PART I.

Introduction and object of the study.

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(A) Introduction:

Historical:-

As early as in the year 1530 a patient was reported to have acquired a hole in his stomach, which communicated with the outside world through the abdominal wall. Mathew Cornax (1564), Professor of Medicine at the University of Vienna and Physician to Emperor Ferdinand I of Austria, described a Bohemian peasant who, while hunting, was bitten in the abdomen by a snake. He developed a gastric fistula and lived with it for a good number of years. Later on other isolated cases also occurred. However, no studies were reported by Cornax (loc cit) and others on such patients of theirs.

William Beaumont (1833) began experiments in the year 1825, after availing himself of the unique opportunity, afforded by a concurrence of circumstances, which enabled him to study the physiology of the stomach at close range through a permanent opening into the stomach of Alexis St. Martin, a French-Canadian voyageur, who had acquired a gastric fistula as a result of an accidental shotgun wound in the abdomen. The accident occurred when St. Martin was 19, and he lived with his gastric fistula, approximately an inch in diameter, until the age of 78. In fact he outlived Beaumont (loc cit) and following the death of the latter, another physician, Francis Gurney Smith (1856) of Philadelphia, studied Alexis St.Martin further. Smith (loc cit) was unable to add perceptibly to Beaumont's (loc cit) results; in fact the former contradicted the finding of the latter of hydrochloric acid as the principal acid of the gastric juice, contending that it existed only in negligible amounts and that lactic acid was the physiologically important one. Beaumont's (loc cit) finding was later confirmed and Smith's (loc cit) publication forgotten.

Beaumont (loc cit) in his studies on Alexis St.Martin, was principally concerned with discerning the processes involved in converting a bolus of food into an amorphous, semi-fluid chyme. He interested himself primarily in the gastric juice; and as Condie (1834), one of the critics of Beaumont's day, remarked, Beaumont did not make an attempt to show whether or not there was a "Vital force" in the stomach which enabled food to be chymified more readily in vivo than when incubated with gastric juice in vitro.

Alexis St. Martin's survival after his accident for about 60 years demonstrated that a gastric fistula is no obstacle to longevity (Peckham, 1940). He did not feed himself through his fistula and it was only after a lapse of about 42 years after Beaumont's publication in 1833 that patients began to do so. As early as in the year of 1875, a successful surgical gastrostomy was performed on a patient with obstructive carcinoma of the oesophagus (Jones, 1875). The palliative operation was successful, the patient, however, died shortly thereafter of bronchopneumonia. The following year, Verneuil (1876), reported another successful surgical gastrostomy. This patient had acquired a benign structure of the oesophagus after having swallowed lye. Following operation he survived, free of gastrointestinal complaints, to be studied and reported two years later by Richet (1878).

Richet interested himself more in the study of the chemistry and physiological properties of gastric juice, although he did explore the sensibility of the gastric mucosa. He confirmed many of Beaumont's findings and added a few of his own. His patient, unlike St. Martin, actually fed himself through his fistula. He poured the food in directly through a rubber tube without taking it into his mouth. Eating in this fashion he gained 5 Kg. in weight during the 6 months following operation. He observed that escaping gastric juice caused severe burning pain when it came in contact with the denuded edges of the skin immediately surrounding the stoma. Richet (loc cit) looked inside and saw a pink undulating surface with tiny bright holes, which were taken by him, like Beaumont, to be orifices of glands. On investi -gating the sensibility of the mucosa, Richet (loc cit) concluded that it did not appreciate touch, that introducing cold fluids evoked a painful sensation, and that alcohol elicited a sensation of heat. The patient could not tell whether his stomach was full or empty. Very rapid filling or emptying of the stomach, however, was regularly associated with hiccough.

Approximately 25 years after the publication of these studies, Pavlov (1910) made use of the fistula technique in the study of gastric physiology in dogs. He separated surgically a portion of the stomach from the rest of the organ so that nothing from the oesophagus or duodenum could gain access to it. The blind pouch was connected to the abdominal wall by an artificial stoma. Thus Pavlov was able to collect pure gastric juice free from contamination with food, saliva, or duodenal regurgitation and without the possibility of loss through the pylorus. This surgically produced gastric pouch has since been known as the

"Pavlov pouch".

The influence of the circumstances surrounding an experiment on the function of the organ under observation formed one of the factors generally ignored by investogators. This held true even after Pavlov (loc cit) had demonstrated in dogs that the effects of environmental situation to which the animals had learned to attach special significance manifested themselves in profound and prolonged alterations in gastric and salivary functions. Pavlov (loc cit) showed that the effects of these situational factors, like other biological phenomena, were subject to analysis and to experimental approach. To consider the stomach not as an isolated organ, but as a functioning unit in a whole integrated organism, was a fresh point of view that arose gradually. Much of the pioneering work in this field was done by Cannon (1909 and 1929). His studies showed that profound disturbances in gastric functioning occurred during emotional stress.

