Functional Constipation

Pathological physiology is, by definition, a damaged physiology of an organ or system. In order to determine its parameters, it is necessary to know the normal physiology, and anatomical limits of the norm.

Part 1. Anatomy and physiology anorectum

1) Anatomy of the anorectum. The rectum is in the pelvis retroperitoneally. It starts from the 3rd sacral vertebrae and ends at the level of the pubococcygeal line, where it borders on the anal canal. From a functional point of view, the rectum begins caudal to the rectosigmoid sphincter. While fecal retention, it performs a cumulative function, and during bowel movements its strong peristaltic wave, which starts from the rectosigmoid sphincter, expels the stool through the open anal canal. Table 1 shows the normal width of the rectum in patients of different ages after filling the colon with barium at least to the splenic angle [1,2].

Table 1. The normal size of the rectum and anal canal in different ages.

Ages	The width of the rectum (cm)	The length of the anal canal (cm)
5 days – 11 months	1.3 – 3.0 (2.24±0.09)	1.7 – 2.5 (2.21±0.15)
1 – 3 years	3.0 – 3.7 (3.21±0.11)	2.3 – 2.8 (2.55±0.10)
4 – 7 years	3.0 – 3.9 (3.43±0.14)	2.5– 3.6 (3.17±0.14)
8 – 10 years	3.2 – 4.1 (3.72±0.05)	2.6 – 3.7 (3.11±0.10)
11 – 15 years	3.6 – 4.6 (3.95±0.07)	3.1 – 3.9 (3.43±0.10)
23 – 64 years	3.5 – 4.8 (3.95±0.21)	3.4 – 4.2 (4.08±0.07)

The anal canal starts from the pubococcygeal line and continues to the anus. Its length is given in table 1. The anal canal consists of several elements, each of which plays an important role in the fecal retention and defecation. In its center is the smooth muscle of the internal anal sphincter (IAS), which is a continuation of circular layer of the rectum. However, IAS are both morphologically and functionally different from the rectum. There is very little or no ganglion cells between IAS and the external anal sphincter (EAS), since there is no motility in IAS. During a bowel movement, it opens all along the length, completely and simultaneously. For 24 hours a day, except for a few seconds, during a bowel movement, IAS is in a closed position, preventing stool and gas from leaking. The loop of the puborectalis muscle (PRM), consisting of striated muscles, is also involved in the retention of feces. During its contraction, the posterior wall of the anal canal is attracted to the pubis, which contributes to the increase of the anal pressure and is accompanied by a decrease in the anorectal angle. All three portions of the striated muscle of EAS (deep, superficial and subcutaneous) during contraction increase the tone of the anal canal [3, 4].

The two striated muscles of the levator plates (LP) are attached on the periphery fanlike to the bones of the pelvis, and the inner ends through the rectum to the longitudinal layer of the anal canal. Levator plates are contracted during bowel movements. They stretch of the anal canal, which leads to a wide its opening during the passage of the stool [5].

Nervous regulation of anorectum is very important. It includes sensitive elements in the rectum and in the anal canal, as well as 3 systems: (1) intramural nerve system of the rectum (myenteric ganglia, cells of Cajal), which coordinates the motility of the intestine; (2) sympathetic and parasympathetic innervation, which coordinate reflexes и (3) somatic innervation, originating from Onuf's nucleus, which is located in the sacral spinal cord, travel in the pudendal nerve, muscular branches and in the coccygeal plexus. Through them, cortical and spinal effects on the anorectum function occur (Figure 1) [3]. An example of the interaction of all neural networks can serve as an act of defecation. When the pressure in the rectum reaches the threshold level of defecation, this information is recorded by the sensitive elements of the rectum and transmitted through the networks. Through the intramural nervous system, the excitation of strong rectal motility and relaxation of IAS occurs. At the same time, there is a reflex relaxation of PRM and EAS, as well as a contraction of LP. Through somatic innervation supply striated muscles are under voluntary control, i.e. the final decision on defecation depends on whether it is possible in the present situation.

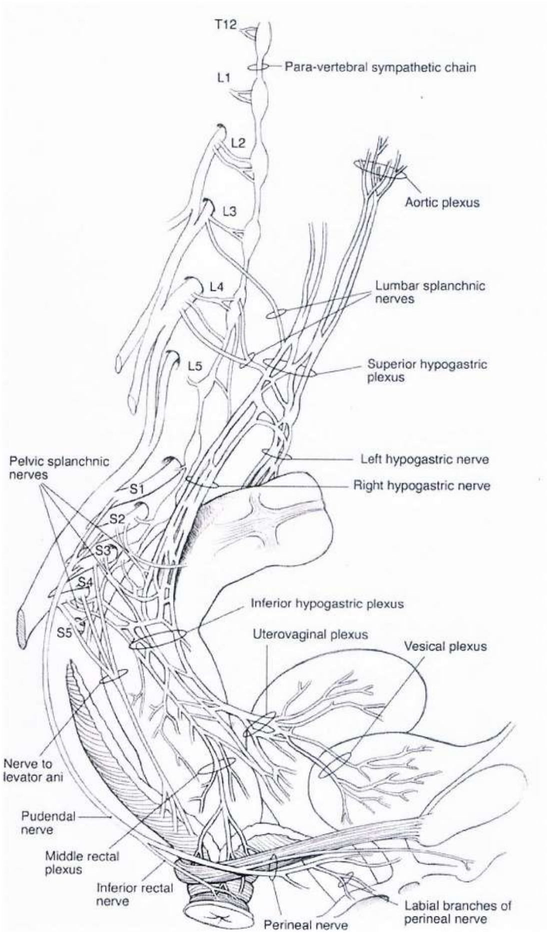

Figure 1. Scheme of the nervous supply anorectum from the article Bharucha [3].

The sensory-motor nerve paths coordinate the work of the internal and external layers of the anal and urethral sphincters [6]. It is obvious that damage (intersection) of the nervous supply will inevitably lead to dysfunction of the anorectum.

Ligamentous apparatus creates a stable framework for the normal function of all elements of the pelvic floor [7].

2) Normal anorectal physiology. There is not a single muscle that would provide a long overlap of the anal canal. Nevertheless, the anal canal is in continuous contraction around the clock. It is known that smooth muscle of IAS is capable of a longer contraction than striated muscle. Meanwhile, the contraction power of the PRM, EAS and LP is dramatically reduced after a few seconds (5-15). Coordination between the nervous systems allows the muscles to retain the feces with the necessary (optimal) force of contraction, depending on the amount and consistency of the contents in the rectum, i.e. with minimal power of contraction with an empty rectum and stronger with a filled rectum, and with fluid contents.

Skeletal muscles are capable of two types contraction: tonic and mechanical. Tonic prolonged contraction of the LP, PRM and EAS explained by postural reflex [8,9]. Each nervous axon has a connection to the muscle fibers scattered throughout the muscle. Therefore, even a small amount of the contracted muscle fibers results in a contraction of the whole muscle. The muscle tone is dependent on the number of fibers participating in the contraction, i.e. from the percentage of axons activating muscle contraction. The prolonged, tonic contraction is due to the continuous replacement of the axons activating the different groups of muscle fibers. At different time the different groups of the muscle fibers are contracted. During the contraction of one group, other groups of fibers restore ability to contract [10,11].

