Review Article

New concepts in the pathophysiology of fecal incontinence

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Abstract: The pathophysiology of fecal incontinence (FI) is often considered to primarily depend on disturbed mechanisms of faecal containment. Barrier mechanisms such as the anal sphincters and puborectalis muscle provide an easily comprehensible model for FI that satisfies some clinical observations in relation to risk, e.g., obstetric trauma, iatrogenic injury during anal surgery and diagnostic findings, e.g., anal contractile pressures and integrity on ultrasound evaluation. However, this barrier-centric containment model is insufficient to explain many lived observations of FI, including the origin of the symptom of urgency and continence development over the life course. It also fails to explain several other major risk factors such as rectal inflammation and irritable bowel syndrome, epidemiological (e.g., roughly equal prevalence in men) and treatment observations, i.e., the general failure of barrier augmentation *vs.* success of a treatment that does not overtly alter barrier closure [sacral neuromodulation (SNM)]. This review presents a revisionist view where reflex control of rectal contractility is considered central to FI pathogenesis and the anorectum is considered a single functional unit that cooperates with the colon and central nervous system (CNS) to maintain continence. This revised understanding implicates the barrier not only as a means of containment but also as a reflex controller of rectal function. Together, this serves as a much more adequate theory to explain human observations of the condition and a better starting point for the development of new treatments.

Keywords: Anal sphincter; disease pathophysiology; fecal incontinence (FI); incontinence; pudendal nerve

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Introduction

Fecal incontinence (FI) defined as the recurrent uncontrolled passage of feces (1) is a relatively common condition with considerable unmet needs in terms of effective treatments. FI may consist of feces of normal consistency, only liquid form, or mostly of flatus. It is not necessarily accompanied by urinary leakage, although the two disorders often occur together. While most new developments in medicine now arise from targeting defined disease mechanisms, progress for FI has been limited by poor understanding of pathophysiology and a dependence on looking for, and trying to treat, the obvious (2). This review questions current dogma and proposes a new approach.

Risk factors for FI

FI can result from a single catastrophic event such as major anorectal injury, but more commonly develops

from accumulated risks (*Table 1*). The majority of patients present in their late 50s when combined exposures to risks, e.g., serial pregnancy, childbirth, and age are sufficient to compromise normal function. What is vital to appreciate is that prevalence of FI (based at least on community survey data) is similar in males and females, and hence risk factors other than obstetric trauma, which is so frequently cited as the primary cause of FI in women, must play a pivotal role. Data for some risks are conflicting.

The classical barrier theory

In medical school, students are often taught the paradigm of 'passage and passenger' to describe the two main contributing risk factors for FI: a dysfunctional barrier (with a focus mainly on the anal sphincters), and liquid stool consistency placing the barrier at increased risk. This paradigm is helpful but not wholly correct. It underpins common treatment approaches such as pads and plugs, stool hardeners, e.g., loperamide, and bulking agents, e.g., ispaghula. As referenced in *Table 1*, there is good epidemiological data that overt injury to the barrier, e.g., through 3rd and 4th degree tears at childbirth and the diagnosis of states characterized by chronic diarrhea, e.g., diarrhea-predominant irritable bowel syndrome (D-IBS) confer a significant risk of developing FI.

Textbook descriptions of the continence barrier include: the resting tone of the anal sphincter, which is conferred by the internal anal sphincter (IAS) ~55–75%, the external anal sphincter (EAS) ~25%, and anal canal vascular columns ~15% (37,38), which interdigitate to provide a hermetic seal with turgor maintained by hydrostatic pressure within the vascular spaces (39). Further factors include resting tone of the pelvic floor musculature that maintains the anorectal angle conferred by tonic puborectalis contraction, and the ability [in response to anorectal sensory function such as sampling (40)] to volitionally contract the EAS (41). However, voluntary contraction of the anal sphincter can be normally maintained only for 15 seconds (42), so this is a 'last resort' reaction. While significant direct injury to the barrier may be sufficient alone to cause a physical gutter (or fistula) through which feces may bypass the continence mechanism, the majority of patients, even those women with obstetric anal sphincter injuries (OASIS) (after primary sphincter repair at the time of childbirth) have no overt ongoing defect.

In the late 1970s and 1980s, it became evident that overt injury to the barrier was insufficient to explain the association of FI with a number of other risk factors including pregnancy (especially with instrumental or protracted labour), chronic straining and pelvic organ prolapse (43,44) and various neurological injuries, e.g., cauda-equina syndrome. A series of seminal studies (45-49) utilized technological developments to directly measure intra-anal pressure (anorectal manometry) (50), or neurophysiological techniques, including electromyography (EMG) and nerve conduction studies (50,51). These demonstrated that poor contractile function of the sphincters, especially of the puborectalis, which like the EAS is in state of tonic contraction, were major factors in FI development with or without direct injury to sphincter integrity (52).

Electrophysiological recordings showed that such changes were at least in part due to pudendal nerve injury, occurring as a consequence of direct sphincter injury, pelvic floor muscle and ligamentous stretching or compression during pregnancy or chronic straining (53) with perineal descent (54). All these factors tend to progress with time after an initial injury (49,52), and all are inter-related. Weak muscles perform even less well when handicapped by floppy, non-elastic ligaments, and 'ballooning' descent of the pelvic floor on coughing and straining. A further factor in coordinated pelvic floor functioning is the central location of the vagina, which is itself an elastic structure. Hence, vaginal prolapse, associated with ligamentous stretch injury and damage to muscles and their innervation, is especially likely to lead to organ prolapse (55) and also urinary and/or FI. Several minimally invasive surgical techniques utilising tape insertions, to generate fibrous tissue support for damaged fascia and ligaments have been developed on this basis for selected patients (56) (with the caveat of the current embargo on use of tapes and mesh in any form in many countries). Together these concepts provide a 'barrier-centric' paradigm for the pathophysiology of FI (*Figure 1*).

