Gut, 1975, **16**, 298-329

Symposium on colonic function[1]

Electrophysiology of the colon

E. E. DANIEL

From the Department of Pharmacology, The University of Alberta, Edmonton, Canada

One approach to an analysis of the electrophysiology of smooth muscle and nerves of the large bowel is to examine small bits of them as examples of smooth muscle tissues, without any consideration of the functions of the whole organ. Another approach, more relevant to clinical problems, involves analysis of how the components of the organ are controlled and integrated to form a functional unit. The large bowel transfers the semiliquid contents it receives from the ileum to the rectum in such a way as to allow for extraction of electrolytes and water and for other changes in composition en route. Since evacuation of contents from the rectum is usually a periodic phenomenon, and input by evacuation from the ileum is probably also periodic, there must be coupling in some way between input and output; and there must also be a system of controls to provide for orderly delays and movements of the colonic contents during transit.

To understand the control system for transit in the large bowel, a systematic approach seems warranted. I believe one should begin with an analysis of the range of responses which its muscle components can execute (Daniel, 1973). This requires consideration of the origin and integration of spontaneous electrical and mechanical activity of the musculature of the large bowel during normal and abnormal motor activity. A question soon arises: Which responses are initiated and integrated by the smooth muscle alone? Answering this question leads to characterization of the properties of the myogenic control system. If complete, this characterization would provide information about the cellular electrical activities, cell-to-cell coupling in muscle layers and coupling between layers, and the translation of these activities into mechanical responses.

A number of gastrointestinal myogenic control systems, particularly of stomach and small bowel (see Daniel, 1973; Sarna, Daniel, and Kingma, 1971, 1972a, b, and c), have been characterized as myogenic systems of mutually coupled relaxation oscillators. These systems are integrated in time and space within the longitudinal muscle layer by having the highest frequency oscillator proximal (in relation to the direction of net transit) and by having appropriate coupling so that distal lower frequency oscillators are pulled up or phase locked (fig 1). This leads either to higher frequency of contraction

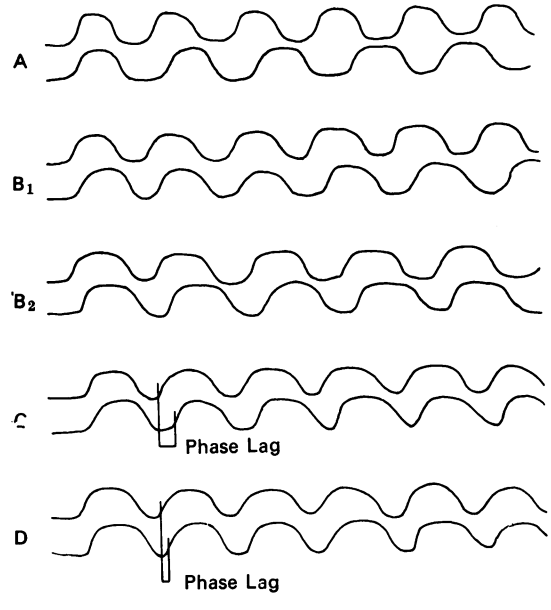

Fig 1 *Effect of increasing coupling on oscillation frequencies of two bowel oscillators. In A, proximal one (top) is shown to have a higher uncoupled (intrinsic) frequency than a distal one (bottom). As the extent of mutual coupling (fraction of the output of one which reaches the input of the other) is increased, the frequency of the lower frequency oscillator can be pulled up (B_1), that of the lower frequency oscillator can be pulled down (B_2), or both changes can occur (not shown). With sufficient coupling, the oscillators become phase-locked (C and D); the greater the coupling, the less the phase lag between them (D).*

[1]The following five papers (pp 298-329) were given at the spring meeting 1974 of the British Society of Gastroenterology.

proximally, or to an appropriate phase lead by proximal over distal regions of muscle. Around the circumference, the coupling is tight so that oscillations of excitability occur nearly simultaneously.

This system of coupled electrical oscillations leads to control[1] in time and space of the excitability of gastrointestinal smooth muscle organs. However, the translation of this excitability into contraction seems usually to be a function of neurogenic and hormonal control or modulation mechanisms.

There is strong evidence for the existence of such systems of coupled relaxation oscillators in the nonfundal portions of the stomach, in the small intestine, and in the large bowel of the cat (see Sarna *et al*, 1971, 1972a, b, and c; Daniel, 1973; and below). In stomach and intestine, oscillatory control potentials originate in the longitudinal muscle and spread into the circular muscle; in the cat colon with neuronal modulation, they originate in circular muscle.

There is a marked contrast between the above hypothesis of a basic control system, dependent on myogenic activity and integration through modulation by nerves and hormones, and the traditional hypothesis of control via an intricate network of nerve pathways for integrated responses such as the peristaltic reflex.

One aspect of the peristaltic reflex model of control of motor function in the gut has been widely accepted for many systems; ie, distal inhibition in response to stretch and to pharmacological and electrical stimuli. There may be tonic activity in such a system. This distal inhibitory response seems to be mediated by an intrinsic neuronal system—non-adrenergic inhibitory nerves (Burnstock, 1972).

These two models are not mutually exclusive, though one or the other may be more applicable to one gut region or to one species. I shall emphasize the model of myogenic control, because it is not yet widely known.

