Gastrointestinal Pathology in Autism: Description and Treatment

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Abstract

This paper, adapted from conference presentations, describes various lesions found in the gastrointestinal tracts of children with autism spectrum disorder (ASD) using endoscopy. Some of these lesions, which are illustrated in color, are common to children with ASD, while others are similar to those found in neurotypical children. While not curable, all of these lesions are treatable. What is exciting is that most of these children respond extremely well to some combination of a restricted diet, anti-inflammatory medication, probiotics, antibiotics, antifungals, and digestive enzymes.

Keywords: gastrointestinal pathology, autism spectrum disorder (ASD), gastrointestinal tract, lymphonodular hyperplasia (LNH), esophageal disease, gastric disease

For the past seven years, I have specialized in treating children who have an autism spectrum disorder (ASD). I have seen many lesions throughout the entire gastrointestinal tract in the hundreds of children in whom I have performed an endoscopy. I will describe for you what I have seen in anatomic order (from the mouth down to the colon) and include figures, all of which were taken in children on the autism spectrum. Some of these lesions are exceedingly common in children with ASD, while others seem to be no more common than in neurotypical children.

Starting in the back of the throat, we find lymphonodular hyperplasia (LNH). LNH means that the lymph nodes—clusters of immune cells—are enlarged (i.e., hypertrophied) in response to a particular immunologic trigger. This response might be caused by contact with everyday viruses or protozoa, bacteria, food allergens, or something unexpected and unusual. Any kind of immunologic response can cause enlargement of the lymphoid nodules, and while that is a normal and appropriate response, it should not be chronic. In other words, one would expect that with the passage of the triggering antigen, the immune response would dissipate.

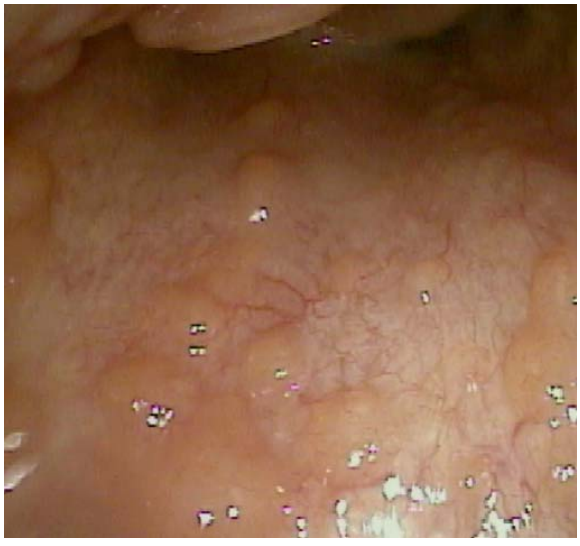

Figure 1. A soft palate with excessive LNH

The bumps in the soft palate shown in Figure 1 are enlarged lymphoid nodules. Any anesthesiologist or ENT will tell you this degree of LNH is excessive—they do not see these in healthy children. This is an indication, at the very top of the GI tract, that these children are mounting a vigorous immune response to something. That's not to say that this is a disease--LNH itself is not a disease, it is an exuberant immunologic response.

Esophageal Disease

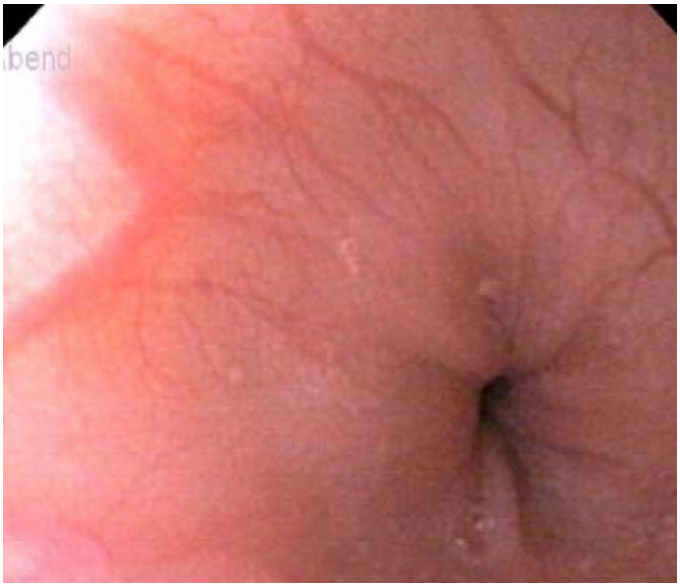

Figure 2. A normal esophagus with healthy mucosal vasculature

The hole in the middle of the normal esophagus shown in Figure 2 is the entrance to the stomach. Notice that it is pink, there is a healthy blood-vessel pattern, and there are no erosions anywhere (Fig. 2).

In the esophagus of these children we most often find “eosinophil-laden” esophagitis. The difference between “eosinophil-laden” esophagitis and eosinophilic esophagitis is determined

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by how many eosinophils (a subpopulation of white blood cells—the inflammatory cells) are found in a high-powered microscopic field. The normal range in the esophagus is between 0 and 2. Most of the children with ASD who come to us for upper endoscopy will have somewhere between 5 and 15 (indicative of eosinophil-laden esophagitis), but we often see over 20. Although acid reflux esophagitis can also cause an increase in the mucosal eosinophil count, the other characteristic features of reflux esophagitis are characteristically absent. If it is over 20 eosinophils per high-powered field, it is classic eosinophilic esophagitis. This is not found in the setting of reflux disease.

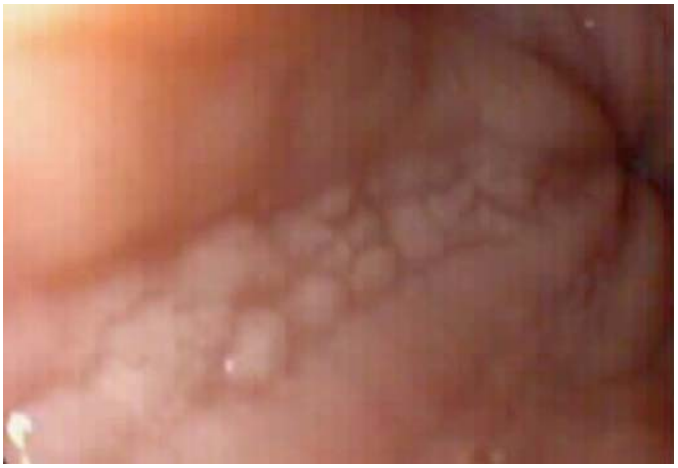

Figure 3. An eosinophil-laden esophagus with linear streaks

One of the common things we see endoscopically in the eosinophil-laden esophagus is these linear streaks of nodularity (Fig. 3). No one would say this exaggerated immune response is normal. Biopsies confirm that it is some sort of immune response, but whether that response is allergic (the term *allergic* always means IgE mediated), or some other non-IgE-mediated immune response is not clear.