In mechanical contraction all fibers are involved, resulting in a significant shortening of the muscle. However, the duration of the muscle contraction is severely limited, typically less than one minute.

Fecal retention. At rest, the IAS and striated muscles of the pelvis floor are in a state of tonic contraction. They help to support the pelvic organs and participate in the continuous retention of feces. The pressure in an empty rectum is equal to the intra-abdominal pressure. It is basal rectal pressure (BRP). Its absolute indices are irrelevant, because, firstly, in different articles, they differ significantly from each other, and, secondly, intrarectal catheters distort the true functional characteristics. When the fecal bolus penetrates from the sigmoid colon into the rectum, it stretches the wall of the rectum and rectal pressure increases above the BRP. This pressure we called the threshold pressure of the first order (TP-1). It causes a reflex relaxation of the IAS and contraction of the EAS and PRM (anorectal inhibitory reflex). The PRM pulls forward the upper part of the anal canal. In front, inside the PRM loop the anal pressure decrease as a result of the IAS relaxation. Between the rectum and anal canal there is narrow opening through which the gas and liquid feces can penetrate the upper part of the anal canal. In the mucosa at this level there are sensors that allow to distinguish the liquid from gas. In the presence of gas is enough to strain the abdominal wall to increase rectal pressure and expel gas through the lower part of the closed anal canal. When the liquid feces penetrate the upper part of the anal canal the tone of the EAS increase, which leads to a contraction of the IAS and crowding out of the fluid from the anal canal into the rectum. During anorectal inhibitory reflex the formed stool remain in the rectum due to acute anorectal angle and the narrow hole between the rectum and anal canal. After a few seconds the rectum adapts to the new rectal volume and relaxes. The rectal pressure drops up to BRP, resulting in the contraction of the IAS and relaxation of the PRM and EAS. After entering the rectum of another bolus of feces this picture (anorectal inhibitory reflex) is repeated. This picture can be observed up to seven per hour. During IAS relaxation, its muscle fibers restore contraction ability. In this period, the fecal retention function is performed by the PRM and EAS. During the rise of the intra-abdominal pressure (rise from the spot, cough, etc.), the reflex contraction of all sphincters occurs. The tone of the IAS increases, since the electric potential from the center outside the rectum increases the number of contracted muscle bundles.

When the volume of stool in the rectum reaches a certain value, the rectal pressure rises from TP-1 to the threshold pressure of the second order (TP-2), in which a need for a bowel movement appears. If this need is does not coincide with the possibility of its implementation, the rectum continues to relax to a limited extent. At the same time, there is an increase in the tone of the recto-sigmoid sphincter, which prevents the further penetration of feces from the sigmoid colon into the rectum.

Defecation. When the need for a bowel movement coincides with the possibility of its implementation, a straining of the abdominal wall and diaphragm increases the abdominal and rectal pressure from TP-2 to the threshold pressure of the third order (TP-3). At the rectal pressure TP-3 the reflex defecation takes place: a strong peristaltic wave of the rectum expels stool through the open anal canal. Wide opening of the anal canal is due to relaxation of the IAS, PRM, and EAS, with a simultaneous contraction of the LAM. Any of pressure levels depend not only on the volume of feces, but also from the tone of the rectum. During the opening of the anal canal, its wall is stretched at the level of deep and superficial portions of the EAS. The subcutaneous portion is relaxed, but it is not connected with LAM (see Figure 2). Therefore, during the evacuation of soft feces, it forms a tape, the diameter of which depends on the viscosity of the feces.

Part 2. Functional studies in functional constipation.

Definition. Chronic constipation (CC) is a common problem. The prevalence of constipation in the worldwide general population ranged from 0.7% to 79% (median 16%). In children prevalence rate was between 0.7% and 29.6% (median 12%) [13]. Different types of CC are divided into organic and functional. Organic causes include Hirschsprung disease, anorectal malformations and spina bifida. The functional reasons of CC include the cases where the cause can be established and made specific correction (hypothyroidism, celiac disease, allergies, elevated levels of calcium and lead) [14]. All other cases of CC covered by the criteria of international groups of experts Rome IV are considered functional constipation **(FC)** [15,16].

Rome IV criteria for diagnostic functional constipation in infants and toddlers must include 1 month of at least 2 of the following in infants up to 4 years of age [16]:

1. 2 or fewer defecation per week
2. History of excessive stool retention
3. History of painful or hard bowel movements
4. History of large-diameter stool
5. Presence of a large fecal mass in the rectum

In toilet-trained children, the following additional criteria may be used:

6. At least 1 episode/week of incontinence after the acquisition of toileting skills.
7. History of large-diameter stool that may obstruct the toilet.

From the analysis of the clinical symptoms of the FC it can be seen that any combination of 2 paragraphs, with the exception of identical 1 and 2, indicates a stool retention in the dilated rectum, since only the passage of a broad stool can cause pain during a bowel movement and only the extended rectum can form a wide stool.

The most common pathogenesis of FC is a vicious cycle that begins in the early childhood with painful defecation and leads to stool-withholding behavior as a result. Functional constipation in children arises in the early childhood results from intentional withholding of stool following a painful experience with defecation [17]. It is believed that the conscious is not paying attention to the rectal urge and / or suppression of the urge to defecation can lead to fecal retention, with the development of the rectal hyposensitivities, increased compliance and megarectum [17,18]. This is the so-called obstructive constipation (OC), the main distinguishing feature of which is the expansion of the rectum (megarectum). Separately considered cases of chronic constipation accompanied by abdominal pain, which, under the Rome III criteria is the irritable bowel syndrome (IBS) [16, 19]. Among the primary functional disorders is distinguished slow transit constipation (STC), which is explained by pathology intracolonic nervous plexus [20].

1) <u>Barium enema.</u>

a) In all children with FC, except for children of the first three years of life with disease up to six months who received appropriate treatment, the width of the rectum was outside the maximum limit of the age norm. Megarectum was always accompanied by expansion and lengthening of the sigmoid colon, and in 70% of patients the descending colon was expended [21].

b) We calculated the integral characteristic of the size of the colon, based on which we divided megacolon into 3 degrees [22]. With age, the percentage of patients with 1st degree megacolon decreased due to the growth of patients with 2nd and then 3rd degree (**Figure 2**).

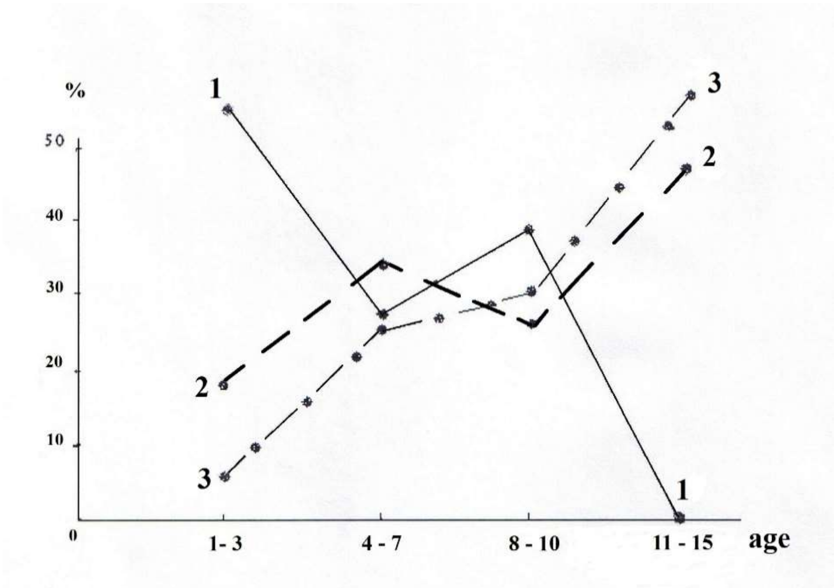

Figure 2. Schedule. Percent the different degrees of megacolon depending on age: (1) - megacolon 1st degree - (C = 32 - 45); (2) - megacolon 2nd degree – C=

46 - 60; (3) - megacolon 3rd degree – C > 60. The upper limit of normal is 31, regardless of age.

c) A significant ($p<0.05$) lengthening of the anal canal as a result of hypertrophy or edema of PRM (**Figure 3, A**) was observed in some patients with FC up to 3 years, which is observed in the initial stage of the FC. In more old children, a significant shortening of the anal canal is sometimes observed (**Figure 3, B**), which is explained by stretching of the pelvic floor muscles (descending perineum syndrome) [1].

