and assume control of the pacemaking activity in the stomach. Whether the external stimuli have acted on neurones in the intramural plexuses or directly on the smooth muscle itself is unknown. Frequency pulling between the site of the external stimulus and the site of the natural pacemaker occurred in such a manner that the external stimulus was able, within certain defined limits, to control the natural pacemaker. This investigation supports Nelsen's hypothesis[94] that gastrointestinal smooth muscle acts like a matrix of loosely coupled relaxation oscillators in which pacemaking sites which oscillate at the highest frequency entrain or couple other areas of electrical activity where the intrinsic frequencies are lower.

SECTION IV. FACTORS WHICH INFLUENCE GASTRIC ELECTRICAL ACTIVITY

We may now consider the factors which are known to influence the BER and action potentials. These may be broadly classified as chemical, mechanical, and neural factors.

A. Influence of Drugs

1. Acetylcholine (Ach)

Several suggestions as to how the BER exerts control over contractile activity have already been outlined. The PP may trigger the release of Ach, or may sensitize the gastric musculature to its effects. Ach may, in turn, initiate action potentials, promote calcium release, and thus lead to contraction. Ach release may also be brought about by distension of the GI tract, which activates mechanoreceptors to set up nervous impulses that impinge on postganglionic cholinergic nerves.[44] Acetylcholine is thought to be the sole transmitter at both pre- and postganglionic cholinergic nerve endings.[93]

Ach may occasionally cause a slight increase in the amplitude of the BER,[14, 43] but otherwise has no consistent effect on its rate. Ach in threshold doses injected intra-arterially (into the gastro-epiploic vessels) during the "susceptible period" (after the refractory period of the initial potential) will produce or enhance action potentials.[37] If injected at an inappropriate time (e.g. immediately after the absolute refractory period of 2.8 seconds, but within 5 seconds of the

onset of the initial potential), it will result in a premature initial potential.[43, 45] This premature PP will be propagated both caudally and in a retrograde fashion. The retrograde propagation results in the loss of the next expected normally propagated PP; the premature potential collides with the normally expected PP, and the latter is unable to pass along the muscle which is refractory as a result of the premature potential. The result is an irregularity of the BER that is analogous in its origin to the compensatory pause which follows a premature ventricular contraction as recorded in the ECG.

2. Atropine

Atropine inhibits or abolishes action potentials and contractile activity by preventing acetylcholine from exerting its action.[14, 42, 43, 98] Generally, it has no effect on the rate of the BER, though it has on occasion been reported to decrease the amplitude of the initial potentials.[37, 39] Atropine does not affect the propagation of the BER, suggesting indirectly that Ach is not essential for the production of initial potentials. High doses of atropine may, however, initiate repetitive bursts of initial potentials. The pattern so described on the gastrogram has been labeled the "sympathetic dominance pattern";[44] this phenomenon is observed whenever there is a dominance of sympathetic over parasympathetic activity.

3. Catecholamines

Catecholamines in threshold doses injected intra-arterially cause temporary inhibition of action potentials and contractile

activity.[37, 42, 43] This effect has been demonstrated with both epinephrine and isoproterenol, suggesting that there are two kinds of inhibitory adrenergic receptors in the stomach: alpha receptors in the myenteric plexuses stimulated by norepinephrine, preventing the release of acetylcholine, and beta receptors in the smooth muscle cells stimulated by isoproterenol, diminishing the effect of Ach on the gastric musculature.[44]

Catecholamines in low dosage do not affect the BER, except by occasionally decreasing the amplitude of the potential.[14, 37] Large dosage, however, results in a series of repetitive triphasic potentials without contraction,[39] and thus suppresses local control activity. Initial potentials are temporarily eliminated distal to the site of local injection,[43-45] and electrical activity which may be generated below the injection site is propagated in both caudad and retrograde directions. In other words, the muscle may be able to propagate pacesetter potentials at a time when it does not initiate them. Moreover, the capability of gastric musculature to propagate potentials in both directions supports the concept of the electrotonic spread of current; the ability to propagate potentials bidirectionally is incompatible with a mechanism involving chemical transmission at synapses.

The phenomenon described as the sympathetic dominance pattern is due in part to a relative deficiency of acetylcholine at the level of the smooth muscle cells. This pattern radically

disorganizes the BER. It is of interest to note that despite the rapid rate of the potentials, the minimum time interval between each potential is 2.8 seconds; this is identical to the duration of the absolute refractory period.[43] Similar patterns have been observed following local injection of high doses of atropine, morphine, and histamine.

4. Hexamethonium

Ganglionic blocking agents have no specific effects on the BER.[14, 37] However, both contractile and relaxant responses to vagal stimulation are abolished by these drugs.[98] This hexamethonium-sensitive relaxation may be mediated via preganglionic vagal fibres which synapse with ganglion cells of adrenergic neurones.

5. Morphine

Morphine causes a spastic, non-propulsive increase in contractile activity and a corresponding increase in the frequency and amplitude of action potentials.[14, 42] It may cause a slight increase in the amplitude of the initial potentials, but its effect on BER rate is variable.[37]

The effect of morphine on contractile activity is limited to the circular muscle layer. Despite the marked increase in the frequency of AP's caused by morphine, a 1:1 ratio is always maintained between the BER and the AP's.

6. Histamine and 5-hydroxytryptamine (5-HT)

Histamine excites cholinergic ganglionic cells presynaptically,[98] resulting in an increase in AP's and contractile

activity. It also has a direct excitatory effect on antral smooth muscle. 5-HT may be either excitatory or inhibitory on intrinsic cholinergic neurones, depending on the prior degree of tonus in the smooth muscle cells.[44] 5-HT may also play a role in vagal inhibition of contractility.[77]

Neither histamine nor 5-HT have consistent effects on the BER.

7. Serotonin

Serotonin causes an increase in the amplitude of PP's, but a slowing of the BER frequency, and some disorganization in its rhythm.[37]

8. Local anaesthetics

Procaine or cocaine in dosage sufficient to paralyse all neural elements does not apparently affect the BER, confirming that the initial potential is not neural in origin.[37, 63]

9. Barbiturates

Anaesthesia with sodium thiopental in low dosage has no appreciable effect on action potentials or on the resting BER. With deeper anaesthesia, sympathetic tone predominates and gastrointestinal atony results.[9, 37, 63] The effects are limited to a decrease in the incidence of action potentials, and a significantly decreased response of intragastric pressure to vagal stimulation. Halogen anaesthetics have similar effects.

Though the effect of barbiturates on the BER is thought to be negligible, one investigation[29] has reported a significant influence. Recordings from unanaesthetized dogs demonstrated

a mean cycle duration of 12.2 ± 0.55 seconds; dogs anaesthetized with sodium thiopental recorded cycle durations of 15.5 ± 3.5 seconds. The prolongation of the BER cycle, and hence the slowing of the BER rate may have been due in part at least to the fall in body temperature which accompanies anaesthesia.

B. Influence of Hormones

1. Insulin

Insulin results in a marked increase in velocity of propagation of the BER, and increases the incidence of action potentials.[71] However, it does not significantly alter the BER rate. The excitatory effect described is vagally mediated.[107]

2. Gastrin

Gastrin has an excitatory effect on gastric musculature. It has been shown to increase the BER frequency by 25-35%.[35, 91] Gastrin causes a marked increase in antral contractile activity via direct action on smooth muscle receptors.[44] It can cause powerful contraction in a totally denervated gastric pouch;[107] this effect is not blocked by anticholinergics, local anaesthetics, or ganglionic blocking agents; nor is it potentiated by anticholinesterases. The effects of increased contractile activity and the associated increase in AP's occur with a dosage comparable to that which will produce a maximal secretory response.[107] Of interest however is a recent investigation[35] which has demonstrated that, despite the increase in contractile activity and actual force of contraction (measured with strain gauges), gastric emptying time is actually delayed

during the infusion of pentagastrin at rates varying from 1-4 ugm/kg./hr.

3. Alkalinization of the duodenum to a pH greater than 8.2 results in increased motility of a totally denervated or autotransplanted gastric pouch, with corresponding increase in the incidence of action potentials.[107] Whether this is due to suppression of an inhibitory hormone such as enterogastrone, or to the production of an excitatory motor hormone is uncertain.

4. A humoral brain factor (Jefferson et al.[67-69]) may be activated or released by stimulation of the central end of a divided cervical vagus nerve, resulting in a reflex increase in gastric contractility. This matter will be discussed further in a subsequent section.

C. Mechanical and Metabolic Factors

1. Body temperature

A fall of 10° C. in body temperature decreases the frequency of the BER by 50%;[14, 37] the amplitude of the PP's and their velocity of propagation are also reduced. Conversely, these parameters are proportionately increased following an increase in body temperature. The slower BER provides an electrical environment conducive to the appearance of ectopic foci of electrical impulse generation, thus rendering the rhythm irregular. This is analogous to the appearance of ectopic atrial or ventricular foci in cardiac muscle during periods of bradycardia.

2. Anoxia

Anoxia results in a progressive reduction in the BER frequency, with decreased voltage and a prolongation of the refractory period. However, during the initial stages of anoxia, contractile activity is increased.[63]

Selective destruction of the intrinsic nerve plexus by local hypoxia results in a lowered BER rate distal to the damaged segment.[14] It is postulated that when the nerve plexus is damaged, the smooth muscle generates an initial potential at its inherent myogenic rate, a rate that is lower than that of the intact bowel wall. One might conclude that a functional myenteric plexus raises the excitability of the myogenic system so that it generates the PP at a faster frequency than its own natural inherent rate.

3. Trauma, in the form of clamping or transection of the antrum, results in a temporary slowing of the BER frequency distal to the site of the insult. Velocity of propagation in the distal segment is permanently reduced. Disorganization of the BER of the distal segment is usually observed for a variable period, and results from the retrograde propagation of potentials originating in the region of the pylorus.

4. Hyperventilation reduces both parietal cell and muscular response to vagal stimulation. It may therefore be accompanied by a reduction in the incidence of action potentials. It probably has no effect on the BER.

Whether or not an action potential and contraction will occur will therefore depend not only on the arrival of a propagated pacesetter potential, but on the local chemical and physical environment of the smooth muscle cells, and whether this environment is receptive to initiating response activity.[44] Local reflexes modulate the response by determining the quantities of transmitters and hormones to be released, and thereby regulate the balance between excitation and inhibition.

D. Neural Influences

The vagi may exert a controlling or stabilizing influence over the gastric pacemaker. Vagotomy in dogs has been shown to cause a temporary slowing of the BER frequency, a disorganization of the regular rhythm,[93, 96] and a permanent slowing of the caudad propagation of the BER.[71] The reduced frequency and disorganization are temporary, lasting on the average 5-10 days. One interpretation of these observations is that vagotomy has removed a controlling influence over the normal pacemaker, allowing it to assume its natural slower rate. Since higher order pacemakers dominate, the lower intrinsic rate provides as already described an electrical environment suitable for the emergence of ectopic foci of impulse generation; hence the disorganized BER with multiple conduction pathways and both caudad and retrograde (antiperistaltic) propagation. The pattern on the electrogastrogram is somewhat analogous to the ECG pattern of slow atrial fibrillation with superimposed multifocal premature ventricular contractions.

Early investigation has suggested that vagotomy results in impaired gastric tone, weakened contractions, disturbed peristalsis, and delayed emptying of solids.[71, 88, 93] Unsynchronized peristaltic waves, not coordinated in time or direction of propagation, would not provide adequate propulsion of solids, though the generalized increase in tone could achieve normal or even accelerated propulsion of the liquid content of the stomach and thus account for the frequently observed rapid "initial emptying time" following vagotomy. The initial emptying of the fluid component of a meal into the small bowel can at times be so rapid as to be considered a form of dumping.[93] The major postvagotomy motor disturbance, however, is retention of the solid portion of a meal for hours or even days. If the pacesetter potential does in fact initiate some change required for the production of the action potential and subsequent contraction, and thus coordinate contractile activity, the irregular, disorganized BER with the associated equally disorganized action potentials so produced by vagotomy may well account for the unsynchronized gastric peristaltic activity, gastric distension, and delayed emptying which so often follows vagotomy. The random disorganization of the BER persists approximately one week; this period is comparable to the duration of significantly impaired gastric emptying and gastric dilatation observed following vagotomy in humans. The entire concept is analogous to the sequence of events observed following acute spinal cord transection, following which lower order reflex activity temporarily prevails.[107]

Further evidence of vagal control over gastric electrical activity is found in the effect of insulin hypoglycemia.[71] Prior to vagotomy, insulin has been shown to cause an increased velocity of propagation of the BER in dogs, and a marked increase in the incidence of AP's and contractile activity. Vagotomy abolishes this effect of insulin induced hypoglycemia. In prevagotomized dogs, gastric instillation of oil slows propagation of the PP, and markedly diminishes the incidence of AP's; once again, vagotomy substantially diminishes and occasionally abolishes this effect of fat on gastric electrical activity. The oil no longer reduces the incidence of AP's or contractile activity.[71] Both investigations support the concept that vagally mediated stimuli exert some control over gastric electrical activity, and that vagotomy removes the cephalic phase of gastric motility in the same manner as it abolishes the cephalic phase of gastric secretion.[93]

To pursue the problem of gastric inhibition by fat, it is likely that both humoral and neural factors are involved.[107] Fat in the upper small intestine, in the presence of bile salts and pancreatic juice, delays gastric emptying by inhibiting gastric motility. This inhibition can occur in both innervated and denervated stomach and in an autotransplanted gastric pouch, suggesting that humoral factors (enterogastrone) are involved.[107] However, procainization of the intestinal mucosa abolishes the inhibitory action of fat, and vagotomy significantly attenuates the inhibitory response, as well as prolonging its latency. One

may conclude that vagally dependent neural mechanisms are also implicated in this phenomenon. It has been postulated that the inhibition by fat is initiated reflexly in a fashion similar to the initiation of the enterogastric reflex, and is then perpetuated via the action of circulating enterogastrone. The action of procaine implies a local reflex mechanism involved in the release of enterogastrone; this reflex may be facilitated or otherwise modified by vagal impulses. A similar mechanism of control exists with respect to gastrin. The participation of both neural and hormonal pathways provides a more complete explanation for the effects of vagotomy on the gastric inhibition by fat.

