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Mechanisms protecting against gastro-oesophageal reflux: a review

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Thomas Willis in his *Pharmaceutice Rationalis* published in 1674-5 clearly recognized that the oesophagus may be closed off from the stomach and described 'a very rare case of a certain man of Oxford [who did] show an almost perpetual vomiting to be stirred up by the shutting up of left orifice [of the stomach]'. His diagrams (Fig. 1) of the anatomy of the normal stomach show a band of muscle fibres encircling the oesophagogastric junction which function to close this orifice. During the 288 years which have elapsed since this description, it has become abundantly clear that a closing mechanism does indeed exist at the cardia but its nature remains the subject of dispute.

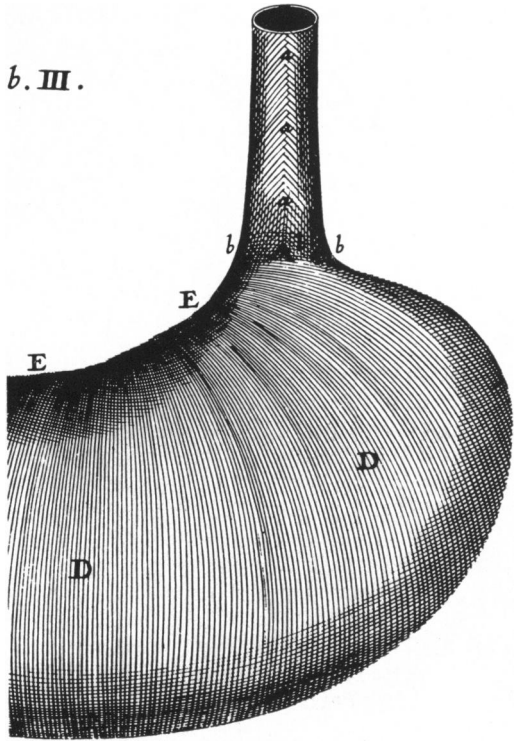

FIG. 1. *The arrangement of muscle fibres in the oesophagus and stomach taken from Willis's* Pharmaceutice Rationalis (1674-5). '*A, the mouth of the ventricle to which the oesophagus aaa is joyned and which the fleshie circular fibres bbb do compass about, and as occasion serves being contracted, do shut up.*'

Willis was chiefly concerned with the failure of this mechanism to open and does not appear to have appreciated its true physiological importance. Although descriptions of oesophageal ulcer are to be found in the writings of John Hunter and of Carswell (1838), the pathogenesis of these lesions remained uncertain until 1879, when Quincke described three cases with ulcers of the oesophagus resulting from digestion by gastric juice. Thereafter peptic ulcer of the oesophagus became accepted as a pathological entity closely resembling peptic ulcer in the stomach in macroscopic and microscopic appearances. The clinical picture of peptic ulcer of the oesophagus was clearly described by Tileston in 1906 who noted substernal pain radiating to between the shoulders, dysphagia, vomiting, haematemesis, and melaena as the principal presenting features. During subsequent years it was recognized that gastro-oesophageal reflux may produce oesophagitis giving essentially the same clinical picture as peptic ulcer of the oesophagus. Winkelstein (1935) drew attention to the clinical presentation of peptic oesophagitis caused by the eroding action of 'gastric juice rising into the lower part of the gullet and held there by mild spasm of the cardia'. With the general recognition of the clinical picture and the increasing use of radiology and oesophagoscopy in the investigation of digestive disturbances, gastro-oesophageal reflux has come to be recognized as one of the commonest disorders of the upper alimentary tract (Lawler and McCreath, 1951). The acute or chronic inflammatory changes of digestion oesophagitis, maximal in the lower oesophagus yet ceasing abruptly at the mucosal junction, and associated with superficial ulceration, leukoplakia, and fibrosis, are the characteristic pathological findings (Stewart and Hartfall, 1929; Allison and Johnstone, 1953; Peters, 1955b).

Although the clinical and pathological features of peptic oesophagitis are now generally accepted, controversy still centres around the question of how reflux is normally prevented and which of the many mechanisms which have been described since the time of Willis are of importance in this respect.

THE EFFECT OF GASTRIC MUCOSA LINING THE OESOPHAGUS

The first question to arise is whether this oesophagitis is always the result of the reflux of gastric juice from the stomach. Ectopic gastric mucosa may be found in the oesophagus; Rector and Connerley (1941) found this in 11·8% of 1,000 consecutive necropsies in which the oesophagus was carefully examined. Oxyntic and chief cells were noted in ectopic mucosa in the oesophagus by Taylor (1927) and the possibility that under these conditions the oesophagus may produce its own acid and so digest its squamous lining has been advanced, a state of affairs analogous to that found in the small intestine with Meckel's diverticulum. Studies in the experimental animal in which gastric mucosa has been transplanted into the oesophagus indicate that small areas (1 to 1·5 cm. in diameter) produce sufficient acid to injure the oesophageal mucosa if left in contact for some time (Arroyave, Clatworthy, and Wangensteen, 1950; Ripley, Leary, Grindlay, Seybold, and Code, 1950), and, as might be expected, the administration of histamine in beeswax aggravated the oesophagitis.

Turning now to the problem of whether the human oesophagus can secrete sufficient acid to digest its own squamous mucosa we are immediately faced with difficulties of definition of the oesophagus, necessary to distinguish the condition from thoracic stomach. Defining the oesophagus as the tubular structure interposed between the pharynx and the bag of the stomach, receiving its blood supply from the aorta rather than the left gastric artery, and having no peritoneal covering, Barrett (1958) states that ectopic islands of gastric mucosa in the oesophagus have never been proved to have caused a pathological lesion. This is presumably because the amount of acid they secrete is small and easily neutralized by swallowed saliva. Distinct from gastric mucosal ectopia is the condition in which the lower oesophagus is lined by columnar epithelium and it is here that the differentiation from hiatus hernia is usually most difficult and controversial. The epithelium of the tubular oesophagus contains mostly mucus-secreting glands but some oxyntic cells may occur in the lowermost portion (Barrett, 1958). In a few of these patients the cardiac closing mechanisms may function normally yet sufficient acid is secreted in the lower oesophagus to cause oesophagitis in the squamous-lined portion of the organ and lead to stricture in the region of the arch of the aorta. The difficulty lies in establishing that the cardiac closing mechanisms are unimpaired, and several radiological examinations, together with manometric observations to demonstrate that the oesophagogastric sphincter is detectable in the normal position in relationship to the diaphragm, are desirable to prove this point with certainty and to exclude reflux from below the diaphragm as the cause of oesophagitis. Ulceration of the columnar epithelium of the oesophagus may develop as a result of acid secreted in the oesophagus. This differs from ulceration of the squamous mucosa of the oesophagus in that it is often deeper and less likely to lead to stricture formation (Barrett, 1950).

SUGGESTED MECHANISMS AT THE CARDIA

In the vast majority of instances peptic oesophagitis is caused by acid produced in the stomach and nearly always results from incompetence of the closing mechanisms at the cardia. The pressure in the intra-abdominal stomach is generally a good deal higher than that in the oesophagus and during a Muller's manoeuvre this difference may reach 80 mm. Hg (Dornhorst, Harrison, and Pierce, 1954a). Straining and retching may increase this gastro-oesophageal pressure gradient to a comparable extent (Atkinson, Bottrill, Edwards, Mitchell, Peet, and Williams, 1961).

