Children's Hospital LOS ANGELES
We Treat Kids Better

Keck School of Medicine of USC

# Neonatal Enteropathies: A review of selected entities with distinct molecular signatures

**Nick Shillingford, MD, FCAP**

Children's Hospital Los Angeles

Keck School of Medicine of USC

# Disclosure statement

## I have absolutely nothing to disclose


Chad Ambo

# Objectives

## At the end of the exercise the audience will be able to:

1. Broaden their list of differential diagnoses in children with refractory diarrhea to include less common entities

2. Describe the salient pathologic features of these enteropathies

3. Discuss the molecular/genetic signatures of microvillus inclusion disease, congenital tufting enteropathy and enteroendocrine cell dysgenesis

4. Implement the appropriate ancillary studies that will aid in the diagnosis of the rarer entities

ARTICLES

# INTRACTABLE DIARRHEA IN EARLY INFANCY

**Gordon B. Avery, M.D., Ph.D., Olmedo Villavicencio, M.D., John R. Lilly, M.D., *and* Judson G. Randolph, M.D.**

*From the Departments of Pediatrics and Surgery, Children's Hospital of the District of Columbia; the Department of Pediatrics, Georgetown University School of Medicine; and the Department of Surgery, George Washington University School of Medicine, Washington, D.C.*

Pediatrics, Vol. 41, No. 4, April 1968

**ABSTRACT.** Twenty infants with intractable diarrhea, whose onset was before 3 months of age, were analyzed. Twelve had identifiable pathological entities sufficient to explain their protracted diarrhea. A systematic diagnostic scheme for such babies is presented.

destruction of the mucosa and inflammatory infiltration. The authors believe that in these latter cases, regardless of the initial cause of the diarrhea, certain vicious cycles came into play which perpetuated the diarrhea. Preliminary evidence suggests that colostomy and, perhaps adrenal corticoste-

# Protracted (Intractable) Diarrhea of Infancy

- Onset before 3 months of age
- Symptom complex characterized by diarrhea >2 weeks
- Repeatedly negative stool cultures
- Varying degrees of villous atrophy
- Exact etiology is often unclear
- Consequent malnutrition

