

The autonomic nervous system and gastrointestinal disorders

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The enteric nervous system (ENS) constitutes the most complex part of the peripheral nervous system. It has been described as the 'brain of the gut', because ENS neurons can function independently of the central nervous system (CNS) to control motility, exocrine and endocrine secretion, and microcirculation in the gastrointestinal tract (GIT) (Gershon et al. 1994; Furness and Bornstein 1995). The ENS also regulates the local response to immune and inflammatory processes (Lundgren et al. 1989). The CNS, however, maintains an important role in coordinating the diverse functions of enteric neurons via sympathetic and parasympathetic motor and sensory pathways.

Disorders of the ENS may result in motor, secretor, inflammatory or immune dysfunction of the GIT. Loss of enteric neurons is characterized by abnormal motility causing disturbed transit and sphincter control; secretor responses in the GIT may also be suppressed, although a secretor deficiency often remains clinically unrecognized. Pathological activation of motor and secretomotor enteric reflexes (e.g., by toxins or inflammation) generally presents as secretor diarrhoea, in the absence of morphological abnormalities of the ENS.

DEVELOPMENT OF THE ENS

The ENS is derived from neural crest cells that migrate and colonize the intestinal wall during em-

bryogenesis. Neuroblasts are first detected in the proximal foregut of the human embryo on gestational day 24. Three different regions of the neural crest (vagal, truncal and sacral) contribute to the precursor cells which differentiate into intestinal neuroblasts or Schwann cells; they also give rise to neuroblasts which colonize distinct GIT regions (Hoar and Monie 1981). Progenitors of vagal origin colonize the entire GIT and reach the terminal hindgut, while cells originating from the truncal and sacral regions migrate to the rostral foregut and to the postumbilical bowel, respectively (Gershon 1997). Hindgut ganglia receive an additional contribution from cells of the sacral segment of the neural crest. These cells are most numerous in the distal colon, where they represent as much as 17% of the ENS (Burns and Douarin 1998). The precursors for the intestinal nervous plexus migrate individually or in small clusters and intermingle with mesenchymal cells of the intestinal wall. They redistribute in Auerbach's and Meissner's plexuses when the muscular layers of the gut start to differentiate.

Several genes are involved in the migration and development of neuroblasts (Table 1). The *Ret* proto-oncogene codes for a tyrosine kinase receptor involved in the development of enteric ganglia (Takahashi et al. 1985). During embryogenesis *Ret* mRNA and protein are expressed widely in the central, peripheral and enteric nervous systems. *Ret* is also expressed outside the nervous system, on the

TABLE 1
Genes involved in the development of the enteric nervous system.

Gene	Locus	Effect of gene deficiency on the enteric nervous system
<i>Ret</i>	10q11.2	absence of plexuses in small and large bowel
GDNF	5p13	absence of plexuses in small and large bowel
Endothelin 3	20q13.2–q13.3	aganglionosis of the distal colon
Endothelin receptor B	13q22	aganglionosis of the distal colon
<i>Mash1</i>	12q22–q23	aganglionosis of the rostral foregut and absence of serotonergic neurons

growing tips of renal collecting tubules. In humans, mutations of this gene may be found in Hirschsprung's disease, in MEN2a and MEN2b syndromes, and in medullary and papillary thyroid carcinoma (Mulligan et al. 1994; Romeo et al. 1994). In the latter cancer syndromes, *Ret* mutations activate receptor phosphorylation (Mak and Ponder 1996). However, in Hirschsprung's disease, mutations inactivate tyrosine kinase, the ligand binding domain, or the membrane transport of the receptor (Edery et al. 1994). There is no correlation between *Ret* gene mutation and the topography and severity of aganglionosis (Attie et al. 1995); this indicates that either an unknown gene influences the clinical phenotype or that receptor activity is subject to other factors.

Glial cell line derived neurotrophic factor (GDNF) is a functional ligand of *Ret* (Jing et al. 1996) and a member of the growth factor- β superfamily (Lin et al. 1993). It is potent in stimulating growth and recovery of dopaminergic neurons, and it is also active on central cholinergic neurons and motor neurons in the spinal cord and facial nerve (Henderson et al. 1994). A defect of the GDNF gene results in the absence of kidneys and in severe deficiency of GIT innervation (Sanchez et al. 1996). GDNF acts on specific receptors of the GDNF family receptor $\alpha 1$. It is believed that the formation of the signalling receptor complex implies the binding of a GDNF–GDNF family receptor $\alpha 1$ complex to a *Ret* dimer.

The interstitial cells of Cajal are not neurons; they act as pacemakers and are responsible for the spontaneous, rhythmic, excitatory activity of smooth muscles in the GIT. These cells also modulate communication between the nerve and the muscle. The *Kit* gene is involved in the develop-

ment of interstitial cells (Huizinga et al. 1995); abnormal intestinal motility, due to lack of interstitial cells, has been observed in mice with mutations in the *Kit* gene (Maeda et al. 1992).

Endothelin-3 and endothelin receptor B genes also play a role in the migration and development of the ENS (Lahav et al. 1998). *Endothelin-3* is a 21-amino acid peptide that determines smooth muscle contraction (Chakder and Rattan 1999). Endothelin receptor B is expressed in the brain, kidney, lung, heart and endothelium, and it is also found in the human colon – in the myenteric plexus, the mucosal layer, the ganglia and the blood vessels of the submucosa (Inagaki et al. 1991). Mutations of the *endothelin-3* gene cause aganglionic megacolon (Baynash et al. 1994). A similar phenotype results from disruption of the gene encoding for the endothelin-B receptor (Puffenberger et al. 1994).

Glutamate, acting on *N*-methyl-D-aspartate receptors, promotes neuronal migration, differentiation and plasticity, and controls neuronal survival in the developing nervous system (Ikonomidou et al. 1999). Regulation of nerve growth is also mediated by inositol 1,4,5-trisphosphate receptors. The inhibition of these receptors prevents neurite extension, while microinjections of heparin, a competitive receptor blocker, induce neurite retraction (Takei et al. 1998).

ORGANIZATION OF THE ENS

See also Part I, Chapter 1.

Anatomy

The ENS is composed of nerve cell bodies and their processes embedded in the gut wall. In humans,

the number of enteric neurons is estimated to be 10–100 million cells (Furness and Costa 1980). Nerve cell bodies are grouped in the enteric ganglia, which form two main ganglionated plexuses: Auerbach's myenteric plexus and Meissner's submucous plexus.

Myenteric and submucous plexuses

The myenteric plexus lies between the longitudinal and circular layers of the muscularis externa to form a continuous network around the circumference of the GIT, from the upper oesophagus to the internal anal sphincter (Fig. 1A). The submucous plexus of ganglia predominates in the small and large intestines.

Myenteric ganglia, usually 1–4 nerve cells thick, are connected to each other by small bundles of nerve fibres, the internodal strands. The meshwork formed by the ganglia and the internodal strands is the primary component of the myenteric plexus. Nerve strands joining with the primary plexus and running circumferentially constitute the secondary component of the plexus. The myenteric plexus is connected to the submucosal plexus and the mucosal plexus by nerve fibre bundles running through the circular muscle. These penetrating fibres arise from the ganglia, from strands of the primary plexus or from secondary strands, to run almost directly through the circular layer (Furness et al. 1990). Their main targets are the muscularis externa, which receives most of its innervation from the myenteric plexus, the submucous ganglia, and other myenteric nerve cells. Myenteric nerve cells also provide nerve fibres to the mucosa; many of them are constituted by sensory nerve endings, and nerve fibres that project to sympathetic prevertebral ganglia.

Numerous small ganglia are found in the submucosa of the small and large intestine. Submucous ganglia are smaller and less regularly arranged than myenteric ganglia. Most secretomotor neurons have their cell bodies in the submucous plexus; some of them project to the myenteric plexus (Kirchgeßner and Gershon 1988), while others supply the muscularis mucosae of the small and large intestines. Enteric vasodilator neurons also have cell bodies in submucous ganglia. The stomach almost entirely lacks submucous ganglia; therefore, the intrinsic innervation of the mucosa and muscularis mucosae derives from the myenteric plexus.

Non-ganglionated plexuses

Other, non-ganglionated, plexuses supply GIT layers (Fig. 1B). These are the longitudinal muscle plexus, the circular muscle plexus, the plexus of the muscularis mucosae, and the mucosal plexus. In addition, perivascular plexuses are found around arteries and arterioles in the gut wall (Furness and Bornstein 1995).

Ganglia of biliary system and pancreas

The biliary system and the pancreas arise from a diverticulum of the small intestine, and the ganglia located in their walls are part of the ENS. Ganglia are present in the gall bladder, in the cystic duct, and in the common bile duct (Kirchgeßner and Gershon 1990); numerous nerve fibres are found in the muscle, around blood vessels, and in the mucosa of the biliary tract. Pancreatic ganglia are connected to each other by small nerve bundles and are scattered to form a 3-dimensional plexus around the acini, the blood vessels, and the islets. In the gall bladder, intrinsic neurons control motility, water and electrolyte exchange; in the pancreas, they control endocrine and exocrine components.

Microscopic structure

Nerve cells of the enteric ganglia can be classified by their shape. Dogiel (1899) proposed that shapes of nerve cells be related to their function and defined types I, II, and III. Most neurons are Dogiel type I or type II, although a variety of other shapes can be found. Type II neurons have more than one axon, while the other types are uniaxonal.

The ganglia are composed by compactly arranged nerve cell bodies, by nerve fibre terminals, by bundles of nerve fibres, by glial cells and by their processes (Gabella 1994). Unlike other autonomic ganglia, they do not contain blood vessels or connective tissue cells, although septa of connective tissue cross the ganglia. Nutrients are supplied via the surrounding interstitial fluid. Hormones or drugs act on the enteric ganglia by the same route; cell bodies of enteric neurons often present large surface areas not covered by glia and exposed to the extraganglionic space (Pompolo and Furness 1990).

Nerve fibres are of two types: fibres of relatively

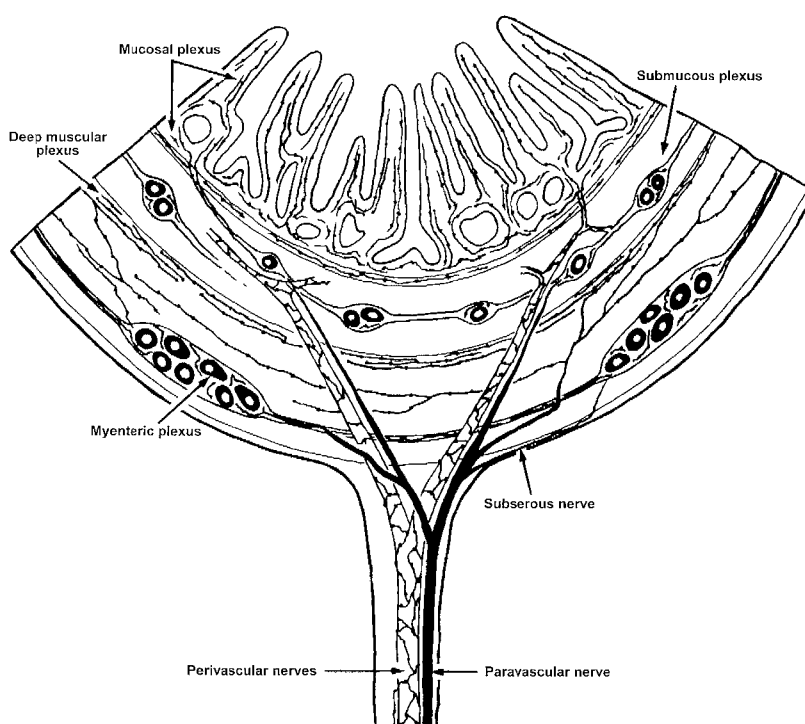
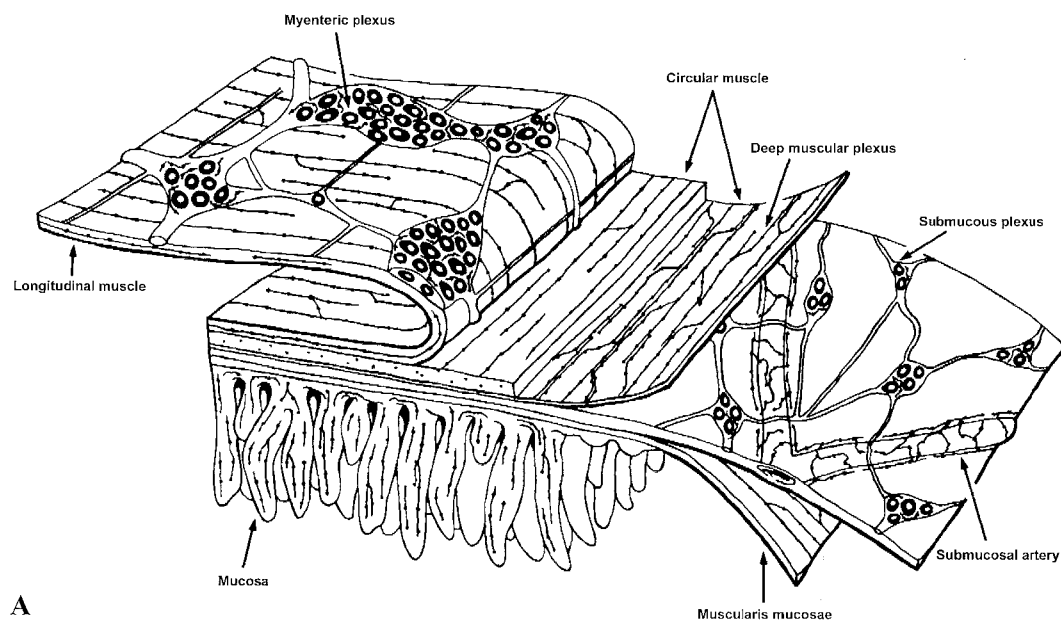


Fig. 1. Organisation of the myenteric and submucous plexuses (A) and of non-ganglionated plexuses (B). (Modified from Furness and Costa 1980.)

uniform diameter (0.2–0.5 μm) and others consisting of varicosities (1–2 μm in diameter), connected by short intervaricose segments 0.2–0.5 μm thick. Varicosities, which are considered the site of transmitter release, are present on the terminal part of the axons, which may vary greatly in length up to a few mm. A single axon may impinge upon several neurons. Close contacts with nerve cells or dendrites are of two types: synaptic specialization, consisting of presynaptic vesicles in close contact with the cell, without postsynaptic densities, and contacts with non-specific vesicles and postsynaptic densities.

Noradrenergic axons in the myenteric plexus have a distinctive ultrastructure, not shared by axons of other chemical classes, and contain numerous flattened vesicles.

Nerve fibres that innervate the muscle and epithelium are contained in bundles where individual fibres are partially surrounded by enteric glial cells (Gabella 1994). There is no clear postjunctional specialization, but varicosities make close contacts with muscle cells and have prejunctional specialization. Such close contacts have not been observed in the mucosal epithelium.

Biochemistry and neurotransmitters

See also Part I, Chapter 3. Acetylcholine (ACh) is the major transmitter for excitation at neuroneuronal synapses in the ENS. It is also a transmitter for excitatory motor neurons to intestinal muscles and for secretomotor neurons. The other autonomic transmitter, noradrenaline, is located in sympathetic nerves that supply the GIT from extrinsic ganglia. Other transmitters are found in the ENS, and many

other transmitter candidates have been recently identified (Table 2).

Purines such as adenosine triphosphate (ATP), amino acids such as γ -aminobutyric acid (GABA), and peptides such as vasoactive intestinal polypeptide (VIP) act as neurotransmitters in the ENS. More recent is the identification of a role for nitric oxide (NO; Goyal and Hirano 1996). Each one of these substances may be found in different neurons performing different functions (Furness and Bornstein 1995).

ENS neurons may contain more than one neurotransmitter (Morris and Gibbins 1992). Different substances may be co-released from a nerve, only one of them having the primary role in transmission (Furness et al. 1992). The relative contribution of co-transmitters may vary, depending on the location and the activity of a neuron. Neurons may contain more than one primary transmitter and several co-transmitters or neuromodulators.

Functional organisation

Intrapancreatic neurons of the ENS encompass motor neurons, enteric interneurons and intrinsic enteric sensory neurons (Fig. 2). Sympathetic and parasympathetic neurons innervate also the GIT.

Motor neurons

Excitatory motor neurons innervate the longitudinal and circular muscles and the muscularis mucosae of the GIT. Their primary transmitter is ACh, which acts on muscarinic receptors located on muscles. Tachykinins, substance P, neurokinin A, neuropeptide K, and neuropeptide Y are also released from excitatory motor neurons (Brookes et al.

TABLE 2
Neurotransmitters in the enteric nervous system.

Amines	Acetylcholine, norepinephrine, serotonin
Amino acids	γ -aminobutyric acid
Purines	adenosine triphosphate
Gases	nitric oxide, carbon monoxide
Peptides	calcitonin gene related peptide, cholecystokinin, galanin, gastrin-releasing peptide, neuromedin U, neuropeptide Y, neurotensin, opioids (dynorphin, enkephalins, endorphins), peptide YY, pituitary adenyl cyclase activating peptide, somatostatin, substance P, thyrotropin releasing hormone, vasoactive intestinal polypeptide

Modified from Goyal and Hirano 1996.

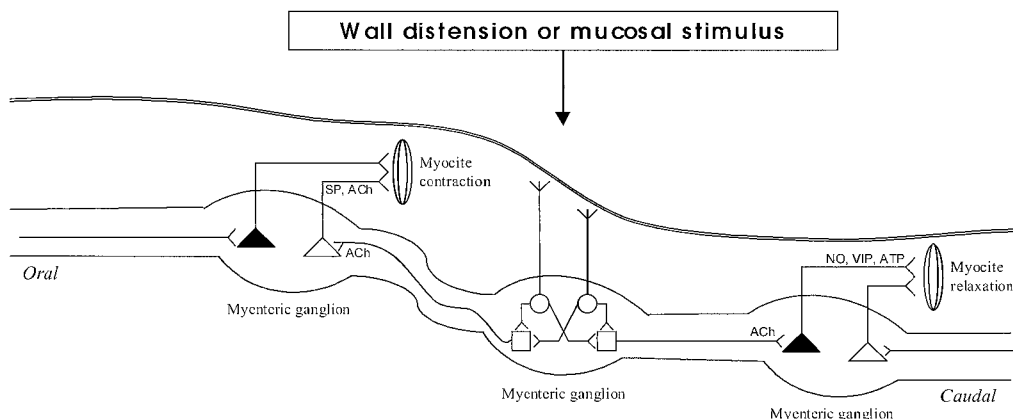


Fig. 2. The reflex of peristalsis is schematically illustrated. Three identical ganglia are represented with simplified connections. Wall distension or a mucosal stimulus (e.g., chemical) activates afferent intrinsic neurons (circular perikarya) that stimulate cholinergic interneurons (squared perikarya). The latter ascend orally, to stimulate excitatory motor neurons (hatched triangular perikarya) to induce muscle contraction (mediated by substance P and ACh), and descend caudally to stimulate inhibitory motor neurons (filled triangular perikarya) to induce muscle relaxation (mediated by NO, VIP and ATP). Abbreviations: hatched symbols = excitatory neurons; filled symbols = inhibitory neurons.