Three types of antireflux barrier have been suggested. 1 One or more sphincters at or immediately above the oesophagogastric junction, which may be defined as a line separating the saccular cavity of the stomach from the tubular lumen of the oesophagus (Ingelfinger, 1958). The mucosal junction commonly lies a little above this point, *i.e.*, in the tubular gullet or oesophagus (Neumann, 1933). 2 The pinchcock action of the crura of the diaphragm; 3 a structure which functions as a mechanical valve formed by the oblique entry of the oesophagus to the stomach, by the flaccid intra-abdominal portion of the gullet or by mucosal folds. A formidable amount of anatomical, physiological, pharmacological, and clinical evidence concerning the importance or otherwise of each of these mechanisms has been collected. Conflict between morphology and function has been one of the greatest stumbling blocks: for example, the inconspicuous circular muscle fibres at the cardia seem scarcely sufficient to constitute the sphincter which physiological studies demonstrate.

SPHINCTER AT THE OESOPHAGOGASTRIC JUNCTION

Willis's anatomical diagrams clearly showed circular muscle fibres binding the oesophagus immediately above its point of junction with the stomach. In the cadaver Laimer (1883) found an isthmus or constriction about 2 to 3 cm. in length in the lower oesophagus 3 to 4 cm. from the cardia and just above the diaphragmatic hiatus. A constriction in this situation can often be seen in blood clot casts of the oesophagus and stomach in patients dying of gastrointestinal haemorrhage (Lerche, 1950; Peters, 1955a). Others have confirmed that such a narrowing may exist (Mosher, 1930; Nauta, 1955) but most would agree that this is an inconstant finding in human necropsy material (Lendrum, 1937). This narrowing is presumably brought about by thickening or agonal contraction of the musculature in this situation. Lendrum (1937), after studying multiple sections of the muscle coats at the oesophagogastric junction, came to the conclusion that no morphological evidence of a sphincter is to be found in this region. The most careful anatomical study of this region in recent times was made by Lerche (1950) who, contrary to the general experience of others, found a localized muscular thickening at the site of luminal constriction just above the diaphragm. This he named the 'inferior oesophageal sphincter', and at the junction of the tubular oesophagus with the saccular stomach he described a second sphincter, the 'constrictor cardiae' (Fig. 2). The intervening segment, which he regarded as being distinct from either the oesophagus or stomach acting as an entrance to the latter, he named the 'vestibule'. This vestibule is encircled by the diaphragmatic hiatus to which it is attached by the phreno-oesophageal ligament.

Whilst the anatomical evidence for a sphincter at the human gastro-oesophageal junction is both slender and controversial no such doubts exist in certain animals. Thus, the bat, which spends much of its existence in the inverted position, has a prominent sphincter at the gastro-oesophageal junction, said by Fischer (1909) to be five to six times as thick as the musculature of the gastric wall.

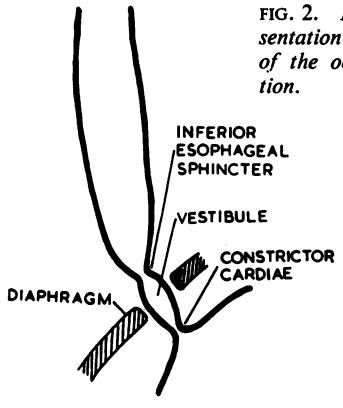

FIG. 2. *Diagrammatic representation of Lerche's conception of the oesophagogastric junction.*

Physiological studies place the existence of a sphincter at the gastro-oesophageal junction beyond dispute. Magendie (1822) noted that morsels of food tend to be held up in the lower oesophagus, and with the introduction of radiological methods it became certain that the food bolus is delayed in the lower oesophagus before passing into the stomach. The resulting distension of the lower oesophagus was mistaken for an anatomical structure and called the 'phrenic ampulla', but it is now generally recognized that this bears no relationship to the vestibule of Lerche and is located higher in the oesophagus (Wolf, Marshak, Som, Brahms, and Greenberg, 1958). Fleshler, Hendrix, Kramer, and Ingelfinger (1958) found that the mechanism at the gastro-oesophageal junction was able to withstand a hydrostatic force obtained by layering fluid in the oesophagus. Oesophageal distension evoked a secondary peristaltic wave and reflex relaxation of the sphincter before a pressure high enough to force the closing mechanism was reached. Diaphragmatic contraction did not appear to be responsible since the hold-up in this situation was seen in expiration as well as in inspiration. Creamer and Pierce (1957) found that delay in the lower oesophagus occurred during isolated swallows when the bolus had been held in the mouth before swallowing but when the same quantity was drunk from a cup no hold-up was seen. Inhibition of the sphincter apparently occurred earlier during drinking than during swallowing.

Direct observation of the cardia in animals and man from above or below confirms the presence of a constriction in this situation (Kronecker and Meltzer, 1883; Som, 1956). At oesophagoscopy the constriction at the oesophagogastric junction noted by von Mikulicz (1903) and Som (1956) is not invariably present. Difficulty may arise in distinguishing this narrowing from that brought about by the diaphragmatic pinchcock (Jackson, 1922; Allison, 1951) which usually shows a pronounced respiratory rhythm. The explanation of the apparently ephemeral nature of this sphincter in man during oesophagoscopy may lie in the nature of the anaesthetic employed since the closing mechanisms often relax under general anaesthesia. Observations from the gastric side of the dog's cardia at operation indicated that this is closed, puckering the mucosa to form a rosette which is pulled upwards during swallowing before opening to allow the oesophageal contents to enter the stomach (Nauta, 1956). The

cardia is drawn upwards before opening in a similar manner in the cat by vagal stimulation and before vomiting induced by apomorphine (Torrance, 1958). Studies in the experimental animal indicate that this constriction is still detectable after the oesophagogastric junction has been freed from the diaphragm or after phrenic nerve section (Fulde, 1934). That the diaphragm is not solely responsible for constriction of the human oesophagogastric junction is clearly demonstrated by manometric studies in patients with hiatus hernia (Atkinson, Edwards, Honour, and Rowlands, 1957b) or with phrenic palsy (Atkinson and Sumerling, 1959) (*vide infra*).

The application of pressure-recording techniques to the investigation of the function of the oesophagus and the oesophagogastric junction dates from the ingenious studies of Kronecker and Meltzer (1883) before the advent of radiology. Using themselves as experimental subjects a double lumen tube was passed into the lower oesophagus. One lumen communicated with a small balloon near the tip of the tube which was used to register the arrival of the peristaltic wave. The other lumen opened into the oesophagus near to the balloon and through this a piece of litmus paper attached at its tip adjacent to the opening of the tube could be withdrawn. The subject was then given a swallow of vinegar and the litmus paper when withdrawn a few seconds later indicated that the bolus had arrived in the lower oesophagus long before the peristaltic wave had reached this region.