However, this schema is not the whole story. *Table 2* lists some of the main limitations of this model. The major factor missing from this conceptualisation is recognition of the sensation of urge that is described by the majority of patients before they become aware of incontinence. Urge-related episodes of incontinence were recently reported by 75% of 2,452 patients presenting with FI to a tertiary center (7) While, it is acknowledged that reduced anal tone may lead to transgression of fecal content into the highly sensitive upper anal canal causing urge (just as trigone stimulation and upper urethral entry of urine causes bladder urge), this explanation is incomplete as a link between

Table 1 Risk factors for FI

Risk factor	Mechanisms	Notes
Advancing age	Reductions in coordinated muscle function, cognition and mobility. Changes in stool consistency	Demonstrated by almost all epidemiological studies (3,4). Major determinant of nursing home referral (5)
Female sex	Vulnerability due to loss of vaginal support and elasticity after childbirth, hormonal	Majority of patients seeking care are female (6,7) but community surveys (3,4) suggest unexplained similar prevalence between sexes
Parity with uncomplicated vaginal delivery [and Caesarean section (8)]	Stretch/compression injury leading to pelvic floor laxity (muscular, ligamentous and fascial) and neuropathy leading to muscular weakness, pelvic floor descent on straining or pelvic organ prolapse	Controversial: considered major risk factor in clinical populations with FI (7,9,10) and a risk based on obstetric cohorts (11,12); however weak or no risk in population surveys, even with prolonged 2nd stage of labour (4,13,14)
OASIS (3rd and 4th degree tears)	Difficult delivery with direct injury to sphincter musculature; increased risk of fascial/ligamentous stretching and nerve injury (as above)	Significant risk factor in isolation (9,15) although time to symptom onset is dichotomous (immediate or in older age) (8). Majority of women with OASIS do not develop FI in short-term (16)
Iatrogenic and traumatic anal sphincter injuries	Direct injury to sphincter musculature (IAS and/or EAS). Major trauma may covertly damage pelvic floor and innervation	Textbook causation, especially where internal anal sphincter is injured at fissure (sphincterotomy and anal stretch), haemorrhoidal or fistula surgery
Menopause	Low oestrogen levels alter neuromuscular functions of anorectum and pelvic floor leading to reduced muscle contractile force	Difficult to distinguish from age effects. Oestrogen replacement may not be effective (17)
CNS diseases, e.g., dementia, multiple sclerosis and stroke	Decreased cognition, immobility; loss of higher control of spinobulbar reflexes	Dementia leads to 4x risk in cohort studies (18). Identified as an independent risk factor for FI in several epidemiological studies (19-21) FI major problem in nursing homes (21)
Spinal cord and peripheral nerve injury	Loss of reflex control of anorectal functions. Loss of volitional pelvic floor contraction; anal sphincter not controlled by higher centers	Textbook causation in spinal cord injury (including occult) and cauda equina injury; severe diabetic motor-sensory and autonomic neuropath
Loose stool/diarrhea	Liquid stool more easily overcomes barrier. Some specific conditions may have effects on rectal urge and contractility, e.g., irritable bowel syndrome and post-cholecystectomy diarrhea	Cross-sectional (1,22-24) cohort studies (25) and case-control studies (26) uniformly support loose stool or chronic diarrhea as risks
Colonic resection and LARS	Factors include bowel shortening and rapid transit. LARS may have direct effects on anorectal sensory and motor functions	Observational data including prospective cohort studies (27)
Constipation	Occurs with or without impaction/overflow: failure to keep rectum empty risks FI if other risks present; chronic retention may affect afferent functions, e.g., to CNS	Incomplete evacuation a risk factor in some studies (24,25); cross-sectional data show substantive overlap of FI and functional constipation (7)
Rectal inflammation (proctitis) by any cause	Increased rectal afferent (urgency) and motor (hypercontractility) functions. Crohn's disease may also affect anus	Textbook causation supported by epidemiology, e.g., IBD (28) and pelvic radiation (25,29)
Diabetes	Autonomic (30) and enteric neuropathy (31), with effects on colonic motility (32), pelvic floor (33), anorectal (34) and smooth muscle function as well as on mucus secretion and blood flow/turgor in anal valves	Textbook association supported by observational data

Table 1 (*continued*)

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Risk factor	Mechanisms	Notes
Obesity	Increased pressure on pelvic floor; possible alterations in sphincter functions (but also other secondary effects of metabolic syndrome)	Conflicting data but most large population surveys support (3,25,35,36)
Chronic illness (disease burden)	Poly-mechanistic including constipation	Comorbidity count, especially conditions like depression

FI, fecal incontinence; OASIS, obstetric anal sphincter injuries; IAS, internal anal sphincter; EAS, external anal sphincter; LARS, low anterior resection syndrome; CNS, central nervous system; IBD, inflammatory bowel disease.

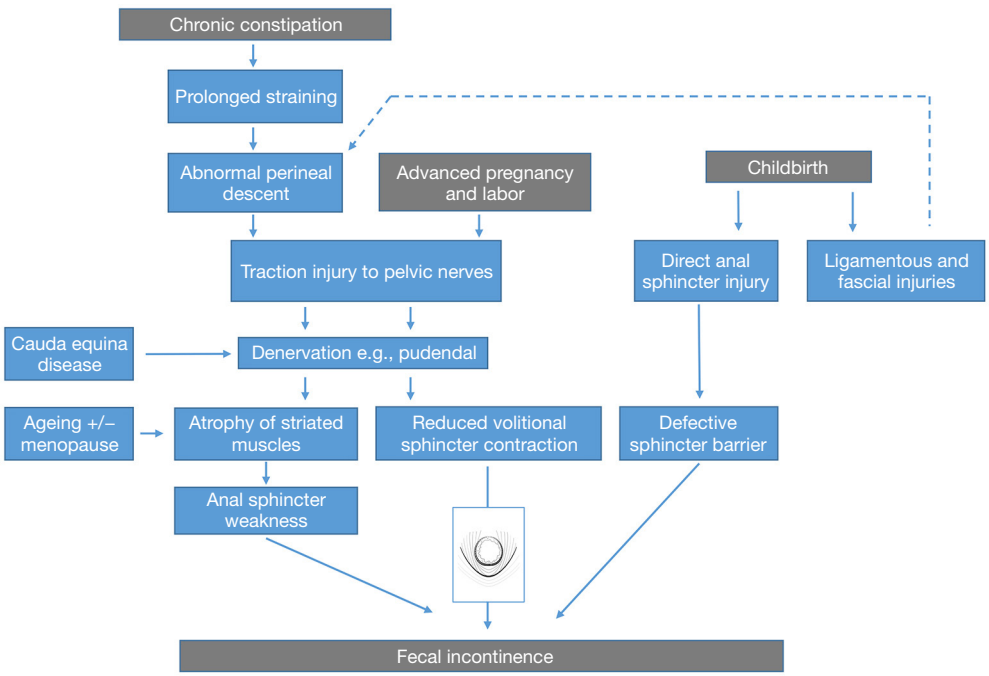

Figure 1 Barrier-centric schema for the pathophysiology of Fecal incontinence. The anal musculature is considered central to pathophysiology.

urgency and EAS injuries (see below). Tied to this is the recognition that no motor system, such as the pelvic floor musculature and its sphincter systems, can function without modulation by sensory input. Information about rectal content and readiness to defaecate is thus sent to the spinal cord, brainstem and brain. Disturbed anal sensation is a feature of many anorectal disorders, including incontinence, prolapse, haemorrhoids and slow transit constipation (65). There is therefore a need for a better model. A starting point is the rectum.