SECTION V. VAGAL PATHWAYS AND EFFECTS ON GASTRIC CONTRACTILE ACTIVITY

Much of the work in tracing vagal afferent and efferent pathways through the central nervous system has been accomplished by studying gastric tone and motility. Though the effects of vagal stimulation on gastric electrical activity have not been specifically studied, it is probably justified to apply many of the concepts formulated by the study of motility to the examination of gastric electrical activity, as the two parameters of study are closely related.

In order that contractions may serve a useful purpose, they must be coordinated and brought into harmony with the needs of the organism, and must conform to a pattern which will

serve the purposes of digestion. Regulation of this activity, whether in the form of augmentation or inhibition, is accomplished via local and central neural pathways, and via the effects of circulating hormones. The only known direct innervation of gastric smooth muscle cells (except for a few postganglionic sympathetics) is via efferent neurones in the local intrinsic plexuses. These motor neurones constitute the final common path in a reflex arc in which the afferent neurones are also located in the same intrinsic plexuses.[107] The long reflex arcs through the central nervous system are comprised of both vagal and sympathetic visceral afferents plus their corresponding efferent fibres traveling in the same nerves. The extrinsic nerves do not in fact innervate the gastric smooth muscle directly, but serve as connecting links between reflex centres in the CNS which are concerned with regulating gastric function and the local reflex centres in the myenteric plexuses, through which the activity of the muscle is coordinated. The visceral efferent nerve fibres are in reality afferents to the local but diffuse reflex neural centres in the visceral organs.[28, 107] Thus, extrinsic neural influence is primarily directed at either facilitating or inhibiting the local axon reflexes mediated through the intrinsic myenteric network.

A. Gastrointestinal Receptors

Before discussing the autonomic nerve pathways, it is relevant at this point to briefly outline the various gastrointestinal receptors and indicate the role of the extrinsic nerves in modifying their responses.[107]

1. Osmoreceptors

These are located in the duodenal and upper jejunal mucosa, and are sensitive to osmotic forces. Solutions having greater or lesser activity than the osmolar concentration of blood plasma stimulate these receptors with resultant slowing of gastric emptying. The role of the extrinsic autonomic network in this phenomenon is uncertain.

2. Hydrogen Ion Receptors

These receptors are situated in the upper intestinal mucosa, and operate with a threshold of pH 2.0-3.5. Acid in the upper intestine inhibits gastric motility and delays gastric emptying. Recording from single vagal fibres, Iggo[65] has found that the electrical activity of the nerve is increased when solutions with a pH of less than 3.0 or greater than a pH of 8.0 are applied to the gastric mucosa. The function of these gastric pH receptors is unknown.

3. Other Chemoreceptors

Amino acids, products of protein digestion, and peptones in the upper intestine inhibit gastric motility via neural pathways, probably via specific receptors. Fats and products of fat digestion in the upper intestine also inhibit gastric motility; both enterogastrone and vagal pathways are involved in this phenomenon.

4. Mechanoreceptors

Contact (pressure) receptors and stretch receptors are each present in the gastrointestinal tract, and are involved in

local reflexes which regulate motility. Stretch receptors in the gastric wall, when stimulated, result in impulses detectable in afferent vagal fibres. These impulses influence motility via long reflex arcs through the CNS.[64, 97] Youmans[111] has described an "intestino-intestinal" reflex in which overdistension of a segment of intestine results in generalized intestinal inhibition, presumably due to stimulation of stretch or tension receptors. This in turn has an inhibitory effect on gastric peristalsis. The situation is not clear, however, when one attempts to draw parallels between the reflex effects of stimulating these receptors and the responses obtained by stimulation of extrinsic nerves. Integration of local axon reflexes with long reflex arcs through the CNS probably provides the most suitable explanation for the role assumed by the various mechanoreceptors.

5. Miscellaneous Receptors

Pain, thermal, and special sense receptors all have direct or indirect effects on gastrointestinal motility. Their effects are mediated in part at least by their influence on electrical activity. Noxious stimuli such as excessive muscular contraction, mechanical trauma or chemical injury result in non-specific inhibition of visceral function. Body temperature has already been discussed insofar as it affects electrical activity.[37]

B. Afferent Nerve Pathways

1. Vagal Afferents

Afferent vagal fibres are concerned with the autonomic

regulation of gastrointestinal function. Pavlov, in his account of the nervous regulation of digestion,[59] emphasized the importance of a discharge down efferent vagal fibres to the abdominal viscera. This discharge was thought to be a reflex impulse initiated in a "secretory centre" in the brain stem following stimulation of cephalic nerve endings which in turn had been excited by visceral afferent inflow along the course of the abdominal vagi (and sympathetics as well). Existence of this reflex was queried when McSwiney[88] and Alvarez[7] demonstrated that gastric secretion and motility could be altered in the absence of an extrinsic nerve supply. Nevertheless, several investigators have described the effects of electrical stimulation of vagal afferent fibres, measured as a change in the tonus or contractile activity of the gastric musculature.

Babkin and Kite[9] have demonstrated inhibition of antral contractile activity following central (reflex) stimulation of one divided cervical vagus, the other nerve remaining intact. However, a similar degree of antral inhibition was usually observed following central stimulation of femoral, sciatic, or splanchnic nerves. The authors postulated several mechanisms to account for this inhibition:

(i) depression of lower vagal centres in the medulla, hypothalamus, or reticular substance;

(ii) stimulation of vagal inhibitory neurones;

(iii) stimulation of the sympatho-adrenal system.

The central pathways involved in this reflex inhibition were thought to include the cortex, medulla, and hypothalamus.

In these experiments, a chloralose-urethane anaesthetic mixture was used. This particular combination has been shown to stimulate vagal secretory centres in the CNS,[9, 54] and may likewise stimulate vagal motor centres in the region of the dorsal vagal nucleus and reticular substance. These effects are abolished by vagotomy. The influence of the anaesthetic agent may be of significance in interpretation of the observations as recorded by these investigators.

Harper and his colleagues[59, 77, 107] have studied the effects of both afferent and efferent vagal stimulation in cats. Using square wave impulses of 0.1-10.0 millisecond duration, 5-40 V., applied at 30-50 impulses per second for periods of 10-30 seconds, as well as curare or high (C_2) spinal cord section to eliminate retching movements,[59, 60] they have demonstrated an increase in acid and pepsin secretion upon stimulation of the central end of one divided vagus while the other vagus remained intact. Central stimulation of one divided vagus resulted in an overall decrease in tone of the gastric musculature in the majority (80%) of experiments, though there was evidence of slight superimposed contractile activity in one-half of these cases. The overall decrease in tone outlasted the period of stimulation by up to 15-20 minutes. In the remaining 20% of experiments, there was no background decrease in tone, but only slight increase in contractile activity

as measured by water manometry. The latent period of this response was 5-10 seconds.

Efferent stimulation of these same nerves using similar stimulation characteristics also resulted in enhanced acid and pepsin secretion, but primarily a strong contractile response of the gastric musculature. In approximately 50% of this group, there was no loss of gastric tone; in the remainder, the overall loss of tone upon which the contractions were superimposed was only slight and variable. Once again, the latent period of this response was 5-7 seconds.

The effect of afferent or reflex stimulation on gastric motility as described in this investigation was primarily inhibitory, whereas efferent stimulation was primarily excitatory. By way of contrast, both afferent and efferent vagal stimulation on intestinal motility was excitatory. Following complete vagotomy, Harper demonstrated a progressive increase in gastric tone associated with an increase in spontaneous contractile activity. This could be interpreted as a removal of the inhibitory effects of the vagi. The entire concept of vagal inhibitory fibres will be discussed in more detail in a subsequent section. Harper has therefore demonstrated that vago-vagal reflex effects can be obtained by direct stimulation of afferent vagal fibres, and that the secretory and motor changes as described are abolished by complete vagotomy.

Jefferson[67-69] has demonstrated that electrical stimulation of the central end of the cervical vagus with <u>all</u> vagal fibres severed results in gastric contraction localized primarily

to the area of the cardia and fundus. He suggests that humoral factors liberated from the CNS may be implicated in this contractile response. His investigation has also put forth evidence to suggest that there are extravagal efferent parasympathetic fibres which leave the spinal cord between T_4 and L_2 via dorsal and ventral roots; they travel to the stomach via the splanchnics and other as yet undetermined pathways, and result in a contractile response.[68] That their effect is blocked by atropine suggests that they are probably cholinergic. Jefferson's investigation suggests that complete interruption of cholinergic impulses to the stomach cannot be achieved in the dog by vagotomy.

At the present time, one can only conclude that it is difficult to assess the significance of the conflicting results obtained by electrical stimulation of afferent vagal fibres, primarily because the vagi contain afferents from so many unrelated organs, and account for at least 90% of all vagal fibres.

2. Afferent Fibres Associated with Sympathetic Efferents

Visceral pain fibres usually accompany the sympathetic nerves. Afferents enter the spinal cord via the dorsal roots of the lower thoracic nerves, usually T_{8-12}, though they may be found within the range of T_4-L_2.[68, 107] Support for the existence of these afferent pathways is found in Dragstedt's work in the 1940's. He has demonstrated that though vagotomy relieves the pain of duodenal ulcer, introduction of acid into

the stomach of a vagotomized subject can still elicit pain, indicating that an afferent nerve pathway remains intact.[52]

C. Efferent Nerve Pathways

1. Introduction

The autonomic nervous system regulates two types of gastric response:

(i) pure tonus changes in the form of contraction or relaxation;

(ii) augmentation or inhibition of rhythmic movements.

The tonus of smooth muscle may be defined as "the resistance of its substance to extension". The "all-or-none" law of striated muscle contraction does not apply to plain muscle. A state of tonus may be considered as a continued contraction, or as an inhibition or partially inhibited relaxation. From such an equilibrium, a state of further contraction or further relaxation can be obtained.

It is a gross oversimplification to designate the vagus the motor nerve and the sympathetic the inhibitor nerve of the stomach. Sympathetic and parasympathetic networks each have both excitatory and inhibitory functions.[77] It is the purpose of the subsequent sections to outline some of the early investigation which has lent support to this concept, and to review more specifically the role of the efferent pathways in the regulation of gastrointestinal motility.

Vagal efferent fibres reaching the stomach terminate in arborizations around the neurones in Auerbach's plexus.[88] Cells of this plexus in turn innervate the smooth muscle cells. With the exception of the few postganglionic sympathetics, the extrinsic nerves do not directly innervate the gastric muscle fibres, but serve rather as links between CNS centres and the myenteric plexuses; their influence is primarily one of modification of local axon reflexes.[107]

Investigation in this field has demonstrated over the years almost every conceivable combination of contraction and relaxation in response to extrinsic nerve stimulation.[98] The consensus, put simply, has been that gastric muscle, when stimulated, is more likely to contract if fully relaxed, and to relax if fully contracted. Generally, weak stimuli have favoured contraction, and strong stimulation has favoured relaxation.[28] The body and fundus appear more susceptible to inhibition by vagal stimulation than is the antrum.[107] It has also been observed that the response to sympathetic stimulation is generally not as dependent on the existing state of tonus as is the response to vagal stimulation. To elaborate on this concept, it can be stated that tonus is dependent upon passage of propagated disturbances over the peripheral part of the neuromuscular mechanism, and that the degree of tonus is dependent upon the frequency of these propagated disturbances. When tonus is high, vagal stimulation is thought to decrease the frequency of the propagated disturbance to an inhibitory

value; when tonus is low, the frequency of the propagation is also low, and vagal stimulation will raise this frequency to excitatory values.[88, 109]

McSwiney, in his review of gastric innervation,[88] comments that the immediate results of nerve section may not be of great physiological importance, as they are of brief duration and are often indistinguishable from the effects of shock and anaesthesia. He cites the inhibition of motility and loss of gastric tone following laparotomy as an example of this concept, and suggests that the more remote effects of nerve section are of greater significance. His review of the subject to 1931 concludes the following:

(i) section of one vagus or of one splanchnic has no appreciable effect on gastric tone or motility;

(ii) complete vagal section results in gastric dilatation, decreased tonus, slow and weakened peristalsis, and delayed gastric emptying;

(iii) complete splanchnic section results in accelerated gastric function and effects opposite to those of vagal section;

(iv) complete vagal plus splanchnic section results in a sequence of events similar to, but less pronounced than that which follows complete vagotomy.

