METHODS IN HUMAN ALIMENTARY MOTILITY

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Studies of gastro-intestinal tract (GIT) motility examine the integrated propulsive function of the gut as a whole, or record mechanical or electrical smooth muscle activity in pre-selected areas. Studies of the former modality comprise measurement of transit, i.e. the rate at which ingested material, or markers pass through the GIT, or from one anatomical part to the next. Within specific areas mechanisms which determine transit rates can be investigated with respect to muscle contraction, peristalsis, or the electrical activity of smooth muscle.

The prospective investigator should:

1. Decide the variable that is pertinent to measure to test his hypothesis
2. Select the appropriate technique
3. Appreciate the limitations of the technique
4. Devise a method for analysing the data

Below we outline the principles underlying measurements of various aspects of GIT motility in human subjects and indicate the usefulness of the tests in the investigation of gut function. The clinical applications of these tests will not be discussed, but it is useful to remember that while most tests of motility have been used to study gut function in health and disease, at present they are not used in routine clinical investigations. Conversely, contrast radiology is an important test in suspected disorders of GIT motility, but as the observations are impossible to quantitate and the contrast medium is non-physiological, radiology is not suitable for the scientific study of motility.

Transit studies

Transit can be considered in four phases:

1. Oesophageal clearance.
2. Gastric emptying
3. Small bowel transit
4. Colonic transit

1. Oesophageal clearance

Transit through the oesophagus is so fast that it is not measured. Interest in propulsive activity of the gullet has focussed instead on the clearance of refluxed or instilled material from the body of the oesophagus, and intraluminal pressure measurements. pH monitoring, or scintiscanning have been used to measure this. Pressure recording is described in detail later. The amplitude of oesophageal peristaltic contractions, their conduction velocity and the pressure

of the gastro-oesophageal sphincter have been used to assess oesophageal clearance indirectly (Fisher *et al.*, 1977, Ahtavidis *et al.*, 1981) Intra-luminal oesophageal pH can be recorded by placing a glass pH electrode 3-5 cm above the gastro-oesophageal junction and continuously recording the pH (Atkinson & van Gelder, 1977). The number and duration of episodes of low intraluminal pH quantitates reflux of acid into the gullet. Time taken for the pH to return to baseline after spontaneous reflux, or after instillation of acid measures clearance of refluxed material.

Scintiscanning, described below in studies of gastric emptying, has also been used to measure reflux (Fisher *et al.*, 1976) but it is less sensitive than intraluminal pH monitoring (Corrazari *et al.*, 1980) and the need for expensive equipment and radio-isotopes limits its use.

2. Gastric emptying

Early studies needed repeated intubation of the subject after the ingestion of fluid meals (Hunt & Spurrell, 1951). Modern studies employ meals labelled with radio-isotopes where clearance from the stomach can be measured by an external counter. Initially, scintiscanning equipment was used (Griffith *et al.*, 1966), but this needed laborious manual counts of scans repeated every 10 to 20 min. This is obviated by using a gamma-camera, with which frequent scans can be made (Harvey *et al.*, 1970). The camera is usually coupled to an electronic counter. It also confers the particular advantage that scans can be taken within 3 min of ingestion, permitting an assessment of early gastric emptying. Various radionuclides have been used to label meals, but isotopes with a short $t_{1/2}$ such as ^{113m}In or ^{99m}Tc give more accurate results. Different isotopes are used to label the solid and liquid phases of a meal. This makes it possible to separately determine the rates of gastric emptying of liquid and solid phases (Heading *et al.*, 1976).

After ingestion of a labelled meal, the subject is positioned under the gamma camera. Radio-activity in the intestine must be excluded by defining the outline of the stomach either electronically, or by masking out the area of interest on an oscilloscope screen and making counts with a photomultiplier tube. The assumption made is that there is no change in gastric outline during the period of counting.

Counts can be made at one minute intervals and the measurements continued for long enough to allow at least half the isotope to leave the stomach. Counts are plotted against time and gastric emptying can be calculated and expressed as the half emptying time ($t_{1/2}$). Such observations may not discriminate between subjects who differ only during the early phase of gastric emptying. Alternative forms of analysis, such as the principal component analysis (Barber *et al.*, 1974), has allowed investigators to measure early phases of gastric emptying. For example, differences between controls and duodenal ulcer patients, or before and after vagotomy which were not apparent using $t_{1/2}$, have now been demonstrated (Howlett *et al.*, 1976).