About 10 years after Pavlov's (loc cit) observations, Carlson (1912) studied a patient with a gastric fistula half an inch in diameter. During the succeeding years after the work of Beaumont (loc cit), others, thus, had patients, no doubt, with holes in their stomachs to study, but Carlson's (loc cit) investigation on his patient, Fred V., has compared in scope with Beaumont's (loc cit) work. He worked with a new approach to the investigation which was offered to him by the passage of time. "Mechanism" has taken the place of "Vitalism". A great school of physiologist -s, interested in the behaviour of individual organs and in the mechanisms of interrelationships of organs, had sprung up. Carlson's (loc cit) work was primarily concerned with kinetics.

The majority of the experiments, he performed on the stomach, were directed towards a study of gastric motility and of "hunger contractions" in particular. He made one observation, however, on vascularity; namely, that strong contractions of the stomach were associated with increased redness of the mucous membrane. On secretion, he made several observations, the most striking of which was that the resting, fasting stomach secretes acid gastric juice. This observation was contrary to the findings of Beaumont (loc cit) and Pavlov (loc cit), who held that in the absence of stimuli, mechanical or chemical, the stomach remained empty and failed to secrete. Carlson's patient lived on for years, serving alternately as experimental subject and diener in the laboratory, feeding himself through his stoma, and enjoying good health, free from gastrointestinal complaints.

Rouhier and Soupault (1936) reported the case of a patient who had lived over 40 years in good health after feeding herself through the fistula. Numerous other patients with successfully functioning gastrostomies have been reported by Petrowić (1932), and Gordon and Chernya (1940), and there have been studies on the alterations of gastric physiology by gastrostomy.

King (1937) reviewed a large number of cases from his own practice and all of them were found to show a marked diminution of gastric acidity and in most instances an achlorhydria. The operations, in nearly all of his cases, were done for cancer of the oesophagus. Involvement of the stomach might have been possible in some of these neoplasms and the achlorhydria may have been explained on that basis. All the patients had rubber tubes fixed permanently in place in the stoma and the autopsy examination carried out of their stomachs showed varying degrees of gastritis, which may have explained the achlorhydria in some of them.

"Psychic" stimuli to gastric secretion as well as other aspects of gastric fistulae have been the subject of some investigators like, Kretschy (1876), Bogen (1907), Columbi and Sacchi (1931), Hertz and Sterling (1910). The studies, however, were fragmentary because of limited facilities or because of difficulties in managing the subjects, many of whom were young children.

Cade and Laterjet (1905) had the opportunity of studying a patient who acquired in infancy an epigastric hernia. This contained a portion of the stomach, which became incarcerated with eventual separation of the mucosal surfaces of the pouch and the main stomach. Afterwards the anterior aspect of the pouch ulcerated through to the outside and the patient was left with a spontaneously produced 'Pavlov Pouch'. These workers confirmed the work which Pavlov (loc cit) did on animals in regard to secretion in the pouch in response to the food taken into the main stomach, and in response to 'Psychic' stimuli like that of due to appetizing dishes. They did not, however, make any note of changes in vascularity or in color in the exposed mucous membrane.

About two years later after this work, Hasnelson (1907) was able to confirm Pavlov's (loc cit) sham-feeding experiment on a human being who had an oesophageal as well as a gastric fistula.

Despite the infrequency of suitable fistula cases and the difficulties of obtaining the co-operation of the patients for experiment, a good deal has been learnt by this method of study. The data obtained, moreover, gain significance because such data could be collected without tissue damage and with a minimum of instrumentation.

Beaumont (loc cit), Richet (loc cit) and Carlson (loc cit) had, no doubt, all recognized that changes in gastric function occurred in association with varying emotional states, but no systematic observations on these lines were made by those workers. Neither was the stress laid by them upon the magnitude of these changes and their possible relation to epigastric distress and disease. Finding the significance of psychosomatic relationships and exploring the possibility that serious structural changes in the gastrointestinal tract might occur as a result of prolonged functional disturbances was the theme of study of Wolf and Wolff (1944) on their subject, Tom. For the first time till then, an evaluation of circulatory changes in the gastric and duodenal mucosa was made possible by their work. The wide variations in blood flow and their relation to secretion and contractility were found, through their work, to have dramatic implications for health and disease. Not only the natural activities of the organ - its secretions and motions and associated variations of blood flow, its responses to different stimuli, and its effects on various foodstuffs - but also the influence of many agents commonly employed to alter those functions have been critically examined by Wolf and Wolff (loc cit) in the favourable circumstances which Tom presented. Perhaps the most illuminating of all the observations made by those investigators are those on the intimate relations between emotional states and gastric activity. In that respect the investigators were fortunate, for their subject, Tom, was a sensitive, proud, and independent individual, at different times anxious, fearful, difficult and obstinately decisive. He had an emotional range and responsiveness that permitted nice discriminations which the investigators fully utilized. The interesting fact, which was observed by them was that the frustration and repressed conflict were associated with hyperemia and with increase of motility and secretion. Likewise highly significant was the evidence, brought out by them, that engorgement of the mucosa, whatever its cause, was associated with lessened resistance to trauma, for, as the investigators had pointed out, this condition has importance in explaining the incidence of gastric ulcer.

