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Pseudo-obstruction syndromes

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The term *intestinal pseudo-obstruction* is used to indicate a syndrome characterized by impairment of intestinal propulsion and a clinical picture resembling mechanical obstruction, in the absence of any lesion occluding the lumen of the gut.

Pseudo-obstructive syndromes may be acute or chronic. *Acute pseudo-obstruction* (or paralytic ileus) (Wood, 1981) occurs in the vast majority of patients undergoing abdominal surgery and spontaneously resolves within a few days. It may also be caused by peritonitis (Jones, 1983) and severe infections (especially if induced by Gram-negative bacteria), hypokalaemia (and severe electrolyte imbalance in general), retroperitoneal haemorrhage, spinal or pelvic fractures, and also myocardial infarction. The mechanisms through which these different pathological conditions may temporarily suppress intestinal motility are, as yet, incompletely clarified. One hypothesis suggests that prolonged activity of intrinsic inhibitory neurons driven by neural and/or circulating mediators may be involved (Oliveira et al, 1983). The term *chronic intestinal pseudo-obstruction (CIP)* was first coined by Maldonado and colleagues in 1970 (Maldonado et al, 1970), although patients experiencing episodes of intestinal obstruction in the absence of a mechanical obstacle to transit have been carefully described since the end of the last century (Murphy, 1896). In agreement with Maldonado et al, we feel that the term chronic intestinal pseudo-obstruction should be limited to those syndromes in which symptoms and signs mimic mechanical obstruction. Surgery is often ineffective since the symptoms can recur after bowel resection. CIP may derive from abnormalities of both myogenic (Schuffler and Pope, 1977; Anuras et al 1983, 1986; Leon et al, 1986) and neurogenic (Schuffler and Jonak, 1982; Oliveira et al, 1983; Schuffler et al, 1985; Krishnamurthy et al, 1986; Mayer et al, 1986) control of gut motility. In the former case, the impairment of progression of intraluminal contents is due to a reduction of the force of muscular contractions and in the latter, to a loss of co-ordination of contractions. Both myogenic and neurogenic CIP may be either 'secondary' to a recognized pathological condition, or 'idiopathic' (chronic idiopathic intestinal pseudo-obstruction—CIIP) (Faulk et al, 1978; Schuffler, 1981;

Schuffler et al, 1981). There is evidence for familial forms of CIIP (Wood, 1981).

In order to understand better the mechanisms and consequences of the motor abnormalities responsible for pseudo-obstructive syndromes, the important recent developments in gastrointestinal (GI) motor physiology will be briefly summarized.

PHYSIOLOGY OF GASTROINTESTINAL MOTILITY

The basis of the recent rapid development of our knowledge in the physiology and pathophysiology of gastrointestinal motor activity is the reliability of the techniques presently used for recording the electrical and mechanical activity of gut smooth muscle.

Myoelectrical activity of GI smooth muscle cells

Smooth muscle cells of the distal two thirds of the stomach and of the small bowel and colon of humans and most other mammalian species present spontaneous rhythmic fluctuations of membrane potentials determined by alterations in transmembrane ion fluxes (Szurszewski, 1981). These potentials are termed *slow waves* or *electrical control activity (ECA)*. Their shape depends on the technique used for recording. In *in vivo* recordings, the electrodes employed are relatively large and detect potential fluctuations from many thousands of cells. Recordings *in vitro* are carried out by electrodes implanted into single cells, and each slow wave appears to be composed of an initial upstroke followed by a plateau potential (Kim and Malagelada, 1986). ECA is generated from specific areas in the stomach and intestine called *pacemakers*. The gastric pacemaker is situated on the great curvature, in the region separating the fundus from the antrum (Hinder and Kelly, 1977). The proximal intestinal pacemaker has been located in the descending duodenum (Milton and Smith, 1956), but each region of small bowel can act as a pacemaker. Slow waves propagate directly from one smooth muscle to the adjacent one through gap-junctions (Gabella, 1981). Slow waves, with characteristic frequencies, migrate aborally from the pacemaker areas and 'drive' distal segments of less frequent intrinsic activity. In the human stomach, ECA spreads from the pacemaker to the pylorus at a frequency of 3 cycles per min. In the small bowel, the frequency progressively decreases in a series of plateaux from the duodenum (11 cycles/min) to the distal ileum (8-9 cycles/min) under the control of different pacemakers with decreasing frequencies. The interstitial cells of Cajal, which lie between the circular and longitudinal layers of muscle are thought to be the pacemaker cells.

The smooth muscle contracts only when the membrane depolarization exceeds a hypothetical threshold (Szurszewski, 1981). Under basal conditions slow waves produce only a small muscle contraction, hardly detected by *in vivo* techniques and occurring as the upstroke of the action potential exceeds the threshold. Neurohormonal stimulants such as acetylcholine and penta-gastrin cause a contraction of greater force and duration by increasing the

amplitude of the plateau potentials and by causing bursts of spike potentials or electrical response activity (ERA), superimposed on the plateaux (Szurszewski, 1975, 1981). In contrast, inhibitory mediators such as catecholamines and prostaglandin E₂ inhibit contractions by decreasing the amplitude of the plateau potentials (Szurszewski, 1981; Sanders et al, 1979). Thus the properties of intestinal smooth muscle determine the timing, potential frequency and rate of propagation of contractions, but whether or not contractions occur depends on the release of transmitters from the enteric nervous system (ENS) or the release of hormones. The ENS is largely responsible for determining the pattern of contractions in the small intestine.

Fasting motility

In healthy individuals, interdigestive motility cycles in three successive phases (Code and Marlett, 1975). Phase I is characterized by motor quiescence, phase II by irregular contractility, and phase III (or the activity front) by a burst of contractions occurring at or close to the maximal frequency allowed by the ECA rhythms. The three phases constitute the so-called migrating motor complex (MMC) (Figure 1). The activity fronts of the MMC begin in the gastric antrum or in the proximal small bowel and migrate slowly to the ileum (3–8 cm/min), transporting intraluminal contents (food remnants, exfoliated cells, bacteria and digestive secretions) distally. They usually fade out shortly before they reach the distal ileum, and their spread and periodicity are highly variable (Kerlin and Phillips, 1982). The mechanisms of initiation and propagation of MMCs have been investigated in numerous studies; these have been recently reviewed (Sarna, 1985).

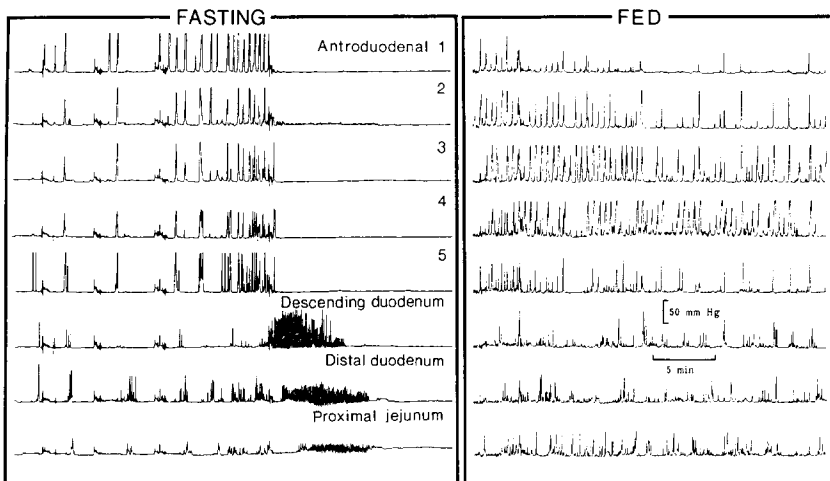


Figure 1. Normal gastrointestinal motility in a healthy subject during fasting (left) and after the ingestion of a meal with solid components (right).

Studies carried out to evaluate the influence of extrinsic neural control have yielded conflicting results (Carlson et al, 1972; Weisbrodt et al, 1975; Marlett and Code 1979; Itoh et al, 1981; Gleysteen et al, 1985; Sarna et al, 1985). It is now generally accepted that neither parasympathetic nor sympathetic nervous supplies are necessary for the onset and spread of MMCs, but both may exert a modulating role on their frequency (Bueno et al, 1979). Hormones such as pancreatic polypeptide, somatostatin, and motilin may modulate MMCs, but a clear cause and effect relationship has not been established (Wingate et al, 1975; Keane et al, 1978; Peeters et al, 1983). It now seems likely that MMC onset and migration are under the control of the ENS. Activity fronts are still present in isolated segments of small intestine and, if the segments are re-anastomized after transection, MMCs occur independently in the different segments (Sarna et al, 1983) until regeneration of intrinsic nerves across the anastomosis restores the original co-ordination.

