Progress report

The oesophagus

A searching review of the literature on the human oesophagus up to the end of 1969 has recently appeared¹ and this report will not attempt to compete. However, there have been several important new concepts published since, the most exciting and challenging of which is the physiology and pharmacology of the cardiac sphincter and its role in the antireflux mechanism. In 1957, my colleagues and I reported a difference in the sphincter pressures in those with hiatal hernia and those without². We thought for a time that this indicated the difference between refluxers and non-refluxers, but there were questions that this theory did not answer. For many years there has been tedious controversy about whether the sphincter was the sole mechanism, a concept tacitly assumed by many workers just because it was there, or whether its biological purpose was to prime the 'flutter valve' by gently closing the lumen of the intraabdominal oesophagus against the small changes in intragastric pressure produced by contraction of the stomach wall³. It was postulated that the main antireflux mechanism was the combination of the intraabdominal oesophagus and the cardiac sphincter³.

The proponents of the 'sphincter alone' theory were on uncomfortable ground because the pressure recorded in the lumen of the closed sphincter segment by an unperfused water-filled, open-tube system was 0-10 mm Hg above that of the intragastric pressure, scarcely enough to overcome the high pressures sometimes developed in the abdomen. Disconcertingly too, when measured by this method, there was little or no difference between the pressures in the sphincters of those suffering from reflux and of apparently normal subjects. A new burst of interest occurred when continuously perfused tubes were used which recorded a higher pressure in the sphincter^{4,5,6,7,8} than unperfused tubes. Confusion temporarily reigned because different workers used different rates of perfusion and some continued to use their small balloons which measured a slightly different property of the muscle and gave a slightly different pressure. Now it seems that the rate of perfusion determines how quickly the pressure is reached but should not influence the height of the pressure⁶. Nor is it likely that the diameter of the tube or its opening is important. Perfusion is necessary if there are leaks or air bubbles in the system, and if the wall of any part of the recording system is compliant; PVC and rubber tubing are particular offenders. Most of the differences between the reports of the range of normal sphincter pressure depend upon differences in the way the pressure is computed, for example, whether it is 'end expiratory' or maximum 'mean sphincter'. Greater excitement occurred when the pressure recorded by continuously perfused tubes within the sphincter of subjects suffering from reflux was found to be less than that in people without reflux^{4,7,9,10} and careful studies began to claim that there was no overlap between the sphincter pressures of those with and those without reflux. The difficulty was still the large discrepancy between the pressure

recorded in the sphincter during the resting state, and the difference in pressure known to be developed across the diaphragm. On the supposition that the sphincter was responsible for competence, but that recording intra-sphincteric pressure might not be the best way of quantitating this competence, the pressure was compared with the force required to pull an almost frictionless 12 mm Teflon ball from the stomach through the sphincter into the oesophagus^{11,12}. The correlation was excellent but still the pressures were disconcertingly too low when measured in the resting state.

Wankling and his colleagues in 1965⁴ and 1966⁹, in papers that few took notice of, reported their measurements of sphincter pressure in subjects with and without reflux and with and without hiatal hernia, together with the effect of challenging the sphincter by increasing intraabdominal pressure. Using continuously perfused tubes they found that some patients with hiatal hernia had sphincter pressures within the normal range, whereas the remaining patients with hiatal hernia had a lower than normal sphincter pressure, as did a small group of patients without a hiatal hernia. Those who had a normal sphincter pressure, whether they had a hernia or not, were found to have few symptoms and no endoscopic evidence of reflux. Those with a low basal sphincter pressure, whether they had a hernia or not, were found to have symptoms and endoscopic evidence of oesophagitis.

Their most interesting observation was that when the sphincter was challenged by increasing intragastric pressure the pressure within the whole length of the sphincter increased by intrinsic muscular contraction in normal subjects, and in those with a hiatal hernia provided that the resting sphincter pressure was in the normal range. When the sphincter had a low basal pressure the pressure in the sphincter rose only to the level of intragastric pressure; the intraoesophageal pressure rose almost as much, suggesting that reflux occurred, and the sphincteric zone became incompetent during the abdominal compression. The point of particular importance is that the whole length of the sphincter contracted more forcibly, and to a similar degree, whether the whole or only part of the sphincter was within the thorax, where it was subjected to intrathoracic, not intraabdominal pressure. Their evidence indicated that the increase in pressure in the sphincter segment could not be simply a reflection of the increase in intraabdominal pressure. They also demonstrated that the hiatal opening in the diaphragm allowed intralocular pressure to equal intraabdominal pressure. These observations and conclusions, together with their evidence that the presence of a hiatal hernia was not essential for the occurrence of reflux, proved to be a major step forward in thinking.