We see a great deal of classic gastroesophageal reflux disease (GERD) in ASD children. Reflux is a *symptom*, not a primary diagnosis—it occurs because something is not going right. If the intestines are unable to move food effectively from the mouth down to the anus, then it comes up as reflux. Hypomotility in the gastrointestinal (GI) tract in ASD children is so common that almost all of those I have scoped have some degree of clinical (but not necessarily histologic) reflux.

Erosive esophagitis occurs when the damage from the acid reflux is extreme. The esophagus is not designed to handle the stomach's hydrochloric acid; prolonged exposure invariably causes damage to the esophageal lining. If untreated for a long period of time (months to years) there's an increased chance Barrett's esophagus will develop; the cells of the mucosa in the lower esophagus actually change from one type to another, usually as a result of the chronic exposure to acid. Once Barrett's mucosa has formed, there is an increased statistical chance of developing esophageal cancer. The vast majority of Barrett's patients in the adult data do *not* develop cancer, but there's very little pediatric data. Finding Barrett's esophagus in children is practically unheard of—it's a very, very rare phenomenon. Ordinarily it's the result of years and years of reflux; we found it in a number of ASD children, suggesting either that their reflux is excessive, or that some other immunologic trigger is causing an inflammatory response.

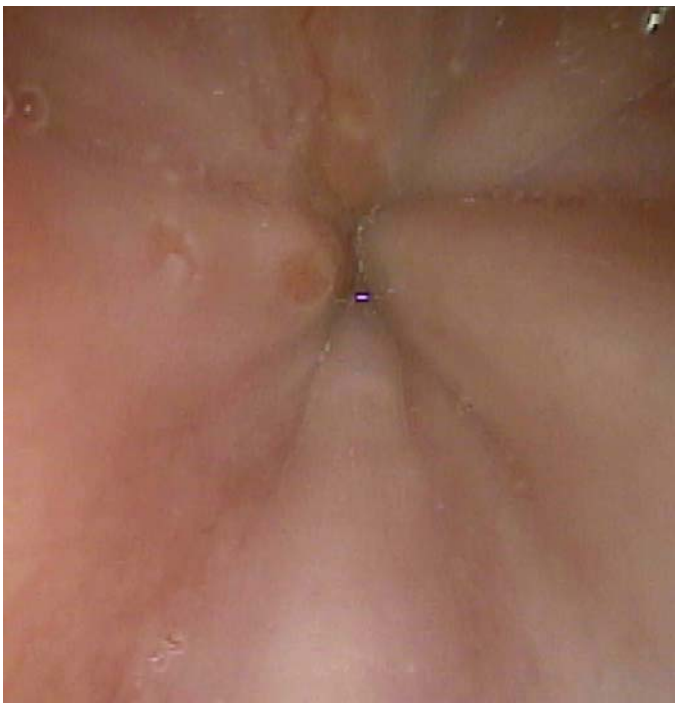

Figure 4. Barrett's Esophagus with salmon-colored patches

Around the entrance to the stomach, there are salmon-colored patches visible—that is the Barrett's mucosa, our signpost (Fig. 4). Microscopically it consists of different types of cells than those seen in normal esophageal mucosa. The Barrett's we are seeing in these children is somewhat unusual, because it is often not accompanied by other changes of reflux—ordinarily you find a very macerated, red, inflamed, oozing esophagus in the area of the Barrett's, but here the surrounding tissue looks pretty good (Fig. 4).

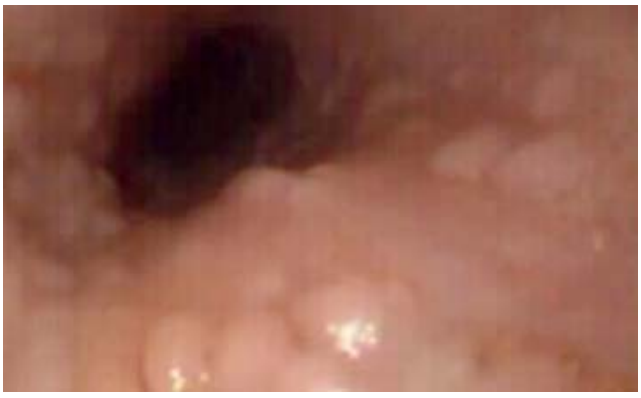

Figure 5. Nodular esophagitis

Figure 5, showing nodular esophagitis, was taken in an autistic 38-year-old man. He had endured more than thirty years of ongoing GI symptoms before he was finally scoped and biopsied. This was the worst I have ever seen—his symptoms were very, very intense and he had tremendous pain. Did he

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remain autistic after we started treating him? Yes, absolutely, he was very low functioning, but his pain disappeared. He could not talk and he could not look you in the eye, but he could e-mail, and he was very insightful and intelligent. He knew about politics and he commented on everything—a very interesting man. Treatment changed his life, because when he had pain, his OCD would make him take off all his clothes, regardless of where he was. Since he was an adult, people frequently got scared, and called the police. Essentially he became a shut-in. Since he was very intelligent and liked to be out in the world, getting rid of his pain and the resulting behavior made major improvement in his quality of life possible.

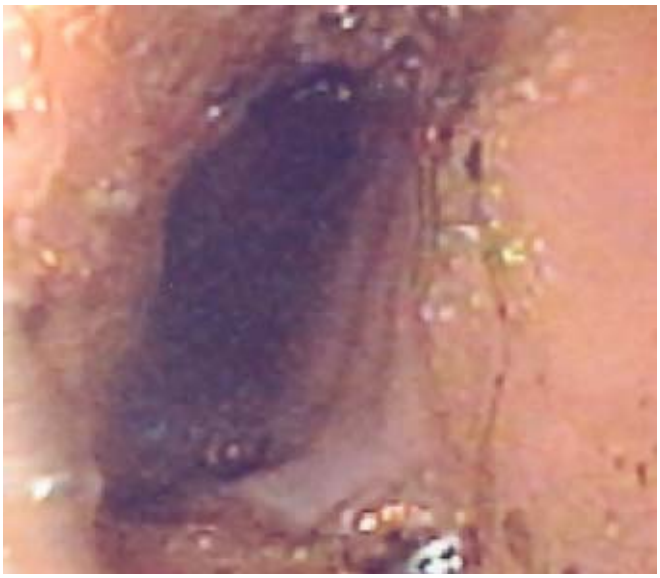

Figure 6. Bile reflux esophagitis

Figure 6 depicts bile reflux esophagitis. Looking down the esophagus, you can see a mix of bile and fecal contents (Fig. 6). The hypomotility (abnormally slow movement) was so severe that fecal waste actually came back up. This child's breath smelled like feces.