Postprandial motility

After ingestion of food, the fasting motor pattern motility is rapidly replaced by an irregular contractile pattern which homogenizes gastrointestinal contents by mixing food and digestive secretions, and transports the resultant chyme slowly in a net aboral direction.

The duration of the fed motor pattern depends upon the amount of nutrients ingested and on their physical and chemical composition (Weisbrodt, 1981). Gastric fed motility is characterized by a series of intense phasic contractions (Figure 1) which must accomplish the important task of breaking down digestible solids into particles with diameters of approximately 1 mm (Meyer et al, 1981). In the small intestine the fed pattern is represented by irregular phasic contractions which often propagate over short distances (Figure 1). As with other patterns of contractile activity, the postprandial motor activity is thought to be determined by the ENS, and modulated by hormones and the extrinsic nerves. Intravenous infusions of several hormones (gastrin, GIP, CCK, secretin, insulin) disrupt the MMCs and induce patterns found in the fed state (Valenzuela, 1976; Mukhopadhyay et al, 1975, 1977; Eeckhout, 1978). Vagotomy only slightly influences the response to feeding (Marik and Code, 1975). However, vagal cooling in dogs interrupts the fed motility and induces an MMC-like pattern (Diamant et al, 1980). Similar results have been obtained by applying stressful stimuli to healthy subjects (Stanghellini et al, 1983), and these effects are at least partially mediated by the release of opioids and catecholamines (Stanghellini et al, 1984). The role of the intrinsic nerves is illustrated by the ability of glucose solutions to disrupt MMCs in isolated perfused loops of small intestine but not in the other regions of small intestine (Eeckhout et al, 1979). However, in the same animal model, ingestion of food induces the fed motor pattern in both the intact small intestine and the isolated loop (Mukhopadhyay et al, 1977), illustrating the action of extrinsic mechanisms.

CLINICAL FEATURES OF CIP

CIP is characterized by recurrent bouts of abdominal pain, nausea and/or vomiting, distension and/or bloating, mimicking mechanical occlusion. Between two occlusive episodes, patients may be asymptomatic, but more often they complain of symptoms of variable intensity. When the disease mainly affects the proximal portions of the gut, nausea, vomiting and weight loss predominate, while in colonic pseudo-obstruction, the clinical picture is mainly characterized by diffuse abdominal pain, severe distension (mimicking 5th to 9th month of pregnancy) and constipation. Diffuse disorders present with variable combinations of symptoms. Diarrhoea and steatorrhoea may occur secondary to bacterial overgrowth of the small bowel (Pearson et al, 1969). Dysphagia is present in a minority of patients with CIP, but it is relatively frequent in those affected by pseudo-obstruction secondary to progressive systemic sclerosis (Schuffler, 1981).

The syndrome occurs in patients of all ages, with a certain female predominance. Of 42 patients with idiopathic CIP recently studied at the Mayo Clinic, 28 were women and 14 men; their ages ranged between 5 and 76 years (Stanghellini et al, 1987). At presentation, the main symptoms were: nausea and vomiting (83%), abdominal pain (74%), distension or bloating (57%), constipation (36%), diarrhoea (29%), and urinary tract symptoms (17%). Interestingly, similar clinical presentations have been found in patients affected by CIP, secondary to other conditions (Schuffler, 1981; Schuffler et al, 1981). Involvement of the pupillary sphincters has also been described (Schuffler, 1981).

The onset of CIP is generally insidious, the first pseudo-obstructive episode being preceded by many years of dyspepsia and constipation of increasing severity. More rarely, however, CIP commences for the first time after operations. Jejunio-ileal anastomosis, carried out to treat obesity has been particularly associated with CIP (Fikri and Cassella, 1974; Barry et al, 1975), but this may be caused by ileal inhibition of small bowel motility due to the increased ileal content of unabsorbed food (Read et al, 1984). Oesophageal sclerotherapy may also precipitate CIP through unknown mechanisms (Rasbridge et al, 1986). Most patients have undergone repeated laparotomies in the vain attempt to eliminate the cause of the repeated occlusive episodes. In the series seen at the Mayo Clinic (Stanghellini et al, 1987), only nine patients were seen prior to abdominal surgery; of the remaining 33, 12 had simple exploratory laparotomies, 10 had also gastric surgery (vagotomy in all, partial resection in 8), seven had segmental small bowel resections and four had colectomy with ileoproctostomy. None of these surgical measures improved the patients symptoms.

Differential diagnosis of CIP must take into consideration mechanical obstruction on the one hand and severe dyspepsia and/or constipation on the other. During obstructive episodes, it is very difficult to exclude the existence of a mechanical occlusion. The symptoms are almost identical, except that pseudo-obstructive episodes are compatible with the passage of flatus (Code and Marlett, 1975). A history of similar episodes that either resolved spontaneously or recurred in spite of repeated laparotomies strongly suggests

CIP, although the possibility of adhesions induced by laparotomies or other concurrent mechanical obstruction, such as occult hernias, cannot be ruled out. Abdominal radiology usually shows air–fluid levels and distended abdominal loops in both conditions. Diagnosis is established by demonstrating the absence of mechanical obstruction by endoscopic or radiological investigations using contrast media (see below). Also gastrointestinal manometry can help in differentiating mechanical from functional obstructions (see below). Between occlusive episodes, patients with CIP may have symptoms indistinguishable from those of severe dyspepsia or intractable constipation, and neither radiology nor manometry help in establishing the diagnosis (see below).

DIAGNOSTIC APPROACH

Laboratory investigations

Laboratory tests do not help in establishing the diagnosis, but are important in identifying possible causes and monitoring the patient's condition.

Immunological tests (ANA-binding titre, autoantibodies, rheumatoid factor) and complement levels may suggest the presence of progressive systemic sclerosis or other collagen vascular diseases. Monoclonal gammopathies may predispose to amyloidosis which will be diagnosed by histology (biopsies of rectum, gums, bone marrow). Twenty-four-hour monitoring of glucose and plasma insulin levels or glucose tolerance tests are important and may reveal the presence of diabetes. Viral antibodies should be assayed in all CIP patients. Abnormalities in circulating levels of tri-iodothyronine (T_3), thyroxine (T_4) and thyroid-stimulating hormone (TSH) may signal thyroid dysfunction. Abnormal urinary concentrations of catecholamines and their metabolites may indicate pheochromocytoma. Diarrhoea is generally due to small bowel bacterial overgrowth and is accompanied by malabsorption of fat, lipid-soluble vitamins, vitamin B_{12} , folic acid, iron, calcium, and other minerals. Even low degree malabsorption may lead to clinically relevant imbalances if associated with poor dietary intake.

Radiology

Erect or supine abdominal x-rays show air–fluid levels in the intestine during obstructive episodes, but do not differentiate pseudo-obstruction from mechanical obstruction.

Contrast examination is the most readily available diagnostic tool capable of demonstrating the presence of a mechanical occlusion of the intestinal lumen. Radiographical studies of the oesophagus, stomach, small intestine, and colon should be obtained in all patients (Schuffler, 1981). The most frequent findings include dilatation and abnormal peristalsis of the oesophagus (Nahai, 1969; Schuffler and Pope, 1976; Schuffler et al, 1977, 1978, 1981; Schuffler and Deitch, 1980; Bannister and Hoyes, 1981; Soffer et al, 1984; Shaw et al, 1985; Anuras et al, 1986a, b; Bruyn et al, 1986), and of small

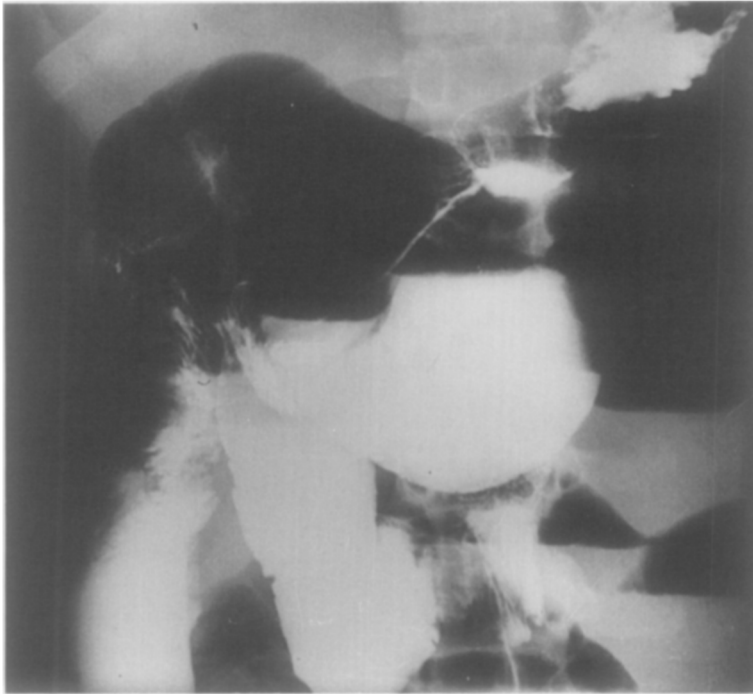


Figure 2. Barium radiograph of a man with chronic intestinal pseudo-obstruction. Note the severe dilatation of duodenum and small bowel loops. Several air-fluid levels are also present.