Anatomy of the Large Bowel

The anatomy of any system provides basic constraints on the nature of any control systems which operate. There can be no control without communication between elements of the system; eg, nerves cannot control muscles unless they have endings sufficiently close to allow chemical communication to occur. Also, one muscle cannot pace another without the means to communicate a signal to it. There is surprisingly little information about the structure of the basic myogenic system, ie, the nature of pathways of electrical or chemical communications (the cell-to-cell contacts) have not been studied within muscle layers or in different regions of the large bowel, nor have arrangements for communication between muscle layers been agreed upon (Elsen and Arey, 1966; Pace, 1967; Schofield, 1968; and Pace and Williams, 1969). Substructure within the circular muscle layer of human colon has been examined in a preliminary way (Pace and Williams, 1969), with the suggestion that there are bands about 1 mm wide divided by transverse septa; within these bands, there are reported to be further subdivisions into fasciculi. The longitudinal muscle is a continuous layer, thickened at the three taenia which are in turn partially subdivided by incomplete grooves running in their long axes. The connexions between taenia and circular muscle are quite controversial. The loci of nerves in human colon in limited studies seem fairly typical of the rest of the gut (Schofield, 1968): preganglionic cholinergic as well as postganglionic adrenergic fibres synapsing on postganglionic cholinergic ganglia, dendrites and axons in the myenteric and submucous plexuses (Gannon, Noblet, and Burnstock, 1969; Garrett, Howard, and Nixon, 1969). There are also non-adrenergic inhibitory ganglia in the plexuses. The extrinsic and intrinsic connexions of non-adrenergic inhibitory fibres are unknown.

There are two basic anatomical patterns in the large bowels of different species. One is characteristic of herbivores such as rabbits and guinea pigs: a large proximal part is sacculated with the longitudinal muscle partially absent. The remainder of the colon is narrower, devoid of sacculation, and has a uniform muscle coat. In omnivores like the cat and dog, the colon is short, without sacculations, with a uniform longitudinal muscle coat and a vestigial caecum. Man, an omnivore, is in between—closer to herbivores in structure. In the species in which myogenic control systems have been most extensively analysed (the cat colon) there are no taenia; instead, the longitudinal muscle is everywhere a uniform, continuous coat. Howard and Garrett (1973) have pointed out that in the cat there are direct adrenergic fibres innervating longitudinal muscle in distal colon and rectum, and circular muscle in lower rectum and internal sphincter. In colon, the same neurone organization as in the human seems to exist, except for the direct adrenergic fibres to muscle. Whether this arrangement of muscles and nerves is structurally and functionally equivalent to the human system with its taenia is unknown; so studies from cat colon cannot yet be extrapolated to the human large bowel.

[1]For this reason we refer to the oscillatory potentials as control potentials. These potentials are also known descriptively as slow waves, pacemaker potentials, BER, etc. The term 'control potentials' should not be used for these potentials unless they do in fact control the integration of motility.

	Cat		Human		Guinea Pig	
	LM	CM	LM	CM	LM	CM
Parasympathetic and/or acetylcholine	↑	↑	↑	↑	↑	↑
Sympathetic and/or noradrenaline[2]	↓	↓	↓	↓	↓	↓
Nonadrenergic inhibitory	?	?	?	?	↓	↓

Table I *Responses to nerve mediators*[1]

[1]See Heulten (1969), Wienbeck and Christensen (1971a), Bucknell and Whitney (1964), Bennett and Whitney (1966), Belisle and Gagnon (1971), Burnstock (1972).
[2]Low doses of noradrenaline or higher doses in the presence of a β-adrenergic antagonist may cause contractile responses in the cat or human.

How activity of the various colonic nerves modulates the electrical and contractile responses is summarized in table I. Thus vagal and sacral nerve activity would activate colonic response potentials and motility either directly or by coupling of response spikes to control potentials; and sympathetic nerve activity might relax or uncouple contractions by inhibiting acetylcholine release or by acting directly to inhibit muscle. Stimulation or tonic activity of nonadrenergic neurones could inhibit muscle contraction directly.[1]

Cat Colon

MYOGENIC CONTROL SYSTEM

Two electrical control systems for the colon will be discussed: that of the cat has been most extensively analysed; it may or may not be similar to that of man.

[1]There is evidence suggesting that in the myogenic system contraction would normally be coupled to control potentials but for the tonic activity of inhibitory nerves. Though multiple neurological derangements occur in aganglionosis of the large bowel (loss of intrinsic cholinergic and of intrinsic nonadrenergic inhibitory ganglia as well as of sensory cell bodies, plus overgrowth of extrinsic nerves), the fundamental defect may be loss of tonic inhibitory control.

Nature and origin of control waves (slow waves)

Christensen and colleagues showed that the cat colon *in vitro* showed the characteristics of coupled relaxation oscillators. The circular muscle generates slow waves, which are periodic depolarizations and repolarizations when recorded with microelectrodes (figure 2a, b). They can easily be recorded by simple glass-pore as well as by other types of electrode (fig 2) in preparations from which the mucosa has been stripped. Slow waves so recorded are control waves in the sense that when action potential spikes and contractions occur under the influence of cholinergic and other drugs, they occur in bursts phase-locked to the slow potentials; and the duration of the slow wave increases (fig 3). However, it should be noted that slow waves recorded with microelectrodes show few superimposed spikes. Some spikes recorded with extracellular electrodes may originate in longitudinal muscle.

Circular muscle cells throughout the cat colon are capable of generating control potentials. The size of the unit generating oscillations is unknown, but it is less than 4 mm—probably less than 0·5 mm, and maybe as small as a single cell (Christensen and Rasmus, 1972).