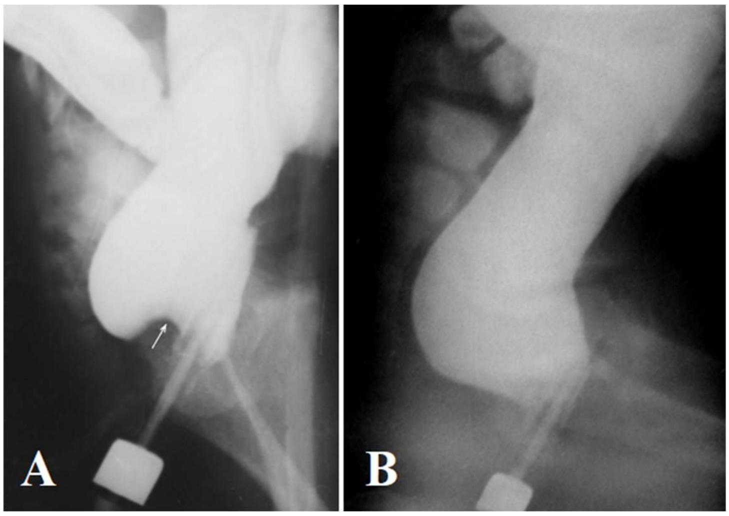

Figure 3. Lateral roentgenograms of anorectum in children in different stages of the FC. The true diameter of the marker located near the anus is 1.6 cm. **A.** Child of 3 years. There is a typical concavity (arrow) on the lower contour of the rectum due to hypertrophy and/or edema of the PRM. The length of the anal canal is 3.6 cm (the maximum normal limit is 2.8 cm. The width of the rectum is 4 cm (the maximum normal limit is 3.7 cm. B) In a patient of 8 years, the width of the rectum is 5.6 cm (the maximum limit of the norm - 4.1 cm). The length of the anal canal is 2.1 cm (the minimum limit of the norm - 2.6 cm). The upper part of the anal canal, including the PRM and IAS, are in constantly stretched state, i.e. are not involved in the feces retention.

d) In most cases, the disease begins in the first 3 years of life. Complaints to encopresis appear on average after 6 years with a peak of 8-10 years (**Figure 4**). It is surprising that by the age of 15 the number of complaints for encopresis decreases sharply. Meanwhile, by this time there is a progression of the disease, as evidenced by the increase in the number of patients with megacolon 2nd and 3rd degree (see Figure 3). This contradiction can be explained by the fact that older children begin to be ashamed. They wash their underwear themselves and hide the encopresis. It is also possible that before admission to the hospital with fecal disorders, they used treatment.

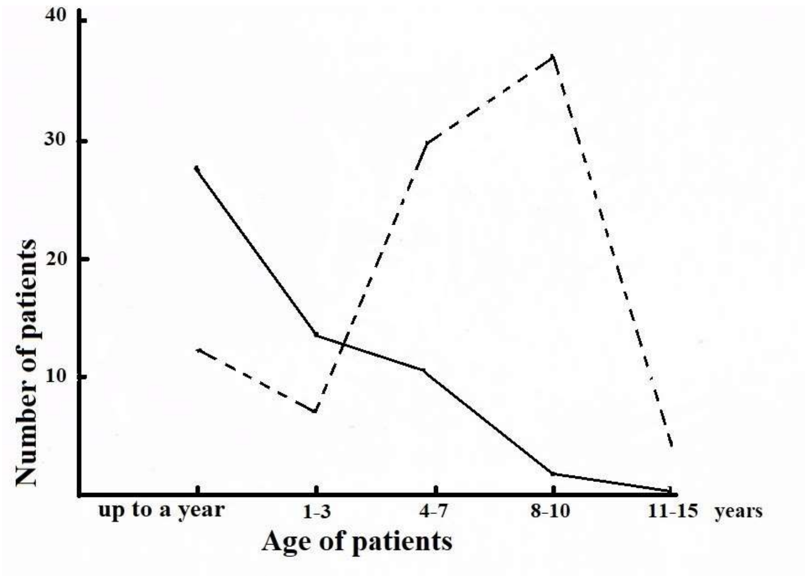

Figure 4. The number of patients with the FC (solid line) and the frequency of patients with encopresis (intermittent line), depending on age.

Studies with barium enema show that FC in childhood occurs because of stool retention in the rectum. This leads to the expansion of the rectum (megarectum), as well as expansion and lengthening of the sigmoid colon (dolichosigma). The descending colon expands in 70%. Megarectum always combined with megacolon.

2) Manometric studies include anorectal manometry with balloon expulsion test and colonic manometry.

A) Anorectal manometry is considered to provides assessment of dyssynergia and its subtypes together with assessment of rectal sensation, reflexes, and compliance It is essential for a diagnosis of dyssynergic defecation. First, it excludes the possibility of Hirschsprung's disease. Second, it detects abnormalities during attempted defecation. Normally, when a subject bear down or attempts to defecate, there is a rise in rectal pressure, which is synchronized with a relaxation of the IAS, EAS and PRM. The detection of anal relaxation impairment during attempted defecation is an important manometric tool in FC patients since it identified dyssynergic defecation. The paradoxical contraction or impaired ability to relax the pelvic floor muscles during defecation change the normal sequence of the pelvic floor muscle activity during any stage of complex mechanism of defecation. Patients have a significantly higher conscious rectal sensitivity threshold than controls ($p<0.02$) [20]. Inability to pass a 50-mm^3 balloon is highly specific and 50% sensitivity for pelvic outlet dysfunction [23].

All the manometric symptoms of obstructive constipation and the pathological balloon expulsion test can be explained by the expansion of the rectum (megarectum), because this is indicated by:

- increased rectal compliance [24];

- higher rectal sensitivity threshold, because in the wide rectum it is necessary to inflate a balloon of larger diameter in order to induce TP-3 for the defecation reflex;

- a balloon with a volume of 50 mm^3, which normally causes rectal pressure PT-3, in patients with FC, it causes pressure PT-1, at which the IAS relaxes and the EAS with PRM contract (anorectal inhibitory reflex). This is a normal sphincters reaction in the presence of megarectum;

- the possibility of defecation occurs when in the rectum is collected large-diameter feces and the rectal pressure reaches PT-3. This leads to a mismatch between the width of the stool and the width of the open anal canal. This is the main reason for the obstructive constipation. Stelzner and Hansen came to the same conclusion: -"Based on the fact, that constipation never occurs in patients with a colostomy, reason for the development of FC are presumed in a disturbance in the anal canal and the rectum. A possible explanation for the malfunction of defecation could be a different caliber between the usually tight pelvic colon (anal canal) and the wide rectum". Based on this conclusion, they "... did a deep resection of the rectum instead of the dilated and elongated colon" [25].