intestine (Nahai, 1969; Hines and Davies, 1973; Luderer et al, 1976; Schuffler et al, 1977, 1978; Anuras et al, 1979, 1986; Schuffler and Deitch, 1980; Bannister and Hoyes, 1981; Conklie and Anuras, 1981; Soffer et al, 1984; Shaw et al, 1985; Bruyn et al, 1986) (Figure 2), as well as dilatation and elongation of the colon (Schuffler et al, 1977, 1981; Anuras et al, 1979, 1986a, b; Sutcliffe and Deitch, 1980; Waterfall et al, 1981; Schuffler and Jonack, 1982; Soffer et al, 1984; Shaw et al, 1985). The stomach usually appears normal: the most common abnormality being a delayed emptying of radio-opaque substances (Naish et al, 1960; Dyer et al, 1969; Schuffler et al, 1978, 1985; Bannister and Hayes, 1981; Waterfall et al, 1981). Contrast enemas are of diagnostic importance in patients with symptoms suggestive of colonic obstruction (diffuse abdominal pain, severe distension and constipation). In a recent study (Koruth et al, 1985), water-soluble contrast enemas were used in 91 of these patients. Twelve of them were thought, on clinical grounds, to have pseudo-obstruction. Radiology confirmed the diagnosis in 10 but showed the presence of large bowel carcinomas in two. In the remaining 79 patients, a mechanical obstruction was suspected; this was confirmed in 61. A negative study prevented surgery in the remainder. Although radiology is an essential tool for diagnosing CIP, it can yield false positive and false negative results and the physician should evaluate critically the radiological findings. The

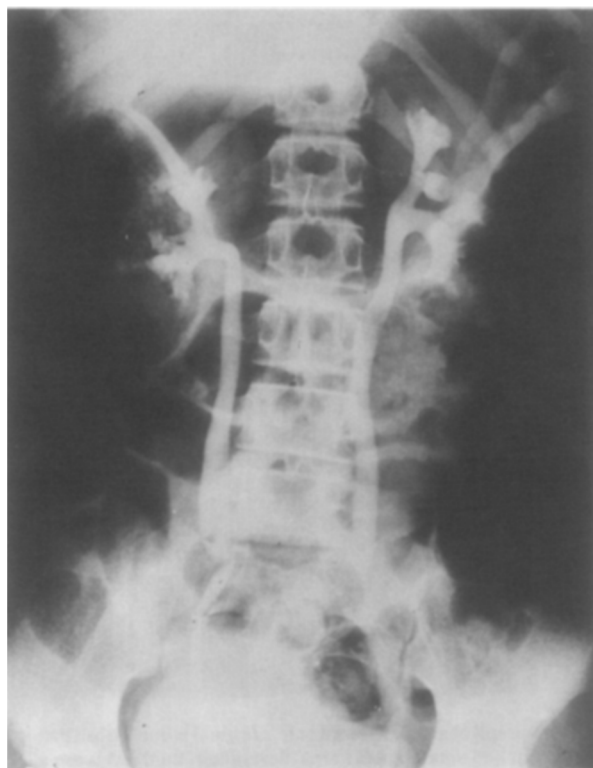


Figure 3. Excretory urogram of the same patient as shown in Figure 2, showing bilateral dilatation of calyces, pelvis and ureters.

urinary tract should also be studied, as evidence of dilated calyces, pelvis, ureter and bladder in patients with recurrent obstructive symptoms is strongly suggestive of a diffuse disease involving the myogenic or neurogenic control of smooth muscle (Figure 3).

Finally, careful radiographical and cineradiographical studies may also give some suggestions about the nature of the disease responsible for CIP. Systematic radiological evaluation of the whole digestive canal was performed in 34 patients with CIP, the origin being established by clinical and histological criteria (Rohrman et al, 1981). Eighteen patients had progressive systemic sclerosis (PSS, scleroderma), 11 visceral myopathies and five visceral neuropathies. Patients with PSS presented characteristic packed valvulae in the small intestine. Other features of PSS were oesophageal hypoperistalsis, and strictures or sacculations of both the small and large bowel. Histology showed fibrosis and atrophy of the smooth muscle, especially of the circular layer. This may lead to predominance of longitudinal fibres with consequent 'packing' of the intestinal wall. Decreased circular muscle force may also explain lower oesophageal sphincter (LOS) weakness, increased gastro-

oesophageal reflux and oesophageal strictures. Myogenic pseudo-obstruction was characterized by oesophageal hypoperistalsis and enlargement of the small and large intestine. Only a few patients with neurogenic pseudo-obstruction were evaluated; both hypo- and hypermotility were observed in the oesophagus; dilatation of the intestine was present, but generally to a lesser degree than in PSS or myogenic CIP. Intestinal hypercontractility with 'spasm severe enough to mimic true obstruction' was also described in some cases.

In conclusion, well conducted radiological studies of the digestive canal may be regarded as useful tools in the diagnosis of CIP despite some shortcomings: for example, interpretation cannot rely on standardized parameters and is based mainly on the experience of the radiologists; furthermore, mechanical obstruction can be overestimated and differential diagnosis among the different types of CIP by radiology alone is very difficult.

Endoscopy

Oesophagogastroduodenoscopy and colonoscopy may represent valid alternatives to radiology in the diagnosis of obstructing processes involving the proximal and distal portions of the gut. They also have the advantage of allowing mucosal specimens to be obtained for pathological diagnosis of conditions such as intraluminal neoplasm, amyloidosis and non-tropical sprue.

Oesophageal manometry

Many reports have described oesophageal manometric findings in patients with CIP (Schuffler and Pope, 1976, 1977; Schuffler et al, 1977, 1978, 1981, 1983, 1985; Sullivan et al, 1977; Anuras et al, 1978, 1979, 1983, 1986b; Faulk et al, 1978; Lewis et al, 1978; Schuffler, 1981; Wood, 1981; Schuffler and Junak, 1982; Booth et al, 1983; Smouth et al, 1985; Krishnamurthy et al, 1986; Mayer et al, 1986). In some patients no abnormality has been detected (Anuras et al, 1978; Schuffler et al, 1981; Krishnamurthy et al, 1986) but variable patterns of dysmotility have been found in most patients, confirming that pseudo-obstruction is a diffuse disorder. Oesophageal dysmotility is not necessarily accompanied by suggestive symptoms and should be looked for in every CIP patient, regardless of the clinical presentation. Manometric features do not necessarily allow us to differentiate myogenic from neurogenic pseudo-obstruction, although some differences may be found. In the myogenic forms, the proximal portion of the oesophagus generally presents post-deglutitive normal peristalsis, while the distal tract shows either low-amplitude, simultaneous contractions (Schuffler and Pope, 1977) or no contractions at all (Anuras et al, 1979, 1986b). The LOS pressure has been reported to be decreased (Anuras et al, 1979) or increased (Anuras et al, 1986b), and relaxation is sometimes reduced or absent. The mecholyl test is generally negative (Schuffler and Pope, 1977; Schuffler et al, 1981). In neurogenic pseudo-obstruction, LOS pressure has been found both increased (Mayer et al, 1986) and decreased (Schuffler and Jonak, 1982; Schuffler et al, 1985;

Smooth et al, 1985), and failure of complete relaxation has been frequently reported (Schuffler et al, 1978, 1983; Mayer et al, 1986). The mecholyt test is generally positive (Schuffler et al, 1978, 1981). Other abnormal findings in neurogenic pseudo-obstruction include repetitive contractions after swallows (Schuffler et al, 1978, 1983), sometimes simultaneous and with low amplitude (Schuffler and Jonak, 1982) and sometimes intense and unco-ordinated (Schuffler et al, 1981). In a patient with co-existence of smooth muscle and neuronal abnormalities, only low amplitude, simultaneous contractions were recorded and the LOS was of normal pressure but relaxed incompletely (Smooth et al, 1985). In pseudo-obstruction caused by PSS, LOS shows reduced pressure, but normal relaxation; swallowing is not generally followed by peristalsis but produces low amplitude contractions (Schuffler et al, 1981) in some patients.

