Functional Diagnosis

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Besides aganglionosis, there is no clear correlation between histomorphology and function of the bowel. Therefore functional diagnosis of chronic constipation is of great importance for the diagnosis and treatment of Hirschsprung's disease (HD) and allied disorders.

12.1 Anorectal Motility

The musculature of the gastrointestinal tract and the draining urinary tract is composed primarily of smooth muscle cells. Because of their low resting membrane potential, these cells tend to depolarize spontaneously. The electrical impulses arising from the spontaneous depolarization and repolarization, the basal electrical activity (basal electrical rhythm, BER), are responsible for the muscular tone. Any major shift of the membrane potential fluctuations in the direction of depolarization leads to the occurrence of stronger electrical impulses in the form of volleys of action potentials, which present as spikes in the slow basal rhythms. These rapid action potentials are responsible for the segmental and peristaltic contractions of the smooth musculature (Fig. 12.1). Both the origin and the propagation of the progressive contractions, that is the propulsive waves, and in all probability the segmental contractions, that is those confined to one bowel segment, of the gastrointestinal tract are regulated via the intramural bowel wall plexus. Distension of the bowel wall by a stool bolus produces an excitatory impulse which, after traversing the submucous plexus and being transmuted by the myenteric plexus, leads to a cholinergic contraction oral to the bolus and to nonadrenergic–noncholinergic (NANC) relaxation, mediated by inhibitory neurons containing nitric oxide (NO), aboral to the bolus [1–3]. Adrenalin modulates the acetylcholine release at cholinergic synapses. NO has recently been recognized as a neurotransmitter that mediates relaxation of the smooth muscles of the gastrointestinal tract [4]. It is identical to nicotinamide-adenine-dinucleotide-phosphate-diaphorase (NAPDH-diaphorase) [5] which can therefore be used as a diagnostic marker for HD. It is suggested too, that a lack of NO synthase in pyloric tissue is responsible for pylorospasm in infantile hypertrophic pyloric stenosis [6] (Fig. 12.2).

At the time of circular muscle relaxation, contraction of the longitudinal muscles, and thereby shifting of the bowel contents, occurs. Beside NO-containing inhibitory neurons, many other peptidergic neurons, storing vasoactive intestinal peptide (VIP), substance P (SP), enkephalin, neurokinin A (NA), histidine isoleucine, gastrin-releasing peptide (GRP) and many other factors are involved in the peristaltic reflex. They are lacking or abnormal in HD and allied disorders [3, 7]. Also a decreased expression of nerve growth factors (NGFs), fibroblast growth factors (FGFs), extracellular matrix (ECM) such as laminin, and cell-adhesion molecules (CAMs)

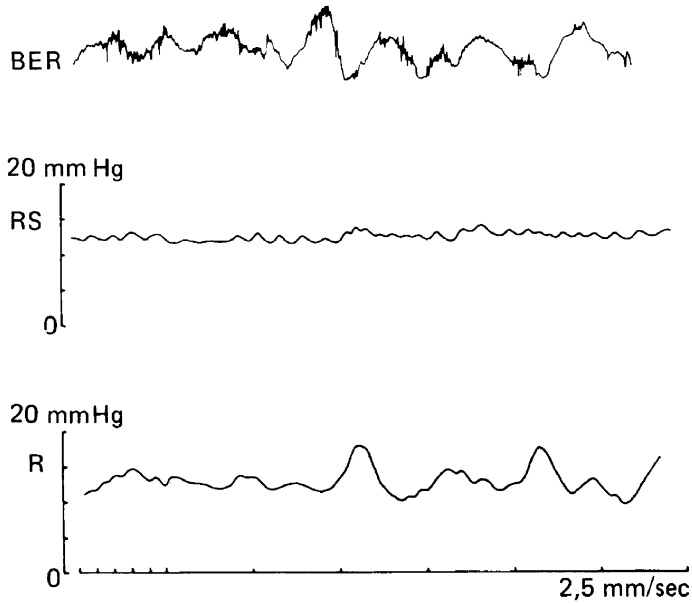


Fig. 12.1 Spike potentials on the top of the slow waves in the colon of a healthy child (*BER* basal electrical rhythm, *R* rectum, *RS* rectosigmoid)

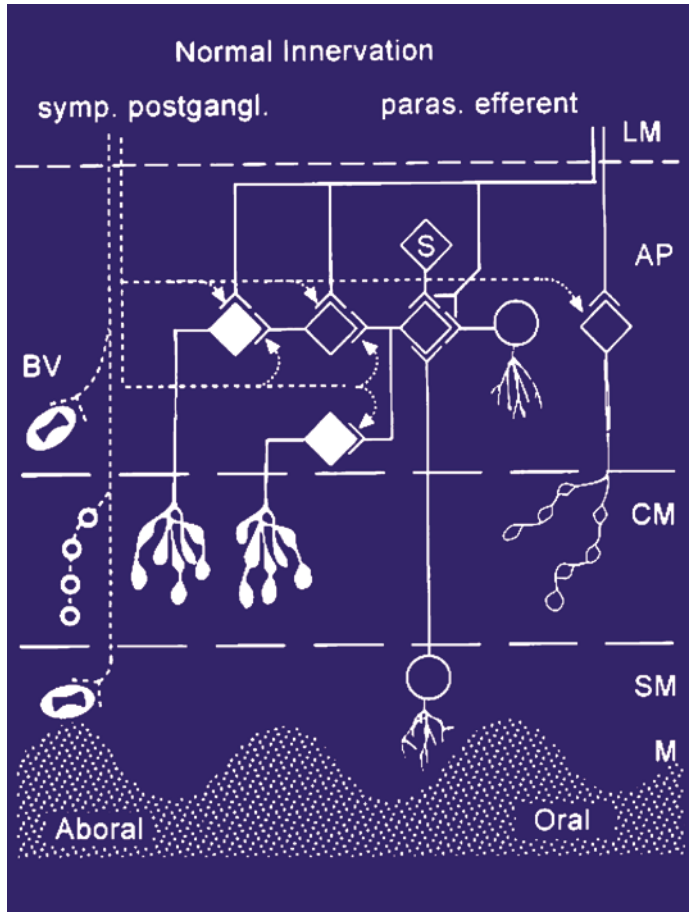


Fig. 12.2 Schematic diagram of the peristaltic reflex, showing the intramural plexus and the efferent postganglionic adrenergic and preganglionic cholinergic axons entering the bowel. The impulses from the mechanoreceptor cells are transmitted via interneurons (*white squares*) over cholinergic synapses to the NANC inhibitory neurons (*dark squares*). The finely drawn neuron with white circles in its terminal axons represents a postganglionic adrenergic axon. Stimulation of the NANC neurons leads to a neurogenically produced and peptidergically transmitted relaxation aboral to the bolus. Oral to the bolus, a myogenically produced contraction of the circular muscle occurs (rebound excitation). The sympathetic system acts as a modulator of the acetylcholine release at the cholinergic synapses. *AP* Auerbach's plexus, *asterisks* peptidergic transmitters, *BV* blood vessels, *circles* sensory neurons, *CM* circular muscle, *S* pacemaker neuron with spontaneous activity situated in the ICCs of Stach's plexus (plexus submucosus extremus), *SM* submucosa

such as neural cell adhesion molecule (NCAM), NCAM L1 (L1CAM), and N-cadherin lead to neuronal abnormality in HD. CAMs play an important role in cell–cell interactions, which regulate the development and maintenance of multicellular organisms. FGFs can induce diverse cellular responses in multiple biological systems including neurite outgrowth. Yoneda et al. [8] showed that there is an altered interaction between FGF-CAM and FGF receptors (FGFR) in aganglionic segments of HD. The number of CAM-positive fibers in aganglionic segments is markedly decreased compared to ganglionic segments, whereas there is not such a difference in FGF and FGFR expression. This suggests that CAM-FGF signaling is altered in HD and may be responsible for the failure of neural cell migration in the intestinal tract.

Beside the submucous and myenteric plexus, interstitial cells of Cajal (ICCs) have important regulatory functions in human gut musculature [9]. These cells are pacemaker cells which generate slow waves and facilitate active propagation of electric events and neurotransmission of the gastrointestinal tract. The ICCs can also be recognized immunohistochemically by the demonstration of their surface-receptor-tyrosine-kinase-kit (c-kit). Mesenchymal ICC precursors which carry the c-kit receptor require the kit ligand provided by neuronal or smooth muscle cells. The ICCs develop as either myenteric ICCs (ICC-MY) or intramuscular ICCs (ICC-IM). Solari et al. [10] demonstrated in c-kit immunoreactive ICC-IM in the circular and longitudinal muscle layers in normal sigmoid colon and ganglionic bowel in patients with HD and in those with total colonic aganglionosis (TCA). These long, thin, bipolar cells are connected to each other via one or two processes, whereas ICCs-MY create a dense mesh-like network surrounding the myenteric plexus. This characteristic 3D network can only be visualized with the whole-mount technique where the mucosa is separated in one layer from the muscularis mucosa attached to the submucosal layer. In aganglionic bowel only sparse and single ICC-MY were observed between the circular and longitudinal muscle layers. Similarly, in whole-mount preparations ICC-IM were markedly reduced. Wu et al. [11] reported that neurons might be necessary for development of highly differentiated ICC-MY and a mature ICC network. This could explain the absence or reduction of c-kit-immunopositive cells in HD. Nemeth and Puri [12] found that the characteristic 3D network observed in normal colonic mucosa is replaced in HD by thick nerve trunks that do not form any network and run up and down in a serpentine manner.

12.2 Physiology of the Internal Anal Sphincter

The internal anal sphincter is influenced by five nervous mechanisms:

1. Alpha adrenergic excitatory nerves
2. Beta-adrenergic inhibitory receptors
3. Cholinergic neurons
4. Nonadrenergic noncholinergic neurons
5. Peptidergic nerves

Alpha Adrenergic Excitatory Nerves

Alpha adrenergic excitatory nerves travel in the hypogastric nerves and maintain sphincter tone via alpha excitatory receptors [13]. In the basal state hypogastric nerves do not play a significant role in the resting internal anal sphincter pressure and rectoanal reflex-induced relaxation. However, there is a significant sympathoexcitation in response to higher volumes of rectal balloon distension [14]. Yamato and Rattan [15] conclude that alpha-2 adrenoreceptors exert important neuromodulatory influences on the rectoanal inhibitory reflex, while alpha-1 adrenoreceptors may exert modulatory effects on the resting internal anal sphincter tone. Adrenergic influences via the hypogastric nerves contribute to the tone of the internal anal sphincter.

Injury to the hypogastric nerves leads to reduced sphincter contraction to 70% of baseline and increased activity in the rectum, whereas after lumbar colonic nerve resection internal sphincter tone decreases to 32% of baseline [16]. Spinal anesthesia or blocking of the pudendal nerves is followed by a decrease of the sphincter tone as is known from patients with myelomeningocele.

Beta-adrenergic Inhibitory Receptors

The pharmacological stimulation of beta-adrenergic inhibitory receptors leads to relaxation of the muscle [17–20].

Cholinergic Neurons

The influence of cholinergic neurons on the sphincter is not yet adequately understood because parasympathetic drugs act differently in different animal species and in the upper and lower segments of the sphincter.

Nonadrenergic Noncholinergic Neurons

NANC inhibitory neurons are situated in the myenteric plexus, and contact neurons of the cholinergic system. They are of great importance both in the peristaltic reflex and in internal sphincter relaxation. This is evidenced by the fact that the rectoanal inhibitory reflex can still be elicited after both sacral nerves and both hypogastric nerves have been severed and the blood supply to the anorectum has been isolated [21]. Their absence causes pathophysiology of the narrow segment and anal sphincter achalasia [5, 22–25]. The NANC innervation of the

internal anal sphincter involves an inhibitory substance generated from the l-arginine-nitric oxide pathway [26–30].

Peptidergic Nerves

Peptidergic nerves seem to play an additional role in internal sphincter relaxation by modifying adrenergic and cholinergic transmission. Neuropeptide Y (NPY), VIP, SP and metenkaphalin lead to relaxation of the colonic smooth muscle [31]. VIP and nitric oxide synthase are present and frequently coexist in neurons of the internal sphincter of the opossum. These neurons may be important too in mediating rectoanal reflex-induced relaxation [26, 32, 33]. According to Fujimoto et al. [34], there are only a moderate number of these fibers in normal internal anal sphincter tissue, whereas these peptide-containing nerves are abundant in the sphincters of patients with neurogenic internal sphincter achalasia. NPY causes an increase in internal anal sphincter pressure and inhibits internal anal sphincter relaxation [31].

The relaxing phase of the peristaltic reflex, mediated by the ganglion cells, manifests itself at the caudal end of the gastrointestinal tract as relaxation of the internal anal sphincter. Manometric evidence of internal sphincter relaxation can therefore be considered as proof of the presence of intramural ganglion cells and a normal neurotransmission in the most caudal segments of the terminal anorectum, and places the diagnosis of aganglionic HD out of the question.

12.3 Comparison of the Internal Anal Sphincter and the Rectum

The internal anal sphincter cannot be regarded as a simple terminal convolution of the circular muscle of the rectum. O'Kelly et al. [35] demonstrated that the response in vitro of the human anal canal longitudinal muscle layer to cholinergic and adrenergic stimulation also shows evidence of sphincter specification of the longitudinal muscle coat. Comparing the histological and pharmacological properties of the rectum and the internal anal sphincter, the following are particular to the anal constrictor. The internal anal sphincter has no or far fewer ganglion cells at least in its lower two-thirds than the adjacent rectum. Tafazzoli et al. [36] provided reference data about the quantitative distribution of nerve cells and ganglia within the submucosal plexus of the

Table 12.1 Summary of the most important anatomical, physiological and pharmacological data on the internal anal sphincter, rectum and aganglionic segment in HD. Inhibitory influence: NANC neurons, peptidergic neurons, inhibitory β-receptors. Excitatory influence: cholinergic neurons (?), α1 and α2 receptors, high norepinephrine content, no spike potentials (*BER* basal electrical rhythm, *GFA* glial fibrillary acid protein, *GRP* gastrin-releasing peptide, *MetEnk* metenkephalin, *NANC* nonadrenergic-noncholinergic neurons, *NCAM* neuronal cell adhesion molecule, *NO* nitric oxide, *NPY* neuropeptide Y, *SP* substance P, *VIP* vasoactive intestinal peptide)

Internal anal sphincter	Rectum	Hirschsprung's disease
Only a few ganglion cells in the uppermost part of the muscle [113]	Normal distribution of ganglion cells (18,000/cm²) [117]	Ganglion cells absent [119]
Dense sympathetic nerve fibers [114]	Normal nerve fiber distribution [113]	No inhibitory NANC neurons [5, 22–24]
No NANC-inhibitory neurons [5, 22, 23]	Low norepinephrine content (0.23 μg/g fresh weight) [114, 116]	No peptidergic neurons storing Enk, GRP [120]
Peptidergic inhibitory neurons storing NPY, VIP, SP, MetEnk, and other peptides	Inhibitory NO storing NANC-neurons [1–4]	Fewer VIP and SP-containing nerve fibers [7, 20]
Inhibitory β-receptors [20, 115]	Peptidergic neurons storing VIP, SP, MetEnk, GRP, histidine, isoleucine, neurokinin A [31–34]	Hypertrophied sympathetic nerve fibers [121]
High norepinephrine content (0.46 μg/g fresh weight) [116]	Few α-excitatory receptors [118]	Hypertrophied parasympathetic nerve fibers [122]
Many α1- and α2-excitatory receptors [13–15]		High norepinephrine content (0.4 μg/g fresh weight) [115, 123]
Cholinergic neurons [21, 115]		Lack of GFA [124]
No spike potentials on the BER [37]		Abnormal expression of NCAM [125]

human anorectum from healthy subjects showing that there is no uniform distribution pattern of ganglia or nerve cells, but a continuous decrease towards the anus. Morphometric analysis has demonstrated the presence of nerve cells and ganglia even in the most distally located segments of the rectum, the region of the anal canal. Although the number of nerve cells and ganglia in these segments is less than 50% of the numbers found in the remaining segments, the distal anorectum is characterized by hypoganglionic conditions and not by aganglionic conditions. It has a denser adrenergic innervation than the neighboring rectal segment and double the norepinephrine content. It is rich in alpha-excitatory receptors, and the NANC inhibitory neurons are absent from its lower two-thirds. In humans the tonic sustained contraction of the muscle is not induced by bursts of spike potentials, in contrast to the findings in many animal species and to the proximal rectum [37–39]. Therefore, the internal anal sphincter cannot be characterized as a megacolon-like narrow segment [40] (Table 12.1).