When isolated colon circular muscle was cut into 2-cm rings (Christensen, Anuras, and Hauser, 1974), there was a gradient of intrinsic frequencies increasing distally (fig 4). When intact and electrically coupled, the proximal oscillators were pulled up in frequency by the higher frequency distal one, and the distal oscillators were pulled down slightly. As a consequence of the characteristics of coupled relaxation oscillators, distal oscillators (especially in proximal colon) contracted more frequently, and in phase-locked regions usually had phase lead over proximal ones (Christensen and Hauser, 1971a). As a result, in the isolated intact cat colon, control potentials usually were propagated orally (fig 5a), but spread in either direction could occur (fig 5b). When

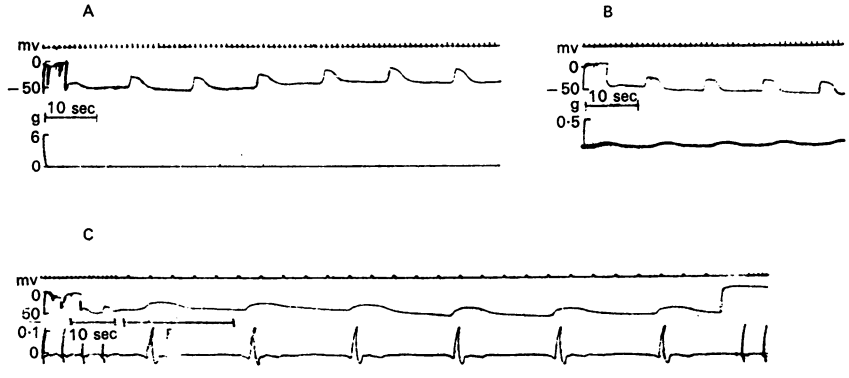

Fig 2 *From Christensen et al* (1969). *A and B: Intracellular recordings and tension from circular muscle of distal colon. Note that slow wave amplitude is independent of presence or absence of contractions. C: Intracellular and extracellular recordings from circular muscle of proximal colon of the cat. Extracellular recording with a glass pore electrode. Time constant 0·3 sec.*

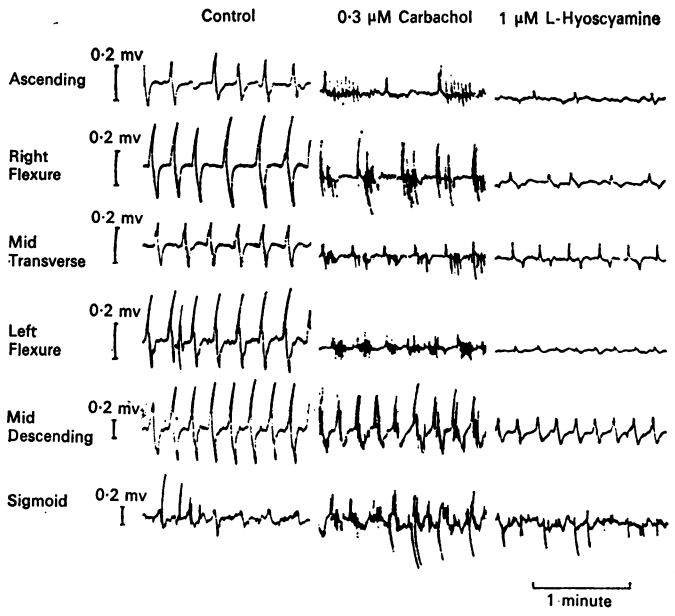

Fig 3 *From Wienbeck and Christensen (1971). Simultaneous records from the six areas of circular muscle of the cat colon* in vitro *as described in the text. The colon slow waves, recorded from glass pore electrodes through AC amplifiers, time constant 1 sec, show at all sites the first positive component followed by a second negative component. During the control period, in the record at the left, there are almost no spikes present. After addition of 0·3 μM carbachol to the tissue, in the middle record, the slow wave duration (the interval between first and second slow wave components) is prolonged, and numerous spikes become apparent, superimposed on slow waves. At some recording sites the frequency of slow waves decreases. Consecutive addition of 1 μM l-hyoscyamine to the tissue, in the record at the right, shortens slow wave duration and suppresses spike activity.*

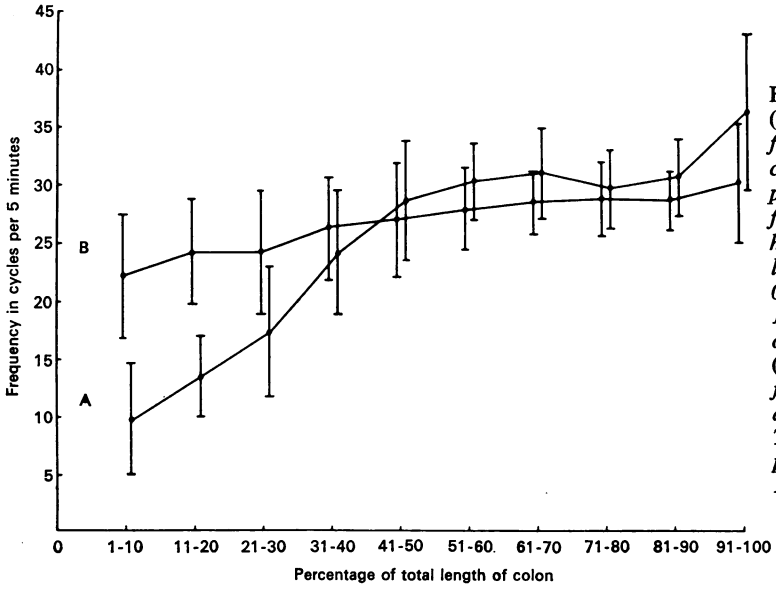

Fig 4 *From Christensen* et al *(1974). A plot of the average frequency of slow waves along the colon* in vitro *before and after partition. The vertical axis indicates frequency in cycles per 5 min. The horizontal axis shows normalized length of the 14 colons examined, 0% at the ileocaecal junction and 100% at the anal verge. The plot of average frequencies before partition (plot B) shows a slight gradient in frequency, frequency increasing with distance from the ileocaecal junction. The plot of average frequencies after partition is labelled* A. *Brackets show 1 SD above and below the mean.*