Much less common, we have seen *H. pylori*, the painful bacterial infection that is associated with stomach ulcers, at the junction of the esophagus and the stomach in the ASD kids we have scoped—a very unusual location; furthermore, three or four have had candida in the esophagus, typically seen in adults who are immune-suppressed (e.g., cancer and chemotherapy patients, and recipients of organ transplants).

A neurotypical child with any of these esophageal lesions would complain bitterly, but even very high-functioning children with ASD usually have difficulty interpreting and expressing what they feel physically—never mind the children who cannot speak at all. Since they can't explain what is wrong, the children I see have tantrums, they point to their throats and bang on their chests, they are irritable after meals, and they avoid food because swallowing hurts. These children are not stupid, as the parents well know; they are usually highly intelligent, and when they do things, they do them for a reason. I believe that even their "stims" have some logic, some precision, but putting that issue aside, certainly when they avoid food they are doing it for a reason. Some children with (and without) ASD have pathologic food avoidance for a psychiatric reason, but you cannot assume it is psychogenic until you have proven that the lesions in the preceding photos are not present in the child.

Gastric Disease

Some of the lesions we see in the stomach are called reactive gastropathy. This is a microscopic finding; anything that enters the stomach can theoretically cause a reactive gastropathy. In practice it is not something we find very often in normal adults, but about 80-90% of the ASD children I scope have it. At first I thought the reactive gastropathy might be caused by supplements or vitamins they were taking, but now I have a very large population of children who were treatment-naïve when they came in for their endoscopy but who nonetheless have it, and that suggests that it is something inherent to the disease process itself, i.e., it can't be from anything done as a treatment, since the subjects have not yet been treated. Figure 7 depicts the microscopic appearance of reactive gastropathy.

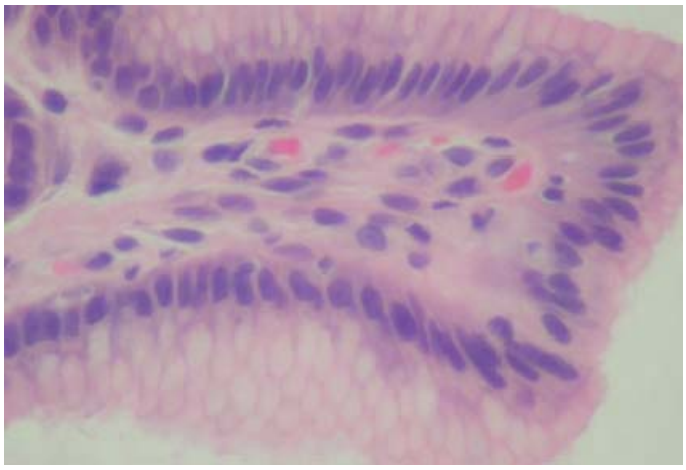

Figure 7. Microscopic view revealing reactive gastropathy

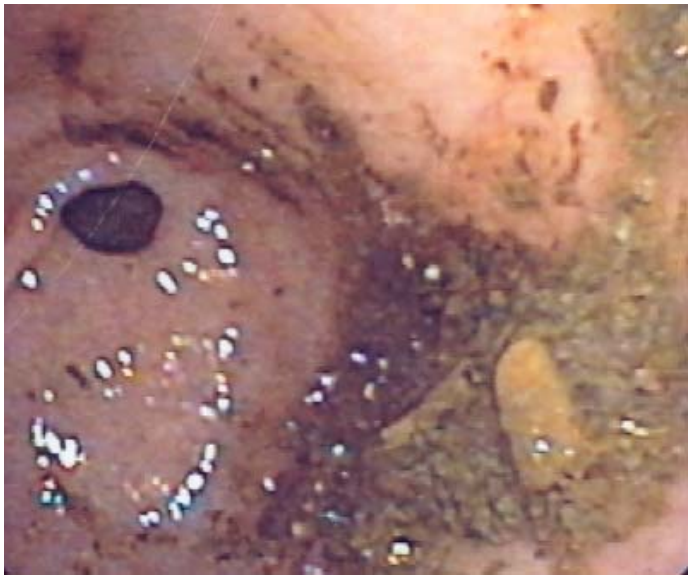

Figure 8. Stomach with bile reflux and stool.

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Figure 8 shows the hole leading from the stomach down into the duodenum. As mentioned above, when the motility is poor the consequence is that the intestinal contents can come back up into the stomach and sometimes even out the mouth. Most ASD children have hypomotility—they do not move things well from the mouth down to the anus. It occurs primarily in the colon, which is why they are so often constipated.

We have a subset of children whose hypomotility occurs from the antrum to the duodenum, and these children have very distended bellies. We see two types of distention: lower abdominal, like a pregnant woman, indicating that the intestines or the colon themselves are full of gas or stool, and upper abdominal, just below the rib cage. Upper abdominal distention usually occurs because food contents are not moving out of the stomach; we have two children who needed feeding tubes in the jejunum to bypass the stomach for this reason.

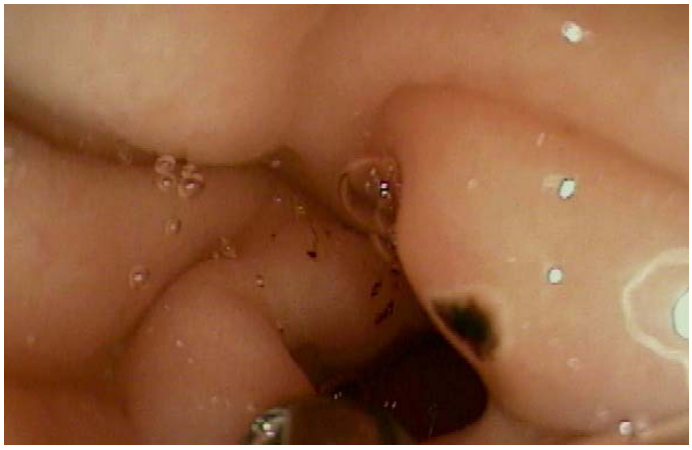

Figure 9. A classic acid peptic ulcer.

Figure 9 depicts a classic acid peptic ulcer. The ulcer is the area that looks like a black patch with a white rim. It was bleeding; it caused a lot of swelling in this child, and he was vomiting a lot. Before the endoscopy, the parents heard several opinions on the cause of the vomiting: reflux, food intolerance/allergy, and willfulness—"just another autistic behavior." I cannot emphasize enough how important it is to thoroughly investigate GI symptoms in a child on the autism spectrum.

