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# Small Intestinal Motor Activity – Its Role in Gut Homeostasis and Disease

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## INTRODUCTION

Recent years have witnessed a considerable resurgence of interest in gastrointestinal motor activity, both in the physiological laboratory and in clinical medicine. Technological advances in both recording techniques and analytical methods have led to considerable advances in our understanding of small intestinal motor activity, both *in vitro* at the level of the smooth muscle cell and its neural connections and *in vivo* in the whole animal. Stimulated by these physiological studies and spurred on by the large number of clinical problems which have been traditionally regarded as reflecting disordered 'gut motility', though often on the basis of little good evidence, the clinician is increasingly attempting to study intestinal motor patterns both in normal man and in various disease states.

## THE PHYSIOLOGY OF INTESTINAL MOTOR FUNCTION

If properly organized, motor activity should subserve the basic functions of the gut, namely the digestion of food, the absorption of essential nutrients, and the elimination of non-digestible and toxic material. One can visualize contractile activity assisting these processes in a number of ways. Thus, forward propulsion would appear to be a prerequisite for the digestive process. Similarly, compartmentation, by sphincters, of chyme within various parts of the gut would promote storage and increase contact time with the absorptive surface of the mucosa within that segment. Furthermore, to ensure adequate mixing of chyme with digestive juices and enzymes, motor and secretory functions should be closely coordinated.

The motor apparatus which generates such integrated motor patterns consists, in the first instance, of the smooth muscle of the gut wall and secondly, of the neural, hormonal and peptidergic control mechanisms which regulate and integrate smooth muscle activity. Whether a given segment of the gut contracts to achieve propulsion or relaxes to cause stasis depends on a complex, many tiered control system which operates at a number of levels (Fig. 1). At the most fundamental level is the individual smooth muscle cell, the modus operandi of gut motor function, additional tiers of control being provided by the interconnections between individual smooth muscle cells, the intrinsic nerves of the gut wall in the submucosal and myenteric plexsuses, the autonomic nerves with which the gut is so well endowed, and finally, and at the highest level, the central nervous system.

Based in part on a lecture given at the Royal Colleges of Physicians and Surgeons in Glasgow, October 1986, as part of a symposium in honour of Dr Geoffrey Watkinson.

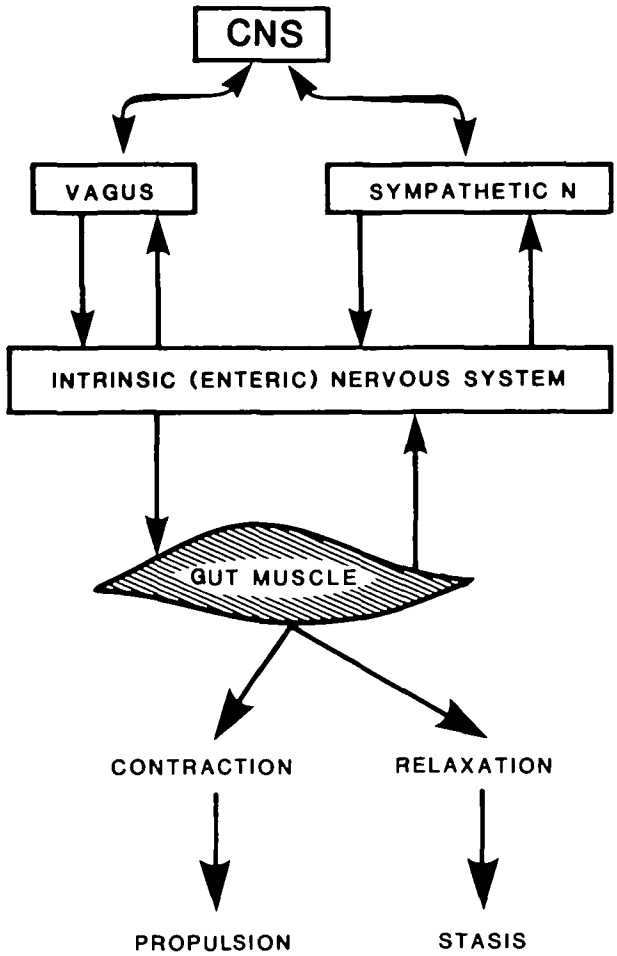


FIG. 1. The various levels of control of intestinal motor activity.