1991). They contribute to the excitation of the longitudinal and circular muscles.

Inhibitory motor neurons relax muscles and are involved in reflexes that facilitate the passage of food along the GIT. Inhibitory neurons release a combination of at least three transmitters (NO, ATP and VIP). In most neurons, NO is the primary transmitter, and the roles of VIP and ATP are variable. VIP and NO synthase, a marker for NO, are co-localized in inhibitory motor neurons (Costa et al. 1992). Inhibitors of NO synthase reduce inhibitory transmission, indicating that the enzyme marks the presence of NO as an inhibitory transmitter (Sanders and Ward 1992).

ATP also relaxes smooth muscles. Levels of ATP metabolites increase in perfusates when inhibitory neurons are active. The activity of ATP containing inhibitory neurons is depressed by suramin, that antagonizes ATP action on P_2 receptors on the intestinal muscle (Hoyle et al. 1990).

It is believed that VIP also contributes to inhibitory transmission in some GIT muscles. Other members of the VIP family, which are encoded by the same gene, peptide histidine methionine and pituitary adenyl cyclase activating peptide, also relax intestinal muscles and are found in enteric neurons. They may contribute to enteric inhibitory transmission.

Secretor neurons

The mucosa of the small and large bowel is supplied by cholinergic and non-cholinergic secretor neurons that adjust water and electrolyte secretion (Fig. 3). ACh released from cholinergic neurons acts on muscarinic receptors located on the epithelium. VIP is the putative primary transmitter of non-cholinergic secretor neurons (Ito et al. 1988); administration of VIP provokes a dramatic mucous discharge abolished by tetrodotoxin. Cholinergic secretor neurons control gastric acid secretion; they stimulate parietal cells through muscarinic receptors. In a porcine model, it has been found that GABA containing neurons are involved in the control of secretor processes, rather than of peristalsis (Timmermans and Scheuermann 1998).

NO controls intestinal fluid and electrolyte secretion (Mourad et al. 1999). Endogenous NO is a pro-absorptive molecule and NO synthase inhibitors reverse fluid absorption to secretion. In resting conditions, NO controls absorption by maintaining microvascular perfusion of villi and activates neurotransmission in the ENS. In some pathological conditions, NO may be synthesized at a higher rate to evoke secretion by direct action on epithelial cells, or through cyclooxygenase and serotonin (5-hydroxytryptamine – 5-HT) dependent pathways. Under these conditions, NO may induce free radi-

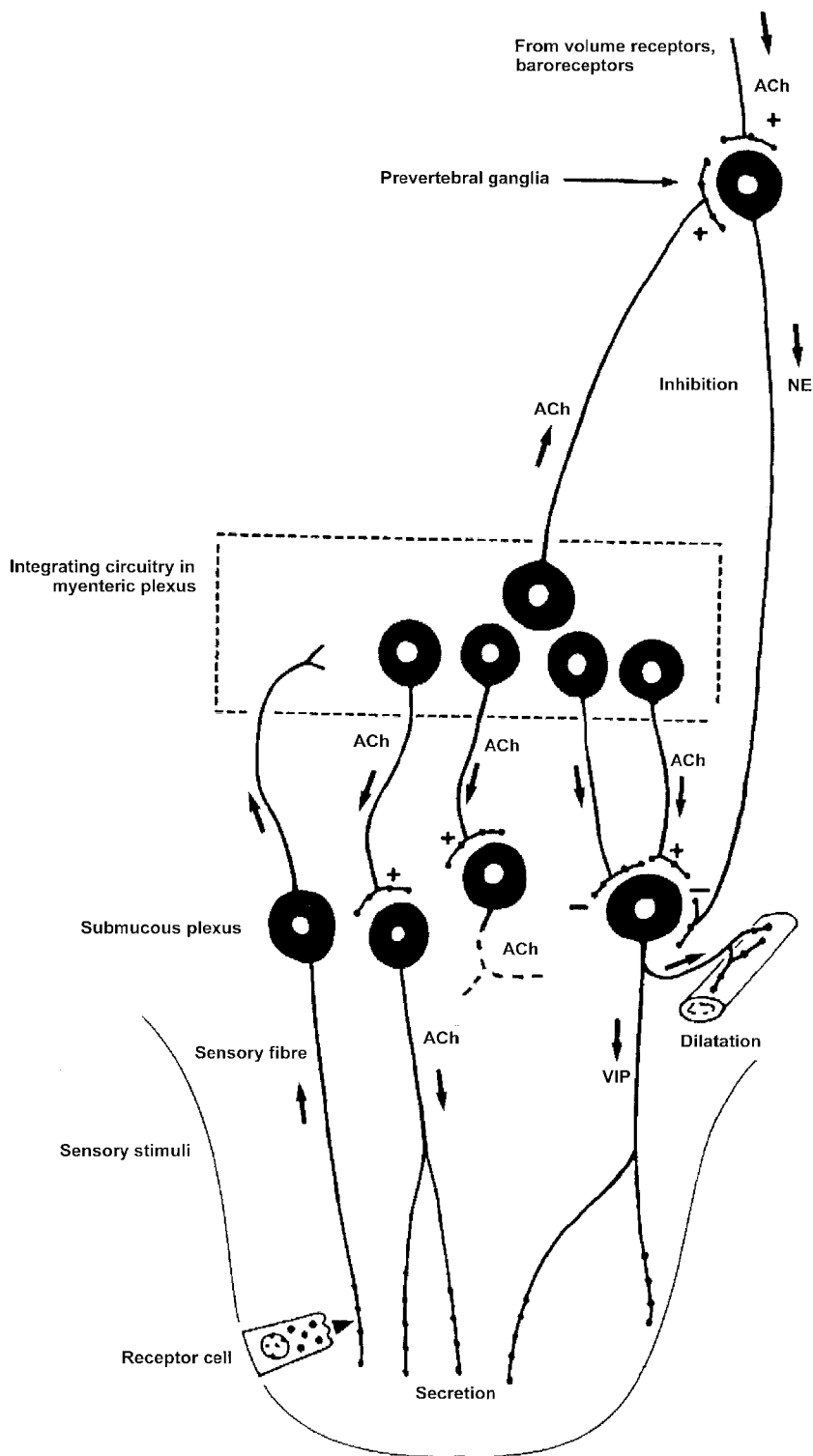


Fig. 3. Enteric pathways for secretomotor control. (Modified from Furness and Bornstein 1995.)

cal formation and stabilize enterochromaffin cells, mast cells, and intestinal motility. The laxative action of several intestinal secretagogues (including bisacodyl, magnesium sulfate, bile salts, senna and cascara) is exerted through their action on NO (Izzo et al. 1998).

Vasodilator neurons

Enteric vasodilator neurons are present in the small and large intestines and in the stomach. Local vasodilator reflexes can be elicited by mechanical or chemical irritation of the mucosa. Stimulation of cholinergic and non-cholinergic vasodilator neurons, whose cell bodies are located in the submucous plexus, changes the diameter of submucous blood vessels mediated by cholinergic and non-cholinergic neurons (Galligan et al. 1990). If the vagus nerve is stimulated, acid secretion and blood flow are enhanced; these effects are reduced by muscarinic antagonists. Secretion-independent increase of blood flow is antagonized by atropine.

Neurons to endocrine cells

The GIT mucosa which contains a variety of endocrine cells is densely innervated, and most cells have nerve fibres in their proximity. With the notable exception of gastrin cells, little information is available on the neural control of enteric endocrine cells. The secretion of gastrin is controlled by the vagus and by intrinsic pathways. Neurons in both pathways are located in the stomach wall, and utilize gastrin releasing peptide (Makhlouf et al. 1989).

Interneurons and intrinsic neurons

Cholinergic interneurons are involved in the motility and control of secretion. 5-HT is the transmitter for interneurons located along descending pathways in the small intestine and it is also present in interneurons reaching the sphincter of Oddi, where it stimulates 5-HT₃ and 5-HT_{1P} receptors (Hillsley and Mawe 1998).

Intrinsic reflex pathways involved in the control of movement, blood flow, and secretion are activated by neurons that are sensitive to several stimuli (distension, endoluminal chemicals, mechanical stimulation of the mucosa). Intrinsic sensory neurons have their cell bodies in the myenteric

and submucous plexus. Sensory neurons located in the myenteric plexus probably use substance P as a transmitter; those located in the submucous plexus are probably cholinergic. The distribution of substance P and of neurokinin-1 receptors has been recently outlined in the gastric antrum and in the duodenum by immunocytochemistry. Neurokinin receptors are present on myenteric and submucous neurons; in the submucous plexus neurokinin-immunoreactive neurons are surrounded by substance P containing terminals (Smith et al. 1998). Substance P probably acts upon neurokinin-1 receptors, that are coupled by a G-protein to the inositol phosphate signal-transduction pathway (Otsuka and Yoshioka 1993). L-754-030, a trisubstituted morpholine acetal, is a potent and selective non-peptide neurokinin receptor antagonist, which prevents delayed cisplatin induced emesis (Navari et al. 1999).

The GIT also contains extrinsic sensory neurons, that have their perikarya in the dorsal root ganglia or in the sensory ganglia and are constituent of the parasympathetic system.

Sympathetic neurons

Sympathetic pathways to the GIT affect blood supply, motility, water and electrolyte secretion. Sympathetic neurons that supply the splanchnic vasculature are noradrenergic; they constrict the arterioles, the arteries and the major mesenteric veins. Their role is primarily to adjust the yield of cardiac output to digestive organs. Sympathetic neurons inhibit GIT motility by constricting the sphincters and by inhibiting the general contractile activity of the gut. Inhibition of non-sphincteric muscles is exerted by means of a presynaptic action on the myenteric plexus.

Parasympathetic neurons

A variety of central effects, including relaxation of the proximal stomach, enhancement of gastric peristalsis, secretion of acid, and promotion of gastrin secretion, are mediated by the vagus. Vagal neurons do not act directly, but form synaptic connections with neurons whose cell bodies are in the intrinsic ganglia of the GIT. Vagal input neurons are involved in complex circuits which integrate various enteric reflexes with signals deriving from the CNS and from other parts of the GIT; this

transmission is mainly mediated by ACh acting on nicotinic receptors. The effects of vagal stimulation are blocked or reduced by anti-nicotinic drugs.

The primary action of the pelvic nerves is to change GIT motility, secretion, and blood flow in the distal colon and rectum. This corresponds to the action exerted by the vagus on the proximal GIT. Pelvic neurons, whose cell bodies are located in the sacral spinal cord, form excitatory cholinergic synapses on enteric neurons containing nicotinic receptors.

Physiological features of enteric neurons

Enteric neurons can be classified physiologically into afterpotential hyperpolarizing and synaptic neurons (Hirst and McKirdy 1974). Afterpotential hyperpolarizing neurons have the morphology of type II neurons, they display large action potentials (75–110 mV), which are normally followed by two separate phases of hyperpolarization. The first phase has a shape similar to the hyperpolarization curve of most CNS neurons; it results from the activation of a voltage-sensitive K^+ channel. The second phase lasts for 4–25 s and is associated with the opening of a Ca-sensitive K^+ channel. Synaptic neurons have smaller action potentials followed by a rapid hyperpolarization that is blocked by tetrodotoxin. In response to electrical stimulation of internodal strands, synaptic neurons exhibit prominent fast excitatory postsynaptic potentials (EPSP), mediated by nicotinic receptors. EPSP are blocked or markedly reduced by hexamethonium and tubocurarine. As a rule, afterpotential hyperpolarizing neurons do not exhibit fast EPSP in response to electrical stimulation, but may occasionally display fast EPSP of small amplitude. The large multiaxonal type II neurons, located in the myenteric and submucous plexuses, are afterpotential hyperpolarizing neurons. All the other neurons, which are uniaxonal with various cell morphologies, are synaptic neurons. In the submucous plexus, but not in the myenteric plexus, synaptic neurons all have a similar shape (Bornstein et al. 1986). Afterpotential hyperpolarizing and synaptic neurons can be found in the GIT also outside the myenteric and the submucous plexuses. They are located in small ganglia associated with branches of the parasympathetic nerves, where they enter the oesophagus, the stomach, and the large

bowel. Afterpotential hyperpolarizing neurons and synaptic neurons have similar physiological features. Neurons in the gall bladder wall are also similar to synaptic neurons (Mawe 1992).

Sensory neurons are afterpotential hyperpolarizing type II neurons; secretomotor neurons are synaptic-like uniaxonal neurons and possess a variety of synaptic inputs. Both types of secretomotor neurons produce fast EPSP; non-cholinergic synaptic neurons also produce inhibitory and slow excitatory potentials.

The principal forms of synaptic transmission in ENS are cholinergic fast excitatory inputs to neurons located in the submucous plexus. Slow EPSP and inhibitory postsynaptic potentials (IPSP) are also observed in GIT ganglia. Slow EPSP usually last between 15 and 120 s and are seen in at least 75% of synaptic-like uniaxonal neurons and 40% of afterpotential hyperpolarizing type II neurons.

In the myenteric plexus, slow EPSP are the result of several superimposed responses, each one producing a similar synaptic potential. In the submucous plexus, the vast majority of neurons exhibit fast EPSP, and a large proportion of them also exhibit slow EPSP, similar to those observed in myenteric neurons. Fast EPSP are presumably mediated by ACh, acting through nicotinic receptors. Slow EPSP in the submucous plexus are probably elicited by the combined action of different neurotransmitters, just as in the myenteric plexus. IPSP are commonly observed in submucous neurons, but not in the myenteric plexus following a stimulation of the internodal strand. Neurons displaying such activity are thought to be non-cholinergic secretomotor neurons containing VIP (Bornstein et al. 1988).

Presynaptic inhibition is the mechanism by which sympathetic nerves diminish the contractile activity of the gut. Sympathetic nerve stimulation reduces the amplitude of fast EPSP in GIT neurons, decreasing the release of ACh (Edwards et al. 1976). This also reduces presynaptic ACh action to stimulate further the release of ACh and of other transmitters mediating slow EPSP (Morita et al. 1982). Several other enteric neurotransmitters (dynorphin, enkephalin, GABA, 5-HT) may reduce transmitter release in the GIT, but no physiological role has been established for any of these substances.

Control of GIT motility

Smooth muscles and the interstitial cells of Cajal

The main function of smooth muscles in the GIT is to mix and to propel the intraluminal content and so allow an efficient food digestion, a progressive absorption of nutrients and the evacuation of residues. These functions depend on the intrinsic electrical and mechanical properties of GIT smooth muscles and are regulated by the ENS and by sympathetic and parasympathetic influences. Smooth muscles have an endogenous rhythmic activity corresponding to regular oscillations of their membrane potential (Sanders and Publicover 1989). These are called slow waves.

Interstitial cells of Cajal are non-neural cells, which act as local pacemakers to generate the rhythmic activity of intestinal muscles, particularly in the circular muscle layer throughout the GIT. Motor neurons control the musculature indirectly through their action on Cajal's cells, which are innervated by the myenteric plexus in the stomach and in the small intestine and by the sub-muscular plexus in the colon (Der-Silaphet et al. 1998). The interstitial cells of Cajal are lost in

Hirschsprung's disease and in infantile pyloric stenosis (Vanderwinden et al. 1996a,b); this deficiency contributes to the motor abnormalities associated with such diseases. In inflammatory bowel diseases, Cajal's cells are morphologically altered in the colon; their functional impairment contributes to the motor abnormalities associated with chronic inflammation (Lu et al. 1997).

Muscle activity is regulated by intrinsic and extrinsic neurons (namely ENS neurons, sympathetic and parasympathetic nerves), by hormones and autoacoids. These factors influence the occurrence and the characteristics of GIT motility.

Control by the ENS

The electrical and mechanical properties of smooth muscles are modulated by transmitters released from ENS neurons (Makhoulf 1995). Intrinsic sensory neurons are activated by mucosal stimuli. Intrinsic motor neurons regulate the local pattern of motility (Table 3) and generate the interdigestive migrating motor complex (MMC). This is the best organized contraction, which in humans lasts for about 90–120 min and is generated by the ENS (Furness and Bornstein 1995). MMC activity mi-

TABLE 3
Organized contractions of the gastrointestinal tract.

Site	Contraction	Purpose	Frequency
Oesophagus	primary wave	deliver food to stomach	quiet
	secondary wave	housekeeping of oesophagus	irregular
	tertiary wave	housekeeping of oesophagus	irregular
Stomach	fundic tone	accommodate food, deliver liquid to duodenum	constant
	antral peristalsis	shearing of food, delivery of solids to duodenum	every 100 min
Small bowel	phasic contraction	basic unit of contraction	2/h
	MMC	interdigestive housekeeper	every 100 min
	migrating cluster contraction	postprandial propulsion	5–10/h
	giant migrating contraction	housekeeping of distal small bowel	irregular
	retrograde giant contraction	deliver bolus to antrum for vomiting	irregular
Large bowel	phasic contraction	mixing of lumen content	2–13/min
	short duration	slow anterograde and retrograde propulsion	0.5–2/min
	long duration	rapid anterograde propulsion	1/h
	organized contraction		2–4/day
	propagating MMC		
	non-propagating, MMC-like		
	giant migrating contraction		

Modified from Zenilman 1993.

grates caudally from the gastric antrum throughout most of the small bowel with an approximate speed of 6–8 cm/min. Four MMC patterns are recognized. In phase I there are no muscular contractions and slow waves pacesetter potentials persist. Phase II is characterised by irregularly spaced, clustered contractions, with increased frequency. Phase III has the peak frequency of contractions, that characterise each slow wave. In phase IV, contractions decrease in frequency and return to phase I.

The motility of the intestine is the result of contractions and relaxation of the external longitudinal and circular muscles and of the muscularis mucosae (Table 4). The pattern of mixing and propulsive movements is principally determined by the circular component of the external muscle. In isolated segments of the intestine, distention, chemical or mechanical stimulation of the mucosa elicit reflex depolarizing potentials in the circular muscle oral to the site of the stimulus and hyperpolarizing potentials caudally.

MMC elicited as a response to stimulation or to distention of the mucosa do not pass along the gut if the myenteric plexus is cut (Fig. 2); however, they persist following a lesion of the submucous plexus. MMC elicited by non-distending stimuli of the lumen disappear if the mucosa is removed, while those evoked by distention of the same site persist. Reflex activity excited by stimulation of the mucosa is relayed by a direct connection of the mucosa to the myenteric plexus. It is likely that separate sensory neurons mediate responses to stimulation or to distention of the mucosa, although no such evidence has been found anatomically (Smith et al. 1992).