Gastrointestinal manometry

Pseudo-obstruction is due to disordered gastrointestinal motor activity (Anuras et al, 1983, 1986a, b; Booth et al, 1983; Schuffler et al, 1983; Summers et al, 1983; Soffer et al, 1984; Smooth et al, 1985; Mayer et al, 1986). In a recent paper, gastrointestinal manometric studies were carried out during fasting and after feeding in 42 patients with CIIP, seen consecutively at the Mayo Clinic (Stanghellini et al, 1987). In this group, radiological studies detected gastrointestinal abnormalities in 57% of patients; manometric studies were abnormal in all the patients. Four major patterns of intestinal dysmotility were detected: (a) aberrant propagation and/or configuration of activity fronts; (b) bursts of non-propagated phasic pressure activity; (c) sustained, unco-ordinated intestinal contractions; and (d) inability to convert fasting into fed pattern.

Propagation of activity fronts was regarded as abnormal when phase III appeared simultaneously at different recording sites along the small bowel or migrated in an oral direction (Figure 4). The configuration of activity fronts was considered abnormal when tonic elevations of baseline pressure were higher than 30 mmHg and lasted at least 3 minutes. Bursts were defined as periods of at least 2 minutes duration with continuous high amplitude (> 20 mmHg) and high frequency (close to the frequency of ECA typical of the segment involved) phasic contractions that were not propagated and not followed by motor quiescence (unlike typical phase III activity of the MMC). Phasic contractions were sometimes associated with tonic elevation of baseline pressure. Bursts were recorded during both fasting (Figure 5) and fed periods. Sometimes intense phasic contractions similar to those characteristic of bursts were recorded for very prolonged (> 30 min) periods of time. Unlike short bursts, this sustained contractility was localized to one segment of small intestine, while normal or reduced activity was recorded simultaneously at other levels of the intestine (Figure 6). In some patients, fasting motor patterns were not modified by ingestion of a meal (Figure 7). Six patients showed only one motor abnormality during the 5 h recording period (3 h during fasting and 2 h postprandially), but motility was severely disrupted in the majority of cases and two or more abnormal patterns were often recorded on the same

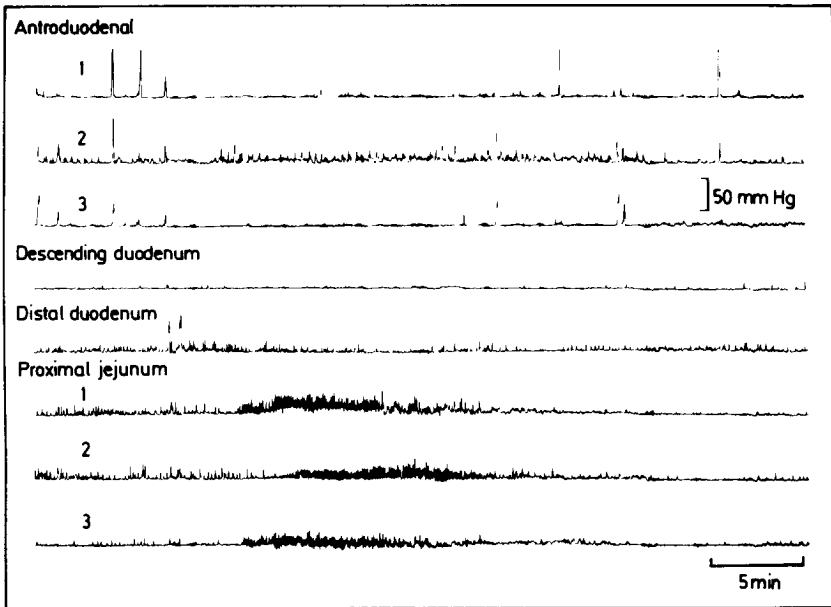


Figure 4. Abnormal propagation of interdigestive motor complex in a CIP patient: simultaneous appearance in different jejunal recording sites of a phase III-like activity which is not followed by quiescence. From Stanghellini et al (1987), with permission.

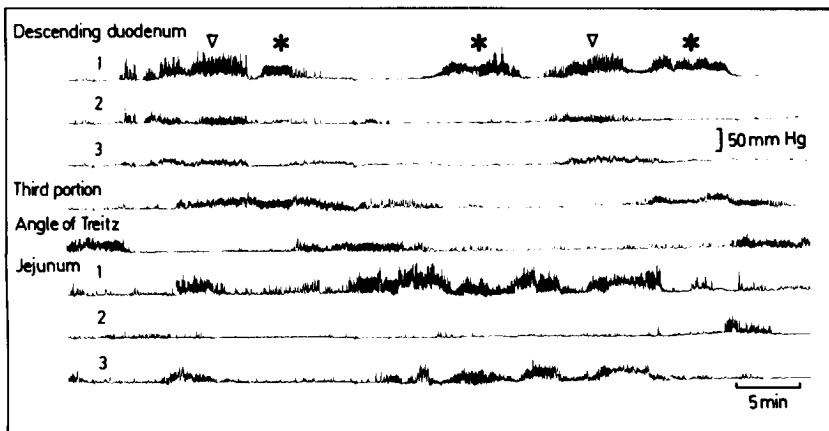


Figure 5. Bursts of non-propagated (*) pressure activity in the small bowel of the same patient as shown in Figure 4. Arrows indicate propagated bursts. From Stanghellini et al (1987), with permission.

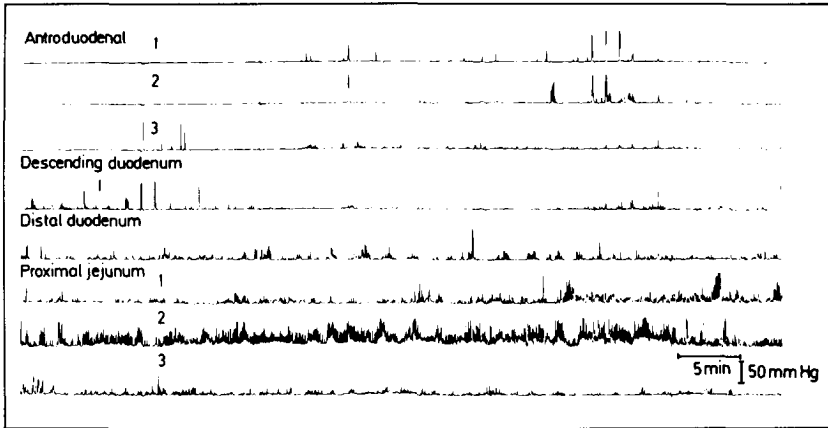


Figure 6. Sustained unco-ordinated intestinal pressure activity in a CIP patient. Note phasic contractions superimposed on tonic activity at one jejunal recording site, unco-ordinated with adjacent segments. From Stanghellini et al (1987), with permission.

tracing. No relationship was observed between the manometric patterns and either the nature or the severity of the patient's symptoms and number of abdominal operations.

Similar intestinal motor abnormalities have been described in sporadic cases of pseudo-obstruction reported in the literature. Booth et al (1983) studied duodenal and jejunal motility in a three-year-old girl with CIP secondary to a ganglioneuroblastoma secreting noradrenaline and vaso-inhibitory peptide (VIP). During fasting, the young patient presented series of

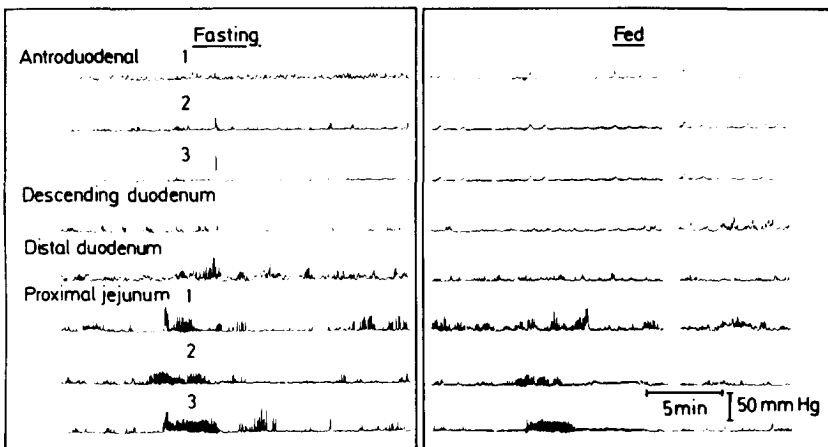


Figure 7. Inability of the meal to convert fasting into fed motor pattern in a CIP patient. Note the almost identical appearance of the tracings before and after feeding. From Stanghellini et al (1987), with permission.

