PEPTIC
ULCER

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BY

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PREFACE

Peptic ulcer is a common disease, painful, incapacitating and not free from danger. While not one of the main killing diseases, it ranks high on the list of chronic disabling affections, and its frequent occurrence in young adults adds to its social and economic importance.

Despite much research, our knowledge of its causes is still incomplete, while in treatment the record of recent years gives no assurance that finality is in sight. Yet essentially it is a curable disease and, if its causes were understood, it might well be preventable. Undoubtedly, therefore, it is a subject well deserving of further study.

In these circumstances it seemed useful to bring together the more important elements of present-day knowledge and present them in the form of a monograph. In doing so, I have not written as a surgeon but rather as a student of disease, attempting to set down what is known about the problem in all its aspects from the point of view of the physician no less than the surgeon, the practitioner equally with the researcher.

The literature on peptic ulcer is immense and not all ponderable, so while I have consulted it extensively I have quoted with discrimination, preferring a few reliable facts to a host of opinions. So far as possible, I have tried to write on the basis of my own experience, and even where I have had to rely mainly on the writings of others the interpretation has doubtless been coloured by my own beliefs and prejudices. The more important references have been listed and, except where otherwise stated, they have been read and verified personally, so any errors are mine alone.

Although I have preferred to write the whole text, I know well that I cannot claim sole credit for it. Peptic ulcer has been the main clinical interest and research problem in my hospital wards and University department for a long time, and I am but the mouthpiece of a large team of associates and assistants who, by their zealous collaboration, have given me the knowledge from which to speak. Some of their publications are mentioned in the text, but I owe even more to the daily debates and arguments which provoke thought and crystallise belief. Their co-operation has made my task easy.

C. F. W. I.

Glasgow,
October, 1953.

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CHAPTER I

THE GASTRIC SECRETION

Since peptic ulcer forms only in the presence of acid juice, it is clear that whether we seek the cause of ulcer or its cure, the process by which the acid is secreted must be a subject deserving our close attention.

The history of observations in this field begins in 1752 with Réaumur's discovery of the acid character of the gastric juice. Réaumur, a French gentleman of scientific inclination, is best known to fame by the temperature scale which bears his name, but after the fashion of those times he turned his attention to many different aspects of natural philosophy. Having in his possession a tame buzzard, he took advantage of the well-known habit of this bird of vomiting anything it could not digest, and trained it to swallow, hold and in due course return small perforated metal tubes containing various kinds of foodstuffs. By such experiments he obtained fresh gastric juice, which he found capable of turning blue paper red, and he also made other simple observations on the process of digestion, distinguishing it clearly from putrefaction and attributing it to the solvent power of the juice.

The first scientific study of the process of digestion in the human subject was made by Dr. Stevens of Edinburgh, whose thesis for the degree of Doctor of Medicine, published in 1777, gives an account of a series of experiments which for simplicity and directness of purpose are only matched by the brevity of their presentation.

Dr. Stevens' subject was a man of weak understanding, "stolidus et miserandus," who since the age of seven had possessed the aptitude for swallowing stones in such numbers that they rattled within his belly, and gained a miserable livelihood exhibiting this feat for the amusement of the common people. Stevens persuaded him to substitute perforated silver capsules with multiple compartments containing various meats and foodstuffs, and to harbour them within the stomach for 24 to 48 hours before expelling them. As a result of these experiments, he concluded that digestion is not the effect of heat, trituration, putrefaction or fermentation alone, but of a powerful solvent secreted by the coats of the stomach; to which he added the interesting surmise that probably every species of animal has its peculiar gastric liquor, capable of dissolving appropriate types of foodstuff.

The acid of gastric juice was first identified as muriatic (hydrochloric) acid by Prout in 1824. It is interesting that Prout not only identified the acid but also discussed its mode of formation, concluding that it is derived from the common salt of the blood, which dissociates so that the chloride is excreted while the sodium is left behind. Since that time many other theories have been propounded as to the intrinsic mechanism of parietal cell secretion, but very little exact knowledge has been forthcoming, and indeed it is true to say that Prout's view still remains almost the sum total of our understanding of this vital process.

Another early method of studying the digestive process in the living human subject was by direct observation of the stomach through accidental wounds or surgical fistulas.

The most notable early example of this type of observation was carried out by Dr. William Beaumont (1833), a surgeon in the U.S. Army, on the young French-Canadian voyageur Alexis St. Martin. St. Martin had sustained an extensive musket wound of the abdominal wall and viscera which left him with a large gastric fistula. Beaumont, who had been called in at the time of the accident, " received, kept, nursed, medically and surgically treated and sustained him, at much inconvenience and expense, for nearly two years " . . . and subsequently retained him for the special purpose of carrying out many interesting and ingenious physiological experiments.