TABLE I

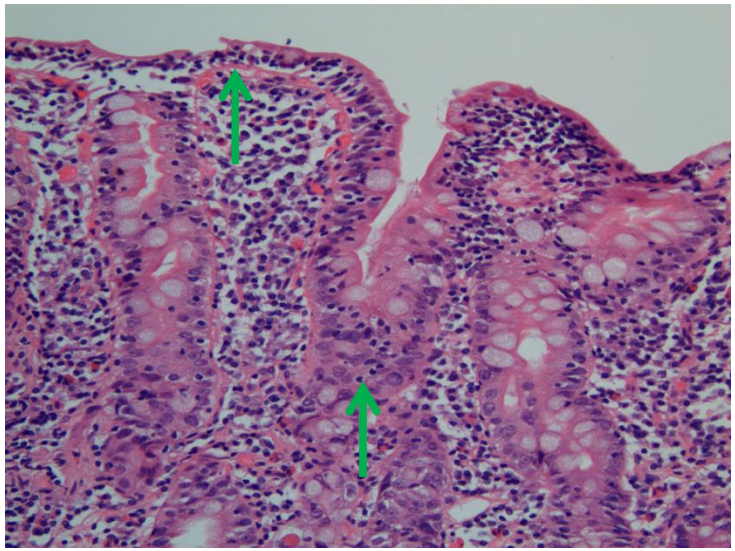
20 CASES OF INTRACTABLE DIARRHEA

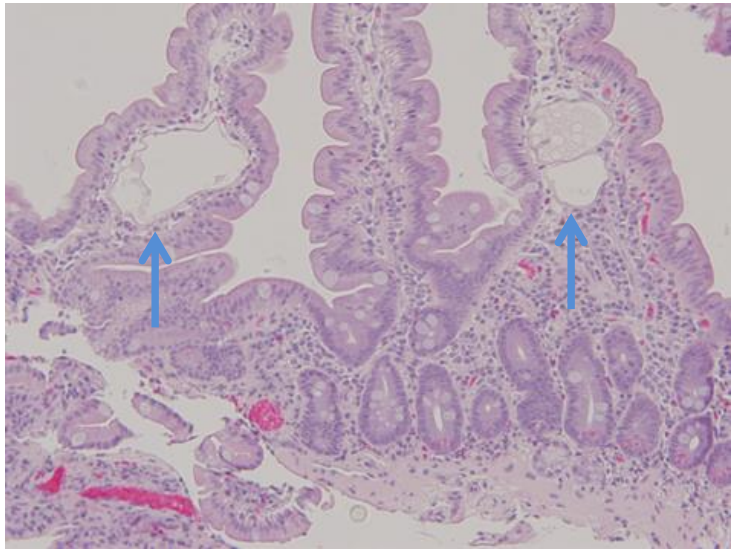
| *Name* | *Diagnosis* | *Onset* | *Duration (da)* | *Special Treatment** | *Other Intravenous Therapy* | *Confirmatory Tests* | *Outcome* |
|---|---|---|---|---|---|---|---|
| A.H. | Disaccharide intolerance | Birth | 180 | Monosaccharide formula | Blood | Lactose tolerance + acid stool pH stool reducing sugars, response monosaccharide formula | Improved |
| T.B.† | Disaccharide intolerance | 30 da | 150 | Monosaccharide formula | Blood; gamma-globulin; vitamins | Stool reducing sugars, response monosaccharide formula | Improved |
| T.D.‡ | Disaccharide intolerance | Birth | 85 | Monosaccharide formula | Blood; albumin; plasma vitamins | Lactose tolerance, response monosaccharide formula | Improved |
| L.B. | Cystic fibrosis | 14 da | 210 | Enzymes | Vitamins; antibiotics | Sweat test, absent trypsin | Improved |
| S.S. | Cystic fibrosis | Birth | 120 | Enzymes | Blood; vitamins; antibiotics | Sweat test; cystic fibrosis at autopsy | Died |
| K.W. | Salmonella enteritis | Birth | 45 | Antibiotics | | Stool positive for salmonella after many negatives | Improved |
| D.L. | Ulcerative colitis | 3 da | 25 | Supportive | | Sigmoidoscopy and barium enema | Improved |
| K.G.§ | Perinephric abscess | 15 da | 48 | Antibiotics | Blood; plasma; albumin; Mg; vitamins | Perinephric abscess at autopsy | Died |
| D.W. | Urinary tract infection | 14 da | 16 | Antibiotics | Vitamins | Several cultures 100,000 *E. coli* in urine | Improved |
| G.M. | Adrenal insufficiency | Birth | 36 | Supportive | Blood; albumin | Adrenal atrophy at autopsy | Died |
| D.R. | Ileal stenosis | Birth | 75 | Stenotic segment resected | Blood; albumin; vitamins | Confirmed at laparotomy | Improved |
| A.P. | Hirschsprung's disease | Birth | 21 | Colostomy | Blood; albumin; vitamins | Barium enema; rectal biopsy | Improved |
| A.W. | Non-specific enterocolitis | 21 da | 54 | Steroids | Blood; plasma; vitamins | See Table II | Died |
| S.M. | Non-specific enterocolitis | Birth | 48 | Colostomy | Blood; plasma; vitamins | See Table II | Died |
| G.C. | Non-specific enterocolitis | 10 da | 22 | Steroids | Blood; albumin; vitamins | See Table II | Died |
| M.F. | Non-specific enterocolitis | Birth | 14 | Steroids and colostomy | Blood; plasma | See Table II | Died |
| B.B.H. | Non-specific enterocolitis | 4 da | 63 | Steroids | Blood; plasma; albumin; vitamins; Mg; casein hydrolysate (Amigen) | See Table II | Died |
| P.H. | Non-specific enterocolitis | 28 da | 54 | Steroids and colostomy | Blood; plasma; albumin; vitamins; Mg; casein hydrolysate (Amigen) | See Table II | Died |
| M.M. | Non-specific enterocolitis | Birth | 35 | Steroids and colostomy | Blood; albumin; vitamins | See Table II | Improved |
| D.D. | Non-specific enterocolitis | Birth | 105 | Colostomy | Blood; plasma; vitamins | See Table II | Improved |

# Enteropathies Presenting with Profuse Diarrhea:

## Those with detectable histologic changes

- Lipid malabsorption
- Celiac disease
- Cystic fibrosis
- Autoimmune enteropathy
- IPEX Syndrome
- Intestinal lymphangiectasia
- Enteroendocrine Cell Dysgenesis
- α6β4 integrin defects (some with epidermolysis bullosa)
- Congenital Tufting Enteropathy
- Microvillus Inclusion Disease