We are finding inflammatory polyps in these children. They are not pre-cancerous, they are caused by stomach inflammation. The polyp in Figure 10 suggests ongoing inflammatory activity in the stomach, and perhaps elsewhere.

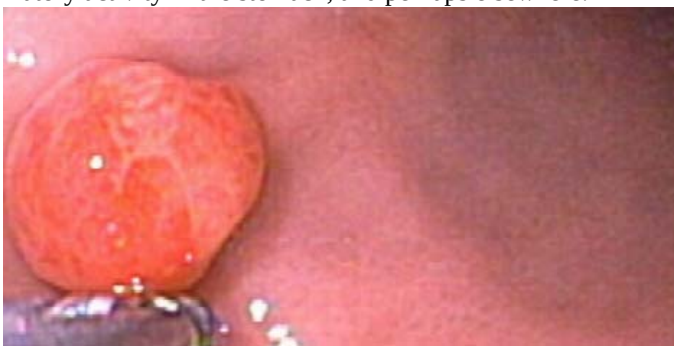

Figure 10. An inflammatory polyp

Figure 11 shows gastric ulcerations, but they are not acid-peptic—these are more punctate (characterized by dots or points); there is an area of redness around a small central core. We see a lot of these in ASD children.

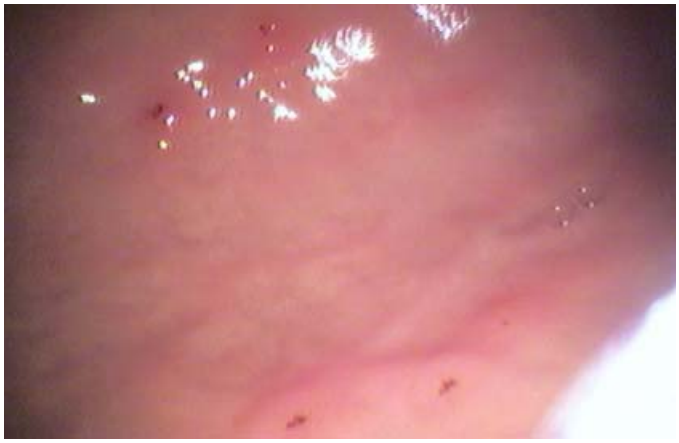

Figure 11. Gastric ulcerations

We have seen nodular gastritis that is not *H. pylori. H. pylori* is a bacterial infection, and children who have it in their stomach will have a very nodular gastritis. We are seeing the nodular gastritis both in the presence of *H. pylori,* and in its absence as shown in Figure 12.

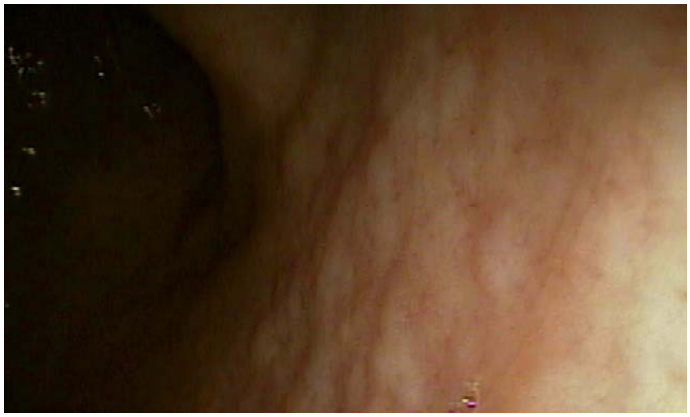

Figure 12. Nodular gastritis

The stomach in this photo is nodular and brownish—it should be smooth and pink; this is an unhealthy stomach (Fig. 12). The biopsy showed inflammation, and we searched high and low but found no sign of any kind of bacterial infection, *H. pylori* or otherwise.

A neurotypical child with any of these lesions would complain, particularly after a meal; maximal output of acid occurs about half an hour after eating. The classic location for acid peptic gastritis is between the belly button and the bottom of the sternum. Symptoms of gastritis include pain after eating, waking at night (irritable, not playful), vomiting, sweating, pallor, and reflux. In non-verbal children, watch for tantrums, irritability, food avoidance, head banging, stomach poking, reflux, and abnormal posturing.

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Figure 13. A child posturing

Figure 13 is a photo of a child posturing. A family from Geneva, Switzerland first brought this behavior to my attention. Their child spent an inordinate amount of time leaning over tables and armrests. We found colitis and other GI pathology in this child, and when he was treated, his stools and his pain normalized and this posturing activity disappeared completely. After that I began paying attention to posturing, and I found that many of these children do it, in all sorts of creative ways. We invariably find disease on endoscopy, and when we treat it properly, the posturing always disappears—it is *not* a "stim." When a child does this, even if there are no other overt symptoms, I assume it is abdominal pain until proven otherwise.

Lesions of the Small Intestine

The stomach leads into the small intestine, comprising the duodenum, the jejunum, and the ileum. It is the longest part of the bowel, important because it is where the body absorbs calories and nutrients. If a child's small intestine is not working, there is growth failure.

Celiac disease is one of the things we sometimes find in this young ASD population, but surprisingly rarely, considering that this group is exceedingly sensitive to gluten. Because celiac can only be diagnosed with certainty while the child is ingesting gluten, it is critical to obtain baseline celiac antibodies ***before*** beginning a gluten-free diet.

The photo in Figure 14 shows a classic duodenal acid-peptic ulcer. There is so much swelling that the lumen of the duodenum is narrowed to about 4 or 5 millimeters, so barely any food can get through. The lower half of the photo shows the exudate, the slimy pus-like material that is being exuded out of the ulcer (Fig. 14).

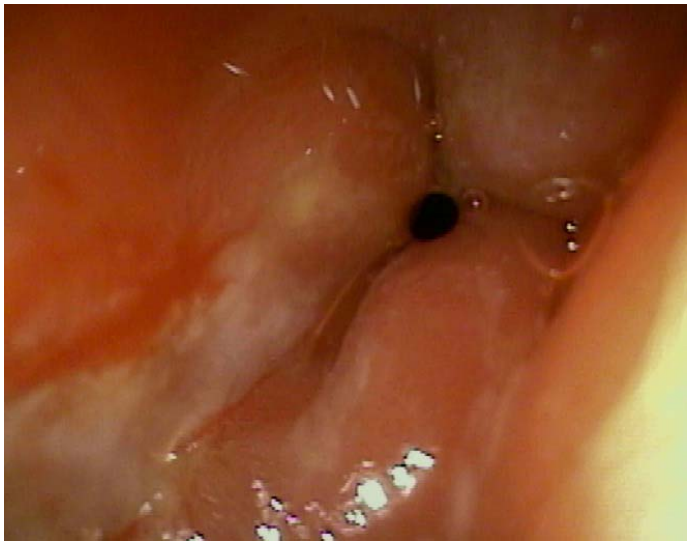

Figure 14. A classic duodenal acid-peptic ulcer

We often see duodenal aphthous ulcers (fig. 15). The term *aphthous* refers to a very small ulcer, surrounded by a ring of redness (erythema). (A chancre sore in your mouth is an aphthous ulcer.) These are very commonly seen in Crohn's disease, but they are not exclusive to Crohn's.