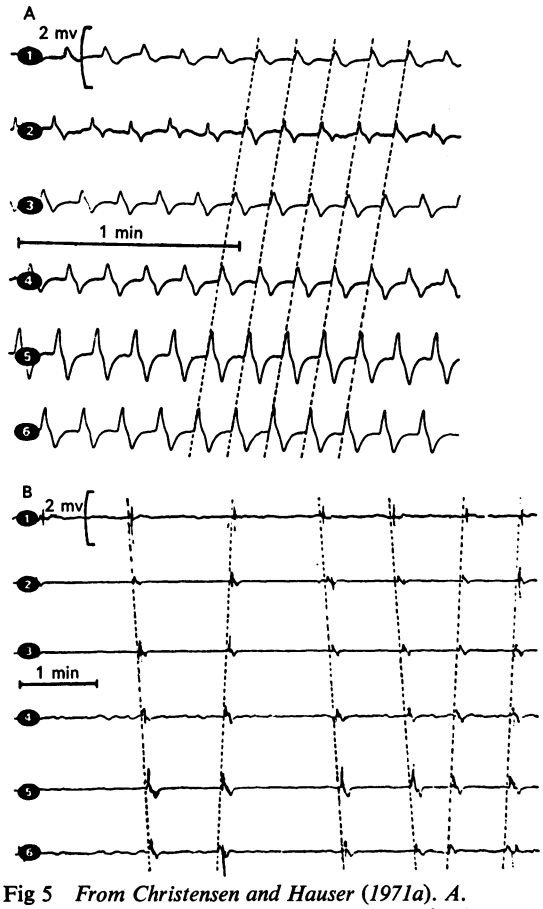

Fig 5 *From Christensen and Hauser (1971a). A. Most common phase relationships in proximal colon of cat* in vitro. *Electrodes from (1) to (6) are 5·8 mm apart on exposed circular muscle. (1) is <2 cm from ileocaecal junction. Occasional occurrence of reverse phase relationships in a similar preparation.*

proximal oscillators had phase lead, conduction velocity was faster (3·6 versus 2·6 mm/sec) than when distal oscillators had phase lead.

In situ, in the unanaesthetized cat with chronically implanted bipolar electrodes (Wienbeck, 1972a), the longitudinal electrical coupling of control potentials seems to be tighter than *in vitro*, since the frequency of oscillation of the proximal colon is higher (5·3 vs 4·8 cpm), and those of the distal colon may be less (5·5 vs 5·7 cpm). These results require confirmation by comparison in simultaneous experiments.

In terms of the coupled relaxation oscillator model of colonic activity, tight coupling is favoured by a high output of coupling current from the driving oscillator, a high coupling coefficient (most of the output of the driving oscillator reaches the input of the driven oscillator, owing to low resistance or impedance between them), a small difference in intrinsic frequencies between driving and driven oscillators, and a short refractory period in the driven oscillator. We do not know what accounts for the tighter coupling of colonic oscillations in the longitudinal axis *in vivo* than *in vitro*.

These results, together with the interaction of proximal and distal oscillators, each to pull the frequency of the other, strongly supports the existence of mutual coupling of colonic slow-wave oscillators, and provide a basis for their integrative and controlling function along the longitudinal axis.

In its transverse axis, when cat colon was cut open, laid flat, and a strip of mucosa removed (Christensen and Hauser, 1971b), coupling between oscillators was sufficient, in conjunction with what are probably very small differences in intrinsic frequency, to keep them phase-locked 93 to 97% of the time. No evidence of spirality of muscle was obtained. Conduction velocity was, as expected from consideration of muscle structure and of the small differences in intrinsic frequencies, greater than in the longitudinal axis: 7·5 to 9·6 compared with 2·3 to 2·6 mm/sec. Transverse coupling, as judged by increased conduction velocities, was greater in the middle colon than in the ascending colon (Christensen and Rasmus, 1972). Tight coupling in the circular axis provides for nearly simultaneous excitation of rings of large bowel, ie, provides a basis for segmental contractions.

Ionic basis of control potentials

The conduction changes and ionic currents which underlie control potentials of cat colon are not known. Early results (Wienbeck and Christensen, 1971b) suggested that they depend directly or indirectly on sodium and/or calcium currents.

NERVE CONTROL SYSTEMS

Study of the actions of nerve mediators provides insight into the potential mechanisms for neurogenic modulation of myogenic control activity. Muscarinic cholinergic agents such as bethanechol (Wienbeck and Christensen, 1971a) which act on smooth muscle, prolonged slow waves, and increased the coupling between control potentials and spikes (or response potentials—fig 3). Spikes and prolonged control potentials were both associated with contractile responses. These responses were all blocked by atropine or hyoscine (fig 3). Similar results (slow wave duration could not be determined accurately) were obtained on intravenous infusion into intact, awake cats (Wienbeck, Christensen, and Weisbrodt, 1972; Wienbeck, 1972b); there were also significant

decreases in frequency *in vivo* throughout the colon, and these were blocked by atropine.

In general, control of the rhythmic, segmenting contractions of colon might be achieved by variations in excitability associated with control potentials and the coupling of increased excitability to contraction by release of acetylcholine from extrinsic or intrinsic parasympathetic activity. Since control wave and contraction frequency would be expected to increase aborally, and since in phase-locked regions the oral regions show phase lag, this system should operate to impede forward propulsion of colonic contents, especially in the proximal colon.