Sensory assessment using balloon distension may not accurately reflect the function of visceral afferents, because the patients with intractable constipation has persistent dilatation of the rectum, in such patients' greater volumes will be required to distend and thus stimulate the rectum [26]. The group from Queen Mary University London showed that 16% had an anatomical megarectum (increased rectal dimensions, but normal compliance), 51% a functional or "pathophysiological" megarectum (increased rectal dimensions and hypercompliance), and the remaining 33% appeared to have true impairment of afferent nerve function (normal rectal biomechanical properties, but abnormal nerve sensitivity) [27]. From this work the criterion for the diagnosis of true impairment of afferent nerve function (hyposensitivity) was a combination of constipation with the normal width of the rectum. However, these authors filled of the rectum with barium of volume to 500 ml under minimal pressure [28]. During introduction of 500 ml under minimal pressure, the width of the rectum on the radiograph in patients with megarectum will more reflect the tone of the rectum, than the true width, since a contrast medium is unable to stretch of the rectum to its maximum size, and will be distributed into the left part of the colon. Analysis of these paper indicates that the authors did not consider the projection magnification of the image on radiographs, significance of which depends on the distance from the object being studied (rectum) to the cassette. The greater the patient's pelvis, the more its image will increase relative to the norm. On the lateral radiograph the rectal size can be 2-fold greater at full and large people than in reality. These authors used barium enema with serious methodological disturbance and therefore mistakenly did not diagnose megarectum in 33% of patients. In the studies using the rectal barostat was shown that no differences in sensory function could be identified in groups of children with functional constipation compared to healthy volunteers [29, 30]. These studies indicate that the appearance of sensation on large volumes of a rectal balloon indicates a megarectum.

B) Colonic manometry, as well as the study with radiopaque markers, detects in some patients with FC slow propagation of peristaltic waves and bowel content. Some authors believe that slow transit constipation (STC) and functional fecal retention are two forms of severe intractable constipation in childhood. It is argued that STC is characterized by delayed passage of fecal matter through the proximal colon whereas functional fecal retention describes delayed transit in the rectosigmoid region only [31]. However, Wessel et al. were not able to categorize all patients as either STC or outlet obstruction [32].

Intraintestinal pressure depends on the tone of the intestine and the width of the lumen. In the extended intestine, pressure cannot be normal, which is why it is called inert. The wider the segment of the colon, the more the pressure in it is different from the norm. Thus, abnormal colonic manometry is an indirect and not entirely accurate way to determine the width of different segments of the colon. I did not manage to find out who was the first and on what basis did he determine that abnormal colonic manometry is an indication of an operation?

3. Scintigraphic evaluation of colonic transit in children with constipation

In the recent article the authors adhere to the generally accepted opinion that "Segmental transit times are measured in the right colon to the right of the vertebral spinous processes and above an imaginary line from the fifth lumbar vertebra to the pelvic outlet. The left colon is the area to the left of the vertebral spinous processes and the imaginary line above the fifth lumbar vertebra and the left anterior superior iliac crest. The rectosigmoid is the area under the imaginary line from the pelvic brim on the right to the superior iliac crest on the left" [33,34]. However, in obstructive constipation, a significant part of the extended and elongated sigmoid colon (dolichosigma) is located to the right of the midline (**Figure 5**).

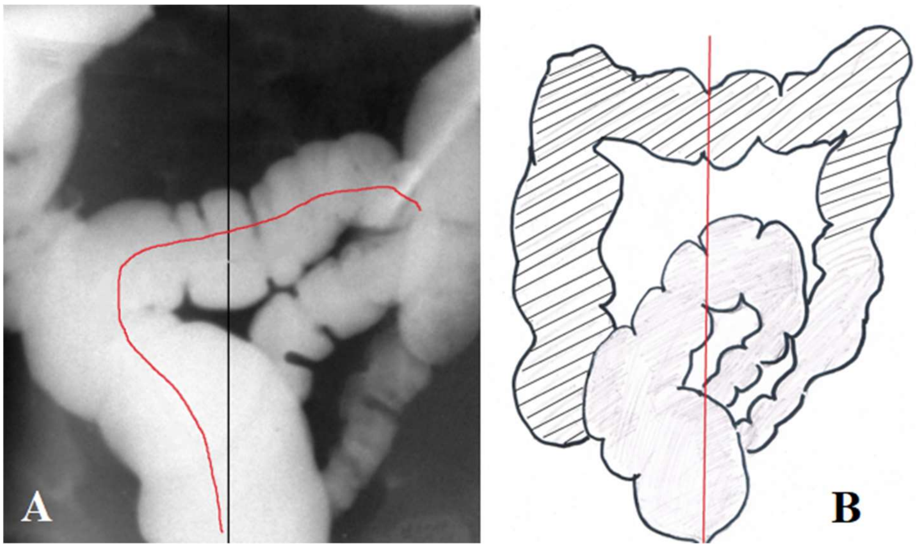

Figure 5. Barium enema of the patient with functional constipation (A) and the scheme to it (B). A significant portion of the extended and elongated sigmoid colon is located to the right of the midline (white line) and it is partially superimposed on the cecum. The configuration (red line) of the sigmoid colon differs from the ascending colon configuration. On figures 2 and 3 it is mistakenly taken as the right half of the colon. Thus, the left half of the colon is in the right half of the abdomen.

In the caption to Figure 6 from the article Calegaro et al [33], the authors signed: "Retrograde transit: The 67Ga-citrate was come back for ascending colon (120 h image) after evacuation". But, 72 minutes after the radiotracer oral administration, marker was concentrated in the transverse colon (t) and in the rectum (r). The marker has already passed through the ascending colon and cannot be there anymore. After 120 minutes, the marker is in the bowel, most of which is located to the right of the midline, but none of its points reaches the level of the hepatic flexure (t). The location and configuration of the intestine correspond to the dolichosigma.

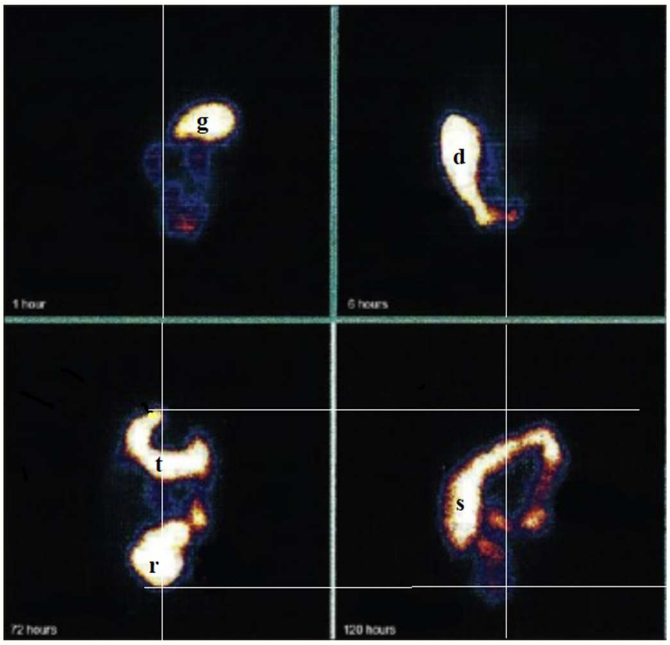

Figure 6. Slow evacuation from the stomach (g). Dyskinesia duodenum (d). Note the location of the hepatic flexure of the transverse colon (t). Extended rectum (r). Through 120 hours, after emptying the rectum, the labeled chyme moved from the transverse colon to the dolichosigma. Conclusion: obstructive constipation. (My notation and interpretation in the figure from the article).