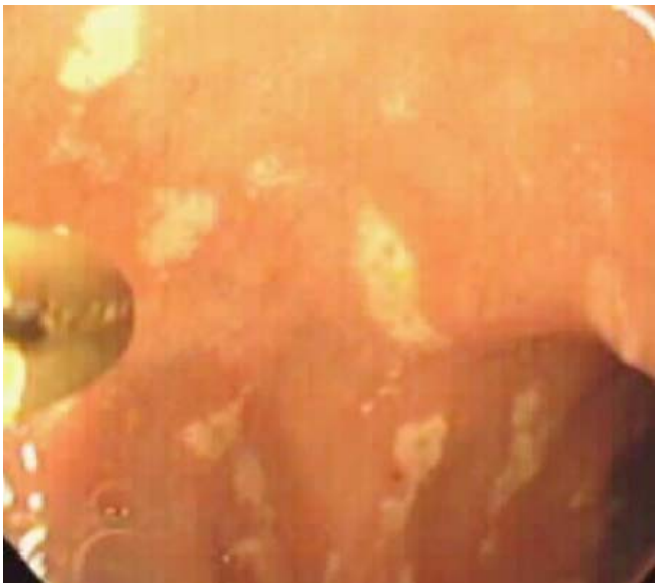

Figure 15 multiple duodenal aphthous ulcerations

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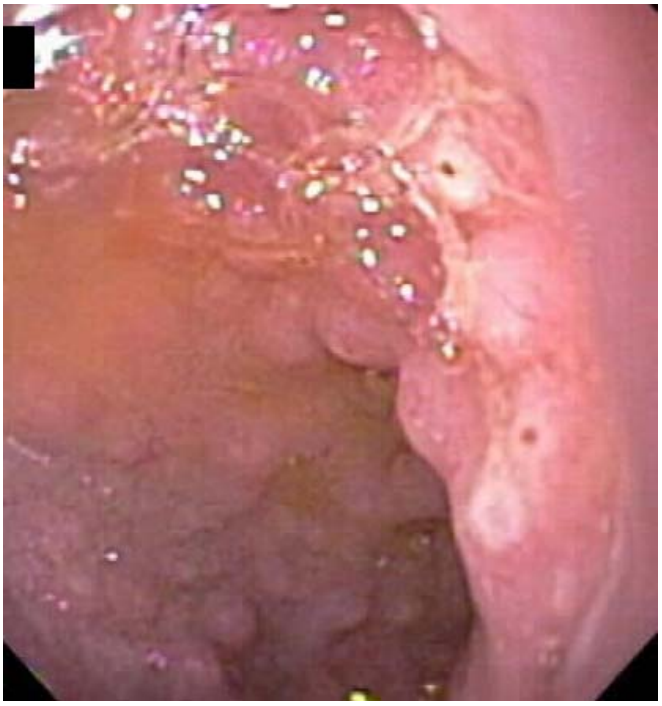

Figure 16. Marked lymphoid hyperplasia of the duodenum

The photo in Figure 16 was taken in a child from California who had tremendous abdominal pain, and growth failure. He had marked lymphoid hyperplasia of the duodenum, including some aphthous ulcerations on the tips of some of the nodules. He is doing well now as a result of dietary restriction.

Non-specific duodenitis is an extremely common finding in ASD children; "-itis" just means inflammation, so duodenitis is inflammation of the duodenum. By inflammation we mean the influx of white blood cells to the area, which in this case are clustered in various layers of the mucosa of the duodenum. The distribution of these white blood cells is not diagnostic of any known disorder, so the condition is termed *non-specific*. The pattern includes villus-tip blunting, intraepithelial lymphocytes, and lymphonodular hyperplasia, and it does not appear to be celiac or acid-peptic in origin. Figure 17 is a photograph of non-specific duodenitis.

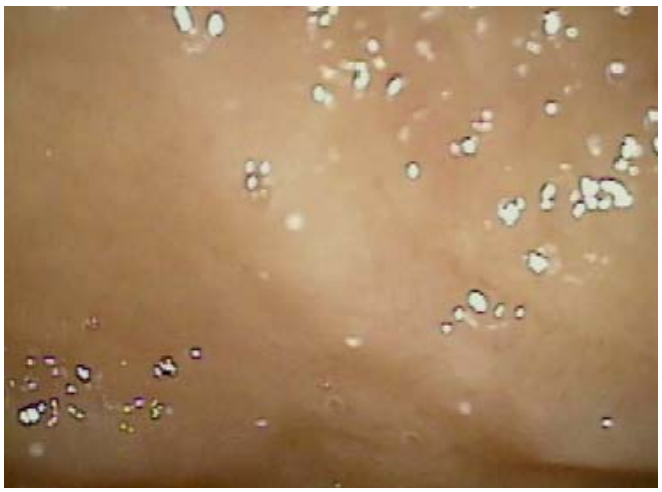

Figure 17. Non-specific duodenitis

It is not pink, and it has a lot of white specks—this is very mild lymphangiectasia, which is a common finding accompanying intestinal inflammation. Figure 18 is the microscopie appearance of figure 17. It shows villous blunting, inflammation at the tip of the villus, and also some intraepithelial lymphocytoses.

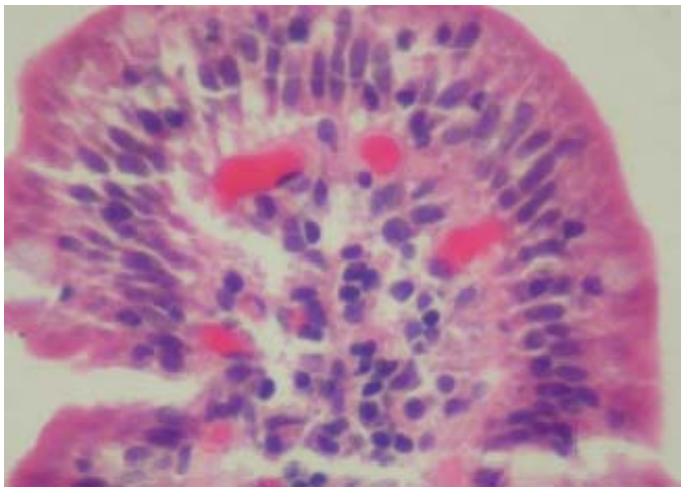

Figure 18. Slide showing villus blunting

These are significant when you find them on biopsy.

