Leading article

The tunnel at the end of the light

While it is only human to prefer the known to the unknown, the proliferation of scientific meetings and publications devoted to colonic epithelial inflammation and neoplasia should not be used as a screen to hide our ignorance of what happens within the colonic lumen. The truth is that physiologists have not yet been able to define the synergy of mucosal and motor function that effects the transformation of enteric residue into faeces, nor the systems that control these functions. Against this background, it is hardly surprising that current therapy for the apparently troubled colon consists, for the most part, of an armamentarium of placebos that work only because doctor and patient alike share beliefs in their efficacy. The fact known only too well to gastroenterologists and family practitioners alike is that the clinical load due to colonic dysfunction is far greater than that due to mucosal disease. For example, using unsatisfactory defecation (too often, too rarely, too soft, too hard . . .) as one marker of colonic dysfunction, and making the reasonable assumption that 10% of the adult population suffer from this problem, we arrive at a total of four million sufferers in the UK. That most will resign themselves to self-medication and only a relatively small proportion will confront gastroenterologists with their problems is no cause for complacency, as it probably only reflects the fact that professional advice founded on ignorance is often ineffective.

Why don't we know more about the colon? Has a social education that inculcates a healthy distaste for excrement discouraged research-minded gastroenterologists from dabbling in the distal murk? Unlikely, since professional training is designed to counter lay prejudice; comparison with the flourishing science of urodynamics suggests that what is wrong with research into colonic function is that it has not increased our understanding of how the colon works. Certainly the colon is not an easy organ to study. The fact that material entering the colon may, in health, remain there from a few hours up to a few days¹ poses peculiar difficulties. Even so, progress seems unduly slow; if, in operational terms, the colon may be regarded as a black box, for scientists it seems to be no more than a black hole into which scientific endeavour seems to disappear leaving no trace. Why should this be? Have we been asking the right questions?

In the past, a considerable volume of research on both the motor and transport functions of the colon seems to have been based on the assumption that the colon is a homogeneous organ. For example, in man, the absorptive properties of colonic mucosa have been studied using total perfusion techniques,² even though evidence of marked regional variation in colonic transmural electric potential difference may be presumed to reflect regional differences in sodium transport.³ This raises questions over

agents that are said to alter colonic mucosal transport; is it safe to assume that dihydroxy bile acids are cathartic in all parts of the colon,⁴ or that they selectively affect different areas? Likewise, studies of muscle activity in the rectosigmoid region have been assumed as representative of overall colonic motor function,⁵ even though this region shows no evidence of the retrograde motor activity which must exist somewhere within the colon to balance caudad propulsion if material is to be retained for significant periods of time.

In the past, assumptions of functional homogeneity have not been challenged because of the obvious problems of studying regional function in the human colon. Two papers in this issue show that by using human tissue *in vitro*, the study of regional function in the human colon can be achieved. Both have relied on tissue obtained from patients undergoing elective surgery. Interestingly, both studies were carried out by British workers on temporary postdoctoral assignments in North American units with considerable experience in the study of the colon; perhaps there is still much to be said for the transatlantic experience.

Sandle and his colleagues⁶ have carried out flux studies on specimens of human ascending and descending colon. Their results demonstrate an important difference in the mode of cation transport between the two regions. Sodium transport in the descending colon appears, from observations of short circuit current, to be solely an electrogenic process, whereas in the ascending colon, although electrogenic transport exists, the primary driving force for sodium may be electroneutral. In contrast, cation transport in the descending colon is wholly electrogenic, but this electrogenic component may include a potassium as well as a sodium transport system. If this is a giant step forward for colonic physiologists, it may also seem to be rather a small step forward for gastroenterologists, but it is a crucial step. The idea that the pathophysiology of colonic disorders may depend crucially upon the site of the mucosal lesion is new. But perhaps more important is the direction indicated for the further study of mucosal function. The ability to harvest biopsy material in health and disease from known sites using the colonoscope offers the physiologist the opportunity to investigate regional variation in depth. The Yale group used the Ussing chamber technique for their studies; this technique as conventionally used demands greater quantities of tissue than are provided by perendoscopic biopsy, but as neurophysiologists have repeatedly shown, and as is evidenced by the current vogue for patch clamping, laboratory techniques for tissue study can be miniaturised. Even using existing techniques, biochemical study of enzyme and peptide function and also of subcellular systems is possible on biopsy material.