*Intestinal smooth muscle physiology*

Contractile activity is based on the intrinsic electrophysiological properties of smooth muscle cells [1]. Like other excitable tissues smooth muscle cells generate a potential difference across their membranes, the transmembrane potential, which lies between 50 and 75 mV. One unique property of the membrane potential of smooth cells is its propensity to undergo spontaneous, slow, transient depolarization to a level below that necessary to generate action potentials [1]. Indeed, electrical recordings from any point in the small intestine will record these omnipresent slow waves (Fig. 2). These slow waves do not in themselves generate contractions – these result from action potentials consequent on further depolarization above the critical level. However, these action potentials, or spikes, occur only on the crest of slow waves (Fig. 2); it can thus be seen that the intrinsic slow wave frequency predetermines the frequency at which gut contractions can occur, a phenomenon often referred to as phase-locking. A further, practical advantage of these close relationships between electrical and contractile events is that the investigator can make some deductions regarding one while only recording the other.

Individual smooth muscle cells come into close contact with one another at regions called nexuses (intercellular connections permitting transmission of electrical signals between cells).

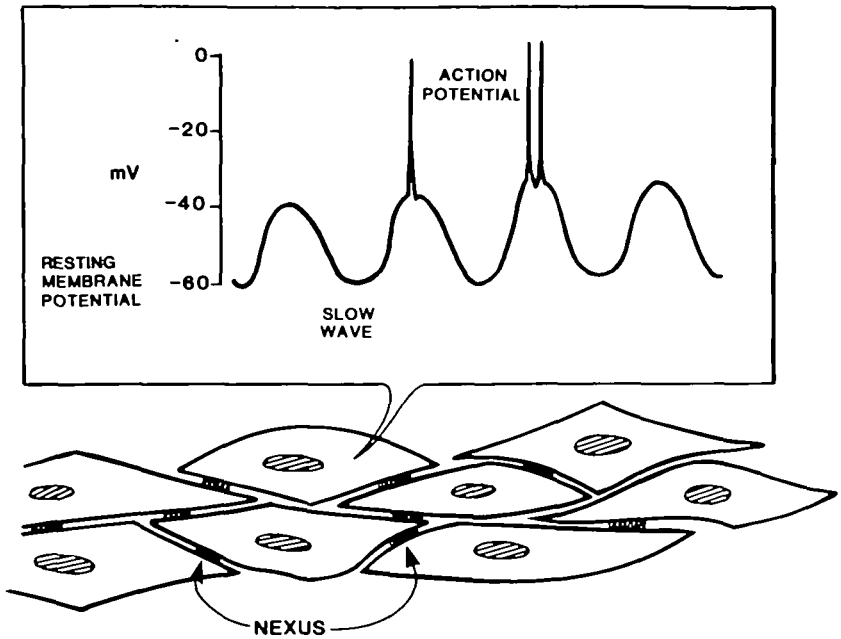


FIG. 2. Smooth muscle electrical activity. Inset represents recording of intracellular electrical activity from a single smooth muscle cell. Note resting membrane potential of −60 mV which regularly undergoes spontaneous depolarization to −40 mV to produce rhythmic slow waves. Action (or spike) potentials which occur only on the summit of slow waves result in muscular contraction. Nexuses permit propagation of electrical signals between individual cells.



By permitting circumferential, radial and longitudinal dissemination of electrical signals, this syncytial property of gastrointestinal smooth muscle is fundamental to integrated motor function [2]. As a consequence of longitudinal propagation of slow waves, regions of the gut with the fastest intrinsic slow wave frequency can effectively dominate and entrain the rest of the intestine [3]. In the small intestine the proximal duodenum has the highest intrinsic frequency and therefore acts as a pacemaker, slow waves being propagated aborally along the gut from this site [4]. Slow wave frequency declines along the gut; in man, for example, it declines from a frequency of 11–12 cycles/min in the duodenum to 8–9 cycles/min in the distal ileum [5].