And of course we also have classic IgE-mediated allergic duodenitis.

Going farther into the small bowel, we have to rely on the pillcam because it is the only means of examining the farthest reaches of the small bowel without cutting the patient open. We find mucosal erosions, ulcerations, polyps, and LNH.

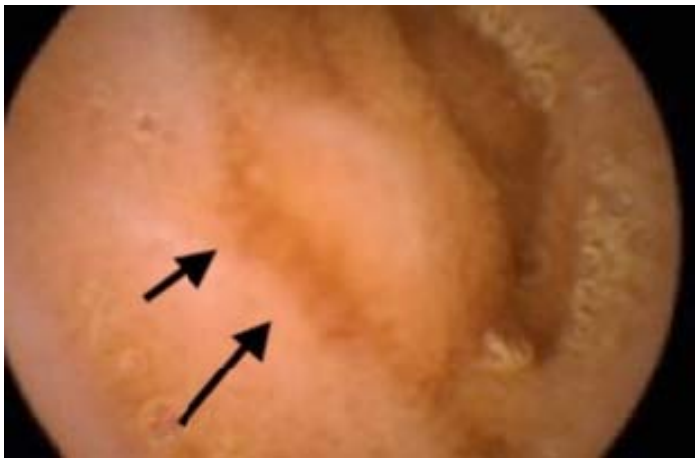

Figure 19. Aphthous ulcers with red crease

Figure 19 is an interesting photo. The arrows point to aphthous ulcers, and there is a red crease from the top left to the lower right. The earliest lesions of Crohn's disease look exactly like this—this is *not* a photo of Crohn's, but Crohn's provides a useful template for comparison because this new variant of bowel inflammation shares many interesting clinical and histological features, and there are overlapping serologic markers (Fig. 19). However, no full-thickness lesions, strictures, or fistulas have been documented to date, and the cytokine population also appears different from that found in Crohn's. None-

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theless, when we extrapolate some of what we know about treating Crohn's and apply it to treating these children, we get very similar responses.

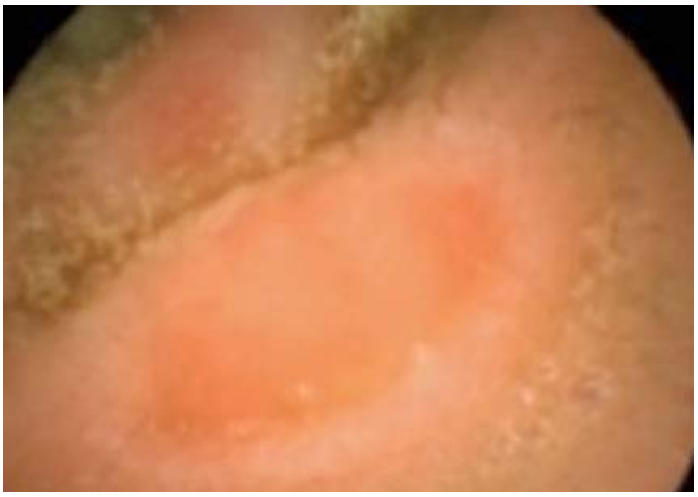

Figure 20. Small-bowel erosive ulcerations

Figure 20, obtained by capsule endoscopy (pillcam), depicts small-bowel erosive ulcerations. In the very center is a large, oval-shaped, dark erosion with a raised rim around it. The upper part of the figure shows another erosion (Fig. 20). This was taken in a child with ASD whose multiple IgE-positive food allergies were so severe that he ended up needing an elemental formula supplied by a feeding tube. This is what happens to the intestine when you introduce food allergens.

At the very end of the small bowel is the terminal ileum, which is an area of great interest to us because it is the most immunologically active; it has the highest concentration of lymphoid follicles per centimeter in the GI tract. An immunologic disease will most likely manifest itself in this area, which is commonly affected by Crohn's disease and other diseases as well. Figure 21 is a photo of moderate LNH in the ileum.

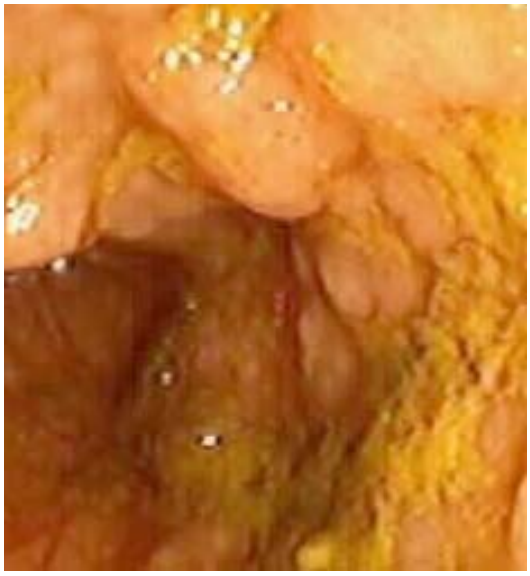

Figure 21. Moderate LNH in the ileum

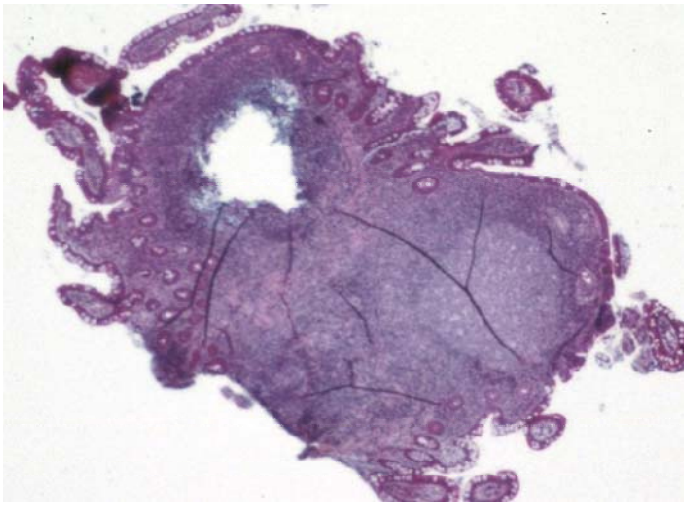

Figure 22. Biopsy showing protruding nodule with pale purple center

Figure 22 shows the biopsy. Toward the right side of this slide is a big protruding nodule with a pale purple center (the germinal center); lymphoid nodules markedly enlarge because they are being excited by some trigger, resulting in expansion of that germinal center. It is very prominent. There is displacement of the villi on the top of the slide. The little finger-like projections are normal villi, but those villi are absent over the surface of the nodule. Villus displacement is an important histopathologic finding.

