The pathogenesis of acute appendicitis is an example of the reaction of the digestive tract to the focal abdominal inflammation.

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The literature describes single scientific facts showing that the tone of the anal canal depends on the tone of different segments of the digestive system. The purpose of this study is to clarify the pathogenesis of acute appendicitis (AA) and to determine the effect of local inflammation of the intestine on the tone of its other parts. Material and method. The present work is a review of 5 own published studies (1984-1989) devoted to different aspects of the etiology and pathogenesis of AA. In the first study, a statistical analysis of AA frequency was carried out depending on age, sex, season, day, menstrual cycle. In the second study, the x-ray examination of 100 appendixes removed during an appendectomy was done. In the third study were made the barium enema to clarify the diagnosis of AA. In the fourth study, the anal canal pressure was measured. In the fifth study on the radiographs of the abdomen, we determined the areas of the stomach and its gas bubble, their perimeters, the shape factors, and the maximum and minimum diameters. Results. It is shown that a local inflammatory process in the gut causes an increase in the tone of the stomach, small and large intestines, as well as the anal canal. Conclusion. The present study allows us to hypothesize that an inflammatory process anywhere in the GI causes an increase in the tone of the entire system.

Key words: acute appendicitis; anal canal tone; increasing tone of all intestine; pathogenesis.

Introduction

Acute appendicitis (AA) is the most common surgical urgency in children, with a developing lifespan risk of 8.6% in males and 6.7% in females. The classical pattern of symptoms occurs only in about 50-60% of cases. Literature reported that rates of appendiceal complications vary depending on age: in the overall pediatric population 17-33%, 10-20% in the 10-17-year-old group, up to 80-100% in children younger than 4 years. Complications increase mortality from 0.002% to 3% and morbidity unnecessary appendectomy is reported in 15-40%. A rate of 10-20% negative appendectomies is considered acceptable and is justified by a surgical approach to the equivocal cases to reduce appendiceal complications. Nevertheless, appendectomy is a procedure performed under general anesthesia and even an unnecessary appendectomy accounts for a complication rate of 3-15%, with 2% of cases requiring a reoperation [1]. Antibiotic therapy for acute uncomplicated appendicitis is effective in adult patients, but its application in pediatric patients remains controversial [2,3]. An in-depth understanding of the pathogenesis of AA will help improve the diagnosis and treatment of this disease .

In the literature, OA is considered only as a local process. However, there is reason to believe that the entire digestive tract, including the stomach, colon, and anal canal, reacts in response to local inflammation in the appendix. And this nonspecific reaction is probably present not only with purulent inflammation in other organs but also with inflammation and irritation of the mucous membranes.

The state of the problem. Classically, appendicitis is described as a dynamic disease process that comprises 5 stages over a 24-36-hour period. **(1)** The primary pathogenetic event in most patients with AA is luminal obstruction. This may result from a variety of causes, which include fecaliths, lymphoid hyperplasia, foreign bodies, parasites, and both primary and metastatic tumors. **(2)** During the second stage, stimulation of the 8th-10th visceral afferent thoracic nerves cause a mild to moderate peri-umbilical pain typically lasts from 4-6 hours. **(3)** As intraluminal pressure increases, appendiceal wall perfusion decreases due to arterial insufficiency. This third stage results in tissue ischemia and mucosal

compromise. **(4)** In the fourth stage, bacteria are then able to invade the luminal wall, leading to transmural inflammation. **(5)** At this final stage transmural inflammation extends beyond the appendix, and the parietal peritoneum and adjacent structures also become inflamed. At this stage, the pain is more severe, continuous, and often associated with anorexia, fever, nausea, and vomiting [4,5].

If at the beginning of the disease a sudden recanalization of the obstruction zone occurs spontaneously or because of antibiotic treatment, the inflammatory process may undergo a reverse development [6].

A rate of negative appendectomy (i.e., appendectomy performed after a false-positive diagnosis of AA) as high as 25%in children has been considered an acceptable means of preventing high perforation rates [4].