### *Enteric neurophysiology*

One of the most significant advances in gastrointestinal physiology has been in our understanding of the intrinsic nerves of the gut [6]. It is now appreciated that the nerve plexuses of the gut wall, together with their interconnecting neurons, play an extremely important role in processing and integrating afferent signals and in coordinating and directing efferent responses. The complexity of this system is still being unravelled, but it is clear that this intrinsic or enteric nervous system, as it is now known, exerts a considerable degree of autonomy and truly behaves as a 'minibrain' within the gut. It is now also appreciated that the neurons of the intrinsic nervous system can project over considerable distances, both longitudinally and circumferentially. Through these interconnections and by drawing upon its impressive armamentarium of inhibitory and excitatory neurotransmitters and neuromodulatory peptides, the enteric nervous system can generate complex and coordinated responses to incoming stimuli from the muscularis or mucosa. Several of these peptides have now been identified and their function in

the enteric nervous system delineated [7], Some, including vasoactive intestinal peptide, Substance P, enkephalins, neurotensin and bombesin, act as classical neurotransmitters; others, by exerting an influence on the release of other neurotransmitters operate as neuromodulators; it has been suggested, for example, that opiates may act by inhibiting acetylcholine release from enteric neurons. Furthermore, it is now widely believed that the intrinsic nervous system not only orchestrates responses to local physiological stimuli such as low-grade gut distention as seen in the peristaltic sequence, but also generates spontaneously and autonomously complex contractile patterns such as the migrating motor complex [8].

As the primacy of the enteric nervous system in the generation and integration of gut motor function has been increasingly recognized, so has that of the classical autonomic nerves receded. It is now clear for instance, that efferent neurons from both autonomic outflows terminate primarily not on smooth muscle cells, but on cells of the enteric ganglia; the final common pathways for excitation and inhibition being those cholinergic and non-cholinergic non-adrenergic neurons, respectively, which originate in the enteric nervous system [6]. It is also evident that the vagus is primarily a sensory nerve and that many afferent signals from the gut pass *via* the vagus through the CNS [9]. In the light of these new neuroanatomical and neurophysiological concepts, it would appear that the vagi and the sympathetic nerves should be viewed as further levels of control above the enteric nervous system capable of modifying enteric neural activity, the principal roles of the autonomic nerves being firstly to mediate the so-called long reflexes such as the intestino-intestinal or entero-gastric reflexes, and secondly to relay sensory information to higher centres [9].

The central nervous system provides the ultimate level of control. While many intestinal functions, including motor activity, can and do occur at a subconscious level, it is now evident that these functions can be modified by signals from the highest levels. Responding to input from the special senses and to somatosensory signals, output from the central nervous system can modify patterns of motor activity generated by the gut wall. Examples of CNS modulation of motor activity include those motility alterations induced by feeding and exposure to physical and emotional stress [8].



*Patterns of contractile activity*

Until recently our understanding of small intestinal motor function was based, in large part, on radiological observations of contractile activity [10]. Direct measurements of intestinal myoelectric or muscular activity were limited to either *in vitro* studies of isolated muscle strips or *in vivo* observations which focused on a short segment of the intestine. Intestinal motor activity was classified, therefore, in terms of the character of individual contractile events, i.e. whether peristaltic, segmenting or pendular, and was quantitated solely in terms of the total incidence of these waves.

With the advent of recording systems capable of monitoring contractile activity along the length of the gut, it became clear that patterns of contractile activity in the small intestine were organized on a more universal basis. Two basic concepts have evolved. First, along the length of the gut, motor activity during fasting and following food differ fundamentally, and second, in the fasted state, motor activity is highly organized into a distinct and cyclically recurring sequence of motor events, now known as the migrating motor complex.

While cyclic activity in the gut had been identified by Boldyreff at the beginning of this century [11], it did not become generally appreciated until the description of the migrating motor complex (in the dog) by Szurszewski in 1969 [12]. Similar patterns have since been recorded from several other species including man [13].