Beaumont was concerned mainly with the process by which food reaching the stomach is converted into chyme. He confirmed Prout's finding that muriatic acid is the main constituent of the gastric juice, and made many other simple observations on the rate and manner of its secretion.

Though the most notable, Beaumont is not quite the first to have made observations of this sort. Corvisart and Leroux had described a similar case thirty years earlier, in the month of Pluviose in the tenth year of the Revolution. This was a woman aged 47 who many years after a severe injury developed a spontaneous gastric fistula. They made a meticulous examination and were about to undertake a study of the digestive processes when unfortunately the patient took pneumonia and died.

Since these early experiments others have followed the same path, and some of the most important recent additions to our knowledge of the gastric functions have come from observations of similar cases by workers such as Wolf and Wolff and their colleagues.

Complementary to observations on the human stomach, a great deal of information on the physiology of the gastric juice has been forthcoming from experiments on laboratory animals.

Foremost in this field come the researches of the great Russian physiologist, I. P. Pavlov, who with his associates and assistants was responsible for bringing to light many of the fundamental features of the acid secretion.

Pavlov was the first to show that the gastric juice is secreted at a constant level of acidity; that the rate of flow varies with the character of the food; that mechanical stimulation and distension of the stomach cause no secretion; and that fats exercise an inhibitory influence. Undoubtedly, however, his main contribution was to distinguish between the two phases of secretory activity (now termed the nervous and the hormonal phases), and in particular to demonstrate the precise nature of the nervous mechanism.

Pavlov's experiments were made on dogs in whom one or more of the following fistulae had been constructed: (1) an oesophageal fistula through which food when swallowed was discharged at the skin surface of the neck, (2) a gastric fistula for feeding or for withdrawing stomach contents, (3) a "miniature stomach" (now

called the Pavlov pouch) physically separate from the main stomach but with its vascular and nervous connexions intact (Fig. 1).

In dogs thus prepared the first critical experiment was that in which sham feeding was found to lead, after a few minutes, to a flow of gastric juice, which persisted as long as the feeding was continued and for three or four hours thereafter. This result was obtained only in animals with the vagus innervation intact; after division of these nerves, sham feeding yielded no secretion.

At first, Pavlov assumed that the secretion was due to a simple reflex excited by contact of the food with the mucous membrane of the mouth. Later experiments, however, showed that the mere sight of food was an effective stimulant to secretion, whereas agents other than food, whether chemical or mechanical, when placed in the mouth, were ineffective. From such observations he was able to deduce that the nervous stimulus to secretion (the " appetite juice ") had its origin in the psyche.

In the forty or fifty years that have elapsed since Pavlov's crucial experiments our knowledge of the physiology of the acid secretion has been advanced by many researches both at the bedside and in the laboratory. The nerve pathway has been made clear by anatomists and the effects of its division by surgeons. The nature of the nerve impulse has been studied by observing the action of atropine, acetylcholine and the ganglion-blocking drugs. The acid secretion has been found to be responsive, by two entirely different mechanisms, to insulin hypoglycaemia on the one hand and histamine on the other. And finally the effects of emotional disturbances have been studied by psychiatric observations as in the well-known experiments of Wolf and Wolff. All these and other aspects will be studied in detail in the following pages.

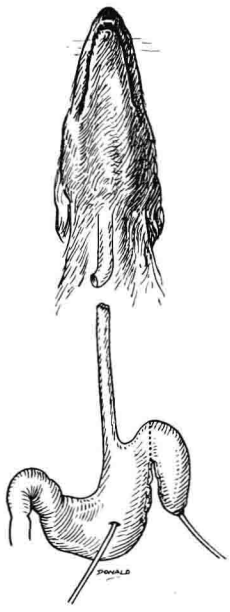


FIG. 1

Pavlov Pouch

The illustration shows the preparation originally used by Pavlov, with oesophageal fistula, gastric fistula and " miniature stomach." Some fibres of the vagus nerves (not shown) were preserved, so the pouch remained innervated. Heidenhain's pouch, in contrast, was deprived of its innervation.

COMPOSITION OF THE GASTRIC JUICE

The gastric juice is a mixture containing hydrochloric acid, the ferments pepsin, rennin and lipase, mucin, the haemopoietic factor and various salts. Apart from rennin and lipase, about whose secretion there is little exact information, it is known that each of these substances is elaborated by its own type of cell which has its own characteristic situation in the stomach wall and responds to its own distinctive forms of stimulation.