3. Small bowel transit

The appearance of hydrogen in expired air after ingestion of a non-absorbable carbohydrate forms the basis of measuring small bowel transit using a non-invasive technique. The underlying principle is that bacteria ferment the carbohydrate to produce hydrogen and that in health this occurs only in the colon (Levitt, 1969).

A standard dose of an unabsorbable carbohydrate, usually lactulose 10 g in water 100 ml, is given by mouth. Lactulose is a synthetic disaccharide consisting of fructose and galactose, which is not split by brush border disaccharidases. End-expiratory samples of air are collected at 10 min intervals using a Haldane-Priestley tube (Metz *et al.*, 1976) and hydrogen concentration determined by gas chromatography. Transit time is measured from the time of ingestion of lactulose to the point at which there is a rise in breath hydrogen concentration of 20 ppm. An early rise in breath hydrogen concentration within 10 min of marker ingestion may be due to emptying of ileal contents in response to ingestion, but the exact mechanism is not understood.

Lactulose is an osmotic purgative, so that it cannot be regarded as a physiological marker of transit. Alternatives are provided by stachyose and raffinose, unabsorbable oligosaccharides contained in baked beans, which have been used to measure small bowel transit of a standard meal (Read *et al.*, 1980). Whichever marker is chosen, the measurement is that of the 'head of the meal' reaching the colon.

Transit time has been shown to vary with the dose of carbohydrate given (Levitt & Donaldson, 1970) and is greatly influenced by rate of gastric emptying (Bond & Levitt, 1972). This has to be borne in mind when interpreting results, as the technique really measures mouth-to-caecum transit time. There is also considerable inter- and intra-subject variation which it may be possible to decrease by giving the marker in a standard meal of a large volume. The technique is best used for comparisons, e.g. before and after a

drug, rather than for absolute measurements.

3. Colonic transit

The variable recorded by most methods is more correctly termed 'whole gut' transit time. However, the time taken by the markers to traverse the oesophagus, stomach and small bowel in health is relatively short compared with colonic transit. Suitable markers are ingested and their subsequent appearance in the stool is detected. Many different markers have been tried, but sections of radio-opaque PVC tubing 3 × 4 mm, are most convenient, as they can be counted on stool radiographs. In prolonged studies, the average sojourn time of a marker in the gut can be calculated after continuous intake of the marker and recording its output in the stool for several weeks (Cummings *et al.*, 1976). This procedure is very demanding on the subject and the observer and has not therefore been widely adopted. The most common method is to administer one dose of 20–40 markers at breakfast. All subsequent stools are timed and collected separately. Transit is expressed as either the time to the passage of the first marker, or the time taken for 80% of the markers to be passed (Hinton *et al.*, 1969). The last few markers may take a long time to be eliminated, hence the adoption of 80% elimination as the point of measurement.

Motor activity

Measurements of intraluminal pressure (IP) have provided much of the data about motility of the GIT. Pressure-sensitive systems generally comprise a pressure sensor, a transducer, an amplifier and a recorder. Intraluminal manometry, miniaturised strain gauges and radiotelemetry capsules have been used to collect pressure data from various parts of the human gut.

1. Intraluminal manometry

This method is most widely used for recording IP and measurements have been made in the entire GIT, although inaccessible sectors of distal small gut and the colon above the distal sigmoid remain grossly under investigated. The pressure sensor can be either a perfused polyvinyl tube with end, or side-opening ports (open ended tube, OET), or a small, air-filled 5 × 7 mm latex balloon mounted on a narrow-bore tube. The pressure is transmitted to an external transducer. The transducer, of which there are many commercially available, is usually of strain gauge type and should be sensitive within a range of –50 to +300 mm Hg. The transducer is connected to a compatible amplifier and the pressure waves recorded are usually

displayed on a multichannel pen writer. OETs record IP accurately, but may be blocked by intraluminal contents, or mucosal folds: artefacts due to tube blockage can usually be easily recognised by characteristic pressure elevations on the pressure trace.