There are two stages in the response which follows vagotomy. Initial inhibition and paresis is followed by a gradual return of function. After a variable period, the peripheral intrinsic nervous network assumes control of the extrinsically denervated stomach, supporting the premise that the vagi (or the splanchnics) are not essential to gastric function, but are instead modulating in their role.

2. Vagal Efferents

Vagal efferent fibres terminate in relation to the cells in Auerbach's myenteric plexus, and are influential in modifying smooth muscle activity, either by exciting the ganglion cells of the plexus to discharge impulses over their axons, or by inhibiting or facilitating local reflexes.[107] As an example, the temporarily disturbed gastric peristalsis following vagotomy suggests that the vagi do have some regulatory influence on local reflex mechanisms.

It has been shown that vagal stimulation can result in either inhibition or augmentation of gastric contractile activity. As early as 1889, Openchowski described a "dilator nerve of the cardia", presumably a vagal fibre which, when stimulated, resulted in relaxation of the cardia.[79, 88, 110] He described both contraction and relaxation of the cardia following vagal stimulation; the response depended upon the strength and frequency of the electrical stimulus. Wertheimer, in 1897,[79] obtained reflex inhibition of the gastric musculature by stimulating the central end of the sciatic nerve or of one

vagus nerve; this inhibition was much less following complete vagotomy. Wertheimer made reference to earlier work by Morat, in France (1882), who apparently observed cessation of gastric motility on stimulation of the central end of the vagus, and attributed this phenomenon to the influence of vagal inhibitory fibres. Langley, in 1898, described a relaxation of the upper portion of the body of the stomach and the esophageal orifice on peripheral stimulation of the cervical vagus.[79] The greater the tone of the sphincter, the greater the effect of vagal stimulation. Langley suggested that the decrease in intragastric and sphincteric pressures was due to active relaxation of the cardiac orifice, rather than an opening of the sphincter by contraction of the longitudinal muscle of the esophagus. At the same time, vagal stimulation was observed to increase contraction in the region of the pylorus. In the presence of atropine sufficient to block the excitatory response, Langley noted a much greater degree of relaxation following vagal stimulation than when atropine was not used. Langley's work has therefore demonstrated both motor and inhibitory vagal efferent fibres.

Subsequent investigation in 1911 by Cannon and Lieb[26] confirmed Langley's observations by demonstrating relaxation of the lower esophagus and cardia following electrical stimulation of the distal end of a divided cervical vagus nerve. They noted further that swallowing was associated with a relaxation of what they termed the cardiac sphincter. The fundus

was observed to relax just prior to the arrival of the esophageal peristaltic wave; i.e., just after the onset of swallowing. Maximal relaxation coincided with the arrival of the esophageal peristalsic wave, resulting in an increased gastric capacity without a concomitant increase in intragastric pressure. This was interpreted as a mechanism designed to allow the swallowed material to be received into the stomach with a minimal increase in esophageal work, and was termed "receptive relaxation". Repeated swallowing was associated with continued relaxation of the cardia and fundus. This phenomenon illustrated the concept of reciprocal innervation of antagonistic muscles, in which opposing muscles act in reciprocal cooperation. Vagotomy resulted in abolition of this reflex receptive relaxation, indicating that it is mediated by inhibitory vagal efferent fibres. Hexamethonium also abolishes this phenomenon.

Cannon and Lieb also noted motor effects following efferent vagal stimulation. Low frequencies and intensities of stimulation were associated with excitatory effects on the gastric musculature, whereas inhibition followed high frequency, high intensity stimulation.

Other investigators studied the inhibitory effects of efferent vagal stimulation. Veach, in 1925,[109] postulated that the inhibitory effects were due to an exhaustion of the transmission mechanism, similar in principle to Wedensky inhibition. McSwiney and Wadge[87] reiterated the concept that the

response to efferent vagal stimulation was dependent upon the basal tone of the stomach at the time of stimulation. Harrison and McSwiney,[61] in 1936, suggested that inhibitory effects were due to adrenergic fibres in the vagi, as inhibition was not abolished by atropine. Paton and Vane[98] were proponents of this view, claiming that they could achieve inhibition of gastric motility on vagal stimulation only in the presence of atropine, and that the inhibitory effect was abolished by sympatholytic drugs. Eliasson, in 1952,[54] elicited gastric inhibition following the stimulation of the orbital region in the brain stem of cats, and established that this response was conveyed via vagal efferents. This response was no longer observed following the administration of atropine.

Needless to say, these conflicting, contradictory results are confusing. More definitive quantitative evaluation of these observations has been offered by Martinson and his colleagues in Sweden.[66, 81-85] Autonomic nervous control of smooth muscle is exerted by a fibre discharge of relatively low frequency, of the order of 1-4 impulses per second at rest, and 8-10 impulses per second during intense excitation.[82] Veach has demonstrated an increase in gastric motility following direct vagal stimulation with impulse frequencies of up to 12 per second.[109] With further increase in the frequency, or increase in the strength of stimulation at higher frequencies, inhibition resulted, and Veach attributed this to Wedensky inhibition. As already described, McSwiney and Wadge claimed

that the initial tone of the muscle was the dominant factor in determining whether vagal stimulation would cause increased or decreased motility; they observed inhibition if the basal tone were high, and augmented contractility if basal tone were low. By applying graded efferent vagal stimulation with variation of impulse duration, voltage, and impulse frequency in a controlled manner, Martinson[82] has described frequency-response curves for changes in gastric tone and secretion which suggest two groups of efferent vagal fibres: "low threshold" excitatory fibres responding to short duration (less than 0.2 msc.) impulses, causing increased tone and contractility, and "high threshold" inhibitory fibres responding to longer duration impulses (1 msc. or longer), resulting in a reduction in tone predominantly in the corpus in fundus, but not in the antrum. The inhibitory fibres have little if any effect on the pyloric region, whereas the excitatory fibres have their greatest effect in this region. The most pronounced excitatory responses occurred with stimuli of 0.1-0.2 msc. duration, 4-5 V, applied at impulse frequencies of 8-10 impulses per second. The strength of the response increased with an increase in the rate of stimulation up to 8-10 per second, and then leveled out; further increase in only the frequency of stimulation did not further alter the character of the response. This observation conflicts with that of Veach which suggests that an increase in the frequency of stimulation <u>alone</u> is sufficient to eventually change the response from excitatory to inhibitory. Veach

observed that gastric motility could be inhibited by increasing either the intensity or the frequency of vagal stimulation. It appears from Martinson's work that inhibition appears only after a certain threshold intensity of stimulation is reached, and then occurs whether the frequency of stimulation is high or low. Certainly a high frequency stimulation will result in some depression of neurogenic influence due to fatigue in some link in the neuroeffector unit, provided that the rate of stimulation exceeds the capacity of the system; this, however, is a non-specific suppression of the effector response.[82]

Atropine abolishes the excitatory response, but does not affect the inhibitory response, indicating that the latter is not cholinergic in origin. Nor is it truly adrenergic, as it is not abolished by sympatholytic drugs. The threshold for inhibition is identical before and after abolition of the excitatory response by atropine. The short latency of the inhibitory response (approximately five seconds) indicates that it must be neural in origin, and that humoral factors are not involved.

The inhibition caused by vagal stimulation has been attributed by some to adrenergic fibres in the vagi, or at least to some adrenergic mechanism.[61] However, the factors as outlined below serve to differentiate vagal from sympathetic inhibition:[83]

(i) vagally induced inhibition is more potent, develops more rapidly, and has a shorter latency (5 seconds v. 30 seconds) than inhibition induced by sympathetic stimulation using comparable stimulation parameters; the response to

infused catecholamines is of even lesser degree than is the response to stimulation of sympathetic fibres;[77, 81]

(ii) the extremely short latency of the gastric inhibitory response to vagal stimulation indicates that humoral mechanisms, including the adrenal medulla, are not involved;[81]

(iii) vagal and sympathetic stimulation produce differing frequency-response relationships; the maximum response to vagal stimulation is achieved with lower impulse frequencies than those required to obtain a maximum response to sympathetic stimulation;

(iv) vagal relaxation is of longer duration than that achieved by sympathetic stimulation; with maximal sympathetic or catecholamine induced inhibition, further relaxation can be achieved by subsequent vagal stimulation;

(v) vagally induced inhibition is confined primarily to the corpus and fundus, whereas sympathetic stimulation inhibits the antrum as well;

(vi) inhibition produced by stimulation of these opposing networks of the autonomic nervous system differs in its response to antagonistic drugs; sympathetic and catecholamine induced responses are abolished by guanethidine, whereas vagal relaxation is not affected by

> either alpha or beta adrenergic blocking agents; vagal relaxation is potentiated rather than decreased by atropine, but is abolished by hexamethonium.[66, 77, 81]

The abolition of vagal relaxation by hexamethonium suggests that the mechanism involves a ganglionic transmission step.[83] That atropine enhances the relaxation suggests that it may act here at a ganglionic level, rather than only at the periphery. It appears that vagally induced gastric inhibition is not mediated by an adrenergic mechanism, though there are in fact adrenergic fibres which enter the vagus within the thorax and abdomen; their effect is considered negligible.[56] Sympathetic stimulation at high stimulation frequencies results in inhibition more on the basis of a non-specific overflow of adrenergic transmitter substance from vasoconstrictor nerve endings than anything else, accounting for the longer latency and shorter duration of the response.[82] The long-lasting specific relaxation of the stomach on excitation of high threshold vagal efferents is mediated via preganglionic vagal fibres which are neither adrenergic nor strictly cholinergic. The peripheral mechanism may involve the local release of a stable, smooth muscle relaxing transmitter[66] which is more potent than the catecholamines, and is eliminated at a slower rate. Effects of this type have not been described with histamine, bradykinin, serotonin, or gastrin, but it has been suggested that perhaps 5-hydroxytryptamine may be implicated in the ganglionic transmission step of this vagal inhibitory pathway.[77, 83]

The cephalic phase of gastric secretion, mediated via the vagi, results in increased secretion of hydrochloric acid and pepsin. This is an energy consuming process, requiring increased blood flow. The secretory response is achieved via stimulation of high threshold fibres, as is gastric vasodilatation which would provide the increased blood flow necessary for the secretory response. Martinson has proposed that stimulation of these high threshold vagal efferents initiates a physiologic, gastric peripheral response pattern comprised of the secretion of hydrochloric acid and pepsinogen, vasodilatation, and relaxation of the corpus and fundus (receptive relaxation) in association with swallowing.[84, 85] The individual components of this response pattern cannot be separated by means of the electrophysiological properties of the fibres involved. At the same time, antral activity is enhanced, with effective mixing and propulsion of the stomach contents. The relative fewness of efferent vagal fibres suggests that though they initiate the pattern of response, the final response is governed by the far greater number of neurones in the myenteric plexuses, and probably by local hormone action as well.

It has been demonstrated that repetitive stimulation of nervous tissue at high frequencies can result in increased responsiveness to subsequent stimulation.[19, 103] Rapid, repetitive stimulation is thought to cause a persistent hyperpolarization of the terminations of the presynaptic or motor fibres involved at the level of Auerbach's plexus, with a consequent increase

in the amount of transmitter substance released in response to subsequent stimulation. Potentiation of gastric contraction in response to efferent vagal stimulation has been achieved by preceding a regular test stimulus (at for example 5-10 impulses per second) by a thirty second period of stimulation using the same voltage and impulse duration, but applied at a considerably higher impulse frequency, of the order of 20-50 impulses per second. Similar potentiation of efferent vagal stimulation on intestinal contractility has also been observed. Potentiation of afferent or reflex vagal stimulation was effective in increasing intestinal contractility following the regular test stimulus; however, slow stimulation of afferent vagal fibres had no significant effect on gastric contractility either before or after the application of a potentiating stimulus. The increased response of intestinal (but not gastric) muscle to slow afferent vagal stimulation after a potentiating stimulus is an example of potentiation mediated via an autonomic reflex arc through the CNS.

Potentiation is increased in degree and duration when all vagal connections are severed. This has been interpreted as being due to the removal of the reflex inhibition mediated via vagal afferents. Post-activation potentiation of either acid or pepsin secretion has not been demonstrated, but perhaps this could yet be achieved using different stimulus parameters.

The potentiation is produced by impulse frequencies (20-50 per second) at which the vagal fibres may be expected to

conduct. Iggo[64] has recorded impulse frequencies of 30 per second in non-myelinated vagal afferents in cats. It has already been noted that in cats, approximately 3,000 efferent vagal fibres are given the task of coordinating or at least modifying gastrointestinal secretion and motility. This concept of potentiation and facilitation of contractile activity may account for the economic achievement of at least the motor functions of the vagi with the relatively small numbers of efferent fibres available, and is a simple means of reconciling the multiplicity of actions attributed to the efferent vagal supply to the abdomen.

3. Sympathetic Efferent Pathways

Sympathetic visceral efferent fibres also consist of low threshold excitatory fibres which are cholinergic and probably synapse at the myenteric plexus level, and high threshold inhibitory fibres which are probably adrenergic, and synapse in the sympathetic ganglia.[107] Kure has described myelinated efferent fibres emerging in the dorsal spinal roots from levels T_4-L_2, passing through the prevertebral ganglia without synapse, and reaching the stomach via the greater splanchnic nerves.[78, 88] These excitatory sympathetic fibres have been shown to be cholinergic, as response to their stimulation is blocked by atropine.[107] They have been termed "spinal parasympathetics", and may be the same extravagal parasympathetic outflow alluded to in Jefferson's work.[67-69] Splanchnic stimulation generally results in gastric inhibition, but when the inhibitory fibres

are blocked by the application of nicotine to the sympathetic ganglia, splanchnic stimulation has an excitatory action, mediated presumably via the fibres just described.

