RECENT ADVANCES IN 5 GASTROENTEROLOGY

Edited by Ian A.D. Bouchier

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Recent Advances in
GASTROENTEROLOGY

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Preface

The generally favourable reception of the fourth volume of Recent Advances in Gastroenterology has encouraged me to repeat the presentation. Consequently Volume 5, too, presents a survey of the gastrointestinal and hepatobiliary literature covering mainly the years 1979 to 1981. I have been fortunate in being able to maintain the same team of experts who contributed so ably to the previous volume.

There have, however, been changes in content and format in Volume 5. Dr R. E. Pounder contributes to the chapter on the stomach and duodenum. There is a new chapter on the small intestine which covers particularly the exciting and rapidly changing field of the gut hormones and peptides. It has been written by Drs J. E. Hegarty and D. B. A. Silk.

Such has been the expansion in paediatric gastroenterology that it has become necessary to separate gastrointestinal disease from hepatology, and Professor John T. Harries and Dr Alex P. Mowat are each responsible for a chapter covering these topics. Gastrointestinal fibreoptic endoscopy is very much part of everyday practice and I have felt it unnecessary to devote a separate chapter to the topic in this edition. Instead each contributor has included such advances in fibreoptics as appropriate.

The contributors form a skilled and effective team. They have performed their difficult and arduous task with efficiency and understanding. I am grateful to them for their cooperation and tolerance. Mrs Joan Brown, Ms Maureen Hughes and Miss Alison Scott cheerfully and efficiently undertook the extensive secretarial work necessary in the preparation of the manuscript.

Dundee, 1982 I.A.D.B.

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Contents

1. The oesophagus

Michael Atkinson

The past three years have seen small but significant advances in the understanding of oesophageal physiology and pathology. The mechanisms controlling oesophageal motility continue to be investigated intensively and an ever increasing number of agents are being shown to affect these under pharmacological if not physiological conditions. More sophisticated investigational methods have revealed physiological gastro-oesophageal reflux to be a more common occurrence than had previously been suspected and there has been an increasing awareness of oesophageal damage caused by drugs. Endoscopic interest has concentrated on the improvement of therapeutic procedures to relieve the various types of dysphagia and to sclerose oesophageal varices.

OESOPHAGEAL PHYSIOLOGY

The control of oesophageal peristalsis

Oesophageal peristalsis during swallowing or in response to oesophageal distension is initiated by neural stimuli. In the striated muscle of the upper oesophagus each muscle fibre is innervated by a single motor end plate and peristaltic sequential contraction results from the pattern of discharge in the dorsal vagal nucleus in the medulla, those nerve fibres supplying the more proximal oesophageal striated muscle being discharged before those to the distal muscle.

The smooth muscle of the oesophagus is more complex and differences in response to electrical field stimulation are demonstrable in the opossum between longitudinal and circular muscle fibres (Christensen, 1976). The 'on' response consists of muscle contraction during electrical field stimulation and is seen in the smooth muscle longitudinal fibres. The 'off' response is a contraction occurring after cessation of the stimulus and is present in circular smooth muscle fibres. There is a gradual increase in the latent period for the 'off' response from the more proximal to the distal part of the smooth muscle circular coat. Hence a single simultaneous stimulus produces a progressive circular muscle contraction resembling a peristaltic type of wave.

The latent period of the 'on' and 'off' responses can be modulated by changes in potassium concentration (a rise causing shortening and a fall causing prolongation) and by various drugs. Carbachol, bethanecol and isoproterenol all cause shortening while hexamethonium and d tubo curarine, tolazoline, propranolol, norepinephrine and dopamine have no effect (Christensen et al, 1979).

The instillation of a bolus into the body of the oesophagus may excite either secondary peristalsis or simultaneous non-propulsive contraction in normal subjects. The bolus volume needed to elicit secondary peristalsis has been shown to be reduced by increasing its acidity but this is not so for tertiary contractions (Corazziare et al, 1978).