During the past decade, manometric methods have been intensively applied to the problems of oesophageal function, notably in the laboratories of Ingelfinger and of Code. In a comprehensive review Ingelfinger (1958) made a critical appraisal of these methods and their contribution to our knowledge of oesophageal motor function. Using open-ended, water-filled tubes attached to capacitance manometers recording electronically, Sanchez, Kramer, and Ingelfinger (1953) and Ingelfinger, Kramer, and Sanchez (1954) demonstrated a different pattern of motility in the vestibule of Lerche from that obtained higher in the oesophagus which had already been described by Butin, Olsen, Moersch, and Code (1953). During deglutition the essential changes noted in the body of the oesophagus were an immediate rise in pressure, coinciding with the arrival of the bolus at the recording point and persisting to form a plateau of positive pressure, and a final positive deflection indicating the arrival of the peristaltic wave. In the vestibule this plateau did not occur suggesting that this region remained closed off in the early phases of swallowing. Subsequently Fyke, Code, and Schlegel (1956) demonstrated a zone of increased intraluminal pressure at the oesophagogastric junction analogous to that which had already been demonstrated at the pharyngo-oesophageal junction and which is brought about by the tonic contraction of the pharyngo-oesophageal or cricopharyngeal sphincter (Fyke and Code, 1955; Atkinson, Kramer, Wyman, and Ingelfinger, 1957c). The presence of a zone of raised intraluminal pressure at the oesophagogastric junction was confirmed by others (Botha, Astley, and Carré, 1957; Atkinson, Edwards, Honour, and Rowlands, 1957a). This zone (Fig. 3), extending over a total distance of 1 to 4 cm. below and above the level of the diaphragm, has the physiological characteristics of a sphincter; in contradistinction to the body of the oesophagus, in this zone there is a transient fall in pressure during swallowing, suggesting relaxation of the sphincter (Fig. 4). An alternative explanation of the zone of higher pressure would be that it was brought about by external compression of the oesophagogastric junction by the diaphragm. Three observations indicate that this is not the case; first, the zone of higher pressure can still be detected in patients with hiatus hernias in whom the oesophagogastric junction lies well above the level of the diaphragm (Atkinson *et al.*, 1957b); secondly, the zone can still be detected in patients with diaphragmatic paralysis (Atkinson and Sumerling, 1959); and thirdly, it is diminished in magnitude or absent after cardiomyotomy (Atkinson, 1959). The height of the elevation of pressure in this zone bears a relationship to the tone of the sphincter. One of the difficulties which arises is the variability of the pressure elevation in the same subject often from minute to minute. This necessitates making many observations and taking the maximum value obtained, a method not altogether free from criticism. The reason for this variability may lie in the fact that the volume of fluid in the sphincter is small and may at times be insufficient to drive the pressure sensing device. To overcome this difficulty a closed system using small balloons has been used (Code and Schlegel, 1958) and certainly by this means a more convincing rise in pressure is recorded. How much of this pressure rise is caused by the greater diameter of the balloon stimulating the sphincter to contract is open to question.

Reid in 1838 noted stasis in the oesophagus after vagal section in the neck and this observation was subsequently confirmed by others (Cannon, 1907). Langley (1898) found nerve fibres in the rabbit's vagus, stimulation of which caused relaxation of the cardia. This work was borne out by subsequent studies. In a series of experiments on cats, Knight (1934) found that vagal section caused a disorder resembling cardiospasm whereas vagal stimulation led to relaxation of the cardia. Excision of the

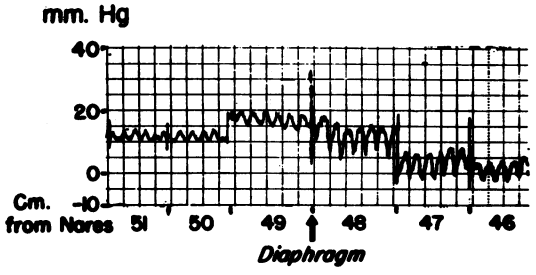

FIG. 3. *Pressure record obtained during withdrawal of an open ended tube in one centimetre stages from the stomach (51 cm.) to the oesophagus (47 cm.). Note the segment at the oesophagogastric junction in which intraluminal pressure is raised.*

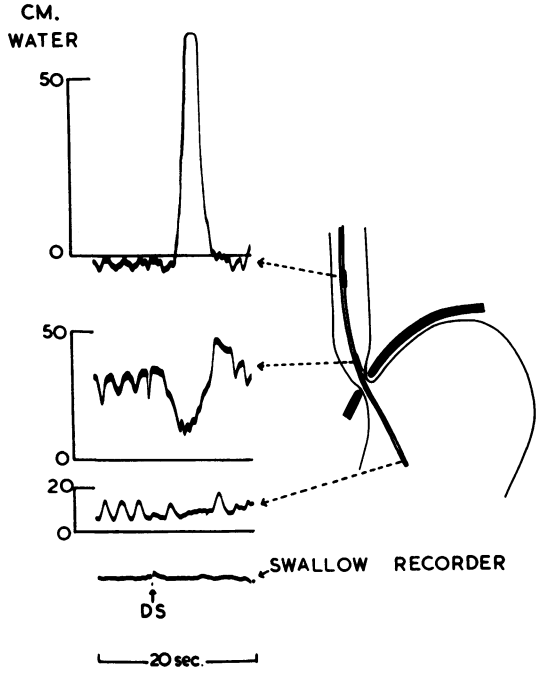

FIG. 4. *Simultaneous pressure records from the oesophagus, oesophagogastric junction, and stomach during a dry swallow (d.s.). Note the temporary fall in pressure in the junctional zone which occurs during swallowing.*

sympathetic fibres round the coeliac axis caused the cardia to relax and led to reflux. In keeping with these observations is the fact that dysphagia may follow vagotomy carried out for the treatment of peptic ulcer (Bruce and Small, 1959).

Pharmacological studies have given results apparently at variance with the results of nerve section. Anticholinergic drugs cause a fall in the height of the pressure elevation at the human oesophagogastric junction and favour the occurrence of gastro-oesophageal reflux whereas this pressure is augmented after cholinergic drugs (Bettarello, Tuttle, and Grossman, 1960). It must be pointed out, however, that studies in the cat have suggested that acetylcholine causes relaxation of the circular muscle of the oesophagogastric junction (Schenk and Frederickson, 1961). Further light has been cast on this rather confused picture by the careful studies of Ellis, Kauntze, and Trounce (1960), using isolated muscle samples taken from the human oesophagus at operation. They found that the isolated circular muscle contracted in response to acetylcholine and that this response could be prevented by atropine. No evidence of a cholinergic mechanism producing relaxation could be found. The response to adrenergic drugs was more complex in that, although contraction usually occurred, blockage of these receptors by phentolamine led to relaxation. This dual response suggested two types of adrenergic receptors, one causing contraction, the other relaxation. The circular muscle of the cardia differed from that higher in the oesophagus in that nervous stimulation by short pulse waves or nicotine caused relaxation, which, they suggest, is mediated by noradrenaline and masks a cholinergic mechanism causing contraction. These findings go a long way towards reconciling the results of nerve section and of pharmacological studies.