The role of the rectum in the pathophysiology of FI

It is surprising that the apparent main storage organ for feces receives relatively little attention compared to the anal sphincters. This is not so for urinary incontinence and the bladder. For instance, a quick PubMed search reveals that 37.2% of studies of urinary incontinence (UI) incorporate bladder in the title compared to only 24.4% of those on FI incorporating the rectum. While clearly a crude approach, this is interesting because, on basic physical principles alone, the rectum should have a greater role in incontinence than the bladder. Feces, unlike urine, is a non-Newtonian fluid, even in liquid form (66,67). Its flow behaviour does not obey the law of viscosity (68) but is something akin therefore to a bottle of tomato ketchup, i.e., it does not come out with basic actions such as shaking or sudden moderate squeezing, with such forces producing a shear

Table 2 Observations that question the classical barrier theory

3rd and 4th degree tears only occur in 3% deliveries (16,57) and only a minority of parous women with FI have major (overt) sphincter injuries. Epidemiological data show that the majority of women even with 3rd and 4th degree tears do not develop FI (16), and those that do present only when other risk factors such as age (8) have accumulated
FI is almost as common in men as women in surveys (3,4). Only a small proportion of men (~25%) (58) have evidence of sphincter injury (usually from anal surgery or trauma) (58)
Changes over the life-course: infants develop continence when unmodulated spinal reflex activity becomes controlled by mature central connections with assimilation of acquired behavioural patterns of cognition. In senility, continence may deteriorate with decreasing cognitive capacity. Whether this is always a frontally-mediated deficit, or relates to basal brain white matter small vessel disease (far more likely) is a matter for debate and research. Either way, it is well accepted that the control of social defecation and continence is centrally mediated by cortical influences on spinal and bulbar reflexes (equally for micturition and the bladder)
Most FI is classified as urge incontinence (7) defined as "incontinence occurring with a strong, sudden need to defaecate that is difficult to delay". Urgency is a conscious perceived, i.e., cortical, event. Urge incontinence is considered a marker of external sphincter dysfunction (59-61). However, while a disrupted barrier may explain incontinence, it does not fully explain urgency
FI has a strong link with functional conditions such as IBS (62). This link is not confined to patients with loose stool. Urgency of normal stool is also common (63)
Surgical attempts at augmenting the continence barrier are almost all now obsolete (2). Some of these suffered from infection and erosion of foreign bodies but use of native muscle, e.g., posterior repair and graciloplasty also led to unacceptable functional consequences especially in causing obstructed defecation. Even sphincteroplasty, while still has outcomes that deteriorate significantly with time (2) and the role of injectable biomaterials (bulking agents) is not established (2)
In contrast, the dominant therapy, SNM does not augment sphincter structure and has no obvious effects on anal motor function (64)

FI, fecal incontinence; SNM, sacral neuromodulation; IBS, irritable bowel syndrome.

effect through the fluid rather than flow (69).

This may account for the very low incidence of stress FI with only ~2% of patients having isolated classic stress symptoms on coughing, sneezing, movement (7) [compared to 50% of patients with UI having isolated stress UI (70)]. When stress FI does occur it is frequently for flatus (7), explained by the gas phase shearing through the fluid as it changes viscosity in response to stress (69). Much as the rest of the colon requires forceful contractions to move feces in an abroad direction, the corollary is that for feces to leak, there must be an organized contraction of the rectum (+/– conscious compression by Valsalva).

The urethra and the bladder as a model for the anorectum

In the field of UI, 11% of patients have pure urge UI (UUI) and a further 36% have mixed urge and stress UI (70). The pathophysiology of UUI, and its main sub-diagnosis: overactive bladder (OAB), is almost exclusively concerned with the bladder and its reflexes, and treatments, e.g., drugs, intra-vesical botulinum toxin A injection and sacral neuromodulation (SNM) are focussed on stabilising the detrusor muscle to prevent contraction and unwanted micturition. Considering the general scientific principle of parsimony, it is odd that two very similar muscular organs sharing embryology (both have two systems derived from the cloaca), basic functions (storage and emptying) and single 'exit pipes' passing through a common sheet of muscle (pelvic floor) would come to have very different mechanisms of failure leading to incontinence. Of course they do not.

Both the bladder and rectum utilise smooth muscle contractile forces (peristalsis and bladder contraction) to expel contents. Both have smooth muscle sphincters controlling 'sampling' via upper anal canal and upper urethra respectively, and striated sphincters as minor players. Both use tension on the efflux pipe (urethra and puborectalis/rectum/anal canal) to oppose anterior and posterior walls (kinking) to maintain continence. Finally, the nervous system controls of both systems are very similar and this may account for the shared utility of SNM, which is currently considered the gold-standard procedure for both OAB and FI using an identical procedure (electrode placement and stimulation parameters) (71).

The rectum should therefore not be considered a passive reservoir. Rather, it is a contractile and sensate organ, that like the bladder, is subject to fine reflex control.

Understanding the fine balance between filling and expulsion phases is key to understanding FI.

Abnormal anorectal afferent function

Active defecation can be considered to commence with the urge to pass feces. Continence is ultimately dependent upon an awareness of lower bowel content and warning of impending defecation. Hence, intact sensory functioning and integrity of anorectal afferent mechanisms are fundamental to both processes.