In recent years, the frequency of recurrent and chronic appendicitis is described on average as 10% and 1%, respectively, of the total number of patients with appendicitis [7,8]. Almost all patients with recurrent or chronic appendicitis can recall at least one episode of an acute attack of abdominal pain resembling an AA that went through without surgery. This suggests that the patient can be operated on AA, while, in fact, there was an exacerbation of the chronic process [5].

This theory of the pathogenesis of appendicitis leaves several questions open. Why fecal masses stagnate in the appendix (AX) up to the formation of fecal stones? What causes significant differences in AA frequency by age, sex, season, etc.? How does the digestive tract react to the inflammatory process in the AX? **Purpose** of this study to explain the difference in the frequency of AA depending on age, sex, season, etc., as well as determine the reaction of different parts of the digestive tract to inflammation in the AX.

Material and methods

The present work is a review of 5 own studies [9-11, 13-14] devoted to different aspects of the etiology and pathogenesis of AA. It analyzes the medical history of 3282 children aged 0.5 to 15 years who applied to the Belarusian Children's Surgery Center with suspicion of AA in 1970-1998. Patients were divided into 5 groups depending on the method of study.

The first group consisted of 2932 patients hospitalized with suspected AA. We performed a statistical analysis of the results of histological studies of the AX, depending on the age, gender, season, time of day, and the presence of menstruation. The census conducted in the same year made it possible to calculate the actual incidence of AA in different age groups. This was also facilitated by the fact that the children's surgical center was the only institution providing emergency surgical care to children in Minsk [9].

The second group consisted of 100 appendixes removed during appendectomy. They were selected by the blind method. The X-ray examination was done both without contrast medium and after injection of the barium into their lumen [10].

The third group consisted of 111 patients admitted from January 1984 to August 1985 in whom the clinical symptoms of AA were doubtful. To clarify the diagnosis the barium enema was accomplished [11].

The fourth group includes 52 patients aged 7-10 years with complaints of pain in the right ileal region, in which anal canal pressure was measured, according to the method described by us earlier. The measurement was performed using an endotracheal tube with a latex cuff, which was connected to a manometer [12]. The obtained data were compared with the results of anal manometry of 20 children of the same age who entered the hospital for scheduled operations (control group) [13].

The fifth group consisted of 87 patients aged 7-15 years, hospitalized with suspected AA. The radiograph of the abdomen was done in an upright position 10 minutes after taking 50 ml of a warm barium. On the radiographs, we determined the areas of the stomach and its gas bubble, their perimeters, the shape factors (the degree of difference of the measured area with the area of the circle), and the maximum and minimum diameters. The contours from the radiographs were taken with the help of a coordinate graph with subsequent computer statistical analysis [14].

Statistical analysis was performed by the method of the Student's t-test. The level of significance was set as $P<0.05$.

Results

The first group. Out of 2832 hospitalized patients with suspected AA, 1694 children were operated (7 appendectomies per 1000 child population -7 ‰). The incidence increased from 2.8‰ at the age of 0-4 years to 8.8‰ at 5-9 years and 10.8‰ at 10-15 years. A more detailed analysis revealed a sharp increase in the incidence at 6 years. From 6 to 8 years, it practically did not change, further increased with a peak of 10-11 years, and then incidence decreased quite sharply (**Figure 1**). Similar graphs were obtained in a separate analysis by the sex. The second peak of frequency increase in girls was observed at 10 years, and in boys at 11. The same graphs with small fluctuations were characteristic of both destructive and non-destructive (catarrhal) forms of AA, as well as for non-operated patients in whom AA was excluded. At the age of 6 and 9 years, the frequency of enlarged lymph nodes in the mesentery increased, especially in girls. A sharp increase in the incidence was in February-May and September. The lowest incidence rate was in the summer months (June-July) when the incidence was more than 2 times lower than in February.