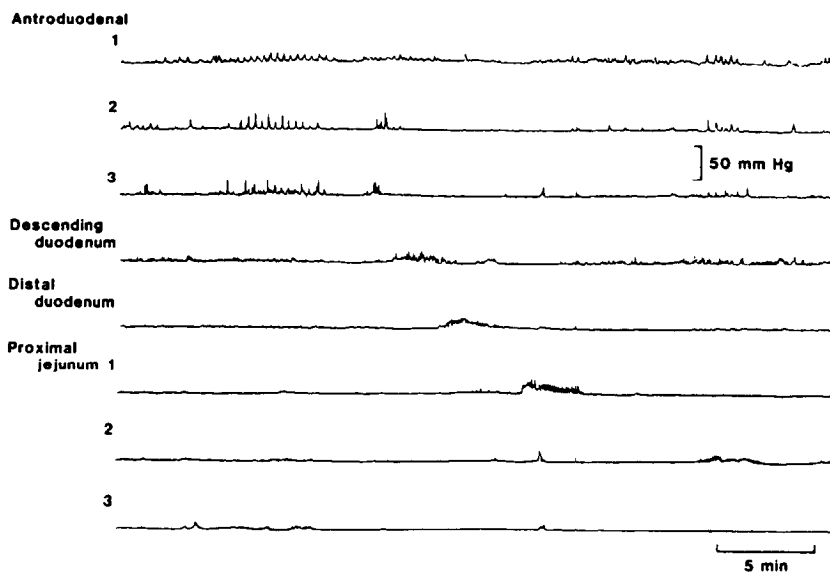


Figure 8. Interdigestive manometric recording in a patient with myogenic CIIP. Normal propagation but low amplitude of activity front. From Malagelada et al (1986).

non-propagated 'rhythmic contractions' (bursts?) and 'abnormal migrating motor complexes' which were propagated more slowly than in control children. Furthermore, intraduodenal instillation of glucose failed to induce a fed motor pattern. In another study, interdigestive and postprandial motility were recorded from the duodenum and proximal jejunum in six patients with pseudo-obstructive symptoms and elevated anti-nuclear titres (Soffer et al, 1984). One patient showed a retrograde phase III, and in a second, the normal fasting cycling activity was replaced by a continuous series of unco-ordinated contractions that continued unchanged after feeding.

Unco-ordinated motility with normal or augmented contractile force is suggestive of a preserved myogenic activity, but abnormal neurogenic control. This has been confirmed in mice with a genetically transmitted depletion of enteric neurons. The affected animals show frequent unco-ordinated phasic contractions superimposed upon tonic contraction of the circular muscle layer (Wood, 1973). On the contrary, when the damage is limited to the muscularis propria, manometric recordings are characterized by weak contractions that are normally co-ordinated (Anuras et al, 1986a; Malagelada et al, 1986) (Figure 8) or, if the myopathy is more severe, by absolute absence of detectable contractions (Anuras et al, 1983, 1986b; Malagelada, 1986). In patients with impairment of both myogenic and neurogenic control of intestinal motility, manometric studies show low amplitude unco-ordinated contractions (Nowak et al, 1984).

Intestinal manometry may also exclude mechanical obstruction of the intestinal lumen. Experimental studies carried out in dogs (Summers et al, 1983b) have shown that artificial obstruction of the intestine causes an

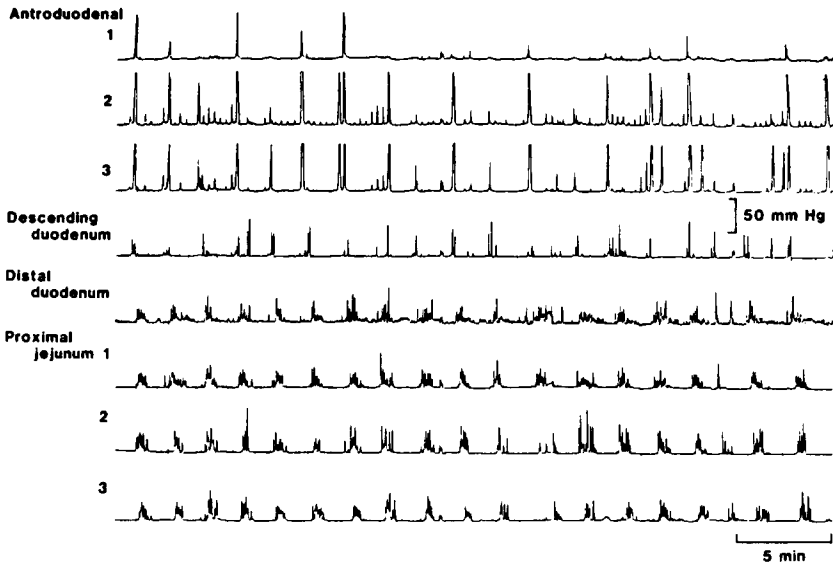


Figure 9. Partial mechanical obstruction of the distal small bowel. Regular 'clusters' of contractions separated by quiescent periods of about one minute each. From Malagelada et al (1986).

immediate decrease of spike bursts (the electrical counterpart of muscle contractions) distal to the site of obstruction, and intense continuous proximal spiking activity proximal to the obstruction. After approximately five hours, the spiking activity takes the form of clusters of spike bursts separated by periods of quiescence. Clustered contractions have also been observed during both fed and fasting periods in subjects with short-duration mechanical occlusion of the small bowel (Malagelada et al, 1986) (Figure 9). In long-term mechanical obstruction, smooth muscle cells lose their contractile force, clusters disappear and motor activity consists of low-amplitude, unco-ordinated contractions indistinguishable from those seen in myogenic disorders (Malagelada et al, 1986).

Summers et al (1983) evaluated jejunal manometry in nine patients with mechanical obstruction and in three with suspected CIP. In the patients with mechanical obstruction, they recorded postprandial clusters of contractions. A similar pattern was detected also in one of the patients with CIP, though the remaining two had infrequent and low-amplitude contractions reminiscent of long-term mechanical obstruction. It was concluded that manometry cannot differentiate the two syndromes. However, the patients with reduced intestinal contractions had muscle degeneration and replacement with fibrosis; this may have led to the reduced amplitude of contractions. The recording of postprandial clusters of contractions in a patient with apparent CIP is difficult to explain. Such a pattern was never observed in the large series evaluated at the Mayo Clinic. However, one must keep in mind the possibility of the presence of both pseudo-obstruction and mechanical obstruction in the same

patient even when repeated radiological tests have failed to demonstrate mechanical occlusion (Smouth et al, 1985). The existence of mechanical occlusion in the patient described by Summers and colleagues was not ruled out, as exploratory laparotomy was not performed.

We feel that gastrointestinal manometry may help in the diagnosis of pseudo-obstructive syndromes and may also indicate the aetiology of the condition. However, abnormalities similar to those recorded in CIP patients may be observed in a variety of different disorders. Approximately 80% of patients with severe dyspeptic symptoms of unknown origin have recognizable motor abnormalities (Malagelada and Stanghellini, 1985), such as bursts of phasic contractions, which may be superimposed to a tonic component, and activity fronts with abnormal configuration and/or propagation. Similar abnormalities have also been recorded in patients with disorders involving the extrinsic nerve supply of the gut, such as diabetic neuropathy (Camilleri and Malagelada, 1984), orthostatic hypotension (Camilleri et al, 1985), brain stem infarcts (Malagelada et al, 1986) or tumours (Wood et al, 1985). Furthermore, disappearance of MMC and episodes of abnormally irregular motility have been recorded during fasting in patients with irritable bowel syndrome (IBS), both in basal conditions and under the effect of stressful situations. Perception of typical symptoms (abdominal discomfort and pain) invariably occurred during at least one of such episodes (Kumar and Wingate, 1985).

Manometric studies of the small bowel reinforce the opinion that primary and secondary dyspeptic syndromes, IBS and CIP, are related conditions, but the reasons for the different clinical presentations remain obscure.

PATHOGENIC MECHANISMS

Despite the fact that numerous cases of intestinal pseudo-obstruction have been carefully described, only a handful of studies have directly investigated the possible causes of the syndrome. Defects at any level of control of intestinal propulsion may determine pseudo-obstructive syndromes. Abnormalities of the smooth muscle cells, the ENS, the extrinsic autonomic nervous supply, and the central nervous system may separately, or in various combinations, cause pseudo-obstruction.

The smooth muscle and the enteric nervous system are so close to each other that both may be affected by the same disease. Similarly the extrinsic and intrinsic nervous supplies are often damaged by the same disease. In spite of these considerations, Table 1 has categorized the causes of CIP on the basis of the main regulatory mechanism altered.

Smooth muscle diseases

The smooth muscle of the gut may be involved with myotonic dystrophy and progressive muscular dystrophy, and, in myotonic dystrophy, may precede the somatic disease by months or years (Kohn et al, 1964). Gastrointestinal symptoms are frequently present in these patients, but they do not usually have severe obstruction (Harvey et al, 1965). In a recent case-report, Leon et al

Table 1. Causes of chronic intestinal pseudo-obstruction.