Firstly, it is important to consider where the urge to defaecate originates. Most evidence (principally involving distension studies, which mimic filling) points to the rectum as the primary organ responsible for this sensation (72-74). However, in the seminal 1951 study by Goligher and Hughes (72), although the majority of patients likened the sensation of balloon distension to "that of wind or motion in the rectum requiring evacuation", other patients stated that they had "never experienced anything quite comparable before", suggesting either simple rectal distension may be incapable of recreating the normal urge or that other organs are involved. This is supported by observations that those without a rectum [e.g., following surgery (75-77)] still perceive an urge to defaecate, though the quality of that sensation may be altered (77). Lane and Parks, for example, reported that the majority of 12 patients who had undergone rectal resection with colo-anal anastomosis described a normal sense of "perineal fullness" to distension, indicating that receptors responsible for the appreciation of impending evacuation may also lie outside the bowel (76). Indeed, Broens *et al.* using a combined manometry and proctographic study showed that the exquisitely sensitive proximal anal canal and/or its surrounding structures (e.g., muscle spindle and tendon organ stretch-sensitive receptors in the levator ani/puborectalis) played an important role in the desire-to-defecate sensation (78).

Taking available evidence together, the 'call to stool' is likely a complex, multifactorial process with perception of urge regulated by distal colonic, rectal and extra-rectal sensory mechanisms (the 'early warning system'), with the rectum principally responsible for graded sensations of filling, and the anal canal and pelvic floor musculature providing discriminatory function and sensory 'fine tuning' crucial to continence (including through the 'sampling' reflex) (40). Distension of the anus is not associated with an urge-sensation (72).

Rectal distension results in deformations of the rectal wall, which induce alterations in tension encoded by mechanoreceptors. Specialized intraganglionic laminar endings located in the myenteric plexus (79) are the mechanotransduction sites of extrinsic sacral spinal afferent neurons in the guinea pig rectum and these have recently been characterized in human tissue (80). When a sufficient volume of stool distends the rectum, the perception of rectal fullness is communicated to the cortex via such afferent pathways. Rectal mucosal chemoreceptors (to substances like capsaicin) likely also involve afferent signalling via spinal afferents. Urge sensation is abolished with bilateral loss of sacral nerves (81).

Rectal sensation is inextricably linked to rectal biomechanical factors (e.g., capacity and compliance). In a normally functioning rectum (like the bladder) the urge to defaecate will dissipate, in the absence of further distension, due to the mechanism of 'receptive relaxation' [i.e., its 'reservoir' function (72,82)]. The degree of this relaxation is considered to be an important independent factor in the pathogenesis of fecal urgency and FI. A non-compliant (i.e., 'stiff') or small capacity rectum [as classically seen in inflammatory bowel disease (IBD) (73,83,84), post-pelvic irradiation (85), or following rectal surgery (27,86), but also in idiopathic FI (87)] is less able to adapt to filling, with urgency occurring at an earlier stage. Several studies have shown that reduced rectal compliance is commonly associated with rectal hypersensitivity (reduced thresholds to sensory stimuli) in patients with urge FI (88-93). In such patients, the rectum may also be hypercontractile, or hyper-reactive (87,90,94). Clinically, these patients have increased urgency and frequency of defecation, and greater lifestyle restrictions than those FI patients without rectal hypersensitivity (87,88).

Conversely, a large capacity, 'lax' (or hyper-compliant) rectum is frequently allied to rectal hyposensitivity (elevated thresholds to sensory stimuli) (95). Such patients invariably present with constipation and evacuatory difficulties associated with an impaired or absent urge to defaecate (96,97), though a sizeable proportion also have coexistent FI (presumed to be 'overflow') (53,95,97), manifest primarily as fecal seepage (10,98). It has been postulated that in patients with impaired rectal sensation, the normal compensatory EAS contraction to filling (excitatory reflex) is delayed or absent, allowing FI to ensue in the presence of low anal tone due to relaxation of the IAS (inhibitory reflex) which occurs at lower distending volumes than that of first perception of rectal distension (90,99-101).

Overall, rectal sensory disturbances in FI are common (~20% overall) with hypersensitivity more frequently found in females, and hyposensitivity in males (102). Neurophysiological studies have shown that impaired conduction through anorectal afferent pathways and reduced cortical activation are very common in FI (103). In patients with rectal hyposensitivity, latencies from rectal stimulation to cortical response are prolonged (104).

Rectal reflexes and the control of rectal contractility

The above discourse implicates the rectum as a sensate organ, and disturbances of rectal afferent function as important biomarkers of FI in a variety of conditions. However, as already noted, the rectum must contract or be compressed to evacuate fecal contents. The control of rectal contractility, like the bladder, is subject to intrinsic reflexes. It is well established that the rectum provides afferent information for the rectoanal inhibitory reflex (RAIR). The IAS has an important role in 'guarding the anal canal'. It relaxes briefly several times per hour (105,106) to allow sampling of rectal contents. It is also known, although widely neglected, that rectal distension elicits a (reflex) rectal contraction to generate a conscious defecatory urge (101,107). Sun *et al.* showed that in healthy subjects, the onset of a rectal contraction always occurred at the same time that a rectal sensation was perceived, and that the duration of rectal sensation correlated strongly with the duration of the rectal contractile response (RCR). Rectal sensation was always perceived at volumes well below those required to cause a sustained or deep anal relaxation [RAIR, conversely to the situation with rectal hyposensitivity (108)]. The RCR is probably a local reflex mediated by the rectal wall (enteric nervous system) however some historic data support a spinally-mediated reflex (107). It is best appreciated through rapid distension of an intra-rectal bag using the barostat (*Figure 2*). During both rapid phasic (109) and ramp inflation paradigms (93), a transient reduction in volume and concomitant increase in pressure within the bag is consistently observed in the early phase of distension, attributed to the RCR. Such contractions may be repetitive in health (90,93,109) and exaggerated in conditions such as IBS, characterized by urgency (94). Conversely, if perception of rectal distension (a sensory phenomenon) is indeed associated with the rectal contractile (motor) response, then it would be reasonable to speculate that the RCR may be attenuated in patients with rectal hyposensitivity. There is limited evidence to support this (110,111).