Acid.—Hydrochloric acid is the product of the parietal or oxyntic cells which fringe the " fundic gland " tubules lying in the fundus and body of the stomach. It is secreted only by these cells and is their sole natural product. The nervous,

hormonal and other factors controlling the acid secretion will be discussed at length on later pages. Here it will be sufficient to state that available evidence indicates that at its source the acid is maintained at a remarkably constant concentration, with a strength of approximately 0·5 per cent. or 160 milli-equivalents per litre. Consequently, variations in the acidity of the stomach contents as a whole do not reflect differences in the level of acidity at its source, but in the quantity of acid secreted in relation to the quantity of neutralising or buffering fluids with which it is mixed. It is not yet known whether the product of the individual parietal cell may vary in quantity, but on the whole the evidence suggests that it cannot do so, but that if the cell secretes at all it must secrete at maximum output (see also p. 40). If this view is correct, variations in the total acid output must depend upon the number of parietal cells at work. As will be shown later, the total number of parietal cells varies enormously in individual subjects. In any one subject, moreover, the proportion of parietal cells engaged actively in the secretion of acid at any given moment varies enormously. Under strictly basal conditions, that is to say, in the absence of all nervous and chemical stimuli, the secretory activity is in abeyance; under average resting conditions we may assume that something like 20 to 30 per cent. of the cells may be actively secreting; after a suitable meal the proportion may rise to something like 70 per cent., or even higher; simultaneous secretory activity by all the parietal cells is rare in health but may be provoked by stimulation, as for example by large doses of histamine (p. 40).

Pepsin.—Pepsin is formed by the principal or chief cells lining the depths of the fundic tubules. It thus arises from the same tubules, though not the same cells, as hydrochloric acid. Like the acid, its secretion is stimulated by cholinergic (vagal) nerve impulses, but, at any rate in the dog and cat, it differs from the acid in not responding to the administration of histamine. In these animals, therefore, vagus-stimulated gastric juice contains both acid and pepsin, whereas histamine-stimulated juice contains much acid but only traces of pepsin washed out from the tubules. It is not certain whether this differential effect holds good also for the human subject (see p. 23).

Mucin.—Mucin is found in two forms in the stomach. The visible, relatively insoluble mucus which probably contains hexosamine is secreted by the surface epithelium of the mucous membrane. The other, soluble mucus, which is believed to contain uronic acid, is mainly a product of the cells lining the neck of the fundic gland tubules.

Acid and Alkaline Components.—Thus three types of product are formed in the gland tubules of the body and fundus of the stomach, namely, hydrochloric acid, pepsin, and soluble mucin. This "fundic secretion" is typically acid in reaction and is known as the acid component of the gastric juice.

In contrast, the racemose glands found in the pyloric antrum and canal, and also in a small area fringing the cardia, secrete a watery, slightly alkaline fluid which is known as the alkaline component (Fig. 2). According to Berger (1934) the transition from acid to alkali is an abrupt one, at a level just above the angulus

on the lesser curvature. Above this point the parietal cells are distributed fairly uniformly over the body of the stomach but diminishing towards the cardia.

As has already been stated, if such factors as swallowed saliva and regurgitated duodenal contents are left out of count the resultant acidity of the gastric contents depends principally on the ratio between the volume of acid secreted by the fundic glands and the volume of the "alkaline component" of the pyloric region. While the volume of the fundic secretion varies enormously, that of the alkaline component appears to be less changeable, and little is known of the factors which control it.

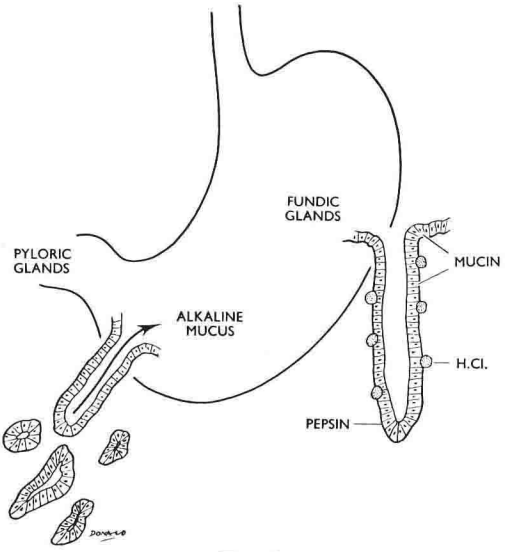


FIG. 2
The Gastric Secretion
The straight tubular glands of the fundus secrete acid, pepsin and mucus. The racemose glands of the pyloric part of the stomach secrete an alkaline mucoid fluid.