D. Central Integration of Autonomic Nerve Pathways

Experimental electrical stimulation studies of the brain have demonstrated loci in many cerebral areas which have both excitatory and inhibitory influence on gastric motility.[107] These effects are conveyed by sympathetic and parasympathetic visceral efferent fibres, each of which contain both excitatory and inhibitory fibres. They function reciprocally to regulate motility by imposing a higher control. The effects are guided by impulses which originate in visceral and somatic receptors which respond to osmotically active substances, pH, pressure and muscle stretch, and by intracerebral inputs. Somatic and visceral pain receptors, special sense receptors, and receptors involved with emotional responses contribute to initiating these reflexes. The afferent limb of each reflex is incorporated into vagal and sympathetic afferents. Efferent impulses initiate activity which will best prepare the stomach for its functions, and modify its ongoing activity in accordance with the needs of the organism as a whole. Cortical influence is funnelled through the subcortex and brainstem. There are feedback mechanisms at each level of control to provide for a hierarchy permitting any given region to exhibit a dual role in influencing regions more central or more distal to it, thus

securing homeostasis in the regulation of gastric motility. In interpretation of these concepts, one must consider that the response to stimulation of any given area is related to the species of animal studied, the degree of tonus of the organ at the time of stimulation, the stimulus parameters, the effect of anaesthesia, and many other factors of this nature. It is valid to compare the results of different studies only if these circumstances are taken into consideration.

Eliasson[54, 107] has concisely described many of the intracerebral pathways involved in the regulation of gastric motility. He has traced fibres from each of the cortical areas which influence contractile activity to the region of the anterior commissure, thence to the thalamic nuclei and hypothalamus. Fibres pass from behind the diencephalon to the corpora quadrigemina and reticular substance. Here the fibres separate into a primarily excitatory dorsal bundle and a primarily inhibitory ventral bundle; both are then traced to the vagal nuclei. The medulla, which is comprised in part from the dorsal motor nucleus of the vagus and the bulbar accessory nerves, receives fibres from the nodose ganglion, which is in turn the site of cell bodies of some of the visceral afferent fibres from the abdominal cavity.

Stimulation of these varied regions has confirmed the concept that the vagi and sympathetics each contain both excitatory and inhibitory fibres. With Martinson's investigation in mind, it is likely that the conflicting results obtained by other

investigators following stimulation of these pathways have been due to a mixed peripheral effect of simultaneous activation of both types of fibres.

The following examples serve to illustrate some of these principles.[107] All effects on gastric motility following stimulation of the thalamus are abolished by bilateral vagotomy or by atropine, but not by splanchnic section. Thus, the gastric motor impulses elicited by thalamic stimulation are carried by the vagi. Stimulation of the dorsal column of anaesthetized dogs results in an excitatory response, whereas ventral column stimulation causes inhibition of gastric motility. This effect is abolished by bilateral splanchnicotomy, and suggests that motor pathways in the dorsal roots connect the splanchnics to the medulla. Jefferson's work, described in a previous section, has demonstrated an excitatory response to stimulation of either dorsal or ventral spinal roots in the region from T_4-L_2; he has suggested that both roots convey motor fibres to the stomach.[68] This particular phenomenon is not abolished by removal of either the stellate or celiac ganglia. Jefferson has also observed gastric contraction upon stimulation of the isolated vagus nerve in the thorax (sectioned both in the neck and above the diaphragm);[107] from this observation he concludes that there are efferent, extravagal motor fibres to the stomach, cholinergic in their action, which leave the cord between T_4 and L_2, and reach the stomach via the splanchnics and perhaps other pathways as yet uncharted. Following section of the vagi and the spinal

cord, supra-spinal stimulation registers no effect on gastric motility.[77] Generally, inhibitory impulses, particularly those initiated in somatic afferents and those associated with emotional disturbances, are conveyed via the sympathetic nerves. Excitatory responses are generally carried in the vagi. Vagal inhibition is concerned more with specific inhibitory reflexes, such as receptive relaxation. Thus all levels of the CNS have been shown by stimulation and ablation studies to influence gastric motility; successive ablation from higher to lower levels of control is generally accompanied by increased motility.[107]

It is evident that the integration of control of gastric motility and the associated electrical phenomena are complex. Once again, it is prudent to consider that the response to stimulation may be modified by the numerous factors outlined at the beginning of this section; it is therefore difficult if not impossible to draw any sweeping or dogmatic conclusions in this field of study.

SECTION VI. THE GASTRODUODENAL JUNCTION

Though the major focus of this review is concerned with gastric contractile and electrical activity, the function and control of the gastroduodenal junction is relevant to this discussion.

The details of anatomical continuity of the pylorus and duodenal cap are essential to understanding the possible

integration of function of this area. There are basically three functional units to be considered: the pylorus and antrum operating as one unit; the duodenal bulb above the entrance of the common bile duct; and the duodenum proper below that level. Circular muscle on either side of the pyloric ring is discontinuous; however, approximately 20% of the longitudinal muscle fibres from the antrum continue into the duodenum, primarily along the lesser curve.[10] The myenteric plexus, which remains largely in association with the longitudinal fibres, is also partly continued into the duodenum.[53] The outer subserous plexus containing vagal and sympathetic fibres is also continuous across the pylorus, but the degree of continuity of the submucous plexus is uncertain.

Duodenal electrical activity is controlled by two separate pacemakers. The duodenal bulb has an erratic, irregular, low voltage BER; approximately 70% of BER cycles are associated with action potentials and contractile activity.[10] This percentage is substantially higher than that which is observed in association with the gastric or main duodenal pacesetter potentials. The main duodenal pacemaker is situated at the level of the common bile duct,[14] but a specific, localized pacemaker node has not as yet been identified. This pacemaker has an inherent frequency (in dogs) of 17-19 per minute,[53] and is propagated initially at 20 cm. per second, with a progressively decreasing rate of propagation in the more distal small bowel such that ileal slow waves become independent of this pacemaker

and originate instead within the distal small bowel wall itself.[36]

The duodenal pacemaker is affected by factors similar to those which have been discussed with reference to the gastric pacemaker.[14, 53, 89] Vagotomy has no appreciable effect on the duodenal BER. Localized duodenal heating increases the BER frequency, and may precipitate ectopic foci with retrograde conduction of potentials. Localized cooling, transection, or clamping of the duodenum below the site of the pacemaker decrease the BER frequency by interrupting conduction pathways.[14]

Duodenal pacemaker activity in humans has been correlated with thyroid function; hyperactivity is associated with an increased BER frequency; conversely, a slowing of the BER is observed in association with decreased thyroid function.[30-32] The influence of the thyroid gland supports the view that cellular metabolic processes are involved in governing the slow wave frequency.

Daniel[45] has recently compared the control activity or BER of the stomach with that of the duodenum, and has observed the following similarities:

(i) both arise in longitudinal muscle, and are propagated electrotonically into the underlying circular muscle;

(ii) both are inherent and spontaneous in origin, and are not related to contractile activity; a

higher intrinsic frequency is found in the proximal regions of each organ;

(iii) both exhibit control over distal frequencies, such that the lower distal frequencies are "pulled in" or coupled to the higher proximal frequencies;

(iv) both are sensitive to inhibitors of ATPase, indicating a possible common mode of origin.[38]

There were, however, appreciable differences between the two PP's. Though the duodenal potential is capable of both caudad and retrograde propagation, it does not demonstrate the following characteristics that are observed with the gastric PP:

(i) there is no measurable refractory period following the duodenal slow wave;

(ii) premature PP's cannot be induced by acetylcholine;

(iii) catecholamines do not abolish the PP at either local or distant sites.

These observations suggest that perhaps the mechanisms underlying the initiation of slow waves in the stomach and duodenum are not in fact identical.

Opinion varies as to the degree of coordination between antral and duodenal activity.[43, 53] It would seem reasonable to suggest that mechanisms exist to formulate a coordinated motor unit which would promote gastric mixing and emptying, and at the same time prevent duodenal reflux. The gastric PP,

originating in the proximal greater curve, sweeps down the gastric musculature with increasing velocity, attaining a rate of 3-4 cm. per second in the antrum due to the greatly increased conductivity in this region. The rapid progress of this initial depolarization permits the entire antrum to contract virtually simultaneously. The terminal antral contraction so produced, in conjunction with the closed, contracted pyloric ring, is well designed for retropulsion and thorough mixing of the gastric chyme.[29, 53] The frequency of the terminal antral contraction is rate-limited by the frequency of the BER. The pyloric ring musculature per se does not influence resistance to flow except in association with antral activity. It is not so much a sphincter as part of a pumping mechanism which regulates gastric ejection of chyme into the duodenum.[53]

According to many investigators, the gastric pacesetter potential continues as far as the connective tissue septum between the antrum and duodenum, and there ceases. It has been suggested that this "hypomuscular zone" acts as an electrically silent insulator, and that there can be no electrotonic spread of current through this segment. However, some studies have recorded occasional evidence of duodenal electrical activity in the antrum, and rarely antral electrical activity in the duodenum.[43] These studies have suggested that the electrotonic spread of current across this junction occurs by way of the contiguous longitudinal muscle fibres. This observation lends support to the myogenic theory of origin and conduction of the

slow wave potential. In view of the muscular and neural connections across the gastroduodenal junction as outlined above, it is difficult to conceive of this region as an electrically silent insulator.

Allen[2, 53] has provided evidence to suggest a possible mechanism whereby antral and duodenal activity are interlocked. Most work has shown that there is no consistent temporal relationship between the antral and duodenal BER, or between antral and duodenal contractions, in either fasted or fed animals (dogs). In fasted animals, there is similarly no relationship between duodenal action potentials (and associated contractile activity) and the antral BER. However, in fed dogs, a relationship does exist between the antral BER and duodenal <u>contraction</u> in which the antral BER suppresses a duodenal contraction when a duodenal BER cycle begins synchronously with the <u>onset</u> of an antral BER cycle. Instead, the duodenal contraction is associated with either the second or third duodenal BER cycle following the onset of the <u>antral</u> BER cycle. The interlocking of antral and duodenal activity is somehow brought into play following the ingestion of food. Integration may occur via electrical impulses transmitted within the myenteric plexus, via hormonal pathways, or via the stimulus of the gastric chyme ejected into the duodenum. It has also been suggested that because the duodenal BER is usually a 3:1 or 4:1 harmonic of the gastric BER, there may be a coupling of the gastric and duodenal rhythms; the two pacemakers may function as coupled relaxation oscillators.[43]

With respect to surgical alteration of the gastroduodenal junction, an interesting concept has been put forward to explain the efficacy of pyloroplasty in association with vagotomy. Vagotomy has been associated with a disorganized BER during the first postoperative week, due to the emergence of ectopic foci of impulse generation. It has been suggested that pyloroplasty may reduce the excitability of ectopic pacemakers in the region of the pylorus which may have initiated randomly propagated potentials. The net effect would be less disorganization of the BER than would occur without pyloroplasty, and hence less disturbance of gastric peristalsis and improved gastric emptying following vagotomy.[43, 104]

SECTION VII. THE SMALL INTESTINE

From the point of view of comparison, the following section briefly outlines some of the features of small bowel motor and electrical activity.

There is a gradient of electrical rhythmicity progressing distally along the course of the small bowel, with the dominant pacemaker located in the second part of the duodenum.[14, 62] BER frequency decreases progressively towards the ileum, at which point the duodenal pacemaker no longer assumes control of the electrical activity.[36] The concept of segmental pacemakers collectively forming a series of coupled relaxation oscillators provides the most plausible explanation for entrainment throughout the small bowel, and accounts for normal caudad peristalsis.[62, 105].

Intestinal motility is regulated by both extrinsic and intrinsic nerve pathways. The more prolonged latent period of response, the relative paucity of nerve endings in intestinal versus gastric muscle, and the disproportionately high number of impulses required to effect a response suggest that excitation or inhibition of intestinal smooth muscle results from a generalized diffusion of transmitter substance, rather than liberation of the transmitter at discrete nerve endings in the muscle substance.

The intrinsic system is much more readily activated in the small intestine than in the stomach.[77] The myenteric reflex has been referred to as the "law of the intestine" as long ago as 1899 by Bayliss and Starling.[15, 16] Local stimulation of the intestine results in excitation above and inhibition below the site of stimulation. Radial stretching of sensory receptors rather than increase in transmural pressure is the effective stimulus. Transmission in this phenomenon is cholinergic.

The extrinsic innervation of the small intestine is concerned with the modulation of intrinsic reflexes. Both vagal and sympathetic fibres may act in either an excitatory or inhibitory capacity, depending on factors analogous to those discussed with reference to gastric motility.[108]

The sympathetic system is essentially inhibitory. Inhibitory adrenergic alpha receptors are located in the ganglion cells innervating the smooth muscle, while inhibitory beta

receptors reside in the smooth muscle fibres themselves.[14, 77] Stimulation of sympathetic efferents generally results in inhibition of intestinal tone and contractility, with the most pronounced effect occurring in the terminal ileum.