Cohen and Harris^{11,13} used a similar procedure and obtained essentially similar results. With continuously perfused tubes and a carefully standardized procedure they compared the maximal *increment* in sphincter pressure with the *increment* in intragastric pressure. They found that the increment of sphincter pressure always *exceeded* the increment in gastric pressure in subjects *without* symptoms of reflux and that there was a close linear relationship between the two increments. Conversely, in subjects *with* symptoms of reflux *but no hernia* (that is, supposedly an intraabdominal sphincter segment) the increment in sphincteric pressure was *less* than the increment in gastric pressure, that is, they did not record the expected simple increase in sphincteric pressure directly transmitted from the intraabdominal pressure. The same linear relationship between sphincter pressure and the force

required to pull a Teflon ball through the sphincter was maintained in those with or without a hiatal hernia, and in those with or without reflux ^{11,12}.

From this study they drew several conclusions which support those of Wankling and his coworkers^{4,9}. First, that the common sliding hiatal hernia does not predispose to gastrooesophageal reflux by causing the lower oesophageal sphincter to become weaker. Second, that the pressure surrounding the lower oesophageal sphincter does not affect its strength but, third, that, as intragastric pressure increases, the sphincter becomes stronger. Fourth, the ability of the sphincter to become stronger as gastric pressure is increased is not affected by the sphincter's location above or below the diaphragm but seems to depend on the initial resting pressure. Their results support the physician's admonition to avoid increasing intraabdominal pressure, but they question the usual explanations advanced for the success of hernial repair, for example, restoration of the angle of entry, or of the intraabdominal section of oesophagus. They do not deny that surgery sometimes helps to reduce the symptoms of reflux but they emphasize that a more sensible goal of treatment for gastrooesophageal reflux would be to increase the strength of the sphincter rather than just change its location or surroundings.

Pharmacology

If the sphincter is so important, what determines its state of contraction? Innervation of the muscle from the medulla and the myenteric plexus accounts for the temporary relaxation following a swallow and for the temporary 'after swallow' contraction above the resting level, but what determines the resting level and how may it be modified?

A spate of papers records the effect of pentagastrin and human gastrin on the intact sphincter. There seems little doubt that gastrin increases the tone of the resting sphincter, and there is a strong probability that secretin antagonizes this action¹⁴. A particular person's sphincter is not just open or closed but varies considerably in strength^{12,15}. In their search for a physiological mechanism to explain this, Castell and Harris^{16,17} assessed the effect of altering gastric acidity. When acid secretion was stimulated by betazole, the sphincter pressure consistently *increased*, but when gastric acidity was increased by instilling 0.1 N HCl, the sphincter pressure consistently *decreased*, and some subjects got heartburn. When 0.1 N NaOH or 0.1 N NaCO₃ or commercial antacids were instilled into the stomach, the sphincter pressure *increased*, as it did when peptone broth¹⁸ or 10% ethanol was instilled. They postulated that the increased contraction might be produced by an increased serum level of endogenous gastrin, and the decreased contraction by reduction in this level. Castell and Harris were not able to measure serum gastrin, so they gave pentagastrin and within two minutes of a subcutaneous injection the sphincter pressure began to rise, even when one sixth the maximal secretion inducing dose was given. When sphincter pressure was increased by endogenous gastrin or injected pentagastrin the sphincter still relaxed normally in response to a swallow. Giles and his coworkers¹⁸ got similar results with injections of hog gastrins and they¹⁸ and others¹⁹ found that atropine blocked the effect of gastrin. Castell and Levine²⁰ have taken the study further and shown striking relationships between the change in sphincter pressure and the change in pH of the gastric contents. There is a

delay of five to 10 minutes between the change in *pH* and the change in sphincter tone. The same range of effect was produced by a variety of alkalis and seems to result simply from the neutralization of gastric contents. When a group of six patients with an abnormally low mean resting sphincter pressure of 5.5 mm Hg, that is, to well within the normal range of resting pressures. They suggest that the effect of alkali in the treatment of heartburn is not so much to neutralize the acid refluxed from the stomach as to increase the amount of endogenous gastrin and so tighten the sphincter.