ROLE OF THE DIAPHRAGM The oesophagus passes through a slit-like tunnel in the right crus of the diaphragm to enter the abdomen and is attached to the hiatal opening by the phreno-oesophageal ligament. This tunnel is approximately 3 cm. in length (Milstein, 1961) and the oesophagus is angulated as it runs through. The anatomy of this region has been described in detail by Collis, Kelly, and Wiley (1954b) who dissected 50 diaphragms at necropsy and found that in 66% all the fibres forming the oesophageal opening came from the right crus, in 32% some fibres came from the left crus, and in 2% most of them came from the left crus. A band of fibres from the left crus (the muscle of Low) runs behind the oesophagus to the region of the inferior vena caval hiatus and together with the right crus of the diaphragm is said to exert a scissor-like action in closing off the oesophageal hiatus (Fig. 5).

The phreno-oesophageal ligament, consisting chiefly of fibrous and elastic tissue, arises from the under surface of the diaphragm and invests the oesophagus in the region of the narrowing of Laimer. Sycamore (1956) attributed an annular indentation of the lower oesophagus just above the diaphragm, which he visualized radiologically, to the attachment

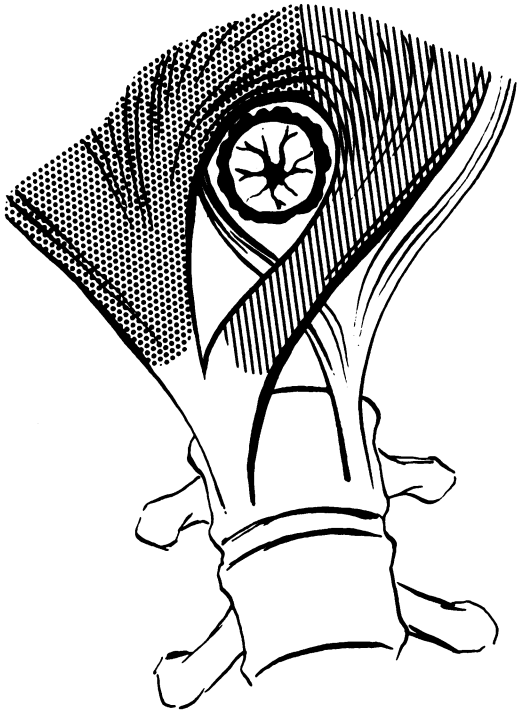

FIG. 5. *Diagrammatic representation of the muscular arrangements at the oesophageal hiatus of the diaphragm modified from Collis* et al. (1954b). *Note the sling formed by the right crus of the diaphragm, the left portion of which (hatched area) is supplied by the left phrenic nerve and the right portion (stippled area) by the right phrenic nerve. The muscle of Low runs from the left crus behind the oesophagus.*

of the phreno-oesophageal ligament. The structure and functional significance of this ligament are extremely controversial and the subject has been well reviewed by Peters (1955a). Anders and Bahrmann (1932) noted many elastic fibres in the ligament and also found some striated muscle fibres to be present. Many believe this ligament to be a substantial structure which plays an important role in maintaining the position of the oesophagus and stomach in relation to the diaphragm and to which particular attention must be directed in the operative repair of hiatus hernia (Harrington, 1955; Allison, 1951). Others, however, consider the eye of faith to be required for the dissection of this structure, which is felt to be too delicate to play any part in preventing sliding hiatus hernia (Barrett, 1952).

The innervation of the diaphragm in the region of the oesophageal hiatus was examined in 14 cadavers by Collis, Satchwell, and Abrams (1954a), who found that the portion of the right crus which passes behind and to the left of the hiatus is supplied by the left phrenic nerve whereas the right portion of the right crus is supplied by the right phrenic nerve (Fig. 5). Perera and Edwards (1957) confirmed that the left portion of the right crus is supplied by the left phrenic nerve; Botha (1957) concurred with this view and could find no evidence of vagal or intercostal nerve innervation in the region of the hiatus.

Two roles have been attributed to the diaphragm in maintaining closure of the cardia. The first of these is direct compression from side to side by what Chevalier Jackson graphically described as a pinchcock action. This compression is easily visible at oesophagoscopy and can be identified by the radiologist as an inspiratory indentation or interruption of the column of barium in the oesophagus and stomach (Johnstone, 1955). The second role which has been suggested is that the diaphragm maintains the oesophagogastric angle. Normally the oesophagus turns forward and to the left through the tunnel in the diaphragm. This angulation will be increased by the contraction of the right crus which forms a sling round the oesophagogastric junction, likened by Allison (1951) to the puborectalis sling at the anorectal junction. This diaphragmatic sling might compress the oesophagogastric junction directly or serve to maintain the angle of entry of the oesophagus to the stomach and enable this to function as a mechanical flap valve (Collis *et al.*, 1954b). There is no general agreement about the degree to which the oesophagogastric junction is compressed by the diaphragm. Squeezing of a finger inserted into the gastric side of the cardia at operation was noted by Joannides (1929), by Allison (1951), and by Wooler (1952) who found that phrenic nerve stimulation increased the degree of constriction. On the other hand, Dornhorst *et al.* (1954a) and Braasch and Ellis (1956) could feel no such constriction and Nauta (1956) thought it unimportant. Records of intraluminal pressure show increased respiratory deflections in the region of the hiatus which would be in keeping with direct compression by the right crus of the diaphragm but it is possible that these are brought about by the recording tip being forced against the wall of the oesophagus in this situation without luminal closure.

Most observers are agreed that the diaphragmatic pinchcock only comes into operation during the inspiratory phase of the respiratory cycle or during diaphragmatic contraction on straining and heavy lifting.

CARDIA AS A MECHANICAL VALVE Von Gubaroff (1886) believed the diaphragm to have but a weak constricting action on the oesophagogastric junction and suggested that the oblique entry of the oesophagus into the stomach was the major factor in

preventing reflux. This angle at which the oesophagus enters the stomach has subsequently become known as the angle of His (1903). Dick and Hurst (1942) stressed the importance of this angle and the prevention of reflux, and this view has been elaborated by Barrett (1952 and 1954), who maintained that in the normal subject a barrier against reflux exists in the form of a flap of mucous membrane situated on the greater curvature aspect of the cardia and depending for its efficiency upon the muscularis mucosae, which moves the mucosa and causes it to pout into the orifice.

Increase in intragastric pressure would thrust this flap against the lesser curvature aspect of the oesophago-gastric junction which is supported externally by the liver, and so close off the orifice. It is difficult to believe that this mechanism could form an effective barrier unless the angle of His were maintained by some active means. Many believe that the diaphragm fulfils this role and certainly in the presence of sliding hiatus hernia this angle is often lost. Furthermore the angle appears to be maintained by an active mechanism since it is usually absent in the cadaver (Atkinson and Sumerling, 1959). That the diaphragm is not necessarily the most important factor is suggested by the observations that the oesophagogastric angle in the anaesthetized dog is maintained after the oesophagogastric junction has been completely freed from the diaphragm (Smiddy and Atkinson, 1960). If the oesophagus and stomach are then removed from the animal the oesophagogastric angle will gradually disappear as the musculature loses its tone and the oesophagogastric junction then takes on the funnel shape found at necropsy. These observations provide strong evidence that in the dog the angle is maintained by an intrinsic mechanism in addition to any part the diaphragm may play. Observations on patients with progressive systemic sclerosis, a disease in which paralysis of the smooth musculature of the upper alimentary tract is prominent, suggest that the angle of His is frequently lost. In this disease striated muscle is infrequently involved and radiological and manometric observations show nothing to suggest diaphragmatic paralysis yet the angle often disappears (Atkinson, Rowell, and Sumerling, 1962). However, Botha (1958a) has stressed the variability of this angle, which, together with the difficulties inherent in making an accurate assessment of it by radiological means, necessitates some caution in interpretation of apparent alterations during life.