The migrating motor complex consists of three distinct phases of motor activity which occur

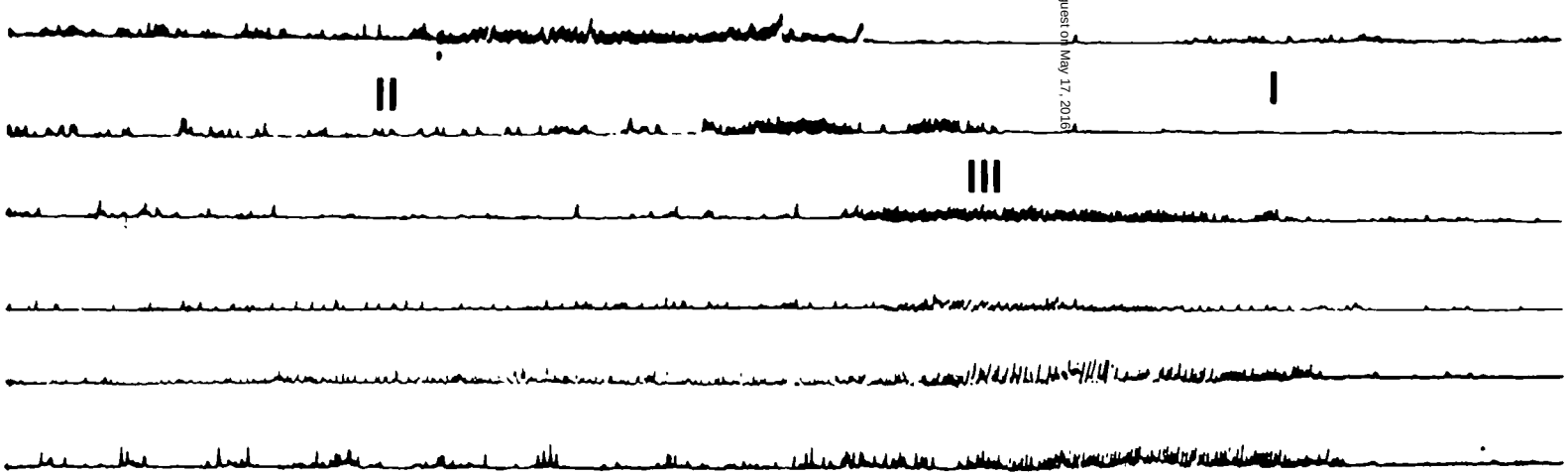


FIG. 3. The migrating motor complex. Recording of intraluminal pressure from the small intestine of a fasted human volunteer demonstrates the three characteristic phases: Phase I – quiescence, Phase II – irregular contractions, and Phase III – uninterrupted phasic contractions. Aboral propagation of Phase III is clearly evident.

in sequence and migrate slowly along the length of the small intestine [13]. Each sequence (Fig. 3) begins with a period of motor quiescence (Phase 1). This is followed by a period of apparently random and irregular contractions (Phase 2) and culminates in a burst of uninterrupted phasic contractions (Phase 3 or the activity front), the last being the most clearly recognizable component of the sequence. Individual cycles last between one and two hours in man and continue to recur as long as the subject remains fasted. In man, the majority of migrating motor complexes orginate in the proximal small intestine and migrate aborally, velocity of propagation slowing as the activity front progresses distally [14].

Following ingestion of food, this cyclical pattern is abolished and replaced by apparently random contractions – the so-called fed pattern [13]. This fed pattern may last from as little as 2.5 to over 8 h in man, at which time the fasted pattern resumes, assuming, of course, that no further meals are taken.

## SMALL INTESTINAL MOTILITY IN MAN – WHAT IS NORMAL?

Employing miniaturized radiotelemetry capsules, Wingate's group have performed several prolonged studies in human volunteers and have clearly shown that the migrating motor complex is not only a feature of intestinal motor activity in ambulant, active individuals who continue to eat and sleep in a relatively normal fashion, but also that they occur both by day and by night [15].

It has become clear and indeed worthy of particular emphasis, that the human migrating motor complex is subject to considerable inter-individual variation, both in terms of the relative duration of the various phases of the cycle and of the contractile events within these phases. Furthermore, intestinal motility is subject to considerable regional variations [14]. This variability is particularly evident in the distal intestine. In man [16], in contrast to the dog, [17], the migrating motor complex usually fades in the distal small intestine. Indeed, the dominant motor pattern during fasting in the distal small intestine of man is characterized by continuous random irregular contractions periodically punctuated by slowly-propagating clusters of phasic contractions and high amplitude rapidly-propagated contractions [16].