Mucosal stimuli elicit MMC by activating afterpotential hyperpolarizing type II neurons of the submucous plexus, which contain substance P and ACh and have terminals in the mucosa and in the myenteric plexus. Afterpotential hyperpolarizing type II neurons of the myenteric plexus (also containing substance P and ACh), relay the reflex to the muscle layers. Myenteric afterpotential hyperpolarizing neurons are thought to receive inputs from the central, sympathetic and parasympathetic nervous systems. Slow synaptic potentials to myenteric afterpotential hyperpolarizing neurons provide a mechanism through which enteric reflexes can be augmented.

Enteric MMC often extend for several cm along the intestine from a single point stimulus, beyond the anatomical extension of sensory and motor neurons, which typically do not exceed 2 mm. This requires the involvement of interneurons. There is one population of orally directed interneurons and several populations of cholinergic, caudally directed interneurons (Costa et al. 1992). Ascending and descending interneurons are morphologically homogeneous, constitute a long chain, and have connections with motor neurons. When a small area of the mucosa is stimulated or when the intestine is distended locally, a segment of the myenteric plexus is activated by means of axons of the primary sensory neurons directed sagittally. Excitation is diffused from the stimulated region along ascending and descending pathways.

Sensory neurons located in dorsal root ganglia are activated by muscle stretch. Extrinsic neurons of the sympathetic and parasympathetic systems influence smooth muscles indirectly by acting on

TABLE 4
Main gastrointestinal reflexes.

Name	Stimulus	Effect	Purpose
Gastrocolic	feeding	increase in motility in the colon	rapid colonic emptying
Enterogastric and enteropyloric	intestinal stimulation	inhibition of gastric emptying and stimulation of pyloric motility	reduction of intragastric pressure
Intestino-intestinal	vigorous distention	inhibition of intestinal motility	protective function
Ileal brake	chemical stimuli	inhibition of duodenal and jejunal motility	protective function
Colocolonic	distension of the ileum distension of the colon	inhibition of the distal colon and vice versa	—

neurons of the myenteric plexus. Non-adrenergic neurons in prevertebral and paravertebral ganglia synapse with cholinergic and non-cholinergic neurons of the myenteric and submucous plexuses to inhibit their activity.

Hormonal and humoral control

As a rule, hormones influence smooth muscle activity during meals and in between meals. After ingestion of a meal several hormones are released. Cholecystokinin (CCK), released into circulation by the upper small intestine, induces a direct contraction of the gall bladder and a VIP mediated relaxation of the sphincter of Oddi. Motilin contributes to the regulation of smooth muscle activity between meals. In humans, the interdigestive MMC typically begins in the stomach and migrates caudally throughout the small intestine. Motilin peaks as MMC phase III starts in the stomach.

Humoral agents produced by non-neural cells in the muscle layers can influence smooth muscle activity. These include histamine, serotonin, adenosine and eicosanoids, such as prostaglandin, thromboxanes, and leukotrienes. Receptors for most of these agents have been identified on smooth muscle cells in the gut (Table 5). The influence of these agents is thought to be most pronounced when the smooth muscle is inflamed or hypersensitized by parasitic antigens (Vermillion et al. 1988). The cells from which they are released lie in proximity to muscle cells to myenteric neurons and to their ter-

minals. These agents can act directly on muscle cells and indirectly by stimulating or inhibiting the release of neurotransmitters.

Enteric secretomotor control

The density of innervation in the intestinal mucosa suggests that enteric neurons of the submucous plexus control water and electrolyte exchange. Sensory neurons have their perikaryon in the submucous ganglia and nerve endings in the mucosa. Secretomotor neurons may produce vasodilatation, concomitant with secretion, through collateral to submucous arterioles (Bornstein and Furness 1988). They are cholinergic and non-cholinergic; the latter mediate most local reflex responses.

Secretomotor reflexes are normally triggered by a chemical or a mechanical stimulus in the lumen. Intraluminal toxins are a well recognized trigger. In the small intestine, an important physiological stimulus is the active uptake of nutrients; this reflex is inhibited by sympathetic neurons that are tonically active. Cutting sympathetic pathways releases the enteric secretomotor reflex and results in paralytic secretion (Hasler 1995). The activity of sympathetic secretomotor inhibitory neurons responds to variations of whole-body water content and electrolyte status; sympathetic activity increases while water and electrolyte secretion are reduced in response to haemorrhagic hypotension, unloading of the baroreceptors, or a decrease of pressure in the right atrial pressure (Furness and Bornstein 1995).

Digestive neural reflexes

Vagal input is required to maintain the fed motor pattern. The vagovagal reflex controls moment-to-moment motor adjustments for optimal digestive function in the upper GIT. The afferent and the efferent branches of this reflex are contained in the vagus nerves (Fig. 4).

The dorsal vagal complex has extensive connections with the forebrain and the brainstem. Sensory information delivered to the nucleus tractus solitarius and to the area postrema is relayed rostrally to centres which feed back to the dorsal vagal complex.

A variety of chemical neurotransmitters are contained in the dorsal vagal complex. Glutamate and

TABLE 5

Humoral regulation of smooth muscle function.

Substance	Receptor	Site	Effect
Serotonin	5-HT ₂	stomach and small bowel	contraction
	5-HT ₄	stomach and small bowel	relaxation
Histamine	H1	stomach and small bowel	contraction
	H2	stomach and small bowel	relaxation
Adenosine	A1	small bowel	contraction
	A2	small bowel	relaxation
Peptidoleukotrienes	two receptors	stomach	contraction

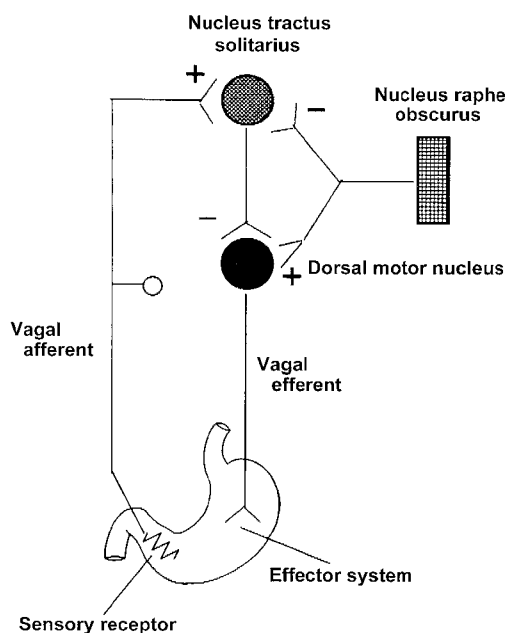


Fig. 4. Vagovagal reflex circuits. Abbreviations: + = excitatory synapses; - = inhibitory synapses. (Modified from Wood 1995.)

GABA (the former excitatory, the latter inhibitory) are contained in the dorsal vagal complex (Gillis et al. 1989); ACh is located in dorsal vagal neu-

rons, while serotonin and a variety of neuropeptides are contained in terminals.

Sympathetic inhibitory reflexes decrease motility and inhibit fluid secretion. They are initiated at one point in the GIT, pass to another gut segment and feed back via the prevertebral ganglia. Two reflexes crossing the sympathetic ganglia have been recognized: one reaches the spinal cord and the other is peripheral; they can only be studied when the central pathways have been experimentally inactivated. A diagram of the peripheral enteroenteric reflex pathways and their associations with other sympathetic pathways is shown in Fig. 5.

INTERACTION BETWEEN THE ENS AND THE CNS

The ENS can function independently of the CNS, but the latter coordinates its diverse functions. The ENS is connected to the CNS autonomic network by motor and sensory pathways of the sympathetic and the parasympathetic nervous system. The hierarchy of digestive neural reflexes is shown in Fig. 6.

The brain-gut axis includes structures of the nervous system with their signalling devices and the effector systems involved in determining the moment-to-moment behaviour of functionally specialized regions in the GIT.

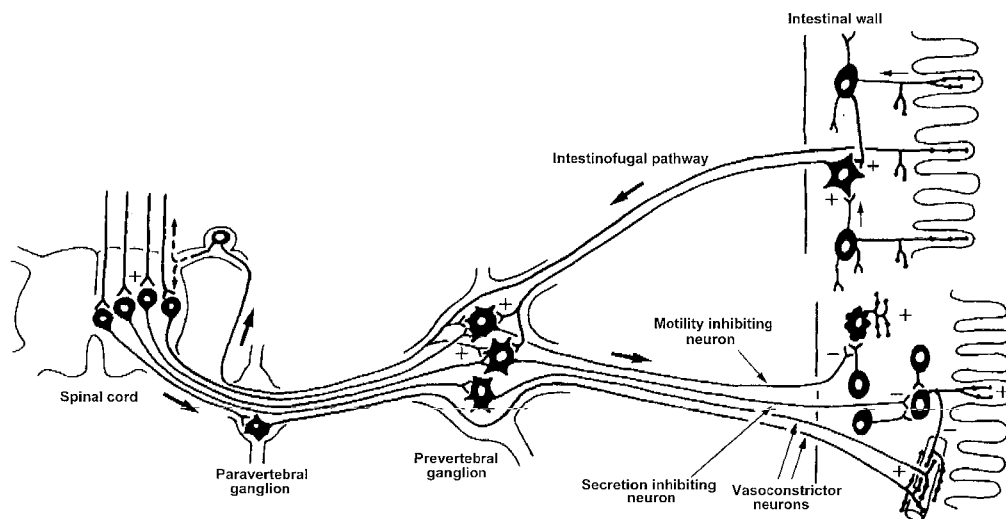


Fig. 5. Schematic view of sympathetic pathways that regulate the enteroenteric inhibitory reflexes. Sympathetic pathways affect intestinal motility, fluid exchange and blood flow. Intestino-fugal neurons have cell bodies in the intestinal wall and are probably directly sensitive to stimuli and indirectly activated by other enteric neurons. (Modified from Furness and Bornstein 1995.)

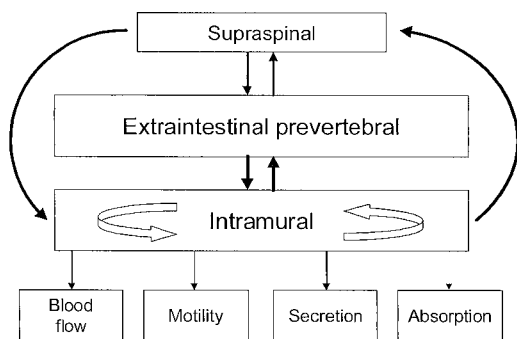


Fig. 6. Hierarchy of digestive neural reflexes.

Organization of the brain–gut axis

Autonomic brain centres control the pattern of alimentary behaviour associated with digestive and interdigestive states and other specialized GIT functions, such as retrograde peristalsis during emesis and the organized muscle activity during defaecation. Brain–gut integration includes sensory, endocrine, and neuroimmune communication (Fig. 6).

Dedicated pathways relay information between the brain and the ENS. The vagus is a mixed nerve containing afferent fibres that provide information to integrative centres in the medullary region of the brain and efferent fibres that transmit information from the same regions. Afferent and efferent centres in the spinal cord are equivalent to the vagus in the brainstem. Efferent centres in the spinal cord receive descending commands from the brain which they relay via efferent fibres to the gut.

Brain regions responsible for autonomic integration exchange information with the ENS (Gillis et al. 1989). The frontal cortex, the bed nucleus of the stria terminalis, the paraventricular hypothalamic nucleus, and the central nucleus of the amygdala project to specialized centres in the medulla oblongata. These nuclei exchange information with limbic regions, where emotional and autonomic responses are integrated. The relationship between emotional states and GIT disorder is well established (Drossman 1995). Emotional stress can result in conditions such as diarrhoea, pain due to irritable bowel syndrome, or gastric ulcer.

Vagus nerve

Sensory afferent fibres comprise most axons (>90%) in the vagus nerves. Their cell bodies are found in the nodose ganglia near the base of the skull on either side of the neck. Nodose ganglion cells give rise to a bifurcated process projecting rostrally to the brain and caudally to the gut and to other thoracic and abdominal organs. Upon entering the CNS, vagal afferent fibres synapse with second-order interneurons in the medulla oblongata (Leslie et al. 1992).

Vagal efferent fibres are less numerous than afferent fibres. The efferent fibres represent the cranial component of the parasympathetic division of the autonomic nervous system and convey commands that trigger activity in integrated units within the ENS. Sensory fibres in the vagus are not considered part of the autonomic nervous system (Wood 1995). Cell bodies of efferent vagal neurons are located in the dorsal motor nucleus of the vagus and in the nucleus ambiguus. The latter is composed of multipolar neurons that innervate the striated muscles of the larynx, the pharynx, and the oesophagus. The dorsal motor nucleus sends efferent fibres to the smooth muscles in the oesophagus, to the entire stomach, the small intestine, and the proximal colon. Most efferent fibres conveyed by the vagus nerves project to the oesophagus and to the stomach, a minority of them project to the small intestine and still fewer to the colon (Gillis et al. 1989).

Sympathetic spinal cord centres

Signals are transmitted from the CNS to the gut along descending spinal pathways to efferent centres in the thoracolumbar and sacral regions of the spinal cord. Centres in the sacral cord correspond to the so-called sacral component of the parasympathetic division of the autonomic nervous system. Efferent cell bodies are located in the intermediolateral cell columns and usually project to the large intestine via the second and third sacral ventral roots. As a rule, spinal sympathetic neurons suppress motor functions to maintain the bowel in a quiescent state; paralytic ileus may be a consequence of hyperactivity of these pathways.

To achieve defaecation, descending commands from the brain are transmitted to the sacral parasympathetic neurons, that initiate a motor program

in the colon. The ENS in the colon is responsible for coordinating contractions of the smooth muscles and of some striated pelvic floor muscles. Motor neurons located in the anterior column of the sacral spinal cord innervate, via the pudendal nerve, the striated anal sphincter and the pelvic floor musculature. Tonic discharges of these neurons cause contraction of the external anal sphincter and of pelvic floor musculature which maintain continence. Inhibition of their discharge is necessary for defaecation.

Cell bodies of spinal sensory neurons that innervate the gut are located in dorsal root ganglia, all along the spinal cord. Sensory fibres reach the gut along pathways common to mesenteric blood vessels and sympathetic postganglionic fibres. They transmit a variety of sensory information to the spinal cord and the brain. Sensory fibres that travel aside the sympathetic fibres of the periaarterial mesenteric nerves are not considered part of the autonomic nervous system.

Endocrine communication

Nervous function is directly influenced by several hormones released from GIT endocrine cells. Among them two hormones, pancreatic polypeptide and CCK, influence CNS functions. Circulating pancreatic polypeptide acts on the dorsal vagal complex, and suppresses efferent vagal signals that enhance pancreatic secretion as digestion progresses. This negative feedback mechanism controls neurally evoked pancreatic secretion; receptors for pancreatic polypeptide are present in the area postrema and in the dorsal vagal complex (Whitcomb et al. 1990).

CCK is another example of a brain-gut peptide released from enteric endocrine cells as part of the integrated response to a meal. Paracrine signalling occurs when the peptide acts on neural elements in the intestinal wall; endocrine signalling occurs when CCK is released in the blood to influence neural microcircuits in other organs such as the gall bladder. CCK-A receptors are present on sensory afferents that constitute the vagovagal reflex arc, particularly those that transmit mechanosensory and chemosensory information from the gastric and the upper intestinal mucosa. These receptors are synthesized in vagal sensory neurons of

the nodose ganglia and transported by axons to the terminal projections in the intestinal wall and in the nucleus tractus solitarius. CCK signalling contributes to the mechanisms of satiety and appetite suppression associated with food intake. This effect is abolished by lesions that interrupt vagal afferent fibres from the GIT to the CNS.

Neuroimmune communication

Detection and paracrine signalling are functional properties of the GIT mast cell population. Detection involves cross-linking antigens to specific antibodies attached to the surface of mast cells. Signalling involves antigen evoked release of chemical messages that are received and interpreted by the ENS (Wood 1991). Mast cells also have receptors for neurotransmitters and can be activated by neural input to release chemical mediators.

Mast cells in the GIT mucosa are strategically positioned in close contact with the lumen, where they are repeatedly exposed to a variety of stimuli, such as food antigens, pathogenic organisms, and enterotoxins. Mast cells recognize agents that threaten the homeostatic integrity of the host, alert the ENS and trigger an appropriate response (Wood 1993). Once activated, the ENS generates a stereotyped sequence of secretion and power propulsion in the affected bowel segment. This provokes the rapid clearance of material from the lumen, with the possible side-effect of producing lower abdominal malaise and diarrhoea. In addition, the autonomic nervous system may influence the ENS by way of the mast cells. This special brain-gut interaction may provide an explanation for the link between psychological variables and GIT irritable states.

MOTILITY DISORDERS IN GIT DISEASES

The five primary targets for the enteric nerves are smooth muscle cells (that are responsible for GIT motility), secretor cells in the mucosa, endocrine cells, the microvasculature (that maintains blood flow in the mucosa during intestinal secretion), and the immunomodulator and inflammatory cells of the gut (that are involved in immune, allergic and inflammatory responses in the mucosa). Disorders of the ENS may result in motor, secretor,

inflammatory or immune dysfunction of the GIT. Degeneration or deficiency of enteric neurons are primarily characterized by disturbed intestinal transit or by functional obstruction. Secretor responses may also be suppressed, but remain clinically unrecognized. Abnormal excitation of motor and secretomotor enteric reflexes (e.g., by toxins or inflammatory mediators) generally leads to secretor diarrhoea. Hyperexcitation of an axonal reflex involving intramural splanchnic primary afferent neurons may activate a reflex triggered by immune and inflammatory bowel diseases. Pain is a common symptom of visceral distension, occurring as a consequence of abnormal motility, rather than of spasmodic muscle contracture.

A primary role of the ENS is to control GIT motility. Deficiency of enteric neurons causes obstruction and lack of intestinal propulsion. Motility disorders involving the ENS can be classified according to the gut segment involved, but in most cases the motility dysfunction is generalized or involves more than one segment. Systemic diseases, congenital or acquired, account for the majority of cases observed in clinical practice.