On Figure 7, which is shown as «Example of right stasis (ascendind and transverse colon)", a gut is visible, which is filled with labeled feces after 48 hours after the radiotracer oral administration. It is located to the right of the midline but does not reach the location of the ascending colon. By location and typical form, it corresponds to dolichosigma.

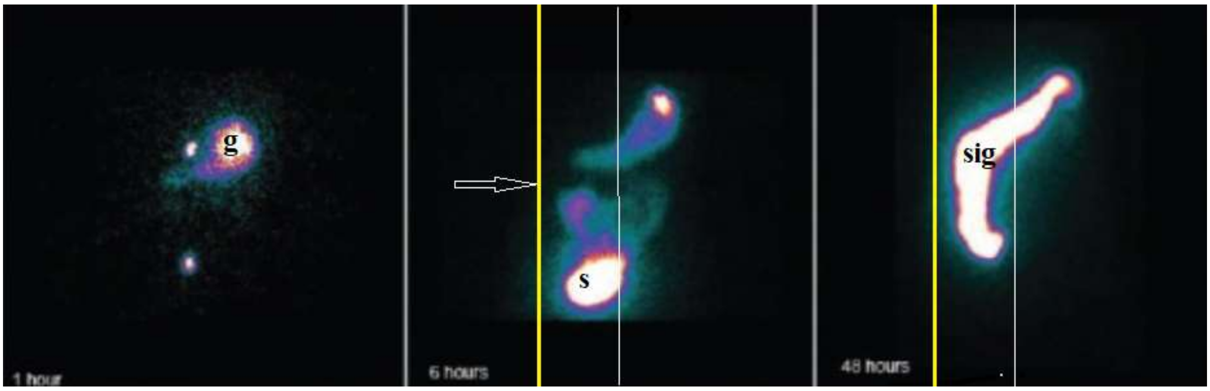

Figure 3. My tagging. Slow evacuation from the stomach (g). The small intestine loops conglomerate (s) is located to the left of the cecum. The cecum and ascending colon must be located to the right of the yellow line. Although the sigmoid colon (sig) is located to the right of the midline (white line), it does not reach the location of the ascending intestine. Its shape does not even resemble to the hepatic flexure of the transverse colon.

Conclusion. The authors made two fundamental errors. First, there is no retrograde fecal movement in the colon. Secondly, there is no predominantly right slow transit constipation. An analysis of the literature indicates that functional constipation in all children has an obstructive nature. Gradually, evacuation from the stomach slows down. There is a slower advance of chyme in the small intestine and the colon. The difference in the image in different patients is due to the different value of megacolon and dolichosigma. The wider and longer the sigmoid colon, the more size of tagged feces are observed on the right, i.e. in the right half of the abdomen is the left half of the colon.

Accurate measurement of the normal width of the rectum in children of different ages has allowed us to prove that all children with FC have megacolon, and therefore obstructive constipation. Methodological errors in the measurement of the width of the rectum led other authors to a completely unrealistic conclusion that children under 5 years of age have the same maximal border of the rectal width as an adult (6.5 cm) [35]. Because of this error, all patients with megarectum, in which the width of the rectum was less than 6.5 cm, were excluded from obstructive constipation and attributed to STC [31,32]. Colonic dysmotility (STC) as a special kind of constipation without the rectal enlargement is only in adults and especially in elderly. In children, STC is a symptom of obstructive constipation. Manometry differences depend on the degree of megacolon, the duration of the disease and the presence of mucosal inflammation.

4) <u>Defecography and dynamic MRI defecography</u>. In children with FC, there are no severe forms of lesions of the rectum and pelvic floor muscles as in adults, and especially in women after childbirth. For example, out of 14 children with chronic intractable constipation, 12 of which were operated (total abdominal colectomy), "...defecography was consistent with isolated pelvic floor dysfunction in 1 patient, abnormal motility and anatomy in 1 patient, pelvic floor dysfunction and abnormal motility in 2 patients, and found abnormal motility only in 5. Defecography study was normal in 5 patients. "All of the patients with abnormal colonic manometry underwent a surgical procedure" [36]. All the described symptoms are characteristic of the FC and indicate obstructive nature. Neither anal manometry nor defecography revealed any damage to the muscles of the pelvic floor, rectocele, etc. Only an abnormal colonic manometry indirectly indicated a marked expansion of the large intestine, which was the reason for the removal of the entire colon. Why? Secondly, were all of these studies needed if the exact condition of the rectum, colon, and pelvic floor muscles can be obtained by performing a hydrostatic barium enema?

Structural abnormality includes excessive pelvic floor descent with an intra-rectal intussusception, rectocele and rectal prolapse [37]. Rectocele is an abnormal protrusion of the wall of the rectum into perineum in front of or behind the axis of the anal canal (anterior or posterior rectocele). It is rarely been described in the literature in children younger than 18 years of age so far. Hussain et al. described 3 cases of rectocele with obstructed defecation in the pediatric population [38]. Figure 5 shows an example of the posterior rectocele from the article Dietz [39].

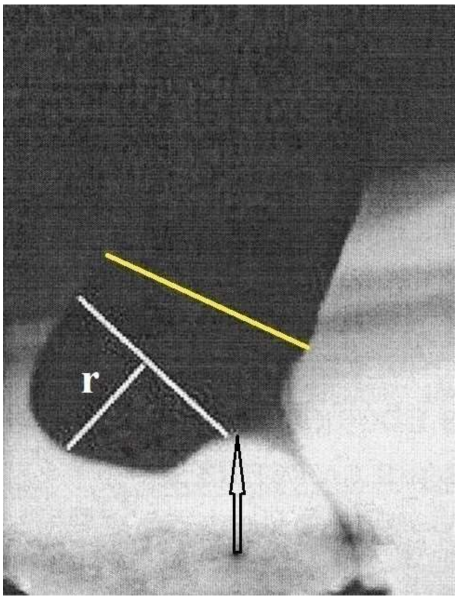

Figure 5. Posterior rectocele on defecation proctography is defined. The author noted the depth (r) of the lowering of the posterior wall of the rectum. The absence of the horizontal branch of the rectum indicates megarectum. During an attempt at defecation, relaxation of IAS occurred (barium penetrated the anal canal in the form of a cone) and contraction PRM, as evidenced by an indentation (arrow) in the anorectal angle.

X-ray picture suggests megarectum. The volume of contrast material in the rectum is insufficient to induce a defecation. Rectal pressure (TP-1) caused reflex relaxation of the IAS and contraction of PRM and EAS (anorectal inhibitory reflex). This study added nothing to what we know of the FC, which always has an obstructive nature and is accompanied by an expansion of the rectum.