Air filled balloons are not prone to blockage, but measure the pressure within the balloon rather than within the gut lumen. Compression of the balloon wall by mucosal folds as happens within narrow-bore intestinal lumen and within sphincters, or by intestinal contents will produce artefacts, which are even more likely to occur with water filled balloons. Air filled balloons can be useful in special circumstances, e.g. for investigating the anal sphincter where the circumferential sphincter squeeze can be recorded (Henry & Parks, 1980). Advantages of OETs perfused with water at a constant rate, over air, or water filled OETs have been documented (Williams & Harris, 1967) and perfused OETs are now generally used for intraluminal manometry. The pressure measuring assembly of OET and water pump must be as rigid as possible, so that the compliance of the system is low. Leaks and air-bubbles must be rigorously eliminated. The internal volume must be as small as possible. The rate of perfusion must allow water to escape through the OET without elevating the pressure within the system. The rate at which water is perfused through OETs is important. On blocking the OET, pressure should rise faster than the rate of rise likely to be encountered in the intestinal lumen. Rapid rates of perfusion are therefore needed for sphincters, or for high amplitude pressure waves. Generally the rate of perfusion is between 1 and 3 ml min⁻¹ which will normally give a response rate 100 mm Hg s⁻¹.

Either motor-driven syringes, or gas-driven pumps can be used to perfuse the system. Gas-driven pumps are superior because of lower compliance and smooth action, which decreases the chances of artefacts. However, mechanical pumps using glass syringes with carefully lubricated barrels can give satisfactory results.

The OETs should be radio-opaque, so that their localisation can be checked with fluoroscopy. Polyvinyl OETs with an internal diameter (ID) of 1–2 mm are commonly used. OETs with smaller IDs are prone to artefacts produced by capillary forces, larger IDs are more cumbersome, have greater internal volumes and require perfusing with larger volumes of water, which accumulates in the intestinal lumen. Single OETs can be used, but usually several are cemented together with the pressure ports at fixed intervals to each other in order to measure IP over a pre-determined length of the gut. Alternatively ports may be at the same level, positioned at 90° to each other for investigation of sphincteric function, as single ports have been shown not to give reliable

information about sphincter pressure (Kaye & Showalter, 1971).

OET assemblies can be tailored, depending on which part of the GIT is studied. For example, a multi-lumen assembly suitable for the oesophagus may have three, or four co-axial ports to record oesophageal sphincter pressure, while two other ports open proximally at 5 cm intervals to measure peristalsis. Similar assemblies can be used in the stomach, or the intestine. Gut pressures are generally recorded using anchored OET assemblies, but sphincteric function can be investigated using either stationary (Cohen & Harris, 1971) or rapid (Waldeker *et al.*, 1973; Dodds *et al.*, 1975) pull-through techniques. It has been suggested that stationary, or slow pull through techniques give more accurate and reproducible results (Welch & Drake, 1980). The upper GIT is accessible to OETs introduced per-nasally, or orally. Pressures in the recto-sigmoid colon are measured by placing OETs through a sigmoidoscope which is then withdrawn, leaving the OETs *in situ* (Painter *et al.*, 1965). The more proximal colon has been studied by introducing tubes through colostomy stomas (Cohen *et al.*, 1968), or per-orally using soft fine bore tubes weighted with a mercury bag (Kerlin *et al.*, 1982).

2. Strain gauges

Strain gauges can record either pressure, or forces generated by muscular contractions. They work on the principle of changes of electrical resistance with stretch, or compression of a suitable conductor. The change in resistance can be measured using a Wheatstone bridge. Strain gauges have the advantage over manometric systems of measuring pressure at site, obviating the need for OET assemblies and their inherent problems. Unfortunately, the response may not always be linear and is temperature dependent.

There are two types of strain gauge: firstly miniaturised transducers which record pressure. Secondly, when mounted on silastic or similar material and in a 'winged' configuration they can record mechanical events, but to do so the strip must remain in contact with the bowel wall. Miniaturised transducers can be positioned in the same way as OETs and provide reliable records in the upper GIT (Stef *et al.*, 1974; Humphries & Castell, 1977). However, they are prone to blockage by solids and are probably not so useful in the colon. Winged strain gauges are perhaps most useful when attached to the serosal surface of the gut wall, but ethical considerations limit their use in man (Bass & Wiley, 1965).