The RCR and RAIR, which both favour emptying, i.e., a pro-expulsive state, co-exist with reflexes that suppress defecation and promote a basal state. The rectoanal excitatory reflex (RAER) is mediated by parasympathetic pelvic afferents and the pudendal nerve (112,113) and is disturbed in patients with FI especially when pudendal neuropathy is present (112). Similarly, the sympathetic nervous system via the hypogastric nerves is inhibitory to rectal motor activity (114-116). In this way, the rectum is subject to a fine balance of local reflexes (pro-expulsion) and autonomic reflexes (pro-basal state) (*Figure 3*). In the bladder, the urethra and bladder are considered as a single functional unit for which a similar balance of local and autonomic reflexes are considered key to the switching between filling and voiding phases. The control of this switching is tightly regulated by the central nervous system (CNS) and this is discussed below.

The role of the colon in the pathophysiology of FI

It is a truism that FI cannot occur with an empty rectum (there may of course still be flatus incontinence or leakage of mucus) and some therapies focus on keeping the rectum empty on this basis, e.g., trans-anal irrigation. Although, the rectum has already been described as a storage organ in this monograph, it is actually questionable whether the rectum really is the main storage organ for feces. This is likely to be true only in the very late stages of continence, i.e., just prior to defecation; in health at least, the rectum is usually empty (117). There is evidence that that the main storage organ for feces is in fact the descending colon/sigmoid, where retrograde motor activity acts as a functional barrier by repelling feces.

The colon fills the rectum with feces as a precursor to evacuation but may also have a role in keeping it empty. From the earliest human colonic manometric recordings, periodic, rhythmic colonic contractions have been described (118). Occurring at 2–8/min, with a primary site of origin at the rectosigmoid junction (119) this cyclic motor pattern has been shown to propagate over short regions of the colon in a predominately retrograde direction (120). While the physiological role of this cyclic motor pattern has not been clearly defined, it seems to play a role in normal colonic transit. Scintigraphic studies have linked these rhythmic contractions to subtle movement of colonic content (121-123), and radiologic studies have shown that content within the rectosigmoid

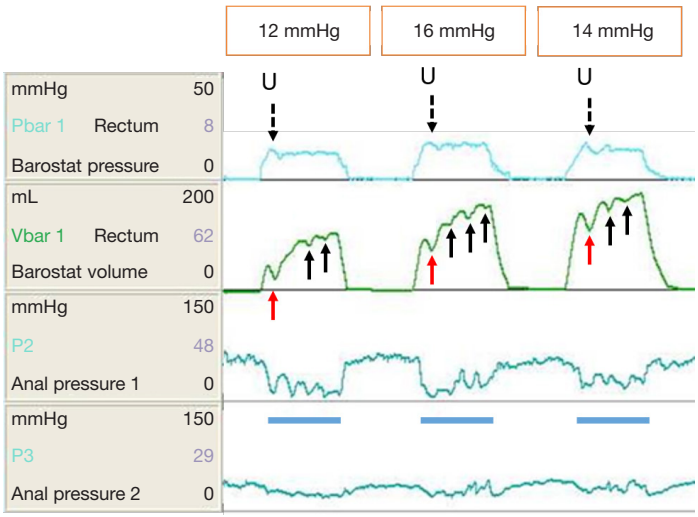

Figure 2 The RCR. The upper two channels represent intra-bag pressure and intra-bag volume, respectively, from a rectal barostat recording. Concomitant upper and mid-anal canal pressures are shown in the bottom two channels (solid-state manometric recording). Isobaric distensions at 12, 16 and 14 mmHg (1 minute duration) can be seen to elicit a RCR (transient reduction in intra-bag volume and concomitant increase in intra-bag pressure) at the onset of distension (upward red arrow and downward black dashed arrow, respectively), associated with the urge to defaecate (U), and a reduction in upper anal canal pressure for the duration of the distension (RAIR; blue lines). Further rectal contractions occur throughout the distension phase (other upward black arrows). Adapted from Vasudevan SP, MD (Res) Thesis, 2013. RCR, rectal contractile response; RAIR, rectoanal inhibitory reflex.

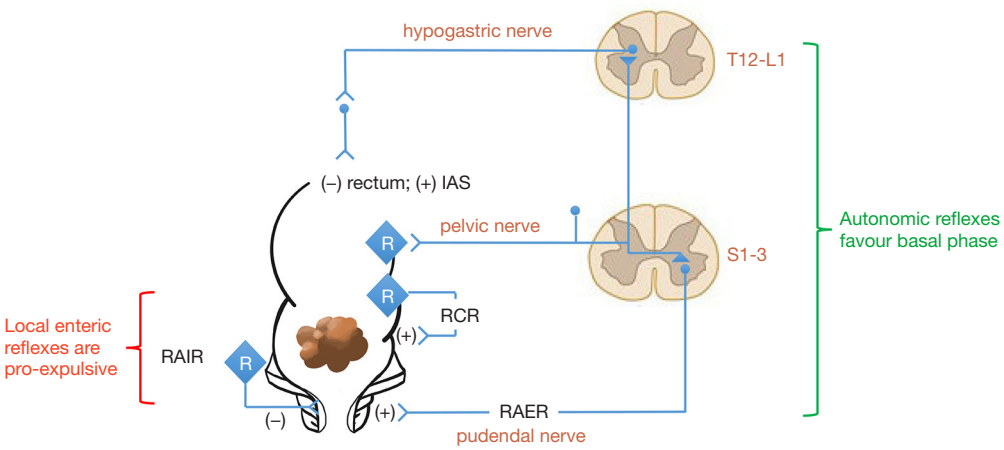

Figure 3 Balance of rectal and anorectal reflexes in the control of rectal expulsion. The mainly autonomic reflexes on the right are pro-expulsive whereas local (mainly enteric) reflexes on the left favour the basal state. IAS, internal anal sphincter; RCR, rectal contractile response; RAIR, rectoanal inhibitory reflex; RAER, rectoanal excitatory reflex.

junction can be moved back into the descending colon with rhythmic retrograde propulsion (124). More recently, studies utilizing high-resolution impedance manometry, have shown that a sub-sensory, low volume (60 mL) of air, infused into the sigmoid colon can trigger these cyclic motor patterns, which prevent the introduced air from reaching the rectum (125) (*Figure 4A*).