Haemopoietic Factor. — The secretion of the haemopoietic factor has little relevance to the subject of peptic ulcer except as regards the extent to which it might be affected by operations on the stomach. The old idea that megaloblastic anaemia is a likely, or even a possible complication of partial gastrectomy for ulcer, must be abandoned. Even after complete removal of the stomach, megaloblastic anaemia is not inevitable (presumably because some intrinsic factor is secreted by the jejunum) and when it does occur its appearance is delayed for a long time—even five or ten years—until the initial store is gradually used up (Conway, 1951). In the rare cases in which megaloblastic anaemia supervenes after operation for ulcer its occurrence must be regarded as fortuitous.

Inorganic Salts.—Among inorganic salts contained in the gastric juice there are appreciable quantities of sodium and potassium chloride and bicarbonate and traces of many others. Recent studies on the use of radioactive isotopes serve only to emphasize our ignorance of the significance of these constituents and of the manner in which they are secreted. Honour and his colleagues (1952) have studied the secretion of radioactive iodine (^{131}I) in the gastric juice, while Lenihan and Stevens have shown that phosphorus (^{32}P) and potassium (^{42}K) behave in the same way, and probably many other ions do likewise. Phosphorus, which they studied most fully, after being injected intravenously appears in the gastric juice within a few minutes, and its rate of secretion mounts rapidly so that within half an hour its concentration in the juice (as estimated by a Geiger counter), is considerably greater than in the plasma. The amazing speed of this process served to emphasize that the gastric mucosa is not merely a secretory organ but also a

semi-permeable membrane through which simple molecules can and do pass with the greatest of ease. Early observations show that the passage of phosphorus isotope into the gastric juice is independent of the secretion of acid. This is indicated by the fact that the isotope count tends to vary inversely with the acid level, and always falls when the secretion of acid is provoked by histamine. Moreover, the isotope is secreted in considerable quantity in patients with complete achlorhydria.

THE INTIMATE MECHANISM OF THE PARIETAL CELL SECRETION

The ability of the parietal cells to secrete such a powerful inorganic component as hydrochloric acid in a strength to rot fibres and tarnish metals is a quite remarkable phenomenon. The intimate mechanism of this secretory process is difficult to study owing to the anatomical disposition of the parietal cells as widely dispersed units scattered among other cells with quite different secretory effects. It is a process which has attracted immense interest among physiologists and biochemists, and has been the subject of numerous theories. For a review of the more notable ones the reader is referred to the recent paper by Davies (1951).

Formerly it was only possible to deduce the behaviour of the parietal cells by analysis of the total gastric secretion under various conditions, or by histological observations of the cells at various stages of secretory activity. A great advance in the methods of study was made in 1930 by Delrue, who showed that the thin mucous membrane of the frog's stomach when divested of its muscular and serous coat would continue to secrete *in vitro*. Delrue mounted the frog mucosa between two glass chambers. Davies later improved on this technique by tying the frog stomach at both its apertures to form a closed bag which could be suspended within a bath containing suitable medium. Under such conditions, when histamine is added to the medium the stomach within a few hours becomes distended with fluid containing hydrochloric acid, while the surrounding medium becomes correspondingly alkaline in reaction. Incubation of such specimens in Warburg's apparatus has made it possible to study the respiratory processes involved in acid secretion and has led to much more precise information about the metabolic requirements of the parietal cells.

Since hydrochloric acid is so powerful a destructive agent it was suggested by Claude Bernard that the actual secretion of the parietal glands was an inert precursor which became activated only on reaching the lumen of the tubule. This view, however, has long been discarded, and it is now established that the parietal cell secretion is pure hydrochloric acid. Indeed, as Bradford and Davies (1950) have shown, during active secretion the contents of the intra-cellular canaliculi give the staining reactions of an acid.

One of the most attractive theories in recent years was based upon the discovery, by Davenport and his colleagues (1943), that the parietal cells contain large quantities of the enzyme carbonic anhydrase. This is the enzyme that catalyses the reaction by which carbon dioxide and water are combined to form

carbonic acid, according to the equation $CO_2 + H_2O = H_2CO_3$. According to Davenport, carbon dioxide derived from metabolites broken down within the parietal cells is hydrated in this way; the carbonic acid thus formed becomes ionised, setting free hydrogen ions which become available for the acid secretion.

This carbonic anhydrase theory appeared to be confirmed by the observation that substances such as thiocyanate which inhibited the enzyme also inhibited acid secretion, but was abandoned when other enzyme-inhibitors such as sulphanilamide were found to have little or no effect on the secretion of acid. Recently Davies has refuted this latter finding, but on other grounds the theory as put forward by Davenport is no longer sustained. It is believed that the large amount of enzyme contained within the parietal cells is concerned not with the process of secreting acid but with the hydration of CO_2 to form bicarbonate ions which are exchanged for chloride ions from the blood.