This child did not just have LNH, he also had inflammation of the ileum (Fig. 23).

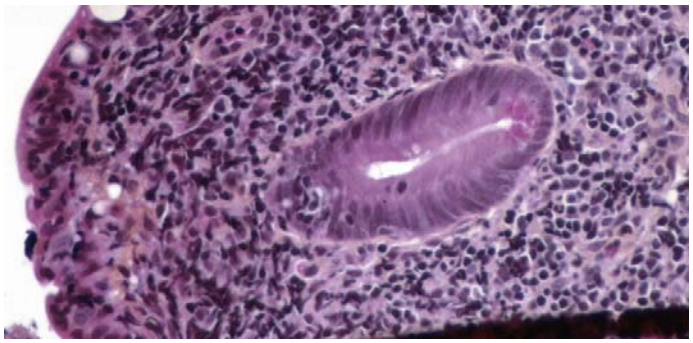

Figure 23. Inflammation of the ileum

That circle in the middle is called a crypt, and the invasion of the little black cells called neutrophils into the crypt is called cryptitis, a common finding in these children (Fig. 22).

Lastly, as shown in Figure 24, we have found four or five granulomas, the kind that are found in Crohn's disease—another interesting overlap of findings with ASD bowel disease.

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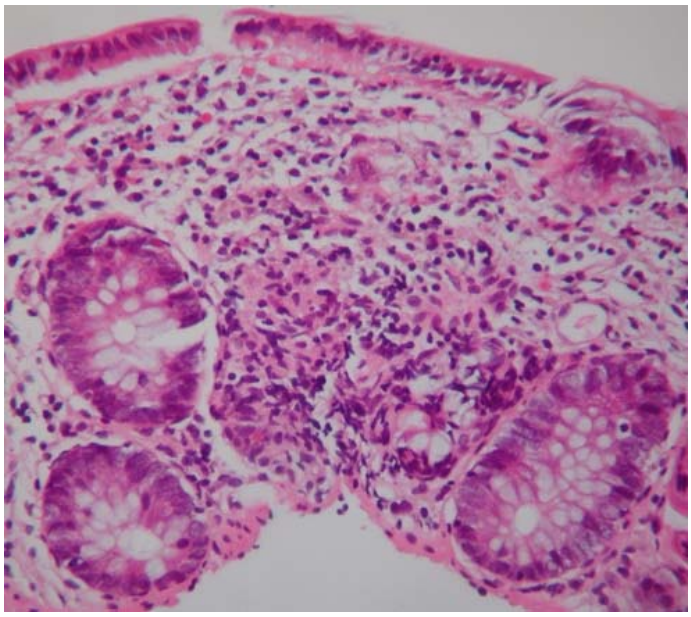

Figure 24. Granulomas characteristic of Crohn's disease

Possible symptoms of disease in the small intestine include diarrhea, food avoidance, self-injurious behavior, poor sleeping, stool incontinence, vomiting, constipation, mucus in the stool, vomiting, malabsorption, poor growth, and low blood serum levels of the protein albumin. It is imperative to keep a sharp eye on any child on the autism spectrum for these symptoms.

Lesions in the Colon

Proceeding to the colon, we see colitis, ulcerations, inflammatory polyps, ulcerative colitis, Crohn's disease, and marked LNH. Figure 25 is a photograph of a patently unhealthy colon in a patient with ASD and diarrhea—it is tubular and it has patchy erythema.

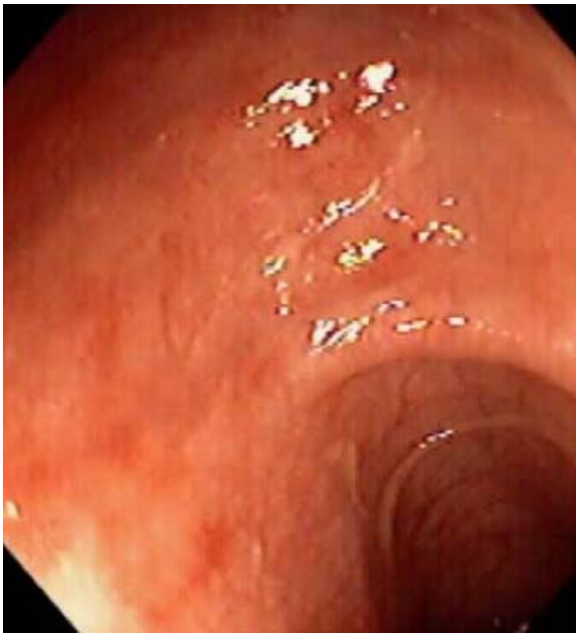

Figure 25. An unhealthy colon

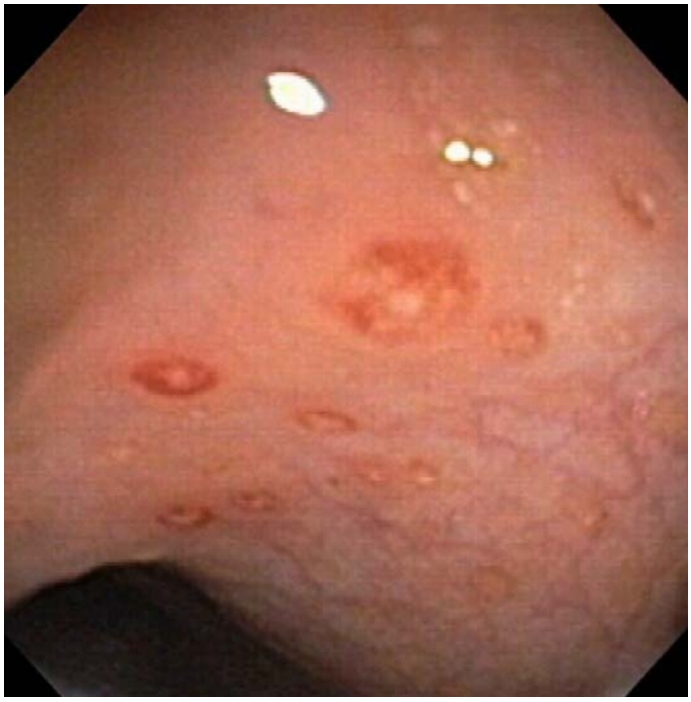

Figure 26. Aphthous ulcers in the colon

Figure 26 depicts aphthous ulcers, like those found in the small intestine. The central ulcers are surrounded by red halos of erythema (Fig. 26). These are all classic colonic lesions. Although some bowel preps may cause isolated lesions that resemble these, the sheer number of individual lesions seen in the ASD children greatly exceeds the numbers that are reported due to the bowel prep.