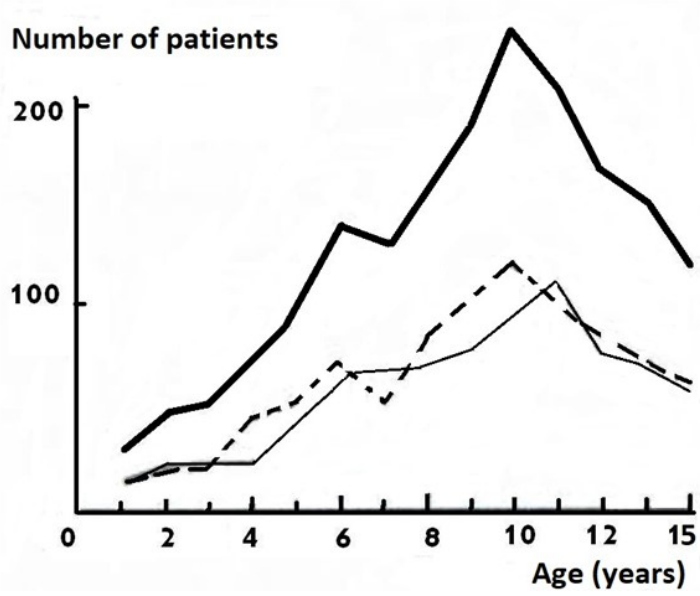

Figure 1. Dependence of frequency of acute appendicitis on age and sex.

Legend: _____ total number;___ males; - - - females.

In daily analysis of the time of occurrence of abdominal pain, two peaks were found: at 7-10 and 16-21 hours. In 125 consecutive girls aged 9-15 years, the incidence of abdominal pain from the onset of the last menstrual period was recorded. In the first days after menstruation, the incidence was minimal. It increased sharply by the 15th day of the cycle, after which it decreased somewhat and increased again after 28 days or more, i.e., after the delay (**Figure 2**).

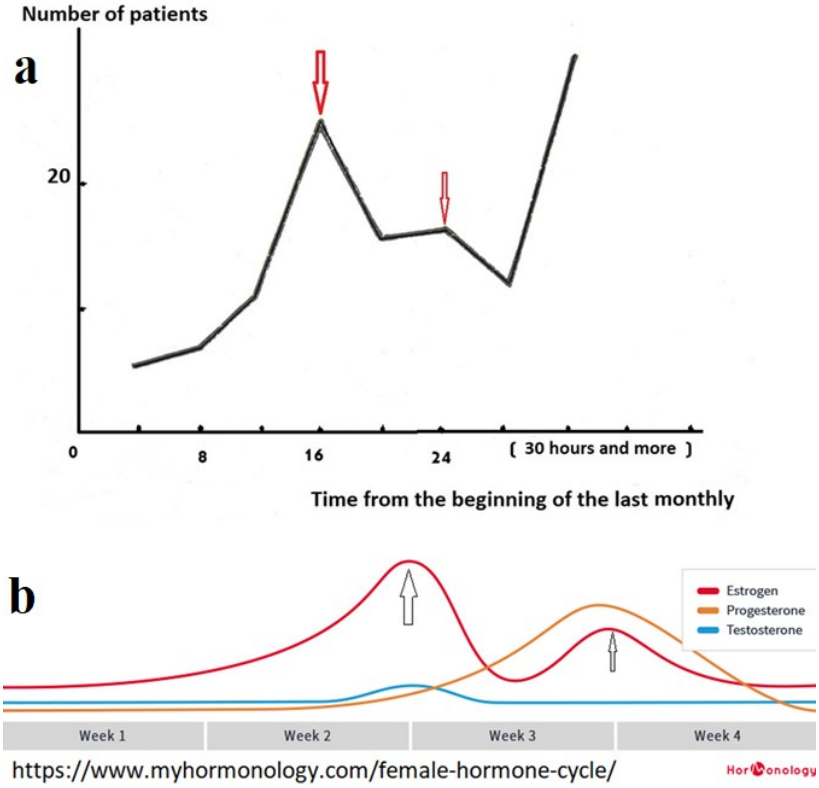

Figure 2. Dependence of frequency of AA on time passed after the last menstruation. An increase in the frequency of acute appendicitis (**a**) corresponds to two peaks of the estrogen excretion (**b**).

The second group. In 65 out of 100 remote AX by macroscopic study was established destructive AA, and in 35 cases was the so-called "catarrhal" or "simple" appendicitis. The results of measurements on radiographs of AX are given in **Table 1.**

Table 1. Results of X-ray studies of appendices (AX).