Main level of altered control of intestinal motility	Primary forms	Secondary forms
Smooth muscle	Sporadic visceral myopathy (Rohrman et al, 1981; Waterfall et al, 1981; Anuras et al, 1986b; Malagelada et al, 1986), familial visceral myopathy (Sarna et al, 1978; Anuras et al, 1986a)	Myotonic dystrophy (Harvey et al, 1965), progressive muscular dystrophy (Leon et al, 1986), Bannister and Hoyes (Kapila et al, 1975; Bannister and Hoyes, 1981)
Smooth muscle + enteric nervous system	Sporadic visceral neuromyopathy (Smouth et al, 1985)	Progressive systemic sclerosis (De Marino et al, 1973; Faulk et al, 1978), dermatomyositis (Faulk et al, 1978), Ehlers-Danlos syndrome (Hines and Davis, 1973), amyloidosis (Faulk et al, 1978), myxoedema (Faulk et al, 1978), jejunal diverticulosis (Schuffler et al, 1981; Krishnamurthy et al, 1983), radiation enteritis (Malagelada et al, 1986)
Enteric nervous system	Sporadic visceral neuropathy (Dyer et al, 1969; Sullivan et al, 1977; Schuffler and Jonak, 1982; Schuffler et al, 1985; Krishnamurthy et al, 1986), familial visceral neuropathy (Roy et al, 1980; Mayer et al, 1986)	Hirschsprung (Faulk et al, 1978), Chagas (Faulk et al, 1978), Von Recklinghausen (Phat et al, 1980), extraintestinal carcinomas (Ogilvie, 1948; Ahmed and Carpenter, 1975; Lhermitte et al, 1980; Schuffler et al, 1983), viral infections (Sonsino et al, 1984), drugs (anthraquinones) (Smith, 1972)
Extrinsic nervous supply		Calcification of basal ganglia (Cockel et al, 1973), Parkinson (Faulk et al, 1978), stroke (Reynolds and Eliasson, 1977), encephalitis (Bruyn et al, 1986), orthostatic hypotension (Camilleri et al, 1985)
Undetermined	Normal appearing smooth muscle + enteric nervous system (Sullivan et al, 1977; Sarna et al, 1978; Wood, 1981)	Phaeochromocytoma (Booth et al, 1983), hypoparathyroidism (Faulk et al, 1978), lymphoid infiltration (McDonald et al, 1985), sprue (Dawson et al, 1984), drugs (clonidine, phenothiazines, tricyclic antidepressants, antiparkinsonian medication, ganglionic blockers, bronchodilators, anti-neoplastic agents) (Faulk et al 1978; Catchpole, 1986; Malagelada et al, 1986)

(1986) described a boy affected by Duchenne's muscular dystrophy who suffered recurrent attacks of intestinal occlusive symptoms; there was no radiological evidence of mechanical occlusion. The patient died in a car accident when he was 16 years old. At autopsy, the muscularis mucosae and muscularis propria of the gut wall showed fibrotic replacement of varying degrees. In the small bowel this abnormality was restricted to the longitudinal muscle. The remaining smooth muscle cells appeared enlarged and contained many eosinophils. The myenteric plexus appeared quite normal.

Disturbances of visceral smooth muscle are not necessarily associated with systemic disease. These conditions may be termed *visceral myopathies* and may be sporadic (Rohrmann et al, 1981; Anuras et al, 1986a; Malagelada, 1986) or familial, with both dominant and recessive autosomal transmission (Anuras et al, 1986b). Histology of the affected muscle generally shows vacuolar degeneration, thinning, and fibrotic replacement of the smooth muscle layers; in children, deposits of lipofuscin can be found in the muscle layers (Anuras et al, 1986a).

In patients without evidence of morphological abnormalities of the gut wall, the causes of pseudo-obstruction may be identified as myogenic or neurogenic on the basis of manometric or myoelectric provocative tests.

Kapila et al (1975) performed 'in vitro' studies on apparently normal smooth muscle of an infant with CIIP. The cells responded normally to caerulein (ceruletide) and nicotine, indicating that the receptors for these stimulants and the contractile mechanisms were intact, but failed to respond to acetylcholine. A few years later, Bannister and Hoyes (1981) reported a young woman with CIIP who failed to respond to cholinergic and anticholinesterase drugs and also lacked the denervation hypersensitivity to these drugs, typical of postganglionic cholinergic neuropathies (Hopkins et al, 1974; Harik et al, 1977). The authors did not carry out any in vitro study, but concluded that the 'most reasonable' cause of the impaired motility was a postjunctional defect of the muscarinic receptors, which prevented the smooth muscle cells from responding to cholinergic stimulants.

In 1978, Sarna et al (1978) recorded jejunal myoelectrical activity in a patient with familial CIIP. Electrodes were implanted during an explorative laparotomy and recording was carried out for 7 days postoperatively. For all except the first 2 hours of recording ECA was present only during the occurrence of MMCs, when spike potentials were superimposed upon every slow wave. The authors suggested that this abnormality may be due to primary hyperpolarization of smooth muscle cell membranes. Absence of phase II appears to be associated with some cases of CIP but these findings need to be confirmed.

Another case of CIP attributable to abnormalities of myogenic control, with any histological abnormality, was reported by Waterfall et al in 1981. The patient was a 12-month-old child with a life-long history of vomiting, constipation and impaired physical growth. Radiological examination of the small bowel showed unco-ordinated motility of the proximal jejunum and an apparent mechanical obstruction in mid-jejunum. At laparotomy, small bowel loops appeared markedly distended, but there were no mechanical occlusions. The myoelectrical activity of the small bowel was abnormal. The

frequency of the ECA was reversed just above the occluding segment. In this tract ERA was also abnormal, being present throughout the control wave cycle. This type of continuous ERA may result in 'tonic' prolonged contractions which would occlude the lumen and were presumably caused by an ectopic pacemaker which possibly prevented the normal aboral transport of contents.

Diseases of the smooth muscle and ENS

Collagen vascular diseases are the most frequent causes of secondary CIP. Cases of CIP have been described in association with PSS, dermatomyositis, systemic lupus erythematosus (Faulk et al, 1978), and Ehlers-Danlos syndrome (Hines and Davis, 1973).

The mechanisms of pseudo-obstruction in PSS have been carefully investigated by Di Marino et al (1973), by evaluation of duodenal myoelectric activity in 13 patients. Myoelectrical recordings were performed under basal conditions and after stimulation induced by either pentagastrin or secretin or luminal distension. Patients presented normal slow wave frequency and propagation velocity under basal conditions, but a reduced incidence of spike bursts or ERA was observed after luminal distension, suggesting an abnormal function of intrinsic neural reflexes. The response to direct smooth muscle stimulation with pentagastrin and secretin was normal in seven patients with disease of short duration, but markedly reduced in those who had had scleroderma for longer periods of time. Scleroderma therefore primarily impairs the functions of ENS and may later affect smooth muscle contractility (Rees et al, 1982).

Lupus erythematosus may induce severe arteritis in intestinal vessels and CIP could be a consequence of tissue ischaemia (Faulk et al, 1978), which can reduce slow wave frequency (Szurszewski and Steggerda, 1968; Kyi and Daniel, 1970), and impair the electrical coupling of smooth muscle cells (Szurszewski and Steggerda, 1968).

Pseudo-obstruction in infiltrative diseases such as amyloidosis and myxoedema may be caused by a mechanism similar to that described in scleroderma, although in amyloidosis the infiltration may be primarily both of the nervous supply (Ikeda et al, 1982) and the muscle cells (Intriere and Brown, 1956).

Jejunal diverticulosis is a heterogeneous disorder that can be caused by abnormalities of both the smooth muscle and enteric nervous system (Krishnamurthy et al, 1983) and may be accompanied by pseudo-obstructive symptoms (Schuffler et al, 1981).

Radiation may induce CIP (Malagelada et al, 1986). Smooth muscle is relatively radioresistant and low doses of radiation primarily affect the ENS. Radiotherapy for abdominal neoplasms, however, generally requires doses which damage both neurons and smooth muscle (Malagelada et al, 1986).

One case of apparently sporadic CIIP with concomitant involvement of muscular and nervous tissues has been described (Smouth et al, 1985) (sporadic visceral neuromyopathy).

Diseases of the ENS

Certain diseases selectively affect the ENS without damaging other components of the intestinal wall. Some, such as Hirschsprung's and Chagas' diseases, have been the object of several studies (Faulk et al, 1978); others are less frequent, but may induce ENS abnormalities which are severe enough to lead to pseudo-obstructive syndromes. Von Recklinghausen's disease is characterized by the presence of cutaneous neurofibromas and café-au-lait spots. These may be associated with neurofibromas scattered throughout the body, angiomas and other multi-visceral congenital malformations often involving endocrine glands. Neurofibromatosis of the digestive tract may be responsible for mucosal ulcerations and mechanical occlusions (Lukash et al, 1966). Von Recklinghausen's disease may also be associated with megacolon (Phat et al, 1980). One patient, who has been described (Phat et al, 1980), had diffuse angiomas of the colon and marked alterations of the myenteric plexus (hyper-hypoganglionosis, and abnormalities of ganglion cells and dendritic processes). Symptoms disappeared after colectomy.