12.4 Electromanometry

Electromanometry allows the recording of pressure changes around hollow muscular organs of the gastrointestinal tract and the bladder. The intraluminal pressures of the rectosigmoid, rectum and anorectum are transformed into electrical impulses and after appropriate amplification registered by a recorder. This permits the function of the anorectal continence mechanism to be assessed. Of foremost interest are the propulsive motility, and the contractile and opening abilities of the internal anal sphincter. Electromanometry is a screening investigation for chronic obstipation and anal incontinence and should be performed before other examinations such as radiography or transit-time studies are performed, or suction biopsies are taken [41].

12.4.1 Technique of Anorectal Manometry

Electromanometry is a combination of pull-through and three-point measuring procedures. Polyvinyl feeding tubes closed at the tip and with a lateral opening 3 to 5 cm from the tip are usually used as pressure receivers. These are connected to a recording system via pressure transducers and amplifiers. Another type of manometric device is the anal pressure vectography. The advantage of this system, in contrast to other methods, is the three-dimensional reconstruction of the intrasphincteric pressure. This may be useful for measuring the anorectal pressure profile in patients with anorectal malformations after sphincter reconstruction operations and in children with stool incontinence after sphincteromyotomy. However, for the recording of internal sphincter relaxations or propulsive waves one has to switch to other probes. Besides, the pressure values recorded by six circularly arranged single tubes inside one probe differ enormously (Fig. 12.3). Therefore, the calculated mean values are not representative.

Other measuring procedures utilizing large-volume single-balloon systems and small miniballoons connected in series [42, 43] have also proven useful. They only allow the recording of internal sphincter relaxation, not the other manometric parameters, and cause, particularly in small children, marked irritation due to their foreign body effect [44]. For this reason, measurements made with feeding tubes have prevailed. Measuring catheters are introduced into the rectosigmoid, rectum and anorectum, respectively. In addition a stimulating catheter is placed in the rectosigmoid and a Foley catheter with a balloon volume of 30 to 50 cm^3 in the rectum to simulate a bolus effect. Introduction and reliable placement of the rectosigmoid catheters is achieved using an intestinal tube which is withdrawn over the carefully positioned catheters back to the anus. The anorectal catheter is then placed in the rectum and in the sense of a pull-through procedure is slowly withdrawn toward the anus. By this means, the height of the anorectal pressure plateau can be determined and hence accurate positioning of the catheter in the area of the internal anal sphincter achieved. The appearance of typical anorectal fluctuations, that is, slow fluctuating waves expressing the basal electrical activity of the sphincteric smooth muscle cells, confirms the accuracy of the positioning.

12.4.2 Anorectal Pressure Profile

An irrigation catheter withdrawn from the rectum down through the anal canal at a constant rate reveals a constant rise in pressure with the maximum pressure plateau in the caudal portions of the sphincter. At a standardized speed of withdrawal, the length of the pressure profile corresponds to the length of the sphincteric high-pressure zone and its height to the anal constrictive pressure produced under resting conditions mainly (85%) by the internal anal sphincter [41, 45]. The length of the high-pressure zone ranges in normal individuals from 3 to 7 cm (Fig. 12.4).

12.4.3 Internal Sphincter Relaxation

The muscle tone of the internal anal sphincter is myogenic in nature and maintained by the basal electrical rhythm. In contrast to the colon, the slow waves give rise to phasic contractions which are not accompanied by spike potentials (Fig. 12.5). The amplitude of the slow waves in vitro are about 10 mV, and in vivo 200–500 μV. However, there is interindividual variation and most pa-

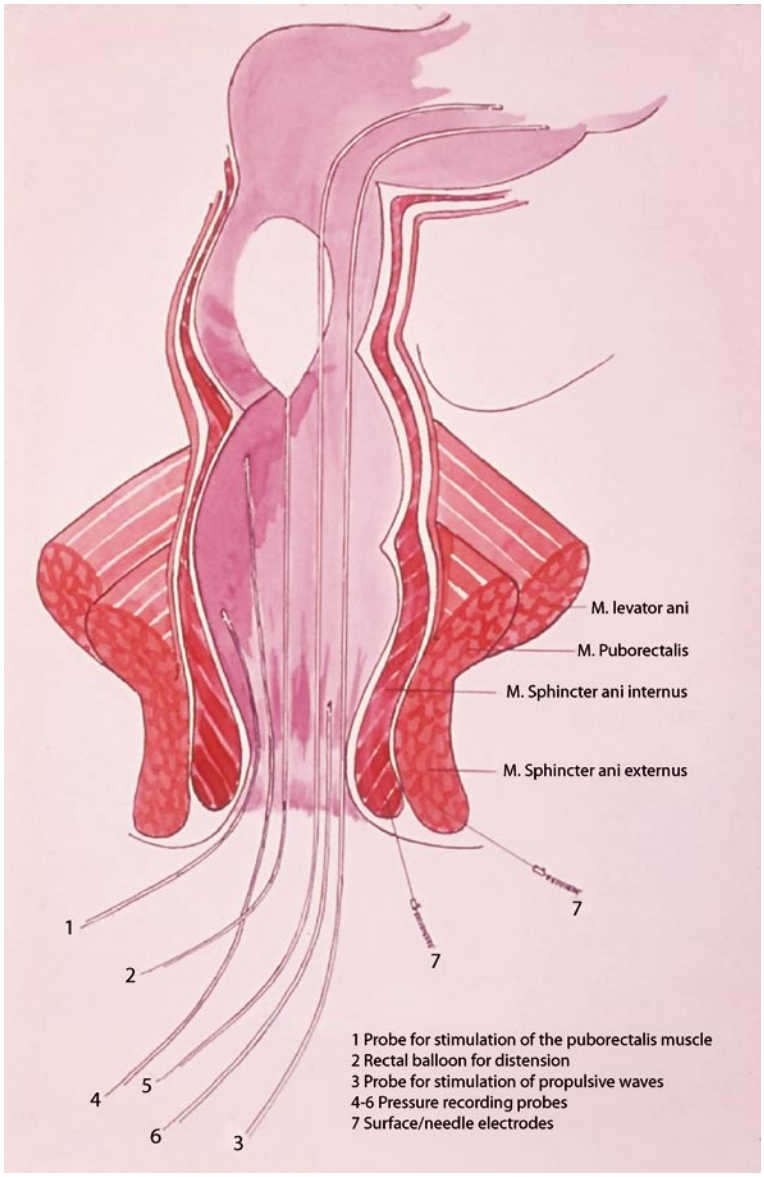


Fig. 12.3 Schematic diagram of the position of the manometric catheters in the rectum and anorectum

tients show a rhythmic increasing and decreasing pattern. According to Wienbeck and Altaparmakov [46], however, the frequency of these pacemaker activity waves remains constant in each individual. The slow wave potentials and mechanical contractions migrate in the oral direction. The frequencies of the electrical control activity are 20 cycles/min at the dentate line, 13.5 cycles/min at the anorectal junction, and 5 cycles/min in the rectum, indicating pacemakers in the smooth sphincter muscle.

The relaxation reflex, a physiological criterion for sphincters, corresponds to the relaxing portion of the most caudal peristaltic reflex, and can be manometrically demonstrated by showing relaxation of the muscle when a balloon is simultaneously distended in the rectum (Fig. 12.6).

The basal electrical activity of the sphincteric smooth muscle becomes desynchronized, and at the same time the mechanical pressure drops. The summation effect is lost, and electrical activity is no longer demonstrable via extracellular leads (Fig. 12.7). As soon as the lowest pressure drop occurs, the electrical and mechanical rhythms reappear, the pressure rises, and sphincter tone is restored. The mean intrasphincteric pressure profile in children is 47±18 mmHg, and the resting pressure in the rectum is 7.5±2.5 mmHg. A rectal distension of a 10-ml balloon should evoke a relaxation of 6 seconds duration.

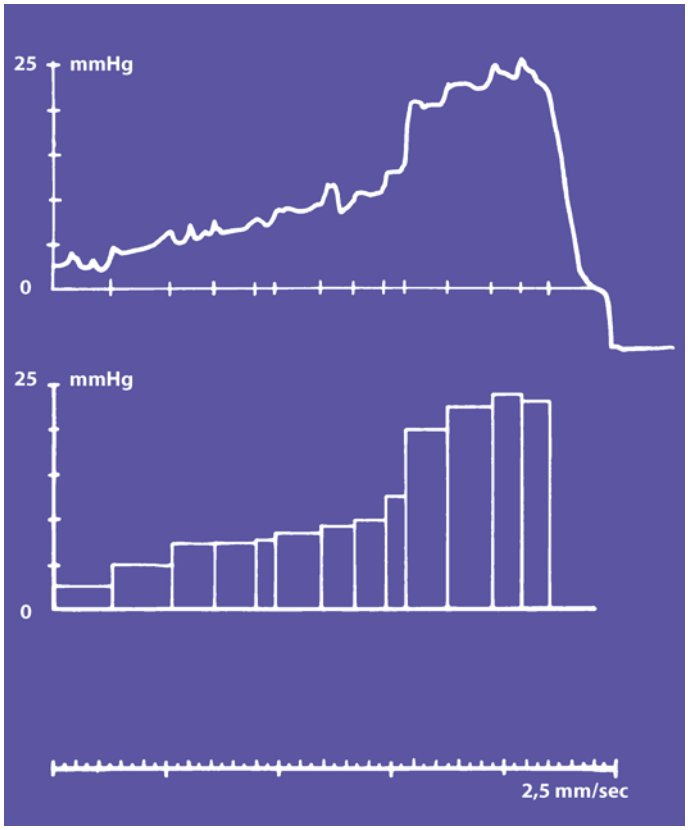


Fig. 12.4 Schematic diagram of the anorectal pressure profile. One horizontal notch represents 1 cm

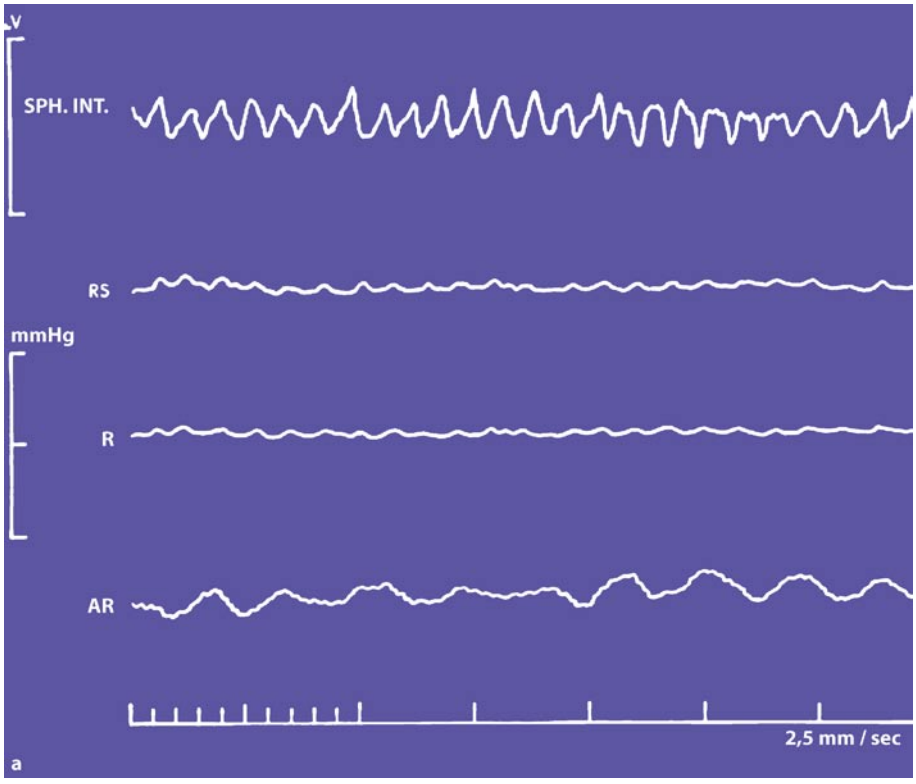


Fig. 12.5a,b Basal electrical rhythm of the internal anal sphincter (SPH.INT) : **a** constant pattern of the slow waves; **b** *see next page* (*RS* rectosigmoid, *R* rectum, *AR* anorectum)

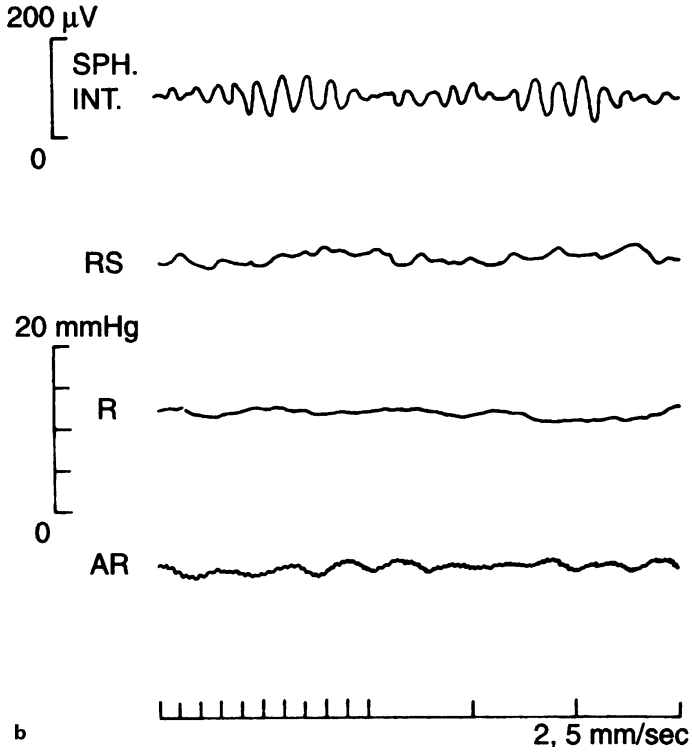


Fig. 12.5a,b *(continued)* Basal electrical rhythm of the internal anal sphincter: **b** wave-type pattern (*AR* anorectum, *R* rectum, *RS* rectosigmoid)