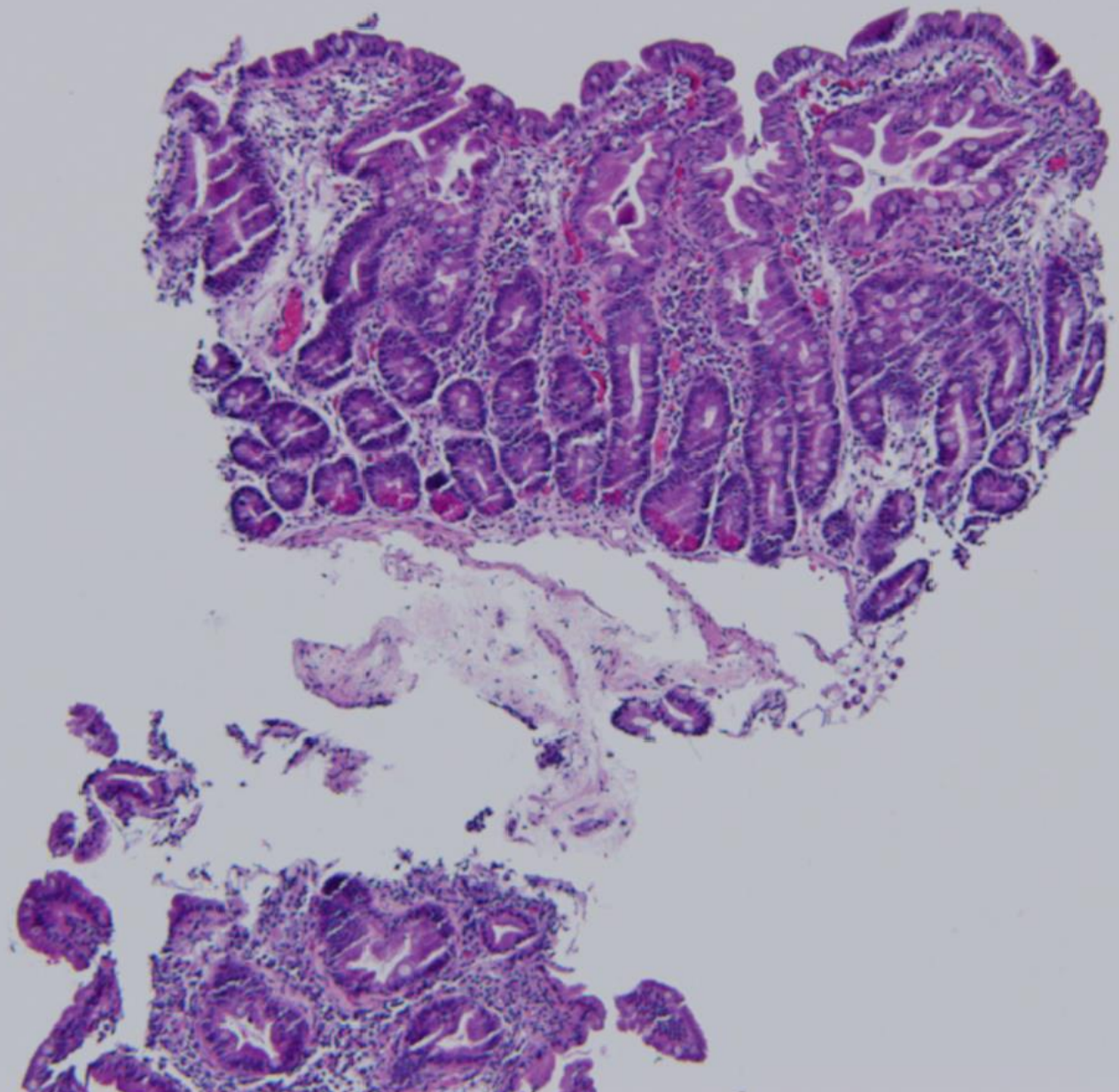




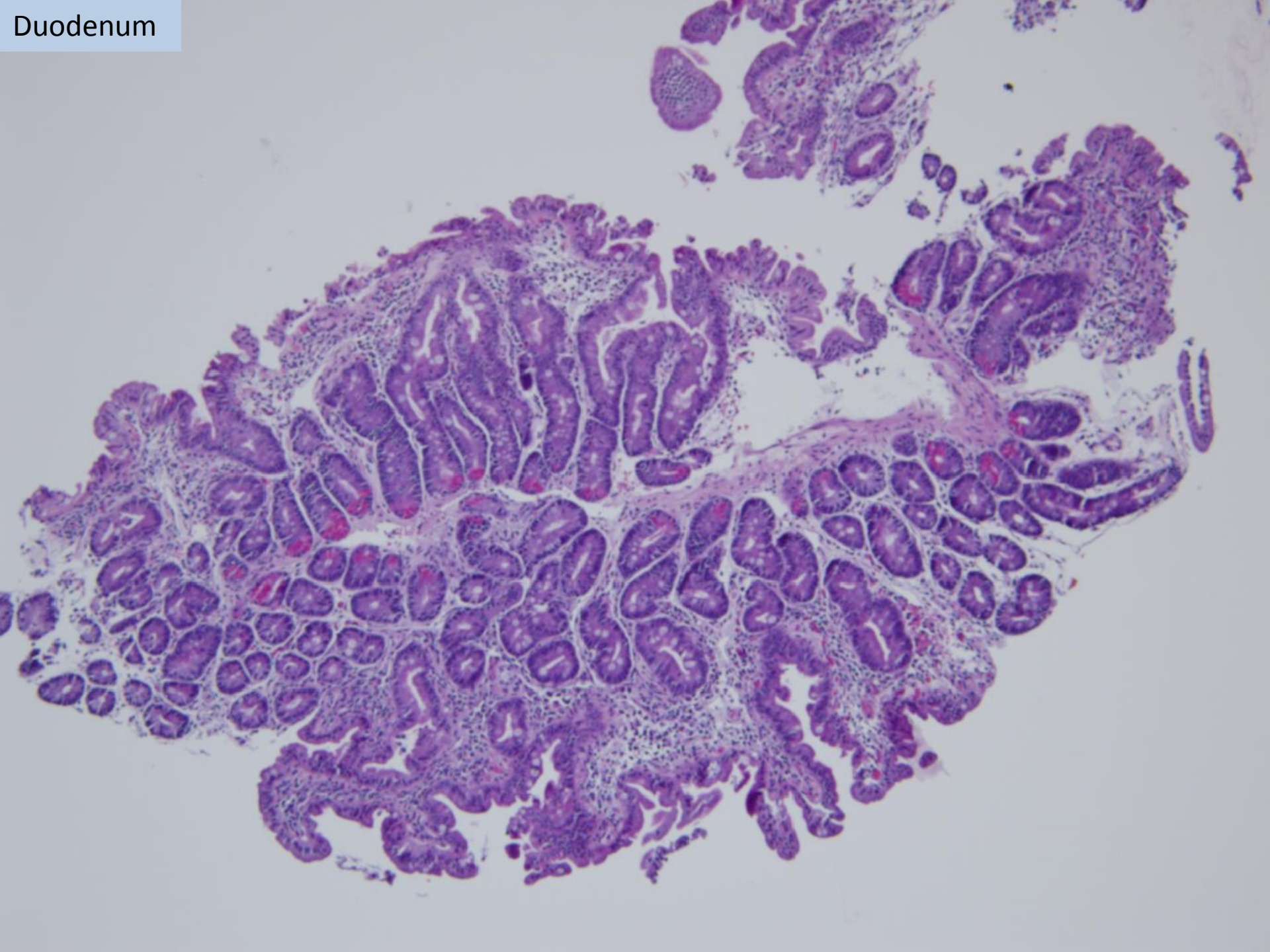
# Case 1

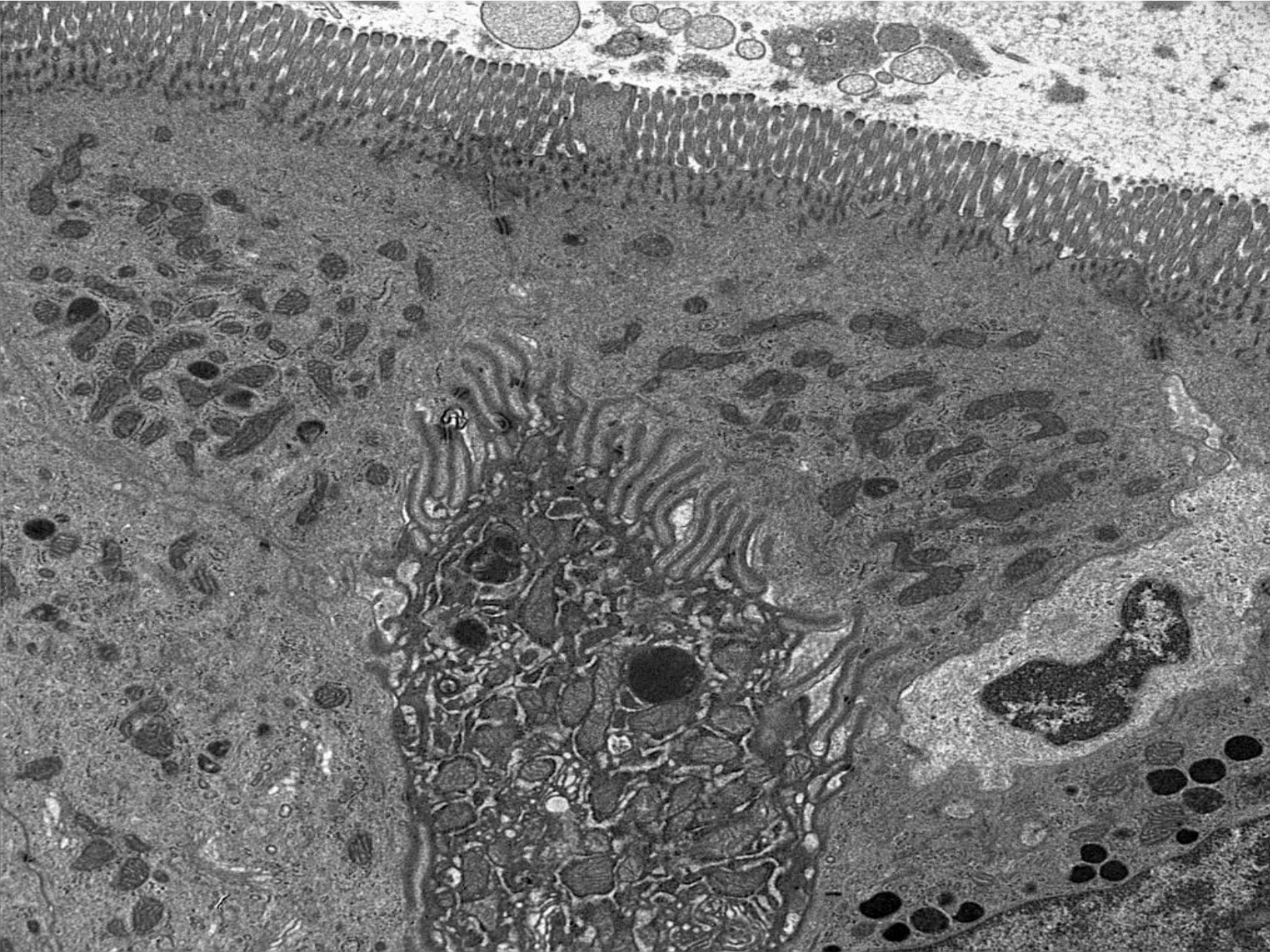
- **25 day old boy presented with severe watery diarrhea**
- **He was referred to gastroenterology at an outside hospital where a grossly malnourished appearing child was described**
- **Endoscopic examination showed normal appearing duodenum, stomach, esophagus, terminal ileum and colon however biopsies were taken**
- **The biopsies were read as normal**
- **It was recommended that he be switched from breast milk to cow's milk based formula, then soy based formula**
- **He continued to have protracted diarrhea and was categorized as failure to thrive**
- **He was referred to our institution**
- **The slides from the duodenum from his initial biopsy were reviewed at our consensus conference**