The sphincter also seems to respond to changes in the *pH* of the fluid in contact with the mucosa surrounding the cardiac orifice; acidity round the orifice increased sphincter tone but the optimum *pH* seemed to be 3.0²¹. The response was blocked by intravenous atropine. It is fortunate that the investigators limited the perfusion of acid to the fundus; had they perfused the antrum they might have obtained a different answer.

Is there any vagal drive to the antrum and to gastrin production and will this mean that a vagotomy would predispose to reflux and a lower sphincter pressure? Studies of the effect of vagotomy on sphincter pressure have produced conflicting results. The symptom is usually dysphagia and this has been shown not to be due to denervation of the sphincter but probably to tissue changes²². Mechanical factors due to the manipulation of the lower oesophagus at the time of vagotomy may be responsible for some reflux. Some authors claim a reduction in sphincter pressure after vagotomy^{10,23}; others found no change^{24,25}. Measurement of serum gastrin suggests a 75% reduction after vagotomy and antrectomy, but no reduction after vagotomy and pyloroplasty²⁶.

Patients with reflux symptoms often complain of heartburn associated with smoking: the cardiac sphincter pressure falls at the time²⁷. Atropine reduces sphincter pressure^{28,29} and it might be sensible not to use it in patients suffering from reflux. Metoclopramide, however, when given in an intravenous drip doubles resting sphincter pressure without increasing gastric secretion, without increasing gastric fundic pressure, and without reducing the relaxation in response to a swallow³⁰. A clinically useful effect of an oral dose remains to be demonstrated and if the sphincter is initially weak, the increment in pressure may be inadequate to stop reflux.

All previous comments have been about the human cardiac sphincter. The opossum's sphincter has many similarities and is being used as a model for the human. Dose response curves have been obtained at the length of optimal tension development for acetylcholine, noradrenalin, and synthetic gastrin I using muscle strips from the circular fibres of the sphincter, the body of the oesophagus, and the gastric antrum³¹. The sphincter muscle developed more than twice the tension and responded at a lower threshold dose of all three substances. The sensitivity to gastrin I was 100 times that of the other muscles and the molar potency of gastrin I was 10⁷ times that of acetylcholine or noradrenalin. The intrinsic cholinergic and adrenergic innervation of the sphincter did not differ from the adjacent oesophagus. The circular fibres of the sphincter in the opossum have different mechanical properties from other smooth muscle fibres and also a specialized receptor mechanism. The mechanical properties enable it to develop optimal tension with minimal distension, ie, it can contract well even at its shortest length. The specialized receptor mechanism enables the sphincter to respond at a lower threshold and attain

a greater response to each stimulant; and the marked selective sensitivity to gastrin suggests an important role for this hormone.

One can speculate in many ways on the mechanism of 'heartburn'. Do 'acid' fruit juices and fatty foods cause dyspepsia by inhibiting gastrin release? After a meal of minced beef the sphincter pressure rises but when the beef is mixed with HCl to give a mixture of pH 1.2 to 1.3 the pressure falls. When glucose is given the pressure rises a little, but a meal of corn oil produces a striking decrease in pressure which is even more striking when the corn oil is instilled directly into the duodenum. Because this latter effect was greater than the decrease in pressure recorded after an intravenous injection of secretin given alone in fasting subjects, the decrease of pressure was thought to be produced by some other enterogastrone and not by secretin¹⁴. These findings fit the pattern of reflux symptoms in many people, but why does not everybody suffer heartburn after a fatty meal?

The Assessment of Reflux

RECORDING INTRAESOPHAGEAL pH

These pharmacological studies raise some interesting problems in the assessment of reflux. What is the likely state of the sphincter and the serum gastrin level at the time of the radiological examination for reflux, after a minimum of 12 hours fasting? Should we not examine for reflux in circumstances in which the symptoms of it are most likely to occur? The commonly used assessment of reflux by recording intraoesophageal pH in the supine or head-down position, after instilling 300 ml of 0.1 N HCl into the stomach, is being unkind to the sphincter because endogenous gastrin production, and consequently the sphincter tone, will be reduced, and the sphincter will fail to respond to intraabdominal pressure as powerfully as a sphincter with a normal tone. Continuous pH recording from the oesophagus of patients during 12 or 24 hours of hospital life³² shows that during the day, when they are sitting or standing, reflux of gastric contents of low pH occurs almost as commonly in people without symptoms of reflux as in those with symptoms³³. Those who suffer from reflux, however, reflux much more frequently when lying on the right side than do those who do not suffer³². Is the challenge of intragastric pressure any greater in this position?