This ability to recognise and expel acid is of obvious importance in the protection of the oesophageal mucosa against refluxed gastric contents.

Modification of oesophageal peristalsis by cholinergic and anticholinergic drugs has long been recognised to occur in humans and has important therapeutic implications in the management of gastro-oesophageal reflux. Bethanecol increases the amplitude of the peristaltic wave but reduces its speed of propagation while atropine has the reverse effect (Phaosawasdi et al, 1981). The net effect on oesophageal clearing is determined by the amplitude of the peristaltic wave rather than by its velocity.

The amplitude of oesophageal peristalsis has been thought to decline with advancing age leading to disorganisation of oesophageal motility, impairment of oesophageal clearing and even to dysphagia. Previous studies have revealed a reduction of amplitude of oesophageal peristaltic waves. However these views have been challenged by Csendes et al (1978) who, in a group of normal subjects ranging in age from 2 months to 74 years, could find no variation in oesophageal peristaltic amplitude with age. Previous studies had been made on older patients, mostly nonagenarians, and it may well be that motility changes only occur very late in life. Histological studies have revealed loss of ganglion cells in Auerbach's plexus in the elderly in the absence of smooth muscle atrophy, which may account for the motor disturbance (Eckart & Lecompte, 1978).

The upper oesophageal sphincter

The pharyngeal phase of swallowing and upper oesophageal sphincter function have been studied by measuring the velocity of a swallowed liquid bolus reaching the oesophagus from recording of intra-luminal electrical impedance. Fisher et al (1978) found that the velocity of the front face of the bolus increased with increase in the volume of liquid swallowed and this novel technique provides a means of examining the function of the upper oesophageal sphincter in health and disease.

Reflex increase in the tone of the upper oesophageal sphincter follows oesophageal distension so providing protection for the pharynx and respiratory tract when the oesophagus contains food and fluid in patients with obstruction or gastro-oesophageal reflux. In the dog localised oesophageal distension caused by inflating a balloon in the lumen caused an increase in upper oesophageal sphincter pressure of up to 400% and the sphincter response to both distension and oesophageal acid perfusion fell off when the stimuli were applied more distally in the oesophagus (Freiman et al, 1981). The reflex control of the upper oesophageal sphincter appeared to be mediated through its vago-symphathetic nerve supply since cooling of these nerves, after they had been isolated in skin loops in the neck, greatly reduced or abolished the effects of distension or acid perfusion. Surprisingly however the resting tone of the upper oesophageal sphincter, which has been related to a constant stream of vagal impulses interrupted only by swallowing, was unaffected.

The lower oesophageal sphincter

During the past three years the lower oesophageal sphincter has continued to attract attention although many of the problems it poses are by no means new. Methodology continues to excite controversy and the difficulties have been ably reviewed by Dodds & Hogan (1980). Whilst Welch & Drake (1980) and Goodall et al (1980) found the reproducibility of lower oesophageal sphincter pressure recordings to be significantly

greater when the rapid pull through method was used as compared with the station pull through, the interobserver scoring error was greater with the station pull through method. In a study from five centres a good correlation ($r = 0.89$) was found between values obtained by the two methods (Castell, 1980). At the present time it would seem that either method offers an acceptable means of measuring lower oesophageal sphincter pressure. Radial variation of the pressure in the sphincter compounds the technical difficulties of recording reproducible lower oesophageal sphincter pressures because it is impossible to know which way a single side opening is facing. To overcome this problem some have recorded simultaneously from several different directions but this may simply cause further variability for such probes are thick and probe diameter affects the pressure recording (Wallin et al, 1980). The use of end opening tubes would seem to offer a means of simplifying such complexity.