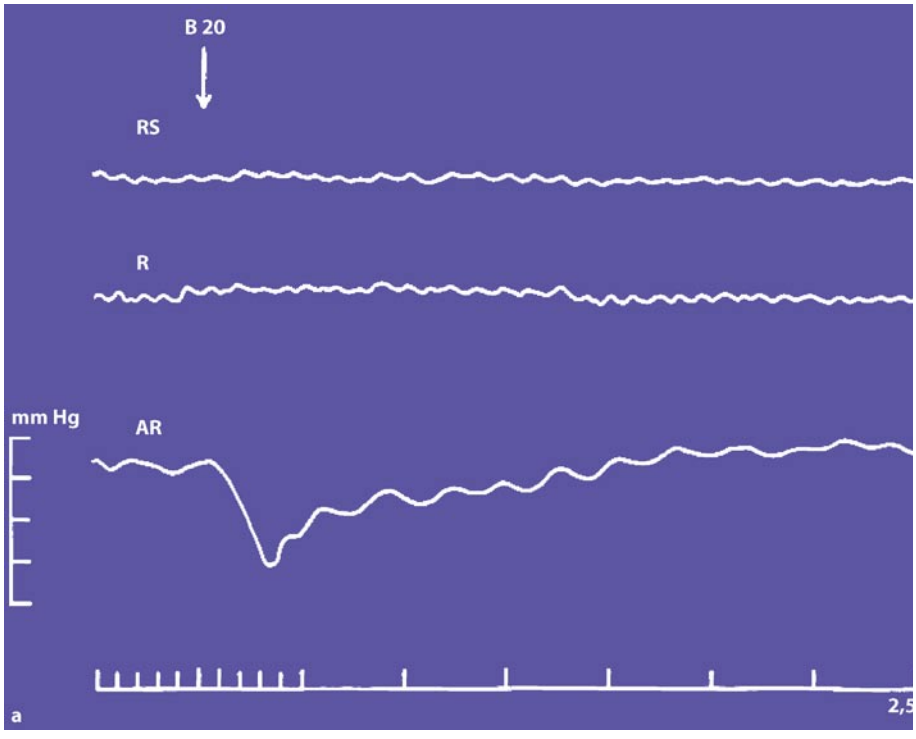


Fig. 12.6 Normal internal anal sphincter relaxation after distension of a rectal balloon (B) with 20 ml of air (*RS* rectosigmoid, *R* rectum, *AR* anorectum). Note: the fluctuating waves of the anorectum resume at the deepest point of the relaxation!

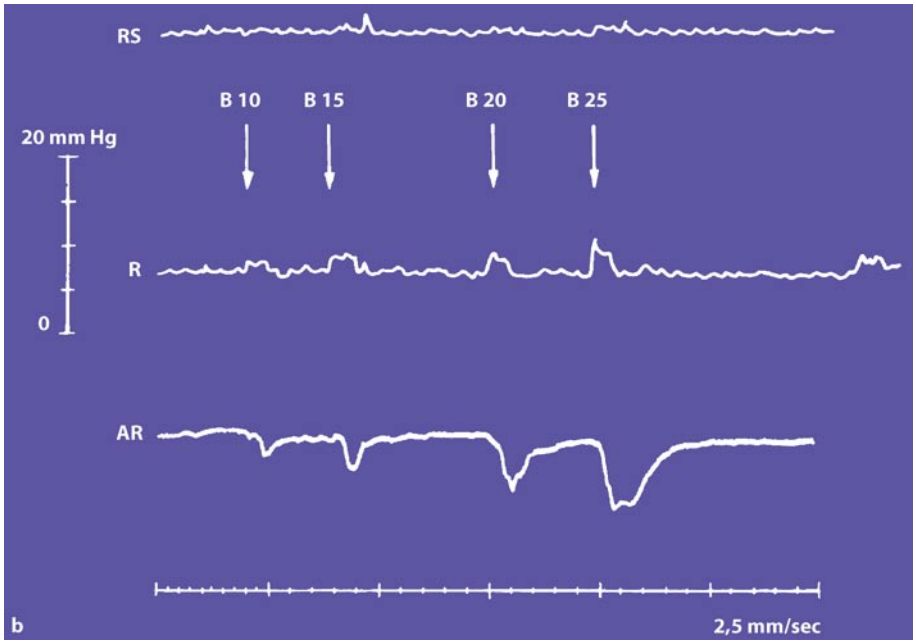


Fig. 12.6 (*continued*) **b** Direct proportionality between the rectal distension volume and the depth and length of the internal sphincter relaxations (*AR* anorectum, *B* balloon, *B10* distension volume 10, 15, 20, 25 ml, *R* rectum, *RS* rectosigmoid)

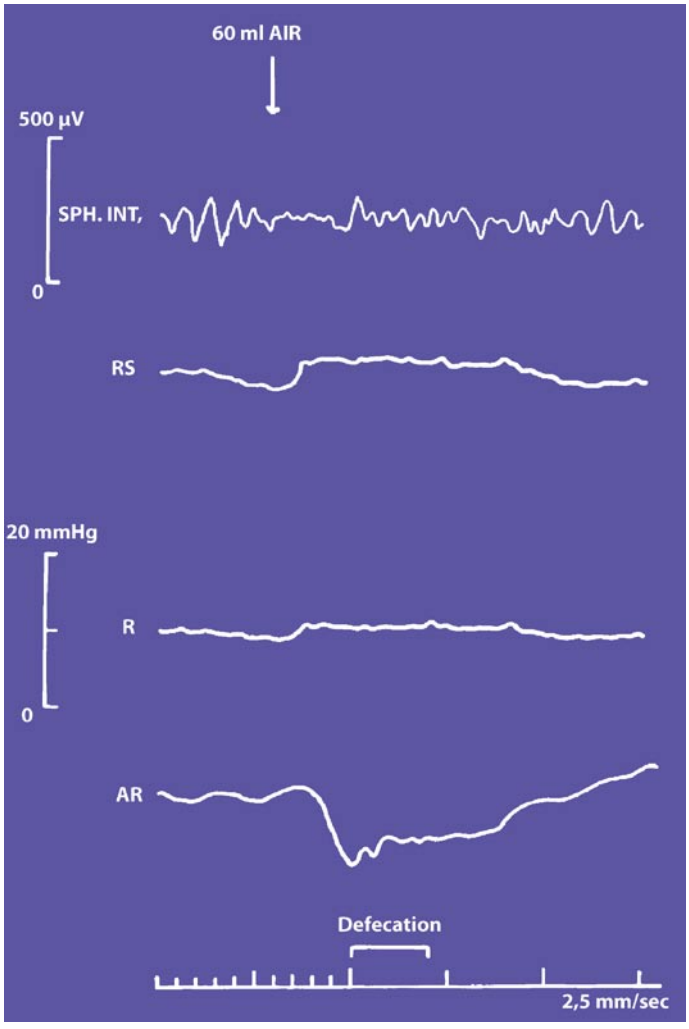


Fig. 12.7 Simultaneous inhibition of electrical and mechanical activity of the internal anal sphincter (SPH.INT) after injection of 60 ml air into the rectosigmoid (*RS*). Slight adaptation reaction in the rectosigmoid and rectum (*R*). Once the lowest point of relaxation is reached, electrical and mechanical activity resumes (*R* rectum)

12.4.4 Continence Reaction

Simultaneous recording of electrical activity in the striated sphincter muscles reveals a substantial increase in activity during internal sphincter relaxation. This is the rectosphincteric reflex (Fig. 12.8).

This reflex serves to constrict the anal canal opened by the relaxation in order to prevent stool soiling. Transient opening of the anal canal for a few stool particles is necessary so that discrimination of gaseous, liquid or solid bowel contents in the upper anal canal is possible. Manometrically, this reflex contraction of the external anal sphincter is expressed as a contraction spike during or at the end of internal sphincter relaxation, which is termed the continence reaction. The simultaneous contraction of the puborectalis muscle is also included in this continence reaction (Fig. 12.9). The simultaneous contraction of the puborectalis muscle, however, can be tested more exactly by direct stimulation of the muscle with 0.1 ml of physiological saline solution [47]. Under resting conditions the external anal sphincter contributes only up to 15% to the anorectal pressure barrier, but up to 60% during sudden rectal distension. The tone of the sphincter is reflected by the intensity of its spike potential discharge and increases even with breathing. The only exception to this very sensitive increase in spike potential is during defecation which is induced by contraction of the abdominal wall muscles followed by simultaneous interruption of the electrical and mechanical activities in both the internal and external anal sphincters (the defecation reflex; Fig. 12.10). The striated muscle contains two types of muscle fibers: type I fibers for tonic contraction and type II fibers for phasic contraction. The proportions and distribution vary from fetal life to adulthood [48] (Figs. 12.11 and 12.12).

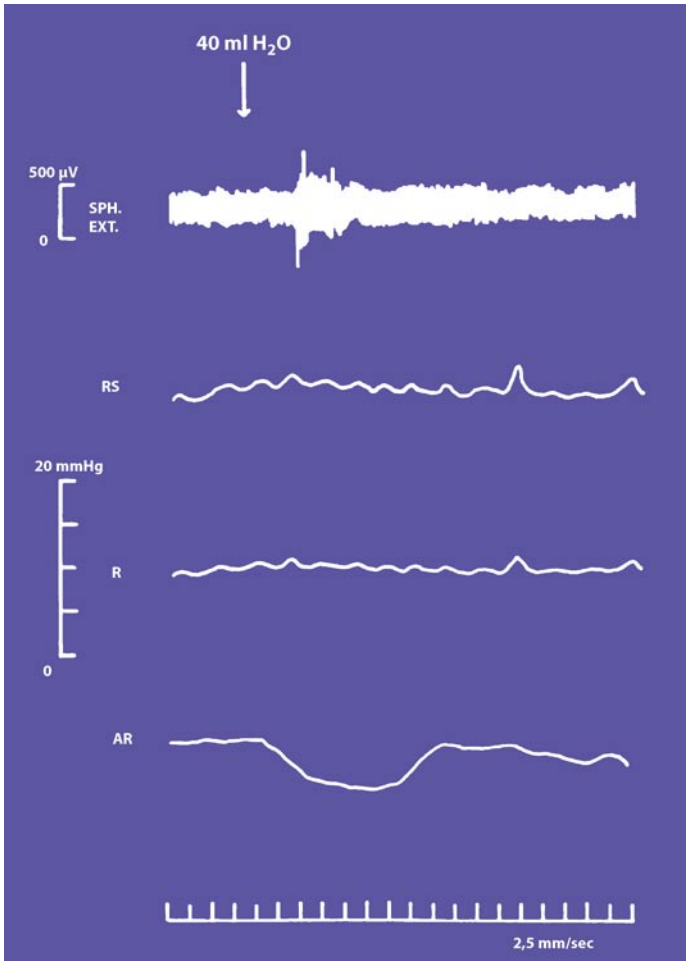


Fig. 12.8 Increased activity in the external anal sphincter during internal sphincter relaxation produced by injection of 40 ml water into the rectosigmoid (rectosphincteric reflex) (*AR* anorectum, *R* rectum, *RS* rectosigmoid)

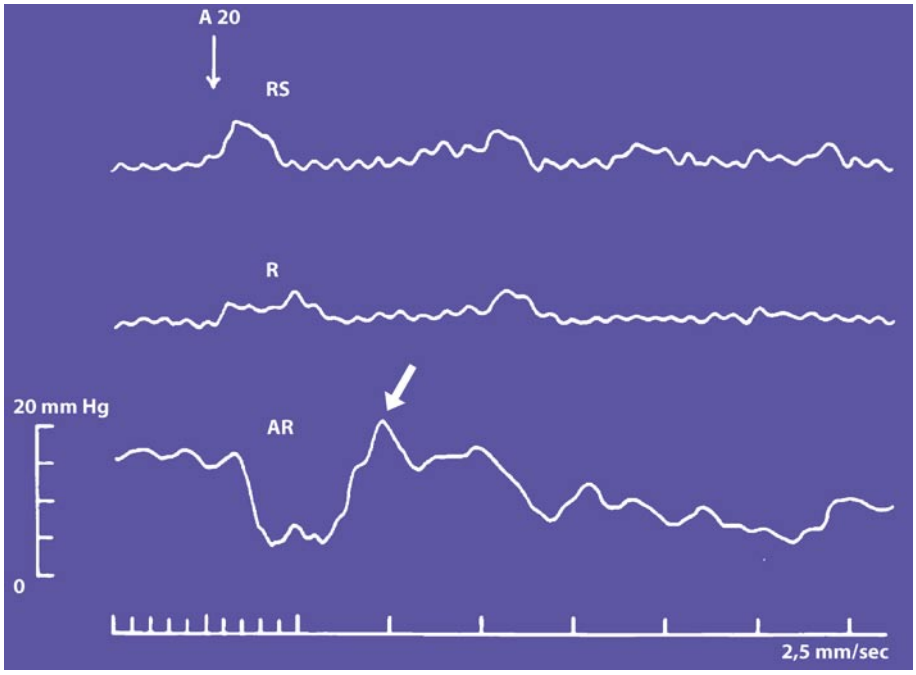


Fig. 12.9 Continence reaction (*CR*): the injection of 20 ml air (*L20*) into the rectosigmoid (*RS*) is followed by deep relaxation in the anorectum (*AR*). There is a subsequent distinct contraction spike in the anorectum (*arrow*), expressing the contraction of the striated sphincter and puborectalis muscles (*R* rectum)

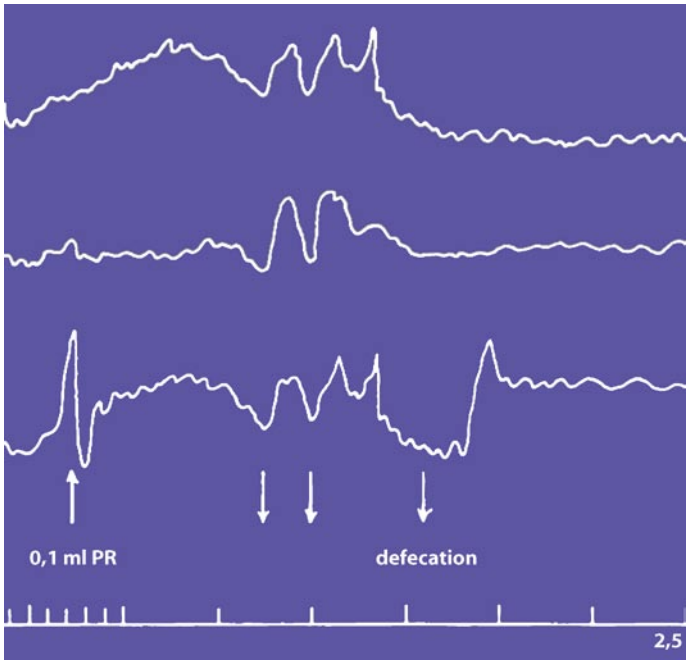
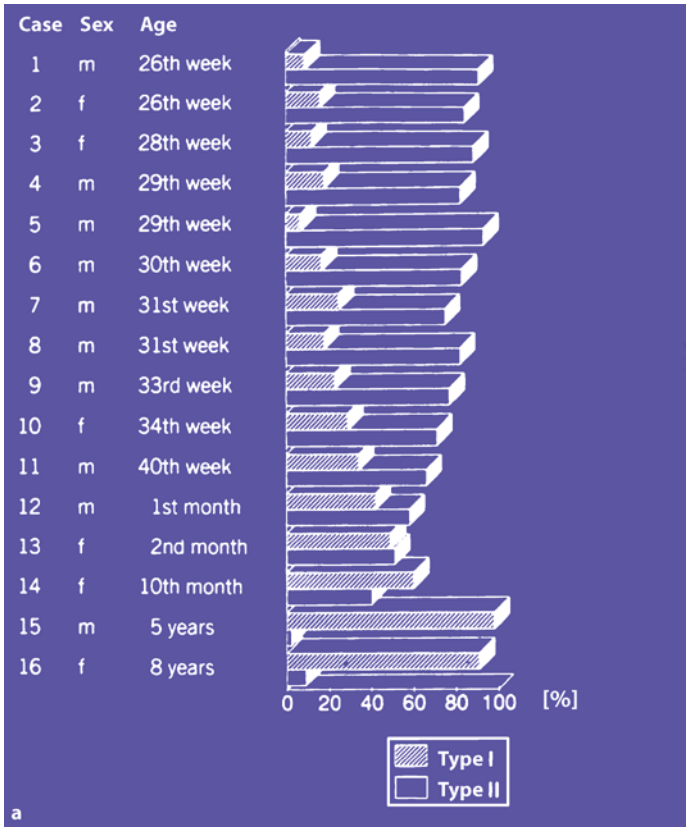