Intestinal pseudo-obstruction secondary to damage of the myenteric plexus has been reported in patients with carcinomas outside the gastrointestinal tract (Ogilvie, 1948; Ahmed and Carpenter, 1975; Lhermitte et al, 1980; Smouth et al, 1985). Ogilvie first described two patients who had colonic pseudo-obstruction associated with metastatic carcinoma (Ogilvie, 1948) and malignant infiltration around the coeliac plexus. He ascribed the pseudo-obstruction to 'sympathetic deprivation'. The possibility that CIP may derive from degeneration of the myenteric plexus and constitute an expression of a paraneoplastic syndrome has been proposed more recently. Pathological studies carried out on a woman with oat-cell carcinoma of the lung, who presented with CIP and died from rapidly progressive autonomic insufficiency, showed similar abnormalities of the enteric and autonomic nervous systems with neuronal degeneration and lymphocytic infiltrates. Since oat-cell carcinoma of the lungs present antigen determinants that are also expressed in several areas of the nervous system, including the myenteric plexus, an autoimmune mechanism may be responsible for the neural degeneration (Schuffler et al, 1983).

Viral infection may be a cause of CIP (Sonsino et al, 1984). Different groups of viruses are known to induce severe gastrointestinal motor abnormalities in experimental animals (Burrows and Merritt, 1984) and in humans (Meeroff et al, 1980). Cytomegalovirus infection may induce important morphological abnormalities of the myenteric plexus, including intranuclear inclusions, focal axonal dilatation with pyknotic debris, and hyperplasia of inflammatory cells and Schwann cells (Sonsino et al, 1984).

Abuse of laxatives (especially those containing anthraquinones) has been claimed to induce CIP. Barbara Smith demonstrated abnormal morphology and a decreased number of neurons of the colonic myenteric plexus in patients abusing these drugs (Smith, 1972). Similar abnormalities however, have been observed also in patients with severe idiopathic constipation (Krishnamurthy et al, 1985) who are just the patients who may abuse laxatives. Severe constipation, as well as severe dyspepsia, may sometimes occur in pseudo-

obstructive syndromes. The actual role of laxatives in damaging the intrinsic plexuses and inducing CIP remains to be clarified.

Involvement of ENS may be isolated, or may be part of a more widespread neurological disease. Isolated idiopathic visceral neuropathies may be familial (Roy et al, 1980; Mayer et al, 1986) or sporadic (Dyer et al, 1969; Sullivan et al, 1977; Schuffler and Jonak, 1982; Schuffler et al, 1985; Krishnamurthy et al, 1986; Mayer et al, 1986). In 1977, Sullivan et al. diagnosed neurogenic CIIP in four patients by measuring the myoelectrical and mechanical activities of the oesophagus, small bowel and colon. Causes of secondary CIP were excluded on clinical grounds. In one of the four patients CIP had previously been attributed to elevated levels of prostaglandins (Luderer et al, 1976), but on re-evaluation severe gastrointestinal motor disturbances were still recorded even when prostaglandin levels had returned to normal. These patients had a normal slow-wave frequency, but more spike bursts (ERA) were associated with the slow waves suggesting a reduction of inhibitory control. A normal increase of spike bursts was observed after direct stimulation of smooth muscle cell receptors by secretin, but no response followed stimulation induced by luminal distension, suggesting impairment of intrinsic reflexes (Rutin et al, 1953).

In other studies, abnormalities of ENS have been directly shown by histopathological studies. Intrinsic nerve plexuses are not demonstrated clearly by conventional stains and the silver-staining proposed by Barbara Smith (Dyer et al, 1969) is currently considered the best technique to display neural morphological abnormalities. The abnormalities include: decreased number of neurons (Dyer et al, 1969; Schuffler and Jonak, 1982); swelling of neurons (Dyer et al, 1969; Schuffler and Jonak, 1982; Schuffler et al, 1985; Mayer et al, 1986); abnormal staining of neurons, showing either a perinuclear ring of unstained cytoplasm (Schuffler et al, 1985) or an uneven silver deposition (Schuffler and Jonak, 1982); reduced number of axons and abnormalities of the remaining ones in the presence of normal number and appearance of cell bodies (Krishnamurthy et al, 1986); inflammatory or Schwann cell proliferation that may (Dyer et al, 1969; Schuffler and Jonak, 1982; Krishnamurthy et al, 1986) or may not (Schuffler et al, 1985; Mayer et al, 1986) occur as a response to neural injury. Smooth muscle layers are normal (Schuffler and Jonak, 1982) or thickened (Dyer et al, 1969; Schuffler et al, 1985; Bruyn et al, 1986; Mayer et al, 1986) in neurogenic CIP, probably as a consequence of chronic unco-ordinated hypercontractility. Whether these different histological abnormalities correspond to different aetiological mechanisms or represent different aspects of a single disease remain to be clarified.

Diseases of extrinsic nervous supply

Several diseases affecting the autonomic nervous supply of the digestive canal are associated with severe gastrointestinal motor abnormalities and may induce CIP.

The first report of pseudo-obstruction possibly related to CNS disorders was published by Cockel et al (1973). The authors described four siblings who

presented a syndrome characterized by mental retardation, calcification of the basal ganglia, malabsorption and recurrent pseudo-obstruction. Whether CIP was secondary to the basal ganglia calcification or whether these disorders represented two separate expressions of an unrecognized underlying metabolic disorder was not clarified.

Cases of CIP have also been reported in Parkinson's disease (Faulk et al, 1978), but it remains to be clarified whether the intestinal disorder is attributable to the disease or to its treatment.

A more convincing relationship between CNS diseases and CIP is represented by the possible onset of the syndrome, shortly after cerebrovascular accidents. Four cases have been reported by Reynolds and Eliasson (1977) but the possible mechanisms involved are not known. Several autonomic nuclei of the CNS are involved in the regulation of gastrointestinal motility. Some are located in the brain stem and control the discharge of vagal efferent fibres (Kalia and Mesulam, 1980; Pagani et al, 1984), others are in the medullary reticular formation and inhibit, through serotonergic and noradrenergic mediators, the outflows of thoracolumbar sympathetic and parasympathetic pathways (Coote and MacLeod, 1974; Loewy, 1981). The overall influence exerted by the autonomic nervous system on gastrointestinal motility is inhibitory and patients with diseases affecting efferent fibres (Camilleri et al, 1985) or central autonomic nuclei (Wood et al, 1985) have abnormal unco-ordinated hypermotility similar to that observed in CIP.

In some patients, the ENS disturbances responsible for CIP may be part of a diffuse neurological disorder involving both central and peripheral nervous systems. A good example of this is represented by the case reported by Bruyn et al (1986). They observed a patient with recurrent episodes of intestinal obstruction which started several years after a bout of measles encephalitis and a subsequent neurological syndrome characterized by severe mental retardation, parkinsonism and epilepsy. Histology showed severe atrophy of both enteric nerve plexuses, associated with lymphocytic infiltration and Schwann cell proliferation. Neurological consequences of encephalitis are known to develop slowly (Felby, 1968), probably due to slow progression of the viral disease or delayed cellular immunoreaction, and it is quite likely that the autonomic involvement seen in this patient may derive from spread of the encephalitis.

Other interesting cases of CIP accompanied by extraintestinal neurogenic involvement are those of patients with generalized autonomic failure. Camilleri et al (1985) described nine patients with orthostatic hypotension of different origin accompanied by severe gastrointestinal motor abnormalities. One of them presented with clinical features of pseudo-obstruction, while the others reported a variety of symptoms including dysphagia, heartburn, early satiety, abdominal pain, weight loss, constipation and diarrhoea. Manometric motor abnormalities were similar to those described in neurogenic pseudo-obstruction with bursts of contractions, sustained unco-ordinated hypermotility and abnormal MMCs. Impairment of splanchnic sympathetic outflow is thought to occur in several diseases (primary amyloidosis, Shy-Drager syndrome, pan-dysautonomia, familial dysautonomia). Impaired efferent sympathetic pathways were indicated by abnormalities of thermoregulatory

sweating. In a previous report (Schuffler et al, 1978), two patients were described with a familial nervous disease presenting as CIP and orthostatic hypotension. These patients presented with unco-ordinated gastrointestinal hypermotility suggesting loss of inhibitory control, but the component of nervous supply responsible for this disorder was not identified. Pathological neurons characterized by eosinophilic intranuclear inclusions, in fact, were detected throughout the nervous system, including brain, spinal cord, coeliac ganglia and the enteric ganglia.