Manometric studies have shown that under normal circumstances the cyclic colonic motor pattern is inhibited by high-amplitude propagating contractions associated with defecation. This has been demonstrated in both healthy controls (126) and in patients with FI (22). However,

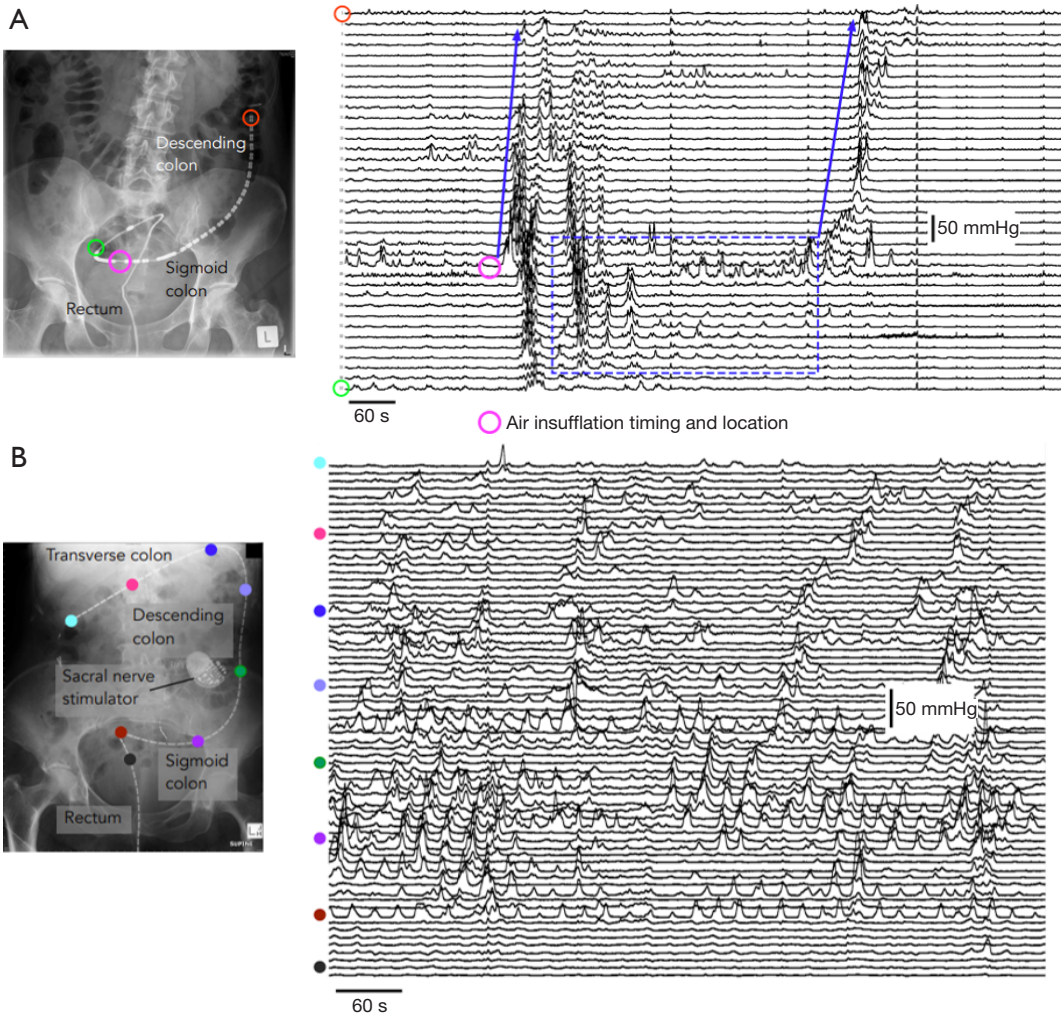

Figure 4 Colonic contractile activity. (A) Manometric recording from the sigmoid and descending colon of a healthy female control. The red and green circles on the manometry trace correspond to the same coloured circles on the X-ray image and indicate the colonic regions they were recorded from. The circle in magenta on the X-ray image indicates the location of air insufflation. This location is also shown on the manometry trace, with the magenta circle also indicating the timing of the start of the insufflation. 60 mL of air was introduced over a 2-minute period. The air triggered a rapid colonic response, inducing retrograde propagating contractions (blue arrows) and the cyclic motor pattern (area within the blue hatched rectangle). These motor patterns prevented air from reaching the rectum and the subject reported no fatal urge or any abdominal discomfort [see (1)]. (B) Fibre-optic manometry catheter positioned in the colon of a female patient with fecal incontinence. This patient has a sacral nerve stimulator implanted. During the stimulation, the cyclic motor patterns can be seen predominantly in the sigmoid colon region.

general evidence linking the cyclic motor pattern with bowel continence/defecation remains mostly circumstantial. In the 1940s, diarrhea, induced with a subcutaneous injection of Mecholyl, a cholinergic drug, was seen to be associated with an increase in proximal colonic contractions with a concurrent inhibition of sigmoid contractions (127). Similarly in patients with ulcerative colitis, high stool frequency was associated with inhibited or absent contractions in the sigmoid colon (128). Studying the potential causes of diarrhea associated with alcohol ingestion, it was demonstrated that intravenously-infused alcohol caused significant inhibition of sigmoid contractility (129). In patients with low anterior resection syndrome (LARS), a significant reduction in the sigmoid cyclic motor pattern has been shown in comparison

to healthy adults (130). In contrast, patients who underwent a low anterior resection but did not develop LARS, had a normal cyclic motor pattern in the sigmoid colon (131). Post-operative ileus has also been associated with sigmoid hyper-contractility (132).

Collectively, the studies discussed above suggest that motility in the sigmoid colon may act as a recto-sigmoid brake helping to control rectal filling and normal bowel continence (133). Importantly the cyclic motor pattern can be initiated by sacral nerve stimulation (134) (*Figure 4B*), which may also help to explain, in part, symptomatic improvement in patients with FI undergoing SNM treatment, especially in those with an anal sphincter defect (135-137).

The neural control of continence

Humans, like many other mammalian species (rats, cats and dogs), have a pattern of social defecation. This was teleologically advantageous: it has enabled us to live in groups, eat away from the bacterial hazards of feces and to wear warm clothes without soiling them. Key to this function is the ability to suppress defecation to a point of convenience and privacy (although defecation was historically communal). Such deferral is not, at least in health, conferred by the volitional continuous contraction of the anal sphincter against ongoing urge. As already noted, most people can maintain maximal squeeze, based on manometry, for only about 10–15 seconds (42). Rather, the sensation of urge dissipates after an initial stimulus (consider with-holding flatus in a crowded lift). The absence of ongoing distractive sensory input is common to the whole digestive system below the pharynx and also has a teleological benefit so that early humans could resume physical activity, e.g., hunting and protection without cognition being disturbed by visceral inputs.