Motility disorders of the oesophagus

Achalasia

Achalasia is characterized by a failure of the lower oesophageal sphincter to relax. It remains tonically contracted, which results in a functional obstruction of the oesophagus. The lower two-thirds of the oesophagus, which contain smooth muscle, are affected and no peristaltic contractions occur (Mittal and Balaban 1997). Achalasia may be due to a non-selective loss of all myenteric neurons or to a selective loss or dysfunction of inhibitory VIP-NO neurons located in the oesophageal myenteric plexus (Mearin et al. 1993; Goldblum et al. 1996). NO synthase is absent in the myenteric plexus and in the nerve fibres of the oesophagus, the cardia and the gastric fundus musculature (Lui et al. 1997). Oesophageal ganglion cells and neurons of the dorsal motor nucleus of the vagus are decreased in number, and wallerian degeneration of the vagus takes place (Goyal and Hirano 1996). The aetiology is not known. NO containing neurons are primarily involved, while cholinergic neurons may be spared.

An autoimmune reaction may occur as two-thirds of patients with achalasia have autoantibodies against DARPP-32, a dopamine carrier protein present on the cell surface in the myenteric plexus (Singaram et al. 1994).

The preserved cholinergic innervation to the lower oesophageal sphincter produces a high sphincter pressure that is a characteristic feature of this disorder (Gaumnitz et al. 1995). Local injections of botulinum toxin may block such unopposed cholinergic activity and may represent a remedy for patients with achalasia (Pasricha et al. 1995).

The manometric findings in achalasia include absent peristalsis in oesophageal body, incomplete lower oesophageal sphincter relaxation, elevated resting lower oesophageal sphincter pressure, and elevated intra-oesophageal pressure relative to intragastric pressures. Complete but short-lived relaxation may be seen in early stages. The degenerative neural damage of achalasia is not corrected by the symptomatic treatment. Peristalsis rarely recovers; therefore therapy is aimed at reducing lower oesophageal sphincter pressure by drug therapy, by forceful dilatation, or by surgical myotomy. The main goal is to overcome distal oesophagus obstruction by improving gravitational oesophageal emptying through a reduction of sphincter tone, while still maintaining an adequate barrier against gastro-oesophageal reflux.

Diseases that cause enteric neural dysfunction and result in secondary achalasia include paraneoplastic syndromes, Chagas' disease, and Parkinson's disease (PD). Herpes virus has a preferred tropism for the squamous epithelium lining the oesophagus; these infections have been reported with increased frequency in the myenteric plexus of patients with achalasia (Robertson et al. 1993).

Familial achalasia also occurs. The severity of clinical features may vary among family members. A positive association with the HLA allele DQw1 has been reported in the Caucasian population (relative risk 4.2) and in the African-American population (relative risk of 3.6). DRw53 is reduced among Caucasians (relative risk of 0.23; Wong et al. 1989).

Cricopharyngeal dysfunction

Cricopharyngeal dysfunction occurs when there is a difficulty in propelling liquid or solid food from the oropharynx into the upper oesophagus. The

cause is variable and includes abnormalities of the central and peripheral nervous systems, metabolic and inflammatory myopathy, gastro-oesophageal reflux, and other still undefined factors (Table 6).

The clinical presentation is remarkably constant (Orringer 1997). Patients complain of cervical dysphagia localized between the thyroid cartilage and the suprasternal notch, of a sense of constriction around the neck, and occasionally of radiating pain. Expectoration of saliva is common in patients who are unable to swallow the 1–1.5 l of saliva produced each day. Concomitant intermittent hoarseness and weight loss due to impaired caloric intake are also common. Gastro-oesophageal reflux occurs in 30–90% of patients with cricopharyngeal dysfunction. It is not clear whether refluxed gastric acid directly causes local irritation of the upper oesophageal sphincter or if distal oesophageal reflux produces loss of coordination of the pharyngo-oesophageal junction.

TABLE 6

Disorders associated with oropharyngeal dysphagia.

Neurological disorders	cerebrovascular accidents
	poliomyelitis
	amyotrophic lateral sclerosis
	Parkinson's disease
	multiple sclerosis
	spinocerebellar degeneration
	syringobulbia
	progressive bulbar paralysis
	Wilson's disease
	tabes dorsalis
	Sydenham's chorea
	Huntington's disease
	brainstem tumours
	cranial nerve injuries
Musculoskeletal diseases	peripheral neuropathies
	stiff man syndrome
	tetanus
	inflammatory myopathy
	muscular dystrophy
Local conditions	myasthenia gravis
	metabolic myopathy
	sarcoidosis
	systemic lupus erythematosus
	inflammatory diseases
	tumours
	congenital webs
	Plummer–Vinson syndrome
	extrinsic compression
	surgical resection of postsurgical changes

Barium oesophagogram may be normal, particularly in those with intermittent symptoms, or it may show hypertonus of the upper sphincter, a specific posterior cricopharyngeal bar (Dantas et al. 1990), or pharyngo-oesophageal Zencker's diverticulum. A complete oesophagogram may help to rule out other relevant oesophageal pathology (e.g., hiatal hernia with gastro-oesophageal reflux or a distal tumour). Oesophageal function analysis (manometry, pHmetry) shows lack of temporal co-ordination between pharyngeal contraction and cricopharyngeal relaxation, abnormalities of thoracic oesophageal peristalsis (in one-third of patients), and gastro-oesophageal reflux. The treatment must be individually targeted. Severe cervical dysphagia may be successfully treated with cervical oesophagomyotomy, which relieves symptoms in 65–85% of patients (Orringer 1980, 1997).

Abnormal relaxation of the upper oesophageal sphincter

Three forms have been described: incomplete relaxation, delayed relaxation and premature closure. Primary abnormal relaxation (the so-called cricopharyngeal achalasia) has been described occasionally in cases of CNS lymphoma or oculopharyngeal muscular dystrophy, after neck surgery or tracheotomy placement. Delayed relaxation is a clinical feature of familial dysautonomia, it is caused by autonomic dysfunction and is usually present from birth. Premature closure of the upper oesophageal sphincter leads to pharyngo-oesophageal Zencker's diverticulum (Cook et al. 1992).

Diffuse oesophageal spasm and related hypermotility disorders

Diffuse oesophageal spasm is a poorly understood hypermotility disorder where patients experience chest pain or dysphagia as a result of repetitive and simultaneous oesophageal contractions of high amplitude. The aetiology is unknown. A history of irritable bowel syndrome, pylorospasm, spastic colon, or other functional GIT complaints is common, suggesting an involvement of the ENS. Many patients with oesophageal spasm have an underlying psychiatric disorder.

Diffuse oesophageal spasm is characterized by intermittent spasms that are detected by oesophageal manometry. The manometric crite-

ria of primary oesophageal motility disorders are reported in Table 7. Antispasmodic drugs (such as anticholinergics, sometimes combined with a benzodiazepine) are occasionally helpful. Response to sublingual nitroglycerin is variable and sometimes dramatic. Calcium channel blockers (nifedipine, diltiazem) may also be of benefit. Oesophageal dilatation may relieve dysphagia and chest pain for several weeks to some months and can be repeated as required. Thoracic oesophagomyotomy has been performed in cases of unresponsive oesophageal spasm (Vantrappen and Hellemans 1980), but the results are less reliable than those observed in achalasia (Orringer 1997).

The 'nutcracker' oesophagus is characterized by prolonged (> 6 s) peristaltic contractions of high amplitude (225–430 mmHg). Similarly to diffuse oesophageal spasm the symptoms consist of chest pain, dysphagia, and odynophagia (Orringer 1997).

Dysmotility after oesophageal atresia repair

Follow-up of patients who have undergone repair of oesophageal atresia in infancy has documented long-term oesophageal manometric abnormalities that persist in adult life (Orringer et al. 1977). Contractions are weak or absent in the oesophagus body and the lower oesophageal sphincter is hypotensive. This motor abnormality is considered to be due to a failure of innervation during development rather than to surgical denervation (Orringer 1997).

Duodenogastric motility disorders

Transgenic and knockout rodent models have allowed the production of experimental replicas of human gut motility disorders. Knockout of NO synthase in mice brings about a GIT motility disorder that has been used as an experimental model of Hirschsprung's disease or pyloric hypertrophic stenosis (Huang et al. 1993). However, it should be pointed out that in this condition dysmotility diffusely involves the GIT. In addition, congenital or acquired motility disorders have been produced by targeting genes expressed in gut neural crest cells (Arbeit and Hirose 1999).

Neonatal hypertrophic pyloric stenosis

Infantile hypertrophic pyloric stenosis is a congenital disorder characterized by a functional gastric outlet obstruction. It is hereditary and occurs in 1/750 births. Pyloric obstruction is the result of a gradual hypertrophy of the circular smooth muscle of the pylorus. Although the myenteric neurons have a normal appearance, neurons that innervate the circular muscle layer of the pyloric sphincter lack NO synthase (Vanderwinden et al. 1992).

Gastric pacemaker dysfunction

Cyclic pacemaker activity originates on the greater curvature at the junction between the proximal and distal parts of the stomach. As in the heart, ectopic pacemakers may generate regular or disorganized electrical activity in other parts of the stomach that

TABLE 7
Manometric diagnostic criteria of oesophageal motility disorders.

Disorder	Criteria
Diffuse oesophageal spasm	simultaneous, non-peristaltic contractions repetitive, at least three peaks increased duration (> 6 s) spontaneous contraction intermittent normal peristalsis contractions may be of increased amplitude
Nutcracker oesophagus	mean peristaltic amplitude in distal oesophagus > 180 mmHg increased duration of contractions normal peristaltic sequences
Hypertensive lower oesophageal sphincter	lower oesophageal sphincter pressure > 45 mmHg but with normal relaxation normal oesophageal peristalsis
Vigorous achalasia	repetitive simultaneous contractions in body of the oesophagus partial or absent relaxation of the lower oesophageal sphincter

supersede the normal organized rhythm. Bradygastria develops when the normal dominant pacemaker fails and other sites in the gastric body generate rhythmic depolarization (Lin and Hasler 1995). The contractile efficiency of the stomach is reduced as a result of a decrease in the maximal number of antral contractions during fasting and after a meal. Tachygastria develops when a rival pacemaker, usually in the antrum, generates an oscillatory pattern at an abnormally high frequency (> 4 cycles/min); with tachygastria, the stomach is usually atonic. In some instances, the ectopic pacemaker activity may be highly variable, either in frequency or location, to produce a gastric slow wave arrhythmia.

The pathogenesis of gastric dysrhythmia is unknown. Gastric slow wave disturbances are antagonized by atropine, suggesting the involvement of a cholinergic pathway. Gastric dysrhythmia can be induced by a variety of substances, including progesterone, insulin, secretin, CCK, pentagastrin, glucagon and prostaglandin.

Non-ulcer dyspepsia

Non-ulcer dyspepsia is characterized by persistent or recurrent pain or discomfort characterized by postprandial fullness, early satiety, nausea, or upper abdominal bloating (Talley 1995). The majority of patients with chronic or recurrent dyspepsia do not have a peptic ulcer or any other recognized structural or biochemical abnormality (Fisher and Parkman 1998).

The pathophysiology remains poorly understood. Three main disease subtypes have been defined (Table 8), namely, ulcer-like, dysmotility-type and reflex-like dyspepsia. In dysmotility-like dyspepsia, 25–50% of patients have postprandial antral hypomotility and delayed gastric emptying (Malgelada et al. 1986). Antral pressure waves are de-

creased in frequency, amplitude or both. Occasionally, they are increased in number and decreased in amplitude. Abnormal pacemaker activity, such as tachygastria or tachyarrhythmia, also occurs in these patients. Gastric dysrhythmia generates weak or no contractions; activity may propagate orally rather than caudally, producing impaired transit.

The cause of motility disturbances in non-ulcer dyspepsia is unknown. A viral infection or a direct association with *Helicobacter pylori*, although strongly suspected, has not been established. Autonomic cardiovascular responses are usually normal. Whether the autonomic nervous system contributes is unclear.

Duodenogastric reflux

Abnormal alkalization of the foregut is responsible for many foregut complaints. Physiological duodenogastric reflux in normal subjects usually occurs early in the morning or postprandially and involves the late phase II of MMC. Phase III antral activity clears away the refluxate. Pathologic duodenogastric reflux is most commonly seen following gastric surgery (Perdikis et al. 1994), especially after distal gastrectomy and Billroth II reconstruction. Pathologic duodenogastric reflux has also been demonstrated in patients with an intact stomach (Perdikis et al. 1994; Civello et al. 1998). Antral hypomotility and poor duodenal phase III propagation are found in these patients and may play a role in the pathogenesis of primary duodenogastric reflux disease.

Postvagotomy dumping syndrome

The dumping syndrome occurs in up to 25% of patients after a surgical operation for peptic ulcer disease (Pappas 1997). This syndrome appears after meals and is characterized by tachycardia,

TABLE 8
Subtypes of non-ulcer dyspepsia.

Dyspepsia subtype	Symptomatology
Ulcer-like	pain often relieved by food or antacids, periodic or nocturnal pain, or pain before meals or when hungry
Dysmotility-like	nausea or vomiting, bloating and distention, anorexia or weight loss, pain aggravated by food or after meals and pain relieved by belching
Reflux-like	pain with heartburn or acid regurgitation
Unspecified	

hypotension, and abdominal pain. The cause is thought to be a loss of receptive relaxation in response to a gastric load. High-carbohydrate meals worsen symptoms. The hyperosmolar chyme dumped into the small intestine causes: (1) an activation of the distention reflex, leading to stimulation of motility; (2) the osmotic shift of fluid from the intravascular compartment to the gut, further aggravating the distention and contributing to relative hypovolaemia and to haemoconcentration; and (3) the release of vasoactive substances, such as VIP, bradykinin, 5-HT, substance P and neurotensin, that cause peripheral vasodilatation. Dietary treatment is usually effective. The long acting somatostatin analogue octreotide improves symptoms (Pappas 1997).

Vagotomy may also produce dysphagia or gastric atony. Dysphagia occurs in 1–4% of patients undergoing truncal vagotomy, primarily as a denervation injury of the distal oesophagus. Selective vagotomy is associated with a slightly higher (4–12%) incidence of dysphagia. Manometric studies demonstrate lack of lower oesophageal sphincter relaxation with swallowing and abnormal distal oesophageal peristalsis. Gastric atony is an uncommon condition, affecting 1–9% of patients after gastric surgery. The pathogenesis of postvagotomy gastric atony is obscure; abnormalities of antral peristalsis and fundic tone have been demonstrated.

Small intestine motility dysfunction

Paralytic ileus

Paralytic ileus is characterized by a lack of motor activity in the intestine. It is a common disorder observed in most patients following an abdominal operation. There are several theories on the pathophysiology of postsurgical ileus. (1) The activation of inhibitory spinal and inhibitory sympathetic reflexes, anaesthesia, humoral agents, and inflammation have been implicated (Livingstone and Passaro 1990). (2) Psychological factors or direct caecal manipulation may cause the release of corticotropin releasing factor in the paraventricular hypothalamic nucleus and in the dorsal vagal complex, stimulating the efferent inhibitory motor pathway (Taché and Monnikes 1993). (3) Increased production of NO, due to activation of the non-neuronal, inducible NO synthase, may produce

acute intestinal ileus; the involvement of VIP1/pituitary adenylyl cyclase activating peptide receptors in the pathogenesis of postoperative ileus has been documented (De Winter et al. 1998). (4) Inflammation may be a contributing factor.

A dense network of macrophages has been found in the intestinal muscularis mucosae. Endotoxin administered systemically may activate these leukocytes and produce paralytic ileus. Recent data support the hypothesis that abdominal surgery may initiate inflammatory events resulting in the common clinical phenomenon of post-surgical ileus (Kalff et al. 1998). Paralytic ileus may complicate the acute stage of high spinal cord injury (Mathias and Frankel 1999); the cause is unknown.

Jejunal diverticulosis

Altered small bowel motility may cause diverticula leading to bacterial overgrowth, malabsorption and steatorrhoea. That dysmotility is the cause of diverticula formation, and not vice versa is supported by the observation that the resection of the bowel segment containing diverticula fails to resolve symptoms of pseudo-obstruction. Manometry shows that all MMC phases are present in the small bowel; phase I is dominated by spasmotic contractions, which may be antegrade, simultaneous, or retrograde (Case Record Massachusetts General 1990).

Small bowel transplantation

The maintenance of normal intestinal motility is of particular importance after small bowel transplantation (Mousa et al. 1998). Animal models confirm that intrinsic nerves can be preserved and transplanted, while extrinsic nerves are severed from their targets (Taguchi et al. 1998). Complete section of extrinsic nerves is an inevitable consequence of transplantation, which may lead to poor functioning of the grafted gut. Reinnervation of the intestinal wall is appreciably limited even 1 year after transplantation. Besides, the ENS is damaged by the procedures of preservation and reperfusion of the small bowel (Gatti et al. 1998). There are no visible changes in nerves and ganglionic cells of the submucous and myenteric plexuses following hypothermic preservation at 4°C, after cold perfusion for 20 h; preservation at room temperature

causes major changes. After reperfusion, ENS damage is evident only when sufficient re-warming is allowed. Severe acute rejection causes evident changes in the myenteric plexus.

Interdigestive motor activity with normal manometric features occurs in 62% of the grafted small bowel in children, and may be recognized as early as 3 months post-transplantation. Discontinuation of the ENS at the level of the sutures between the host gut and the grafted gut disrupts the orderly propagation of MMC across the anastomosis. Abnormal post-meal motility is present in the majority of patients, and contributes to abnormal intestinal transit and mixing, leading to diarrhoea and malabsorption (Mousa et al. 1998).

NO neurons are markedly decreased soon after transplantation, but recover more rapidly than peptidergic neurons (Taguchi et al. 1998). NO neurons might play an important role in the adaptation process of the graft in the early period.

Motility dysfunction of large bowel and rectum

See also Bruyn et al. 1998.

Ogilvie's syndrome

Idiopathic intestinal pseudo-obstruction is characterized by signs of recurrent intestinal obstruction without any demonstrable mechanical occlusion of the bowel (Corman 1998). The condition is hereditary. Motor response to intestinal distention is reduced, but the duodenal and colonic slow waves may be normal. Koch et al. (1988) have found that Ogilvie's syndrome is often associated with decreased levels of VIP in the colon. In some patients peristalsis in the oesophagus is absent and the lower oesophageal sphincter fails to relax.

Symptoms include cramping abdominal pain, vomiting, distention, diarrhoea, and sometimes steatorrhoea. No surgical treatment is recommended for this condition (Corman 1998); intravenous hyper-nutrition may help manage these patients. Based on the assumption that Ogilvie's syndrome is associated with excessive sympathetic tone, Lee et al. (1988) blocked the splanchnic sympathetic by epidural anaesthesia. This procedure was successful in 63% of patients. Similarly, intravenous neostigmine, aimed to achieve colonic decompression in patients with Ogilvie's syndrome,

provided satisfactory results in 11 of 12 treated patients (Stephenson et al. 1995). In a series of 21 patients with acute colonic pseudo-obstruction who had not responded to conservative therapy, 11 were treated with neostigmine. In 10 a rapid decompression was observed (Ponec et al. 1999). This evidence suggests that the clinical syndrome may be due to excessive large bowel parasympathetic inhibition (Corman 1998). Acute colonic pseudo-obstruction may result from dysregulation of colonic motor activity controlled by the ENS.