Apart from these investigations on gastric secretion which were made by the method of study of fistula, the early physiologists had arrived at the idea of the chemical action of the gastric juice by somewhat heroic methods. Spallangani (1929-99), originally Professor of Mathematics and Greek at Reggio, swallowed sponges tied to strings and pulled them up again to obtain samples. Stevens (1777) in Edinburgh persuaded a man to swallow small perforated boxes containing meat, which were later regurgitated. Lavoisier in Paris swallowed linen bags and even perforated boxes filled with meat and examined them after they had been voided per rectum. He also had obtained samples of gastric juice by making himself vomit before breakfast and had shown that it brought about digestion in vitro.

Structure of the Stomach in relation to its function:

In view of the consideration which will have to be given to the various components of the gastric juice, and their origin in the stomach, it will be in the fitness of things to describe in short the structure of the stomach in relation to its function.

The glands of the mucous membrane are of three varieties: (a) cardiac, (b)fundus and body, and (c) pyloric.

(a) Cardiac glands around the opening into the stomach are (1) simple tubular glands lined by short columnar granular cells, (2) small tubulo-racemose glands, only found quite close to the cardiac orifice. They probably secrete mucus.

(b) Fundus and body glands are found throughout the remainder of the stomach except the pylorus. They are arranged in groups of four or five which are separated by a fine connective tissue. Several tubules open into one duct, which forms about a third of the whole length of the tube and opens on the surface. The ducts are lined with columnar epithelium. The gland-tubules are lined with coarsely granular polyhedral cells (central cells). The central cells are mingled with a variable number of cells with clearer protoplasm which are sometimes called mucoid cells. Between these cells and the basement membrane of the tubes are large oval or spherical cells, opaque or granular in appearance, with oval nuclei bulging out the basement membrane; these cells are called oxyntic or parietal cells. They do not form a continuous layer.

The central cells elaborate the pepsinogen granules which may be dissolved out of the wall of the stomach in alkali solution. Such a solution is not, however, active until made acid and prefer -ably pepsin added.

During secretion they discharge their granules, those which remain being chiefly situated near the lumen, leaving in each cell, a clear outer zone. The rennet enzyme that causes the curdling of milk is also formed by the central cells.

The oxyntic cells undergo merely a change of size during secretion, being at first somewhat enlarged, and after secretion they are somewhat shrunken. They are so called because they secrete the hydrochloric acid of the juice.

(c) Pyloric glands - These are found in the pyloric antrum, and have longer ducts than the fundus glands. Two or three tubules open into each duct by very short and narrow necks and the body of each tubule is branched and convoluted. The lumen is large. The ducts are lined with columnar epithelium, and the tubules with shorter and finely granular cubical cells, not at all unlike the mucoid cells of the fundus glands. The pyloric glands have no parietal cells. As they approach the duodenum the pyloric glands become larger, more convoluted and more deeply situated. They are directly continuous with Brunner's glands in duodenum. These glands secrete a viscid alkaline juice containing no pepsin.

Gastric function:

The purpose of the stomach as a digestive organ has been known for centuries. The process whereby it receives aliment, mixes it, starts the process of chemical breakdown of carbohydrates, proteins and fats, and finally passes it on to the small intestine for further digestion and absorption, has been worked out gradually since the publication on the subject by Young (1903). A rapid advance occurred as a result of the studies of Beaumont (loc cit) about 30 years later and the process has been greatly clarified by the more recent studies of a quantitative chemical nature.

Briefly, the facts which are currently available are as follows:- The first mouthful of food when it enters the cardiac orifice of the stomach drops into the hollow of the greater curvature, and subsequently ingested mouthfuls lie on top of it and central to it, forming a sort of stratification. The digestive juices reach the outer layers first, and these are milked along by peristaltic waves, peeled off the more central layers, as it were, and delivered to the region of the pyloric antrum. Here, the abundant mucous secretion neutralises partially the acid chyme which has reached the pyloric antrum, and the mixture is squirted into the duodenum by strong contractile movements. The pylorus, which is usually open, closes as the waves of contraction pass over it and thus prevents regurgitation of the food back into the stomach (Cowgill, 1941).

The Actions of Gastric Juice:

The following table represents the average composition of human gastric juice. The table is based in part on figures by Gray and Bucher (1941).

Hydrochloric acid	0.5 % (= 136 m.eq./l)
Other chloride	0.107% (= 30 m.eq./l)
Na	0.05% (= 22 m.eq./l)
K	0.028% (= 7.2 m.eq./l)
Ca	0.02 % (= 0.5 m.eq./l)
Total solids	0.43 to 0.65 %
Enzymes and other organic solids	- to 0.45 %
Total nitrogen	0.05 to 0.08 %

Acid:

By the action of the hydrochloric acid, certain changes are induced in the foodstuffs. Cane sugar is inverted to glucose and fructose; a small amount of hydrolysis also takes place in the dextrins and maltose produced by the action of ptyalin on starch.