In many ways, the lived experience of FI (at least of the most common urge FI) can be considered a failure of the deferral of defecation—an inability to switch off urge and expulsion when it is inconvenient and return the colon, rectum and anus to a physiological basal phase from a pre-expulsive phase (41). This is also true for the bladder which has two described phases: filling (99% time) and voiding (1% time). Bladder smooth muscle is continuously active during filling, but in an uncoordinated way, keeping the pressures very low. Isolated bladder experiments show the existence of micromotions (138)—small areas of muscle that contract while others relax without conferring a pressure increase. This constant motion is considered facilitatory for rapid adaptation to acute pressure changes, thus helping to maintain continence. However, the continuously active smooth muscle fibres also lead to continuous afferent firing which, in absence of protective mechanisms, could lead to continuous intrusions from desire to void. One implication of this spontaneous activity, however, is that central control must be mainly inhibitory.

The neural control of micturition (139-141) has been much better studied than defecation. During bladder filling, afferent information is conveyed through pelvic and hypogastric afferents up to the mesencephalic periaqueductal grey (PAG). Hypogastric efferents inhibit the bladder; pelvic efferents are silent during filling; and the pontine micturition center provides the switch between filling and voiding phases. The PAG connects to higher brain centers to provide the conscious perception of filling, desire or urge to void. If the situation is suitable for voiding, the pontine micturition center is activated leading to a synergic voiding (bladder contraction and at the same time urethral sphincter relaxation). If the time or place is inappropriate, the pontine center is inhibited by frontal brain activity and the desire to void is suppressed.

Switching in the pons between these phases occurs by differential afferent firing states in bladder sensory fibres. A low afferent firing state permits subconscious bladder filling, with inhibition of any sensory information to the cortex and suppression of detrusor activity. When the bladder fills toward capacity, a high afferent firing state ensues in which afferent information is no longer gated from the cortex (urge to void is experienced) and detrusor activity is promoted rather than suppressed by activation of detrusor pathways acting via suppression of Onuf's nucleus in spinal cord and activation of parasympathetic efferents through the lumbosacral nuclei.

The plausible notion that the rectum behaves like the bladder in terms of differential firing states is not only based on parsimony. The bladder and rectum share the same peripheral nervous system organisation with similar inhibitory and excitatory reflexes. Furthermore, at least in animals, there is afferent convergence between both systems (142,143), and supraspinal control centers are located in the same brain regions (144-147). This appears also to hold for humans based on functional imaging studies that show common activation of the cortical insula during bladder filling and rectal distension (148).

The barrier in the neural control of continence

At the beginning of this review, the role of the sphincters and pelvic floor were described in respect of their contributions as a barrier to contain feces. This contribution was then set alongside the key role of the rectum and colon as arbiters of whether emptying could occur—this requiring active rectal emptying not just failure of the barrier.

The lived experience of urge incontinence implicates the volitional, although short-lived, contraction of the anal sphincter as a means of suppressing urge. It is possible, although unproven, that such contraction clears the upper anal canal after sampling thus reducing activation of mucosal receptors (78,149). A failure to clear the upper anal canal could therefore link EAS injury to ongoing stimulus-driven urge (59-61). However, this could not be the mechanism for the bladder where urine cannot be displaced and yet the urge to void also is suppressed. Abundant experimental and clinical urological literature show that stimulation of the urethra has marked effects on bladder physiology through some of the seven Barrington reflexes (those between urethra and bladder) [reviewed (150)]. Several of these are excitatory in nature and explain increased bladder activity originating from the urethra. Their normal role is to ensure complete bladder emptying as long as urine is flowing through the urethra. The downside of these reflexes is that they can be activated by sudden pressure impulses in the bladder, e.g., a cough (151) in the case of an insufficient internal sphincter causing bladder neck opening. However, others mediated by the pudendal nerves inhibit bladder contractile activity.

The critical role of the pudendal nerve in micturition has been well demonstrated in experimental animals since the 1930s. Since that time, a series of >100 high quality studies from Duke University and the University of Pittsburgh over a period of about 30 years have carefully unravelled the differential effects of pudendal nerve stimulation (PNS) on the bladder in alpha-chloralose-anesthetized cats. Such studies demonstrate that depending on stimulation frequency, electrical stimulation of pudendal afferents evokes spinal reflexes that either inhibit the bladder and promote continence or excite the bladder to promote micturition, the latter with the caveat that experiments were performed after spinal cord transection. Bladder inhibition by peripheral afferent PNS (experimentally via surface or needle stimulation of dorsal genital nerve) arises from activation of hypogastric efferents and subsequent synaptic and ganglionic inhibition of parasympathetic efferents (152,153) whereas the mechanisms of bladder excitation (above) are uncertain but may be due to convergence of pudendal and pelvic afferents (154) in the spinal cord. Increased urethral tone may have particular importance in gating urge sensation and inhibiting voiding in certain bladder emptying syndromes, e.g., Fowler's syndrome (155) although the pathophysiology of this condition is far from assured (156).

The anal sphincter is also known to be richly innervated by afferent fibres (157) and these too signal anal tone. The pelvic floor muscles, and the EAS itself contain muscle spindles that have similar structures to those in skeletal muscles. These will have modulating effects on postural control of these muscles, by signalling muscle stretch and rate of change of stretch (45). In addition, there are Golgi tendon organs in the tendinous and fascial attachments of pelvic floor muscles, that signal muscle tension. The pelvic floor fascia, the perivaginal fascia and ligaments, and the peritoneum above the pelvis is liberally innervated by Pacinian corpuscles, that signal displacement and pressure. Pacinian corpuscles are also found in the fascial and peritoneal attachments of the anus and rectum respectively. These could play a role in detecting pressure changes due to filling of these organs.

Surface and needle stimulation of the dorsal genital nerve in humans has therapeutic effects for urge urinary (158) and urge FI (159,160) with demonstrable reductions in unwanted detrusor contractions (the motor correlate of urgency) in several studies of patients with UUI (158). Further, PNS using implanted electrodes on the pudendal nerve trunk, may have greater treatment effects in OAB than SNM (161,162) and has been trialled successfully for selected patients with FI (mainly those failing SNM or those with cauda equine syndrome) (163).