Conclusion

Functional constipation in children occurs at an early age as a result of a delay in defecation. This leads to the expansion of the rectum (megarectum). The obstructive nature of the disease is caused by the discrepancy between the diameter of the stool formed in the extended rectum and the width of the open anal canal. Barium enema with a marker near the anus and the rentgenometric analysis is a simple, accurate and safe method for diagnosing FC and its complications [37].

Part 3. Pathogenesis of functional constipation.

1-4 years. Functional constipation begins in early childhood. A large-diameter stools accumulate in the rectum as a result of a delayed defecation. Subsequent attempting to defecate causes pain, what leads to fear of defecation and suppression of urge. So, there is a vicious circle, as a result of which the rectum stretched (megarectum). Large volumes of fecal masses accumulate in the left half of colon, causing expansion and lengthening of the sigmoid colon (dolichosigma). The total volume (capacity) of the colon increases significantly (megacolon).

4-8 years. The chronic colonic obstruction in FC less severe than in Hirschsprung's disease and therefore causes less severe inflammation (colitis) [38]. “A microscopic inflammation in the colonic mucosa may hypothetically be the reaction to all the irritants the colon is exposed to in daily life” [39]. Enhanced peristalsis and the release of fluid into the lumen of the colon causes abdominal pain and a symptom of encopresis.

9-18 years. The likelihood of complete recovery decreases with age. There are 3 options for older children and teenagers for the development of the pathological process.

1st. Clinical and pathological stabilization. This is a constipation, which is controlled by the periodic or permanent use of laxatives.

2nd. Descending Perineal Syndrome. Wide fecal masses under the influence of a strong peristaltic rectal waves stretch the muscles of the pelvic floor (PRM and levator plates) (**Figure 6.A**). Weak PRM does not overlap the anal canal during relaxation of BAC (anorectal inhibitory reflex), which leads to fecal incontinence. Weak levator plates do not stretch the walls of the anal canal when attempting to defecate, which dramatically increases the resistance during move the stool through the anal canal [1,7].

3rd. Irritable bowel syndrome (IBS). Colitis caused by stagnation of feces in the colon and / or the intake of stimulant laxatives causes an increase in the tone of the entire intestine. This is manifested by a narrowing of the intestinal lumen. The narrowing of the rectum gradually occurs. Besides, with an increased tone of the rectum, smaller amounts of feces are necessary to create a rectal defecation pressure - TP-3. Therefore, the stool passes more easily through the anal canal. Constipation becomes less severe, but there is pain in the abdomen. Chronic constipation and abdominal pain are recognized symptoms of IBS [16]. There are two proofs of this hypothesis. First, there are no significant diagnostic differences between the FC and the IBS [40]. Secondly, when examining patients with chronic abdominal pain with a history of chronic constipation, the expansion and lengthening of the sigmoid colon in combination with the symptoms of colitis (Figure 6 B) was found (Figure 6 B) [41].

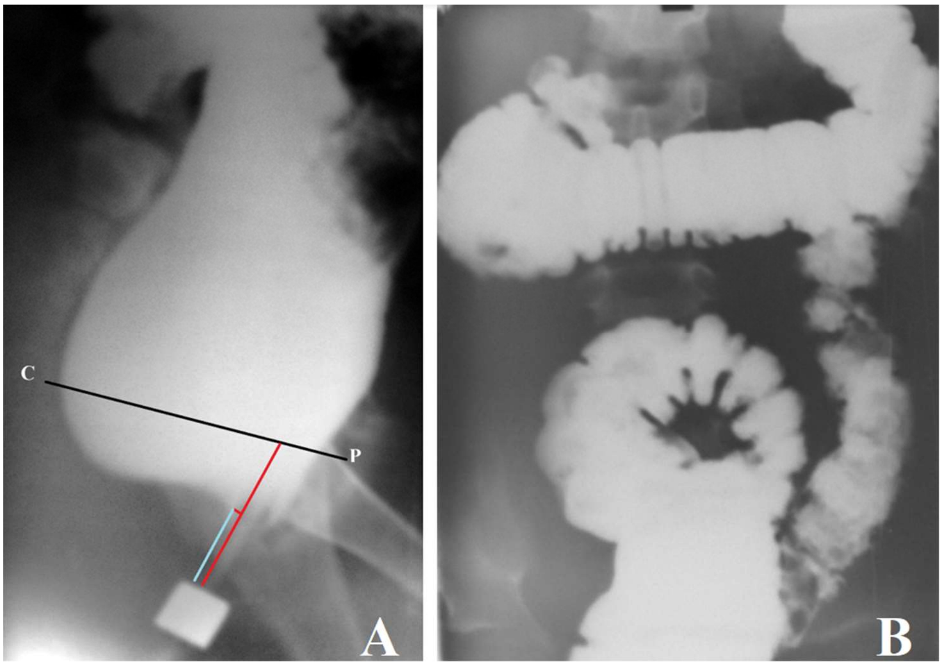

Figure 6. **(A)**. Patient 12 years old with FC and soiling. The length of the functioning anal canal (blue line) is almost 2 times less than the normal length of the anal canal at this age (red line). The upper part of the anal canal is open as a result of stretching (weakness) of the pelvic floor muscles. Conclusion: DPS. (A) 13-year-old patient with complaints of abdominal pain with history of chronic constipation. The sigmoid colon is enlarged and extended (dolichosigma). In the sigmoid and descending colon, areas of spasm and unequal haustration. The contours of the descending colon are not clear. These are radiological symptoms of colitis. Conclusion: IBS.

Conclusion: The variety of the clinical picture of the FC is due to different directions of pathogenesis.

Part 4. Diagnosis of functional constipation.

Rome IV criteria are a good basis for the initial diagnosis of the FC. If the treatment is not effective or a patient is admitted with fecal impaction, X-ray examination is a safe and accurate method of diagnosis FC, determining the degree of megarectum and pathogenesis factors.

Method. The study was conducted by the hydrostatic barium enema [37]. Only in infants up to 3 months the bowel filling was made from a rubber bulb. In other cases, a barium was introduced from the graduated bag. The bottom of this bag at the beginning of the study was located 40 cm above the deck of the table. A barium was introduced into the colon up to the splenic flexure. The radiopaque marker is strung on the tip of the enema. It is in contact with the anus during the study. At least two radiographs (frontal and lateral) have been made after the filling of the colon. On a frontal radiograph the widths of the different parts of the colon are measured. On a lateral radiograph of the anorectum were measured the maximum width of the vertical portion of the rectum, as well as interval not containing contrast medium between the rectum and a contrast marker on the posterior contour of the tip. This gap is a contracted anal canal. Figure 7 shows examples of the analysis of radiographs.