Having faced the formidable technical difficulties of recording lower oesophageal sphincter pressure the question remains as to whether this provides any useful information in view of its considerable random variation (Pope, 1981). The wide overlap in values obtained in patients with and those without gastro-oesophageal reflux makes the measurement of lower oesophageal sphincter pressure effort wasting in the routine clinical assessment of this disorder, although it is of proven value in investigating its basic pathophysiology. Thus Dent et al (1980) have shown during overnight oesophageal pH recording that episodes of reflux coincide with transient relaxations of the lower oesophageal sphincter. In clinical practice manometric assessment of lower oesophageal sphincteric function is of considerable value in the diagnosis and management of oesophageal motor disorders such as achalasia.

Hitherto there has been much doubt about whether the lower oesophageal sphincter constitutes a morphological entity except in the bat which spends long periods in the head down position. In the opossum, light and electron microscopic studies have revealed thickening of the circular muscle coat with muscle fasciculi interspersed with abundant connective tissue in the area of the lower oesophageal sphincter. These changes are not seen higher up in the oesophagus (Seelig & Goyal, 1978). In the human cadaver thickening of the circular muscle coat over a length averaging 3.1 cm has been found between the diaphragm and the angle of His (Liebermann-Meffert et al, 1976) and this was greatest on the left posterior aspect in which direction of course lower oesophageal sphincter pressure is greatest.

Neurotransmitters in the oesophagus

Between the smooth muscle fibres of the oesophageal wall run nerve fibres with localised swellings of varicosities along their length. These contain synaptic vesicles from which neurotransmitters are released. Burnstock (1981) has identified by electronmicroscopy eight morphologically distinguishable types of synaptic vesicle in the nerves of the alimentary tract and has attempted to relate vesicle morphology to neurotransmitter content of acetylcholine, noradrenaline, adenosine triphosphate, 5 hydroxytryptamine, gamma aminobutyric acid and various peptides respectively. A variety of peptides are demonstrable by immuno-cytochemical methods in the nerve elements of the gut but their role if any in the physiological control of oesophageal motility is still uncertain.

In non-adrenergic non-cholinergic nerves supplying the gastrointestinal tract adenosine triphosphate (ATP) appears to be the principal neurotransmitter

(Burnstock, 1972). But Rattan & Goyal (1980) noted that in the opossum tachyphylaxis to ATP did not inhibit vagally stimulated relaxation of the lower oesophageal sphincter, suggesting that ATP is not the relevant neurotransmitter. In the oesophagus acetylcholine is the principal excitatory neurotransmitter found in the varicosities in nerve terminals supplying smooth muscle but noradrenaline containing vesicles are mainly concentrated in the interneurones of the myenteric plexus.

Table 1.1 Neurotransmitters in gut wall

Type of neurone	Neurotransmitter		
1. Cholinergic	Acetyl choline		Established
2. Adrenergic	Noradrenaline		
3. Purinergic	Adenosine triphosphate		
4. Serotonergic	5 Hydroxytryptamine		
5. Peptidergic	Vasoactive intestinal peptide	Bombesin	Putative
	Substance P	Neurotensin	
	Somatostatin	Pancreatic polypeptide	
	Enkephalins	Cholecystokinin	
6. Other	Gamma aminobutyric acid		
	Histamine		
	Dopamine		

Many other potential neurotransmitters have been demonstrated in the oesophagus and these are listed in Table 1.1. Autoradiography reveals both 5 hydroxytryptamine (Dreyfus et al, 1977) and substance P (Jenssen et al, 1979) to be taken up by enteric nerve cells. Substance P increases lower oesophageal sphincter pressure in the opossum and this effect is not blocked by tetrodotoxin, phentolamine, hexamethonium or methysergide (Mukhopadhyay, 1978). Nerves showing immuno reactivity to vasoactive intestinal peptide have been found in the oesophageal muscle coat and also in the myenteric plexus in the cat and the pig particularly in the region of the lower oesophageal sphincter (Uddman et al, 1978). These are deficient in patients with Chagas' disease which is probably a non-specific reflection of myenteric ganglion cell destruction. Vasoactive intestinal peptide acts directly on smooth muscle causing relaxation because its effect is not blocked by tetrodotoxin (Behar et al, 1979).