Fig. 12.10 Defecation reflex: simultaneous interruption of the electrical and mechanical activities in both the internal and external anal sphincters stimulated by injection of 0.1 ml of physiologic saline solution at the puborectalis sling (*PR*), lead to the propagation of a propulsive wave which is followed by a drop in the anorectal pressure and recurrent defecation of small amounts of liquids



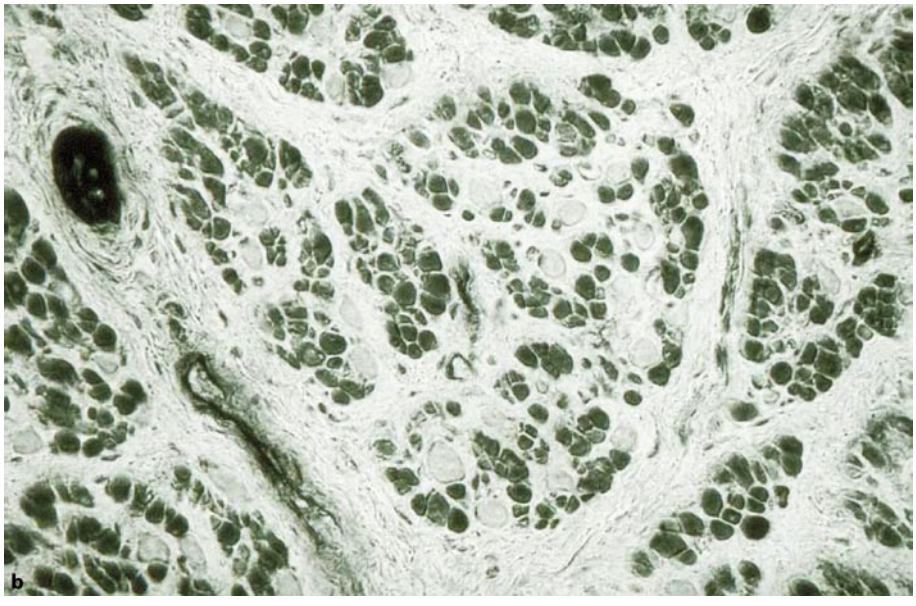
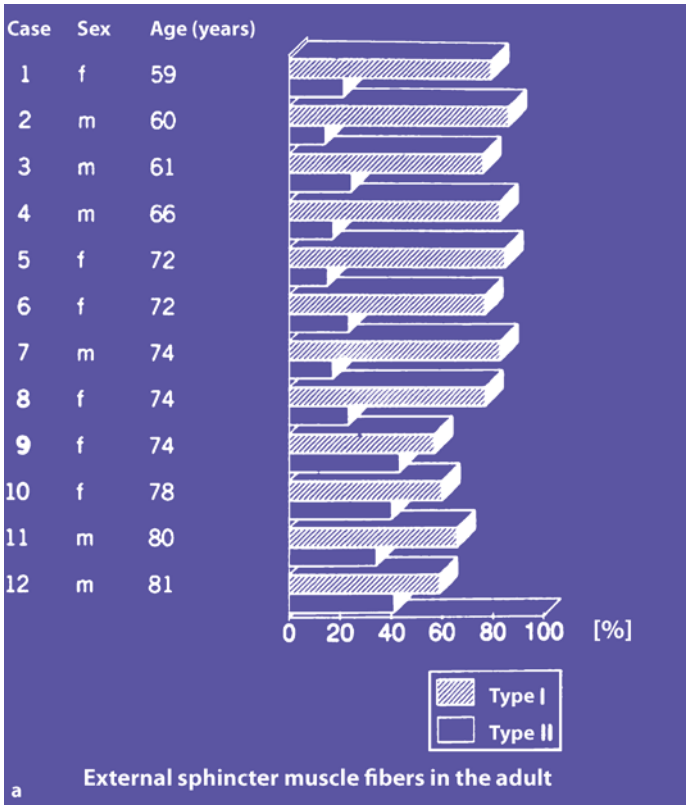


Fig. 12.11 **a** Relative Distribution of type I (tonic) and type II (phasic, rapid) fibers in infants, fetuses and children. **b** Cross-section through external anal sphincter of 29-week fetus. Large type I fibers (clear) surrounded by small type II fibers (dark). ATPase reaction at pH 10.4, enlarged 100× (taken from 48). In Fetuses rapif Type II muscle fibers predominate. With increasing age infants Type I fibers increased and showed a predominace in adults



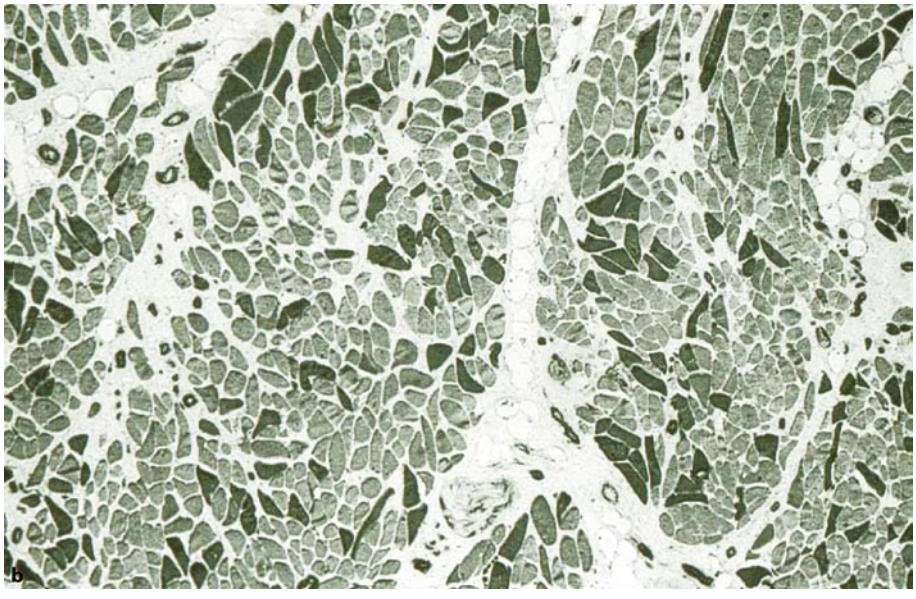


Fig. 12.12 **a** Relative distrubution of Type I and Type II muscle fibers in adults; **b** Predominace of Type I fibers (clear);

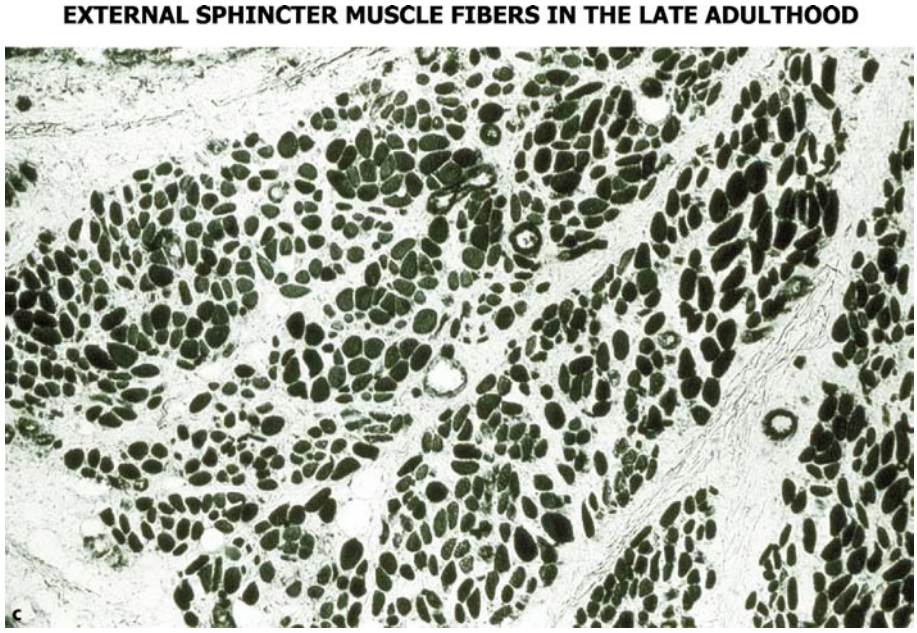


Fig. 12.12 *(continued)* **c** Increasing proportion of Type II (rapid, dark) muscle fibers. The pattern of late adulthood corresponds to the findings in newborns

12.4.5 Rectal Motility

Insertion of one measuring catheter into the rectum and another about 5 to 10 cm above the first into the rectosigmoid, or insertion of a probe with at least three sideholes placed at a distance of 3 to 5 cm according to the age of the patient permits observation of the segmental and propulsive contractions of the colon. When the rectosigmoid is stimulated with water or air, a rapid pressure increase followed by a slow pressure decrease occurs in the rectum, an expression of the plastic adaptive ability of this organ to sudden changes in pressure. Manometrically, this reaction is called the adaptation reaction (Fig. 12.13). The quotient of volume difference and pressure difference is designated as rectal compliance, and can to some extent indicate the elasticity of the rectum (Fig. 12.14). Thus, the compliance is distinctly elevated in a greatly dilated secondary megacolon, while it is below 1 ml/mmHg in a "rectal colon" after abdominoperineal pull-through.

12.5 Pathological Electromanometric Criteria

Indications for anorectal manometry are the differential diagnosis of HD and chronic constipation and for the functional analysis of fecal incontinence.

12.5.1 Habitual Chronic Constipation

In habitual chronic constipation, marked segmental contractions are found in the rectum which lead to spontaneous internal sphincter relaxations. The amplitude of the relaxations is directly proportional to that of the contractions in the rectal waves (Fig. 12.15).

12.5.2 Neurovegetative-Psychogenic (Functional) Anal Sphincter Achalasia

In neurovegetative-psychogenic or functional anal sphincter achalasia, the opening ability of the internal anal sphincter is interrupted or prevented by a simultaneous voluntary contraction of the striated sphincters and pelvic floor muscles. Even with large stimulating volumes, only rudimentary relaxations accompanied by voluntary contraction spikes before, during or after internal sphincter relaxation can be observed. Their appearance is a sign that the child is not willing to defecate, but is retaining stools. If the patient's attention is diverted, however, normal internal relaxation patterns can be observed during the same session (Fig. 12.16). Decisive in the diagnosis of functional anal sphincter achalasia is thus the simultaneous appearance of both rudimentary and normal relaxation patterns. About 90%

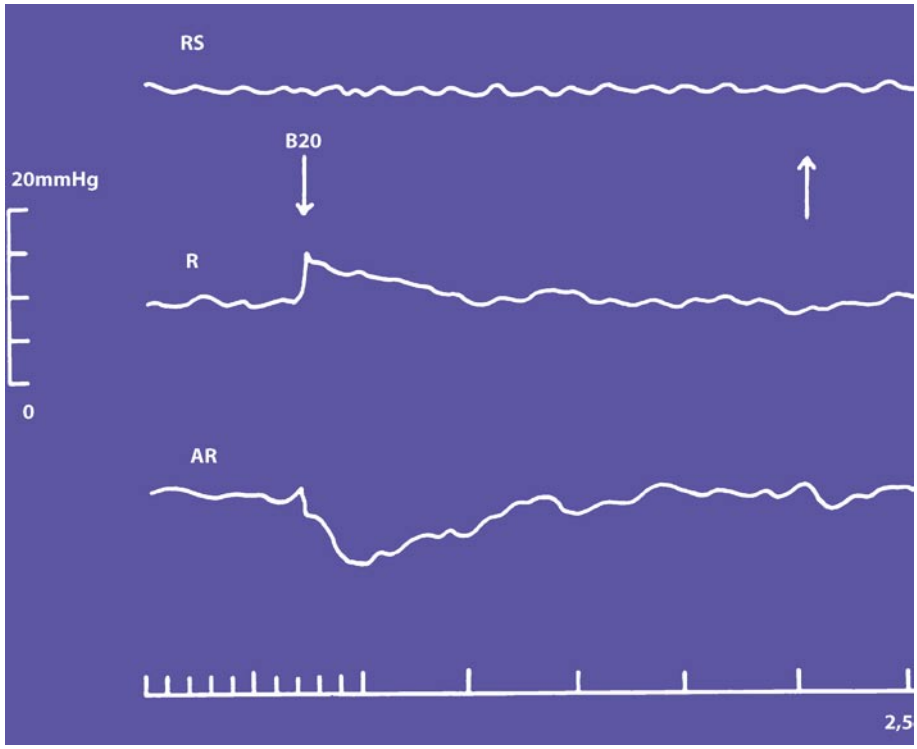


Fig. 12.13 Adaptation reaction: after distending a rectal balloon (B) with 20 ml of air. Definite adaptation reaction is seen in the rectum (*R*), with a rapid pressure increase and slow decline to resting values. In addition, there is relaxation in the anorectum (*AR*), (*RS* rectosigmoid)

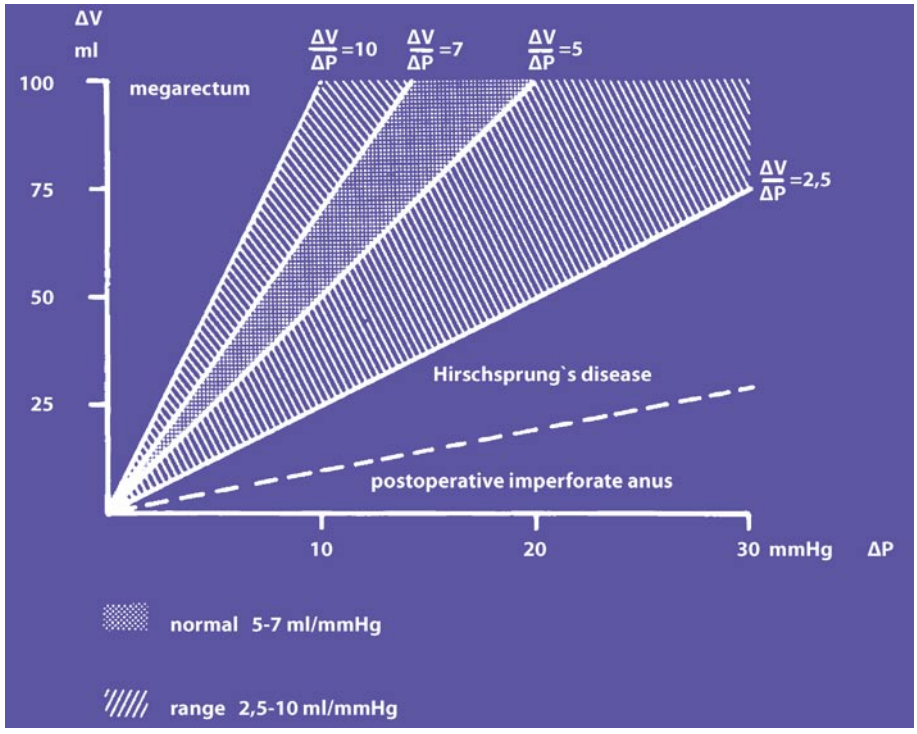


Fig. 12.14 Schematic diagram of rectal compliance: >10 ml/mmHg in the distended rectum in HD, <2.5 ml/mmHg after surgical correction of high anal atresia, 2.5–10 ml/mmHg normal range