Motor function is also subject to major modification by many of the 'normal' variants of every-day life. Thus, the intensity of the contractile response following a meal is influenced by the nature of the meal ingested; the greater its caloric density [18] and fat content [19], the more intense the response (inclusion of fibre will prolong the duration of this response [20]). Recent studies have also revealed significant diurnal variations in motor patterns [21]. Furthermore, studies in normal volunteers have revealed quite dramatic changes in motility patterns following exposure to various physical and mental stresses [22, 23].

## MOTILITY AND GUT FUNCTION

The relationships between motor activity and other intestinal functions are highly complex, and to a large extent, poorly defined. Thus, for example, definition of the precise relationships between gut contractions and intestinal transit and absorption are complicated, in the first instance, by the considerable theoretical and conceptual problems in applying the laws of hydrodynamics to such an ever-changing environment as the intestine and, second, by the practical difficulty of making direct correlations beween changes in transit or absorption defined over a given length of intestine and motor events recorded at a particular point within that segment. The relationship between the various phases of the migrating motor complex and transit has been an area of considerable interest. As one would predict, the phase of intense contractions (Phase 3) is distinctly propulsive [24]. However, it is now appreciated that Phase 2

includes discrete bursts of contractions which propagate rapidly through short segments of the intestine and are intensely propulsive [25]. Furthermore, transit is fastest in the fed state when, of course, no migrating motor complexes occur [24].

Motor patterns also regulate the rate of entry of food into and exit of chyme from the small intestine. At the proximal end, antro-pyloro-duodenal motor coordination serves to ensure delivery of solid food particles to the duodenum in a size small enough to permit optimum digestion and also to minimize reflux of potentially irritant duodenal contents into the stomach [26]. At the distal end of the small intestine distinctive terminal ileal contractile patterns combine with fluctuations in tone at the ileocaecal sphincter to promote the special absorptive functions of this region and also to clear the small intestine of refluxed colonic bacteria [16, 17].

Phases of motor activity are also closely related to intestinal secretions – peaks of gastric acid output, duodenal bile acid content and trypsin secretion being noted in relation to Phase 3 activity in the duodenum [27]. Gallbladder contractions [28] and phasic activity at the sphincter of Oddi [29] also synchronize with duodenal Phase 3, thus ensuring that bile will flow into the small intestine at a time when intense phasic contractions are propelling chyme into this area.

## SMALL INTESTINAL MOTOR ACTIVITY IN DISEASE

Inter-species, inter-individual and inter-regional variations in normal intestinal motor activity must be fully appreciated before ascribing pathophysiological importance to a given motor event in a symptomatic patient. Many disorders where abnormalities in motor function are clearly of fundamental pathogenetic importance have now been well characterized, and an even greater number of 'functional' disorders, long thought to have a motility basis, are being investigated.



### PROBLEMS AFTER SURGERY

#### *Vagotomy*

The state after vagotomy is characterized by a failure of food administration to interrupt cyclic migrating motor complex activity [30], which may predispose to the dumping syndrome, and also by an acceleration of small intestinal transit [31]. By resulting in an increase in the postprandial bile acid and osmotic loads entering the colon, the latter abnormality may contribute to the pathogenesis of diarrhoea after vagotomy.

#### *Roux-en-Y syndrome*

Creation of a Roux-en-Y gastrojejunostomy results in isolation of the Roux limb from the duodenal pacemaker [32]. As a consequence, the Roux limb is electrically asynchronous with the stomach and distal small bowel and acts, in effect, as a functional obstruction, thus explaining the frequent occurrence of symptoms such as abdominal pain, nausea and vomiting in such patients.

#### *Short bowel syndrome*

Remington and colleagues found that in comparison to normal subjects, both the duration and frequency of migrating motor complexes were increased in patients who had undergone extensive small intestinal resections [33]. They postulated that this increased frequency of cyclic activity might contribute to the occurrence of nocturnal diarrhoea in these patients.

## AUTONOMIC NEUROPATHY

Loss of gastrointestinal autonomic control appears to uncouple the coordination and integration of gastric and intestinal motor events. Thus, a combination of an inappropriate antral response to feeding and disorganized fasting small intestinal motility appears to be common to all forms of intestinal denervation [34, 35].