Duodenum



Duodenum





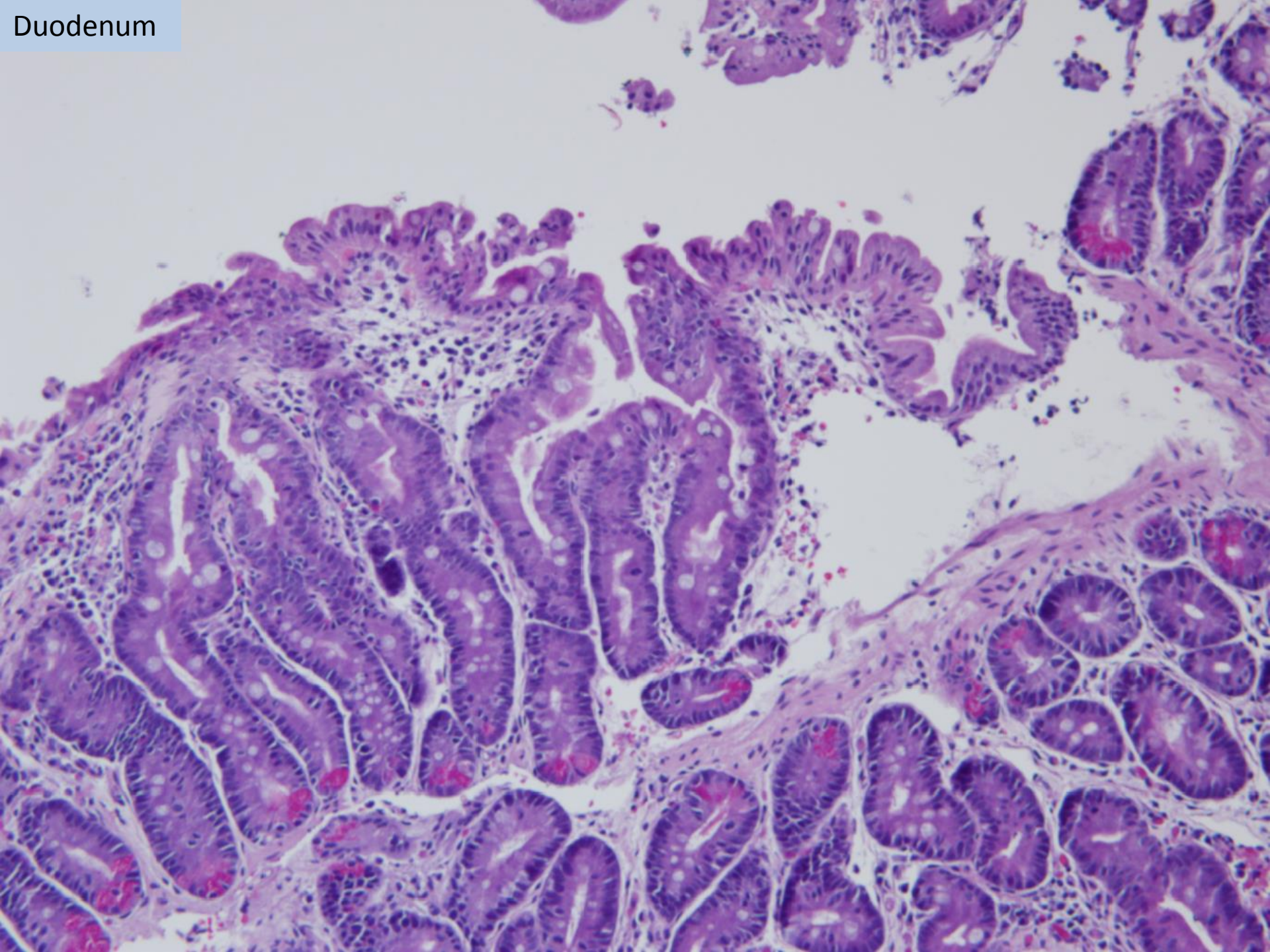
# DIAGNOSTIC IMPRESSION

- **Microvillus inclusion disease**
- **Congenital tufting enteropathy**
- **IPEX syndrome**
- **A6β4 integrin defect**
- **Enteroendocrine cell dysgenesis**