Summary

Integrated theory of FI pathophysiology

The important functions of the rectum, colon and CNS can be integrated with the classical barrier-centric model of FI pathophysiology. So doing treats the anorectum as a single functional unit in the same manner applied to study of the bladder and urethra. This unit requires contraction +/– external compression of the rectum for incontinence to occur but the control of rectal contractility is intimately dependent on reflexes from the anus, pelvic floor and probably other pelvic organs such as the vagina. This new version of the barrier is more than just the goalkeeper (it

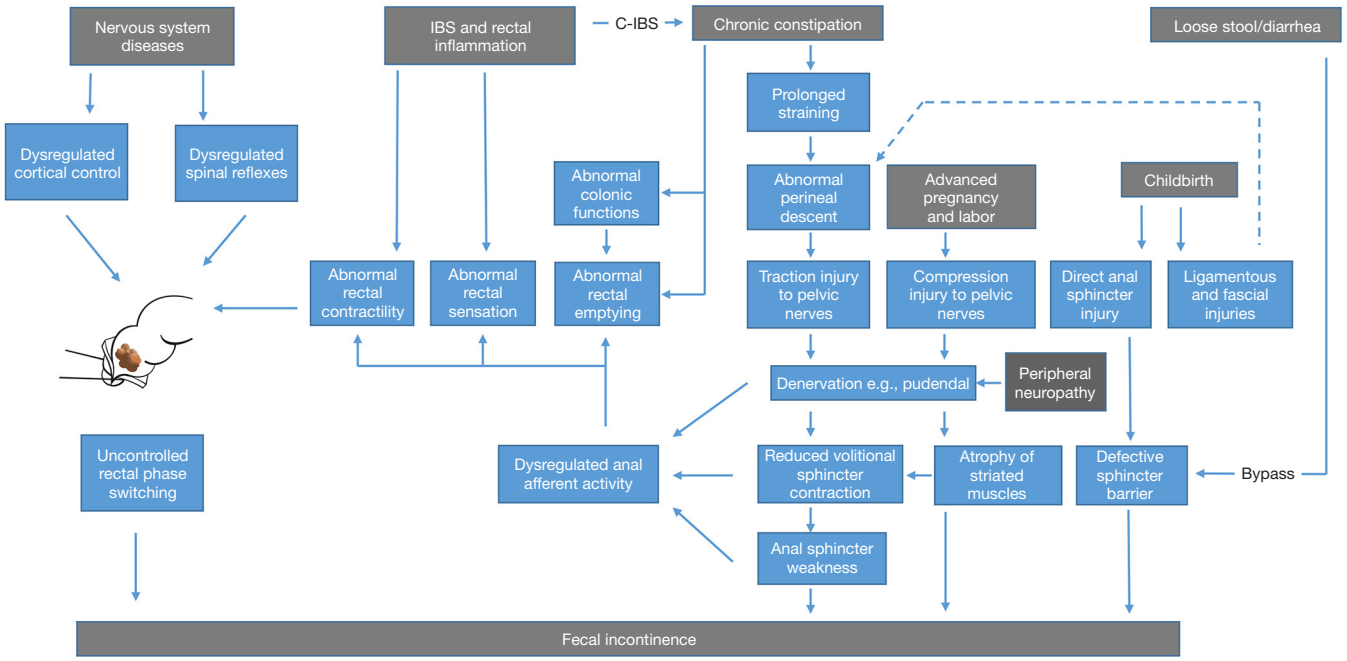

Figure 5 New rectum-centric schema for the pathophysiology of FI (see summary text). IBS, irritable bowel syndrome; C-IBS, constipation-predominant-IBS; FI, fecal incontinence.

Table 3 Performance of new rectum-centric theory of FI

Original criticism of barrier theory	New theory
Epidemiology of FI in parous women	FI can occur as a consequence of subclinical injury to sphincters and to pudendal/pelvic nerves. Subtle neuropathic or myopathic changes lead to change in reflex control of rectal contractility
Epidemiology of FI in men	The majority of FI in men is associated with problems of rectal sensation (generally hyposensation), and anorectal coordination (functional evacuation disorders) +/– IBS
Changes in continence over the life course	Key role of the CNS as controller of switching between basal and pro-expulsive phases. These require cortical, midbrain and spinal functions that develop in infancy and may be disturbed by disease or injury in later life
Lived experience of urgency	Central role of the rectum and particularly of rectal sensory functions in mediating both local reflex contractility and urge perception
Link to functional conditions such as IBS and functional evacuation disorders	These conditions are associated with demonstrable changes in rectal motor and sensory functions
Failure of direct repair and augmentation of the barrier	Static compression or constriction of the anal sphincters reduces dynamic variations in anal tone required for normal anorectal reflex activity leading especially to rectal evacuation problems
Success of SNM as therapy for FI and UUI	SNM, as studied to date, has effects that are predominantly on gating of spinal reflexes and central processing of urge perception

FI, fecal incontinence; IBS, irritable bowel syndrome; CNS, central nervous system; SNM, sacral neuromodulation; UUI, urge urinary incontinence.

also controls play in the defence and midfield). The CNS controls switching this play between attack and defence. Together a new rectum-centric schema (*Figure 5*) provides a much better theory for explaining the pathophysiology of FI in terms of epidemiology and risk factors as well as the lived experience of urgency (*Table 3*).

Areas for future research

- Revisiting work started in the 1980s, but discontinued, on fundamental anorectal excitatory and inhibitory reflex functions (the 'Barrington' reflexes of the anorectum) with concomitant but separate recordings of IAS, EAS and puborectalis contractile activities.
- Studies of the origins of anorectal sensation, especially of urgency.
- Functional brain imaging studies to further assess afferent functions of the anus, rectum, pelvic floor and distal colon.
- Continued studies of the relationship between the distal colon and the rectum as pertains to control of rectal filling, both in health and FI.
- Further integrated high-resolution studies of contractility and intra-luminal movement to better understand flow of solid, liquid and gas through the distal colon and anorectum in relation to perceived sensations.
- Experimental studies to better characterise the RCR and its relationship with cortical activation.
- Studies to determine the mechanism of action of SNM for therapy understanding but also as a means of better understanding the pathophysiology of incontinence.
- Mechanistic studies of PNS (nerve trunk and distal afferents) on anorectal functions.
- Pharmacological and physiological studies of the parasympathetic and sympathetic innervation of the distal colon, rectum and IAS.

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