The source of the hydrogen ions destined for the acid secretion has been the subject of much speculation. According to Bull and Gray (1945) and other workers, they are derived from lactic and pyruvic and other organic acids which are known to be formed from glucose within the parietal cells. Biochemical observation makes this view appear unlikely, however, for studies of the rate of oxygen uptake indicate that the acid secretion is much greater than could be explained by this mechanism.

According to Davies, while some of the hydrogen ions could come from glucose, the only source sufficient to supply equivalent amounts of acid and alkali in quantities sufficient to account for the known rate of secretion is water. A mechanism such as this, involving the dissociation of H and OH ions, can only be brought about by the expenditure of much energy, and according to Davies this is derived from the oxidation, within the parietal cells, of glucose and its derivatives, and probably stored in the form of " high energy " phosphate bonds.

THE NERVOUS PHASE OF GASTRIC SECRETION

The significance of a neural factor in the secretion of gastric juice had been suspected for many years before Pavlov and his colleagues provided conclusive proof. It is now established that secretory impulses originating in the parasympathetic centre of the hypothalamus pass exclusively by way of the vagus nerves to their ganglia in the stomach wall, whence post-ganglionic fibres proceed to the fundic tubules (Fig. 3). Stimulation of the hypothalamic centre may be of psychic origin (the " appetite juice "), it may occur as a reflex following contact of food with the mucous membrane of the mouth, tongue and throat, or it may be produced by biochemical changes, for example in hypoglycaemia.

It is interesting that, however the vagus stimulation is brought about, it is effective only after a latent period of five to ten minutes. The explanation of this unusual feature is not known. Once the secretion has started it persists for a long time even after the cause of the stimulation has ceased to operate. This seems to be due to the continued discharge of impulses from the centre, for, as Pavlov showed, if the vagus nerves are divided immediately after sham feeding the secretion promptly stops.

The place of vagus impulses in controlling the gastric function has been clarified by surgical experience following the operation of vagotomy. Several observers have reported that the operation regularly leads to reduction in the volume and acidity of the nocturnal secretion. Generally this effect persists for a year or more, when in some cases the acidity returns to its pre-existing level. Vagotomy not only interferes with the nervous phase of gastric secretion, but also reduces the response to histamine and probably it affects the response to gastrin too. These observations suggest that in man the effect of vagotomy is a general inhibitory effect rather than a specific action on the psychic phase.

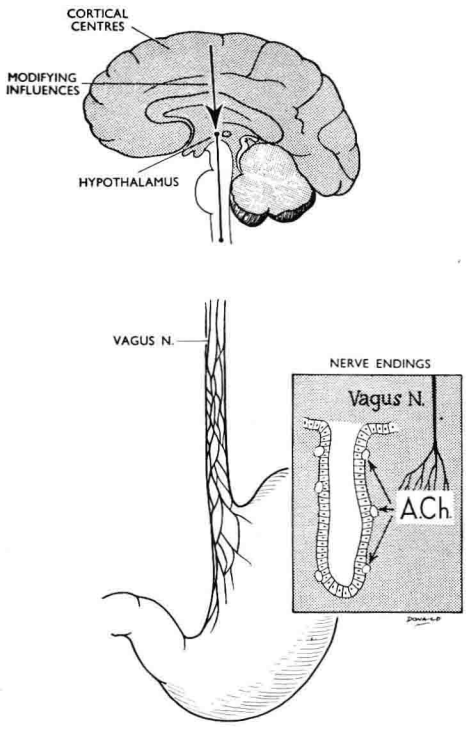


FIG. 3
The Nervous Pathway
Stimuli originating in the hypothalamus (subject to cortical control) pass by way of the vagus to the stomach wall.

The mechanism by which vagus impulses actuate the secretory cells of the fundic glands appears to be a complex one. It is believed that at this point, as at the ganglionic synapses, the transmission of impulses is effected through the agency of acetylcholine. In the secretion of pepsin, it is generally thought that acetylcholine is the sole agent involved, and that it stimulates the secretory cell directly; in the secretion of acid, on the other hand, it is almost certain that acetylcholine acts through the mediation of histamine, which is well known to be capable of stimulating the parietal cells even in the absence of extrinsic innervation.

At first thought it seems strange that this one operation should require the action of two such different chemical substances as acetylcholine and histamine, but it is a fact that this is only one of many instances, of wide occurrence in plant as well as animal physiology, in which these two substances are closely related.[1]

The proportion of the gastric secretion attributable to nerve stimulation is not easy to determine, for under normal conditions the nervous phase is quickly followed by the chemical phase, and for the greater part of the period of secretion they are combined. Dragstedt (1951), on the basis of pouch experiments (p. 11) estimates that in dogs the nervous and gastric phases each account for something

[1] The common nettle contains both acetylcholine and histamine. Acetylcholine causes the burning pain of the sting, but can only do so after dilatation of the skin capillaries by histamine (Feldberg, 1950).

of the order of 45 per cent. of the total output of acid, the remaining 10 per cent. being attributable to the intestinal phase. These estimates are admittedly tentative, and it may be remembered, moreover, that conditions in the human subject may well be different from the dog. Indeed, Jamieson's (1950) observations on a man with an isolated gastric pouch appeared to indicate that the " appetite juice " was quite small in amount.