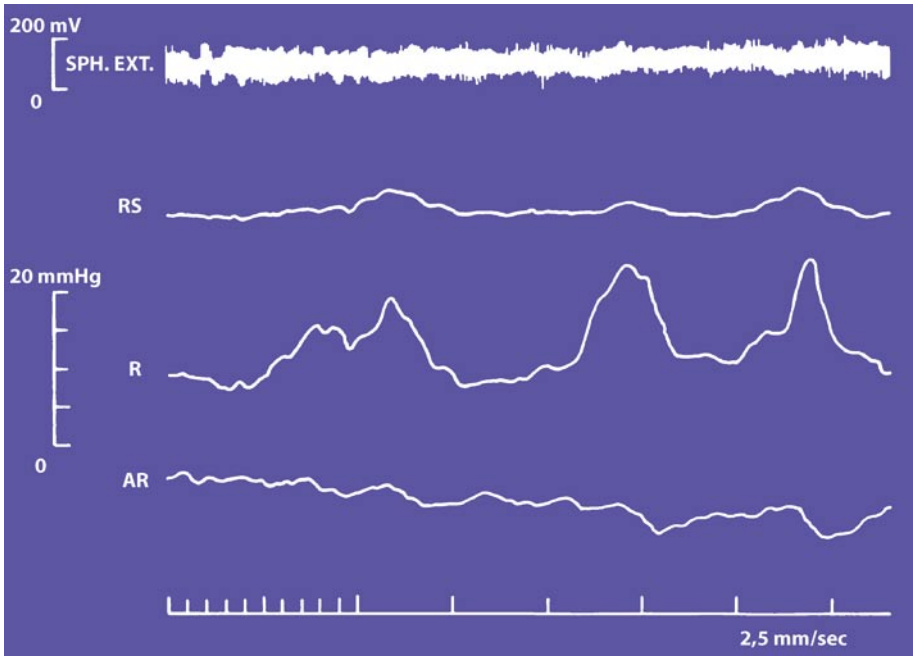


Fig. 12.15 Habitual constipation: high segmental and propulsive contractions in the rectum (*R*) lead spontaneously to internal sphincter relaxations in the anorectum (*AR*), whose amplitude is proportional to the intensity of the rectal contractions, (*RS* = rectosigmoid, SPH.EXT. = external anal sphincter EMG)

of all constipated children suffer from functional anal sphincter achalasia.

12.5.3 Myogenic Anal Sphincter Achalasia

In organic-myogenic anal sphincter achalasia, the sphincter muscles have fibrosed due to previous inflammations, abscesses, fissures, fistulas, chronic diarrhea, lacerations etc. The sphincter can no longer open wide enough to allow adequate defecation to occur. The inflammation spreads to the internal anal sphincter, causing progressive fibrosis of the smooth muscle [49] which can proceed to total sclerosis. Electromanometrically, rudimentary sphincter relaxations with reduced amplitude and shorter duration are found in this form of anal sphincter achalasia. The direct proportionality between the amplitude and duration of relaxation and the rectal distension volume is abolished (Fig. 12.17). Normal patterns of relaxation are no longer observed, although the relaxation reflex is still demonstrable. Myogenic sphincter achalasia is however very rare in children. Since our report in 1973, we have operated on no further patients with this diagnosis [50].

12.5.4 Neurogenic Anal Sphincter Achalasia and Hirschsprung's Disease

Neurogenic anal sphincter achalasia occurs to a different degree in all patients with neuronal intestinal malformations such as aganglionosis, intestinal neuronal dysplasia (IND), hypoganglionosis, immaturity of ganglion cells, hypogenesis and others. In children with aganglio nosis restricted to the sphincter and lowermost parts of the anal channel it corresponds to a megacolon with an ultrashort segment, and behaves manometrically like a congenital Hirschsprung's megacolon. Since the basic pathophysiology in aganglionic megacolon is the absence of intestinal nervous plexus and thus neither ganglion cells nor inhibitory NANC neurons are present, the intestinal inhibitory reflex of the internal anal sphincter cannot be elicited [41, 45] (Fig. 12.18). Normal peristalsis is not possible. Whereas the demonstration of internal sphincter relaxations excludes the presence of HD, the absence of the relaxation reflex is only pathognomonic when the anorectal fluctuations typical of the smooth muscle cells of the internal anal sphincter are observed prior to and after relaxation and when the patient is not a newborn less than 14 weeks of age [51]. In newborns the internal sphincter relaxation reflex may be absent or rudimentary due an immaturity of its nerve supply. According to Wood [52], the discharging frequency of the action potentials in the aganglionic segment increases from its proximal to its distal parts. This leads to an increased contractile tendency in the aganglionic bowel segment and to manometrically demonstrable multisegmental mass contractions (Fig. 12.19).

12.5.5 Intestinal Neuronal Dysplasia

In patients with IND no pathognomonic morphology of the relaxation reflex exists. The reflex mechanism may be

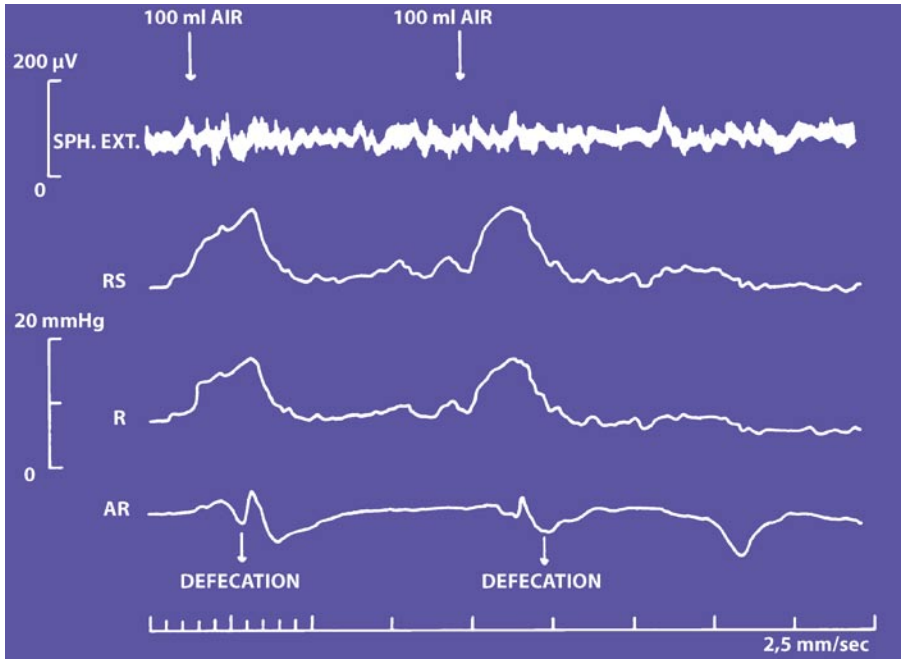


Fig. 12.16 Neurovegetative-psychogenic (functional) anal sphincter achalasia: simultaneous occurrence of spontaneous normal internal sphincter relaxation and rudimentary relaxations take patterns in the anorectum (*AR*) after injection of 100 ml air into the rectosigmoid. The rudimentary relaxation takes place due to simultaneous voluntary contraction of the puborectalis muscle and external anal sphincter, meaning an increased continence reaction, during internal sphincter relaxation, (SPH.EXT. external anal sphincter EMG, *RS* rectosigmoid, *R* rectum, *AR* anorectum)

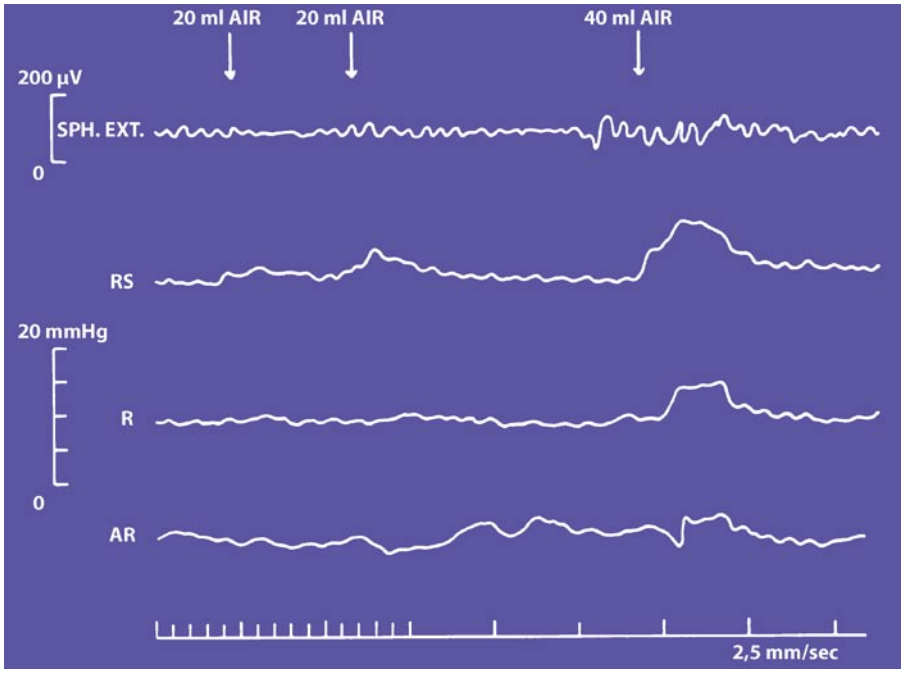


Fig. 12.17 Myogenic anal sphincter achalasia: rudimentary internal anal sphincter relaxations after injection of 20–40 ml air into the rectosigmoid (*RS*). The direct proportionality between the distending volume and the amplitude of the relaxation is abolished. Unobtrusive relaxations, such as those seen in functional achalasia, are not observed, (SPH.EXT. external anal sphincter EMG, *RS* rectosigmoid, *R* rectum, *AR* anorectum)

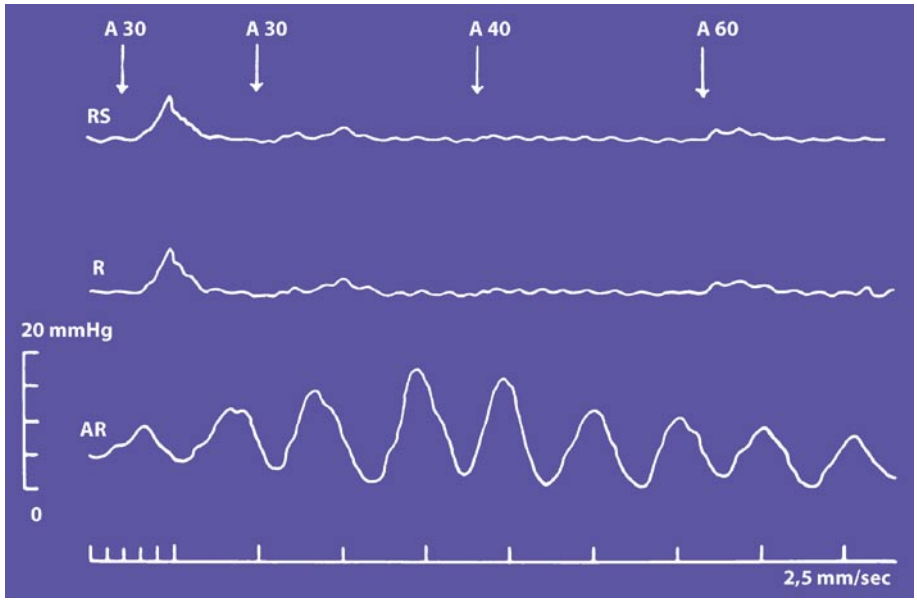


Fig. 12.18 Congenital Hirschsprung's megacolon: absence of internal sphincter relaxation during the injection of increasing volumes of air into the rectosigmoid (*RS*). Strikingly high anorectal fluctuations are apparent in the anorectum (*AR*), (*R rectum*)

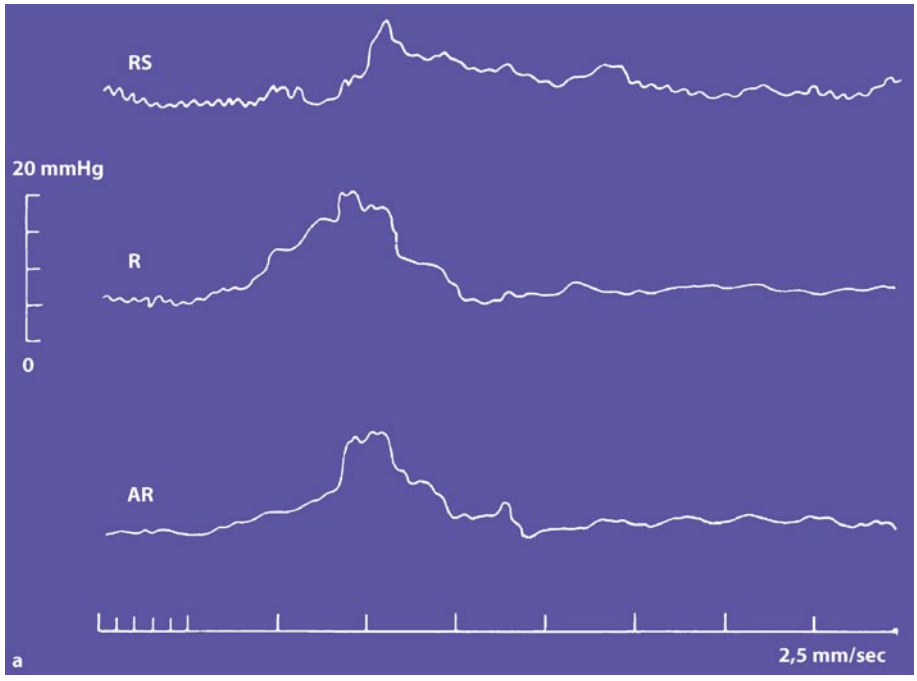


Fig. 12.19 **a** Spontaneous multisegmental mass contractions in the rectosigmoid, rectum and anorectum in congenital Hirschsprung's megacolon, **b** *see next page*

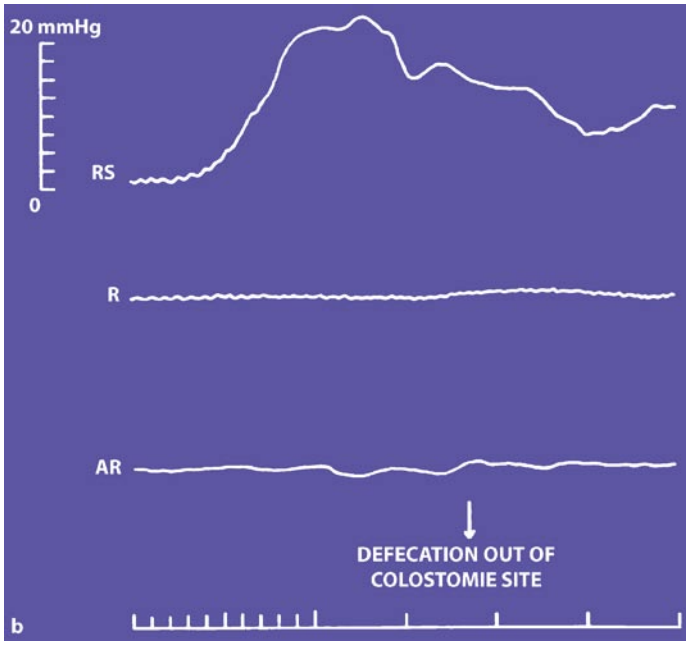


Fig. 12.19 *(continued)* **b** Spontaneous multisegmental mass contractions in the rectosigmopid (*RS*); no propagation of the wave in the rectum (*R*) and anorectum (*AR*); Defecation out of the colostomie site.

normal, rudimentary or absent (Fig. 12.20). The same is true for hypoganglionosis and immaturity of ganglion cells.

