OBSERVATIONS ON THE CLINICAL USE OF RADIO PILLS

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The invention of the transistor made it possible to design a self-contained radio-transmitter with a transducing system for modulating it which is small enough to be swallowed as easily as a pill. The radio signal is picked up by an aerial, and the output of the receiver is fed into a loudspeaker and a pen recorder (Fig. 1). Radio pills containing transducers sensitive to pH, temperature, and pressure have already been used for telemetering continuous information about one or other of these variables from the lumen of the gut (Fig. 2).

Advantages and Limitations of Telemetering

This development seemed to herald a tubeless era for gastro-intestinal investigations. The news was welcomed by patients and doctors alike because the nausea and emotional distress associated with the swallowing of tubes must affect the results of the tests and may well have vitiated a

great deal of clinical investigation. Wireless telemetering not only eliminates the discomfort but makes it possible to study the effect of emotional factors on gastro-intestinal functions both in patients and in normal subjects because they can be studied in their natural surroundings, almost oblivious of the fact that they are being studied at all. Moreover, the small intestine and proximal colon are just as accessible to telemetering as the oesophagus or rectum.

Despite these advantages, telemetering is still a long way from replacing the use of tubes either in clinical investigations or in research. This is partly because of electronic problems; to show that a new technique can be made to work under certain ideal conditions is only the first step (Mackay and Jacobson, 1957; Farrar *et al.*, 1957; Rowlands and Wolff, 1960). It was inevitable that many difficulties would arise in the process of developing the method and adapting it for routine clinical use, but as these electronic problems were gradually being solved it became clear that physiological considerations would constitute the most important limiting factors to the clinical use of radio pills (Connell and Rowlands, 1960). At the present time it would be fair to regard tubes and telemetering as complementary techniques: tubes remain the method of choice for investigating the oesophago-gastric and recto-sigmoid area, whereas radio pills have distinct advantages in the small and large intestines, and not only because these areas are so inaccessible to tubes.

In 1959, when we started using the pressure-sensitive radio pills which were constructed for us in the Bio-engineering Laboratory of the National Institute for Medical Research, we encountered a series of electronic problems. Although most of these have been solved the technique is more elaborate and capricious than the well-established manometric methods using open-ended tubes. Tubes are therefore preferable for studying oesophageal disorders where it is necessary to position the pressure-detecting device accurately and to record from several points in the body of the oesophagus and sphincters simultaneously. For this purpose it is both more difficult and illogical to use a radio pill tied on to a thread as some enthusiasts have advocated.

The anchoring of a radio pill nullifies the two main advantages of telemetering—namely, that it is tubeless and that the pill moves about freely in the lumen of the gut. The mobility of the pill makes it unsuitable for recording oesophageal motility, but it is a great advantage in studying the problem of gastric motility and intestinal propulsion. Pressure waves recorded by means of tubes and balloons in the stomach or intestine are commonly classified empirically into three "types," according to their amplitude, duration, and frequency, but this is not very helpful because these wave patterns cannot be correlated with the movements of the intestinal contents. The radio pill, on the other hand, provides a freely mobile observation platform within the lumen, telemetering pressures and its own movements simultaneously,

FIG. 1.—Schematic diagram showing method of using the radio pill.

FIG. 2.—Showing cross-section of the three types of radio pill.

and a more complete picture can be obtained by synchronizing the telemetered data with fluoroscopy and judicious cineradiography using an image intensifier. In this way it should be possible to resolve the fundamental problem of the relationship between pressure and propulsion, and between intestinal movements and absorption.

The method should also prove useful for studying the mechanism of abdominal pain and of simple recurrent diarrhoea of unknown aetiology, and assist in differentiating between small-intestinal and large-intestinal causes of symptoms such as these, which constitute a large and obscure group of intestinal disorders. Work along these lines is now in progress, but, as described below, the technique is complicated and requires a formidable array of electronic equipment. However, a much simpler method will suffice for studies in which it is only necessary to record changes of pressure and the effect of drugs or meals on the pressure waves. For example, radio pills have been used to measure the duration of small-bowel paralysis after various operations (Watson *et al.*, 1962). They are also being used to record motility in bus drivers while at work on their usual London routes, the signal being recorded on tape and transcribed at leisure to a pen recorder.