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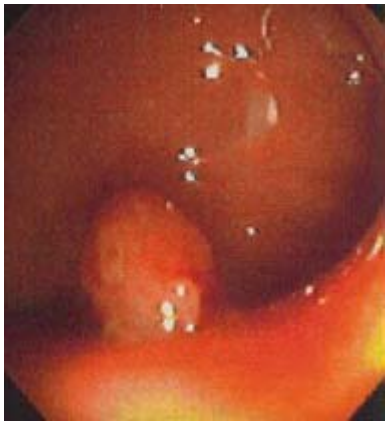

Figure 27. An inflammatory polyp of the colon

Figure 27 depicts an inflammatory polyp of the colon. A key symptom of colonic disease is stool urgency, which is why a lot of non-verbal children cannot be potty-trained. Loose, stinky, yellow stool suggests colonic inflammation. Constipation is less commonly a sign of potential colitis. Figure 28 depicts a very common type of stool for this population.

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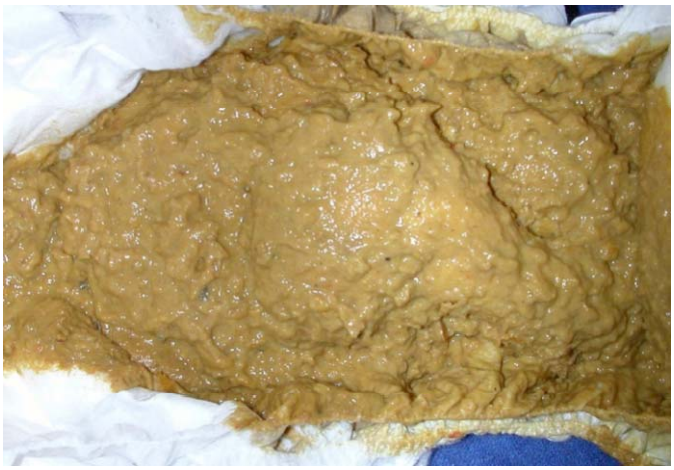

Figure 28. An unformed stool common to ASD children

It is not the watery diarrhea we sometimes experience as adults. Though some ASD children do have watery, explosive stools, most of them have stools that resemble the one in this figure. All children and adults occasionally have unformed stools, but if most or all of the stools are unformed, it is pathologic. Many parents have said to me, "My child has never had a formed stool, ever."

Figure 29 depicts a child who was experiencing so much pain that he was engaging in self-injurious behavior. This child was admitted to the hospital for three days of narcotic-induced sleep, to provide a respite for him. Self-injurious behavior is not a normal part of autism—it should be assumed the child is in pain until proven otherwise. The same child is shown after treatment in Figure 30.

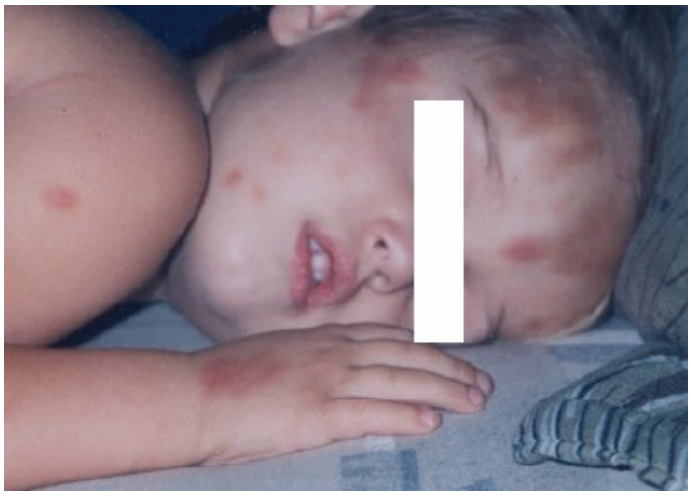

Figure 29. A child engaging in self-injurious behavior due to pain

Treatment

If GI symptoms persist, the ASD child needs a full evaluation, including a very careful history, a physical exam, and baseline screening tests. If those are normal, and temporary, empiric use of drugs like Zantac, Prevacid, Tums, or motility drugs do not alleviate the symptoms, then the above diagnoses should be considered, and it becomes essential to look at the mucosa of the GI tract. If a gastroenterologist dismisses the symptoms as "behavioral"—expected in a child on the spectrum—then the parents should find another gastroenterologist.

The exciting thing is that while not curable, all of these lesions are treatable. Most of these children respond extremely well to some combination of a restricted diet, anti-inflammatory medication, probiotics, antibiotics, antifungals, and digestive enzymes. While some experience a corresponding improvement in autistic behavior, the question of whether treatment of the bowel disease is correlated with improvement in cognitive function is the subject of current research at Thoughtful House Center for Children. At the very least, it is simply intuitive that a child who feels good will have greater benefit from the myriad of available behavioral interventions than the child who is experiencing flatulence, diarrhea, urgency, and abdominal pain.

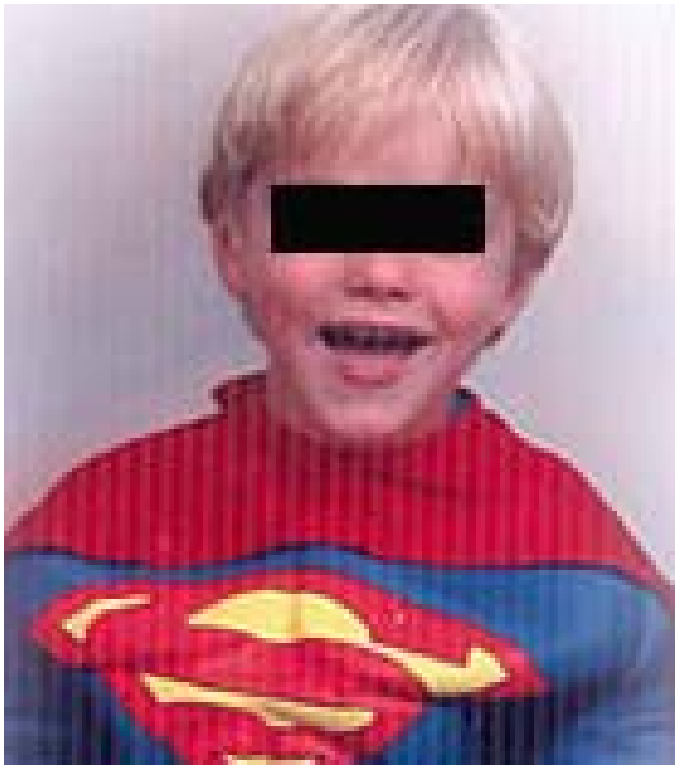

Figure 30. Same child as shown in Figure 29 after treatment

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