Some proteins such as blood fibrin, and the collagen of the connective tissues, are swollen up to form a jelly-like mass.

Pepsin:

The chief digestive function of the gastric juice is dependent on the action of the enzyme pepsin. According to Freudenberg (1940), Cathepsin, a proteolytic enzyme functioning at pH 4-5 and having a maximal activity in presence of certain activators e.g. cysteine etc is present also.

Pepsin, which is inactive in neutral medium, is actively proteolytic in strongly acid solution, with the optimum pH 1.5-2.0, hydrochloric acid being the natural acid. Its effect is on the proteins. Its action on blood fibrin is best studied which shows that the products obtained are acid-meta-proteins, proteoses and peptones. Proceeding from primary through secondary proteoses to peptones, there is a continuous diminution in the size of the molecule. During the time, over which gastric juice can act, a maximum, say, of eight hours, the breakdown generally does not pass beyond the proteose and peptone stage, and it is in this form, and as acid-meta-protein, that the proteins of the food pass on into the small intestine. Analysis of gastric contents in man shows that, whereas carbohydrates may have been largely converted into reducing sugar in an hour, less than 3% of the protein nitrogen had been resolved into non-protein derivatives (Beazell, 1941).

Action on particular proteins:

1) Collagen: The connective tissues, e.g. areolar tissue, tendon and bone, are made up chiefly of collagen. On prolonged boiling it is converted into gelatin. The gastric juice dissolves collagen, converting it, probably through the stage of gelatin,

into gelatoses and gelatin peptones, bearing the same relation to the original substance as is borne by the proteoses and peptones to the other proteins. On account of this action adipose tissue is broken up. The cellular envelopes are dissolved, and the fat floats freely in the gastric juice.

2) Elastin: The chief constituent of elastic fibres, may be regarded as indigestible.

3) Mucin: This forms a considerable proportion of the ground substance of connective tissues and it is converted by gastric juice into peptone-like substances, and into reducing bodies allied to glucosamine.

4) Nucleoproteins: These are first dissolved by the acid of the gastric juice and are then broken up into two moieties. The protein half is converted into proteoses and peptones, while the nucleic moiety is precipitated as nucleic acid.

Chymosin:

Caseinogen of milk is present in the form of calcium-caseinogenate. (In U.S.A. and in some parts of Europe, caseinogen and casein are respectively called casein and paracasein). The first effect of gastric juice, even in neutral medium, is to convert the caseinogen into an insoluble form called casein. This action is often in part due to the presence of a distinct enzyme named chymosin or rennin. Although crystalline pepsin also clots milk, an active chymosin preparation can be obtained which has no peptic activity; it is a thioproteose and in various other respects differs chemically from pepsin (Tauber and Kleiner, 1932 and 1934). It has been stated by Dotti and Kleiner (1945) that adult human gastric juice contains no chymosin. For the clotting of milk by chymosin, the presence of calcium ions is necessary. The addition of chymosin to oxalated milk apparently produces no effect, but clotting ensues if calcium chloride is then added to the mixture. It is therefore thought that, in the clotting of milk, the caseinogen first undergoes conversion into casein, the calcium salt of which is insoluble. Under the further action of the acid gastric juice, the clot of casein first formed is dissolved.

Action on Carbohydrates:

The chief digestion of carbohydrate which takes place in the stomach is that of starch, since the amylase of the swallowed saliva continues to act until the contents become definitely acid. It seems probable that the hydrolysis of cane sugar and some other carbohydrates e.g. inulin, which takes place in the stomach can be completely accounted for by the action of hydrochloric acid present, and that there is no need to assume the presence of a special enzyme.

Action on fats:

The chief action of this juice on fats is the solution of their connective tissue framework and protoplasmic envelopes, so as to set the fat free in the gastric contents. After a fatty meal it is found, moreover, that a proportion of the fat in the stomach has undergone hydrolysis with liberation of free fatty acids. In this hydrolysis three factors are involved: (1) The action of the warm dilute hydrochloric acid; (2) The action of a lipase, which is secreted by the walls of the stomach, and acts especially in the beginning of gastric digestion before the contents have attained a high degree of acidity. The action of this enzyme is conspicuous only if the fat be present in a finely divided form, as in yolk of egg; (3) The action of lipase regurgitated from the duodenum. In any case, the chief digestion of fat takes place in the duodenum.

Anti-anaemia factor:

Gastric juice contains an important principle called the intrinsic factor (haemopoietin) possibly an enzyme, differing from pepsin or chymosin, formed in the stomach itself (Castle, Heath and Strauss, 1931; West, 1935). This reacts with an extrinsic factor, present in certain foods, e.g. meat, yeast, rice-polishings, eggs, which is, however, not identical with any vitamin B component. The reaction between these two factors produces a substance, haematinic factor which is essential for haematopoiesis ie. proper maturation of red blood corpuscles (Castle, 1934).