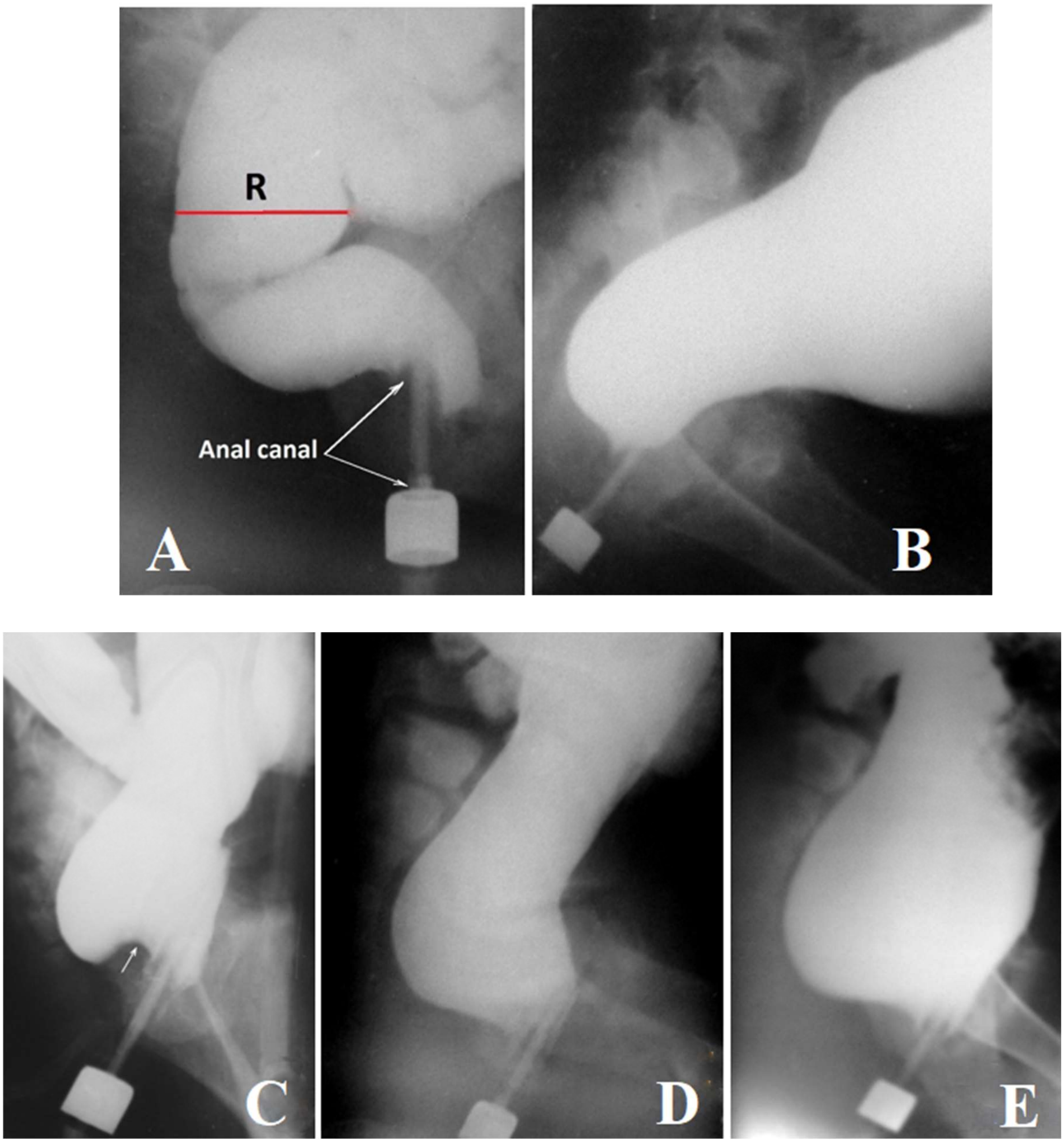

Figure 7. Lateral x-ray images of the anorectal zone. (**A**) In a healthy child, the rectum of normal width has vertical and horizontal branches. As a result of IAS relaxation, barium penetrated the upper part of the anal canal in front of the enema tip. The posterior wall of the anal canal is pressed to the tip as a result of the PRM contraction. The axis of the anal canal is shifted forward relative to the axis of the rectum. (**B**) Patient with Hirschsprung disease. Due to the absence of ganglia in the rectum, there is no neural connection between the rectal wall and PRM. As a result of this, PRM is not contracted and is not relaxed. Therefore, the rectum is represented only by the vertical branch. The aganglionic rectum has a normal

width since there is no colitis. Recto-sigmoid index <1, which indicates the absence of peristalsis in the rectum. (**C**) Early stage FC. As a result of the expansion of the rectum, its horizontal branch disappeared. The anal canal seems long due to PRM edema. This is evident by the impression on the lower wall of the rectum (arrow). (**D**) Due to weakness of PRM, the contrast agent penetrates the upper part of the anal canal behind the enema tip. (**E**) Descending perineum syndrome. A sharp expansion of the rectum is combined with a sharp shortening of the functioning anal canal.

<u>Conclusion:</u> Anorectal inhibitory reflex (reflex relaxation of IAS and contraction of PRM and EAS) is a reliable symptom excluding Hirschspring's disease. The X-ray picture displayed in Figure 7. A. (relaxation of IAS and the contraction of PRM) is the radiological equivalent of the anorectal inhibitory reflex. Thus, barium enema reliably differentiates FC and Hirschsprung's disease. Accurate determination of megarectum, dolichosigma, megacolon, irritable bowel syndrome and descending perineum syndrome allows to choose the correct treatment strategy without resorting to other methods.

Part 5. Treatment

<u>1. Conservative treatment</u> of the FC consists of numerous laxatives. There is strong evidence that stimulant and osmotic laxatives, intestinal secretagogues, and peripherally restricted μ-opiate antagonists are effective and safe. Lubiprostone, acupuncture, anal sphincter botulinum toxin injection, transanal irrigation, biofeedback therapy, pelvic physiotherapy, prucalopride, sacral nerve stimulation, fecal microbiota transplantation - this is not a complete arsenal of tools and methods for treating FC.

Since pathological changes in the rectum, the colon, and pelvic floor muscles increase with age, there is every reason to believe that the likelihood of recovery or clinical and pathological stabilization in childhood is possible as a result of conservative treatment. All pediatricians are unanimous in the opinion that treatment of the FC should be started as early as possible by Polyethylene Glycol. All pediatricians are unanimous in the opinion that treatment of the FC should be started as early as possible by Polyethylene Glycol (PEG). There is no generally accepted treatment program in cases if PEG is not effective. Studies to determine such a program is a priority, because completely unreasonable methods are published. For example, some authors prescribed treatment with high doses of Senna for 7 days for patients with an average age of 8 years with a duration of illness on average 4.3 years. By changing dosages through trial and error with long term radiologic monitoring, they identify patients as nonmanageable cases and operate them, "...to attempt to make laxatives more effective in these patients" [45]. It is known that Senna in conventional doses increases the tone and increases the motility of the colon. But there are no studies on how high doses of Senna act on the colon. It is very likely that by increasing the tone they suppress peristalsis, that "... provoked severe symptoms of abdominal distension, cramping, and vomiting, without producing bowel movements" [35]. It is possible that they increase the tone of the anal canal, that prevents bowel movements. There is no justification for the use of high doses of Senna in general and for diagnostics on this basis of this allegedly nonmanageable cases. There are no excuses "long term radiologic monitoring". Neither this method of conservative treatment, nor the indication for surgery proposed by these authors have any scientific substantiation.

2. The surgical treatment of FC in children

It is known that some heads of pediatric surgical departments do not operate children with FC. Anyway, after my letter was published in Journal of Pediatric Surgery [46], 3 professors reported to me that they are not operate children with FC. I believe that all children have a chance to achieve an acceptable state of the intestine by conservative methods. The task of scientists is to develop a scientifically based program where surgical treatment is an exceptional method in those rare cases when conservative treatment cannot meet the patient's acceptable life.