In recent years two complementary methods have been introduced by means of which the vagus activity may be assessed. The first is the insulin test, which is effective only when the vagus innervation is intact; the second the use of methonium compounds by means of which all vagus transmission can be inhibited.

The Insulin Test (see also p. 36) depends upon the ability of insulin to induce hypoglycaemia sufficient to stimulate the vagal centres in the brain. The degree of stimulation—and consequently the volume and acidity of the secretion thus provoked—appears to depend largely on the rate of fall of the blood sugar, and is related less to the sugar content *per se* than to the resulting changes in the acid-base ratio. In general, however, it is necessary to reduce the blood sugar level to 40 mgms. per 100 ccm., and for this purpose the usual dose required is 15 - 20 units of crystalline insulin. Under such conditions, if the vagus innervation is intact, after a period of about thirty minutes there is an abrupt increase in the flow of gastric juice, which is highly acid and contains an abundance of pepsin and mucus.

The Methonium Test depends upon the fact that hexamethonium (hexamethylene bis-trimethyl ammonium) blocks the acetylcholine synapses and thus obstructs the vagus stimulation. Although individual susceptibility varies greatly, in most cases when given intramuscularly in doses of 100 mgms. it reduces the fasting secretion of acid to zero for periods of an hour or more (see p. 17).

CHEMICAL PHASE OF GASTRIC SECRETION

Pavlov's experiments (p. 2) distinguished three phases of gastric secretion, the cephalic phase mediated by the vagus, the gastric phase when food came into contact with the gastric mucosa, and the intestinal phase when food passed beyond the pylorus.

The gastric phase is now commonly called the chemical or humoral phase, by which it is implied that the parietal cells are stimulated by chemical or humoral agents transmitted by the blood stream. These agents include secretagogue substances contained in many foodstuffs, and may also include hormones, notably the hormone gastrin which is believed to be formed when food comes into contact with the mucous membrane of the pyloric antrum. It should be emphasised that while the secretagogue action of various foodstuffs has long been established for certain the existence of the hormone gastrin has only recently been proved, and that not to the satisfaction of all authorities.

The evidence on this point comes from two quite different types of investigation, namely, studies of the effects of various tissue extracts and experiments based on various types of gastric pouches in animals.

Tissue Extracts.—Edkins in 1905 claimed that extracts of the mucous membrane from the pyloric region, when injected intravenously, provoked a flow of acid juice, whereas similar extracts from the fundic region were inactive. By analogy with the recently discovered secretin, he concluded that the extract (" gastrin ") was a hormone produced by contact of the mucous membrane with food.

Subsequent workers failed to confirm Edkins' findings, and it has been suggested that his extract probably contained histamine, which is now known to occur in high concentration in the stomach wall. More recently, however, Komarov (1938) has claimed that by means of an extraction process similar to that used for secretin it is possible to obtain a histamine-free extract capable of provoking acid secretion. Komarov's findings have been confirmed by Uvnäs (1942) and others, and his extraction process is used regularly in many laboratories with success. It is clear, therefore, that a potent substance other than histamine is normally present in the pyloric mucosa. Whether this substance is a true hormone, or a secretagogue absorbed from food, still remains in doubt, though on the whole the evidence favours its hormonal character.

Whatever its precise nature, its secretory effect is similar to that of histamine, the juice being a watery fluid with a high acid content, and with (in the dog) little or no pepsin. This finding suggests that the hormone influences the parietal cell through the mediation of histamine, though some doubt is cast on this theory by the observation that the hormone continues to provoke acid in animals from whom the greater part of the histamine content has been " liberated " or withdrawn (p. 16).

Pouch Experiments.—Studies on the production of the hormone " gastrin " have made use of many types of pouch, including the original Heidenhain and Pavlov pouches, the total stomach pouch perfected by Lim and others (1925) and separate pouches made from the fundus and pyloric parts of the stomach.

In order to prove the existence of blood-borne agents capable of stimulating acid secretion it was necessary to prepare a completely denervated pouch. This proved difficult, but was eventually achieved by Ivy and Farrell (1925) who carried out a free transplant of gastric mucosa to the submammary region.

The fact that this completely denervated graft secreted acid when the animal was fed gave final proof of the existence of a humoral mechanism but of course left open the question whether the agent was a true hormone or a secretagogue absorbed from the food.