The oblique fibres which form the deepest muscle coat of the stomach wall serve to maintain the oesophagogastric angle by acting as a sling around the lateral side of the cardia, variously known as the sling of Willis or the collar of Helvetius. These were noted by Lendrum (1937), and Barrett (1952 and 1954) attaches great importance to them in accentuating the angle of His and maintaining the competence of the cardia after cardiomyotomy. These muscle fibres receive little attention in most textbooks of anatomy yet form a distinct bundle which in the dog at least can be clearly identified (Fig. 6). In this animal they are closely attached to the mucous membrane on the lateral side of the cardia and so their sling action is difficult to destroy by simple section of the bundle. The arrangement of the mucosal folds at the dog's cardia to form an arc on the cranial aspect would be in keeping with such a sling mechanism (Nauta, 1956).

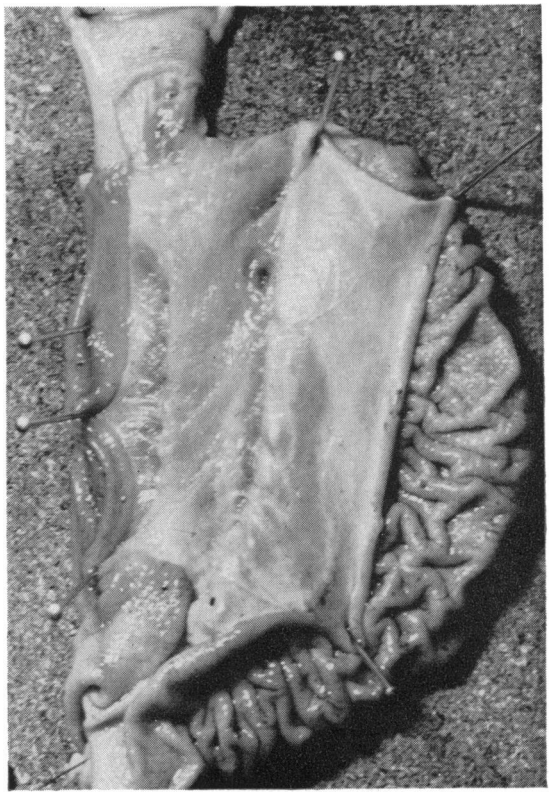

FIG. 6. *Dissection of the invaginated dog's stomach to show the oblique muscle fibres looping over the lateral side of the oesophagogastric junction.*

The second type of mechanical arrangement which has been suggested to contribute to the prevention of gastro-oesophageal reflux concerns the flaccid intra-abdominal position of the oesophagus. The very existence of this structure has been denied by some (Allison, 1948) but the difficulties here are largely those of definition already discussed. Most would agree that a tubular segment, perhaps capable

of dilatation to form a funnel, partially or completely lined by gastric mucosa, lies below the diaphragm. This would comprise the lower portion of the vestibule of Lerche. The abdomen behaves as a fluid-filled cavity in terms of alteration in intra-abdominal pressure with change of posture. In the head down position the external pressure applied to the flaccid-walled intra-abdominal oesophagus at the bottom of the abdominal cavity would be greater than intragastric pressure and hence the segment would remain closed (Cannon, 1911; Fyke *et al.*, 1956). This concept has been developed further by Creamer and Pierce (1957) and by Creamer, Harrison, and Pierce (1959), who by carefully correlating radiological and manometric techniques, were able to show that the point of hold up of barium on swallowing coincided with the effective diaphragmatic hiatus, *i.e.*, the point at which the inspiratory pressure changes reverse in direction. The sphincteric zone identifiable by manometry extends over this intra-abdominal segment of gullet and its contraction converts the segment into a narrow tube supported externally by intra-abdominal pressure. Edwards (1961) believes that a similar mechanism may play some part in preventing flow from the infra to the supra diaphragmatic portions of the stomach in patients with hiatus hernia. It is generally agreed that this flaccid segment could only function as an anti-reflux mechanism if intragastric pressure does not exceed intra-abdominal pressure. Yet in normal subjects the stomach will retain air when inflated during the course of gastroscopy.

MUCOSAL ROSETTE AT THE CARDIA When the cardia is viewed from the gastric side through a gastrotomy opening the mucosal folds can be seen to be drawn together to form a rosette. On distending the stomach these folds are ironed out as the cardiac orifice begins to open (Nauta, 1956). About this there is general agreement but controversy centres around the means whereby these folds are drawn together and whether the mucosa itself is of intrinsic importance in the prevention of reflux. Hughes (1955) showed that the muscularis mucosae is thicker in the lower than in the upper oesophagus in the cat, rabbit, and rat, and Creamer (1955), finding a localized thickening of the muscularis mucosae at the oesophagogastric junction, suggested that this drew together the mucosa in a purse string manner. This, he suggested, formed a mechanical valve upon which carminatives exert their action by altering mucosae pliability. Botha (1958a), after making dissections in various animal species, came to the conclusion that the mucosal rosette is actively supported by the muscularis mucosae as well as by the sphincter in the muscular coat of the oesophagogastric junction. Cinefilms of this region during swallowing showed that the mucosal folds moved independently of the muscular coat suggesting that the muscularis mucosae was binding these folds together.

It seems difficult to believe that in man the mucosa itself is of intrinsic importance in the prevention of reflux since gastric mucosal atrophy, as, for example, in pernicious anaemia, does not cause the cardia to lose its competence. The mucosal rosette is a consequence of closure of the lumen but in itself hardly seems sufficient to provide a barrier to reflux. Allison (1956) expressed this view more graphically. 'There are those who assert that the mucosa is gathered up into a rosette which itself mechanically prevents reflux. This is surely putting the cab before the horse. Anyone old enough to have actually ridden in the cab knows that a mucosa lined tube big enough to allow the passage of a mass will, when closing, form a rosette. Competence does not depend upon the mucosal rosette but upon the muscular action which produces it.'

EFFICIENCY OF THE ANTIREFLUX BARRIERS Whilst the mechanisms outlined above bring the mucosa of the oesophagogastric junction into apposition this does not mean that each necessarily constitutes an effective barrier to gastro-oesophageal reflux. Too often interruption of the column of barium has been interpreted by the radiologist as an effective closing mechanism without any accurate knowledge of the magnitude of the force of closure or the pressure gradients this mechanism can withstand. Countless ergs have been expended in abdominal palpation in efforts to raise intragastric pressure and produce reflux, yet simultaneous manometry frequently shows an insignificant increase in intragastric pressure as a result of these exertions. Quantitative measurements of the forces involved are of the greatest importance in this field. Such measurements may be difficult or impossible to make in the human subject under physiological conditions. It may be argued that the presence of a fine tube running through the oesophagogastric junction will interfere with normal function or cause nausea which in itself may relax the cardia. These limitations although sometimes exaggerated are real and must be accepted. The introduction of the radiopill goes some way towards overcoming them (Connell and Rowlands, 1960).