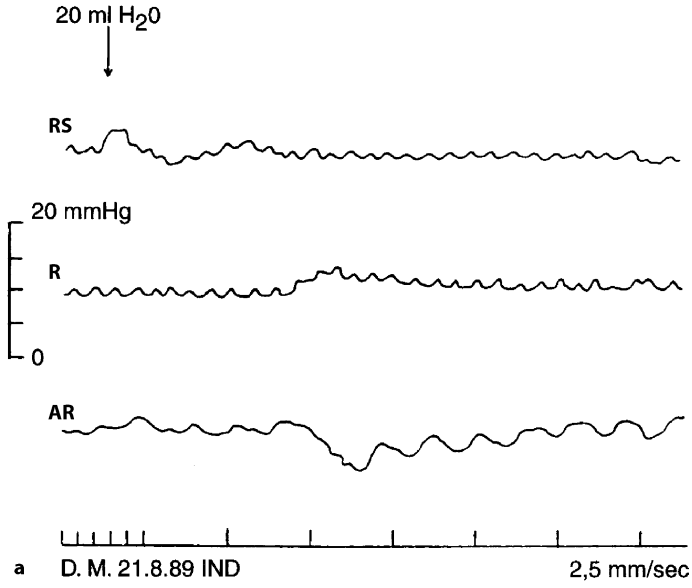
The internal anal sphincter sometimes also has an elevated tone with an increased anorectal pressure profile (Fig. 12.21). This can be true in HD as well as in hypoganglionosis and IND [53–55].

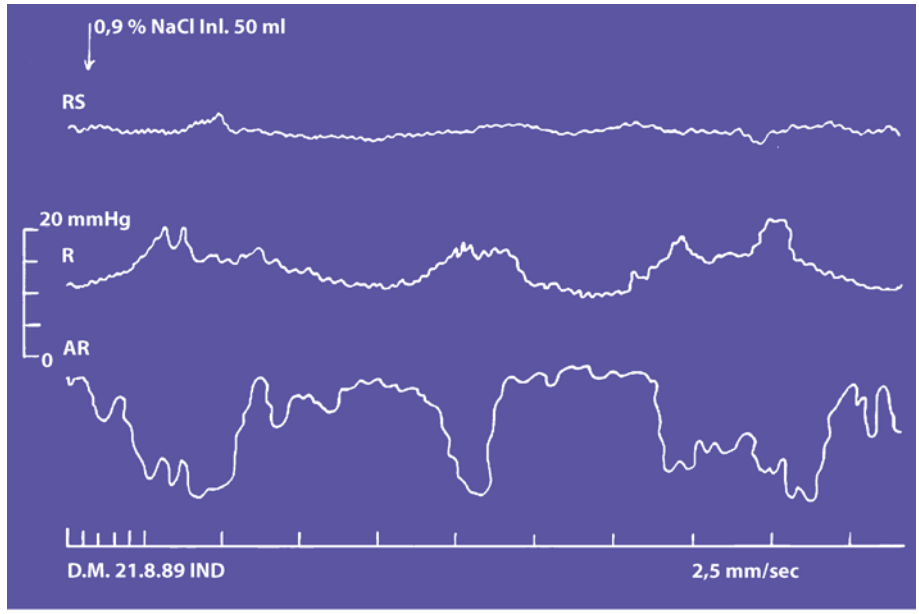
12.6 Potential Electromanometric Errors

The absence of internal sphincter relaxation is, then, crucial for the diagnosis of aganglionic megacolon. Demonstration of genuine internal sphincter relaxation with anorectal fluctuations at the beginning of the relaxation reflex and after return to the resting pressure level excludes the diagnosis of HD. The absence of internal sphincter relaxations cannot, however, be assumed to be reliable evidence of HD. One should keep in mind that in newborns, internal sphincter relaxation can physiologically be absent up to the 14th day of life or longer. It has been shown by measurements in premature infants weighing 1400 to 1900 g at gestational and composite ages of from 35 to 51 weeks that there are great variations in the rate of maturing of anorectal reflex activity which is dependent on both individual and environmental factors [51]. In that study, we found some premature infants who had internal sphincter relaxations as early as 35 weeks of age and others who lacked it after the 41st week. Traumatic skull fractures at delivery [56] and respiratory diseases [57], by way of example, can lead to delays in the maturing of the intramural plexus due to intrauterine hypoxia, causing signs of intestinal obstruction in the newborn.

In addition, the pre- and postnatal development of the rectal ganglion cells and nerve fibers varies enormously from one individual to another [58]. According to studies by Munakata [59] the acetylcholinesterase-positive nerve fibers first develop at 6 to 9 months, which likewise speaks for immaturity of the intestinal intramural plexus. For this reason, the authors recommend that the acetylcholinesterase preparation should be omitted and a silver stain done instead. According to Bughaighis and Emergy [60], at birth two-thirds of all intestinal neurons are immature, and maturation is finished not before the 5th year of life.

Electromanometrically, the type of obstruction due to delayed maturing of the nervous plexus cannot be distinguished from other neuronal intestinal disorders. Howard and Nixon [61] reported six newborns in whom laparotomy was performed with the diagnosis of acute abdomen. The configuration of the colon and rectosigmoid was similar to that found in HD: a zone of abrupt narrowing followed by proximal dilatation. Colostomy was performed and a biopsy taken which showed unremarkable bowel with ganglion cells present, so that the colostomy could subsequently be closed. Today we would suggest that these children were suffering from IND. We have observed the same clinical course in three children with histologically proven IND [62]. Besides, it seems possible that the small left colon syndrome may also be related to a similar maturational disorder, whereby in-





b **RS =Rectosigmoid; R = Rectum; AR = Anorectum**

Fig. 12.20a,b Reduced and enlarged internal sphincter relaxations in a patient with IND a normal internal sphincter relaxation, but reduced amplitude; **b** internal sphincter relaxations enlarged in amplitude and duration after injection of 20 ml (**a**) and 50 ml (**b**) of physiologic saline solution into the rectosigmois (RS). (*R* rectum, *AR* anorectum)

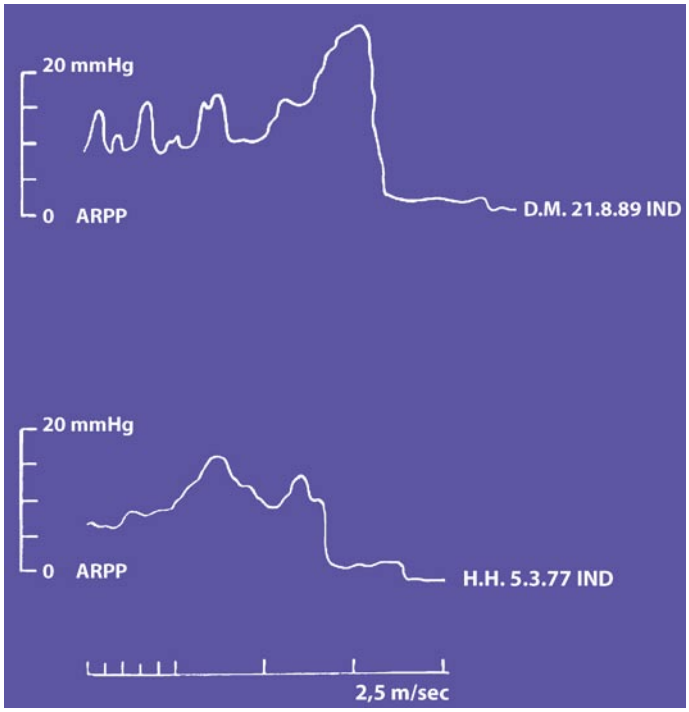


Fig. 12.21 Different values of the anorectal resting pressure profile in two patients with IND

creased condensation of stool due to maternal diabetes may play an additional role.

A further limitation is that catheters which are open at the tip occasionally become occluded. They can only be irrigated very cautiously in newborns, however, since even the small volumes used can induce defecation. For these reasons the value of manometry is limited in newborns whereas it is superior to all other diagnostic procedures except histochemistry in older children..

12.7 Accuracy of Electromanometry

Schnaufer [63] and Tobon et al. [64] consider anorectal manometry to be an absolutely reliable method which can be used with up to 100% accuracy for the diagnosis of aganglionosis. Arhan et al. [65] also reached similar conclusions. Internal sphincter relaxation was demonstrable in all their patients with so-called functional megacolon and was absent in all patients with HD. Frenckner and Euler [66] likewise reached the correct diagnosis of HD with manometry in all their patients with no false results, and similar findings were reported by Tamate et al. [67] and Verder et al. [68]. However, the findings of Meunier et al. [69] and von Issendorff [70] indicate that a certain degree of caution should be exercised in interpreting electromanometric findings in newborns and premature infants. Meunier et al. [69] found nine false-negative and six false-positive results in children from 3 to 31 days of age and seven premature infants. This would mean a diagnostic failure rate of 71.4% in premature infants and 26.4% in infants up to 31 days of age. Penninckx et al. [71] demonstrated 4% false results in 261 consecutive patients. In 11% the manometric result was equivocal. The value of anorectal manometry was most limited below the age of 1 month. According to Iwai et al. [72] a definitive diagnosis in patients with chronic obstruction was obtained in 95% of the patients, whereas in the neonatal period the diagnosis was obtained only in 81% of the children. Sumomito et al. [73] therefore recommend clarifying obscure rectoanal reflexes by the administration of prostaglandin F2 alpha. Since Holschneider et al. [51] have shown that internal anal sphincter relaxation is physiologically not demonstrable prior to the 14th day of life and the maturation of the relaxation reflex can also be delayed, these findings are not surprising.

Studies by Munakata [59] also indicate that acetylcholinesterase staining begins increasing in intensity, and is thus of diagnostic value, between the 6th and 9th month of life. Meunier and co-workers [69, 74] accordingly found only two false-positive and one false-negative result in the 1- to 6-month age group, a distinct failure rate of 7.7%. This rate decreased to 2% to 3% in older children. Von Issendorff [70] studied the value of different anorectal parameters. No normal or atypical internal anal sphincter relaxation could be demonstrated in any of his patients, although atypical or absent relaxations did occur in 5 of 19 patients with chronic constipation. These false-positive results were, in the authors opinion, attributable to technical errors. Mass contractions were never observed in the patients with chronic constipation, but occurred in 40% of those with aganglionosis. The

anorectal pressure profile, at an average of 31.9 mmHg, was definitely higher in the patients with HD than in those with chronic constipation, who showed a pressure of 22.4±7.3 mmHg. Propulsive waves could never be elicited in the patients with aganglionosis and very rarely in children with IND or hypoganglionosis. The adaptation reflex was sometimes normal and sometimes atypical, and the compliance, at an average of 5.1 mmHg, was markedly lower than the average 14.8 mmHg found in the patients with chronic constipation. In a more detailed analysis we came to the same result [41].

We have not managed to achieve the convincing 100% accuracy of Tobon and Schuster [75] in our studies, but have found an electromanometric accuracy of 96% in both comparative histological/manometric studies [49] and comparative roentgenological/manometric studies [76]. The roentgenological misdiagnosis rate, on the other hand, was 25%, and that for histology 4 to 6%. The accuracy of 232 electromanometric tracings in the same number of patients with HD, chronic constipation, anal atresia and myelomeningocele, was 87.2% with only 9.4 faulty classifications [77]. Boston and Scott [78] attained an accuracy of 92% in 63 newborn infants.

The differing results from anorectal manometry are undoubtedly due to different degrees of experience of the individual authors with the manometric technique, to technical difficulties, particularly in the newborn period, and to the physiological range of variation in the appearance of internal sphincter relaxation. Since manometry is an innocuous and simple examination, however, it should definitely be employed as a screening method for all types of defecation disorders. Martin et al. [79] prefer total colonic manometry to measure directly intraluminal pressures and contractile functions of the entire colon in patients with functional colonic obstruction. Manometric tracings were obtained while fasting, after feeding, and after pharmacological stimulation. They concluded that total colonic manometry can be valuable in deciding the need for and timing of diversion, the extent of resection required, and the suitability of the patient for restoration of bowel continuity in refractory functional obstruction. In all uncertain cases, suction biopsies should be taken. In addition radiographic and transit-time studies are essential in order to dry to determine the length of the aganglionic bowel segment and bowel motility.

Yang and Wexner [80] evaluated 50 consecutive patients with fecal incontinence by anal pressure vectography, electromyography and anal sonography during the same visit. Of the 50 patients, 34 (68%) showed global defects of the sphincters on cross-sectional vectograms. out of 46 patients, 36 had isolated decreased electromyographic activity in a single quadrant. However, only 5 of 38 patients (13.2%) had the same defect localized by anal pressure vectography. In addition, 33 of these patients had anal ultrasonography, and 27 of them showed anal sphincter defects. However, only 3 of these 27 patients (11.1%) had the same defect localized by anal pressure vectography. The authors concluded therefore that anal pressure vectography has a poor correlation with other physiological tests and is of no greater value than normal anorectal electromanometry as described above.

12.8 Anorectal Manovolumetry

Anorectal manovolumetry is a method for simultaneous recordings of anal pressures and rectal volumes in response to graded rectal distension pressure [81, 82]. The technique enables recording of rectal compliance and may therefore provide further insight into rectal wall elasticity. It can be especially helpful in incontinent patients. A further possibility for investigating rectal reservoir function is fecoflowmetry introduced in 1990 by Shafik and Khalid [83, 84]. The principle of this method is similar to that of uroflowmetry.

12.9 Electromyography

The reports of Marin et al. [85], Inon et al. [86], Holschneider [45, 87] and Vanasin et al. [88] generated some enthusiasm for anorectal myography in the diagnosis of HD. By means of intraluminal electrodes slow wave activity was recorded from the rectal wall. Strict contact to the mucosa is mandatory but difficult to achieve. Slow wave activity was recognized as regular with 12–20 oscillations per minute. If no spikes are seen on the top of the slow waves, the test is interpreted as being consistent with a diagnosis of HD (Fig. 12.22).