Hirschsprung's disease

Hirschsprung's disease is a congenital megacolon associated with the absence of ganglia in the myenteric and submucous plexuses. It may be sporadic (80%) or familial (20%) (Knowles et al. 1999). The absence of inhibitory neurons containing NO and VIP probably accounts for the lack of relaxation in the diseased segment (Szurszewski and Miller 1994). Peptidergic nerves containing VIP and substance P play an important role in impaired motility of the internal anal sphincter, the so-called anal achalasia (Tomita et al. 1999).

Hirschsprung's disease affects approximately 1/5000 live births and occurs in any race. The male:female ratio ranges from 3:1 to 5:1 (Oakley and Lavery 1995). In approximately 80% of patients aganglionosis is limited to the rectum and the sigmoid colon (classical form), in 10% it extends to the left colon, and in about 8% there is complete colonic involvement, with or without aganglionosis in the small intestine (Ikeda and Goto 1984). The aganglionic segment can be very short (ultra-short-segment Hirschsprung's disease), a condition which is sometimes difficult to recognize. There have also been reports of zonal or segmental aganglionosis in the rectum or in the sigmoid colon; very rarely, a total intestinal aganglionosis, which is uniformly fatal, has been observed (Di Lorenzo et al. 1985).

Hirschsprung's disease has a familial occurrence in about 4% of cases (Ikeda and Goto 1984). Between 0.6% and 18% of the sibs can be affected. The lowest risk is for the sisters of a male proband; the highest is for the brothers of a female proband with long-segment disease (Oakley and Lavery 1995). The type of transmission is variable as is the degree of penetrance; genetic heterogeneity has

been documented (Stannard et al. 1991). Hirschsprung's disease is considered a multifactorial disorder, where multiple genes and the environment play a role (Wartiovaara et al. 1998). Further evidence of a possible genetic aetiology is provided by the finding of chromosomal abnormalities in Hirschsprung's disease patients, of which trisomy 21 (Down's syndrome) is the most frequent (Canniano et al. 1990). Cases with partial trisomy, with a deletion or translocation affecting other chromosomes (e.g., a deletion of chromosome 13 or of chromosome 10 – Lamont et al. 1989; Martucciello et al. 1992; Fewtrell et al. 1994) may be associated with Hirschsprung's disease. Congenital abnormalities occurring in patients with Hirschsprung's disease are listed in Table 9; cardiac, urinary and GIT defects are the most common (Ryan et al. 1992).

The reason why ganglion cells should be absent in the bowel wall remains obscure. Defects in migration differentiation or maturation of neural crest cells could result in aganglionosis in the bowel (Tam and Lister 1986). It has been proposed that aganglionosis in classical, extensive and zonal Hirschsprung's disease may result from later destruction of neural crest cells after migration (Tennyson et al. 1986). It is therefore difficult to provide an unifying molecular pathogenic theory of the disease. Familial cases often show more extensive involvement than sporadic ones. Some patients with the autosomal dominant form have mutations in the *Ret* gene (Edery et al. 1994; Romeo et al. 1994), and many patients with the autosomal recessive form have a mutation in the gene encoding for the endothelin receptor B (Puffenberger et al. 1994; Milla 1999). Some patients with Waardenburg–Shah syndrome have also mutations in the gene encoding for the transcription factor *Sox 10* (Pingault et al. 1998).

Other congenital disorders of colonic innervation

This is a group of conditions that clinically resemble Hirschsprung's disease despite the presence of ganglion cells in the bowel wall. The term neuronal colonic dysplasia was introduced in the early 1970s for a disorder characterized by hyperplasia of the submucous and myenteric plexuses, occasional ganglion cells and groups of smooth muscle cells scattered throughout the lamina propria, and

an increase in acetylcholinesterase activity in the parasympathetic fibres of the lamina propria and circular muscles (Meier-Ruge 1971). This is a specific clinical entity, which is sometimes termed pseudo-Hirschsprung's disease, and accounts for 20% of innervation defects of the colon. The term 'hyperganglionosis' has also been used for this condition, which belongs to the larger set of dysganglionoses (Oakley and Lavery 1995).

The use of monoclonal antibodies against neurofilaments allows the identification of different staining patterns in congenital neurogenic abnormalities of the bowel (Molenaar et al. 1989); they encompass: (a) normal bowel, (b) classical Hirschsprung's disease, (c) long-segment Hirschsprung's disease, (d) hyperganglionosis or neuronal dysplasia, and (e) hypoganglionosis. Abnormal staining patterns, similar to neuronal dysplasia, have also been observed in children and adults with chronic constipation, suggesting that some form of dysganglionosis may be the cause of idiopathic chronic constipation (Oakley and Lavery 1995). This evidence also supports the possibility that Hirschsprung's disease is part of a wide spectrum of innervation disorders, collectively described as neuronal dysplasia. Hypoganglionosis not associated with Hirschsprung's disease is rare. Histology includes low acetylcholinesterase activity in the lamina propria, and hypertrophy of the muscularis mucosae and the circular muscle.

Irritable bowel syndrome

Irritable bowel syndrome is characterised by irregular bowel habit with or without abdominal pain in the absence of detectable organic disease (Hasler and Owyang 1995). No clear diagnostic markers exist and all definitions of irritable bowel syndrome are based on clinical presentation. A diagnosis is made when abdominal pain or discomfort, relieved by defaecation or associated with change in frequency and consistency of stool, lasts for at least 3 months (Hasler and Owyang 1995). Using strict clinical criteria, 9–25% of the population note symptoms which would be considered diagnostic for irritable bowel syndrome (Heaton et al. 1992). Intestinal and extra-intestinal symptoms are common (Stark 1999).

The pathogenesis of irritable bowel syndrome is poorly understood. Altered gut motor and sen-

TABLE 9
Congenital abnormalities associated with Hirschsprung's disease.

Condition	Transmission	Gastrointestinal features	Other features
Hirschsprung's disease, microcephaly and iris coloboma	autosomal recessive	aganglionic megacolon	hypertelorism, submucous cleft palate, short stature
Hirschsprung's disease and bilateral bicolour iris	autosomal recessive	aganglionic megacolon	
Hirschsprung's disease with ulnar polydactyly, polysyndactyly of big toes, and ventricular septal defect	autosomal recessive	aganglionic megacolon	
Hirschsprung's disease with hypoplastic nails and dysmorphic facial features	autosomal recessive	aganglionic megacolon	bilateral hydronephrosis, imperforate anus, inguinal hernia
Hirschsprung's disease and Ondine's curse	autosomal recessive or dominant	short segment or total aganglionosis	idiopathic, congenital hypoventilation, abnormality of the neural crest
13-q syndrome	chromosomal, as in Down's syndrome	aganglionic megacolon	growth deficiency, microcephaly, mental deficiency, abnormal facies with prominent nasal bridge, hypertelorism, ptosis, epicanthal folds, microphthalmia, colobomas, retinoblastoma, prominent maxilla, slanting, low-set ears, micrognathia, hypoplastic or aplastic thumbs, cardiac defects, club feet, cryptorchidism
Metaphyseal chondrodysplasia, McKusick's type	autosomal recessive	megacolon with constipation	dwarfing syndrome with metaphyseal dysostosis, fine, sparse and light-coloured hair, anaemia, susceptibility to chicken pox and malignancies
Waardenburg-Shah syndrome	autosomal recessive	intestinal obstruction with dilated proximal ileum, collapse of distal ileum and colon	white forelock, white eyebrows and eyelashes, heterochromia iridis
Waardenburg's syndrome	autosomal dominant	short segment aganglionosis, megacolon	dystopia canthorum, broad nasal root, white forelock, white skin patches, deafness
Santos' syndrome	autosomal recessive	aganglionic megacolon	polydactyly, unilateral renal agenesis, hypertelorism, congenital deafness

sory activity, as well as stress and psychological disturbances, have been implicated (Hasler and Owyang 1995). Either in diarrhoea- or in constipation-predominant forms, the patients present a predominant slow wave pattern of 3 cycles/min, in

contrast to the pattern of 6 cycles/min of normal controls (Snape et al. 1977). Some studies have not confirmed this observation; it has been proposed that irritable bowel syndrome be categorized based on the pattern of spike potentials (Welgan et al.

1988). More recently, using colonic scintigraphy, a selective acceleration in right colonic transit has been found in some irritable bowel syndrome patients with diarrhoea (Vassallo et al. 1992). No similar studies have been reported in constipation-predominant irritable bowel syndrome, although patients with idiopathic constipation exhibit delayed right colon transit (Stivland et al. 1991). Manometric recordings show increased rectosigmoid motor activity, which may persist up to 3 h after ingestion of a meal (Rogers et al. 1989). Provocative stimuli induce exaggerated colonic motor responses in irritable bowel syndrome patients compared to healthy volunteers (Hasler and Owyang 1995).

Motility patterns of the small intestine in basal conditions are organized and well characterized. Under stimulated conditions, the duration of the fed pattern is shorter than that of healthy controls in constipation- or in diarrhoea-predominant irritable bowel syndrome (Kellow et al. 1988). Delayed emptying of the ileum and decreased ileocaecal clearance have been observed in irritable bowel syndrome patients using radiolabelled bran (Trotman and Price 1986).

Irritable bowel syndrome is also associated with motor abnormalities in smooth muscle outside the GIT; bladder detrusor instability has been noted in up to 30% of patients (Whorwell et al. 1986), and excessively reactive airway function is observed after administration of methacholine (White et al. 1991). These findings suggest that irritable bowel syndrome is characterized by a diffuse disturbance in smooth muscle function.

Idiopathic chronic constipation

Constipation is a common primary presenting symptom and one of the most common chronic complaints (Mertz et al. 1999). It is estimated that 12–30% of the general population suffer from constipation and consult a physician for this problem. This percentage does not include the many others who treat themselves and do not seek medical advice. In the early 1990s sales of laxatives in the USA exceeded 700 million dollars. In the great majority of affected patients, no organic cause of the symptom could be identified. A diagnosis of constipation is made when there are less than three bowel movements per week and at least one of the

following occur on a minimum of 25% of occasions: hard faeces, difficulty passing faeces, sense of inadequate defaecation (Wexner and Bartolo 1995). Patients with chronic idiopathic constipation can be classified in two pathophysiological groups: slow transit constipation and pelvic floor dysfunction.

Slow transit constipation is characterized by delayed transit through the colon and the rectum (Mollen et al. 1997); the diagnosis is made if there is neither a pelvic floor abnormality nor a systemic or neurological (Table 10) condition leading to slowed colonic transit (Maria et al. 1995; Corman 1998). It is common to confirm the diagnosis of slow transit constipation by tracing the progression of ingested radiopaque markers through the colon, after all stimulant laxatives and suppositories have been discontinued. Two patterns can be distinguished in this way. The first is characterized by colonic inertia, revealed by a progression from the caecum with holdup of markers along the course of the colon which indicates reduced colonic activity without haustration. The second pattern has normal colonic motility in the right and transverse colon, with stasis of markers and stool in the rectosigmoid; this may indicate an undetected pelvic floor spasm or a primary sigmoid motility disorder.

The aetiology of slow transit constipation remains unclear and is probably heterogeneous (Knowles et al. 1999).

Pelvic floor dysfunction is characterized by a failure of the puborectalis muscle to relax during

TABLE 10

Neurological causes of constipation and of intestinal pseudo-obstruction.

<i>Central nervous system</i>	
	cerebrovascular accident
	Parkinson's disease
	intracranial tumour
	spinal cord lesions (myelomeningocele, trauma, inflammatory disorders)
	cauda equina syndrome
<i>Peripheral nervous system</i>	
	diabetes mellitus
	myotonic dystrophy
	familial dysautonomia
	autonomic neuropathy
	Von Recklinghausen's disease
	Hirschsprung's disease
	toxic neuropathy

efforts to defecate, or by its paradoxical contraction (Wexner et al. 1992; Maria et al. 1997). With an effort to evacuate the rectum, the puborectalis and the external sphincter normally relax to straighten the anorectal angle and open the anal canal (Fig. 7). In the older literature this condition was named spastic pelvic floor syndrome (Kuijpers and Bleijenberg 1985) or anismus (Preston and Lennard-Jones 1985). Based on radiographic and electromyographic assessments of puborectalis activity during straining or defaecation, it has been renamed paradoxical puborectalis contraction or non-relaxing puborectalis syndrome (Fleshman et al. 1992). The diagnosis is suggested by the demonstration of a persistent impression of the puborectalis on the posterior surface of the anal canal during attempted evacuation of barium paste and, more reliably, by the electromyographic evidence of increased electrical activity in the puborectalis muscle during straining.

The aetiology of pelvic floor dysfunction is unclear. As in other forms of constipation, the patients are commonly females who have developed constipation as adolescents or adults. Prolonged efforts to empty the rectum may aggravate the condition. It has been suggested that paradoxical puborectalis contraction during straining represents a focal dystonia, characterized by excessive recruitment of synergistic and antagonistic muscle groups during voluntary activity and lack of reciprocal inhibition (Mathers et al. 1988). Signs of anismus have been noted in normal subjects (Voderholzen et al. 1997), in patients with anorectal pain (Schouten et al. 1997), and even in patients with faecal incontinence (Wexner et al. 1991; Voderholzen et al. 1997).

Anal disorders

Faecal incontinence

Faecal incontinence is the inability to retain rectal content until a convenient time and place. It is a heterogeneous condition, which affects more commonly the elderly and is particularly observed among institutionalized patients, but many young patients are also affected. There are various degrees of incontinence: complete incontinence of solid, liquid, and gas is obviously different from partial incontinence of liquid and gas or of gas alone.

Leakage of mucous is not considered true anal incontinence and can be secondary to haemorrhoids or to mucosal disease. Severe daily incontinence dramatically affects daily living, but frequent loss of gas can be just as socially unacceptable as complete incontinence.

Continence normally depends on a number of factors: mental function, stool volume and consistency, colonic transit, rectal relaxation, anal sphincter function, anorectal sensation, and anorectal reflexes (Corman 1998). Abnormalities of any of these factors can lead to incontinence. For example, excess of liquid stool and enhanced colonic transit, as observed in diarrhoea, can lead to incontinence even if the anal sphincters are normal; similarly, a poorly relaxing rectum (as seen in inflammatory bowel diseases or in radiation proctitis) may preclude adequate reservoir function.

Idiopathic faecal incontinence is caused by denervation of the pelvic floor (Madoff et al. 1992). Histology shows muscle necrosis and fibre grouping indicating reinnervation. Electromyographic studies have demonstrated reinnervation of the pelvic floor muscles and delayed (> 2.2 ms) conduction in the pudendal nerves. Denervation is caused by traction injury to the pelvic nerves, such as that occurring during childbirth (Snooks et al. 1984), or from prolonged straining at stool. An adequate anorectal sensation is necessary for normal continence. The presence of stool is detected by receptors in the pelvic floor, whereas those in the rectal wall play a lesser role (Madoff et al. 1992). Patients with faecal impaction and overflow incontinence have diminished rectal sensation, as do patients with incontinence due to diabetes (Wald and Tunuguntla 1984) or spinal cord disease (Sun et al. 1990; Glickman and Kamm 1996). Patients with traumatic and idiopathic incontinence may have abnormal sensation in the anal canal.

Abnormal function at different levels of the nervous system can lead to faecal incontinence. Incontinent patients with high spinal lesions have better function than patients with low lesions. Patients with high and low spinal lesions have the most severe physiological abnormalities (Sun et al. 1990). Faecal incontinence in diabetes is due to autonomic neuropathy and is exacerbated by diarrhoea (Schiller et al. 1982). Incontinent elderly patients have abnormal rectal sensation and de-

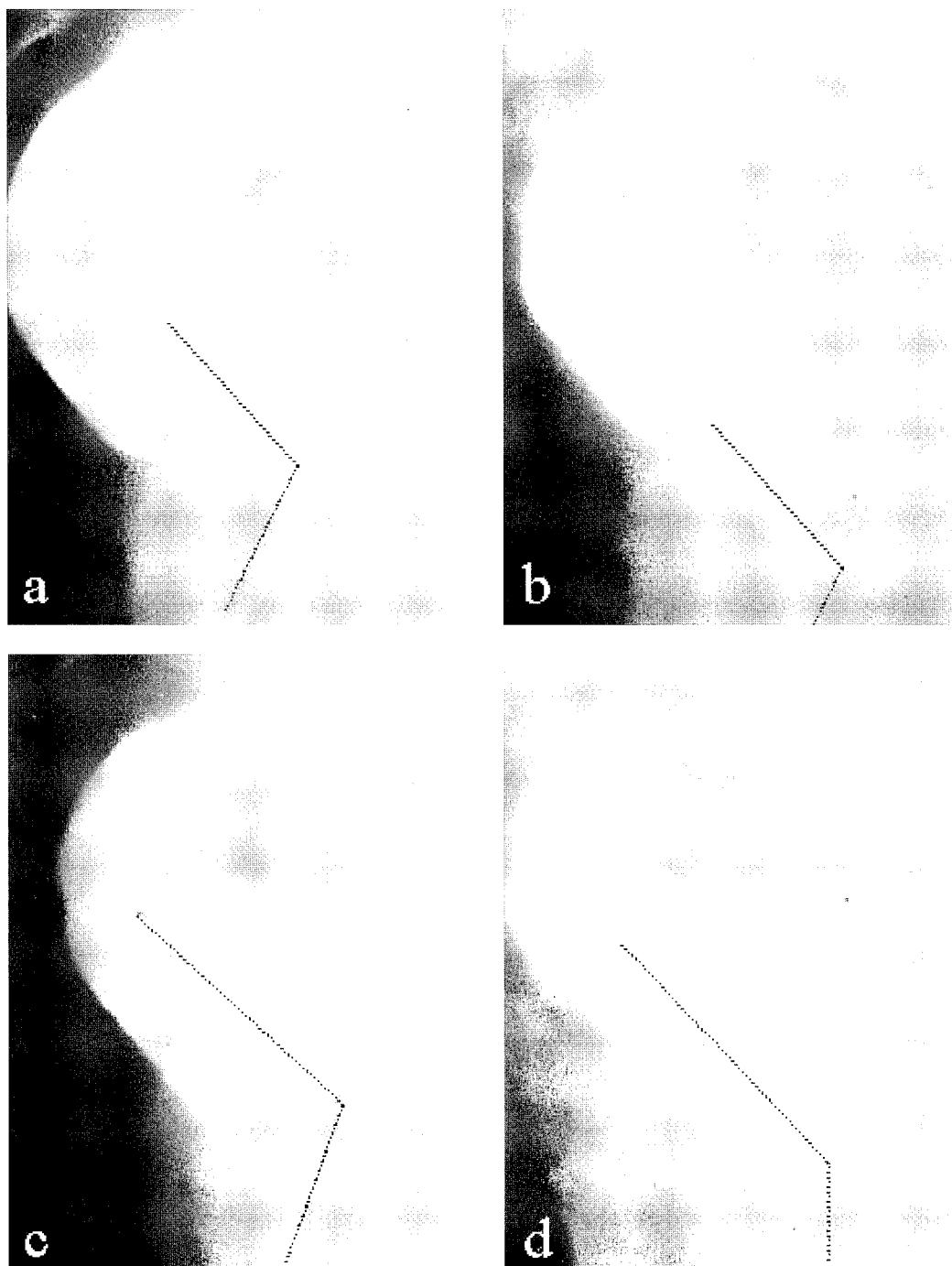


Fig. 7. Treatment of outlet-type constipation in a PD patients by injection of botulinum toxin in the puborectalis muscle. Before treatment, the basal contraction (A) and the contraction at straining (B) show an anorectal angle of 110° and of 110° , respectively. The patient could not evacuate the barium paste. Two months after treatment with botulinum toxin, defaecation is greatly improved, as shown by the correction of the anorectal angle in the basal position (C) and at straining (D). The anorectal angle was 115° at rest and widened, on straining, to 130° . The patient could evacuate the barium paste.

creased resting sphincter pressure compared to age-matched continent patients. Senile dementia, depression, and cerebrovascular accidents all predispose the elderly population to anal incontinence. Despite an abnormal anal sphincter innervation in multiple system atrophy (MSA), faecal incontinence is relatively unknown. Whether diminished motility in the lower gut, associated with constipation, is a contributing factor is unknown.