The study of Gill and his associates,⁸ provides evidence that the length-stress and length-frequency relations of human colonic smooth muscle show marked regional variation. Muscle obtained from the right colon was more distensible than that from the left, consistent with the proposed functions of accommodation, bacterial fermentation and absorption. Further distinction between right and left colonic muscle was evidenced by the aborally-oriented gradient in contractile frequency of the circular muscle layer.

It would seem no more than obvious that colonic motor activity should be explained in terms of patterns of contraction, so why complicate matters

by studying electrical activity? The answer is not that scientists wish to obfuscate matters, but simply that colonic pressure studies have proved, by and large, disappointing; 'normal' patterns of contraction do not appear to be reproducible.⁷ The trouble is that electromyography to date has failed to reveal the expected patterns governing muscle contraction. The conceptual model of myoelectric activity in the gastrointestinal tract is based on the idea that smooth muscle cells are electrically coupled and depolarise synchronously and rhythmically, thereby giving rise to a regular electrical change – the slow wave – that can be detected by large volume electrodes placed on the serosa. According to this model, contraction is determined by the occurrence of action potentials whose timing is precisely determined by the regularity of depolarisation⁹; many workers have symbolised this functional relationship by using the alternative terminology of 'electrical control activity' and 'electrical response activity' to describe slow waves and spike bursts.¹⁰ This model has proved highly effective in unravelling the motor patterns of the stomach and small bowel, but remarkably unsuccessful when applied to the colon; indeed, for much of the time, electrical slow waves cannot be detected using *in vivo* recording methods.^{11 12}

The reasons for this lack of progress are now becoming clear. Even though studies on the isolated feline colon had suggested a functional organisation in some ways resembling the small bowel,¹³ recent work has shown that the model derived from proximal small bowel motor activity is inappropriate. Smooth muscle in the human duodenum, for example, exhibits a slow wave frequency which is virtually fixed at 12 cpm; the only deviations from this that have been observed are in thyroid disorders where the metabolic rate of muscle is altered.¹⁴ Recent studies^{15–17} on human colonic smooth muscle *in vitro* have, in contrast, shown slow electrical oscillations varying between 4 and 28 cpm in circular muscle, and 20 to 36 cpm in longitudinal muscle. Bearing in mind that electromyographic electrodes used *in vivo* derive their signal from all muscle layers, it is small wonder that the interpretation of such data is difficult.

For students of the human colon, the recent data are somewhat daunting. Because of species heterogeneity,¹⁸ extrapolations from data obtained on other species may be unreliable; moreover, it now appears that the methods used hitherto to study function, and muscle function in particular, may be all but useless. Given the anxiety of clinicians to understand how the colon works, we seem to have reached an impasse – 'Those behind cried "Forward!"', while those in front cried "Back!"' – but not quite. First, the use of techniques for prolonged monitoring^{19 20} offers some hope that, as in the small bowel,²¹ clinically relevant data may be obtained; even if electromyographic data are 'noisy', long periods of recording can reveal significant trends. Secondly, collaboration between surgeons and scientists, as the recent studies show, allows *in vitro* study of specific areas of the colon; similar studies on colonic nerves are also feasible.²² And finally, there is the colonoscope. Its value as a diagnostic and therapeutic weapon has been proved beyond doubt, but what remains to be fully exploited is its potential for placing probes and sensors at precise locations in the colon, and retrieving tissue for systematic study.

What is beyond doubt is the potential benefit to be gained from shedding light on the mysteries of the colon. Colonic dysfunction is not lethal, and is

probably responsible for misery that falls short of disability. If the alleviation of this vast mass of minor ailments did no more than allow patients to live in greater comfort and enable physicians to direct their skills to more important illnesses, it would still be worth the effort that is clearly required.

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