Neuro-poietic factor:

There is some evidence that the stomach may also produce a substance which is concerned with the nutrition of the nervous system, for the chronic inflammation and atrophy of the organ, which produce pernicious anaemia, is sometimes associated with degeneration of the lateral columns of the spinal cord (McDowell, 1950).

The factors governing the circulatory, motor and secretory functions of the stomach were studied in details by Wolf and Wolff (loc cit).

Circulatory changes:

Wolf and Wolff (loc cit) concluded that changes in vascularity as evidenced by color changes in the stomach lining actually reflected changes in blood flow. Accelerated blood flow in the mucosa was not merely associated with blushing of its surface. The membrane itself became wet, swollen, and turgid and the rugae were slightly fuller and smoother. These evidences of vascular engorgement were especially obvious in the collar of mucosa exposed on the abdominal wall. During marked hyperaemia, it often doubled in thickness from 5 mm. to 10 mm. and the radial folds in this exposed collar of gastric mucosa decreased in number from 12 or 15 to 5 or 7. The tissue itself under such circumstances felt succulent and boggy.

Motor activity in the stomach:

A comprehensive review on the work done on this aspect of the subject namely the pattern of motility of the stomach, which is provided by the interaction of the circular and longitudinal muscles in its wall, is included in the book by Alvarez (1940). He has concluded that one type of motility consists of gentle waves of contraction which originate in the cardia and progress towards the pylorus. As they do so, the force of contraction increases. They may pass over into the pylorus, or may end in a 'systolic' contraction of the pyloric antrum. A second type of motility pattern is a slow tonic type of contraction in which virtually the whole stomach wall participates, consequently raising the intragastric pressure. These recurring waves were found by Cannon (1912) to be accompanied by pangs of hunger. Hunger has been noted in their absence, however, and it has been observed that contractions of other parts of the gut, as well as the stomach, may give rise to pangs of hunger (Patterson and Sandweiss, 1942).

Normal course of secretion of gastric juice:

We may say that the gastric secretion in response to a normal meal shows three phases: (1) a reflex phase, which begins within five minutes of the taking of the food and is determined by the reflex nervous-mechanism; (2) a second phase, of humoral nature, of later onset and longer duration, due to the presence of products of the digestion of the food in the stomach; (3) a third phase, small and variable and due to the presence of digestion products in the duodenum. These phases may now be discussed in a little greater details as follows:-

(1) Reflex secretion:

In order to form an idea of the normal course of secretion of gastric juice the 'Pavlov Pouch' or the 'modified Pavlov Pouch' (Cope, 1940) was devised. In a dog treated in this way it is found that the amount of juice secreted by the small stomach is always a constant fraction of the amount secreted by the large stomach, while the digestive powers of the two juices are equal. It may, therefore, be regarded that the secretion obtained from stomach pouch is a sample of that produced by the rest of the organ and from the juice collected from the pouch, the behaviour of the stomach i.e. the effects of a normal meal in which the food is swallowed, or of a sham meal in an animal with an oesophagostomy, or of a meal directly introduced into an opening into the large stomach, may be inferred.

The fact that sham feeding causes the production of gastric juice shows that, in the first place, a reflex nervous mechanism is involved. This is an unconditioned reflex. But a secretion, which is at least as vigorous as that produced by a sham meal, can be evoked through a conditioned reflex, by merely providing some stimulus associated with the animal's food habits. If the animal be hungry, it is sufficient to show it the food to produce this effect.

(2) Chemical (Humoral) secretion:

The reflex secretion described above, however, does not nearly account for all the juice which is secreted when a meal is eaten and enters the stomach in the normal way. Although the juice elicited by sham feeding is promptly and abundantly produced, and is rich in acid and pepsin, the flow soon declines after the feeding ceases, and in one to one and a half hour ceases altogether. One can, however, in an oesophagostomised dog with a Pavlov Pouch, imitate the normal course by introducing meat into the lower end of the oesophagus as it emerges from the upper oesophageal opening; the food thus enters the stomach and mixes with the reflex juice which is secreted. It is then seen that the secretion of gastric juice continues for three to four hours, and that much more juice is formed than by sham feeding alone.

It is thus evident that these are two phases of secretion of the gastric juice, the first a reflex phase, occasioned by seeing or eating the food, the second due, in some way, to the presence of the swallowed food in the stomach. Ivy and Farrell (1925) made a totally denervated pouch and transplanted into the mammary region in a dog. When such a dog was fed, the secretion continued for an hour or two. This proved beyond doubt that the second phase is not reflex, but is due to a blood-borne chemical (humoral) stimulus.

Several substances are known which will cause secretion of gastric juice, for instance, alcohol, soup, meat or liver extract and peptone, when given by mouth or histamin or pilocarpine, when given by intravenous injection.