The temperature-sensitive pills designed by the Medical Research Council's Bioengineering Laboratory (Wolff, 1961) have also been used successfully in active subjects under field conditions for measuring body temperature. In these pills the transducer is a toroid made from an alloy known as Mutemp HTC, which changes its magnetic permeability rapidly with changes in temperature (Fig. 2 b).

The development of pH-sensitive pills provides a further illustration of the electronic and physiological problems encountered in telemetering. Jacobson and Mackay (1957) showed that the telemetering of pH was feasible as long ago as 1957, but the copolymer transducer which they used was not accurate enough for clinical purposes. Similarly, the antimony electrode which Nöller (1962) uses in his ingenious pill was superseded long ago in clinical work by the glass electrode, but the technical difficulties of incorporating a glass and a reference electrode in a radio pill proved formidable. However, they appear to have been successfully resolved (Wolff, 1961), and the pills will soon be available for clinical testing (Fig. 2 c). It remains to be seen whether they will respond rapidly to changes of pH in the presence of mucus and food residues and continue to record faithfully after several hours in the gut. If they prove reliable they will be useful not only for recording gastric acidity but also for measuring pH throughout the length of the intestine. The pH of the intestinal contents may well be an important factor in a variety of disorders, but there is very little information available because of the technical difficulties of measuring it. Tubes will still be necessary, however, for measuring the volume of gastric juice secreted, although it may be possible to develop techniques for using the pH pill as an internal indicator as suggested by Nöller.

It is also theoretically possible to construct radio pills sensitive to other variables such as specific chemical reactions or radiation. The latter could be used to detect the presence of radioactive blood oozing into the gut after labelling the patient's red blood cells with a suitable isotope. By this means it might be possible to pinpoint the site of bleeding in those rare but difficult cases of recurrent haemorrhage in which the source of bleeding cannot be found, but the development of a suitable technique presents many serious electronic and physiological problems.

It is too early to say whether telemetering will eventually find a place in routine clinical investigations. If this should

happen, the cost of the equipment would fall and economic considerations would be less important than they are now. Because the pills are expensive and we use a large number of them, we, like Watson *et al.* (1962), have found it necessary to recover as many as possible and use each one several times. A new battery is fitted after each test and a new outer perspex case. Clinical experience so far has been largely confined to the use of pressure-sensitive pills, and some of our own experiences over the past four years may help to illustrate both the practical problems involved in using the method and its value as a research tool for studying motility.

Equilibration and Calibration

The pressure-sensitive pill (Rowlands and Wolff, 1960) consists basically of a transistorized oscillator powered by a mercury battery enclosed in a "perspex" case measuring 22 by 8 mm. (Fig. 2 a). The frequency at which the oscillator runs can be changed (modulated) by the movements of a diaphragm which is sensitive to changes of pressure. The oscillator current flows through an aerial coil which creates an alternating magnetic field in the vicinity of the pill, and this is detected outside the body by an aerial connected to a receiver.

The preparation of the pill before swallowing is somewhat tedious because sufficient time must be allowed for equilibration and calibration. The pressure in the lumen of the gut is measured against the reference pressure of the air trapped inside the pill, which must be brought to body temperature before use by placing the pill in an air incubator at 37° C. A further period of equilibration is then necessary in water at 37° C. because the perspex case is permeable to water vapour. Failure to achieve equilibration is now known to be an important cause of drift of the baseline on the pressure tracing, and this troublesome problem is caused by instability of the oscillator and consequent frequency drift. This must be checked on the loudspeaker, and if drift is still present a further period of stabilization will be necessary. The pill is then ready for calibration in a water manometer, and this too must be done at 37° C. because pressure-sensitive pills also respond to changes of temperature. The performance of the pills has been steadily improved, and in the latest model the battery lasts about three days, but only a few pills have retained enough battery power for recalibration after recovery from the faeces; the results in these have been reasonably good. Identical pressure tracings were obtained with open-ended tubes and radio pills recording simultaneously from exactly the same point in the colon (Connell and Rowlands, 1961).