Dimensions (cm)	Non-destructive AA	Destructive AA	p
Length of the AX	5.5 - 12 7.62±0.24	5.0 - 11.5 7.60±0.20	> 0.2
Width of proximal parts of the AX	0.4 - 0.7 0.61±0.01	0.5 - 1.8 0.72±0.01	< 0.001
Width of distal parts of the AX	0.5 - 0.8 0.61± 0.01	0.7 - 1.9 1.07±0.03	< 0.001
Lumen width of proximal part of the AX	0.2 - 0.6 0.35±0.02	0.2 - 0.09 0.38±0.02	> 0.2
Lumen width of widest part of the AX	0.2 - 0.5 0.31±0.02	0.2 - 0.9 0.59±0.01	< 0.001

All results in the "simple appendicitis" group were the same both in the presence of histological signs of inflammation, and without it. The wall thickness averaged 0.15 cm. This allowed us to estimate the data obtained in this whole group as a norm. The lumen of the AX was passable and uniform throughout its entire length (**Figure 3, a**).

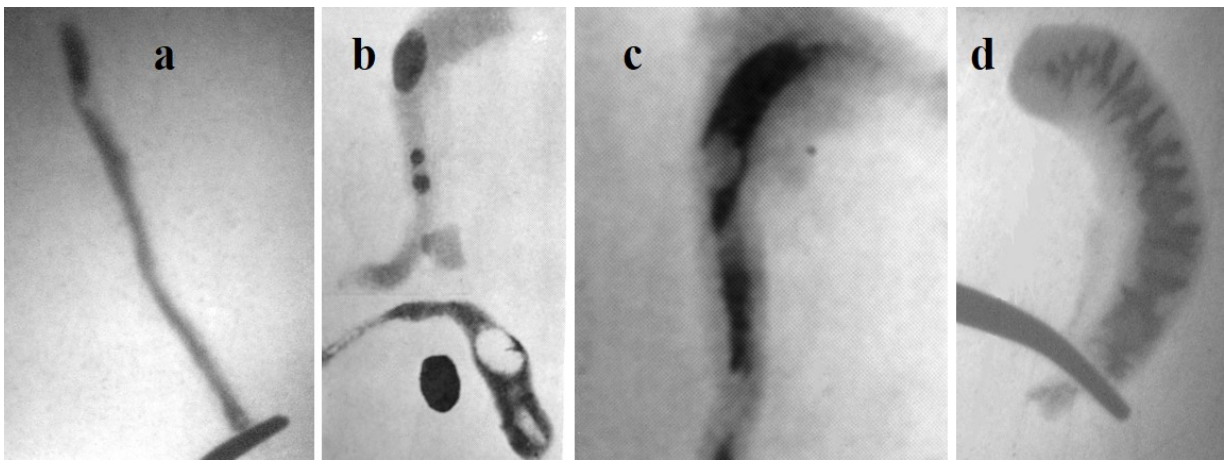

Figure 3. Radiographs of AX. (**a**). Radiograph of unchanged AX uniformly filled with barium. **(b).** In two destructive AX are the radiocontrast (calcified) fecal stones. Areas distal to fecal stones are widened. In the lower AX, after opening the lumen, two cavities. The fecal stone lies next to the AX. **(c).** The oval X-ray-negative formation (fecal

fragment) occludes the enlarged cavity at the apex of the AX. **(d).** Radiograph of destructive AX without foreign inclusions, but with a widened lumen with coarsely modified mucosa.

The width and its lumen at the distal part of the AX in destructive AA were significantly wider than in the norm. The thickness of the wall is on average 0.25 cm. The contrast stones were found in 8 cases, low-contrast - in 12, X-ray negative - in 8, disparate contrast inclusions - in 10, foreign bodies - in 2, and unformed stools 2 observations (**Figure 3, b, c)**. Thus, fecal stones and foreign bodies were found in 42 (65%) of 65 patients with destructive AA. As a rule, the width of the stones was much larger than the width of the lumen of the cranial part of the AX. In 20 observations, despite the absence of any inclusions, the width of the closed cavity was much wider than the norm, or, despite the use of high pressure, it was impossible to introduce a contrast agent into the zone of the greatest inflammation. The relief of the mucosa in them was rough, indicating sclerotic changes (Figure 3, D). Only in 3 (5%) observations with phlegmonous appendicitis, the PX did not differ from normal ones.