Sympathetic activity through release of norepinephrine might have biphasic effects; *in vitro*, low concentrations of norepinephrine (0·1 to 1·0 μM) increased control potential duration and associated spiking with contractions. Higher doses (3 to 100 μM) depressed spike activity (Wienbeck and Christensen, 1971a). The excitant actions were on α-adrenergic receptors. However, Hultén (1966) found that stimulation of sympathetic nerves to the colon of anaesthetized cats caused inhibition of contractile activity, either spontaneous activity or that induced by parasympathetic nerve stimulation, but not that evoked by intraarterial acetylcholine. It is unclear whether sympathetic nerve stimulation could ever lead to excitation of the colon in the awake animal. His results suggest sympathetic control by inhibition of acetylcholine release.

PATHOPHYSIOLOGY OF DIARRHOEA AND CONTROL POTENTIALS

In colons from cats with spontaneous diarrhoea, in colons treated *in vitro* with sodium ricinoleate in low doses ($\geqslant 10^{-7}$ M), in colons treated *in vitro* with quinine or quinidine in low concentrations, but not in colons similarly treated with sodium oleate, phase-locking of control potentials in the longitudinal axis was diminished (Christensen, Weisbrodt, and Hauser, 1972; Barker and Christensen, 1973; Christensen and Freeman, 1972). No consistent changes in conduction velocity or frequency, or in spiking, were found. The authors termed this 'a decrease in congruence' and suggested it might provide an explanation for diarrhoea by interfering with the normal frequency gradients and phase relationships which operate to retard propulsion in the proximal colon. The authors suggest that the underlying mechanism might be either decreased coupling between oscillators, or increased frequencies of driven oscillators, ie, those with lower intrinsic oscillation frequency. The latter explanation seems unlikely, since any decrease in the differences in intrinsic frequencies of oscillators along the large bowel should increase phase locking.

ANOTHER ELECTRICAL CONTROL SYSTEM

In addition to slow waves (or control potentials) and spikes (or response potentials), there is another myogenic electrical event. In early studies (Christensen, Caprilli, and Lund, 1969) fast oscillating potentials with a frequency of 30 to 40 cycles per minute were observed; they were always associated with contractions (fig 6). They have not been observed in intracellular recordings from circular muscle. They were at least partially independent of control potentials, since both types could occur simultaneously (see fig 5). They were usually slower in frequency than spikes. Fast oscillations (30 to 45 cpm) were also observed *in vivo* (Wienbeck *et al*, 1972; Wienbeck, 1972a). They were often preceded and followed by spikes, and sometimes spikes were superimposed on them and they, together with spikes, were associated with contractions. In the distal colon *in vivo*, long spike bursts were found, lasting up to 30 sec, not phase-locked to slow waves, and recurring at 0·7 to 1·5 cpm. Recently, it was observed (Christensen *et al*, 1974) that *in vitro* these spike bursts migrate (70% aborally) and that their electrical signal in the proximal colon is the fast oscillating potential. They were longer in duration in the distal colon. All migrating spike bursts were abolished by transection of the intestine.

It was suggested (Christensen *et al*, 1974; Wienbeck, 1972a) that the migrating spike burst is similar to the 'interdigestive migrating spike complex' of the dog and cat small intestine (Szurszewski, 1969; Weisbrodt and Christensen, 1972), and perhaps better called 'activity front' since they are not suppressed by feeding in all species (Grivel and Ruckebusch, 1972). This has recently been confirmed (Wienbeck and Janssen, 1974); spike bursts migrating into the cat colon *in vivo* from the ileum induce oscillatory potentials in the colon. Spike bursts and/or oscillations usually do not migrate from colon to ileum, but do migrate orad into the caecum. Such spike bursts are induced within 20 minutes by feeding or gastrin, followed by local non-migrating spiking. This may provide a basis for the control of motility called the 'gastro-ileal' and 'gastro-colic' reflexes.

Migrating spike bursts can start within the colon, usually in the mid- or proximal colon, and most often move aborally[3]. They could provide a basis for the control of 'peristaltic' or mass movements, but the propagation velocity seems slow for mass

[3]Recordings with microelectrodes in the distal rabbit colon (Gillespie, 1968) or with glass suction electrodes from the serosal surface of mouse large intestine (Wood, 1974) showed slow waves, usually with phase-locked spikes; sometimes there were in the mouse intestine rapid oscillations usually obliterating slow waves but associated with spikes. Thus the components of the cat electrogram may occur in other species.