It might be supposed, therefore, that the secretion of the chemical phase was due to the absorption, into the blood, of some constituent of the food, which had a secretagogue action. But it is not so simple as that: if a dog is furnished with a gastric fistula and also with a Pavlov Pouch and if meat is introduced through the fistula into the main stomach without the animal being aware of it, there will, of course, be no reflex secretion, but it will be found that there is no delayed secretion either. If the experiment be repeated, but with the difference that, together with the meat, some fresh gastric juice be also introduced into the main stomach, then, although the reflex secretion still remains in abeyance, the second phase secretion begins after the usual interval of time, and continues for a normal period. It is clear, therefore, that the humoral phase depends in some way on the presence, together in the stomach, of food and gastric juice. It must be the products of the action of the gastric juice on the food which act as secretagogues; that this is so is proved by digesting the meat in vitro, with gastric juice, and then giving the solution by stomach tube, when secretion begins almost at once.

The humoral secretion can be elicited by the contact of the exciting substances e.g. liver extracts or predigested meat, for a sufficient time with an adequate area of the mucosa of any part of the stomach or of the small intestine. It has been suggested on the basis of such experiments as mentioned above, that the active substance might be a hormone, liberated into the blood from the gastric or intestinal mucosa, when the chemical excitants formed by partial digestion of the food are brought in contact with it, the liberation of the hormone being inhibited if that mucosa had been previously treated with procaine. Edkins (1906) had made a claim to have identified a gastric hormone to which he had given the name 'gastrin' and he had stated that it was only engendered from pyloric mucosa. But the attempts to repeat his experimental results were unsuccessful.

It has been suggested that histamine is identical with the gastric hormone. This is rendered unlikely by the fact that the action of the chemical excitants of gastric secretion, but not that of histamine, is inhibited by atropine. It is possible that histamine is liberated in the cells by the action, either of acetyl choline from vagus stimulation (abolished by atropine) or by the presence of the gastric excitant (or hormone)(Babkin, 1938).

Pavlov (loc cit) showed that the second phase of the gastric secretion is largely influenced by the character of the contents of the stomach. Thus after the ingestion of large quantities of fat, the secretion of gastric juice during the second phase is greatly delayed and also reduced in amount, in acidity and in pepsin content. Emptying of the stomach is delayed, and there is considerable regurgitation of duodenal contents into the stomach, so that the volume of the gastric contents is subsequently increased. The inhibitory effect of the fat seems to be exerted from the duodenum and not from the stomach itself, as may be shown by the results of introducing fat into stomach or duodenum when these have been separated from one another. The effect is a humoral one and the hormone concerned has been named 'enterogastrone'; it reduces volume and acidity of the juice resulting from a given stimulus: the pepsin content is also reduced when fat is administered, but this is a vagal effect (Gray et al. 1937; Grossman et al. 1944). Enterogastrone also reduces the motility of the stomach. After the preliminary delay, gastric secretion commences often three or four hours late, and may then be quite brisk. This secretion is due to the action of the soaps which have been formed in the stomach by digestion of the fat by the regurgitated duodenal contents.

(3) Intestinal phase:

Certain products of gastric digestion, when they enter the duodenum, act as chemical excitants to gastric secretion. This is true also of water, meat extracts, albumoses, peptones, saponin, soaps and magnesium sulphate. Although a substance ("gastric secretin") which stimulates gastric secretion has been extracted from the intestinal mucosa, it is generally believed that the intestinal phase is due to secretagogues in the food, absorbed from the intestine, the vagus terminals in the wall of the stomach or intestine being involved in the mechanism.

The intestinal phase of gastric secretion is inhibited by fat (before absorption), the acidity, volume and especially peptic activity being lowered. A similar effect is produced by injection-s of extracts of intestinal mucosa or urine; the factors responsible for this effect have been termed enterogastrone and urogastrone respectively (Cantarow and Trumper, 1950).

Other factors:

Insulin (hypoglycemia) stimulates gastric secretion through the vagus mechanism, the volume, acidity and peptic activity of the gastric juice being increased. Mecholyl, pilocarpine and nicotine increase the volume considerably and acidity somewhat. Alcohol is a powerful stimulant (acidity and volume), while acids and atropine are secretory depressants.

Different foodstuffs influence the secretion in different ways. For example, meat produces a juice of high acid, and moderate pepsin content, bread a juice of low acid and high pepsin content, and milk a juice of moderate acid and low pepsin content. Fat depresses peptic activity relatively more than acidity or volume.

It has been suggested that the various secreting cells (chief, parietal, mucous) are stimulated in varying degree by the same as well as by different stimuli. It is more likely, however, that various influences involved (psychic, nervous, chemical) stimulate or inhibit each set of secretory elements separately (Thomas, 1942).

Thus it will be seen from the discussions made above that the normal gastric secretion is mainly due to the cooperation of the various phases. The first and most important is the reflex secretion, determined through the vagus nerves by stimulation of the mucous membrane of the mouth or by conditioned reflexes. The second, next important factor, which provides for the continued secretion of gastric juice long after the reflex effects of feeding have disappeared, depends on the formation of an agent which acts as a chemical messenger to all parts of the stomach, being absorbed into the blood and thence exciting the activity of the gastric glands (Evans, 1947).