Vagal fibres may be either excitatory or inhibitory in their influence. The excitatory effects are more prevalent in the upper small intestine, as the splanchnics have a greater inhibitory influence in the terminal ileum. Post-activation potentiation of intestinal contractility following both afferent and efferent vagal stimulation has already been discussed.[19, 77]

To summarize, the intrinsic neural pathways play a more significant role in the regulation of intestinal motility than in regulation of gastric motility. The extrinsic nerves are primarily geared to facilitate or otherwise modify the intrinsic reflexes.

SECTION VIII. HUMAN BER

The BER of the human stomach has been examined and recorded by means of peroral suction electrodes in contact with the gastric mucosa.[90] It consists of a triphasic complex lasting 2.5-3.0 seconds, is propagated at a velocity of approximately 2 cm. per second in the antrum, and has an inherent natural frequency of three cycles per minute. During the fasting state, approximately 25-30% of the BER cycles are associated with action potentials, which are represented electrically by a burst of rapid spikes of unequal amplitude, beginning 3-4 seconds

after the onset of the BER complex, and lasting 3-6 seconds. The AP's are associated with gastric contractile activity. The electromyographic discharge of the action potential is related both in time and amplitude to the pressure wave recorded by either a strain gauge or intraluminal balloon.[35, 90]

Duodenal BER has been recorded in humans at a frequency of 11.7 cycles per minute.[30-32] There is a descending gradient of BER frequency along the length of the small intestine, with ileal rates recorded at 9.5 cycles per minute.

Human BER is sensitive to temperature change in a manner similar to that described for animals.[14] It is apparently not affected by fasting. The BER frequency has been shown to vary with the activity of the thyroid gland; increased BER frequency is observed in hyperthyroid states, and decreased rates are associated with impaired thyroid function.[30] Insulin induced hypoglycemia has been shown to independently decrease the frequency of the BER.

CHAPTER TWO

METHODS OF INVESTIGATION

1. The Plan of the Experiment

The plan of the experiment aimed at developing an intra-operative test to assess the completeness of vagotomy was essentially twofold:

(i) to determine whether complete vagotomy would alter the gastric electrical activity in some reproducible manner such as would indicate that all vagal connections had been severed;

(ii) to divide one vagus at the level of the esophageal hiatus, assess the effect on the electrical activity of stimulation of its distal or peripheral end, then stimulate the central end with view to eliciting a response in the electrical activity via reflex pathways through the brain stem and vagal nuclei, and hence down the remaining intact efferent vagal fibres; the remaining fibres would then be divided, central stimulation of either vagal trunk repeated, and presumably the previously observed "characteristic" response of the gastric electrical activity would no longer be obtained, indicating complete division of all vagal fibres.

The reflex pathway of vagal impulse transmission through the central nervous system and gastric secretory and motor

responses to afferent vagal stimulation have been adequately documented in the introductory chapter of this review. One may reasonably expect that a corresponding effect on gastric electrical activity could also be obtained via this vago-vagal reflex. To investigate these questions, five groups of animals were studied.

2. Group I. Recording of the BER; the effect of vagal section and vagal stimulation using sodium thiopental anaesthesia

Twenty-six mongrel dogs weighing 15-25 kilograms were studied in acute experiments following an overnight fast. The animals were anaesthetized with sodium thiopental (Pentothal, Abbott), and respiration was controlled by the use of a Bird Mark VII respirator. Anticholinergic drugs were not administered pre-operatively.

Gastric electrical activity was recorded by several methods. In the initial trials, electrodes of both stainless steel and silver wire, 0.006-0.010 inches in diameter, were implanted subserosally perpendicular to the long axis of the stomach. However, recordings obtained in this manner were of unsuitable quality, and this method was consequently abandoned. All electrical recordings evaluated in both this and subsequent groups of study were obtained using monopolar silver wire electrodes. The electrode tip projected 2 mm. from one surface of a flat, double-layered Teflon disc. The silver wire electrode, with the exception of its tip, was insulated by a Teflon sheath, and

was connected between the discs to an insulated copper wire lead. The entire electrode assembly, again with the exception of the electrode tip, was sealed with epoxy resin.

The stomach was exposed through a mid-line laparotomy incision. The electrode discs were sutured via drill holes in each of the four corners to the serosal surface of the greater curve of the stomach in a serial fashion from the fundus to the terminal antrum. Insulated wire leads transmitted the electrical signal to an alternating current amplifier, which in turn was linked to one channel of a rectilinear recording system (Physiograph Six - E & M Instruments). A time constant of 0.3 seconds was selected on the AC amplifier. Calibration was adjusted such that a one millivolt impulse was represented by a 15 mm. pen deflection. A relatively long time constant was chosen to allow accurate recording of the BER and evaluation of the temporal relationship between the BER and any associated action potentials. Shorter time constants were found to deform or even eliminate the BER complex (Fig. 8B). One disadvantage of the longer time constant related to the need to reduce the amplifier gain in order to avoid excessive drifting of the baseline. Shorter time constants and higher amplification allowed better recording of what were interpreted as action potentials associated with contractile activity, but the BER was so distorted as to be uninterpretable. The most satisfactory recordings were obtained when the electrodes were in firm contact with serosa, but not penetrating it. Electrode

tips penetrating the muscle or the gastric lumen produced recordings which were unreadable because of extraneous electrical noise.

After recording the baseline BER, the vagus nerves were dissected at the level of the esophageal hiatus, and were isolated by retraction of adjacent structures. The thoracic cavity was entered on all occasions to facilitate isolation of a 3-4 cm. segment of each nerve trunk. Stimuli to both afferent and efferent vagal trunks were delivered by means of a stainless steel bipolar electrode fashioned in the form of a nerve hook. Electrical stimulation was applied in the form of square wave impulses as delivered by the impulse generator component of the Physiograph Six system. The stimulator provided a range of impulse durations (0.1, 0.5, and 2.0 milliseconds), impulse frequencies (2-200 impulses per second), and voltages (0.1-130 volts). In the initial trial experiments, single volley impulses of various voltages and impulse durations were applied, but these produced little response. Thereafter, stimuli of varied gradations were applied for periods of 60-120 seconds. Impulse durations were varied on the basis of the concept of the existence of excitatory and inhibitory fibres as outlined by Martinson.[81-85] Most of the interpretable responses occurred with impulse durations of 0.1 or 0.5 msc., applied at a frequency of 10 impulses per second. Low voltages (5-20 V) produced minimal effect; therefore, stimuli of up to 120 V, though unphysiologic, were required to detect significant responses.

The BER was recorded in all animals following the division of one vagal trunk (either anterior or posterior), and then following complete vagal section. Following complete truncal vagotomy, the BER in five animals was further studied under the following circumstances:

(i) after esophageal transection;

(ii) following rapid sacrifice of the animal by intravenous administration of potassium chloride.

During the course of several procedures, the regular test stimulus was preceded by a thirty second period of stimulation using the same voltage and impulse duration as the test stimulus in question, but applied at frequencies of 50-100 impulses per second.[60, 103]

The cervical vagi were dissected, divided, and stimulated centrally and peripherally in two dogs. The BER was examined before and during stimulation, and after complete cervical vagotomy.

3. Group II. Effect of the operative procedure on BER

A control group of six animals was studied to determine the effect of the operative procedure per se on the rate of the BER. Five minute tracings were recorded each fifteen minutes over a two hour period under operative conditions similar to those which prevailed in Group I.

4. Group III. Effect of vagal stimulation on BER, using chloralose-urethane anaesthesia

A third series of experiments was undertaken to take into account the reported inhibitory effect of barbiturate anaesthesia on the response of intragastric pressure to vagal stimulation,[9] as it was considered that this inhibition might apply as well to the vagal influence on gastric electrical activity. A mixture of chloralose and urethane was therefore used as a substitute for sodium thiopental.[48] Alpha-chloralose (2 G.) was mixed with urethane (10 G.) in 100 cc of water, dissolved by boiling, and administered intravenously in a dosage of 3.5 mg./kg. Electrical activity was recorded as described in the discussion of the first group of experiments, but in this series, only antral electrodes were applied.

Electrical stimuli to both afferent and efferent vagal trunks were delivered by the stimulus generator already described. Because of disturbing retching movements encountered upon central stimulation of either divided vagal trunk in the initial four animals studied, succinylcholine chloride (Anectine, Dow) in intermittent dosage of 20-30 mgm. was administered intravenously to counteract this effect. Stimulation in the following twelve procedures was applied with the bipolar stainless steel electrode employed in Group I, using the same range of stimulus parameters outlined in that section. In the remaining thirteen animals studied in this group, two innovations were introduced. A stimulus isolator (Tektronix 2620) with a range of 0.01-30.0 milliamperes was added to the stimulator component

with the intent of ensuring precise delivery of the current selected by automatically compensating for any change in the resistance of the experimental model. A new, bipolar phosphor-bronze stimulating electrode with broad, flattened contact surfaces was introduced for the purpose of minimizing heat damage to the nerve during stimulation. The flattened surfaces of the electrode tips were designed to permit the current to be distributed over a considerably longer segment of the nerve fibre.

5. Group IV. Conduction velocity of the BER

Conduction velocity of the BER was studied in four animals. Electrical activity was recorded in a bipolar fashion between two gastric electrodes situated 2 cm. and 5 cm. respectively from the pylorus. Conduction velocity was examined before and after complete vagal section. Electrical stimulation of a peripheral vagal trunk so distorted the BER that conduction velocity during stimulation could not be measured.

6. Group V. Effect of pentagastrin on BER before and after vagotomy

The effect of pentagastrin (Peptavlon, Ayerst) on gastric BER and contractile activity was examined in eight animals before and after vagotomy. Electrical activity was recorded as outlined for the initial experimental groups. Baseline BER was recorded, and pentagastrin was then infused continuously by means of a Harvard pump at a rate of 4 ugm/kg./hr. Twenty

minutes after commencement of the infusion, one vagus nerve (either anterior or posterior) was divided at the level of the esophageal hiatus. The remaining vagal trunk was divided after a further fifteen minutes, and the infusion was discontinued fifteen minutes after complete vagal section. Random five minute recordings at each stage of the procedure were examined to determine the effect on the BER. Electrical stimulation of the divided vagal trunks, utilizing the new phosphorbronze electrode and stimulus isolator, was carried out in three animals during the course of pentagastrin infusion.

CHAPTER THREE

RESULTS AND DISCUSSION

1. Group I. Recording of the BER; the effect of vagal section and vagal stimulation using sodium thiopental anaesthesia

Recordings from the fundus and proximal one-third of the corpus did not reveal any evidence of rhythmical electrical activity. Initial potentials with the greatest amplitude were observed in tracings recorded over the antrum (Fig. 1). This observation is in agreement with previous work which has localized the origin of the pacesetter potential to the junction of the proximal and middle thirds of the stomach.[110] Action potentials were recorded most often at the antrum (Fig. 1), and were followed immediately by visually observed contractile activity. Simultaneous recording of intragastric pressure was not performed in this series of experiments. As many as 50% of the PP's were followed by action potentials in some of the animals studied, particularly after manipulation of the stomach. Electrodes placed serially along either the anterior or posterior aspects of the greater curve demonstrated identical BER rates throughout the length of the distal two-thirds of the organ.

The mean frequency of the BER was calculated from recordings in twenty animals to be 4.41 $\pm$ 0.40 cycles per minute (Table I). Following division of one vagal trunk (either anterior or posterior), the mean frequency was 4.27 $\pm$ 0.55 cycles per minute. Complete vagotomy resulted in a mean frequency of 4.08 $\pm$ 0.51

cycles per minute. Statistical analysis (Wilcoxon's Signed Ranks) indicate a significant difference in the BER frequency before and after complete vagotomy ($p < 0.002$). The difference in the BER frequency with one vagus divided as compared with that following complete vagotomy is also of significance ($p < 0.01$).

In four animals, the BER became disorganized following complete truncal vagotomy (Fig. 2). This disorganization was temporary, reverting to a regular pattern in most instances within ten minutes. Disorganization of the BER was also observed on several occasions following division of only one vagal trunk (Fig. 2); this phenomenon was again only temporary. Sequences of desynchronized BER also occurred spontaneously, perhaps due to anoxia, change in body temperature, anaesthesia, inadvertent traction on the dissected vagi or on the stomach (Fig. 2), or hyperventilation. It therefore appears that an irregular, disorganized BER is by no means pathognomonic of complete vagal section.

Previous reference was made to Daniel's observations which report minor variations in the amplitude of the BER complex secondary to the effect of various drugs.[37, 42-44] The present study has demonstrated that spontaneous changes in the amplitude of the pacesetter potential are often observed within relatively short tracings from the same electrode (Fig. 1). These variations were not apparently precipitated by any manipulation of the experimental model. It is difficult to draw any firm

conclusions with respect to factors which may influence the amplitude of the PP's, other than perhaps the firmness of contact or depth of penetration of the electrode tip into the serosa.[14, 20]

Electrical stimulation of the distal end of either divided vagal trunk, using stimuli of 100-120 V, 0.1-0.5 msc. duration, applied at 5-10 impulses per second for periods of 60-120 seconds, resulted in marked contractile activity of the antrum, a series of AP's, and in most instances an associated disorganization of the BER for the duration of the stimulation and up to 20-30 seconds thereafter (Fig. 3). Stimulation of the central end of one divided vagus (either anterior or posterior) with the other trunk remaining intact had no demonstrable effect on the BER or contractile activity in this series of experiments despite systematic variation of voltage, impulse duration, and impulse frequency across the full range of capability of the stimulator available (Fig. 3). Thus, the model as described in this series has not demonstrated the existence of a vago-vagal reflex whereby one might alter gastric electrical activity or motility by central (reflex) stimulation of either vagal trunk.