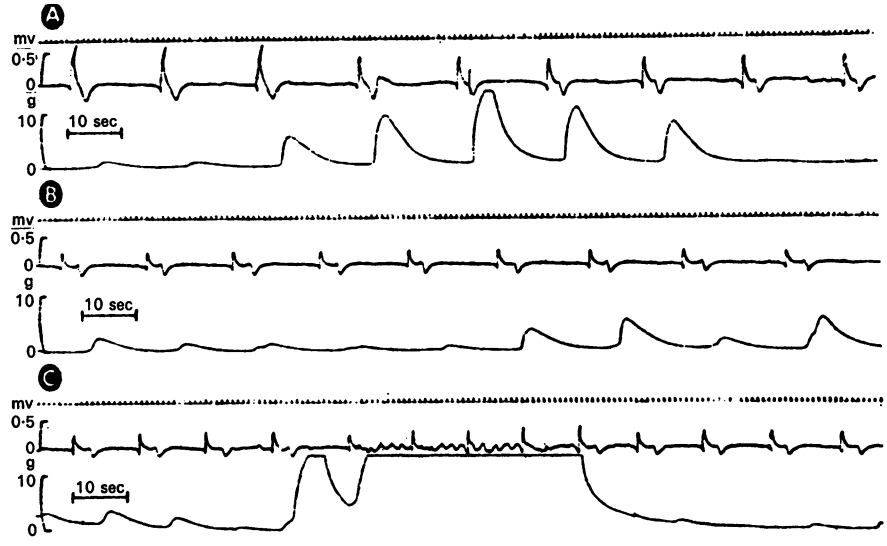

Fig 6 *From Christensen* et al *(1969). Relationship between slow waves, the oscillation phenomenon, and contractions. All three panels represent different segments of a record from a strip of proximal colon. Time scale at top shows seconds. Upper channel is the record from one glass-pore electrode; lower channel records tension of the strip. In A and B, slow waves accompany rhythmic contractions of varying magnitude. In C, a prolonged powerful tonic contraction accompanies oscillations in electrical record which do not prevent occurrence of new slow waves.*

movements, and mass movements are usually associated (in man, at least) with relaxation rather than with contraction of most of the colon.

Human Colon

MYOGENIC CONTROL SYSTEM

At present, we are uncertain about the nature and origins of the human colonic electromyogram. Some recordings in the literature cannot be interpreted because essential information about recording parameters (such as the time constant in RC coupled tracings) were not stated.

Most records *in vivo* have been obtained from the more readily accessible distal large bowel, ie, the rectum or descending colon. They have usually been obtained with monopolar or bipolar suction-type electrodes on the mucosal surface. The intent of such recordings is to force ring electrodes tight against the mucosa, or to push fine needle electrodes through the mucosa and into the circular muscle, and maintain this as a stable contact. Success in such intentions has not been ascertained, ie, it is not clear whether variable contact and short circuiting occur. Also, real differences in electrical activity may occur between regions of fixed segmental contraction and other regions.

Several observations have been made consistently:
1 The slow waves are not recorded continuously, but appear and disappear (Wankling, Brown, Collins, and Duthie, 1968; Kerremans, 1968, 1969; Couturier, Rozé, Couturier-Turpin, and Debray, 1969; Ustach, Tobon, Hambrecht, Bass, and Schuster, 1970; Taylor, Smallwood, and Duthie, 1974), and when present they appear to wax and wane (fig 7). In the distal colon, slow waves were present 5·5 to 21% of the time (Couturier *et al*, 1969; Taylor *et al*, 1974); in the rectum they were present 72 to 92% of the time (Kerremans, 1968, 1969; Ustach *et al*, 1970; Taylor *et al*, 1974). In a very recent study two slow wave frequencies were distinguished: one was 3 to 4 cpm; the other (recorded more frequently) was 6 to 9 cpm; and the frequency showed a tendency to increase with increasing distance from the anus. The percentage of time in which the flow waves could be recorded was 70% at 5 cm from the anus, decreasing to less than 20% at 30 cm above the anus (Taylor *et al*, 1974).

2 In the rectum (Taylor *et al*, 1974) and distal colon (Couturier *et al*, 1969; Kerremans, 1968, 1969) slow waves and spikes are recorded by some investigators. In the distal colon (Couturier *et al*, 1969) slow waves and spikes corresponded in frequency (10/min); spikes occurred at any phase of the low

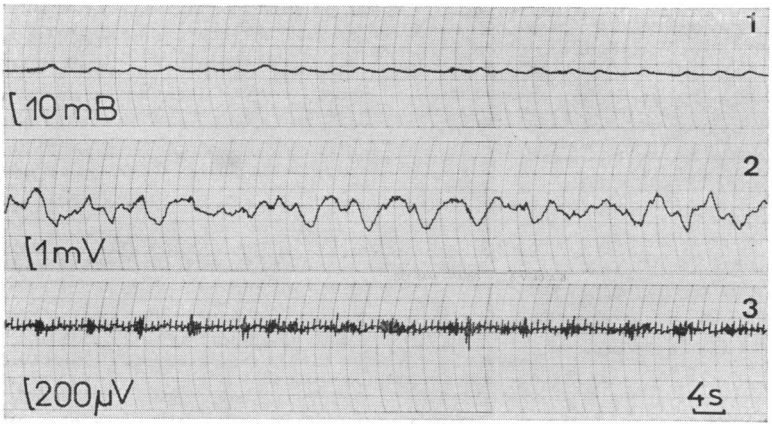

Fig 7 *From Couturier* et al *(1969). Recording from a unipolar suction type electrode (reference electrode on upper thigh) in a normal human colon. Channels 2 and 3 from the same electrode: 2 with a band pass from 0·2 to 100 cps at 3 dB; 3 with a band pass from 5 to 100 cps. Channel 1 shows intraluminal pressure (1 mB = 0·750 mm Hg). In places a clear synchronization of spike bursts (in channel 3) and slow waves (in channel 2) was observed. However, spike bursts were not usually synchronous with pressure increases.*

wave, but in the figures shown (eg, fig 7) were most often at the positive phase of the slow wave (Couturier *et al*, 1969). In the rectum, the slow waves and spike bursts often corresponded in frequency (2·4 to 5·2 cpm), and though spikes usually occurred in the positive phase of the slow wave, they could occur at any phase (Kerremans, 1968, 1969).