In 1975 Hughes isolated an opiate receptor agonist from brain tissue and gut and this has been recognised to be a pentapeptide and named enkephalin. Enkephalin immunoreactive nerves have been demonstrated in smooth muscle and in the myenteric plexus of the oesophagus. Their characteristic distribution suggests they play a part in regulating oesophageal motility possibly by modulating the release of adrenergic neurotransmitters (Uddman et al, 1980). Enkephalin inhibits contraction of the oesophageal muscle and its effect is blocked by naloxone which raises possible therapeutic implications in oesophageal motor disorders.

The arrival of a nerve impulse at the nerve terminal causes a change in ionic permeability of the cell membrane permitting entry of calcium ions from the extracellular fluid which causes the synaptic vesicles to release neurotransmitters. Smooth muscle is poor in the calcium storing sarcoplasmic reticulum and is therefore much more dependent upon extracellular calcium levels for neurotransmitter release. Increase in the serum calcium level causes an increase in the amplitude of the peristaltic wave in the smooth muscle of the oesophagus but not in its striated muscle portion (Danielides & Mellow, 1978). Drugs that block the transmembrane calcium influx such as Verapamil

and Nifedipine have been shown to relax oesophageal smooth muscle (Bortolotti & Labo, 1981).

The physiological importance of these and other possible neurotransmitters revealed by the immuno-histological advances of recent years remains to be accurately defined but obviously their proper understanding is likely to bring significant advances in the management of oesophageal motor disorders. The subject has been ably reviewed by Goyal & Rattan (1978).

The autonomic nerve supply of the oesophagus

The relationship between the nervous system and the gut has recently been comprehensively reviewed by Gershon & Erde (1981). The vagal nerve supply is of central importance in the control of oesophageal motor activity and at the present time the sympathetic nerve supply appears to have only minor influence. In the dog high vagotomy disrupts peristalsis, causes dilatation with stasis and loss of tone of the oesophageal sphincter. Fortunately truncal vagotomy is performed at too low a level for it to affect the efferent nerve supply and neither truncal nor highly selective vagotomy affect the resting tone of the lower oesophageal sphincter (Temple et al, 1981). However the resting tone provides little measure of the sphincter's ability to respond to stress such as an increase in intra-abdominal pressure. After truncal vagotomy the normal response to increase of intra-abdominal pressure is greatly impaired (Angorn et al, 1977) (Fig. 1.1) and this may explain the increased incidence of gastro-oesophageal reflux symptoms after this operation. In the dog proximal selective vagotomy unlike truncal vagotomy, does not impair the response of the sphincter to increase in intra-abdominal pressure (Khan, 1981) but in man it appears to have a variable effect upon the response (Ogilvie & Atkinson, 1982). This may account for the occurrence of reflux in 25% of patients after highly selective vagotomy (Temple & Mcfarland, 1975).

The vagus nerve has a preponderance of afferent nerve fibres and these mediate vagovagal reflexes which have both excitatory and inhibitory effects on the alimentary tract. In addition non-vagal afferent fibres from splanchnic and pelvic receptors mediate reflexes through efferent vagal fibres. It seems probable that the response of the lower oesophageal sphincter to increase in intra-abdominal pressure is mediated through a vagovagal reflex and that truncal (but not necessarily highly selective) vagotomy interrupts the afferent limb of the reflex arc. Recently doubt has been cast upon whether any reflex contraction of the lower oesophageal sphincter does indeed result from increase in intra-abdominal pressure and it has been suggested that diaphragmatic contraction may be a possible explanation of the pressure rise recorded (Lepsien et al, 1980). However this seems improbable as atropine completely abolishes the pressure rise in the sphincter (Ogilvie & Atkinson, 1980).