Following complete truncal vagotomy and esophageal transection, the BER remained unchanged in the five animals so studied (Fig. 4). Rapid sacrifice of these animals by the intravenous administration of potassium chloride (which caused cardiac asystole within 10-15 seconds) did not appreciably alter

the BER in the initial few minutes post-mortem. Following this variable period, the amplitude of the potentials decreased, and some irregularity of rhythm was observed. One dog maintained a regular BER pattern with a rate identical to the pre-vagotomy rate for a full twelve minutes after cardiac standstill.

Attempts to obtain an enhanced response of the BER to either afferent or efferent vagal stimulation by preceding the regular test stimulus with a thirty second period of high frequency stimulation were unsuccessful. It was not possible in this model to confirm the principle of post-activation potentiation as applied to gastric electrical activity.[19]

In two animals, the cervical vagi were isolated, divided, and stimulated. Stimulation of the distal cervical vagus (10-50 V, 0.5-2.0 msc., 10 impulses per second x 60-90 seconds) produced no effect on the BER. Central stimulation of one cervical vagus while the other trunk remained intact resulted only in the characteristic retching movements, but no effect on the BER. Following complete cervical vagal section in one of the animals, a fifteen minute period of gross BER disorganization was observed (Fig. 5). Interestingly, traction on the cervical vagi during dissection but before division of the nerve trunks resulted in this same animal in a prolonged series of repetitive potentials, perhaps an illustration of the sympathetic dominance pattern (Fig. 5).

2. Group II. Effect of the operative procedure on BER

A control group of six animals was examined to determine the effect of the operative procedure per se on the frequency of the BER (Table II). More specifically, this investigation was designed to evaluate the combined effects of time, anaesthesia, and change in body temperature on the BER rate. Sequential five minute tracings obtained at fifteen minute intervals over a two hour control procedure were examined. Statistical evaluation using analysis of covariance and linear regression indicated a significant slowing of the BER over the course of the two hour test period ($p < 0.05$). Slopes fitted for data obtained from each animal indicated that the rate of reduction of the BER frequency was similar in each animal studied ($p = 0.01$).

3. Group III. Effect of vagal stimulation on BER, using chloralose-urethane anaesthesia

The investigation to this point has not taken into consideration the reported inhibitory effect of barbiturate anaesthesia on the gastric contractile response to vagal stimulation.[9] As it was considered that this inhibitory effect may apply as well to the response of electrical activity, a further series of acute experiments was undertaken, in which a chloralose-urethane anaesthetic mixture was substituted for sodium thiopental.[48] Chloralose, though depressing cortical activity,[8] is thought to have an excitatory effect on subcortical structures, and may, via its action on lower cerebral centres,

potentiate gastric motility and secretion.[9]

A total of twenty-nine procedures was assessed in this series. The specific effect of vagotomy on the frequency of the BER was not examined, as the investigation outlined in Groups I and II has satisfactorily demonstrated that vagotomy has no consistent, reproducible effect on the frequency of this potential. Succinylcholine abolished the retching movements caused by central reflex stimulation without altering the BER or gastric contractile responses to efferent vagal stimulation.

In twenty-five animals, both afferent and efferent vagal trunks were stimulated electrically. In the initial twelve procedures (Group IIIA), electrical stimulation was applied using the stainless steel electrode as described for Group I. The remaining thirteen procedures (Group IIIB) differed from the initial twelve in that the stimulus isolator and phosphor-bronze stimulating electrode were introduced into the experimental model.

In Group IIIA, distal stimulation of either vagal trunk (whichever was divided first) usually resulted in strong antral contractions and occasional upper jejunal activity, and was accompanied by a marked distortion of the BER complex for the duration of stimulation and up to 30-60 seconds thereafter (Fig. 6). The latency of this response was less than five seconds. The most pronounced effects were achieved with stimuli of 100-120 V, 0.5-2.0 msc. duration, applied at 10 impulses per second for periods of 60 seconds.

In nine of twelve trials of proximal or reflex stimulation of one divided vagus with the remaining vagus intact, an effect consisting of slight to moderate antral and upper small bowel contractile activity was observed after a variable latent period of 30-40 seconds. The most pronounced effects resulted from stimuli of 120 V, 0.5 msc. duration, applied at 10 impulses per second for more prolonged periods, up to three minutes. In five of the nine animals with a positive contractile response, the BER was significantly distorted during the period of stimulation and for 40-60 seconds thereafter (Fig. 6). However, the distortion of the BER was not observed with <u>every</u> period of proximal stimulation in the same animal. Generally, the increase in small bowel activity was more predominant than the activity of the antrum following proximal stimulation. However, the observations of contractile activity were only subjective impressions, and must be confirmed by measuring either intraluminal pressure change or contractile force before assuming significance.

In seven of the nine animals in which contractile response (and occasional BER distortion) had occurred on proximal stimulation of one divided vagus, proximal stimulation of either vagal trunk after section of the remaining vagus no longer produced these effects (Fig. 6), suggesting that the reflex stimulation had in fact initiated the responses observed via impulses conveyed through the central nervous system and along intact vagal efferents to the stomach and small intestine. This would

seem to confirm the existence of a vago-vagal reflex. In the remaining two animals, however, proximal stimulation of either vagal trunk following complete vagotomy resulted in increased small bowel motor activity, rather than abolishing the response. This may be interpreted as due to either a removal of vagal inhibitory fibres, or perhaps to stimulation of sympathetic cholinergic excitatory efferents.[78]

In one animal, proximal stimulation of the divided anterior vagus nerve with the posterior trunk still intact produced no change in the BER and no contractile activity. Following complete vagotomy, proximal stimulation of either vagal trunk resulted in marked contractile activity of the upper small bowel, but no observable change in the antral BER. Distal stimulation of either trunk in this animal produced the characteristic strong antral contractile activity and distortion of the BER. In the remaining two animals of this series (Group IIIA), proximal stimulation of one divided vagus produced no change in the BER, and no obvious contractile activity, though distal stimulation was effective in eliciting changes in both. Proximal stimulation of either vagal trunk following complete vagotomy in these two animals was also ineffective in eliciting any change in BER or contractile activity.

Efferent vagal stimulation in the animals included in Group IIIB generally resulted in the same degree of BER distortion and antral contractile activity as occurred in Group IIIA. In ten of thirteen animals, afferent or reflex stimulation

of one divided vagus (while the other vagus remained intact) was accompanied by a visually observed increase in antral and/or small bowel contractile activity. However, in only three of these animals was there a definite, simultaneous change in the BER pattern (Fig. 7). The most pronounced effects were obtained using low intensity, low frequency stimuli in accordance with Martinson's concept of low threshold excitatory vagal fibres. The most effective stimuli were of the order of 3-7 ma, 0.1 msc. duration, applied at 5 impulses per second for periods of 60-120 seconds. Higher intensity stimuli generally had less pronounced effects on contractile activity. Preceding the test stimulus with thirty second periods of high frequency stimulation was not effective in potentiating the response to either afferent or efferent stimulation. Proximal stimulation of one afferent trunk was not associated with any observable change in BER or contractile activity in the remaining three animals of this group.

Following complete vagal section, proximal stimulation of either vagal trunk using the same stimulus parameters no longer produced the effects recorded above in nine of the ten animals (Fig. 7). The one exception to this pattern was an increase in small bowel contractile activity following central vagal stimulation, even though all vagal fibres had been severed. Once again, the results tend to support the view that gastric electrical and motor activity can be altered by reflex stimulation of afferent vagal fibres.

4. Group IV. Conduction velocity of the BER

Conduction velocity of the BER complex was studied in four animals by recording in a bipolar fashion from two adjacent antral electrodes (Fig. 8A). The average conduction velocity was 2 cm. per second as measured over the antrum. The conduction velocity was not altered significantly by division of either one or both vagi (Fig. 8A). Electrical stimulation of the distal vagal trunks so distorted the tracings that conduction velocity could not be measured. Central stimulation of one divided vagus, with the other trunk intact, did not alter the conduction velocity of the BER in the animals studied.

5. Group V. Effect of pentagastrin on BER before and after vagotomy

A final group of eight animals was examined to ascertain the effect of a continuous pentagastrin infusion on the BER frequency and on gastric contractile activity. The recordings obtained from six animals were suitable for analysis. The mean resting BER frequency was calculated at 4.06 cycles per minute. Within 15-30 seconds of the commencement of the pentagastrin infusion, antral contractile activity increased markedly, and continued at this heightened level for the duration of the infusion and usually for 15-20 minutes thereafter. A corresponding increase in the BER frequency was observed after the onset of pentagastrin infusion in all cases studied, following a variable latent period of 15-30 seconds (Fig. 9). The increased

BER frequency outlasted the duration of the infusion by up to 40-45 minutes in two animals observed for that length of time.

The mean BER frequency during the initial stage of the infusion, before the vagi were divided, was 5.45 cycles per minute, an increase of 34% over the resting rate (Table III). Following division of one vagus nerve, the mean frequency was 5.51 cycles per minute; after complete vagotomy, the mean rate was 5.45 cycles per minute (Table III).

The 34% increase in BER frequency recorded during pentagastrin infusion is in accord with the similar increases described by Cooke[35] and Monges.[91] However, it seems clear that this effect is not under vagal control, as no appreciable change in the BER frequency was observed following section of either one or both vagal trunks (Fig. 9).

Electrical stimulation of both afferent and efferent vagal trunks was studied in three animals during the course of the continuous pentagastrin infusion. Peripheral stimulation (5-10 ma, 0.1-0.5 msc., 5-10 impulses per second for 60-120 seconds) consistently resulted in marked antral contractile activity and BER distortion, as observed in the previous experimental groups. Central or reflex stimulation, however, produced only inconstant effects on BER rhythm and antral contractility. Gross observations suggest that pentagastrin at this rate of infusion (4 ugm/kg./hr.) does not significantly potentiate the gastric contractile response to reflex vagal stimulation, though fine differences could perhaps be detected by measuring contractile force

with strain gauges. It therefore does not appear that the use of pentagastrin as an adjunct to potentiate vago-vagal reflex activity will be of any significant value in the search for a reliable test to assess the completeness of vagotomy.

CHAPTER FOUR

SUMMARY AND CONCLUSIONS

Electrical activity of the stomach has been recorded in both monopolar and bipolar fashions from the gastric antrum. Basic electrical rhythm (BER) was recorded before and after vagotomy. A significant reduction of the BER frequency was noted after complete vagotomy ($p < 0.002$), but not after the division of only one vagal trunk. Also of significance was a slower BER frequency following complete vagotomy as compared with the rate with only one vagus divided ($p < 0.01$). However, the slowing of the BER as a result of the effects of the operative procedure itself (effect of time, anaesthesia, decrease in body temperature) was also significant when recorded over the course of a two hour period ($p < 0.05$). Therefore, it is not possible to draw any definite conclusions concerning the significance of the reduced BER frequency which follows complete vagotomy. Certainly one cannot claim that this reduced rate is indicative of complete vagal section. Moreover, even if the reduction in BER frequency could in fact be attributed purely to vagal section, the reduction observed in this investigation, though of significance statistically, is of such a low order as to be of very limited value in the assessment of any individual case.

On several occasions, a disorganized BER was observed following complete vagotomy. However, this irregularity was

not only temporary, but could also occur spontaneously, following division of only one vagal trunk, or following traction on the vagi. Hence it is certainly not pathognomonic of complete vagotomy, as has been suggested by Nelsen.[93, 96] Some investigators have reported that the disorganization of the BER following vagotomy is not observed immediately, but develops only after a latent period of several hours or even days.[71] This may explain why this phenomenon was not observed more frequently in the present series of acute experiments. If delay in the onset of BER disorganization is the rule, this principle could not be applied as a sound basis for an intraoperative test to assess the completeness of vagotomy.

Electrical stimulation of the peripheral or distal end of a divided vagal trunk generally resulted in a marked distortion of the BER and considerable increase in antral contractile activity. In the initial experimental series (Group I) using sodium thiopental anaesthesia, it was not possible to elicit a reflex response in gastric electrical or motor activity by central stimulation of one divided vagus while the other vagal trunk remained intact. However, subsequent investigation substituting a chloralose-urethane mixture for sodium thiopental has suggested that vago-vagal reflex effects can be achieved by means of afferent vagal stimulation. Alterations in gastric electrical and contractile activity were produced by afferent vagal stimulation using low intensity, low frequency impulses (5 ma, 0.1 msc., 5 impulses per second); the effects were

presumably mediated via pathways through the central nervous system and along the remaining intact efferent vagal fibres to the stomach. The reported potentiating effect of chloralose on the gastric response to vagal stimulation may have been influential in achieving these results.[9] Nevertheless, the results do demonstrate the existence of a vago-vagal reflex pathway whereby one may modify gastric electrical and contractile activity by stimulation of afferent vagal fibres.