3 In a study of the 'rectal canal' (Wankling *et al*, 1968), slow waves with a frequency of 14·6 to 16·4 cpm were obtained without spikes being recorded. These values were close to those reported (17·5 and 18·9 cpm) in another study from the internal anal sphincter (Kerremans, 1968, 1969); and the description in this paper suggests that in fact both studies were from the internal anal sphincter. If so, both agreed about the absence of any recordable spikes in this region associated with contraction. Both also agree that there are ultraslow variations in electrical potentials in the internal sphincter; one group found a frequency of 2·7 to 3·2 cpm (Kerremans, 1968, 1969); the other found a frequency of 1·2 to 1·6 cpm, and sometimes found them to be associated with contraction (Wankling *et al*, 1969). The former group (Kerremans, 1969) also found ultraslow waves of similar frequency in the rectum, and postulated that they were propagated into the internal sphincter. A third group (Ustach *et al*, 1970) has also recorded from the internal sphincter and reported a frequency of about 17 cpm in normal patients (lower frequencies were found in patients with functional and neurological disorders). This group, too, failed to record any spike activity, even during contraction; and, like one of the others (Kerremans, 1968, 1969), found that slow waves disappeared during relaxation of the sphincter evoked by rectal distension.

From these data it is premature to conclude that the slow waves are, indeed, absent a large part of the time. They may be lost because of asynchrony (absence of phase locking) in the regions from which recordings were made, and because of technical difficulties in recording with constant contact and with adequate sensitivity from the mucosal surface *in vivo*. The higher frequency of occurrence of slow waves in the distal colon and rectum may be related to the fusion in that region of taenia to form a regular and continuous longitudinal muscle.

It is also premature to conclude that the slow waves are also control potentials in the sense already found for stomach, small intestine, and cat colon. The relationships between slow waves and spikes, and between spikes or slow waves and contraction, remain to be established. Possibly slow waves of the human colon, like those of the guinea pig small intestine (Bolton, 1971), are induced by acetylcholine release.

To ascertain the nature and control functions of electrical activity of the muscle layers of the human colon, *in-vitro* studies with and without mucosa, with intra- and extracellular electrode recordings, are needed. Such studies present formidable difficulties, eg, obtaining normal tissues, keeping them in good physiological condition despite their thickness and the need for dissection, etc. None of these difficulties is insurmountable. Data (mentioned above) from

in-vivo studies are subject to difficulties in interpretation which will be overcome only by careful studies *in vitro*.

The nature of neuronal and hormonal controls as they may interact with the myogenic control system in the human colon is also unknown. However, it seems clear that the conceptual and experimental tools for analysis of the myogenic, neuronal, and hormonal control of human colonic motility are at hand, waiting for use. Within the next five years an adequate description of these could be available. Such a description of normal control would help in the understanding of disordered control in disease.

References

Barker, D., Jr., and Christensen, J. (1973). Some effects of quinidine and quinine on the electromyogram of the colon. *Gastroenterology*, **65**, 773-777.

Belisle, S., and Gagnon, D. J. (1971). Stimulating action of catecholamines on isolated preparations of the rat colon and human and rabbit taeniae coli. *Brit. J. Pharmacol.*, **41**, 361-366.

Bennett, A., and Whitney, B. (1966). A pharmacological study of the motility of the human gastrointestinal tract. *Gut*, **7**, 307-316.

Bolton, T. B. (1971). On the nature of the oscillations of the membrane potential (slow waves) produced by acetylcholine or carbachol in intestinal smooth muscle. *J. Physiol. (Lond.)*, **216**, 403-418.

Bucknell, A., and Whitney, B. (1964). A preliminary investigation of the pharmacology of the human isolated taenia coli preparation. *Brit. J. Pharmacol.*, **23**, 164-175.

Burnstock, G. (1972). Purinergic nerves. *Pharmac. Rev.*, **24**, 509-581.

Christensen, J., Anuras, S., and Hauser, R. L. (1974). Migrating spike bursts and electrical slow waves in the cat colon: effect of sectioning. *Gastroenterology*, **66**, 240-247.

Christensen, J., Caprilli, R., and Lund, G. F. (1969). Electrical slow waves in circular muscle of cat colon. *Amer. J. Physiol.*, **217**, 771-776.

Christensen, J., and Freeman, B. W. (1972). Circular muscle electromyogram in the cat colon: local effect of sodium ricinoleate. *Gastroenterology*, **63**, 1011-1015.

Christensen, J., and Hauser, R. L. (1971a). Longitudinal axial coupling of slow waves in proximal cat colon. *Amer. J. Physiol.*, **221**, 246-250.

Christensen, J., and Hauser, R. L. (1971b). Circumferential coupling of electric slow waves in circular muscle of cat colon. *Amer. J. Physiol.*, **221**, 1033-1037.

Christensen, J., and Rasmus, S. C. (1972). Colon slow waves: size of oscillators and rates of spread. *Amer. J. Physiol.*, **223**, 1330-1333.

Christensen, J., Weisbrodt, N. W., and Hauser, R. L. (1972). Electrical slow wave of the proximal colon of the cat in diarrhea. *Gastroenterology*, **62**, 1167-1173.

Couturier, D., Rozé, C., Couturier-Turpin, M. H., and Debray, C. (1969). Electromyography of the colon *in situ*: an experimental study in man and in the rabbit. *Gastroenterology*, **56**, 317-322.

Daniel, E. E. (1973). A conceptual analysis of the pharmacology of gastrointestinal motility. In *International Encyclopedia of Pharmacology and Therapeutics*, Sect. 39a, *Motility and Secretion* edited by Pamela Holton. Vol. 2, pp. 457-545. Pergamon Press, Oxford.

Elsen, J., and Arey, L. B. (1966). On spirality in the intestinal wall. *Amer. J. Anat.*, **118**, 11-20.

Gannon, B. J., Noblet, H. R., and Burnstock, G. (1969). Adrenergic innervation of bowel in Hirschsprung's disease. *Brit. med. J.*, **3**, 338-340.