OESOPHAGEAL INVESTIGATION

Endoscopy

During the past three years advances in endoscopic technique have been largely in the field of endoscopic therapy and these are dealt with later. Important changes in endoscopic design have been made and endoscopes of smaller diameter are now available which facilitate the negotiation of strictures in the oesophagus and at the cardia. Other instruments have wider biopsy channels which permit the introduction of larger biopsy

forceps to obtain larger biopsies and so facilitate histopathological diagnosis. The wider biopsy channelled instruments also facilitate the endoscopic introduction of fine bore feeding tubes (Atkinson et al, 1979). Dye spraying techniques have proved of value in the diagnosis of oesophageal neoplasms, and cytology in expert hands gives a high positivity rate in neoplastic strictures of the oesophagus and cardia. In one series this was greater than biopsy positivity (Witzel et al, 1976).

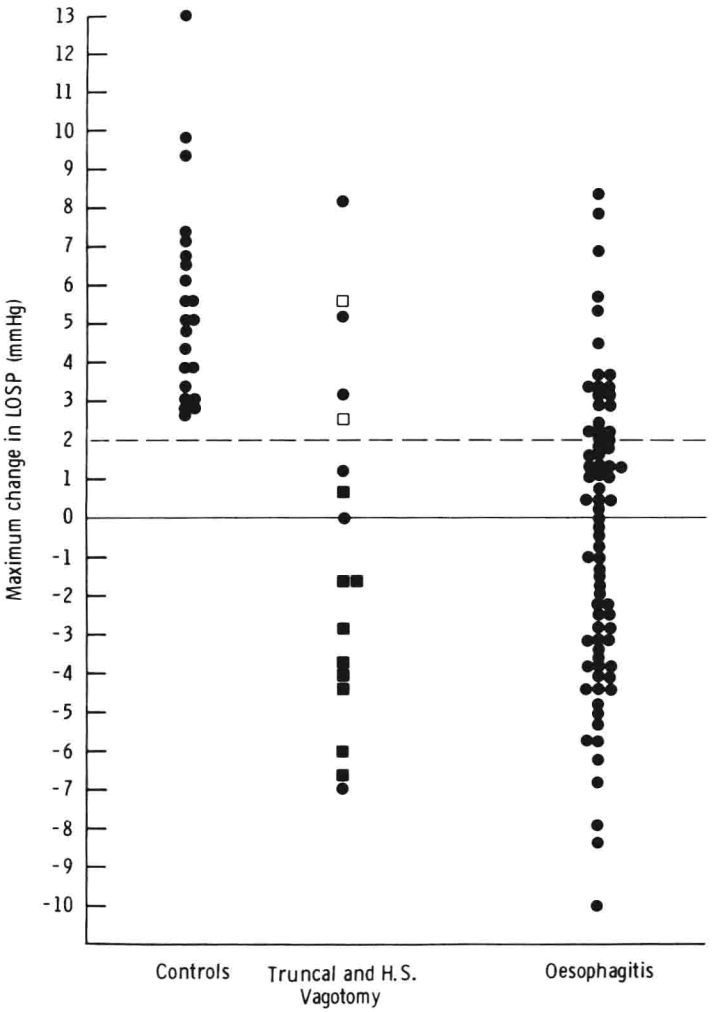

Fig. 1.1 The change in lower oesophageal sphincter pressure with abdominal compression. In the group of patients who had undergone vagotomy, truncal vagotomy is shown as a square and the two open squares represent patients with incomplete vagotomy and recurrent duodenal ulceration. Highly selective vagotomy is shown as a circle. It will be seen that the response of the lower oesophageal sphincter is impaired in the majority of patients after truncal vagotomy but not after highly selective vagotomy. It is also impaired in the majority of patients with reflux oesophagitis. (Ogilvie & Atkinson 1982.)

Although medication with intravenously injected diazepam is used widely, the possibility that it relaxed the lower oesophageal sphincter and so increased the risk of

gastro-oesophageal reflux and pulmonary aspiration was suggested by Hall et al (1975). In a double blind crossover trial oesophageal sphincter pressure was unaltered by intravenous doses of 5 and 10 mg of diazepam but 20 mg caused it to rise (Weihrauch et al, 1979) thus dispelling fears that the drug predisposes to gastro-oesophageal reflux. Vascular irritation caused by the injection of diazepam frequently results in painful localised thrombophlebitis at the site of the injection and far more serious consequences if given intra-arterially by mistake. These risks have been greatly reduced by the use of diazepam in emulsion form (Diazemuls).