The response of the BER to reflex vagal stimulation was very convincing on several occasions, but unfortunately, this response was by no means consistent or reproducible. Far more consistent was the increase in both antral and small bowel contractile activity following afferent vagal stimulation. It would therefore seem more appropriate in the light of these observations to conduct the search for a reliable intraoperative test to assess completeness of vagotomy by investigation of changes in the contractile force of the gastrointestinal smooth muscle subsequent to afferent vagal stimulation. On the other hand, it does not appear that further evaluation of either the effect of vagotomy on the conduction velocity of the BER or the effect of pentagastrin on electrical activity before and after vagotomy will contribute very much of significance to the search at hand.

What then are we left with? The Hollander insulin test no doubt provides a reasonable guide as to who is at risk of recurrent ulceration following vagotomy. The intraoperative tests

developed to date have been neither conclusive nor pathognomonic of complete vagotomy. Perhaps complete parasympathetic denervation is an impossible goal in view of the extravagal cholinergic outflow via splanchnics and thoracic dorsal root ganglia. Perhaps complete anatomic vagotomy is not in fact essential for protection against recurrent ulcer; support for this concept can be found in the incomplete but "adequate" vagotomy which occurs when only a terminal gastric fundic branch remains undivided. Perhaps any of these tests has as its major virtue a stimulus to the surgeon to be more meticulous and exacting in his technique of performing vagotomy, knowing that his work will be put to the "acid" test postoperatively. Nevertheless, the development of such an intraoperative test will be a major factor in firmly establishing vagotomy as a valid operation in the treatment of peptic ulcer disease, and will help prevent this method from falling into disrepute because of a continued high rate of recurrent ulceration.

TABLES

TABLE I

BASIC ELECTRIC RHYTHM BEFORE AND AFTER VAGOTOMY

	BER (cycles per minute)		
Dog	Vagi Intact	One vagus divided	Both vagi divided
1	3.95	3.13	2.76
2	4.13	4.47	4.11
3	4.57	4.56	4.54
4	4.21	4.17	3.99
5	4.83	4.72	4.95
6	4.78	4.36	4.05
7	4.13	4.05	3.76
8	4.51	3.79	3.91
9	4.93	4.65	4.16
10	3.97	4.07	4.19
11	4.77	4.43	4.57
12	4.75	3.60	3.84
13	4.46	4.21	3.75
14	3.91	4.03	3.74
15	4.44	4.12	4.01
16	4.42	4.13	3.95
17	4.20	4.37	3.93
18	3.57	3.65	3.60
19	5.20	5.60	5.00
20	4.40	5.20	4.75
mean	4.41	4.27	4.08
standard deviation	±0.40	±0.55	±0.51

Each recording represents the BER in cycles per minute, averaged over a randomly chosen five minute sequence of recording. The difference in the BER with the vagi intact and that following complete vagotomy was highly significant ($p < 0.002$). The difference between the BER with one vagus divided and that following complete vagotomy also achieved significance ($p < 0.01$). Statistical analysis performed by Wilcoxon's Signed Ranks Test.

TABLE II

THE EFFECT OF LAPAROTOMY AND TIME ON THE BER

Dog	BER	(cycles per minute) at 15 minute intervals							
	0	15	30	45	60	75	90	105	120
1	4.88	4.74	4.70	4.14	3.83	3.82	3.67	3.46	3.97
2	4.82	4.43	5.07	4.87	5.08	5.02	5.07	--	--
3	4.95	4.62	4.54	3.65	4.00	3.87	3.93	3.85	4.20
4	4.12	4.29	4.21	3.96	3.80	3.90	3.94	4.04	3.69
5	4.34	4.42	4.52	4.68	4.79	4.71	4.29	4.21	4.08
6	3.88	4.12	4.20	4.54	3.69	4.39	4.10	--	3.76

Statistical evaluation using analysis of covariance and linear regression indicates a significant slowing of the BER over the two hour test period ($p < 0.05$). Slopes fitted for data obtained from each dog reveal that the rate of reduction in the BER rate is similar in each animal studied ($p = 0.01$).

TABLE III

THE EFFECTS OF PENTAGASTRIN ON THE BER

BEFORE AND AFTER VAGOTOMY

Dog	BER in cycles per minute			
		Course of pentagastrin infusion		
	Baseline	Vagi intact	One vagus divided	Both vagi divided
1	3.76	5.20	5.30	5.50
2	4.04	5.06	5.20	5.20
3	4.34	5.66	5.60	5.60
4	3.80	5.56	5.40	5.52
5	3.80	5.28	5.54	4.88
6	4.60	5.94	6.00	6.02
mean	4.06	5.45	5.51	5.45

The effect of a continuous infusion of pentagastrin (4 ugm./kg./hr.) on the BER of the canine stomach before and after vagotomy. Pentagastrin resulted in a 34% increase in the BER frequency. Vagotomy did not alter this effect.

FIGURES

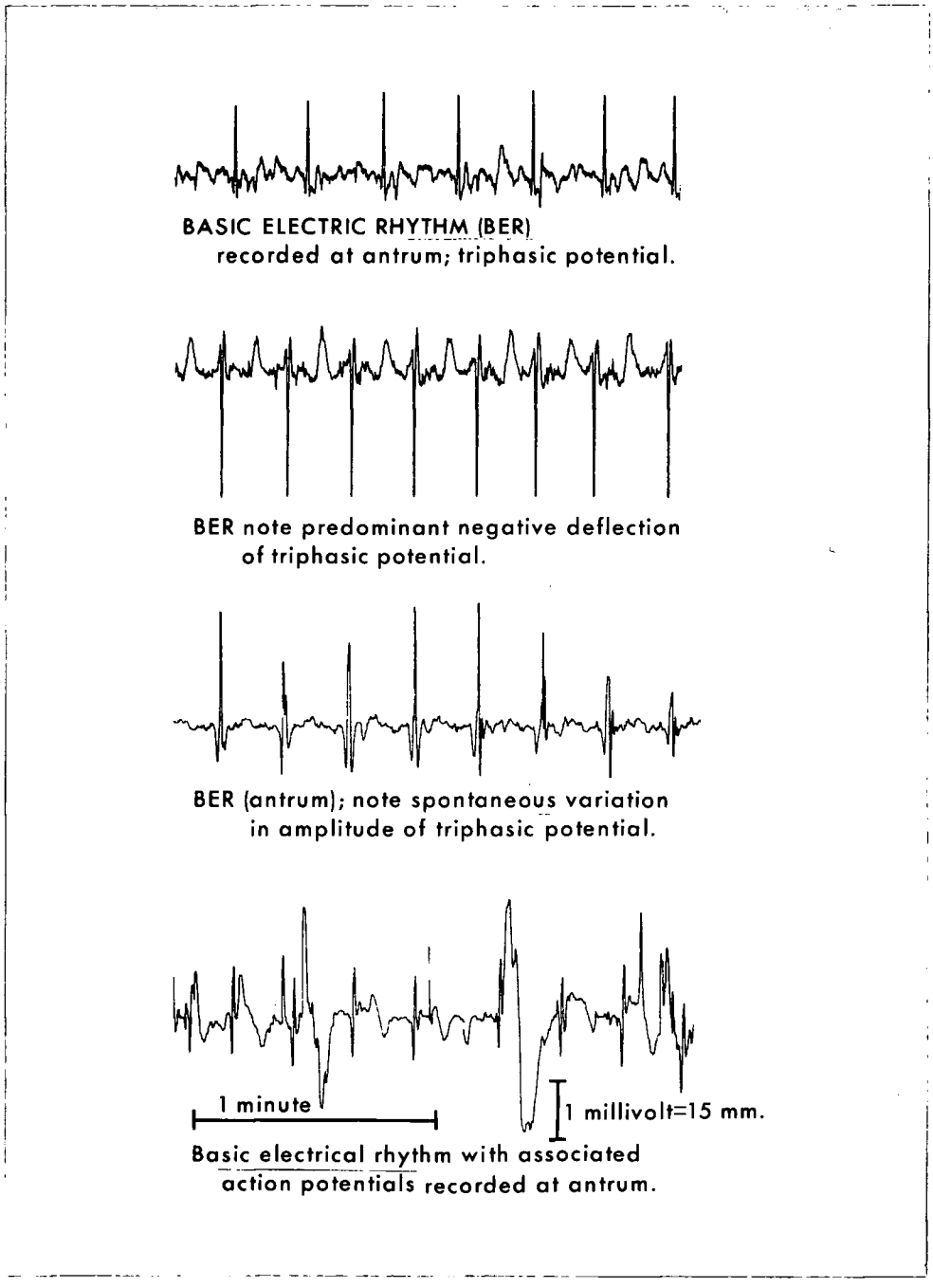


Figure 1. Basic electrical rhythm (BER) recorded at antrum. Variations in configuration of the electrical potential in the resting state. Demonstration of associated action potentials.

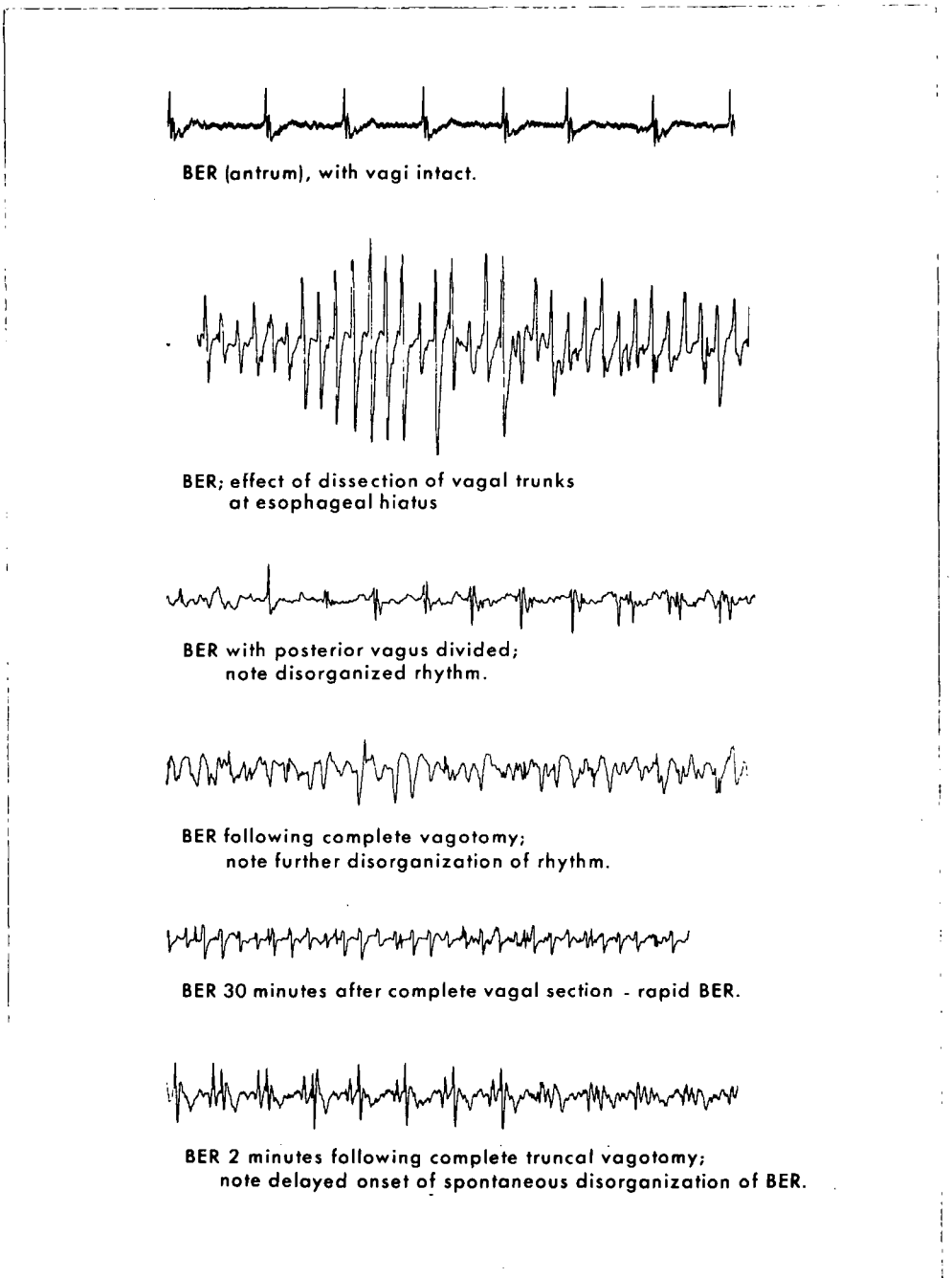


Figure 2. Alterations in the BER following vagal dissection and division.