## INTESTINAL PSEUDO-OBSTRUCTION

A clinical classification of intestinal pseudo-obstruction is outlined in Table 1. Discussion of the various forms of acute ileus is beyond the scope of this review, which will concentrate, instead, on the various forms of chronic intestinal pseudo-obstruction.

The clinical features of this disorder tend to be similar regardless of whether the pseudo-obstruction is a manifestation of a systemic disorder, (secondary pseudo-obstruction) or a primary disorder of the intestinal musculature or its neural apparatus (primary chronic intestinal pseudo-obstruction) [36]. These unfortunate patients present with repeated episodes of suspected mechanical obstruction and are often subjected to more than one diagnostic laparotomy before the correct diagnosis is established. Other features of intestinal pseudo-obstruction include weight loss, diarrhea, constipation, and steatorrhea. Fat malabsorption is due, in large part, to bacterial colonization of stagnant bowel loops. Abdominal radiographs reveal marked dilatation of small intestinal loops and a variable degree of colonic distention. While

TABLE 1. *Intestinal pseudo-obstruction*

| |
|---|
| *Acute intestinal pseudo-obstruction* (acute ileus) |
| May affect small intestine or colon (Ogilvie's syndrome) or both. Most commonly encountered following abdominal and especially, intestinal, surgery but may also complicate pneumonia, pancreatitis, cholecystitis and myocardial infarction. Occasionally occurs in the absence of an identifiable cause. |
| *Chronic intestinal pseudo-obstruction* |
| Primary |
| Visceral neuropathy |
| Visceral myopathy |
| Unclassified |
| Secondary |
| Scleroderma |
| Systemic lupus erythematosus |
| Dermatomyositis |
| Jejunal diverticulosis |
| Myotonic dystrophy |
| Duchenne's muscular dystrophy |
| Autonomic neuropathy (including diabetes) |
| Hypothyroidism |
| Hypoparathyroidism |
| Sclerosing mesenteritis |
| Coeliac disease |
| Radiation enteritis |
| Porphyria |
| Jejuno-ileal bypass |
| Drugs (phenothiazines, tricyclics, vincristine, anti-Parkinsonian drugs, narcotic analgesics, ganglionic blockers) |

these patients certainly demonstrate abnormal motor patterns, none of these patterns appears to be highly specific [37, 38]. Similar abnormalities have been observed both with mechanical obstruction due, for example, to Crohn's disease [37] and in patients with functional dyspepsia and the irritable bowel syndrome [39]. At this stage, therefore, it would appear prudent not to rely solely on intestinal motility studies either to diagnose this condition or to delineate the various types of pseudo-obstruction.

*Chronic idiopathic intestinal pseudo-obstruction*

Careful pathological examination of appropriately stained full-thickness specimens will usually permit definition of the primary abnormality either as a visceral neuropathy or a myopathy. Thus, neuron-specific silver staining will demonstrate patchy but definite abnormalities in the myenteric plexus in cases of visceral neuropathy. Characteristic neuropathological changes include neuronal swelling and axonal fragmentation [36]. Motility recordings in such patients demonstrate chaotic hyperactive contractions similar to the abnormalities observed in patients with systemic autonomic neuropathy.

Histological examination of intestine from patients with a visceral myopathy will, on the other hand, reveal vacuolar degeneration and fibrosis of one or both of the smooth muscle layers [36]. Their intestinal manometric tracings are characterized either by a marked reduction in or complete absence of contractile activity. Several variants of this syndrome have been described. While the occurrence of many cases of visceral myopathy appears to be quite sporadic, in certain instances phenotypic expression is based on autosomal inheritance. The autosomal dominant variant (hereditary hollow visceral myopathy) is highly variable in presentation [36]. The principal abnormality is gross dilatation of the first, second and mid-portion of the third part of the duodenum in association with normal gastric and small bowel function (the idiopathic megaduodenum syndrome). However, it is now recognized that these patients may have more diffuse visceral abnormalities as illustrated by a high incidence of oesophageal aperistalsis, redundancy of the colon and megacystis. The autosomal recessive variant is marked by a more diffuse abnormality of smooth muscle as evidenced by gastric atony, dilatation of the entire small intestine and multiple jejunal diverticula [40].