Oesophageal pH recording

The techniques and clinical usage of oesophageal pH recording has been reviewed by Demeester et al (1980). Oesophageal pH recording is generally accepted to be the most reliable method of detecting gastro-oesophageal reflux but until recently, because of the large and cumbersome equipment involved, measurements could only be made with the patient in hospital either in bed or sitting or standing by the recorder. The development of a new and reliable pH sensitive telemetering capsule (Colson & Watson, 1979) and a portable receiving system (Evans et al, 1980) has enabled oesophageal pH to be recorded during every day activity (Fig. 1.2). The capsule is tethered 5 cm above the lower oesophageal sphincter identified at a previous manometric examination, and its signals received through a 3 aerial chest band and recorded using a portable receiver and Medilog cassette recorder strapped to the patient's waist allowing the subject complete freedom of movement throughout the day. At night the receiver and recorder are placed at the bedside. This method has allowed pH recording under much more physiological conditions and has shown that reflux is commoner than had previously been supposed both in healthy subjects and in patients with reflux oesophagitis (Branicki et al, 1981). Furthermore the method provides a means of determining the times at which reflux occurs in a particular individual and of so identifying activities which precipitate reflux. It will distinguish those who reflux in the upright position from those who reflux mainly when recumbent and so enable appropriate modification of treatment to be made.

Scintiscanning of the oesophagus

This method has been applied to the diagnosis of gastro-oesophageal reflux (Fisher et al, 1976) and oesophageal clearing in oesophageal motor disorders such as achalasia, diffuse spasm and systemic sclerosis (Gross et al, 1979; Tolin et al, 1979). It enables a quantitative estimate to be made of oesophageal retention and may prove of value in monitoring the effects of treatment.

GASTRO-OESOPHAGEAL REFLUX

Pathophysiology

Evidence that the lower oesophageal sphincter shows abnormality in many patients with gastro-oesophageal reflux continues to appear. Antaridis et al (1981) have shown that not only did a group of patients with symptoms of reflux have a lower mean lower oesophageal sphincter pressure but they refluxed acid instilled into the stomach more readily and there was a good correlation between lower oesophageal sphincter pressure and the volume of acid required to cause reflux. This is perhaps surprising because the

resting level of lower oesophageal sphincter pressure is not the best index of its ability to protect against reflux. Thus in a study in which oesophageal pH and manometry, including lower oesophageal sphincter pressure, were recorded simultaneously for 12-hour periods reflux did not appear to be related to low steady state sphincter pressure but to transient falls caused by inappropriate sphincteric relaxation, for example caused by swallowing (Dent et al, 1980).

Fig. 1.2 Ambulatory pH recording equipment showing the 3 band chest aerial in position with a portable receiving system and Medilog recorder attached to the waist (Branicki et al 1982).

Abnormalities of autonomic function have been demonstrated in many patients suffering from gastro-oesophageal reflux. Using the gastric secretory response to insulin-induced hypoglycaemia, expressed as a percentage of that to pentagastrin, as an index of vagal intactness, a quarter of patients with symptomatic reflux were shown by Heatley et al (1980) to have evidence of efferent vagal impairment. No significant relationship was found between the degree of vagal impairment and the intensity of oesophagitis. This, and the fact that abnormalities in pulse rate variability with respiration indicated impairment of cardiac vagal nerve supply, suggests that the autonomic nerve changes were not simply a consequence of severe oesophagitis damaging the adjacent vagal nerves. Autonomic neuropathy might provide an explanation for the failure of the lower oesophageal sphincter to contract in response to increase in intra-abdominal pressure (Fig. 1.1) and could prove to be of aetiological importance in the