In spite of these limitations in the techniques available, clinicians and radiologists have seized the opportunities presented by the effects of disease to obtain an immense amount of information about the functioning of the human oesophagogastric junction and the antireflux mechanisms. This has been supplemented by experimental surgical studies in the animal by which a more precise delineation of the effective-

ness of the different mechanisms may be hoped for. The formidable array of evidence assembled in these studies is sometimes misleading and often conflicting and as yet has led to no view of the functioning of this region that would receive universal acceptance.

EXPERIMENTAL ANIMAL SURGERY At the outset it must be emphasized that the oesophagogastric junction in the animal often differs in important respects from that in man. The subject has been reviewed by Botha (1958b) who dissected out this region in a variety of animals, in few of which, notably the rabbit and the bat, he could find more definite anatomical evidence of a sphincter than in man. The cat resembles the human subject in that the lower oesophagus and oesophagogastric junction is composed predominantly of striated muscle whereas striated muscle extends down to the cardia in the dog, an animal in which much of the experimental work has been carried out. These facts must be borne in mind when applying the results of animal work to man and the subject is fraught with difficulties.

There is much work to suggest that in the dog the antireflux mechanism is intrinsic to the alimentary canal and that the diaphragm is of minor importance in this respect. Feldman and Morrison (1934) found that in the phrenicectomized animal the function of the oesophagogastric junction was unimpaired. Hoag, Kiriluk, and Merendino (1954), performing 50, 70, or 100% gastrectomies on dogs, found that preservation of the oesophagogastric junction prevented the post-operative development of reflux oesophagitis irrespective of loss of the oesophagogastric angle or the diaphragmatic pinchcock. Sacrifice of the oesophagogastric junction led to the almost invariable occurrence of oesophagitis irrespective of the extent of the gastrectomy. They did not consider that the diaphragm played any part in preventing reflux. Braasch and Ellis (1956) performed a Wendel procedure (vertical incisions on either side of the oesophagogastric junction sewn up transversely), a Heller cardiomyotomy, and oesophagogastrectomy in three groups of dogs and found that oesophagitis developed irrespective of whether the oesophagogastric junction was retained in its normal position or transposed to above the diaphragm. Interestingly, in view of the suggestion of a flaccid segment flap valve action in this region already mentioned, they found that no oesophagitis developed when a short segment of intra-abdominal oesophagus was retained. They came to the conclusion that 'the diaphragm is not itself a major factor in the maintenance of gastro-oesophageal continence' and believed that a physiological sphincter at the oesophagogastric junction is of primary importance in this respect. Ingram, Respess, and Muller (1959) came to similar conclusions; they transected the oesophagus 3 mm. above the cardia and closed the distal end, converting the lowest portion of the oesophagus into a blind pouch which was taken through an additional hole in the diaphragm while the proximal end of the oesophagus was taken through the hiatus and anastomosed to the stomach. Oesophagitis developed in the oesophagus proper but not in the blind pouch because the latter was protected by the intrinsic mechanism at the cardia. When the pouch was invaginated into the stomach its mucosa became ulcerated. They thus concluded that the intrinsic sphincter mechanism is responsible for the prevention of gastro-oesophageal reflux. Smiddy and Atkinson (1960), in a series of experiments upon the dog, measured the intragastric pressure necessary to produce reflux at laparotomy. They found that neither freeing the stomach and oesophagus from the diaphragm nor cardiomyotomy had any effect on the cardia's resistance to reflux. Since the resistance of the cardia was minimal after death it appeared that the antireflux barrier was dependent upon muscle contraction. The oesophagogastric angle, retained after both cardiomyotomy and diaphragmatic section, was lost after disruption of the oblique fibres of the gastric muscle coat on the lateral side of the cardia. After this latter operation reflux occurred at much lower levels of intragastric pressure. These findings provide further support for the view that the anti-reflux mechanism in the dog resides in the wall of the alimentary canal rather than in the diaphragm. They are in disagreement with much previous work in suggesting that this intrinsic mechanism is formed not by the circular muscle fibres in the lower oesophagus but by the oblique gastric fibres.

In conflict with these views are the findings of Giuseffi, Grindlay, and Schmidt (1954) that in the dog the creation of a hiatal hernia commonly leads to reflux oesophagitis which is more severe if the diaphragmatic pinchcock is impaired by excision of the left crus of the diaphragm. Rather unaccountably the oesophagitis often tended to undergo spontaneous healing. Further support for these views is provided by the observations reported by Nauta (1956), who found that severance of the diaphragm at the hiatus reduced the level of intragastric pressure required to produce reflux in the dog at laparotomy from 100 to 30 cm. H_2O. It may be significant that the initial pressure was much higher than those encountered by Smiddy and Atkinson whereas that after diaphragmatic section was within the range they found before any operative interference. Adler, Firme, and Lanigan (1958) found that the dog's

cardia became less resistant to reflux after the creation of a hiatus hernia by surgical means. In these dogs shortening of the longitudinal fibres of the oesophagus caused loss of the oesophagogastric angle, and reconstitution of this angle was only effective in restoring competence if the medial side of the oesophagus was supported by an unyielding structure such as the spine.

It is extremely difficult to reconcile this mass of conflicting evidence bearing upon the importance of the diaphragm as an antireflux barrier in the dog. Possibly distension of the stomach at operation is not a satisfactory means of predicting the likelihood of reflux under more physiological conditions. On the other hand, it seems possible that factors other than gastro-oesophageal reflux may have contributed to the rather temporary oesophagitis seen in many of the animals of Guiseffi, Grindlay, and Schmidt. The evidence to support an intrinsic closing mechanism at the dog's cardia appears strong and it could well be that the oblique fibre sling at least becomes inefficient when the oesophagogastric configuration is altered by the creation of a hiatal hernia. The efficiency of the pinchcock action of the diaphragm as a barrier to reflux is questionable and any role the diaphragm may have seems likely to be a supportive one.

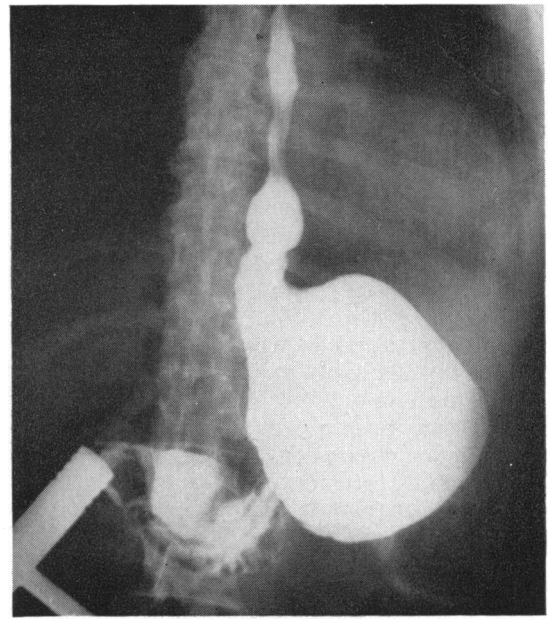

FIG. 7. *Radiograph taken after distending the stomach of the cadaver* in situ. *Note the free reflux of barium into the oesophagus and the loss of the oesophagogastric angle.*

EXPERIMENTS IN THE CADAVER If the main barrier to gastro-oesophageal reflux is formed by a mechanical valve arrangement the cardia might then retain its competence after death, whereas mechanisms involving muscular activity such as an intrinsic sphincter, oblique gastric muscular sling, or diaphragmatic pinchcock would cease to function.