BY RADIOLOGY

The radiological assessment seems still to be a source of confusion. Many papers about the cardiac sphincter and reflux contain information about a group of patients with radiological evidence of reflux but not of hiatal hernia. The relative incidence of this combination in the population under study is not given, but in the author's experience, when examining the group of patients that happen to be sent to him, reflux without herniation is uncommon unless there has been previous oesophageal or gastric surgery. A recent careful study of apparently normal subjects³⁴ without gastrointestinal symptoms demonstrated the capacity of 38 of 73 males and 19 of 73 females to herniate stomach into the chest. Reflux was seen in 15 of the men and 11 of the women with hernia, but reflux was *not* seen in anyone *without* a hernia. They examined 10 to 12 men and 10 to 12 women from each 10-year age span from 21 to 90 years and found no difference in incidence of hiatal herniation with age, and a much higher incidence in men than women. Both these observations

are contrary to ideas widely held about the supposed sex and age incidence of hiatal hernia with symptoms of reflux.

How much herniation and how much reflux is demonstrated by radiology seems to depend as much on what is done and who does it as upon the state of the patient^{35,36} and there is plenty of room for improvement and standardization of radiological technique on both sides of the Atlantic. It is now well within the capacity of radiological examination to determine whether stomach can herniate into the chest in the daily life of the patient, to quantitate the herniation, to assess the size of the hiatal opening, and the ease with which pressure and contents can be transmitted from abdominal to thoracic stomach³⁵. Herniation in most subjects is intermittent and often dependent on their position or upon intraabdominal pressure so that most of the time in most people the stomach is wholly within the abdomen³⁵.

DOES A HIATUS HERNIA CAUSE SYMPTOMS?

It seems highly unlikely that herniation itself causes any symptoms: 33% of a group of symptom-free subjects were found to have a hernia³⁷; and there seems to be no established evidence that the presence of food in an intrathoracic loculus, or 'trapping of air' in a hernia is more than a rare curiosity. Large, even total, herniations of the stomach may occur without symptoms. During a radiological examination in which herniation develops or increases as the patient's position is changed, there are no symptoms referable to this³⁵.

DOES REFLUX CAUSE SYMPTOMS?

There is a group of symptoms with specific associations which are adequate to diagnose reflux and which do not appear to be produced by any other lesion. Other dyspeptic symptoms are common to many dyspepsias and the absence of the specific 'reflux oesophagitis' symptoms should demand a careful search for another explanation of the dyspepsia even if herniation and reflux are seen by the radiologist. Reflux of barium does not produce symptoms unless it breaches the pharyngo-oesophageal closing mechanism. Reflux of acid has commonly been recorded by pH monitoring without associated symptoms. Reflux of barium is seen in patients who do not complain of symptoms of reflux. Symptoms of reflux oesophagitis require an inability of the oesophageal mucosa to resist the material being refluxed and it seems likely that the threshold of sensitivity of the mucosa can vary as well as the noxiousness of the refluxing material³⁶. Some patients suffer intensely for a time and are then free of symptoms for days or weeks. Is this because of a change in the acidity of the refluxing material, or in the tone of the sphincter, or in the sensitivity of the mucosa?

DOES A SLIDING HERNIA CAUSE REFLUX?

The answer to this question is crucial in management decisions but still unavailable. There are many reports of radiological evidence of reflux without herniation, which implies that reflux can occur without herniation, but whether the *capacity to herniate* was also present and relevant is not known because of the possible lack of standardization of radiological technique and of interpretation of the appearances. Most clinicians are likely to think that the worst problems of reflux oesophagitis are always associated with a hiatal hernia, but that in addition there is a group of patients who

complain of the symptoms of reflux oesophagitis but who apparently do not have a hernia or even reflux during a radiological examination. The relationship between herniation and reflux is crucial because if the *herniation or the capacity to herniate* is responsible for the reflux, surgical repair is the only possible long-term cure, and surgical procedures become justifiable. If the *strength of the sphincter* is the important factor and this is unaffected by the presence of herniation or the capacity to herniate, surgery should be confined to relief or prevention of problems arising from the herniation. The management of reflux must then aim to strengthen the sphincter, to reduce the corrosiveness of the gastric contents, and to raise the threshold of the oesophageal mucosa.