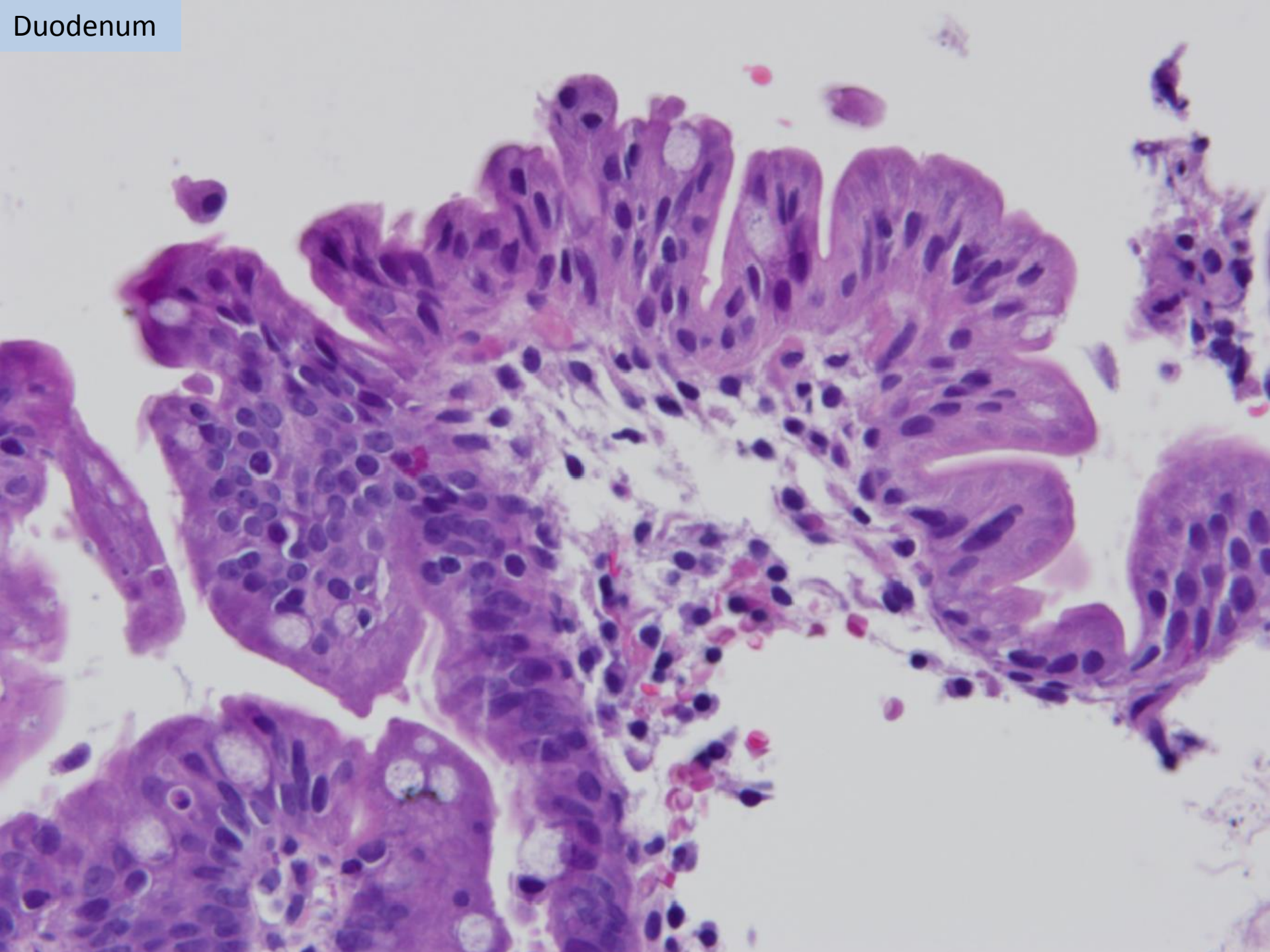
# Diagnostic impression

- **A junior pediatric pathologist suggested the possibility of CTE**

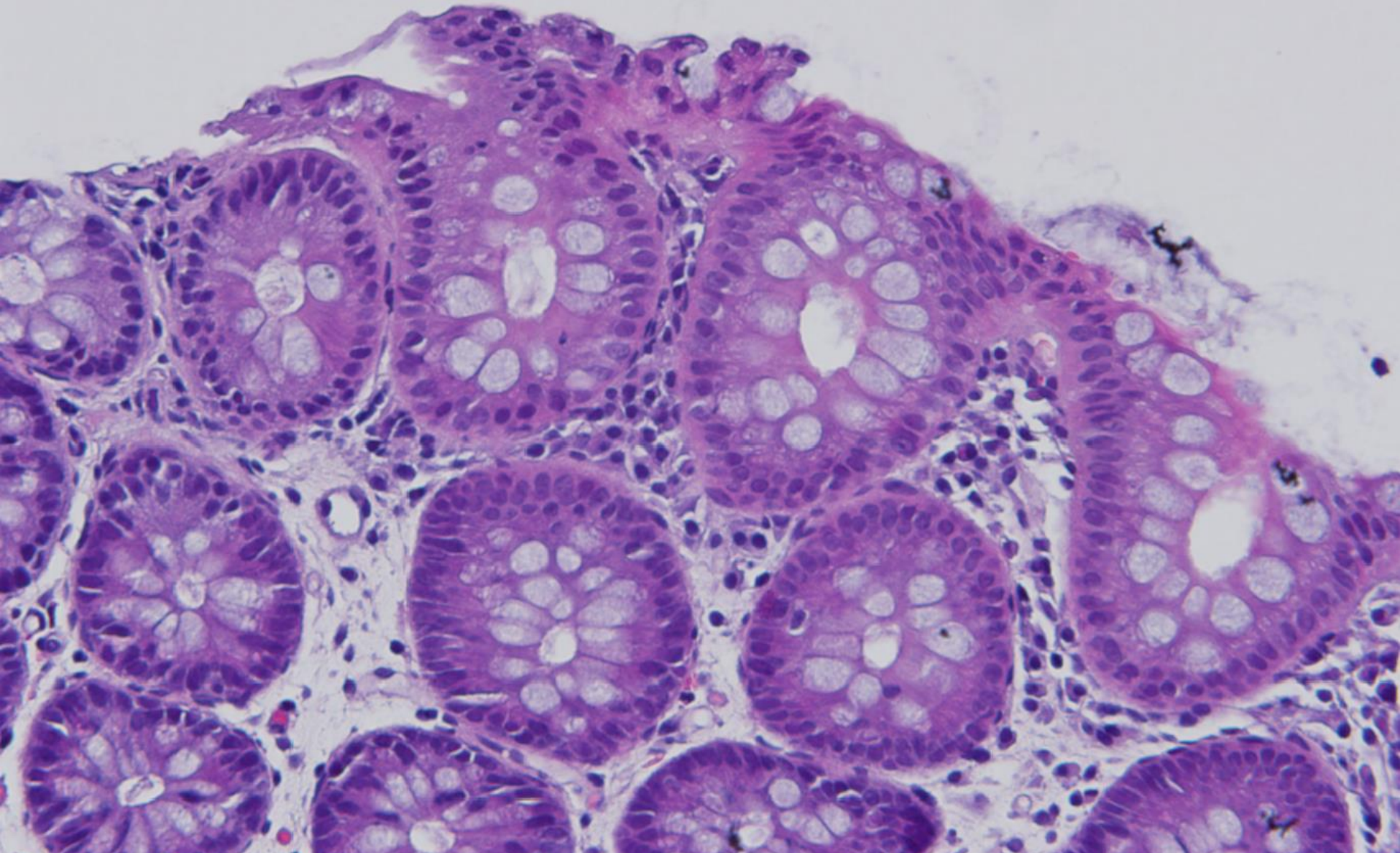
- **The slides were re-examined in greater detail and the remaining slides were retrieved and examined**