(B) Object of the study:

Since the time of Beaumont (loc cit) it has been known that proteins pass out of the stomach more rapidly than fats and that carbohydrates are evacuated still more quickly. Beaumont's observations on the time of evacuation of carbohydrates, proteins and fats, have been confirmed by many workers employing various methods. Penzoldt (1895) passed stomach tubes in a number of men. Pavlov (loc cit) and his pupils used dogs with duodenal and other kinds of fistulae. Cannon (loc cit) made roentgen observations on cats, estimating the degree of gastric emptying from the length of the shadows in the intestine. Fermi (1901) killed dogs at definite intervals after meals and weighed the dried gastric residues. McClure, Reynolds and Schwartz (1920) mixed barium sulphate with food and observed the passage fluoroscopically in man. They found that all substances commence to leave the stomach as soon as ingested, but that the total evacuation of some materials was much slower than that of others.

Pavlov (loc cit) and later Cannon (loc cit) explained the differences in the rate of evacuation by the hypothesis of the acid control of the pylorus. This hypothesis was, in brief, that any acid in the antrum opened the pyloric sphincter, whereas the presence of any acid in the duodenum resulted in closure of the pylorus until such time as the duodenal contents had been neutralized. On leaving the stomach, carbohydrates are neutral and proteins are distinctly acid, whereas fats are broken up into fatty acids and glycerol on arrival in the duodenum. This hypothesis, therefore, fitted in with the known facts and seemed to explain satisfactorily the differences observed.

The following observations, however, raised doubts as to the truth of the acid control hypothesis. Mcclure, Reynolds and Schwartz (loc cit) observed that neutralising the duodenal contents had little effect on the rate of gastric evacuation, and further showed that the pylorus opened and chyme entered the duodenum "on the approach of each antral peristaltic wave". In Cannon's (1898) own experiments the chyme left the stomach as peristaltic waves approached the pylorus, though not with every wave. Carlson and Litt (1924), employing an improved baloon method, found that any substance, acid, alkaline or neutral, when placed in the duodenum caused closure of the pylorus.

As it became evident that acid control is not the only factor, or even the principal influence, in determining the rate of the emptying of the stomach, more and more attention was being turned to the mechanical forces involved, and especially to gastric peristalsis. It, therefore, became of interest to consider the factors which were known to influence peristalsis and gastric evacuation, and the following is a partial list of these.

The physical state of the foodstuff is of considerable importance, as gruel leaves the stomach more rapidly than dry carbohydrates (Hedblom and Cannon, 1909), and large lumps of meat are retained much longer than minced meat (London 1925). Posture and exercise have marked effects as also changes in the carbon dioxide content of the blood have a great influence (Dickson and Wilson, 1924), also the rate of utilization of glycogen has an effect (Bulatao and Carlson, 1924), emotions are having an influence (Hughson, 1925), smoking, drinking water with meals (Ivy, 1919) and many drugs such as strychnine, caffeine etc. are also influencing the emptying of the stomach. It is highly probable that other influences will be found to affect both peristalsis and the rate of emptying and it is possible that the increased fat in the blood after a fat meal (Bloor, 1915) may be one of these. Wilson, Dickson and Singleton (1929) took up a study to throw some more light on this aspect of the study.

Most of our information regarding gastric response, and function is derived from work on animals or human subjects with fistulae. A stomach with a fistula is not a normal stomach. Carlson (loc cit), Cannon (loc cit) and others have done considerable amount of work to determine the pattern of gastric movements and the gastric evacuation time in human subjects. Direct visualisation of the gastric mucosa is made possible after the introduction of gastroscope. But the behaviour of the normal human stomach to various foods to which it is accustomed has been the subject of study of very few observers.

Wilson, Dickson and Singleton (loc cit) estimated in four normal persons the gastric evacuation time of meals of some varieties to which barium was added fluoroscopically. As the hypothesis, then advanced, like the one of the acid control of the pylorus, in explanation of the differences in the rate of evacuation of carbohydrates, proteins and fats from the stomach, appeared to be inadequate, it seemed to Wilson et al (loc cit) advisable to do some further work on this subject, especially with reference to the question why fats are held in the stomach so much longer than carbohydrates. In their investigation, roentgen observation of the human subject was adopted by them as the method which best met their requirements. All the experiments were performed by them on four young men who had no symptoms of gastro-intestinal or other disease, and whose stomachs had previously been found to be normal on fluoroscopic examination. After fasting for at least four hours preceding the experiment, their subject was given a meal containing 40 gm. of barium sulphate made up to 240 cc, with the substance to be investigated. Fluoroscopic observations were made by them during the consumption of the meal, with the object of determining how soon the food commenced to leave the stomach. Subsequent observations were made by them at one and one-half, three and four and one-half hours after beginning the ingestion of the meal and at each examination an estimate was made by them of the percentage of the barium remaining in the stomach. From their results which were expressed by them as the percentage of the meal which had been evacuated from the stomach, they drew some conclusions which are as follows:-

(1) The initial emptying of the stomach depends on two factors: The presence of peristalsis of adequate depth, and the consistency of the meal.