The third group. In 78 (70%) of 111 patients, AA was excluded based on barium enema. The lumen of AX was equally narrow with a length of at least 6 cm. Its contours were parallel and it itself was convoluted (Figure 4, A). The dome of the cecum had convex contours, and its height corresponded to the age norm, which we established in the previous study [12].

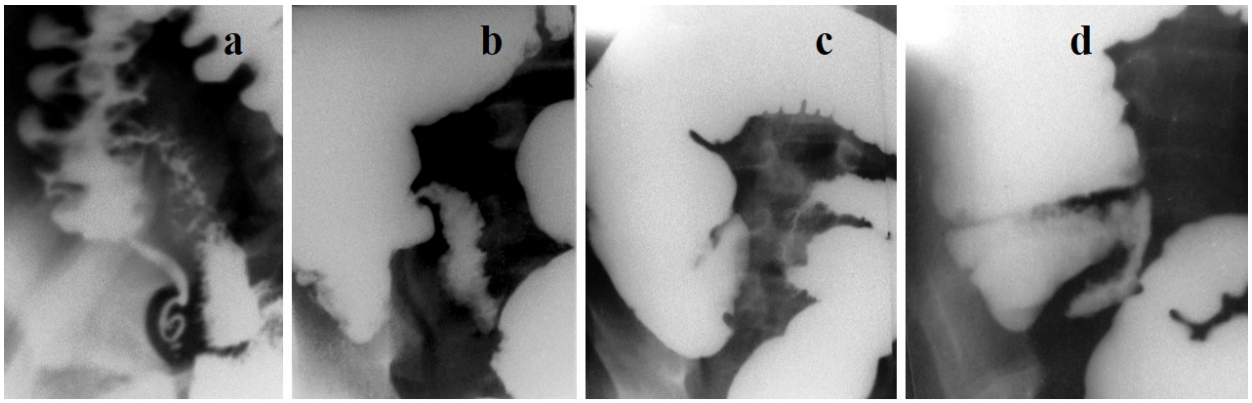

Figure 4. X-ray signs of destructive appendicitis. **(a).** The AX is uniformly and deeply filled with barium. Acute appendicitis is excluded. **(b).** Concavity of the inner part of the dome of the cecum in the patient with destructive appendicitis. The ileum and sigma are removed from the cecum. This is a symptom of the

"window". The distance between cecum and sigma is occupied by an omentum. **(c).** The inner contour of the cecum is slightly concave and uneven. Spasm of sigma located opposite the cecum and symptom of the "window" indicates the presence of inflammation between the cecum and sigmoid colon. **(d).** There is a concavity of the inner contour of the cecum in combination with a sharp shortening of the dome. Spasm of the terminal ileum and symptom of the "window" make the diagnosis of AA obvious.

In 4 out of 78 cases where AA was excluded, appendectomy was performed, but pathology in the AX was not found. In 21 (19%) patients, based on the data of barium enema a conclusion was made about the presence of AA. In 20 of them, a destructive appendicitis was revealed during the surgery. In one patient, the abdominal pain disappeared after the barium enema, which made it possible to abandon the operation. The conclusion about the presence of AA was given based on the detection of radiological symptoms: in 16 patients, the AX was not detected, in 4 cases, the contrast medium penetrated the AX at a depth of 1.1-3.0 cm. In these cases, the internal contours of the AX were uneven, and the AX itself was straightened, which indicates the rigidity of the tissues. More reliable were the symptoms from the dome of the cecum. In 14 patients there was a pronounced concavity of the inner contour of the dome of the cecum, which is considered a convincing symptom of AA (**Figure 4, b, c**) [15]. In 5 children this concavity was not, but we noticed that the height of the dome of the cecum was significantly less than the norm (**Figure 4, d)**. In addition, in 8 cases, a sharp narrowing of the sigmoid colon located near the AX was found. In 6 cases, a spasm of the terminal ileum was determined. Normally, the sigmoid and small intestine are superimposed on the dome of the cecum. At AA, between these intestinal segments, a space was detected - the "symptom of the window".