It may be noted at this point that the substances believed to stimulate the formation of the hormone are the identical substances which are known to have a directly stimulating action when injected intravenously. It is therefore difficult to prove, when they are applied to the pyloric mucosa, that the resulting secretion is not due to absorption of the agents unchanged. There is some evidence (Butler *et al.*, 1943) that such agents are more potent when applied to the pyloric mucosa than when injected intravenously, but there are obvious fallacies in deductions

of this sort. More convincing is the demonstration (Lim *et al.*, 1925) that secretion in a denervated pouch may be brought about by simple mechanical distension of the stomach, as by a balloon.

The Site of Hormone Formation in the dog is generally believed to be in the pyloric antrum, and this also is the most active site for the absorption of secretagogue foodstuffs. Clinical observations appear to suggest that the same disposition obtains in man.

It is unnecessary to review all the many animal experiments performed to decide this question. The most convincing are those described recently by Dragstedt and his colleagues (1951) (Fig. 4) who have shown that in dogs with Pavlov pouches complete removal of the pyloric antrum led to profound reduction of the acid secretion of the pouch, while if the nervous phase was also interrupted by vagotomy the secretion fell almost to zero. Conversion of the antrum into a pouch draining at the skin surface had the same effect as removal of the antrum, and re-implantation of the antrum into the duodenum restored the secretion to its normal level.

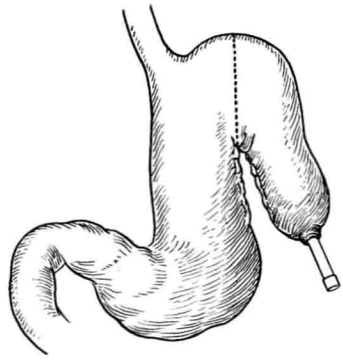
Dragstedt and his colleagues as a final experiment in this series formed the pyloric antrum into a pouch and implanted it into the side of the transverse colon. They expected it in this situation to prove inert but instead, surprisingly enough, it provoked a persistent secretion of high acidity. No explanation of this interesting finding has yet been forthcoming, but it seems clear either that the faeces contained a potent secretagogue or that they contained some substance which after absorption through the antral mucosa gave rise to large amounts of the antral hormone.

Relations of Hormone to Nerve Stimuli.—There is a certain amount of evidence to suggest that while any hormone produced in the antral mucosa must be conveyed to the fundic glands by the blood stream, its action is somehow bound up with nerve stimuli.

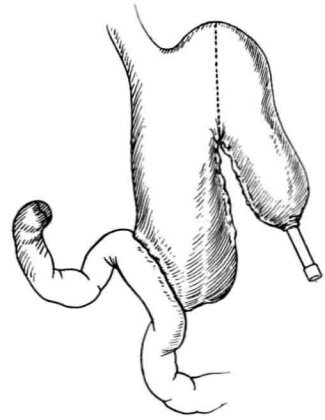
Zeliony and Savich in 1912 showed that when meat extract or sodium oleate was applied to the pyloric mucosa, the secretory effect (presumably hormonal in character) could be prevented by cocainising the mucous membrane or by administering atropine. The cocainisation did not act by causing local vasoconstriction since adrenalin was ineffective, so it was inferred that a nerve inhibition was involved, and since vagotomy does not interfere with the action it must be assumed that the intrinsic nerves are the ones implicated.

Further evidence of a similar nature was put forward by Gregory and Ivy (1941) who noted that in animals with a transplanted (and therefore denervated) pouch of acid-secreting fundic mucous membrane, the chemical phase of secretion produced by applying various secretagogues to the antrum could be prevented by procainisation of the antral mucosa. These and other observations have been taken to indicate that formation of the hormone depends upon an intact intrinsic innervation in the antral wall.

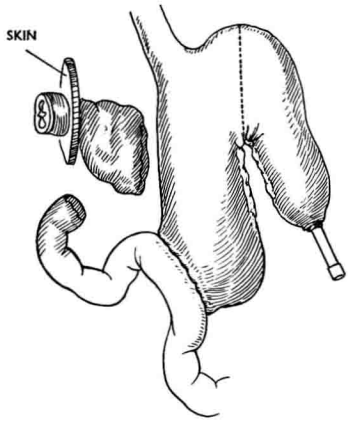
Uvnäs (1942), on the other hand, has suggested a quite different relation between the hormone and the nervous system. In anaesthetised cats and dogs he has shown that the acid secreted in response to electrical stimulation of the vagus is reduced when the pyloric mucous membrane is removed or cocainised,