3. Radiotelemetry

The methods described so far all involve intubating the subject, who subsequently remains tethered to

recording apparatus. The radiotelemetry pill, first described in 1957 by Mackay & Jacobson, provides a means of studying the entire GIT continuously in a non-invasive way. Unfortunately, with the possible exception of the small bowel where tethered pills have been used (Thompson *et al.*, 1980), the interpretation of the pressure record is difficult.

The radio-pill consists of a transducer, a miniature battery and a transmitter. Transducers sensitive to pressure, pH or temperature are available and their clinical use has been recently reviewed (Watson, 1981). The pressure-sensitive radio-pill comprises a transmitter oscillator with a diaphragm-operated variable inductor, which controls the frequency of the signal. The signal is transmitted as a pulse at very low power, making it difficult to receive without interference at a distance of > 1 m. The receiver contains an internal oscillator at the same frequency as the radio-pill; it is very important that this should be stable. Modern radio-pills (Browning *et al.*, 1981) are robust and have a battery life of up to 60 h. Once swallowed by the subject the pill is free to rotate within the gut lumen. Because of the directional nature of the signal emitted by the radio-pill three receiving aeriels are needed, each with its axis of polarisation at 90° to the other two. The aerial and receiver together with a 24 h tape recorder can be worn by the patient on a harness, allowing continuous ambulatory recording.

The major limitation of the pressure-sensitive radio-pill is that it is difficult, or impossible to locate precisely within the GIT and that it is moved about by the very forces it is designed to measure. Serial radio-graphs are only of help in the colon. More useful localising information is provided by the characteristics of the pressure record, which is different in the stomach, jejunum, ileum and colon. The radio-pill is propelled through the GIT, so that unless tethered by a thread, one site cannot be studied for any length of time. Tethering of the radio-pill decreases its main advantage, i.e. freedom from intubation. Motor activity in the GIT is intermittent and it may not always be possible to be certain whether a flat record reflects absence of contractions, or loss of recording from the radio pill. It is possible to identify signal loss by simultaneous loss of the baseline pulse if this is recorded.

The main advantage of pressure radiotelemetry from the GIT is that prolonged records can be made. Major physical activity during the recording will however, produce artefacts which can be troublesome to eliminate.

Analysis of pressure records

Pressure sensitive systems are prone to artefacts caused by tube blockage, somatic movements, or respiration. Characteristic wave forms due to these

forces can easily be identified on the pressure trace and deleted from records prior to analysis. Respiratory movements are commonly monitored with a stethograph, thus aiding artefact elimination. A pneumatic swallow recorder placed snugly around the thyroid cartilage is useful in oesophageal work. Before any analysis can be undertaken, the investigator must be aware of the technical capacities of the pressure recording equipment he has used, the calibration with respect to the amplitude of pressure, and the time base.

So far, there is no universally accepted, or satisfactory method of analysis of records of IP. Intrasphincteric pressures are usually expressed in terms of magnitude of squeeze above the baseline in the adjoining organ. Peristaltic activity (commonly recorded only in the body of the oesophagus) can be defined in terms of the amplitude of the pressure peaks and their velocity. It should be borne in mind that no statements about transit of gut contents can be derived from the analysis of motor activity alone.

The analysis of colonic pressure records is very difficult. This is because pressure waves are more complex, prolonged and unpredictable than elsewhere in the gut. It is possible to analyse the pressure tracings in terms of frequency, duration and amplitude of the pressure events. This is laborious and time consuming, but attempts to digitise the records for subsequent computer analysis (Misiewicz *et al.*, 1968) have not become generally accepted. Attempts have been made to express an overall measure of colonic motor activity by calculating the so-called motility index (MI), a product of mean amplitude of the pressure waves and the percentage of time during which pressure activity occurred. Some workers have integrated the area under the pressure tracing. There is some general agreement that pressure waves with amplitudes of ≤ 10 mm Hg should be excluded from analysis (Connell *et al.*, 1965).