In routine necropsies regurgitated gastric contents are frequently found in the oesophagus suggesting that the closing mechanisms are no longer operative. When the oesophagus and stomach are removed from the body flow through the cardia is equally free in either direction. In contrast Marchand (1955) found that when the stomach was distended *in situ* in the cadaver, the cardia retained a sufficient degree of competence to withstand an intragastric pressure of up to 28 cm. of water. Removal of the left leaf of the diaphragm increased the resistance to reflux to 42 cm. of water whereas freeing of the oesophagogastric junction from the support of the diaphragm and liver, or closing off of the fundus by a clamp so as to obliterate the effective angle, destroyed the antireflux barrier. Marchand accepted the results of these experiments as confirmation of the belief that the angle of entry of the oesophagus into the stomach is of great importance in resisting regurgitation. However, there is a considerable amount of evidence to suggest that in the cadaver the cardia does in fact allow free flow from the stomach to the oesophagus. Repeating Marchand's work, Atkinson and Sumerling (1959) found that in 11 cadavers gastro-oesophageal reflux occurred at an average of 5 cm. H_2O intragastric pressure. When barium was used to distend the stomach radiographs revealed loss of the oesophagogastric angle (Fig. 7). Subsequent studies in the dog (Smiddy and Atkinson, 1960) again revealed that the cardia's resistance to reflux disappears at death as does the oesophagogastric angle.

It is generally agreed that if the acute oesophagogastric angle is maintained by traction applied in a caudal direction upon a loop around the lateral side of the oesophagogastric junction, the cardia's resistance is greatly increased, irrespective of whether the experiment is performed with the stomach and oesophagus *in situ* (Atkinson and Sumerling, 1959) or removed from the body (Collis *et al.*, 1954b). The difficulty lies in deciding whether restoration of the angle or direct compression by the loop is the important factor in increasing the cardia's resistance in these experiments. That the latter is probably the case is suggested by the findings of Adler *et al.* (1958) who, after removal of the stomach and oesophagus at necropsy, reconstructed the angle of His by suturing the fundus to the lateral wall of the oesophagus; they found that this increased the cardia's resistance to reflux only if the oesophagus was

supported medially. Such support would presumably be provided by the liver under normal conditions.

To summarize this work in the cadaver, it suggests that the antireflux barrier is a vital phenomenon which may be related to changes in the configuration of the oesophagogastric junction. A valve arrangement may well be operative in the prevention of reflux but this is probably not a purely mechanical contrivance but one which is dependent upon the functioning of the musculature of the stomach.

OBSERVATIONS UPON PATIENTS WITH DISORDERS OF THE CARDIA

Gastro-oesophageal reflux is common at certain times of life, notably in infancy and during pregnancy. Under these conditions it may be regarded as a physiological phenomenon of temporary duration, which nevertheless may at times be sufficiently severe to cause oesophagitis. Under pathological conditions sliding hiatus hernia accounts for the majority of cases but reflux may occur without displacement of the cardia into the thorax as in systemic sclerosis and occasionally after cardiomyotomy, used in the treatment of achalasia of the cardia. Study of the disturbances present in these various disorders has added considerably to our knowledge of the normal functioning of the cardia.

GASTRO-OESOPHAGEAL REFLUX IN INFANCY Reflux can be detected by radiological means in approximately 50% of normal infants (Blank and Pew, 1956). Most are agreed that hiatus hernia is not present in these infants and the reflux has been variously attributed to blunting of the angle of His resulting from the low position of the diaphragm in infancy (Catel and Garsche, 1956) or to a temporary neuromuscular incoordination (Neuhauser and Berenberg, 1947). In keeping with the latter view is the finding of oesophageal dilatation and impaired peristalsis in a minority of these infants, a condition variously described as lax oesophagus (Forshall, 1955) or chalasia (Blank and Pew, 1956). This condition shows many resemblances to the disorder or oesophageal and gastric motility seen in systemic sclerosis (*vide infra*) in that gastro-oesophageal reflux and widening of the oesophagogastric angle occur often in the absence of hiatus hernia and apparently result from paralysis of the intrinsic musculature of the alimentary tract in this situation.

It is difficult to believe that any gross incoordination of the muscular activity of the oesophagus or oesophagogastric junction occurs in the normal infant; Carré and Astley (1958) found pressure changes, which were essentially similar to those described in the normal adult, in this situation in three infants. The more likely possibility is that the position of the stomach precludes the antireflux valvular mechanism from functioning efficiently, but further studies are obviously required before definite conclusions can be drawn.

PREGNANCY Despite the fall of intragastric acidity occurring during gestation, heartburn has been estimated to be associated with two-thirds of normal pregnancies (Williams, 1941). Symptoms are usually too mild to warrant the risks of radiological investigation but the observations which are available suggest that distortion of the position of the stomach due to its being pushed upwards, atony of the musculature of the oesophagogastric junction, or a small hiatus hernia may be responsible. That positional alteration of the stomach is an important factor in allowing reflux is suggested by the fact that the maximum incidence of heartburn occurs during the sixth to eighth month of pregnancy, and complete relief is often experienced two to three weeks before delivery as the foetal head sinks into the pelvis (Rodway and Shelley, 1935).

While relaxation of ligaments occurs during pregnancy and could conceivably involve the phrenoœsophageal ligament, it seems improbable that two-thirds of pregnant women develop hiatus hernia, particularly since symptoms usually cease abruptly after delivery and do not recur. In a radiological survey of 12 pregnant women with heartburn Williams (1941) could only demonstrate a hiatus hernia in one. On the other hand, hiatus hernia is undoubtedly present in a high proportion of women with severe gastro-oesophageal reflux in pregnancy, and the combination has been recorded by Rennie, Land, and Park (1949), by Dutton and Bland (1953), and by Edmunds (1957). In many instances the hiatus hernia may have been present before conception and persisted after delivery, the pregnancy being merely an aggravating factor. It is of interest, however, that Edmunds (1957) could demonstrate the hernia in only four of eight patients at radiological re-examination after delivery.

HIATUS HERNIA Displacement of the oesophagogastric junction into the chest impairs the antireflux barrier at the cardia and gastro-oesophageal reflux is a common occurrence in hiatus hernia. If the hernia is of the sliding or bell-shaped type the oesophagogastric angle is lost as is any compressive effect the diaphragm may exert. Under these circumstances the oesophagogastric sphincter forms the only barrier to reflux. Radiological observations (Fleischner, 1956; Wolf *et al.*, 1958) and manometric studies (Atkinson *et al.*, 1957b; Carré and

Astley, 1958) indicate that the sphincter may continue to function in the presence of hiatus hernia. Although alone insufficient entirely to prevent reflux the sphincter may continue to play a useful part in restricting the amount of gastric juice entering the oesophagus; Aylwin (1953) was unable to aspirate gastric juice from the oesophagus in a number of patients with sliding hiatus hernia uncomplicated by oesophagitis and suggested that in these the cardiac sphincter had retained a degree of competence. In the mixed type of hernia symptoms of reflux may or may not develop and their presence bears no clear relationship to the oesophagogastric angle seen on *x*-ray films. This latter, however, varies considerably with posture and the degree of reduction of the hernia.