Whereas the basal electrical rhythm continues whether or not the muscles of the bowel wall are contracting, spike potentials can only be demonstrated when an additional contraction of the musculature occurs. Frequency, velocity, and the aboral–oral direction of spread of rhythmic peristalsis are controlled by electrical slow waves. Spike potentials, however, are responsible for additional phasic contractions, but can also be observed without any associated change in pressure [89]. On the other hand, mass movements are correlated to sinusoidal oscillations of several slow wave cycles. Pickard et al. [90] therefore found no spike potentials (what they called abnormal for healthy subjects) in 10 of 41 histologically proven healthy subjects and spike potentials (what they called atypical for HD) in 5 out of 15 patients with HD. Among 45 patients with chronic constipation and HD we found spike potentials on the top of the slow waves of the colon in 31 out of 35 constipated children. In 8 out of 9 patients with HD, in contrast, no spike potentials could be observed. Yanagihara et al. [91] and Shafik [92] also recommend electromyography as a suitable test for HD. However, for the above-mentioned reasons this has to be considered with reservation.

The main role of electromyography in constipation is to exclude anismus as a cause of obstructed defecation.

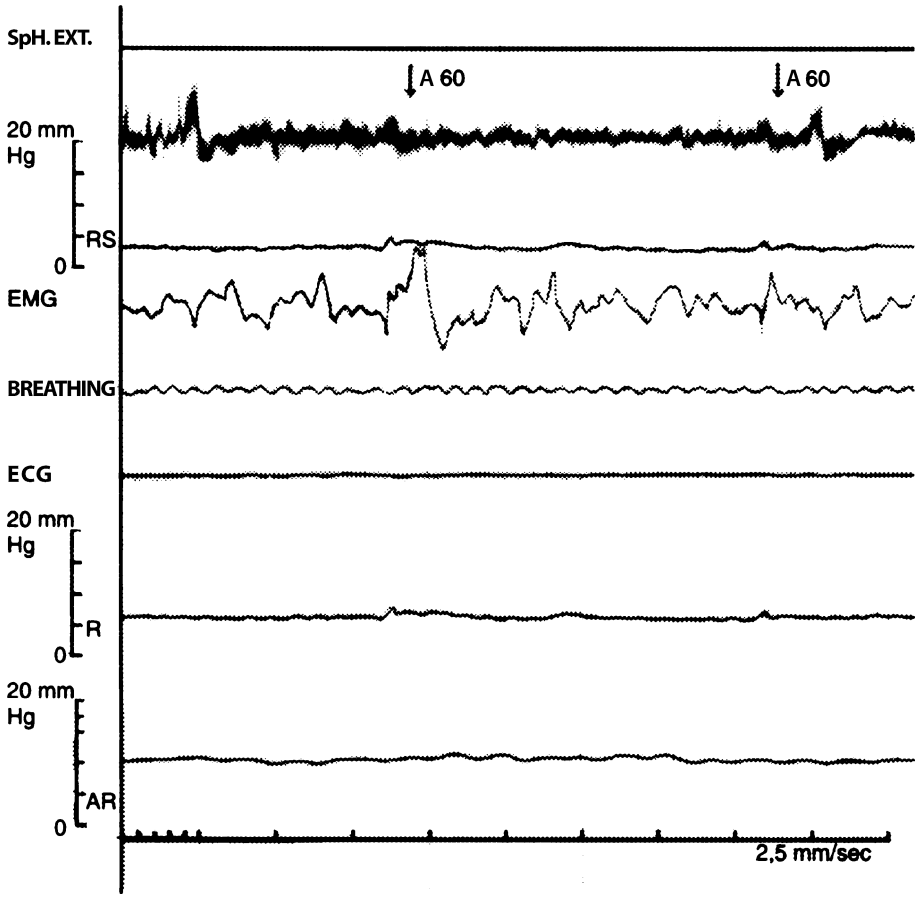


Fig. 12.22 No spike potentials on the top of the slow waves in a patient with HD (*RS* rectosigmoid, *R* rectum, ECG electrocardiography *AR* anorectum, SPH.EXT. external anal sphincter, EMG electromyography of smooth muscle layers)

Fink et al. [93] found anismus in 20% of patients studied. There was, however, a poor correlation between the finding of anismus on electromyography and failure of the anorectal angle to become widened during defecation.

12.10 Endosonography

Endoluminal ultrasonography of the anal canal is of no help in the diagnosis of HD or allied disorders. However, it can be a useful adjunct to physiological studies of anorectal function in patients with stool incontinence after surgical procedures particularly sphincteromyectomy [94–96] and for reproducible estimation of rectal compliance [97]. A combination of endoluminal sonography, electromyography of the external anal sphincter and manometric evaluation is favored by Tjandra et al. [95] and Gantke et al. [98]. Very promising is three-dimensional endorectal sonography which allows three-dimensional visualization of the pelvic floor and anorectal sphincters [99].

12.11 Transit-time studies

Transit-time studies are very helpful in the estimation of the length of the involved segment in patients with chronic intestinal obstruction. We never perform an extended colonic resection without having performed a transit-time examination [62]. Fink et al. [93] also recommend transit-time studies as a necessary requirement before performing a colectomy.

Gastrointestinal transit can be studied by means of indigestible metal particles followed on their way through the gastrointestinal tract by means of metal detectors [100], by transit scintigraphy with ^{111}In-DTPA [101], technetium Tc 99m sulfur colloid [102] or radiochromium (^{51}Cr) [103] or following ingestion of solid radiopaque markers [104–106].

We use a modification of the method of Hinton et al. [104]. A known number of commercially available pellets, usually 20, are swallowed by the patient and the disappearance of the markers from the gut or the appearance of the pellets in the stool is observed by serial radiographs at 24-hour intervals. The children receive normal food. Any laxatives or special diet is avoided. As transit-time studies are performed after X-ray enemas including defecography the bowel is clean at the beginning of the study. Six hours after ingestion the markers can be demonstrated in the ascending colon, where a physiological retroperistalsis can be demonstrated. In children usually, 80% of the pellets have passed after 48 hours. The markers can also be introduced in an enterostoma

to study the transit in the aboral segment of the bowel (Figs. 12.24–12.28). The pellets, usually 20, are inserted into the aboral segment and, according to the method of Hinton et al. [104], the disappearance and appearance of the pellets in the stool is also observed by several radiographs at 24-hour intervals. The ingestion of three sets of distinctive markers on three successive days as suggested by Metcalf et al. [107] has the disadvantage that the passage of the pellets through different segments of the gastrointestinal tract cannot be pursued and the radiograph taken on the 4th day gives just a global overview of bowel motility. According to Evans et al. [106], normal adults retain more than 20% of markers at 12 hours and less than 80% after 120 hours (Fig. 12.23).

Read et al. [102] studied the transit of a meal through the stomach, small intestine, and colon in 14 normal young adults and found that 50% of the markers were eliminated in just over 2 days, while it took just over 3 days to eliminate all the markers. Wagener et al. [108] measured the total and segmental colonic transit time in 22 healthy children without symptoms of constipation using the saturation method of Abrahamsson et al. [109]. The children swallowed ten radiopaque markers at a given time daily for 6 days, and a single abdominal radiograph was taken on the 7th day. The mean segmental transit times were 5.5 hours for the ascending colon, 10.9 hours for the transverse colon, 6.1 hours for the descending colon, and the longest period of 18.2 hours for the rectosigmoid colon. The mean total colonic transit time was 39.6 hours. A pathological transit was observed by Zenilman et al. [105] in 12 women with idiopathic colonic dysmotility and subsequent subtotal colectomy performed according to the results of the transit-time study and histological examinations of suction biopsy material. The use of ^{111}In-DTPA [101, 110] is more difficult due to the radioactivity of the markers with a half-time of 67.4 hours and the necessity to collect and eliminate radioactive stools. However, by investigating the patterns of colonic transit in 23 adults with chronic idiopathic constipation the authors were able to distinguish between two distinct patterns of colonic transit: colonic inertia and functional rectosigmoid obstruction, both of which had different pathogenetic and therapeutic implications.

As mentioned above, we used a modification of the method of Hinton et al. to assess the intestinal transit time in children with intestinal neuronal malformations [111]. In 53 patients with aganglionosis and in 37 out of 53 with other intestinal malformations, the intestinal transit time was prolonged. Of 16 children with IND type B, 8 had an abnormal transit time, 1 underwent anterior resection, and 2 had a temporary colostomy. Also 7 of 8 children with hypoganglionosis and 9 of 10 with a reduced parasympathetic tone showed a prolonged transit time. A resection was performed in 7 and 2 of these children, respectively. But only 11 of 17 children with heterotopia of the submucous plexus, dysganglionosis or immature ganglia had a prolonged intestinal transit time,

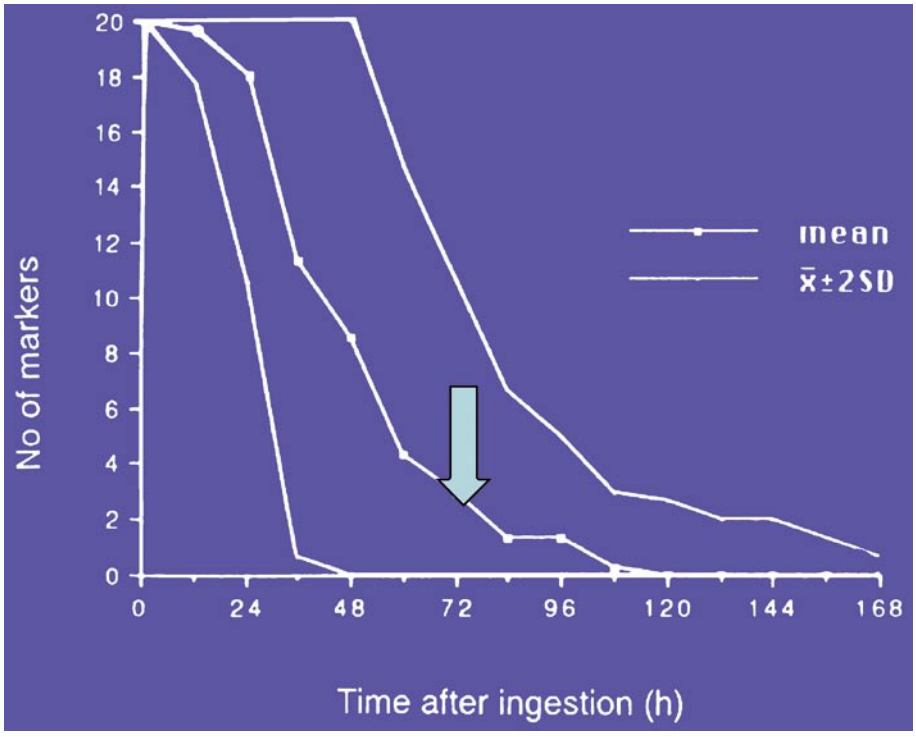


Fig. 12.23 Normal delivery of markers after oral ingestion in adults. The mean delivering time is marked by *arrow*

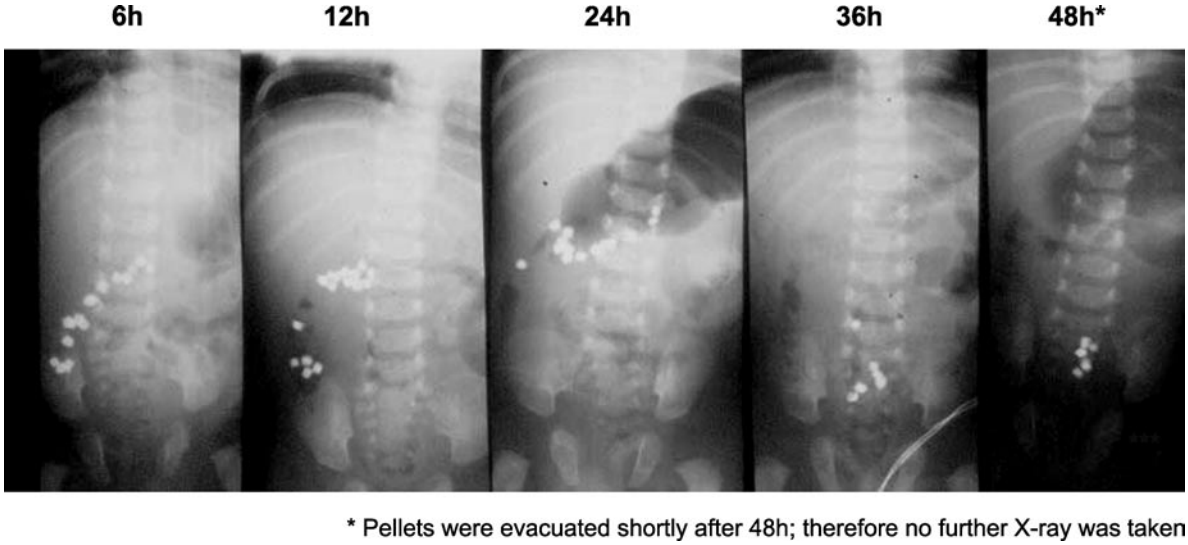


Fig. 12.24 Transit time study in a child with normal transit of markers to the rectum. In the radiograph taken 48 hours after swallowing 20 pellets, only 6 markers are visible in the rectum

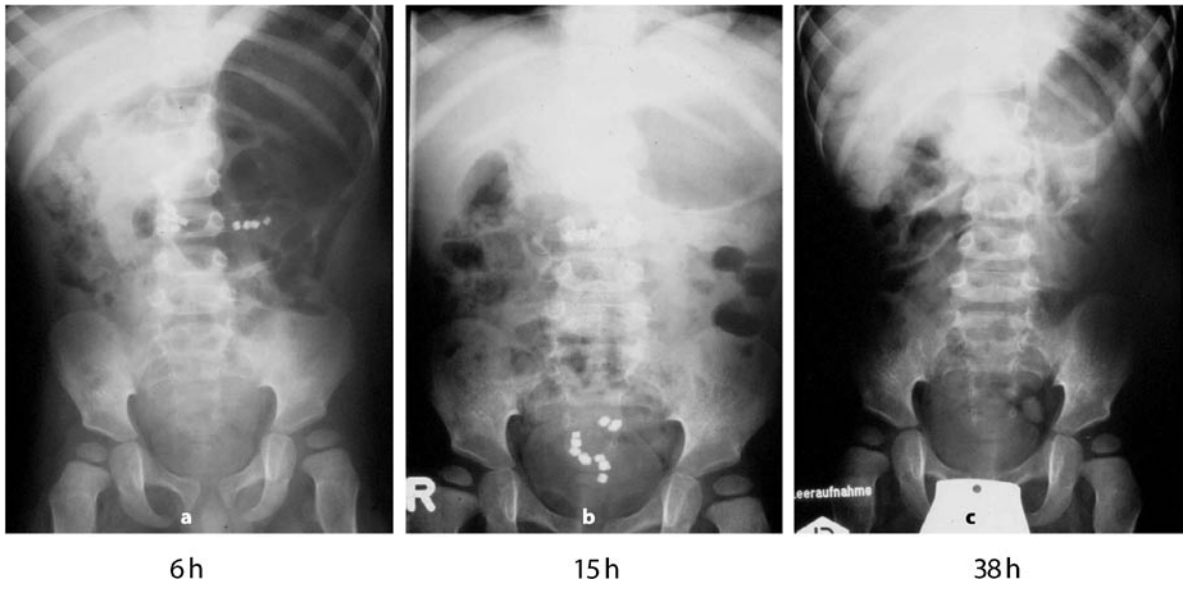


Fig. 12.25 Normal transit of pellets through the colon in a 12-year-old boy with a colostomy and IND after maturation. The radiographs were taken after 6 (*a*), 15 (*b*) and 38 (*c*) hours after ingestion into the aboral part of the colostomy