To add to the confusion, there are reports of patients who have radiological evidence of hiatal hernia but *not* of reflux, yet who freely reflux instilled 0.1 N HCl from the stomach on to an intraoesophageal pH electrode, have positive acid perfusion tests, have low sphincter pressures and are judged to have oesophagitis at oesophagoscopy¹⁰, and similar descriptions are given of patients *without* hiatal hernia but a so-called incompetent sphincter. One gets the impression that some investigators have lost faith in the significance of a radiological report that reflux was not present, and rely upon the recording of intraoesophageal pH^{6,10,38}, although it is not clear what significance is attached to a report that radiological evidence of reflux *was* seen. Some radiologists and some physicians discount radiological evidence of reflux because they say it occurs in normal people. The author's view is that if barium can be seen to reflux consistently when the subject lies down or turns on to one side or bends over to touch their toes, then the *antireflux mechanism* is faulty in the circumstances of the examination, whether the subject experiences symptoms or not. Symptoms will occur if the oesophageal mucosa is also abnormal. Conversely, if the symptoms are right, reflux or regurgitation must be accepted as occurring, at the time of the symptoms, even if, in the circumstances of the radiological examination, the antireflux mechanism is competent and no reflux is seen. Kantrowitz and his colleagues³⁸ found that transient reflux detected by pH recording is not usually accompanied by radiologically visible reflux. Half of their control subjects without hiatal hernia symptoms had isolated periods of reflux. Is minimal reflux or is only massive reflux a cause of symptoms and or oesophagitis?

Is the ability of the oesophagus to clear acid from its lumen at least as important as the reflux itself³⁹ or is the failure to wipe out the acid a measure of the ease of reflux?

SYNTHESIS

There is now strong evidence that the sphincteric pressure recorded by continuously perfused open tubes is less than normal in most people who have symptoms of reflux, and that, by the techniques employed, a normal sphincter responds to the challenge of an increase in intragastric pressure by increasing its contraction by an amount which is greater than the challenge. There is also strong evidence that the circular fibres of the sphincter are extraordinarily sensitive to gastrin. Physiological variations in circulating endogenous gastrin produce variations in sphincter pressure which may include a reduction to levels at which reflux might be expected to occur. It is likely that secretin and other enterogastrones reduce sphincter pressure. The relationships between symptoms of reflux and type of food and time after eating, together

with certain postures, may plausibly be explained by changes in the closing pressure of the sphincter.

The old criticism of the 'sphincter alone' hypothesis that the pressures recorded from the sphincter were too low may be answered by the observations of Lind's and Harris's groups that the effective sphincter responds to a challenge by contracting. There are questions still to answer. Straight leg raising in those with a wide hiatus induces reflux, but does not do so in many with a small hernia who reflux only in certain positions. Of the particular population of people suffering from reflux that the author is asked to see, a large proportion have this failure to reflux during straight leg raising, yet will reflux freely when stooping or when they turn on to their right side. Most of them also fail to reflux when lying on their back or turning on to their left side. Changes in basal sphincter pressure are likely to be small from one position to another, although changes in intraabdominal pressure may be considerable. The contraction response to a challenge of increased intraabdominal pressure is supposed to depend on the basal pressure of the sphincter rather than on the size of the challenge. Why does the response vary from one position to another?

Several other questions remain to be answered by experimental observation. When a normal person is suspended head down on an x-ray table with the stomach full of barium, he does not reflux when he swallows. During straight leg raising when there is an increment in sphincter pressure, swallowing induces relaxation in part of the sphincter⁴⁰. Why is there no reflux? After an extensive cardiomyotomy with bulging mucosa, a denervated sphincter, and free outflow of liquid into the stomach, no reflux can be induced by a variety of manoeuvres including straight leg raising⁴⁰. Why? What is it that some surgeons do when they are fortunate enough to succeed in stopping reflux or in considerably reducing the amount which occurs?

No one will deny that the cardiac sphincter exists and that it has fascinating physiological and pharmacological properties. Nothing that has been observed recently contradicts the role of the sphincter in opposing intra-gastric pressure, and these observations go a long way towards explaining the mechanisms of some forms of reflux, and towards rationalizing some aspects of the treatment, but there is still some way to go. It would be sensible, however, for all of us to learn to dissociate hiatal herniation from reflux in our minds. Each has its causes, effects, and treatment and only sometimes are the two intertwined.

As for methodology, it would also be sensible for all manometrists, at least for the time being, to use continuously perfused tubes as well as their established favourite method. Each method records a particular property of the sphincter as well as the properties of the recording system. We do not yet know which property of the sphincter is the best guide to the solution of a particular problem; when we do, we shall be a little nearer deciding which is the best technique for recording it.

D. A. W. EDWARDS,
MRC Department of Clinical Research,
University College Hospital Medical School,
London

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