(2) All liquid meals start to leave the stomach as soon as ingested, regardless of their composition. Most solids commence to leave the stomach as soon as they reach the pyloric sphincter.

(3) After the first few minutes, proteins are evacuated more slowly than carbohydrates and fats are slowest of all.

(4) In the case of fats this delay is associated with shallower peristaltic waves, due possibly to depression of muscular activity by products of fat digestion circulating in the blood.

Wilson et al (loc cit) thus studied only the rate of evacuation of various foods from the normal stomach and therefore they did not note the nature of the response of gastric secretion. Hawk, Rehfuss, and Bergeim (1926) gave 100 gms. of foods of different varieties and collected samples of material from the stomach at intervals by passing rubber tubes into the stomach and noted the degree of acidity and the evacuation time of these articles. As Mottram and Graham (1949) have remarked, "these observations have not been repeated since the introduction of the fractional method of testing the stomach and they destroy some popular beliefs." Thus 100 gms. of beef and lamb were both digested in about the same time, whereas chicken and lamb took 10-20 minutes longer. Bacon took nearly one hour longer than beef. Their observations on milk were very interesting. The curds from the whole raw milk were larger and tough like rubber; curds of boiled milk soft and small; of pasteurised milk intermediate in character between the curds of raw and boiled milk; and of skimmed milk large and hard. The influence of fat was also shown by them in their studies on cream. It was apparent in these tests that the character of the milk curds was influenced in a direct way by the fat content, that is, the more fat, the less curds. Furthermore, the curds were smaller and softer, the higher the fat concentration. With 40 per cent cream, for example, no curds were formed during the first half hour. Moreover, the largest curds were only about the size of the head of a pin and they did not coalesce to form larger curds as they did with milk of low fat content. It was also noted by them that milks of high fat value left the stomach slowly. They found, in fact, that 475 cc. of material was returned from the stomach two and a half hours after drinking 500 cc. of 40 per cent cream. As exception to the above rule was found in the case of skimmed milk (0.5 per cent fat) which left the stomach somewhat slower than raw whole milk (4 per cent fat). This finding was attributed to the fact that the curds of the skim milk were tough and disintegrated but slowly in the stomach. Their results showing the evacuation time and the highest total acidity for various articles of diet have been summarised in the following table.

(Vide Table 1)

All foods are not digested in the stomach uniformly. Certain articles are better digested and leave the stomach earlier. The lay mind has already recognised this fact and foods have been accordingly classified as light and heavy. Thus milk is held to be lighter than "Shrikhand" or "Basudi", rice is lighter than wheat etc. "Mug" i.e. green gram is believed to be lighter than "Val" i.e. fried bean dry and there are many such other beliefs, without any scientific evidence. And it is on such notions that food is proscribed in health and disease, but the views have not been substantiated so far.

As has been shown above, the rate of digestion, in the stomach, of almost all the Western food preparations has been studied by observers like Hawk et al (loc cit) and such investigations "have destroyed many popular beliefs". Similar study on Indian food preparations had not been undertaken so far and hence a need was felt to compile data in respect of our foods, which will go a long way in advising diet in health and disease. It was therefore thought worthwhile to find out the gastric response, gastric digestion and evacuation time of various Indian food prepa-rations, which forms the subject of this thesis.

Table No.1

Table showing Rate of Digestion of Foods

Evacuation time and highest total acidity for various articles of diet (Quoted from Hawk, Rehfuss and Bergeim, 1926)

Articles of diet (100 Gms. portions unless otherwise stated)	No. of observations	Average Evacuation time Hours	Highest total acidity (average) N/10 alkali to neutralize 100 cc juice
Beef & beef products..	25	3.00	120.0
Lamb & Lamb products..	14	3.00	135.0
Veal:- a. market..	7	2.50	140.0
b. "Bob"..	7	3.20	110.0
Pork & Pork products..	31	3.15	120.0
Chicken..	20	3.15	125.0
Turkey..	2	3.30	140.0
Gunea Hen..	2	4.00	110.0
Fish..	75	2.50	130.0
Cow's milk 75 c.c...	3	1.15	45.0
400 c.c...	50	2.30	100.0
Mother's milk 150 c.c...	5	1.40	60.0
225 c.c...	2	2.25	90.0
Gelatin..	5	2.00	70.0
Eggs & Eggs combinations..	90	2.40	80.0
Vegetables prepared in different ways..	124	2.50	75.0
Fruits..	68	2.00	90.0
Bread and Cereals..	75	2.40	80.0
Cakes..	29	3.00	90.0
Pies..	29	2.30	90.0
Puddings..	23	2.20	90.0
Sugars and candies..	28	2.05	70.0
Icecreams..	7	3.15	100.0
Ices..	4	2.35	65.0
Nuts:- 25 gms. to 50 gms.	22	4.00	100.0

I The other references available in literature are from the work of Cannon, Guiantree, etc. They are on cats and other animals (W.C.Alvarez, 1948).

II The above are the only observations on human beings. Mottram & Graham (1949) state that "they have not yet been repeated since the introduction of the fractional method of testing the stomach"