Electrophysiological studies

The literature dealing with the electrophysiology of the human GIT *in vivo* is confusing. While it is possible to measure intracellular electrical potentials *in vitro* (Bulbring, 1954), such data cannot be extrapolated to the intact GIT *in vivo*. However, electrical activity has been recorded from all parts of the GIT using a wide variety of electrodes. Gut muscle electrical activity in man can be divided into two components. The first is the variously termed basal electrical rhythm (BER), electrical control activity (ECA), pace-setter potential (PSP), or simply as a slow wave. Its frequency differs in various parts of the GIT (Duthie, 1975; Stoddard, 1978). The second form of electrical activity consists of spike bursts occurring for variable lengths of time; there is good association of this type of electrical discharge with

muscle contractions in the oesophagus (Goodman *et al.*, 1966), stomach (Daniel & Irwin, 1960), and small bowel (Bortoff, 1976), but it is less clear in the colon.

The electrodes for the recording of both aspects of electrical rhythm may be made of silver, platinum or stainless steel and are either monopolar, or bipolar. Bipolar electrodes are most commonly used; monopolar recordings require a second electrode on the skin and tend to give more ECG artefacts.

The records can be made either from intra-luminal electrodes, or from electrodes positioned subserosally at laparotomy for some unrelated procedure — e.g. cholecystectomy (Sarna *et al.*, 1981). Intra-luminal electrodes may be of the suction type (Taylor *et al.*, 1974), or consist of rings mounted on polyvinyl tubes (Goodman *et al.*, 1964). Suction electrodes positioned through a sigmoidoscope have been used in the rectum. Ring electrodes have been used in the oesophagus (Goodman *et al.*, 1966) and long (150 cm) polyvinyl tubes supporting 8 groups of 3 electrodes have been placed in the colon using a flexible sigmoidoscope (Bueno *et al.*, 1980). Unfortunately, electrical contact with the mucosa is unpredictable, so that results obtained should be viewed with caution (Daniel, 1975).

Subserosal electrodes, on the other hand, enable more reliable records to be made over a prolonged period (4 days), but interpretation of records made in the early post-operative phase should be cautious. These electrodes are removed by traction at the time the wound drain is pulled out.

The recording is made using a suitable amplifier in much the same way as pressure records. An EEG machine is ideal for this purpose, and the signal can also be stored on magnetic tape for subsequent analysis. The analysis of the record can be made manually, or by computer assisted methods such as digital counting, averaging (Wingate *et al.*, 1977) or Fast Fourier Transformation (Sarna *et al.*, 1980).

Evaluation of drugs acting on GIT motility

Most of the techniques described above have been used to measure the effects of drugs affecting motor, or secretory functions of the GIT in man. Drugs affecting the competence of gastro-oesophageal junction can be probably the best evaluated by prolonged monitoring of intra-oesophageal pH or by

γ -camera studies, but IP in the oesophageal body and the lower oesophageal sphincter are also useful. Measurements of transit rates are useful in documenting the effects of anti-diarrhoeal compounds, or laxatives, although much useful information can be collected by monitoring of 24 h stool weights. Measurements of gastric emptying are employed to assess the effects of preparations that accelerate transit out of the stomach. Records of IP can serve to document the effects and specificity of antispasmodic preparations. The major difficulty in this area is that effects are difficult to demonstrate, e.g. in the colon, when drugs are administered orally, while blood concentration curves are different after parenteral administration.

In designing experimental protocols much attention should be paid to the clinical state of the patient, because the presence, or absence of symptoms and the activity or quiescence of the disease process can affect the results. Attention should be paid to the accurate diagnosis of the patients studied. This general point needs particular emphasis with regard to motility tests, which may involve patients suffering from disorders which are difficult to define precisely and in which laboratory abnormalities, or pathognomonic signs are not available. Environmental and physical conditions, patients' posture during the test, time of day, composition of test meals, route and rate of drug administration must all be standardised. Adequate control periods, inclusion of suitable placebo controls and, if possible, random order of drug administration, are important. Additionally, the patient should not be aware of the sequence at which drugs are administered. Because of the difficulties of analysis of pressure records, this should ideally be performed by an individual who does not know which drug was given when. Side effects of drugs or of experimental procedures (e.g. nausea), must be fully documented, as they can profoundly affect IP or transit rates.

As in other areas, results must be subjected to statistical analysis. Many motility variables are not normally distributed and this must be taken into account in selection of statistical methods. Expression of results as percentage changes from basal, or control levels is generally best avoided, as it may conceal the real magnitude of the changes observed.

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