The diaphragmatic hiatus may present a barrier to passage of gastric juice into the supradiaphragmatic portion of the stomach and oesophagus and conversely may impede emptying from the thoracic part of the stomach, so favouring reflux into the oesophagus. Aylwin (1953) was unable to recover carmine marker placed in the abdominal stomach by aspiration from the oesophagus. Pecora (1956) assessed the size of the diaphragmatic hernia from the resistance to passage of a series of three balloons mounted on a tube and graduated in size, and came to the conclusion that the hiatus was not increased in size in the majority of patients with hiatus hernia. Drake (1957) used paralysis of the left phrenic nerve in the treatment of reflux oesophagitis due to hiatus hernia on the assumption that this facilitated emptying of the supradiaphragmatic loculus.

Controversy has centred round the value of repair of hiatus hernia in controlling symptoms of reflux; although Wells and Johnston (1955) abandoned this operation in favour of vagotomy, partial gastrectomy, and re-anastomosis by the Roux en Y method, and Merendino and Dillard (1955) used a method of jejunal interposition, there is now an increasing amount of evidence to indicate that repair of the hernia will diminish or abolish symptoms of gastro-oesophageal reflux (Allison, 1951; Harrington 1955; Cross, Smith, and Kay, 1959; Barrett, 1960; Wooler, 1961). Amongst the advocates of hernial repair there is, however, no general agreement as to how this helps to reduce reflux; some believe that repair of the hiatus is of cardinal importance (Harrington, 1955; Wooler, 1961) but others lay stress on avoiding a tight hiatus because of the risk of dysphagia and emphasize the importance of reconstituting the oesophagogastric angle (Humphreys, Ferrer, and Wiedel, 1957; Goldberg, 1960).

GASTRO-OESOPHAGEAL REFLUX WITHOUT HIATUS HERNIA Gastro-oesophageal reflux has been considered synonymous with the presence of hiatus hernia by many radiologists, yet it is now generally agreed that the cardia may become incompetent while remaining in its normal anatomical situation. Of 130 patients with free gastro-oesophageal reflux, Cross *et al.* (1959) could find no hernia in 27 and Conway-Hughes (1956) was able to demonstrate a hernia in only 30 of 54 patients with free reflux. Stensrud (1957) attributed incompetence of the cardia without hiatus hernia to loss of the oesophagogastric angle and both he and Hiebert and Belsey (1961) obtained good therapeutic results by suturing the fundus to the oesophagus to re-create the angle. Hiebert and Belsey (1961) suggested that this condition may precede the development of hiatus hernia, a state of affairs analogous to that occurring in systemic sclerosis and suggesting a primary disorder of the musculature of the alimentary tract.

PROGRESSIVE SYSTEMIC SCLEROSIS Progressive systemic sclerosis, also known as scleroderma or acrosclerosis, is a disease in which the motility of the oesophagus and stomach is impaired, giving rise to dysphagia and symptoms of gastro-oesophageal reflux (Lindsay, Templeton, and Rothman, 1943; Bourne, 1949). Paralysis of the musculature of the alimentary tract causes failure of oesophageal peristalsis (Kramer and Ingelfinger, 1949; Dornhorst, Pierce, and Whimster, 1954b) and the oesophagogastric sphincter loses its tone (Creamer, Andersen, and Code, 1956). Although patients with this disease may develop hiatus hernias (Olsen, O'Leary, and Kirklin, 1945) there can be little doubt that many show gastro-oesophageal reflux without a hernia being demonstrable (Harper, 1953) and indeed reflux seems often to precede herniation (Atkinson *et al.*, 1962). Radiological and manometric observations indicate that diaphragmatic function is usually unimpaired in systemic sclerosis and it appears that in this disease gastro-oesophageal reflux develops as a result of an intrinsic lesion of the alimentary tract. In the advanced stage of the disorder the cardia appears widely patent, although still compressed by the right diaphragmatic crus in inspiration, and the oesophagogastric angle is often blunted. The most probable explanation of the cardia's loss of competence is the impairment of the oblique muscle fibre sling and the oesophagogastric sphincter and it is of interest that this occurs in spite of apparently normal diaphragmatic function and in the absence of hiatus hernia.

GASTRO-OESOPHAGEAL REFLUX AFTER OPERATIONS FOR ACHALASIA Operations for achalasia which result in gross anatomical disturbance of the oesophagogastric junction, such as cardioplasty or

resection of the cardia, are followed by a much higher incidence of gastro-oesophageal reflux than is cardiomyotomy (Barrett and Franklin, 1949; Brewer, Barnes, and Redo, 1956). Gammie, Jennings, and Richardson (1958) state that 'cardiomyotomy by itself does not lead to incompetence of the cardia or to gastro-oesophageal reflux' but most would agree that reflux oesophagitis does occur in a small proportion of patients after this operation (Hawthorne, Frobese, and Nemir, 1956). Manometric observations indicate that the sphincter may be completely disrupted yet reflux does not necessarily ensue (Atkinson, 1959) and it seems probable that disturbance of some other mechanism is necessary for reflux to occur. A proportion of patients develop hiatus hernia after cardiomyotomy but reflux may occur with the cardia in its normal position and with the diaphragm apparently functioning normally. In these the valve arrangement at the cardia is presumably disturbed; Barrett (1952) has suggested that if the myotomy incision be placed on the lateral side of the oesophagogastric junction and carried down onto the stomach wall then the oblique muscle fibre sling will be disrupted and the oesophagogastric angle lost leaving a state of affairs similar to that following cardioplasty or resection of the cardia.

EFFECT OF DIAPHRAGMATIC PARALYSIS If the right crus of the diaphragm plays a crucial part in the prevention of gastro-oesophageal reflux, this might be expected after diaphragmatic paralysis. Harper (1938) reviewed gastrointestinal symptoms following interruption of the left or right phrenic nerves used in the treatment of pulmonary tuberculosis, but reported nothing to suggest gastro-oesophageal reflux. After interruption of the left phrenic nerve he found that the stomach occupied a more vertical position with the fundus lying up under the paralysed diaphragm, thus accentuating the oesophagogastric angle. Pickard (1952) could find no radiological evidence of reflux in patients with unilateral phrenic nerve lesions. Manometric studies (Atkinson and Sumerling, 1959) confirm the presence of a zone of raised intraluminal pressure at the oesophagogastric junction but the accentuation of the respiratory deflections normally found in this region was absent after avulsion of the left phrenic nerve, as was the inspiratory interruption of the column of swallowed barium at the oesophagogastric junction. Since the right crus of the diaphragm normally receives its nerve supply from both the left and right phrenic nerves it is conceivable that the pinchcock action may persist after interruption of one or other of these nerves; these manometric and radiological studies suggest that this is not the case after left phrenic nerve avulsion. Certainly muscle relaxants given during anaesthesia cause diaphragmatic paralysis without gastro-oesophageal reflux occurring (O'Mullane, 1954).

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