In 12 (11%) patients, the radiographic data were inconclusive. Although the AX was not filled with contrast medium, the dome of the cecum and the adjacent intestinal sections had normal dimensions and configuration. Eight patients were operated on. In 2 patients a destructive appendicitis was revealed, in 2 a chronic

process was detected. At 2 there was a simple appendicitis, and in 2 observations of inflammatory changes in the appendix was not found.

The fourth group. In children of the control group, immediately after the endotracheal tube with an inflated balloon was lowered into the anal canal, the pressure was raised to 80-100 mm Hg. This so-called reflex pressure is caused by the reflex contraction of the external anal sphincter in response to the stretching of the anal canal wall. Within 0.5 - 1 min, the pressure progressively decreased and was established stably in the range 43.0 ± 0.8 mm Hg. This pressure, called basal pressure, is mediated by a tonic contraction of the internal anal sphincter. After injecting 50 cm^3 of air into the rectum through the channel of the measuring device, a slight increase in pressure to 55-60 mm Hg was immediately observed. We called it reactive pressure. After this, the pressure slowly declined by 10-15 mm Hg. below the basal level with a gradual recovery to the basal level for 4-11 seconds. The drop-in pressure below the basal level is due to the reflex relaxation of the internal anal sphincter - a rectoanal inhibitory reflex **(Figure 5).**

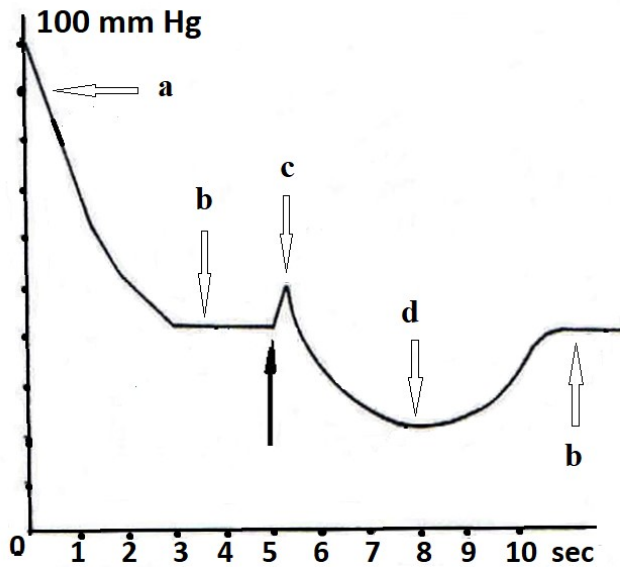

Figure 5. Pressure profile of anal manometry. **(a).** reflex pressure; **(b**). basal pressure; **(c).** reactive pressure, **(d).** anorectal inhibitory reflex. A large solid arrow indicates the moment of air injection into the rectum.

In 19 out of 52 children with complaints of pain in the right iliac region, the diagnosis of AA was excluded (subgroup A). In 15 (45%) of the 33 operated children, a simple AA

was found (subgroup B). In 15 (45%) patients, destructive AA was found (subgroup B). In three cases, no pathological changes in the AX are found (Table 2).

Table 2. Results of the anal canal manometry in children with suspected AA.

Anal canal pressure	Subgroup A (1)	Subgroup B (2)	Subgroup C (3)	P
Basal pressure	45 - 60 53.6 ± 1.1	60 - 80 69.3±1.7	55 - 90 73.0 ± 3.4	P1-2 <0.001 P1-3 <0.001 P2-3 > 0.2
Reactive pressure	45 - 75 58.5 ± 2.5	70 - 130 91.0 ± 2.7	70 - 150 111.3 ± 5.8	P1-2 <0.001 P1-3 <0.001 P2-3 <0.01

Only basal and reactive pressures were significantly higher in patients operated on for, both simple and destructive AA, compared with non-operated children. In patients with destructive appendicitis, the pressure was higher than with a simple one. But statistically significant was the reactive pressure increase.

Fifth group. In 30 out of 87 children with suspected AA, destructive appendicitis was diagnosed after the operation. In 14 cases, superficial inflammation was detected. In remaining, 43 patients diagnose with AA were excluded and they were discharged without surgery. All the parameters, including the area of the stomach and its gas bubble, their perimeters, shape factors, as well as the maximum and minimum diameters with high reliability (P <0.001) were less with destructive appendicitis compared with unoperated children. Differences between the parameters of patients with destructive and simple AA were not significant (P> 0.5).