In patients with neurogenic faecal incontinence there is a decreased sensitivity of the internal anal sphincter to the contractile actions of noradrenaline (Speakman et al. 1990) and of carbachol, but not of 5-HT (Speakman et al. 1992). This fits in with the hypothesis that neurogenic incontinence is associated with abnormal function of extrinsic sympathetic and intrinsic or extrinsic cholinergic innervation of the internal anal sphincter (Speakman et al. 1993).

Anal fissure

Anal fissure is a split in the skin of the distal anal canal. It is common and causes significant complications in the young and otherwise healthy population; it has roughly equal incidence in men and women (Lund and Scholefield 1996). The pathogenesis of this condition is not yet fully understood (Corman 1998). It seems that local ischaemia may play an important part (Schouten et al. 1996). As in other organs, ischaemic damage, promoted by endothelial cell dysfunction (Zeiber 1996), produces vasoactive autacoids with paracrine function on vascular smooth muscle. The endothelial dysfunction is associated with reduced NO synthesis, which is known to be involved in the regulation of local blood flow. Interruption of endothelial continuity does not only remove the anticoagulant and vasodilator functions of the endothelium, but also exposes the subendothelium which has several procoagulant functions (Vane et al. 1990). Furthermore, even in the absence of detectable microscopic changes, endothelial function can change from vasodilator to vasoconstrictor and from anticoagulant to procoagulant. These changes may be induced by inflammatory or immune cytokines (Johnson and Billiar 1998). Activation of the endothelium may express antigens as the endothelial cells can act as antigen-presenting cells. Anti-endothelial cell antibodies have been found

in patients with anal fissure, but not in healthy controls (Maria et al. 1999). In antibody-positive patients, higher resting anal tone, with no change of maximum voluntary contraction, was observed. This supports a role of the endothelium in the pathogenesis of anal ischaemia. Circulating antibodies may activate the endothelium to produce vasoactive autacoids, which could contribute to the increased basal anal tone and aggravate the ischaemia at the level of the posterior anal commissure. The reduction in endothelial NO synthesis is indirectly supported by the observation that the topical application of nitroglycerin ointment induces healing of the fissure in up to 60% of cases (Lund and Scholefield 1997).

Chronic anal fissure is maintained by contraction of the internal anal sphincter (Abcarian et al. 1982), a disturbance which plays a role in the aetiology of the fissure. This view is supported by the detection of myositis in the internal sphincter (Brown et al. 1989). Supersensitivity of the internal sphincter to β_2 -agonists occurs in patients with chronic anal fissure (Regadas et al. 1993). This may be induced by the prolonged absence of the neurotransmitter, or by abnormalities at neurotransmitter or at a metabolic level. Increased adrenergic or cholinergic activity of the internal anal sphincter is likely to take place also in patients with chronic anal fissure; in keeping with this, fissure healing and reduction of resting anal tone have been observed following the injection of botulinum toxin into the internal anal sphincter (Gui et al. 1994; Maria et al. 1998; Brisinda et al. 1999).

Other motility disorders

In internal anal sphincter achalasia, the clinical presentation is similar to Hirschsprung's disease, but rectal biopsy reveals the presence of ganglionic cells (Holschneider 1982). Anorectal manometry is diagnostic when a failure of rectosphincteric relaxation on rectal balloon inflation is demonstrated. This feature is due to deficiency of NO synthase in the internal anal sphincter (O'Kelly et al. 1993).

Hereditary internal anal sphincter myopathy is an autosomal dominant disorder, characterized by severe anal pain and constipation and onset before the 5th decade (Kamm et al. 1991). It is a myopathy specifically involving the internal anal sphincter.

Biliary motility disorders

Biliary tract dysmotility may occur in autonomic neuropathies (e.g., diabetic neuropathy; Lu and Kaplowitz 1995) or in biliary tract diseases.

Biliary cysts and Caroli's disease

Cystic dilatations can occur in any portion of the biliary system. The most common are cystic dilatations of the common biliary ducts; however, isolated cystic dilatations of the intrahepatic ducts (Caroli's disease) or combined with other cystic abnormalities of the extrahepatic ducts are increasingly observed. The prevalence of biliary cysts is highest in Japan (Tan and Howard 1988). A complete and practical classification recognizes five types of bile ducts cysts (Todani et al. 1977).

The aetiology (congenital or acquired) of biliary cysts is disputed. The relevance of the distal duct abnormalities is also unclear. Diminished postganglionic cholinergic activity, observed in the distal portion of choledochus cysts, suggests a pathogenesis similar to that of Hirschsprung's disease.

Dysfunction of the sphincter of Oddi

Sphincter of Oddi dysfunction may be structural or functional and are associated with a variety of signs and symptoms caused by impeded bile flow (Venu and Geenen 1995). True sphincter of Oddi dysfunction is uncommon and accounts for 1–10% of patients who may develop symptoms after cholecystectomy (Bar-Meir et al. 1984), and for 10–20% of patients with idiopathic recurrent pancreatitis (Venu et al. 1989). A variety of microscopic abnormalities, from chronic inflammation to severe fibrosis, have been reported. In a few patients, sphincter of Oddi dysfunction is due to papillary stenosis. Besides structural abnormalities, sphincter of Oddi dysfunction may result from sphincter of Oddi dyskinesia. For unclear reasons, this disorder more commonly occurs among middle-aged women. In most instances there is a history of cholecystectomy, with or without evidence of cholelithiasis, but sphincter of Oddi dyskinesia may also occur in patients with an intact gall bladder.

The most common presenting symptom is abdominal pain, usually postprandial and located in the epigastrium or in the right upper quadrant of the abdomen. This may last for hours and may ra-

diate toward the back or the shoulder. Nausea or emesis may occur, but symptoms of biliary tract obstruction (e.g., jaundice, fever, chills) are uncommon. The diagnosis is based on cholangiography, that shows dilated common bile ducts (> 12 mm) and delayed contrast drainage (> 45 min from the common bile duct to the duodenum). Manometry detects increased sphincter of Oddi basal pressure, greater than 40 mmHg and higher than intraduodenal pressure.

A successful outcome has been reported in patients treated with endoscopic sphincterotomy. Sphincter basal pressure may be reduced by intravenous administration of CCK or glucagon; improvement following amyl nitrite inhalation has been reported in some patients. Responses to drugs suggest that the underlying mechanism is a dyskinesia rather than a papillary stenosis.

MOTILITY DISORDERS IN OTHER DISEASES

Connective tissue diseases

Connective tissue diseases may affect motility due to autonomic neuropathy as to direct involvement of the GIT (Sigurdson et al. 1985).

Ehler-Danlos syndrome is a collection of inherited diseases affecting the synthesis of collagen tissue. At least eight different subtypes have been described; GIT involvement (such as mega-oesophagus, small intestinal dilation and colonic hypomotility) is common in types I and IV (Nardone et al. 1979).

Progressive systemic sclerosis (scleroderma) is characterized by skin hardening, fibrous replacement of smooth muscles and progressive loss of visceral and cutaneous functions. More than 50% of patients have GIT complications, and 70% of these patients present oesophageal involvement. The oesophagus exhibits a reduced number of low-amplitude contractions and weakening of the lower oesophageal sphincter. Disruption of normal oesophageal peristalsis is so common that it is thought to represent a diagnostic sign of progressive systemic sclerosis. It is particularly common in acrosclerosis, a variant associated with Raynaud's phenomenon, that lacks the typical skin changes. Gastric emptying is delayed. The small intestine is also frequently involved and often exhibits exten-

sive gut wall fibrosis, smooth muscle atrophy, and abnormal motility. Commonly observed abnormal motility patterns include loss of interdigestive MMC, and abnormally long MMC cycles, diminished activity of phase III and hypomotility in the fed state (Greydanus and Camilleri 1989; Bortolotti et al. 1991). Patients without GIT involvement have normal small bowel manometry and normal small bowel transit time (Madsen and Hendel 1992). The colon may also be involved; constipation, pseudo-obstruction or volvulus may develop. Treatment with metoclopramide is helpful on occasion; parenteral nutrition is often required in advanced cases. Cisapride and octreotide may benefit patients who fail to respond to other therapies (Soudah et al. 1991). If severe gastro-oesophageal reflux occurs, anti-reflux operations are indicated (Orringer 1997).

Polymyositis and dermatomyositis are characterized by inflammation of striated and, to a lesser extent, of smooth muscles. Dysphagia is often a presenting symptom. GIT may be affected throughout its entire length, but the proximal oesophagus is most commonly involved. Oesophageal and gastric motility may be impaired, leading to oesophageal reflux and gastric stasis (Horowitz et al. 1986). Small and large bowel involvement is also well documented. Megaduodenum and delayed intestinal transit of barium are prominent features. Neurological dysfunction and diminished smooth muscle contractility (as a consequence of muscle atrophy, fibrosis, or inflammation) may contribute to GIT dysfunction (Neil and Weinstock 1995).

Systemic lupus erythematosus is an autoimmune disease characterized by arthritis, myalgia, fever, rash, lymphadenopathy, renal disease, and CNS involvement. It commonly affects GIT motility, and may present with oesophageal reflux, dysphagia, or gastric retention (Hoffman and Katz 1980). Chronic intestinal pseudo-obstruction, usually reversed by treatment, may be either a complication or a presenting feature (Perlemuter et al. 1998). Smooth muscle involvement is probably due to a GIT vasculitis.

Mixed connective tissue disease is characterized by overlapping features of scleroderma, polymyositis, and rheumatoid arthritis. It has the distinct serological finding of high titres of antinuclear antibody against ribonucleoprotein. The extent of GIT

involvement in this disease probably resembles that of scleroderma. Jejunal dilation has been seen radiographically, and pneumatosis cystoides intestinalis has been observed in severe forms (Neil and Weinstock 1995).

Neurological diseases

Familial visceral neuropathies

See also Bruyn et al. 1998. This group of genetic diseases is characterized by a degeneration of the myenteric plexus. Two forms have been identified (Table 11). Myenteric neurons are significantly reduced in number; one-third of neurons contain round, eosinophilic, intranuclear inclusions, which are also present in CNS neurons and glia and in the coeliac plexus. Intestinal smooth muscles are microscopically normal (Anuras and Hodges 1995).

Clinical signs include: intestinal pseudo-obstruction (resulting from visceral neuropathy); CNS abnormalities (such as abnormal pupillary reflexes, ataxia, dysarthria); peripheral nervous system signs (including absent deep tendon reflexes, impaired vibratory and position sense); and dysautonomia (e.g., abnormal cardiovascular reflex tests, loss of thermoregulatory sweating). In a report of a family, the affected members had megaduodenum, generalized dilatation of the small intestine, malabsorption, redundant colon, mental retardation, and calcification of the basal ganglia (Cockel et al. 1973).

Myotonic dystrophy

This autosomal dominant disorder is characterized by abnormal muscular relaxation, muscle weakness, ptosis, cataracts, gonadal atrophy, cardiac conduction abnormalities, and male pattern baldness. The gene is located on chromosome 19p. GIT symptoms are prominent and are caused by abnormal functioning throughout its length. This is the result of degenerative changes in the smooth muscles and of fatty infiltration. Using silver stain, degenerative changes of the myenteric plexus of the colon have been found in myotonic patients presenting megacolon (Yoshida et al. 1988), indicating that intestinal dysmotility may be caused by dysfunction either of smooth muscles or the ENS. A selective loss of substance P and of enkephalin-containing enteric neurons has been observed; neu-

TABLE 11
Classification of familial visceral neuropathies.

Features	Type 1	Type 2
Transmission	autosomal dominant	autosomal recessive
Anatomical lesions	dilatation of the small bowel, megacolon, gastroparesis	hypertrophic pyloric stenosis, dilated short small intestine, malrotation of small intestine
Microscopic changes	degeneration of argyrophilic neurons and decrease in numbers of nerve fibres	deficiency of argyrophilic neurons and increase in neuroblasts
Clinical features		
Age of onset	any age	infancy
Symptomatic cases	>75%	100%
Symptoms	early satiety, abdominal pain and distention, diarrhoea or constipation, intestinal or colonic pseudo-obstruction	intestinal pseudo-obstruction
Prognosis	fair	poor
Non-gastrointestinal manifestations	none	CNS malformation, patent ductus arteriosus

rons containing neuropeptide Y or VIP are preserved (Yoshida et al. 1988).

Dysphagia, diarrhoea and abdominal cramping are the most common symptoms, which occur in up to one-third of the affected patients. Malabsorption and steatorrhoea have been reported in few cases (Chiu and Englert 1962). Constipation is a frequent occurrence and can alternate with diarrhoea. Intestinal pseudo-obstruction is rare (Anuras and Hodges 1995). Abnormal manometric findings at the level of the small intestine include low-amplitude contractions in the fasting state, retrograde propagation or interruption of phase III, and increase of tonic contractions (Nowak et al. 1984).

Mitochondrial neurogastrointestinal encephalomyopathy

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) syndrome is a rare, multisystem disorder characterised clinically by ptosis, progressive external ophthalmoplegia, gastrointestinal dysmotility, leukoencephalopathy, thin body habitus, and myopathy. Gastrointestinal symptoms include recurrent nausea, vomiting, or diarrhoea; MRI scanning allows the detection of altered white matter signal; laboratory studies reveal defects of oxidative-phosphorylation and multiple mitochondrial

DNA deletions frequently in skeletal muscle (Hirano et al. 1998).

MNGIE is an autosomal recessive human disease associated with multiple deletions of skeletal muscle mitochondrial DNA, which have been ascribed to a defect in communication between the nuclear and mitochondrial genomes. Homozygous or compound-heterozygous mutations have been observed in the gene specifying thymidine phosphorylase, located on chromosome 22q13.32-qter. The enzyme activity in leukocytes from MNGIE patients is less than 5% that of controls, indicating that loss-of-function mutations in thymidine phosphorylase cause the disease. The pathogenic mechanism may be related to aberrant thymidine metabolism, leading to impaired replication or maintenance of mitochondrial DNA, or both (Nishino et al. 1999).

Groll-Hirschowitz syndrome

This is an autosomal recessive disorder characterized by dysphagia, nausea and diverticula of the small bowel. It is due to abnormal GIT motility secondary to vagus nerve dysfunction. The distinctive feature of this syndrome is a progressive neurogenic deafness, ascribed to a demyelination (Scheuner et al. 1995).

POLIP syndrome

Polyneuropathy, ophthalmoplegia, leukoencephalopathy and intestinal pseudo-obstruction (POLIP) constitute a syndrome characterized by severe GIT dysmotility due to a visceral neuropathy with chronic malabsorption and malnutrition. Sensorimotor neuropathy affects the cranial nerves and is progressive. Other features include cerebral and cerebellar white matter abnormalities or frank demyelination and endoneural fibrosis (Simon et al. 1990).

Familial dysautonomia (Riley-Day syndrome)

See this volume, Chapter 5.

Down's syndrome

Chromosome 21 trisomy is associated with GIT anomalies. Duodenal stenosis and atresia are most commonly seen. Annular pancreas may accompany congenital duodenal obstruction. Oesophageal stenosis, hiatal hernia, and gastro-oesophageal reflux represent the most common oesophageal abnormalities. Imperforate anus, Hirschsprung's disease, and intestinal malrotation have been repeatedly described (Buchin et al. 1986).

Parkinson's disease

See also this volume, Chapter 6. GIT dysfunction is a common feature of PD and a source of considerable morbidity. The frequency of GIT symptoms in PD is still not precisely known. In PD patients several factors not directly related to the disease process contribute to gut dysfunction; they include diet variations, reduced motor activity, effects of anti-PD medication, and associated autonomic dysfunction (Edwards et al. 1992). In addition, the disease process contributes directly to GIT dysfunction. This may be serious and potentially life-threatening, as in the case of malnutrition, pulmonary aspiration, megacolon or intestinal obstruction. Available data suggest that the primary PD process is the major factor in the aetiology of GIT dysfunction in these patients.

Sialorrhoea occurs in 70% of PD patients in comparison with only 6% of age-matched controls (Edwards et al. 1991); its severity is directly correlated with the severity of motor symptoms because sialorrhoea depends on the reduction of normal swallowing due to akinesia.

Dysphagia occurs more frequently in PD patients than in the elderly population. Dysphagia in PD may result from dysfunction in either the oropharyngeal or the oesophageal phase of swallowing. Dysphagia is most commonly localized to the oropharynx, and solids cause more trouble than liquids. Up to 30% of patients have associated respiratory symptoms, such as coughing, choking or nocturnal dyspnoea. Abnormalities in the oropharyngeal phase include abnormal lingual control, lingual festination, stasis in the anterior and lateral sulci, vallecular stasis, reflux from the vallecula and the pyriform sinuses into the oral cavity, and aspiration. Other abnormalities include abnormal bolus formation, delayed initiation of swallowing, pharyngeal dysmotility, misdirected swallows, and upper oesophageal sphincter dysfunction.

Oropharyngeal dysphagia results from dysfunction at several stages of the oropharyngeal phase of swallowing. Bradykinesia and rigidity directly and adversely affect the motor function of the tongue and pharynx. Improvements of parkinsonian signs are not always associated with a parallel improvement in swallowing. Recent studies indicate that opening of the upper oesophageal sphincter is not coupled with cricopharyngeal relaxation in PD patients, providing a possible pathophysiological basis for dysphagia in PD.