In a systematic review of published studies, Siminas and Losty pointed out the following disadvantages, which did not allow to determine the advantage of any of the methods of surgical treatment. "Forty-one (91%) studies were case series reporting low-quality evidence (level 4). Most studies involved small numbers of patients. Forty studies stated "medical failure" as the primary indication for surgical intervention. Outcomes showed wide variability in the many studies published. Success was defined by study authors as (1) alleviation of clinical symptoms (58%), (2) reduction in requirement for laxatives (45%), (3) improved bowel frequency (43%), and (4) ongoing use of ACE stoma (8%). Median length of follow-up in studies analyzed was 1.5 years" [47].

a) <u>Antegrade continent enema (ACE) and cecostomy.</u>

Although most of the articles are devoted to the results of treatment with ACE, there is no clear advantage in those of them where the comparison between ACE and secostomy is made. Complications from the ACE operation were reported in 22 of 25 studies (88%) and they were rather common. These included pain at catheterization (27%), skin excoriation/granulomata (27%), stoma leakage (24%), stomal stenosis (22%), surgical site infection (17%), ACE revision from malfunction (8%), stomal prolapse (3%), postoperative ileus (3%), gut perforation (2%), and parastomal hernia (1%). Cecostomy was claimed to be associated with fewer complications than the ACE operation—leakage (18%) and excoriation—granuloma (14%). Follow-up mean was 3.6 yr (0.25–14.5) [47].

I have not found a single article that compares the results of using ACE with retrograde colonic irrigation. I agree with Koch et al. that retrograde colonic irrigation is an undervalued but effective alternative treatment for intractable defecation disorders [48]. Physiologically, ACE has no advantage from a retrograde enema. After disimpaction of the colon, the daily intake of chyme accumulates only in the left half of the colon. Regardless of the place of introduction of the liquid, it surrounds the feces completely, thins it and facilitates excretion. In this case, retrograde enema has a great advantage, as it is not accompanied by serious complications.

The authors of a systematic review recommended: "In refractory IC cases with pancolonic slow transit with overflow incontinence, the surgeon should first consider a trial of distal colonic lavage with enemas or Peristeen-type devices before resorting to the ACE appendicostomy or cecostomy" [47]. If the effectiveness of ACE is determined on average through 3.6 yr., how long does a retrograde enema need to be applied, what to switch to ACE? Keshtgar et al. showed 100% efficacy of Botox injections with the need to reintroduce in 19% of patients with average follow-up 1 yr. [49]. We can only suspect, why did these authors not publish articles about the use of ACE.

Conclusion: You cannot follow the fashion without scientific justification.

b) **Sigmoidectomy.** In 2005, Levitt and Pena described 17 patients with chronic constipation who underwent a sigmoid resection [50]. 14 years have passed since then, but the authors have not published the long-term results of this operation. Many surgeons have used this operation throughout the 20th century. Bernard Duhamel summed up many years of experience: "Recto-sigmoidectomy does not improve these children, while recto-rectal pull-through always cures them" [51]. After the resection of sigma symptoms inevitably return, due to the features of the pathological physiology of the FC. It always has an obstructive nature and therefore in all cases there is a megarectum. After this operation, the entire pathologically dilated rectum, located retroperitoneally and it forms large, fecal masses that hardly pass through the anal canal. At first, after the operation, the number of laxatives is significantly reduced, but the stagnation of the feces gradually leads to an expansion of the descending colon and to the return of initial complaints. Pediatric surgeons performing this operation ignore known scientific facts, referring to studies performed with serious methodological violations. As the upper limit of the normal width of the rectum for children under 6 years of age, the indicator was mistakenly set the same as in adults (6.5 cm) [52]. As a result of this error, of the total number of children with chronic constipation, there was a significant part of patients with the width of the rectum was supposedly within the “norm”, while in fact they had a megarectum. Based on this study, a conclusion was made about the "segmental colonic dilation", which serves as the basis for its resection [21]. The question that functional constipation has an obstructive nature is generally accepted in general gastroenterology, although there are disputes about a certain percentage of slow transit constipation in adults and the elderly. Therefore, in the systematic review for adult’s resection of the sigmoid colon is not applied. There are only two types of surgical interventions that can be used in childhood: colectomy and rectal excisional procedures. (Rectal suspension procedures and RV reinforcement procedures are not used in children, and the effectiveness of sacral nerve stimulation is considered unproven) [53,54]. These methods are used by pediatric surgeons [25,36,55]. Ignoring the extensive experience of general surgeons and, moreover, complicating sigmoid resection by the ACE (Figure 8) is not just a mistake.

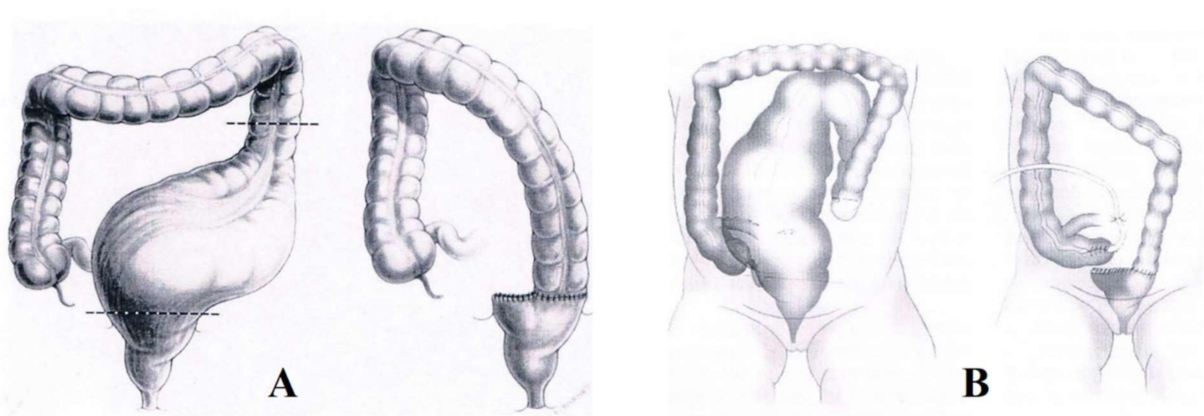

Figure 8. (**A**) Sigmoid resection (2011) [56]. **(B)** Sigmoid resection with ACE (2017) [57].

Posterior resection of the rectum or resection of the posterior rectocele is the most functional method of operation, as it reduces the width of the rectum and thereby eliminates the discrepancy between the width of the feces and the maximum width of the anal canal disclosure.

Indications for surgery in children. "Major colorectal resection and/or stoma(s) should be the option of last resort" [47]. No instrumental methods of research, and especially scientifically unjustified 7-day course of trial and error with high doses of Senna, should not be decisive for a decision on surgical treatment. Only the impossibility of social adaptation with a chronic debilitating condition after using all scientifically based methods of treatment can force the patient to decide. He should be aware that resection of the sigma can only give a temporary effect, that colectomy for slow transit constipation is accompanied by high complication rates and greater long-term post-procedural health utilization than before surgery. It is necessary to consider "...that in surgical studies (usually performed by the proponents of the surgery) bias is both unidirectional (favoring the intervention) and powerful" [47]. The decision on surgery, with very few exceptions, must be made by an adult patient.

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