Garrett, J. R., Howard, E. R., and Nixon, H. H. (1969). Autonomic nerves in rectum and colon in Hirschsprung's disease. *Arch. Dis. Childh.*, **44**, 406-417.

Garry, R. C. (1934). The movements of the large intestine. *Physiol. Rev.*, **14**, 103-132.

Gillespie, J. S. (1968). Electrical activity in the colon. In *Handbook of Physiology*, Sect. VI: *Alimentary Canal*, edited by C. F. Code. Vol. 4: *Motility*, pp. 2093-2128. American Physiological Society, Washington, D.C.

Grivel, M. L., and Ruckebusch, Y. (1972). The propagation of segmental contractions along the small intestine. *J. Physiol. (Lond.)*, **227**, 611-625.

Howard, E. R., and Garrett, J. R. (1973). The intrinsic myenteric innervation of the hind-gut and accessory muscles of defaecation in the cat. *Z. Zellforsch.*, **136**, 31-44.

Hultén, L. (1969). Extrinsic nervous control of colonic motility and blood flow: an experimental study in the cat. *Acta physiol. scand.*, Suppl. **335**, 1-116.

Kerremans, R. (1968). Electrical activity and motility of the internal anal sphincter. *Acta gastro-ent. belg.*, **31**, 465-482.

Kerremans, R. (1969). Morphological and physiological aspects of anal continence and defaecation. In *In vivo Electrical Activity of the Smooth Ano-Rectal Muscles in Man*, ch. III Arscia, Brussels.

Pace, J. L. (1967). The interconnexions of the muscle layers of the human colon. *J. Anat. (Lond.)*, **102**, 148.

Pace, J. L., and Williams, I. (1969). Organization of the muscular wall of the human colon. *Gut*, **10**, 352-359.

Prosser, C. L. (1974). Diversity of electrical activity in gastrointestinal muscle. In *Proceedings of the 4th International Symposium on Gastrointestinal Motility*, edited by E. E. Daniel. Mitchell, Vancouver. (In press).

Sarna, S. K., Daniel, E. E., and Kingma, Y. J. (1971). Simulation of slow wave electrical activity of small intestine. *Amer. J. Physiol.*, **221**, 166-175.

Sarna, S. K., Daniel, E. E., and Kingma, Y. J. (1972a). Simulation of the electric-control activity of the stomach by an array of relaxation oscillators. *Amer. J. digest. Dis.*, **17**, 299-310.

Sarna, S. K., Daniel, E. E., and Kingma, Y. J. (1972b). Effects of partial cuts on gastric electrical control activity and its computer model. *Amer. J. Physiol.*, **222**, 332-340.

Sarna, S. K., Daniel, E. E., and Kingma, Y. J. (1972c). Premature control potentials in the dog stomach and in the gastric computer model. *Amer. J. Physiol.*, **222**, 1518-1523.

Schofield, G. C. (1968). Anatomy of muscular and neural tissues in the alimentary canal. In *Handbook of Physiology*, Sect. VI, *Alimentary Canal*, edited by C. F. Code, Vol. IV: *Motility*, pp. 1579-1627. American Physiological Society, Washington.

Szurszewski, J. H. (1969). A migrating electrical complex of the canine small intestine. *Amer. J. Physiol.*, **217**, 1757-1763.

Taylor, I., Smallwood, R., and Duthie, H. L. (1974). Myoelectric activity in the rectosigmoid in man. In *Proceedings of the 4th International Symposium on Gastrointestinal Motility*, edited by E. E. Daniel. Mitchell, Vancouver. (In press).

Ustach, T. J., Tobon, F., Hambrecht, T., Bass, D. D., and Schuster, M. M. (1970). Electrophysiological aspects of human sphincter function. *J. clin. Invest.*, **49**, 41-48.

Wankling, W. J., Brown, B. H., Collins, C. D., and Duthie, H. L. (1968). Basal electrical activity in the anal canal in man. *Gut*, **9**, 457-460.

Weisbrodt, N. W., and Christensen, J. (1972). Electrical activity of the cat duodenum in fasting and vomiting. *Gastroenterology*, **63**, 1004-1010.

Wienbeck, M. (1972a). The electrical activity of the cat colon *in vivo*. I. The normal electrical activity and its relationship to contractile activity. *Res. exp. Med.*, **158**, 268-279.

Wienbeck, M. (1972b). The electrical activity of the cat colon *in vivo*. II. The effects of bethanechol and morphine. *Res. exp. Med.*, **158**, 280-287.

Wienbeck, M., and Christensen, J. (1971a). Effects of some drugs on electrical activity of the isolated colon of the cat. *Gastroenterology*, **61**, 470-478.

Wienbeck, M., and Christensen, J. (1971b). Cationic requirements of colon slow waves in the cat. *Amer. J. Physiol.*, **220**, 513-519.

Wienbeck, M., Christensen, J., and Weisbrodt, N. W. (1972). Electromyography of the colon in the unanesthetized cat. *Amer. J. Digest. Dis.*, **17**, 356-362.

Wienbeck, M., and Janssen, H. (1974). Electrical control mechanisms at the ileo-colic junction. In *Proceedings of the 4th International Symposium on Gastrointestinal Motility*, edited by E. E. Daniel. Mitchell, Vancouver. (In press).

Wood, J. D. (1974). Physiological studies on the large intestine of mice with hereditary megacolon and absence of enteric ganglion cells. In *Proceedings of the 4th International Symposium on Gastrointestinal Motility*, edited by E. E. Daniel. Mitchell, Vancouver. (In press).