Discussion

A sharp increase in the frequency of AA at 6, 11, and 25 years, as well as the difference in sex completely correlate with the excretion of sex hormones. Up to 7

years, the concentration of estrogens in children of both sexes is the same. Estrogen excretion increases dramatically at 5-7 years, then growth slows somewhat and again increases in females to 10-11, and in males to 12-13 years with a maximum in the third decade [16,17]. After 7 years, the amount of estrogen in females increases more than in males with a one-year lag in males as in AA [18]. Similar changes are also described with respect to androgens, follicle-stimulating, and luteinizing hormones [19]. Meanwhile, the increase in the frequency of AA in males 10-11 years old coincides with the decrease in the concentration of serum cortisol [20].

In our study, there was a significant increase in incidence AA in the middle of the monthly cycle, which also coincides with an increase in estrogen excretion [21]. In modern literature, estrogens are considered as amplifiers of cellular proliferation and humoral immune response [22]. Thus, the influence of sex hormones, including estrogen on the development of AA in children is not in doubt. Probably, hormones are one of the triggers of the volumetric increase of the epithelial and lymphoid tissues of the AX. Given that the absolute level of sex hormones in children is lower than in adults, the observed dependence is not due to the absolute level, but to a sharp rise in the excretion of sex hormones.

As shown by our X-ray studies of the AX, the lumen in the distal part of the AX is expanding in most cases of destructive appendicitis. This is due to obstruction in the more proximal part of the AX and the formation of a closed cavity with high pressure in it. In 42 (65%) of 65 cases, obstruction of the lumen appeared due to the overlapping of the lumen by fecal stones and foreign bodies. In 16 (25%) cases, the expansion of the lumen of the AX indicated that there was a closed cavity with high pressure. In 4 (6%) cases, in spite of the use of high pressure, it was not possible to fill the AX with a contrast agent, which implies obstruction or obliteration of the AX lumen, and only in 3 (4%) cases of phlegmonous inflammation, there were no signs of a closed cavity. All inclusions (fecal stones, foreign bodies) were much wider than the lumen of the proximal part of the AX. This suggests that they could not penetrate the AX on the eve of an acute attack.

Symptoms of the disease appear soon after the onset of obstruction of the lumen. But it is obvious that feces were stuck there, increased in size, and had time to be encrusted by calcium long before the appearance of complete obstruction. This is also evidenced by expressed sclerotic changes in the wall of the AX. The mere fact that the liquid chyme that is ingested in the AX from the ileum was not expelled by the peristaltic wave, indicates serious damage to the neuromuscular function of the AX before the appearance of fecal masses. Di Sebastiano with co-authors applied special methods of studying AX, where there were no signs of inflammation in the usual histological examination. They found neuroproliferation in combination with an increase in neurotransmitters SP and VIP, which could be the cause of pain in the right ileal region. The authors suggested that as a result of the interaction of the nervous and immune systems, neuroimmune appendicitis appears as a separate pathological entity .[23]

Some researchers believe that destructive appendicitis in many cases is the culmination of a process that unfolds because of changes that have occurred in the AX in previous less severe attacks. Repeated attacks AA intensify the phenomenon of sclerosis, right up to the obliteration of the AX lumen [24]. When the AX develops hyperplasia of the mucosa, mainly its lymphoid elements, because of an immunological reaction to a viral infection or an allergic process, this leads to a sharp narrowing of the lumen of the AX. If the complete obstruction of the AX has not occurred, the inflammation undergoes reverse development, but as a result of damage to the nervous apparatus, the peristalsis of the AX is impaired, and scar changes remain in the mucosa that disrupt the normal emptying of the AX. This contributes to the retention of feces in it. They eventually become denser, increase in volume, and are encrusted with salts. Repeated immunological reaction of the mucosa against the background of coprolites and / or scars leads to obstruction of the AX and development of AA in the stages described above.