Other factors may predispose to oesophageal dysfunction in PD, such as disordered neuromuscular junction function in the ENS, degeneration of the dorsal motor nucleus of the vagus, or depletion of peripheral dopamine. Lewy bodies are also contained in the dorsal motor nucleus of the vagus and in the oesophageal myenteric plexus, where they are particularly numerous in the distal third (Qualman et al. 1984). Nausea, but not vomiting, is more common in PD than in age-matched controls (Camilleri 1990). Occurrence of nausea has been traditionally attributed to dopaminergic medication, but a recent study failed to demonstrate differences in the frequency of nausea between a group of PD patients on medication and an untreated group (Edwards et al. 1991).

There are scanty data on the frequency of small intestine dysfunction in PD. Quantitative differences and an abnormal motility pattern have been observed (Bozeman et al. 1990), but their functional significance remains to be evaluated. Lewy

bodies are not found in the small bowel, therefore intestinal motor dysfunction may be due to a direct involvement of the enteric motor apparatus. Manometric studies reveal infrequent MMC, which may be absent in some cases, hypomotility in the fed state, and increased occurrence of retrograde and tonic contractions compared to controls (Bozeman et al. 1990).

Constipation is commonly observed in PD patients. It encompasses either form of idiopathic constipation, colonic inertia or outlet-type dysfunction, which may also be combined (see page 636). Constipation affects over 50% of PD patients compared to 13% of controls; 29% of PD subjects have a bowel movement less than 3 times/week compared with only 10% of age-matched controls (Edwards et al. 1991). The same study also revealed that 67% of PD patients had straining or incomplete evacuation compared to 28% of controls. Case reports have described megacolon (Kupsky et al. 1987) or even sigmoid volvulus in PD, providing evidence for impaired colonic motor function in this disease. Although uncommon, these complications may be life-threatening, and the occurrence of a volvulus should be considered in any PD patient presenting with an acute abdomen.

The use of anticholinergic medication, combined with autonomic dysfunction, the chronic use of laxative, and an improper diet can aggravate colonic dysfunction in PD. The severity of constipation is directly related to PD duration and severity, inadequate diet, to the use of anti-PD medication and inversely to motor activity (Edwards et al. 1991). Lewy bodies have been observed in the colon of PD patients with megacolon (Kupsky et al. 1987); in addition, a dopaminergic deficiency has been demonstrated in the ENS of PD patients with chronic constipation (Singaram et al. 1995).

Abnormalities of defecatory function occurs in PD patients. In a review of 120 consecutive PD patients, we have detected outlet type constipation in 13 (11%) (Albanese and Brisinda, unpublished observations). Ineffective defaecation is associated with a contractile activity of the puborectalis muscle during straining, a paradoxical contraction that may represent a focal dystonia of pelvic floor muscles associated to PD (Mathers et al. 1988). Anal pressure on voluntary squeeze, sustained

squeeze pressure, squeeze duration and squeeze index are all significantly reduced in PD patients compared to controls (Ashraf et al. 1994), suggesting that impaired squeeze response is a specific feature of anorectal dysfunction in PD. Defaecatory dysfunction correlates with the severity and duration of PD and may improve following the systemic administration of apomorphine (Edwards et al. 1993) or a local injection of botulinum toxin into the puborectalis muscle (Albanese et al. 1997a,b).

Multiple system atrophy

See also this volume, Chapter 6. MSA accounts for the largest group among chronic primary autonomic failure syndromes, and is probably the most common neurodegenerative condition affecting the autonomic nervous system in adults (Mathias and Williams 1994; Mathias 1997b). It is a progressive, non-familial sporadic disorder. Its incidence is unknown as there are often difficulties in diagnosis even if the condition is suspected. The GIT is involved in a variety of ways, an early feature being constipation. In many, postprandial hypotension can be elicited. As the disease progresses, disorders of swallowing emerge. These will be discussed individually.

Hypostomia and xerostomia are less common in MSA than other autonomic conditions. Drugs used in this condition can affect salivary secretion. In the parkinsonian form in particular there may be dribbling of saliva more noticeably at night. Whether this is due to the motor deficit and associated swallowing disturbances or due to excessive salivary secretion is unclear. Anticholinergic drugs and, in severe cases, irradiation of the salivary glands or botulinum injections may provide benefit.

As the disease progresses there can be difficulties with swallowing. An initial analysis in MSA indicated that 50% had feeding difficulties, with choking and coughing, especially in relation to liquids (Smith and Bryan 1992; Mathias 1996b). An ideal investigation to assess oropharyngeal dysfunction is videocinefluoroscopy (Fig. 8). This may indicate various abnormalities that include pharyngeal pooling, incomplete laryngeal closure, inadequate laryngeal elevation, penetration of the larynx by contrast medium (a precursor to aspiration), and silent aspiration. The investigation is helpful in providing advice regarding feeding.



Fig. 8. Still from videocinefluoroscopic examination in a subject with oropharyngeal dysphagia showing penetration of the larynx with the potential to lead to tracheal aspiration. (From Mathias 1996b.)

This is of particular importance in MSA where laryngeal paresis may concurrently occur, thus enhancing the potential for aspiration; this may result in recurrent pulmonary infections. If the swallowing deficit is severe enough, a percutaneous enterogastrostomy tube may be needed. In some patients the lower tracts of the oesophagus may exhibit dysmotility. Whether this responds to drugs affecting cholinergic activity is unclear.

Gastric motility disorders in MSA appear uncommon, although a number have fullness post-meal together with gaseous eructation. Whether drugs such as anticholinergics and dopaminergic agents interfere with motility is unclear. Gastric emptying studies suggest increased initial emptying, rather than slowing of motility (Mathias and Bannister 1999). This would favour a form of the 'dumping syndrome' although this does not appear to be the cause of postprandial hypotension, which is a common feature in such patients. This can occur within 15 min of eating, even with the patient

supine, with hypotension persisting for up to 3 h. The reason is likely to be vasodilatation in the splanchnic region, secondary to the release of vasoactive gastrointestinal and pancreatic peptides. This has been demonstrated by measuring mesenteric artery blood flow, as a measure of splanchnic dilatation. Drugs such as octreotide, which prevent the release of gastrointestinal peptides, reduce the degree of splanchnic vasodilatation and prevent postprandial hypotension (Mathias 1997a).

A number of factors are known to enhance postprandial hypotension. The composition of food is of importance, with the greatest fall in carbohydrate, and a lesser fall with lipid and protein meals. The effects of insulin, therefore, may be of importance in the causation of postprandial hypotension. Some patients become intolerant to even small amounts of alcohol. Postprandial hypotension can enhance postural hypotension (Fig. 9), and can contribute substantially to morbidity; some are not aware of the problem, reduce their food intake and can lose a sub-

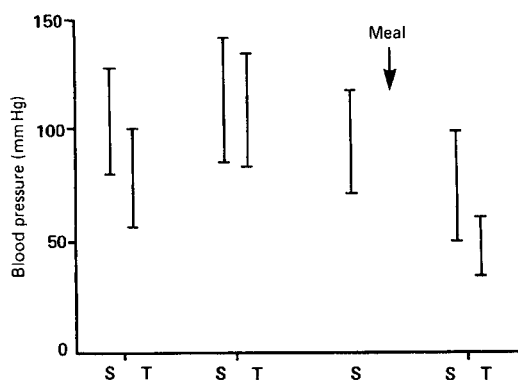


Fig. 9. Systolic and diastolic blood pressure in an MSA subject while supine (S) and after 45° head-up tilt (T) on three occasions. On the first two, food intake was not controlled. The subject had not eaten on the second occasion when the blood pressure fall was negligible. On the third, supine blood pressure was measured while fasting before and 45 min after the meal. Postprandial tilt caused a considerable fall in blood pressure and the subject had to be returned to the horizontal within 3 min. (From Mathias 1991.)

stantial amount of weight. A variety of approaches to treat postprandial hypotension entail non-pharmacological methods (small, frequent meals, avoiding refined carbohydrates and alcohol, and resting after meals), and pharmacological agents that include caffeine, indomethacin, vasopressin analogues (which constrict the splanchnic vascular region) and octreotide (Fig. 10), as described above.

Colonic dysfunction with constipation can be a prominent feature in MSA. Occasionally diarrhoea due to overflow incontinence may occur. There is no specific treatment. As indicated previously, faecal incontinence is an occasional feature only, which is surprising considering the degree of anal sphincter malfunction seen on the anal sphincter electromyogram (Fig. 11). This shows a characteristic pattern of denervation and is suggestive of involvement of Onuf's nucleus, within the sacral spinal cord, which innervates both the anal and urethral sphincters.

Multiple sclerosis

This condition is often associated with anorectal dysfunction, gastroparesis and abnormal colonic motor activity. Constipation is a frequent complaint of patients with multiple sclerosis. The cause is often multi-factorial; ENS involvement, impaired

defaecation secondary to weakened abdominal muscles, and decreased overall physical activity all contribute to decreased bowel activity (Hinds et al. 1990). Transit time through different segments of the colon is usually prolonged. Myoelectrical studies demonstrate abnormal postprandial response and abnormal motor activity. Spontaneous rectal contractions and anorectal manometric abnormalities suggestive of outlet obstruction may also occur.

Management of constipation in patients with multiple sclerosis consists of measures to prompt good bowel function. Sufficient fluid intake, a high fibre diet, regular physical activity, and a daily routine of attempted evacuation are encouraged.

Brain injury

Injuries secondary to stroke, trauma, tumour or surgery may affect the GIT. Acute brain injury may be associated with alteration in the gastric mucosa, which can rapidly result in erosions, ulceration (Cushing's ulcer) or bleeding. Common chronic sequelae include oropharyngeal and cricopharyngeal dysfunction manifesting as dysphagia, aspiration and malnutrition. Anal incontinence and constipation also occur frequently.

Spinal cord injury

Extrinsic denervation due to spinal cord injury produces only mild dysmotility in the small bowel. Patients with injury to the lower spinal cord usually have no abnormalities. In patients with higher spinal cord lesions, manometric study reveals increased phase III contractions, which start from the duodenum rather than from the antrum (Fealy et al. 1984).

Spinal shock, which develops immediately after spinal cord injury, is characterized by a complete loss of all sensory, motor and reflex function below the injury level. Paralytic ileus with abdominal distention follows and usually resolves in few days. Postprandial abdominal distention and discomfort are common sequelae, which occur in more than 40% of spinal cord injury patients (Stone et al. 1990). Their pathophysiology is poorly understood.

Increased amounts of gas are detected in the small and large intestine on abdominal X-ray of patients with stable spinal cord injury. Faecal incontinence is rare, but constipation is frequent (De Looze et al. 1997) and colonic transit time is pro-

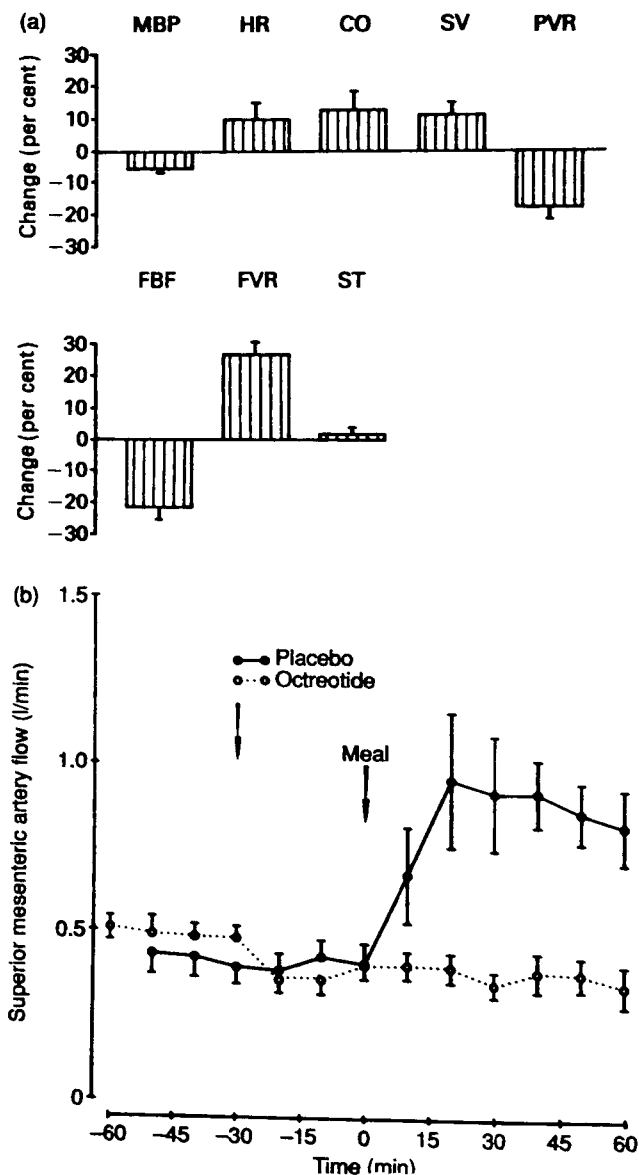


Fig. 10. Superior mesenteric artery blood flow in normal subjects before and after a balanced liquid meal, when given either saline (filled circles, continuous line) or 50 μ g of octreotide (open circles, dotted line) both subcutaneously. In the placebo phase, food ingestion virtually doubles blood flow to almost 1 l/min. The responses are effectively abolished by octreotide. (From Kooner 1989.)

longed in the majority of patients (Geders et al. 1995). Delayed transit has been documented in the left colon and in the rectosigmoidal colon. Delayed colonic transit stands as the most important cause for constipation following a complete spinal cord injury, but other mechanisms may also play a

role, particularly at the level of the anorectum and the pelvic floor. Impairment of evacuation is aggravated by loss of rectal sensation, by loss of anal discriminatory properties, impaired voluntary relaxation, and by inability to generate an adequate intra-abdominal pressure (Sun et al. 1995). Dener-

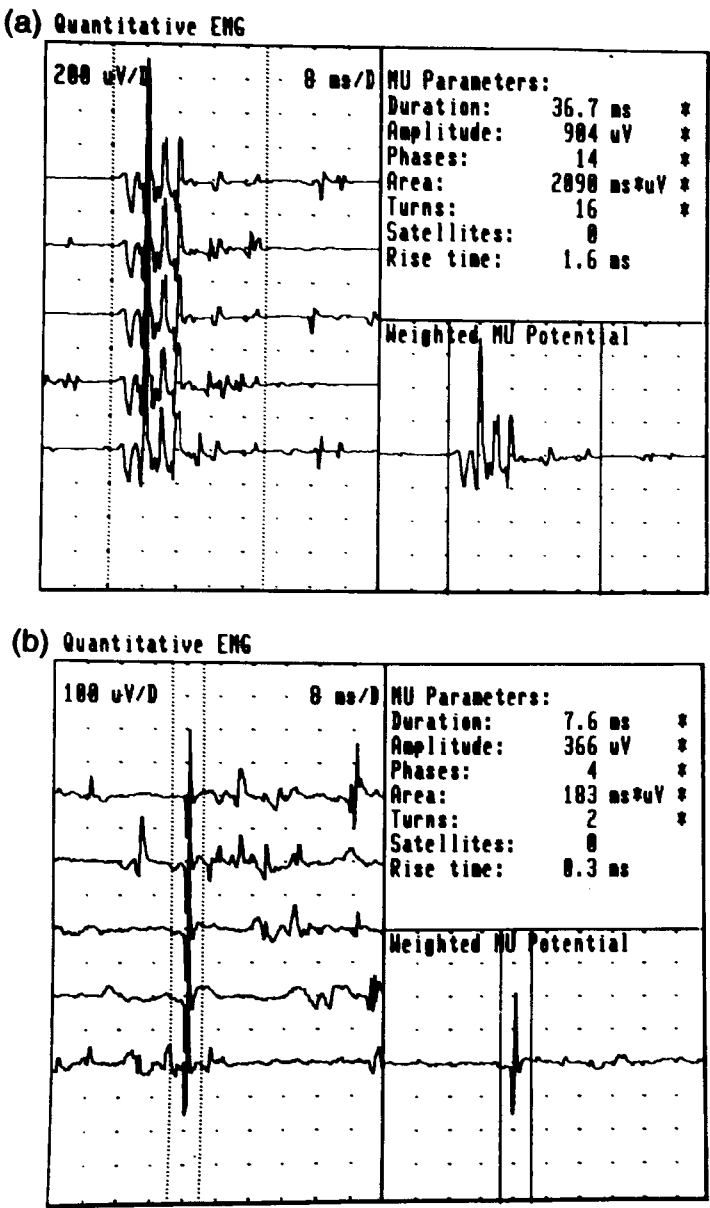


Fig. 11. Anal sphincter electromyogram in a subject with MSA (a), compared with a normal electromyogram (b). In the MSA subject there are polyphasic and prolonged motor units. (From Mathias 1996a.)

vation of the internal anal sphincter has also been described (De Looze et al. 1998).

Diabetic autonomic neuropathy

See also this volume, Chapter 22. GIT dysmotility is common in diabetic patients. Abnormal oesophageal motility occurs in diabetic patients

and can be revealed by radiography or manometry. Manometry reveals a decrease of peristaltic amplitude, non-transmitted peristaltic waves, decreased pressure in the lower oesophageal sphincter and impaired relaxation after swallowing. More than 60% of diabetic patients with autonomic neuropathy have disordered oesophageal motility,

but male diabetics without neuropathic changes may also have dysmotility (Keshavarzian et al. 1987). The clinical significance of these abnormalities is difficult to ascertain, as the majority of the patients are not symptomatic. Oesophageal dysmotility is related to degeneration of the ENS caused by diabetes, rather than to smooth muscle dysfunction.

The complaints of nausea, vomiting and early satiety are often associated with the abnormal gastric emptying that usually complicates diabetes lasting for more than 10 years (Horowitz et al. 1986). It has been estimated that 27% of patients with insulin-dependent diabetes, treated for more than 5 years, had impaired gastric emptying of solid food (Keshavarzian et al. 1987). However, the detection of impaired gastric motor activity did not correlate with the occurrence of symptoms. Delayed emptying is caused by impaired phasic motor activity in the antrum and may be aggravated by an increased outflow resistance from either the pylorus or the small intestine. In advanced diabetes, improperly timed pyloric contractions of abnormal intensity and duration may lead to pylorospasm and to functional outlet obstruction. The pathogenesis of diabetic gastroparesis is poorly understood. Loss of sympathetic nervous function may play an important role in diabetic gastroparesis (Camilleri and Malagelada 1984) and the contractility of smooth muscle cells may be abnormal. In addition, hyperglycaemia, in the absence of an underlying neuropathy or myopathy, can alter gastric motor functions.