Many other patients present with the classical features of intestinal pseudo-obstruction yet do not exhibit pathological abnormalities of intestinal smooth muscle or myenteric neurons. It is possible that these patients have an undefined abnormality of smooth muscle or neuronal function at a molecular level.

*Secondary chronic intestinal pseudo-obstruction*

Of the numerous conditions that may present with this syndrome (Table 1), progressive systemic sclerosis is by far the most prevalent. While these patients often present in a manner indistinguishable from idiopathic pseudo-obstruction, the diagnosis may be suggested by the presence of associated Raynaud's phenomenon and skin changes. Radiological examination will demonstrate dilatation and hypomotility of the oesophagus, stomach, small intestine and colon. Additional radiological features may include oesophageal stricture, jejunal diverticula and sacculation and close-spacing of the valvulae conniventes in the small intestine. The colon may be elongated and show loss of haustrae and sacculation. Pneumotoides cystoides intestinalis is sometimes observed [36].

The prognosis of scleroderma patients is strikingly different from those with chronic intestinal pseudo-obstruction. Schuffler found that the average survival in patients with progressive systemic sclerosis from the time of onset of obstructive symptoms was five to six years. In

contrast, patients with a primary visceral myopathy lived between nine and 50 years after diagnosis [36].

## STUDIES OF INTESTINAL MOTOR ACTIVITY IN FUNCTIONAL GASTROINTESTINAL DISEASE

Textbooks of medicine and gastroenterology describe various functional disorders as reflecting disordered intestinal motility. Thus, for example, patients with the so-called irritable bowel syndrome are frequently referred to as suffering from a 'spastic' colon, despite the lack of any objective evidence that these patients have spasm of any part of the colon. In the search perhaps for 'spasm', elsewhere, patients with various 'functional' intestinal complaints are nowadays increasingly subjected to oesophageal, gastric and small intestinal motility studies.

### *Functional dyspepsia*

In a large study involving 104 patients with unexplained nausea, vomiting and upper abdominal pain, the Mayo Clinic group found that 75 per cent exhibited abnormal upper gastrointestinal motility [39]. They also observed that, while formal psychiatric evaluation frequently uncovered abnormalities in those with normal motility, diabetes and neurological diseases were disproportionately frequent amongst those with motor abnormalities, suggesting that the latter group had an underlying disorder of the intestinal neuromuscular apparatus. It should be emphasized, however, that some of these abnormal patterns were similar to those observed in other studies in patients with intestinal pseudo-obstruction [37] and systemic autonomic neuropathy [35] and in apparently normal human adults [14].

### *The irritable bowel syndrome*

All gastroenterologists wait with bated breath for 'the' diagnostic test for the irritable bowel syndrome. While this still seems some distance away, evidence accumulates to suggest that this syndrome is a disorder of intestinal motility and that the primary abnormality may be in the small intestine, rather than in the colon. Thus, patients with irritable bowel exhibit abnormal patterns of small intestinal motility, both under basal conditions [41] and in response to stress [42]. Furthermore, the occurrence of these aberrant patterns was often closely related to the development of typical symptoms [41, 42]. While these interesting observations do not, of course, prove that abnormal motility is the cause of this perplexing disorder, they have, at the very least, uncovered some measurable and apparently reproducible abnormalities. Whether symptoms and abnormal motor patterns can be suppressed in parallel by pharmacological manipulation remains to be determined.

## SUMMARY

The study of small intestinal motor activity has certainly emerged from relative obscurity to a position where it may indeed become an important clinical tool. Modern technology has led to a considerable increase in our understanding of the physiology of motor function and has brought us to a stage where small intestinal motility is amenable to study in man. It is clear that coordinated motor function of the small intestine is central to integrated digestive function. Normal patterns, and in particular normal variants, are still being defined, and both the investigator and the clinician need to be particularly aware of interspecies, intersubject and

interregional variations. While in some instances, abnormal motility is clearly related to an underlying disorder of intestinal neuromuscular function, in others, and in particular in functional gastrointestinal disorders, the overall experience of intestinal motility recordings in man is still too limited to allow us to declare with confidence whether reported abnormalities are, indeed, truly aberrant patterns or whether they are causally related to a given patient's symptoms.

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