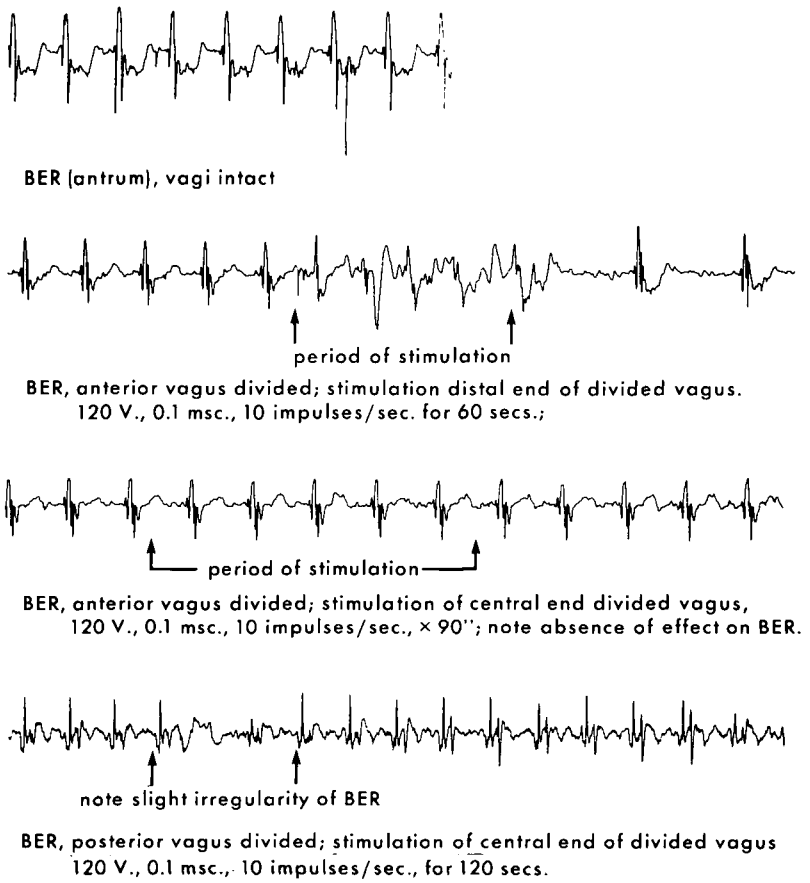


Figure 3. The effect on BER of afferent and efferent vagal stimulation before and after complete vagal section (sodium thiopental anaesthesia).

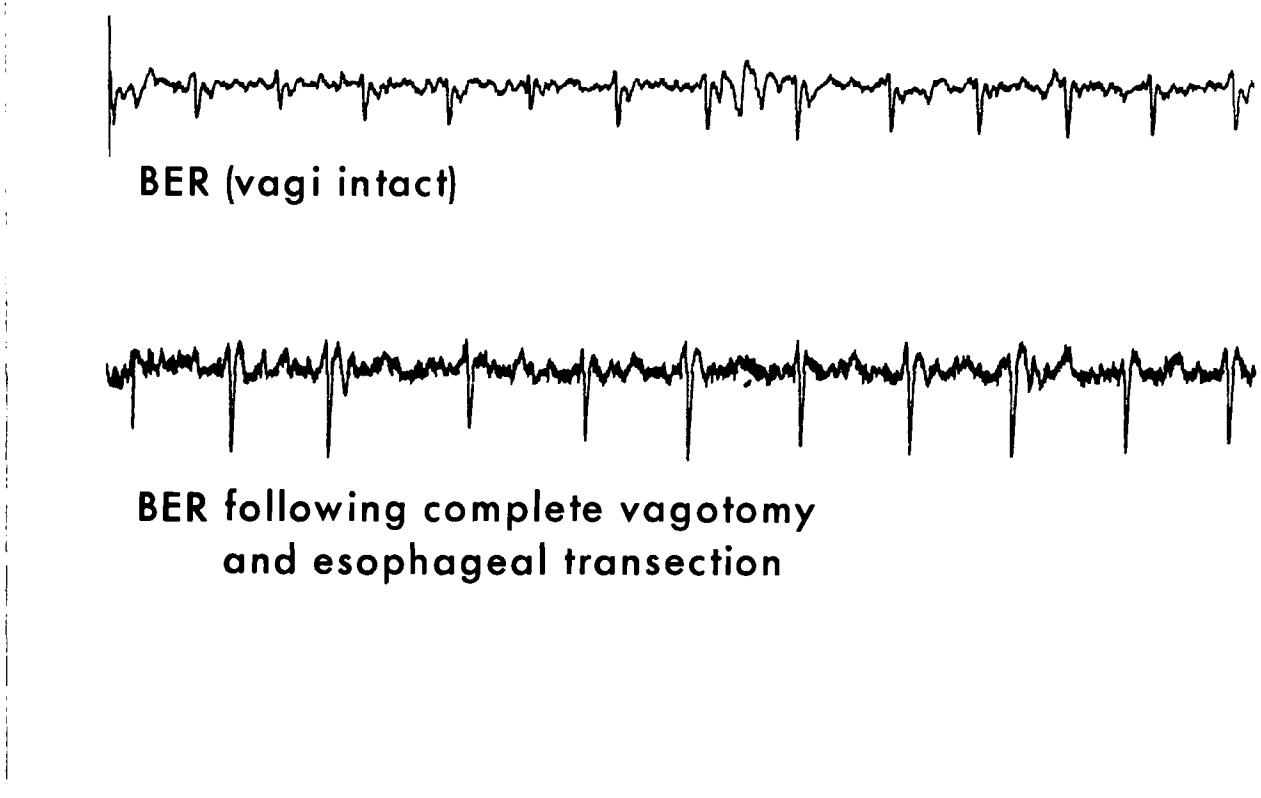


Figure 4. BER following complete vagotomy and esophageal transection.

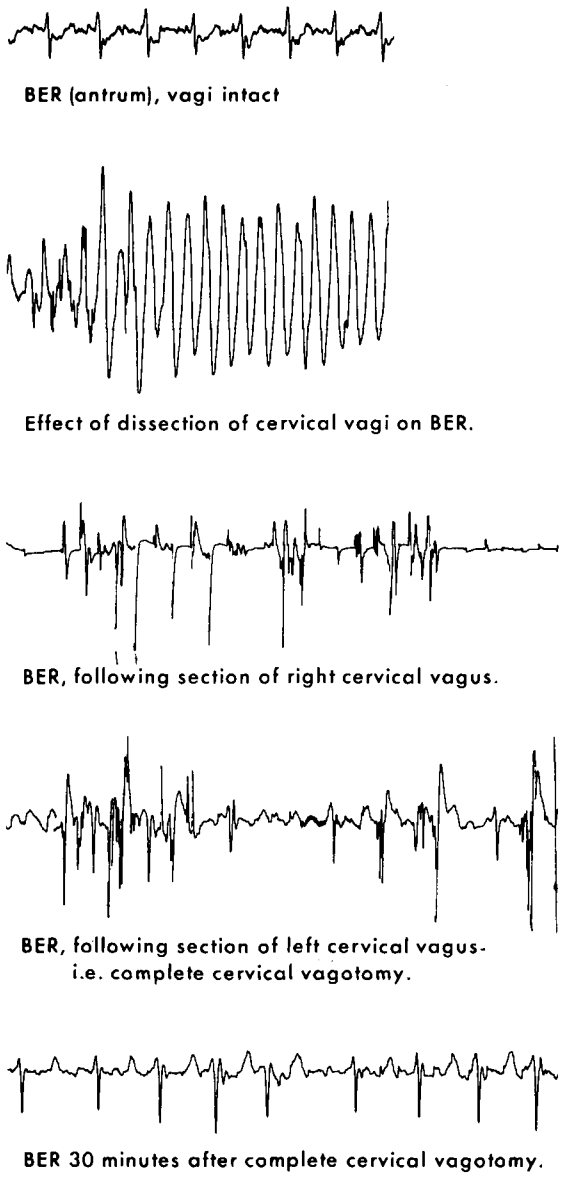
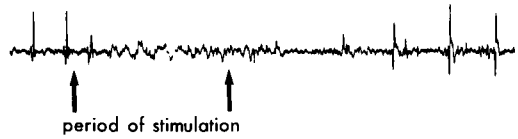
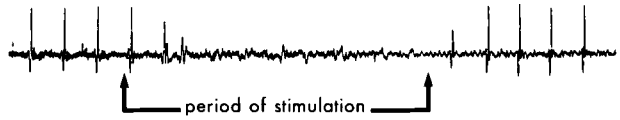


Figure 5. The effect of dissection and division of the cervical vagus nerves on the BER.

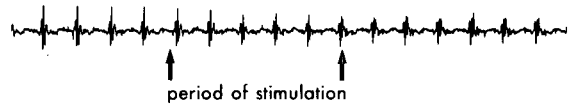
BER, Vagi intact; chloralose-urethane anaesthesia, with supplemental succinylcholine



BER, anterior vagus divided; stimulation peripheral end of divided vagus;
120 V 0.5 msc., 10 impulses/second, for 60 seconds
Strong antral contractions observed during stimulation



BER, anterior vagus divided. stimulation central end of divided vagus
120 V, 2.0 msc., 10 impulses/second for 120 seconds
Strong antral contractions observed during stimulation



BER, both vagi divided; stimulation central end of divided anterior vagus.
120 V, 2.0 msc., 10 impulses/second × 60 seconds
No contractile response in antrum. No change in BER.

BER, both vagi divided; stimulation central end of divided posterior vagus,
120 V, 0.2 msc., 10 impulses/second × 60 seconds.
No contractile response in antrum. No change in BER

Figure 6. The effect on BER of afferent and efferent vagal stimulation before and after complete vagal section (chloralose-urethane anaesthesia).

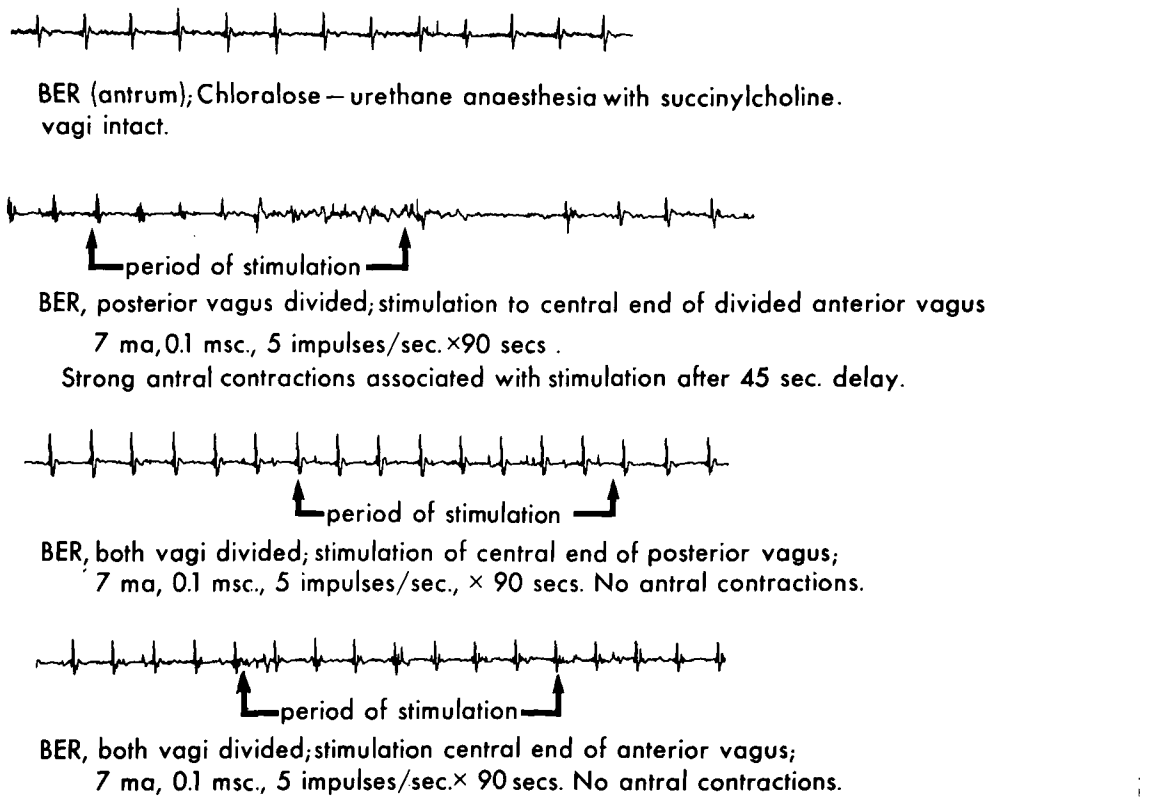


Figure 7. The effect on BER of afferent vagal stimulation before and after complete vagal section (chloralose-urethane anaesthesia, stimulus isolator).

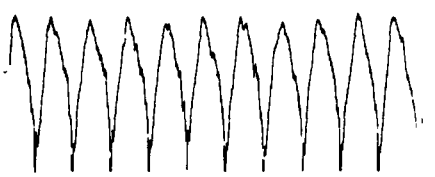
figure A

BER (antrum), vagi intact. Bipolar recording with electrodes 3 cm. apart. Conduction velocity 1.6 cm./sec.

BER, posterior vagus divided. Conduction velocity 1.6 cm./sec.

BER, both vagi divided. Conduction velocity 1.6 cm./sec.

figure B



BER recorded at antrum using a short time constant (0.03 sec.) and higher amplication (1 millivolt= 20 mm. deflection) Note distortion of BER.

Figure 8. A. Bipolar recording of BER, demonstrating conduction velocity of the pacesetter potential before and after vagotomy.
B. BER recorded with high amplification and short time constant.

BER (antrum); vagi intact. chloralose—urethane anaesthesia
BER frequency 3.8 cycles/minute

BER during pentagastrin infusion at 4 ugm/kg/hr.; vagi intact;
BER frequency 5.2 cycles/minute

BER; pentagastrin infusion;anterior vagus divided;
BER frequency 5.3 cycles/minute.

BER; pentagastrin infusion;posterior vagus divided—
i.e.- complete vagal section;
BER frequency 5.3 cycles/minute.

Figure 9. The effect on BER of a pentagastrin infusion, before and after complete vagal section.

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