Data have been published suggesting that only post-ganglionic diseases may lead to severe gastrointestinal motor abnormalities, while central control would simply modulate digestive motor events. Bursts of non-propagated spike potentials have been recorded in the small bowel of dogs, after coeliac and superior mesenteric ganglionectomy, or after complete extrinsic denervation of sympathetic supply (Felby, 1968; Marlett and Code, 1979), but subjects with traumatic spinal cord transection do not present such severe motor abnormalities (Fealey et al, 1984; Aaronson et al, 1985).

Undetermined mechanisms

In some cases, the mechanisms by which inappropriate intestinal transit develops remain obscure. Patients with apparently 'idiopathic' CIP have been described with normal morphology of both smooth muscle cells and intrinsic plexuses (Sullivan et al, 1977; Sarna et al, 1978; Wood, 1981). As already described, however, myogenic and neurogenic abnormalities capable of inducing pseudo-obstruction do not necessarily appear histologically, and may only be demonstrated by manometric or myoelectric tests (Hopkins et al, 1974; Kapila et al, 1975; Luderer et al, 1976; Bannister and Hoyes, 1981; Waterfall et al, 1981).

THERAPEUTIC APPROACH

No treatment has been proven to be effective in the clinical management of CIIP, though the secondary forms of CIP respond to treatment of the underlying disease, if this is possible (Dawson et al, 1984).

Cholinergic and anticholinesterase drugs, noradrenaline, meperidine (pethidine), metoclopramide, domperidone, prostaglandins, indomethacin, xylocaine, somatostatin, serotonin have all been tried unsuccessfully in patients with CIIP (Anuras et al, 1978; Faulk et al, 1978; Waterfall et al, 1981; Read et al, 1985; Smouth et al, 1985). More recently, a placebo controlled trial has been carried out to evaluate the effect of cisapride on intestinal transit times in eight patients with this syndrome. Cisapride significantly accelerated the transit time but it is not known whether chronic treatment with this drug would benefit patients with CIIP (Camilleri et al, 1986).

Electrical stimulation of the muscular layers of stomach and small bowel has been attempted in patients with CIP to restore a normal rhythm of slow waves and to control the frequency of spike potential and contractions.

Pacing, however, cannot induce ECA, when this is absent (Sarna et al, 1978), nor has it succeeded in overcoming abnormal intestinal pacemakers (Waterfall et al, 1981).

Surgery has been proposed as a potentially useful treatment in patients with disease apparently localized to one segment of the digestive canal (Phat et al, 1980; Schuffler and Deitch, 1980). However, no study has reported a follow-up long enough to exclude recurrences of the syndrome. CIP is in fact usually a diffuse disease. Abdominal surgery can eliminate the most severely affected areas and produces a temporary improvement of the clinical picture, but the disease is likely to spread and involve areas of the gut previously unaffected. Surgery, therefore, should be avoided in confirmed cases of CIP, but there are exceptions to this general rule. Firstly, mechanical obstruction cannot always be distinguished from pseudo-obstruction simply on the basis of the clinical presentation and radiological tests (Rohrmann et al, 1981; Schuffler et al, 1981, 1983; Waterfall et al, 1981; Wood, 1981; Malagelada and Stanghellini, 1985; Malagelada, 1986) and, furthermore, the two disorders may coexist in the same patient (Smouth et al, 1985). Accurate endoscopic and manometric studies may help to formulate the diagnosis. Secondly, there are conditions in which the consequences of pseudo-obstruction are life-threatening and surgery becomes imperative; these include the presence of signs of perforation (free air in the abdominal cavity), peritonitis (fever, tachycardia, leucocytosis), or rapid severe distension of the colon (Anuras and Shirazi, 1984; Dudley and Paterson-Brown, 1986). Pseudo-obstructive episodes are severe clinical conditions that always need careful management. After starting gastric suction and fluid replacement, intestinal decompression should be attempted. Colonoscopy has been used successfully to decompress the large intestine (Bachulis and Smith, 1978; Groff, 1983; Starling, 1983). The dimensions of intestinal loops should be marked by plain films of the abdomen. If repeated attempts fail and one of the above-mentioned warning signals of perforation or peritonitis appear, surgery should be considered.

Patients with CIP are difficult to manage even when the occlusive episodes are not present. Their main problems are nausea and inability to maintain their weight when the proximal portion of the gut is predominantly involved, or abdominal bloating and constipation when the disease primarily affects the colon. Symptomatic treatment with small hypercaloric frequent meals (eventually supplemented with liquid formulae, vitamins and salts), antacids, and enemas or mild laxatives has been proposed (Shaw et al, 1985), but no controlled study has proven the validity of these expedients. Patients with intestinal bacterial overgrowth develop malabsorption and diarrhoea which generally respond to antibiotics (Schuffler et al, 1981; Shaw et al, 1985), although relief is only temporary (Smouth et al, 1985). Patients with severe involvement of the stomach and small bowel may become unable to maintain an adequate food intake and must be placed on total parenteral nutrition.

CIP has a variable and unpredictable clinical course and remains an extremely disabling and dangerous disease. The most frequent causes of death are accidents occurring during unnecessary surgery, pneumonia 'ab ingestis', cardiac arrest and malnutrition.

CONCLUSIONS

Only a few years ago in the USA, a correct diagnosis of CIP was achieved after an average period of 20 years from the onset of symptoms (Schuffler et al, 1981). The situation has not radically improved, but recent years have witnessed an increasing awareness of the existence of this syndrome. It is important to recognize the early expression of the disease, especially in those cases with insidious onset. Patients with severe constipation and dyspepsia should be carefully evaluated, especially if surgery is being considered. Specifically, myoelectrical or motor activities of the whole gastrointestinal tract should be thoroughly studied. These studies should also be performed in all patients in whom previous surgery has failed to improve the clinical picture. If diffuse motor abnormalities are detected (particularly if the small bowel is affected), surgery should be avoided, the patients informed of the nature of their disturbances and palliative dietetic and pharmacological therapy attempted.

If laparotomy is performed, it is imperative to obtain full-thickness biopsies from different tracts of the digestive canal, to clarify the diagnosis. Specimens should be prepared for accurate evaluation of both the muscle layer and the intrinsic plexuses. Techniques currently employed fail to detect minimal changes and 'functional' abnormalities and probably detect only the irreversible situation; electron microscopy might yield important information, especially if combined with cytochemical techniques (Burnstock, 1981). Immunocytochemical techniques have rapidly developed in recent years and allow the recognition and quantification of neuropeptides in the ENS (Bishop et al, 1981). Maps of 'normal' alimentary distribution of numerous peptides are available (Bishop et al, 1981) and the effects of these peptides on gastrointestinal motility have been elucidated (Andrews, 1986).

We should now be able to identify an abnormal distribution of neural mediators in diseases with suspected neurogenic pathogenesis. Correlation of the results of each study with myoelectrical motor patterns and with clinical features might yield a better understanding and classification of these intriguing syndromes. This would facilitate the development of new therapies which, if not effective in severe CIP syndromes with irreversible damage of neural and muscular tissues, might help the gastrointestinal motor abnormalities responsible for dyspepsia, irritable bowel syndrome and constipation.

SUMMARY

Chronic intestinal pseudo-obstruction (CIP) is a clinical syndrome characterized by symptoms and signs of intestinal occlusion, in absence of any mechanical obstruction of the gut lumen. It causes impaired transit of intestinal contents and is determined by abnormalities of motor activity. The term CIP is used to indicate a heterogeneous group of disorders with many different pathogenic mechanisms. The defect in the regulation of intestinal transit can be at any level of motility control. Two main types of CIP are recognized, termed respectively *myogenic* (when smooth muscle cells are

affected) and *neurogenic* (caused by abnormalities of extrinsic and/or intrinsic nervous supplies). Both types may be *secondary* to a variety of recognizable diseases or *idiopathic*. In myogenic CIP, intestinal transit is impaired because of lack of propulsive strength; in the neurogenic form, contractions are powerful but not sufficiently co-ordinated to propel intestinal contents aborally in an organized fashion.

CIP belongs to the large and loosely defined group of digestive functional disorders. These disorders probably share common pathogenic mechanisms but with different expressiveness. The reasons why only some patients present recurrent symptomatological bouts resembling mechanical occlusion has not been clarified. This aspect is of great clinical relevance and deserves attention, as CIP patients, unlike other patients with severe functional disorders, may undergo repeated, useless and potentially dangerous operations. The diagnosis of CIP may be suggested by clinical features and is based on radiological, endoscopic, manometric, and histological findings.

Recent technological improvements facilitate the recognition of this intriguing syndrome. In particular, manometric recording of the small bowel motility, which has long been considered an important research technique, can now also be regarded as a useful diagnostic tool.

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