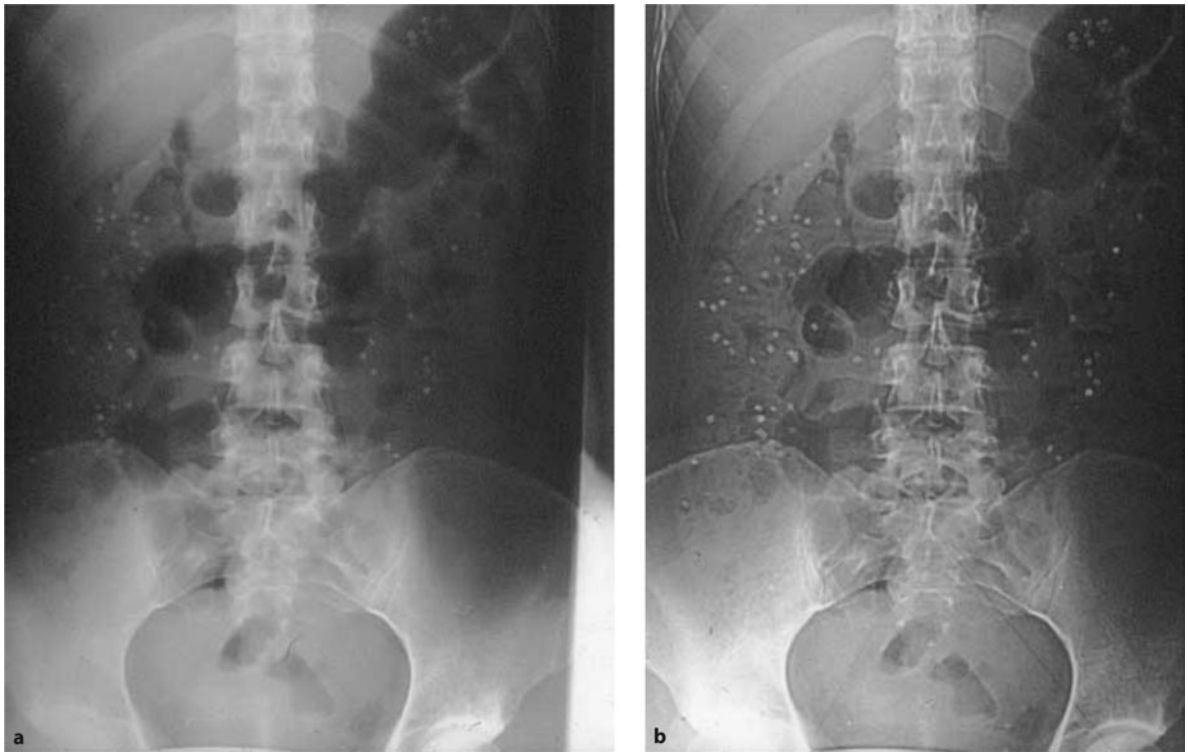


Fig. 12.26 IND in a 36-year-old woman. Twenty markers were ingested on three consecutive days. The radiographs taken at 5 days (*left*) and 11 days (*right*) show a severe transit delay

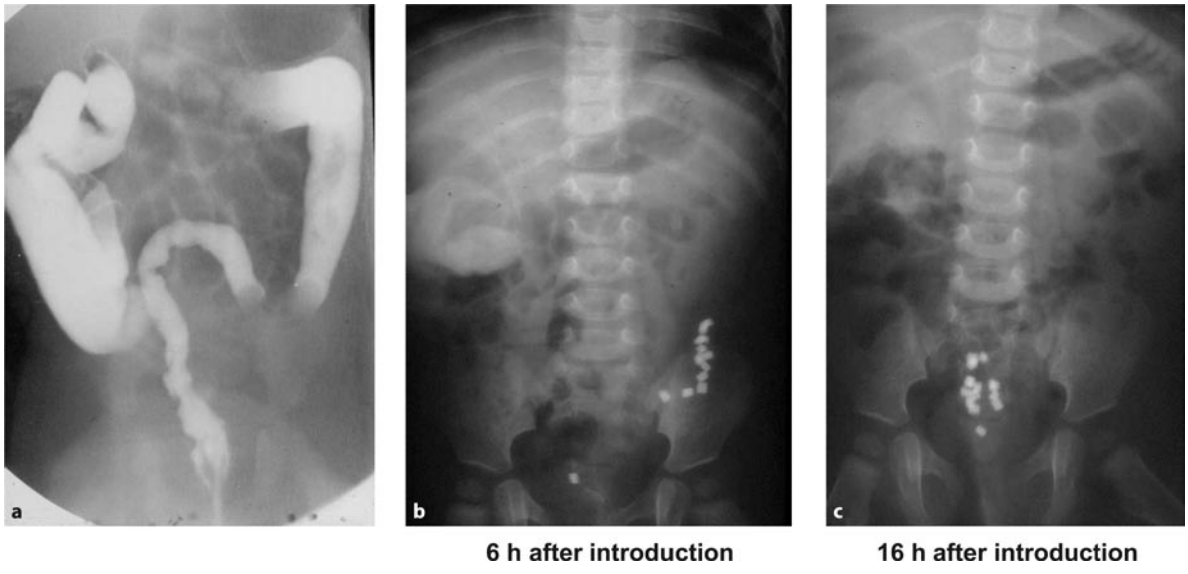


Fig. 12.27 HD and suspected IND in the transitory (unusually long transitory segment of a 10-year-old girl (*left a*). Contrast enema with gastrografin. Pellet study from colostomy site (*center b,* 6 hours after ingestion, *right c,* 16 hours after ingestion)

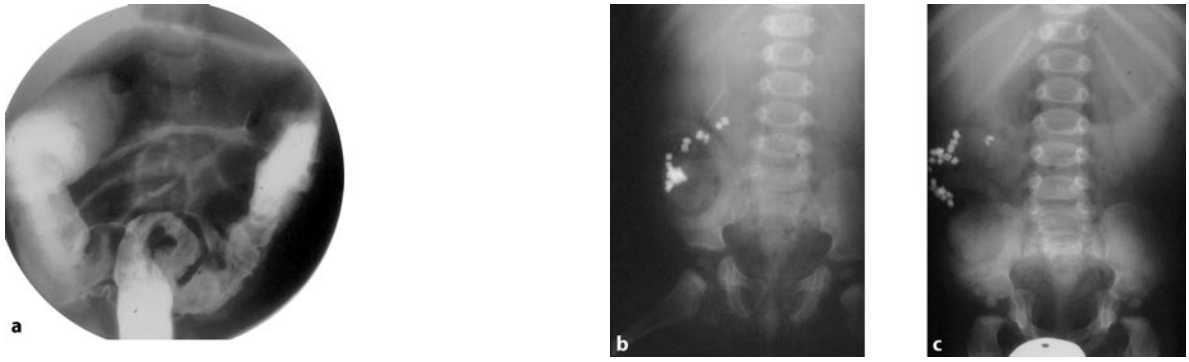


Fig. 12.28 Four month old boy with HD. *Left, a* Typical radiograph with narrow segment. *Top, b 24 hours* after ingestion of pellets into the colostomy, beginning transport through the transverse colon. *Bottom right c,* 48 hours later there is no further movement of the markers. The pellets were delivered by retrograde bowel movements in the colostomy bag

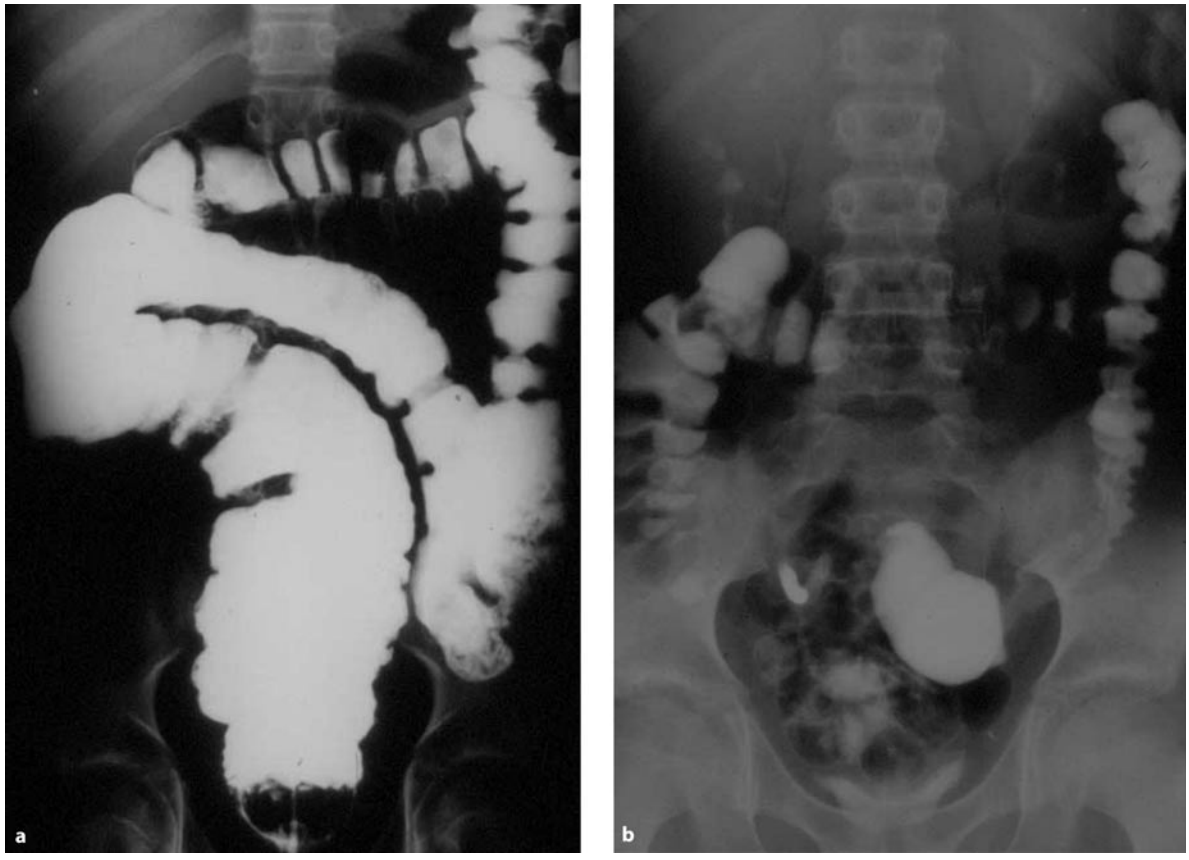


Fig. 12.29 Normal delivery of contrast material. Radiographs taken at the end of the procedure (*left*) and 20 minutes later (*right*)

and 2 underwent sphincteromyotomy. All children who required surgery had a prolonged intestinal transit time, but also 21 of 37 children who were successfully treated without surgery. Waldron et al. [112] used a technique of prolonged ambulant manometry and electromyography as well as transit-time studies in 8 patients with rectal inertia and 14 controls. External sphincter electromyography spike activity did not differ between the two groups. However, a reduced transit of feces to the rectum from the colon over a 24-hour period suggested the presence of a motor neuropathy in the rectum. Finally, late radiographs acquired 6, 12, 24 or 48 hours after contrast enema are very helpful in estimating the transit time of the contrast material (Figs. 12.29 and 12.30).

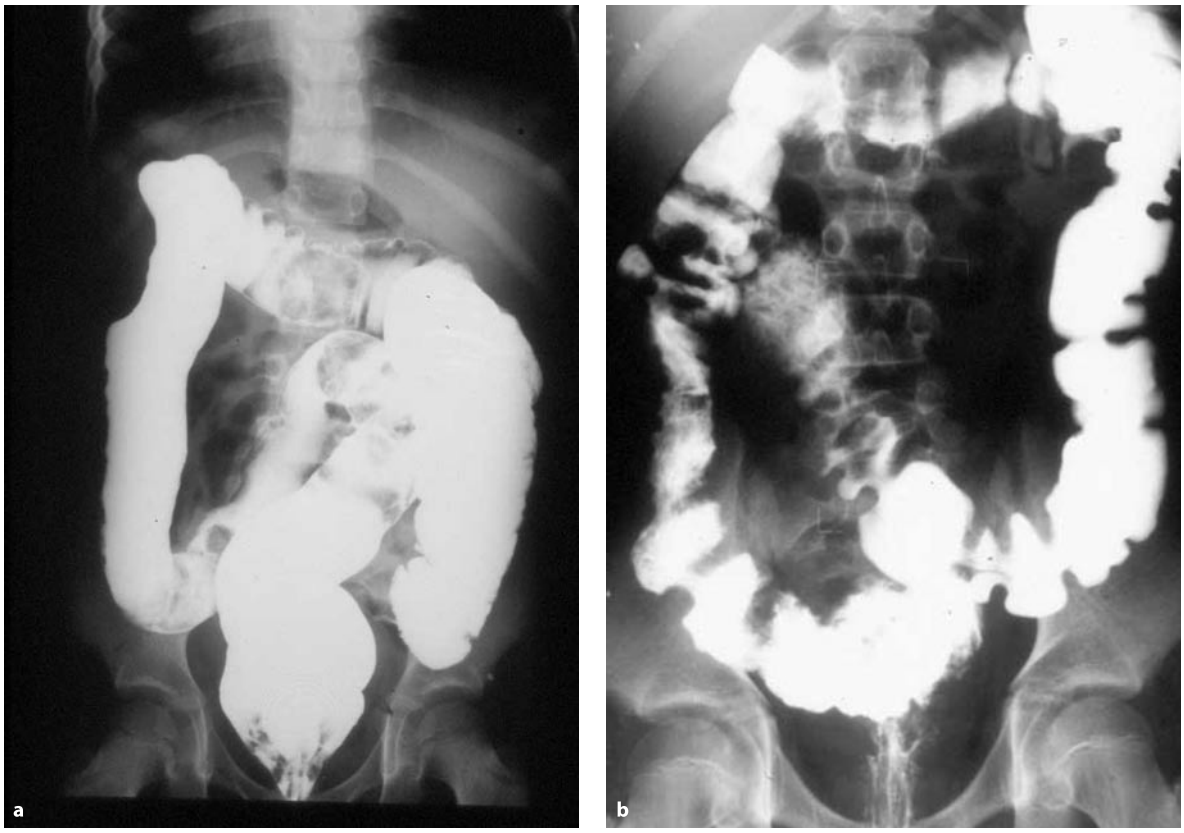


Fig. 12.30 Severe chronic constipation and IND. Radiographs taken at the end of the procedure (*left*) and 20 hours later (*right*)

12.12 Conclusions

Anorectal and colonic manometry are screening methods in patients with chronic constipation and are of high accuracy. Patients with normal internal sphincter relaxations can be treated conservatively. Vague patterns need further evaluation by radiography and transit-time studies. The most important diagnostic tools are histological and immunohistochemical evaluations of suction or full-thickness biopsies and whole-mount preparations of the bowel wall. However, the histological results should always be interpreted with special regard to the clinical symptoms and to the results of the electromanometric, transit-time and radiographic studies to avoid unnecessary surgery.

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