Reception of Signal

Two problems have arisen in connexion with the reception of the signal. The pill radiates only a small amount of energy, and the strength of the signal falls off rapidly with increasing distance from the pill in accordance with the inverse-cube law. A receiver was therefore designed which increases its amplification automatically as the signal fades and indicates correct pressure even at a very low signal level (McCall, 1961). If, however, the level of background interference is high it may produce artifacts which are indistinguishable from the signal from the pill, and therefore all accessible sources of interference must be suppressed. This is usually feasible in all but a few highly industrialized areas where background interference is excessively high, as it is in the area around this hospital. For this reason we were obliged to screen a room completely with copper foil and install a choke filter in the electricity supply.

A more serious electronic problem arises because there are certain critical positions in which the orientation of the pill relative to the receiving aerial is such that little or no signal can be picked up (Connell and Rowlands, 1960). The effect of this is that the signal is apt to fade suddenly when the pill is spinning or tumbling freely in the lumen of the gut, and therefore the pressure record is lost from time to time, although pressure waves may in fact be occurring. This rarely happens when recording from areas such as the colon, where sudden movements of the pill are uncommon, but frequent breaks and artifacts occur when the pill is in the antrum or small intestine.

One method of tackling this problem is to arrange a series of aerials close to the patient with a switch for selecting the appropriate aerial for picking up the signal if and when it fades (Smith and Ridgway, 1962). A better solution was to develop an omnidirectional aerial sensitive to all orientations of the pill. After experimenting with rotating loop aerials of various designs which were so orientated in relation to their axis of rotation that they must pick up the signal for a portion of each revolution, it became clear that the same result could be achieved simply by means of three aerial rods. These are arranged at right angles to each other so that the signal will be received by at least one of them irrespective of the orientation of the pill. They are switched on and off in sequence 50 times every second and a "memory" circuit in the receiver holds the recording pen steady during the very brief period when the signal is lost; this gap is very much shorter than the most rapid pressure changes ever encountered in the intestine.

Recording Pressure and Movement Simultaneously

The troublesome directional effects which occur when a simple unidirectional aerial is used to pick up the signal can be turned to advantage for elucidating the relation between intraluminal pressures and intestinal movements (von Ardenne and Sprung, 1958; Connell and Rowlands, 1961; Smith and Ridgway, 1962). For this purpose we use two separate receivers simultaneously, one of them recording with a unidirectional and the other with an omnidirectional aerial. The latter provides a continuous pressure record regardless of the orientation of the pill, whereas the unidirectional aerial provides a rough index of the movements of the pill. What makes this information so valuable is that changes of pressure and movements of the pill are recorded synchronously on the same tracing. The pill may, of course, move out of range of both aerials and therefore the strength of the signal received by the omnidirectional aerial is also recorded simultaneously on the tracing. Thus the omnidirectional receiver records both the variations in frequency of the radio signal, which reflect changes in pressure, and also the strength of the signal, which is a function of the distance between the aerial and the pill, while the unidirectional receiver records variations in the strength of the signal which depend on the orientation of the pill and its distance from the aerial and thus reflect the movements of the pill. An automatic data-analyser has been developed to assist in the analysis of the records, which are complicated, bulky, and difficult to interpret.

Even this complicated technique does not provide all the data needed for correlating pressures with movements, because the telemetered record does not indicate either the extent or the direction of the movements of the pill, and it is unlikely that the gut handles a pill in exactly the same way as it handles food. Much of this additional informa-

tion may be obtained by intermittent fluoroscopy, using an image intensifier and by taking short pieces of cinefilm synchronized with the telemetered record.