The concavity of the inner contour of the cecum, the narrowing of the lumen of the sigmoid colon and ileum cannot be explained by the pressure of the masses, as

some researchers have claimed [25]. With intra-operative verification of radiologic symptoms, we found that these signs do not depend on the magnitude and rigidity of the AX, which may be out of contact with these parts of the intestine. We believe that these symptoms, as well as the decrease in the height of the cecal dome, is described by us, are due to an increase in the tone of the smooth muscle of these parts in response to the irritation emanating from the inflammatory focus [11]. The "window symptom" described by us is probably due to an omentum that surrounded the inflamed AX and pushed back the bowel loops .

We found that increased tonus extends to other parts of the digestive tract. Basal and reactive anal pressures were significantly higher ($P < 0.001$) in patients with AA compared to non-operated children. In destructive appendicitis, the pressure was higher than with a simple one. But this difference was significant ($P < 0.02$) only for reactive pressure [13]. Since the internal anal sphincter is a thickened continuation of the circular layer of the colon, it can be concluded that its tone reflects the tonic state of the gut.

On the radiographs of the stomach with barium, a highly reliable decrease in the area of the stomach and the gas bubble, their perimeters, shape factors, as well as the maximum and minimum diameters in destructive appendicitis were compared with non-operated children were found. These results indicate an increase in the tone of the stomach in AA. In this way, the appearance of vomiting and pain in the epigastrium in the first hours of the disease can be explained by the contraction of the stomach, because of increasing its tone.

Based on the studies described above, we concluded that the inflammatory process in AX leads to an increase in the tone of the entire digestive tract. Moreover, the closer the intestinal segment is to the inflammation focus, the higher its tone. It is likely that the described phenomenon is not strictly specific for AA. Since the reaction of the intestine, although to a lesser extent, is observed with catarrhal, i.e. not purulent, inflammation, it can be assumed that inflammation in the mucous membrane (ulcers of the stomach and duodenum, esophagitis, gastritis,

duodenitis, enteritis colitis) can lead to increasing the tone of the entire digestive tract .

Shafik's research with co-workers has shown that the motor function of different parts of the digestive tract interacts with each other. They discovered the decline of the intestinal pressure upon rectal distension [26]. They called the left colonic contraction upon rectal distension "recto-colic reflex". This reflex acts at defecation to feed the rectum successively with fecal material until the colon is emptied [27]. Lower esophageal sphincter and pyloric sphincter contraction and esophageal and gastric relaxation during rectal distension appear to delay gastric emptying [28]. Interaction of intestinal segments can be both retrograde and antegrade. When food gets introduced into the stomach, a coordinated response via stretch receptors, neuropeptides, and the enteric nervous system activate the gastrocolic reflex, which in turn increases the motility in the colon to make room for more food [29].

From a scientific point of view, the interactions described above are not reflexes, since there is no reflex arc and extraintestinal centers through which certain intestinal segments are activated. We are talking about the transmission of impulses through the intramural nervous system and non-specific activation of the entire intestinal tract. Several studies have indicated an overlap between gastroesophageal reflux disease (GERD) and functional dyspepsia (FD) and irritable bowel syndrome (IBS). The GERD-IBS overlap ranges from 3-79% in questionnaire-based studies and from 10-74% when GERD has been diagnosed endoscopically [30]. Analysis of the literature and the present study allows us to hypothesize that a chronic inflammatory process in the esophagus causes a stable change in the motor function of the small and large intestine through the intestinal intramural nervous system, i.e., FD and IBS are a consequence of GERD.

The regularity described above suggests that stimulating laxatives, increasing the peristalsis of the rectum to expel feces, simultaneously cause an increase in the tone of the anal canal, which prevents bowel emptying. This explains the recommendations of the pharmacists to treat with

stimulant laxatives in short courses and the senselessness of exceeding the maximum recommended doses. At the same time, a sharp decrease in anal pressure (gaping anus) with intestinal intussusception in children reflects a sharp decrease in the tone of the colon. This condition is dangerous due to the perforation of the colon. Therefore, the pressure and time of conservative reduction of intussusception must be limited [31].

Conclusion

We hypothesize that local abdominal inflammation causes an increase in tone in all parts of the digestive tube. The tone of anal pressure can be an indicator of the state of the intestine.

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