When associated with significant autonomic neuropathy, diabetes may lead to constipation and the risk of faecal impaction, megacolon, stercoral ulceration or perforation and volvulus (Knowles et al. 1999). Diabetic constipation is thought to be associated with an abnormal pattern of smooth muscle contractions, but slow wave activity of constipated diabetic patients does not differ from that of healthy controls (Battle et al. 1980). In insulin-dependent patients with constipation, abnormal postprandial colonic activity occurs and the expected postprandial increase in peristaltic activity is not observed. In diabetic patients without constipation, postprandial peristaltic activity is similar to that of controls (Castro and Cherry 1995). These observations suggest that abnormal colonic

motility of constipated diabetic patients is due to altered autonomic neural control.

The increase of dietary fibres may reduce intestinal transit time and improve constipation in diabetic patients. A diet rich in fibre also improves glucose tolerance and reduces insulin requirements. Lactulose and stool softeners, mineral oil or enemas may be periodically necessary to prevent faecal impaction but these must be used with caution. Chronic use of anthraquinone laxatives is to be avoided, because these agents may be toxic to the intrinsic colonic nerve plexus and may aggravate an existing autonomic neuropathy (Castro and Cherry 1995). Patients with severe diabetic enteropathy may develop constipation unresponsive to these measures. They may benefit, however, from cholinergic agents such as bethanechol (a cholinergic agonist) or pyridostigmine (a cholinesterase inhibitor). Metoclopramide is used for the treatment of diabetic gastroparesis, and may improve severe constipation. Cisapride and erythromycin (see below) may also be helpful (Watkins and Edmonds 1999).

Endocrinological and metabolic disorders

Hypothyroidism

Constipation and gaseous distention are common in patients with hypothyroidism and may be the first indication of the disease. Bowel dysfunction has an insidious onset in most patients; therefore, a high level of suspicion is necessary to diagnose hypothyroidism as a cause of constipation. In all patients with a prolonged or recurrent ileus the diagnosis of hypothyroidism should be entertained.

Hypomotility due to hypothyroidism affects the oesophagus, stomach, gall bladder, small bowel, colon, uterus and bladder. The precise pathophysiology of gut dysmotility is not completely understood. Small bowel transit is significantly delayed compared to normal controls. In treated patients who regain normal thyroid function, transit time also returns to normal.

Paralytic ileus and intestinal pseudo-obstruction can be associated with myxoedema (Salerno and Grey 1978). Dysphagia is a common complaint in these patients. Peristaltic contractions and primary oesophageal peristalsis are decreased in amplitude; the lower oesophageal sphincter may have

decreased pressure and the upper sphincter may not relax completely. These abnormalities also revert to normal when normal thyroid function is regained (Bunevicius et al. 1999).

Hyperthyroidism

Hyperthyroid patients may have diarrhoea and steatorrhoea; more than 7 g of fat is excreted in stools daily in one-fourth of such patients. Accelerated small bowel transit induces rapid gastric emptying (Wegener et al. 1992); oesophageal peristalsis is also increased and normalizes with treatment.

Multiple endocrine neoplasm

The syndromes associated with multiple endocrine neoplasm (MEN) are: MEN1, MEN2a and MEN2b. Medullar carcinoma of the thyroid and pheochromocytoma occur in MEN2a and MEN2b; parathyroid adenomas or hyperplasia occur in MEN1. The genetic mutation of MEN2a is similar to that of Hirschsprung's disease: mutations of genes encoding for *Ret* and for endothelin B receptors have been reported in these patients. MEN2b is a generalized motility disorder characterized by ganglioneuromatosis of the myenteric and submucous plexuses (Goyal and Hirano 1996). Achalasia and pseudo-obstruction are the most common GIT findings. Microscopically, a proliferation of nerves and of ganglion cells is found in the mucosa, the submucosa, and in the myenteric and subserosal plexuses throughout the GIT.

Porphyrias

Abdominal pain, moderate to severe in intensity, localized or generalized, is often the first symptom of porphyria. It is probably due to an underlying autonomic neuropathy causing disturbed motility with regional spasm or dilatation. Constipation is very common. The pathophysiology of the ENS abnormality in the porphyrias is not fully elucidated.

Amyloidosis

Amyloid deposits in the bowel are found in all forms of amyloidosis: primary, secondary, associated with myeloma, and hereditary (i.e., familial Mediterranean fever). The severity of dysmotility is related to the amount and to the distribution of amyloid deposits. In primary amyloidosis and in that associated with myeloma, the muscle layers in

the small bowel are more severely affected than the mucosa. In secondary amyloidosis and in the hereditary forms, the mucosa is predominantly involved causing malabsorption. Amyloid deposits are infrequently found in the myenteric plexus, but in the hereditary forms a neuropathy may result from amyloid deposition in the nerve trunks supplying the bowels. Clinical GIT symptoms include constipation, obstruction and occasional bleeding. The oro-caecal transit time is prolonged to more than twice normal (Matsumoto et al. 1991). In familial amyloid polyneuropathy the GIT is often involved. This can result in xerostomia, nausea and vomiting, postprandial hypotension, diarrhoea or constipation (Jeeves and Mathias 1998).

Anderson-Fabry disease

This is an X-linked glycosphingolipidosis, caused by impaired function of α -galactosidase A. It is characterized by the deposition of ceramide trihexose in the lysosomes of the endothelium, the nerves and smooth muscle cells. GIT manifestations occur in as many as 62% of affected men and 29% of female carriers. They include episodic constipation, diarrhoea, nausea, vomiting, abdominal pain, and, exceptionally, intestinal ischaemia and perforation. The pathophysiology of these symptoms, although unclear, may relate to impaired gut motility (O'Brien et al. 1982). Non-myelinated axons are found in specimens of jejunum and rectum biopsies.

Paraneoplastic syndromes

See also this volume, Chapter 19. Neoplasms can invade the lower oesophageal sphincter and produce achalasia as the result of encirclement or compression of the distal oesophagus or malignant infiltration of Auerbach's plexus in the oesophagus. Paraneoplastic achalasia may be caused by tumours, such as Hodgkin's disease, poorly differentiated bronchogenic carcinoma or hepatoma. It cannot be distinguished from idiopathic achalasia based on manometric findings. Diagnosis is provided by endoscopic biopsy.

A disturbance of gastric motility, without any obvious mechanical obstruction, may be observed in patients with upper GIT malignancies. Chronic intestinal pseudo-obstruction due to a paraneoplas-

tic visceral neuropathy occurs in patients with small cell lung carcinoma (Schuffler et al. 1983). Widespread neuronal and axonal degeneration of the myenteric and submucous plexuses are associated with mononuclear cell infiltration and proliferation of Schwann cells. A neuroimmune mechanism has been postulated in this form (Cuillerier et al. 1998).

Psychiatric disorders

The impact of emotion on the gut has been appreciated since the 19th century. Changes following acute mental stress have even been described in the distal large intestine of a healthy subject (Almy 1951).

Environmental stress plays a pathogenic role in GIT disorders. Response to normal events evoke changes of variable magnitude, depending on personal traits and on the prevailing emotional state. The effects on motility in healthy people are well documented. In the oesophagus, experimental stress induces vigorous spasms; exposure of the skin to cold or to an electrical shock may provoke antral gastric contractions and delayed gastric emptying. Psychological stress may reduce the incidence of fasting state MMC in the small intestine (Valori et al. 1986). These effects usually have rapid onset and revert to normal quickly.

Psychological stress exacerbates symptoms of irritable and inflammatory bowel disorders. These patients have greater susceptibility to psychological and physical stresses than normal subjects. Manometric recordings of small bowel motility reveal normal GIT motor behaviour during sleep, which, upon waking, changes to an irregular pattern that differs greatly from the organized MMC of normal subjects. Patients with irritable bowel disorders are more likely to have stress related changes in bowel motility and abdominal pain than controls (Drossman et al. 1988). These patients present larger motor responses to balloon distention of the rectosigmoid than normal people (Whitehead et al. 1980). Enhanced sensitivity to distention may reflect abnormalities of sensory detection in the periphery or in the central processing of sensory input (Kellow et al. 1988).

A pathogenic role of psychological stress has long been suspected for ulcerative colitis and

Crohn's disease. The beneficial effect of cigarette smoking on ulcerative colitis and its exacerbation after withdrawal may be interpreted as a stress related phenomenon. Studies on an experimental model of ulcerative colitis suggest that environmental stress may be the initiating factor for inflammation.

There is evidence for a higher incidence of personality disorders in patients with GIT motility disturbances, but no specific psychiatric illness is clearly associated with digestive diseases (Clouse and Lustman 1983). Depression and hysteria occur more often in patients with GIT motility disorders than in the general population, but their incidence is the same as that found in people with physical complaints, such as back pain or headache. Anxiety produces a broad range of GIT symptoms. Emotional factors contribute to the symptoms of hysteric globus, oesophageal spasm, nutcracker oesophagus, non-ulcerative dyspepsia, and irritable bowel disorder (Whitehead et al. 1992). Schizophrenia is not associated with GIT disturbances, but neuroleptic agents have a cholinergic blocking activity that may cause gastric retention, megacolon and constipation.

Abnormal gastric motor function must be excluded before establishing a diagnosis of anorexia nervosa when acute dilatation of the stomach is an early manifestation. Impaired gastric emptying of semisolid or solid food is found almost invariably in anorexia nervosa, while liquid emptying is not consistently delayed. Manometry reveals low-amplitude phasic antral contractions in the fasting and fed conditions. The pathogenesis of these GIT motor abnormalities is probably multifactorial. In addition, malnutrition can be associated with delayed gastric emptying, which improves with weight gain.

Other causes of dysmotility

Drug induced dysmotility

Many drugs (such as anticholinergic, opiates, etc.) affect GIT motility. The colon is usually the main target organ for drug induced dysmotility, but the small bowel may be affected as well. Any medication should be considered a possible aetiological agent during the evaluation of a patient with a GIT motility disorder. Constipating remedies warrant

special attention, since their use is ubiquitous in the elderly. Obvious offenders include diuretics, bile acid binders (such as antacids containing calcium or aluminium), cholestyramine, colestipol, analgesics and anticholinergics.

The chronic use of laxatives for severe constipation may be a cause of constipation, although it is difficult to determine their exact role in a given patient. In patients treated chronically with anthraquinone derivatives or bisacodyl, colon biopsy shows neurosecretory granule depletion and reduction in the number of neurotubules in submucosal nerve fibres (Tedesco and DiPiro 1985). The observation of *melanosis coli* at endoscopy may indicate laxative abuse.

Drugs that stimulate bowel motility include cisapride, octreotide, erythromycin, and cholinergic agonists. Erythromycin binds to motilin receptors on the smooth muscle of the gastric antrum and duodenum (Janssens et al. 1990) to induce MMC. Cholinergic agonists (such as bethanechol) increase the amplitude of small bowel contractions and induce motility (Taylor 1985). Octreotide, a long-acting synthetic analog of somatostatin, increases the frequency of MMC, shortening the duration of phase II. Cisapride is a prokinetic agent that increases ACh release in the myenteric plexus, accelerates transit of liquids and solids through the small intestine and is used to treat patients with chronic intestinal pseudo-obstruction. Cisapride induces phase II-type activity in the fasting state and increases small bowel motility after a meal. A recent benzofuran derivative, Ro-93877, facilitates cholinergic and non-adrenergic non-cholinergic neurotransmission (Emmanuel et al. 1998). It is likely that constipation may be favourably influenced by this drug, which also increases the urge to defecate and output of stool. Ro-93877 has a short delay of activity, in contrast to cisapride which produces effects only after several weeks.

Drug abuse can have deleterious effects on the GIT. Alcohol consumption may produce dysphagia and promotes oesophageal reflux. Alcohol enhances lower oesophageal sphincter pressure, decreases the frequency of oesophageal peristaltic contractions, and delays oesophageal emptying. High-amplitude peristaltic contractions have also been reported (Keshavarzian et al. 1987). Alcohol

enhances small intestinal transit, decreases brush border enzyme activity, and impairs absorption of nutrients (Malagelada et al. 1986). Opiates slow colonic peristalsis and thus frequently induce constipation (Castro and Cherry 1995).

Infectious diseases

The most common infectious disorder causing GIT dysmotility is Chagas' disease (see this volume, Chapter 14; De Oliveira et al. 1998). *Trypanosoma cruzi* infection leads to smooth muscle dysfunction, commonly affecting the heart, oesophagus and colon (Ribeiro et al. 1998).

SECRETOMOTOR DYSFUNCTION

Diarrhoea due to abnormal secretion

The pathophysiology of diarrhoea involves abnormal intestinal secretion due to a deranged electrolyte transport. Several chemical compounds and secretagogue toxins may stimulate mucosal receptors exposed to the lumen and activate the intestinal secretor reflexes. Almost half of the intestinal secretion initiated by bacterial endotoxins in vivo is triggered by enterochromaffin cells that release hormones, which in turn activate the ENS and stimulate the enterocyte (Lundgren et al. 1989). Inflammatory mediators released from immune and mesenchymal cells in the lamina propria and in the submucosa may also initiate intestinal secretion. Substances released by mast cells, activated phagocytes, or mesenchymal cells may all directly stimulate enterocytes or may induce the release of prostaglandin from mesenchymal cells in the sub-epithelial layer. These mediators may also activate the ENS.

Toxins bound to receptors activate adenyl cyclase. Elevated intracellular concentrations of cAMP cause chloride and water secretion from crypt cells. In experimental models, the secretion of fluid in response to the application of cholera toxin to the surface of the intestinal mucosa can be reduced by nerve blockers, such as lidocaine or tetrodotoxin, or by nicotinic receptor blockers (Lundgren et al. 1989). This response is also reduced by antagonists of 5-HT₂ and 5-HT₃ receptors (Beubler and Horina 1990), but not by extrinsic denervation or treatment with capsaicin, a drug

that selectively destroys splanchnic primary afferent nerves containing substance P (Buch and Burks 1986). The secretor response to cholera toxin involves an intrinsic secretomotor reflex. Interneurons or secretomotor neurons in the myenteric plexus are probably involved, because the response is reduced by the application of benzyl ammonium chloride, which lesions the myenteric plexus (Herman and Bass 1989).

The secretor effects of a toxin applied to the jejunum are evident not only locally, but in the distal colon. The colonic effect involves intrinsic neural reflexes rather than humoral mediators or extrinsic nerves, indicating a widespread ENS activation (Nocerino et al. 1995). The ENS plays a role in the secretor action of non-invasive secretagogue compounds in vivo. Agents that cause excessive intestinal secretion may also induce motor abnormalities that contribute to diarrhoea. *Escherichia coli* toxin, cholera toxin, and ricinoleic acid elicit giant peristaltic contractions and associated MMC in the intestinal musculature distal to the segment where the toxin is applied (Cubeddu et al. 1990).

Diarrhoea and malabsorption following vagotomy

Vagal denervation affects the upper GIT and the biliary system. Malabsorption that follows truncal vagotomy may be due in part to diarrhoea, poor mixing of food with pancreatic secretions and bile salts, or diminished release of CCK and secretin.

The prevalence of diarrhoea following truncal vagotomy varies from 25 to 70%, and is troublesome in 1–5% of patients. Diarrhoea is often intermittent, with 10–25 watery stools per day. It may result from stasis of food in the stomach and the small intestine, causing bacterial overgrowth, uncontrolled gastric emptying, and exaggerated small intestinal transit. Steatorrhoea is common after vagal denervation. No difference is found between faecal fat content after truncal vagotomy or selective vagotomy.

Absorption and metabolism of glucose are altered by vagotomy and pyloroplasty. The malabsorption is attributed to rapid gastric emptying and decreased transit time in the small intestine, which overload the limited glucose absorbing capacity of the gut.

INFLAMMATORY DISORDERS

Clostridium difficile infection

Clostridium difficile toxin A is known to cause a necrotizing and inflammatory response, with infiltration of neutrophils and increased fluid secretion in the gut. The inflammatory and secretor effects of this toxin involve intrinsic neural pathways and lead to mast-cell degranulation and to the secretion of multiple inflammatory mediators, including prostaglandin, histamine, and 5-HT. These mediators may stimulate secretomotor reflexes, including submucosal vasodilatation (Vanner et al. 1993). The release of calcitonin gene related peptide from primary afferent neurons innervating submucosal arterioles is also involved in vasodilatation (Kurose et al. 1994).

Mast-cell degranulation and inflammation are mediated by neural mechanisms, because they are suppressed by neural blockade (Castaglini et al. 1994). Pretreatment with capsaicin, which selectively destroys substance P containing primary afferent neurons, or with substance P antagonists, also inhibits secretor and inflammatory responses to toxin A (Pothoulakis et al. 1994). This suggests that the action is mediated by substance P containing primary splanchnic afferent fibres. In addition to its secretor effects, *C. difficile* toxin A also produces a pattern of intestinal motility characterized by trains of contractions representing repeated bursts of action potentials (Goyal and Hirano 1996).

Ulcerative colitis and Crohn's disease

Ulcerative colitis and Crohn's disease are immune mediated disorders characterized by chronic, relapsing inflammatory responses. Evidence supports a possible role for the ENS in the pathogenesis of these inflammatory bowel diseases. Psychological stress may exacerbate symptoms of ulcerative colitis or Crohn's disease, suggesting interactions among CNS, ENS, and GIT.

A number of pathways can link key functions of the neuroendocrine and mucosal immune systems. In both Crohn's disease and ulcerative colitis, the immunoreactivity of substance P is increased and binding sites for substance P receptors

are widely expressed (Mazumdar and Das 1992). Substance P probably has a pro-inflammatory action in the gut; substance P-receptor antagonists decrease the infiltration of granulocytes in colitis induced by trinitrobenzenesulfonic acid (McCafferty et al. 1994). An elevation of cytokines, including interleukins 1, 6 and 8, with immunoregulatory and pro-inflammatory activity, has been demonstrated during active inflammatory bowel disease (Sartor 1994; Cominelli and Pizarro 1996). These cytokines may play a role in the initiation and amplification of the inflammatory response and in the pathophysiology of tissue injury. Tissue levels of cytokines are elevated and correlate with the severity of inflammation (Gabay and Kushner 1999).

Abbreviations

5-HT = serotonin; ACh = acetylcholine; ATP = adenosine triphosphate; CCK = cholecystokinin; CNS = central nervous system; ENS = enteric nervous system; EPSP = excitatory postsynaptic potential; GABA = γ -aminobutyric acid; GDNF = glial cell line-derived neurotrophic factor; GIT = gastrointestinal tract; IPSP = inhibitory postsynaptic potential; MNGIE = mitochondrial neurogastrointestinal encephalomyopathy; MSA = multiple system atrophy; MMC = migrating motor complex; NE = norepinephrine; NO = nitric oxide; PD = Parkinson's disease; VIP = vasoactive intestinal polypeptide.

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