Some preliminary impressions may help to illustrate the potential value of this technique, although many more recordings will have to be made and analysed before firm conclusions can be drawn. The pill may spin or tumble about freely in the lumen without any pressure waves being recorded, and it is of considerable interest that when this happens in the stomach the unidirectional receiver usually records three movements per minute, which is the same as the usual rhythm of antral contractions (Fig. 3). There appears to be little or no correlation between individual pressure waves and caudad movements of the pill, and it is our impression that propulsion through the small intestine does not depend on peristalsis in the classical sense of the word.

Once the pill has passed through the pylorus it moves rapidly into the upper jejunum (Fig. 4) and thereafter it may travel considerable distances without any striking pressure changes being registered (Fig. 5). On the other hand, pressure waves may occur with little or no movement of

FIG. 3.—Unidirectional aerial shows regular 3-per-minute movements of radio pill in stomach without any waves in pressure record.

FIG. 4.—Single large pressure wave as radio pill passes through pylorus, followed by rapid waves as pill moves quickly through duodenum.

the pill (Fig. 6), and they are always increased for a time after meals. It seems likely that some of the pressure waves recorded from the small intestine cause delay rather than propulsion as they are known to do in the colon. We are referring here to the simple waves commonly observed in the small intestine and not to abnormal waves with a prolonged rise of baseline which occur, for example, after an injection of morphine and are known to be associated with delayed transit through the intestine (Rowlands *et al.*, 1950).

Jacobson (1962) has devised an ingenious method of tracking the movements of the pill by moving an omnidirectional aerial over the patient's abdomen. The strength of the signal increases as the aerial approaches the pill and decreases as it moves away from it. Because manual tracking was not sufficiently accurate he designed a servo system which tracks the movements of the pill automatically in two planes with the patient lying flat on his back and traces a map of them on paper. This records the position and speed of movement of the pill in relation to the surface of the abdomen, but it does not register every movement in every direction. This again is an elaborate piece of electronic equipment, but it will undoubtedly prove useful

for correlating pressures with movements, although it was originally developed as a means of locating the position of the pill.

Localization

The "surface marking" as judged by the point of maximal signal strength is only a rough guide to the position of the pill, because segments of gut are superimposed on each other and do not bear a constant relation to the body surface. Fortunately, however, it is rarely necessary to be able to pin-point the position of the pill. It can be located with sufficient precision for most purposes by collating information from three sources: the point of maximal signal strength; the pattern of the motility tracing, which is usually sufficiently characteristic to identify stomach, upper jejunum, caecum, and colon; and intermittent fluoroscopy combined with barium markers given before and after the pill is swallowed.

Summary

Tubeless devices have been developed which are easily swallowed and will radio continuous information to an external receiver about pressure, temperature, or pH as they move along the alimentary tract. Practical procedures are described for equilibrating the radio pill and preventing drift, interference, and fading of the signal, and for localizing and tracking its progress.

So far, only the pressure-sensitive pill has been thoroughly tested under clinical conditions. All parts of the gut are equally accessible to investigation, but tubes are more useful for studying oesophageal motility because they can be positioned accurately. The fact that radio pills move freely in the lumen is a great advantage when studying gastric emptying and intestinal propulsion because it is possible to record pressure waves and movements of the pill simultaneously. There is little or no correlation between individual pressure waves and movements of the pill, and propulsion does not appear to depend on classical peristalsis.

This technique is useful for studying motility disorders and the effect of meals, drugs, or surgery on any part of the gut.

We regret that since this article was written Mr. J. McCall has tragically died.

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FIG. 5.—Unidirectional aerial shows vigorous movements of radio pill in jejunum but only occasional waves in pressure record.

FIG. 6.—Pressure waves in colon without any movements of pill.

The Nuffield Foundation has made a grant of £80,000 to the British Industrial Biological Research Association to finance two research projects for the next three years. These relate to the detection and assessment of minor degrees of toxic damage to the liver brought about by chemicals of low toxicity, and to the potentialities of specialized biochemical techniques for studying metabolism and toxicity of food additives.