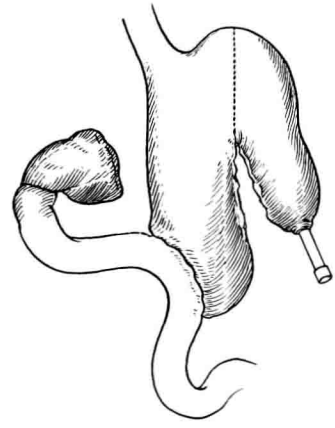
A. ANTRUM INTACT
Pavlov Pouch Instituted



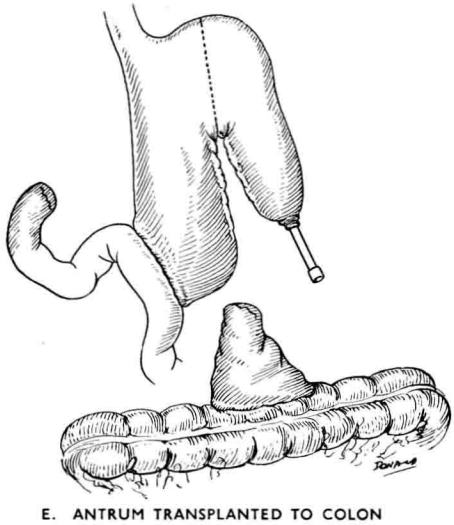
B. ANTRUM REMOVED
Secretion of Pouch Depressed



C. ANTRUM DRAINED TO SKIN SURFACE
Secretion of Pouch Depressed



D. ANTRUM RE-IMPLANTED INTO DUODENUM
Secretion of Pouch Restored to Normal



E. ANTRUM TRANSPLANTED TO COLON
Secretion of Pouch Augmented

FIG. 4
Effect of Antral Transplantation
(after Dragstedt et al.)

and on the basis of this observation has suggested that the vagus acts in part by stimulating the formation of gastrin. It should be added that other workers (Babkin and Schachter, 1944) have doubted the validity of Uvnäs' claims. Recently, however, support has been forthcoming in the observations of Robertson (1950) and his colleagues, who have shown that in dogs with an innervated fundic pouch, irrigation of the pyloric mucosa with acetylcholine leads to increased secretion of juice which could not be due to a direct acetylcholine effect since the juice was deficient in pepsin. In further experiments, moreover, Langlois and Grossman (1950) showed that after removal of the pyloric segment the juice secreted by the fundic pouch in response to an acetylcholine preparation was reduced by 80 or 90 per cent., whereas the histamine-provoked juice was unaffected.

Significance of Antral Mechanism in Ulcer.—If we assume—what is generally regarded as axiomatic—that a highly acid secretion is an important factor in the aetiology of ulcer—it is clearly a matter of some interest to know what part of that secretion is due to the antral mechanism.

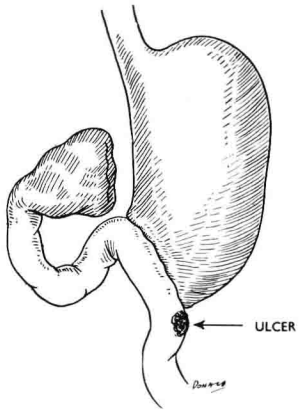


FIG. 5
Resection with Exclusion
Type of gastrectomy particularly liable to ulcer at the anastomosis.

At present there is little accurate information as to the parts played, in man, by the nervous and the humoral mechanisms respectively. Hitherto, owing perhaps in the first place to the dramatic quality of Pavlov's experiments and more recently to the emphasis laid on psychological factors in the aetiology of ulcer, greatest attention has been paid to the nervous factor. This has been reflected also in the methods of treatment which have recently enjoyed popularity, for example, the surgical procedure of vagotomy and the medical use of ganglion-blocking agents such as hexamethonium. Recently, however, a certain amount of evidence has accumulated which tends to show that the antral mechanism may be more important than has been supposed.

A number of surgeons have drawn attention to the great risk of secondary (anastomotic) ulceration after those types of gastrectomy in which the pyloric antrum is not removed (Fig. 5). Wells and Brewer (1948), for example, in a follow-up report of cases of duodenal ulcer treated by gastrectomy, showed that among the 34 cases traced who had undergone the operation of "resection with exclusion" no fewer than 11 developed ulcers at or close to the gastrojejunal anastomosis. This is, of course, a very much greater incidence than would be expected after other types of gastrectomy. Wells and Brewer also showed that in these cases when the pyloric antrum was removed subsequently there was almost invariably a prompt and permanent healing of the stomal ulcer. Isolated cases of a similar nature have been reported by Allen (1943) and by Wangensteen and Lannin (1942).

The part played by the pyloric antrum in such cases is difficult to understand, for it is almost certain that food cannot regurgitate through the whole length of