Duodenum

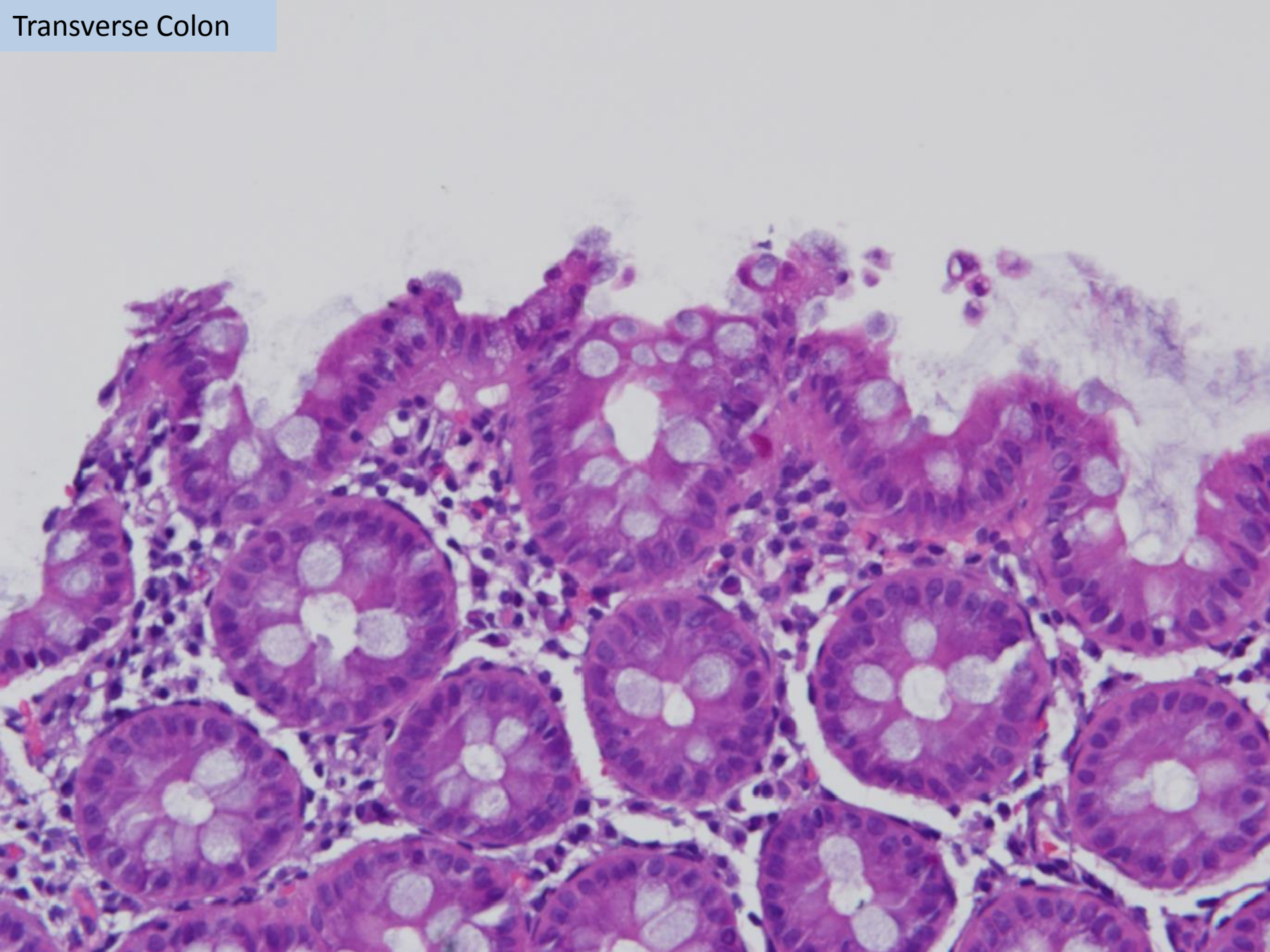
Duodenum



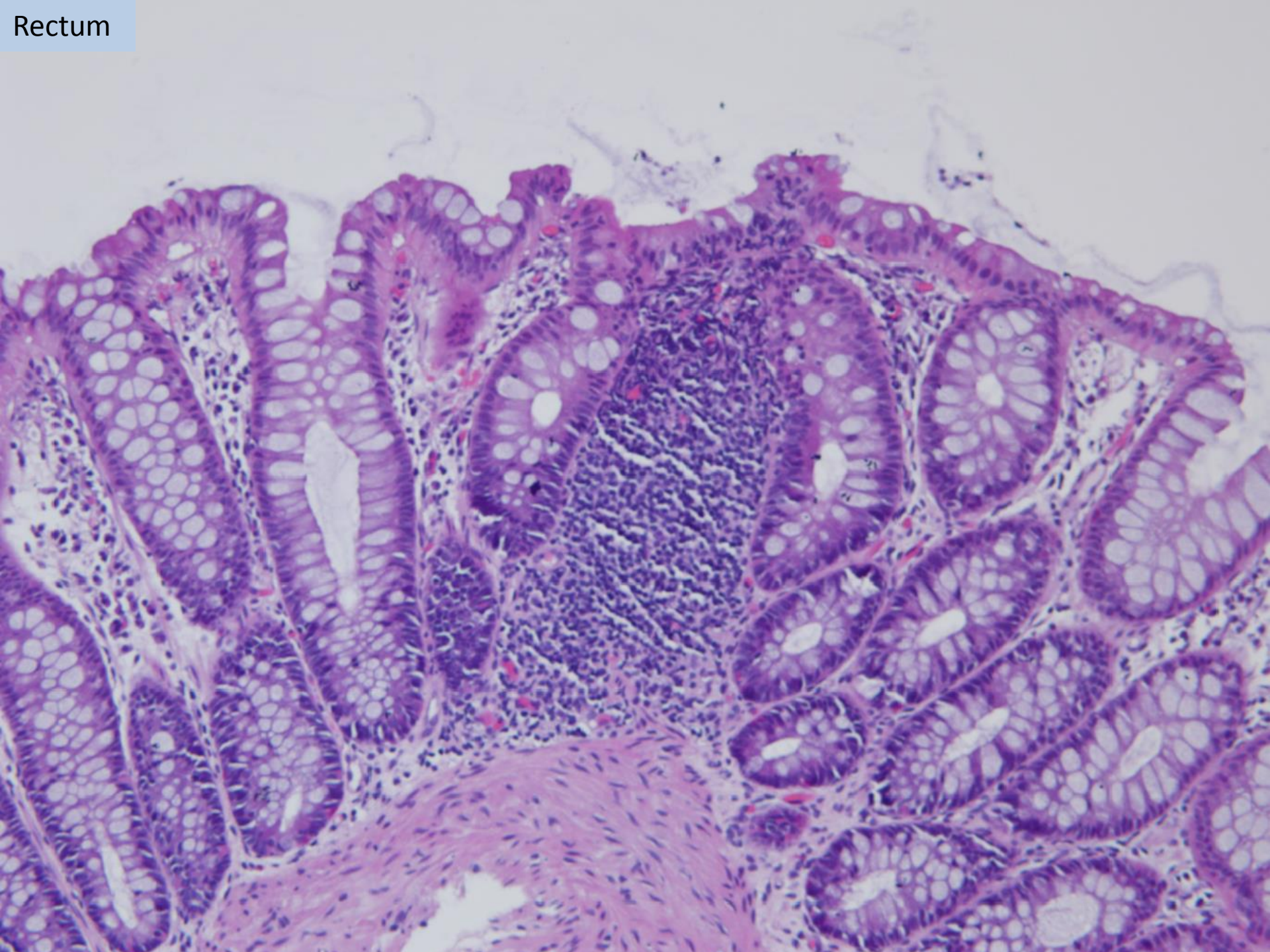
Ascending colon



Transverse Colon



Rectum



*Journal of Pediatric Gastroenterology and Nutrition*
**18**:379–385 

Case Report

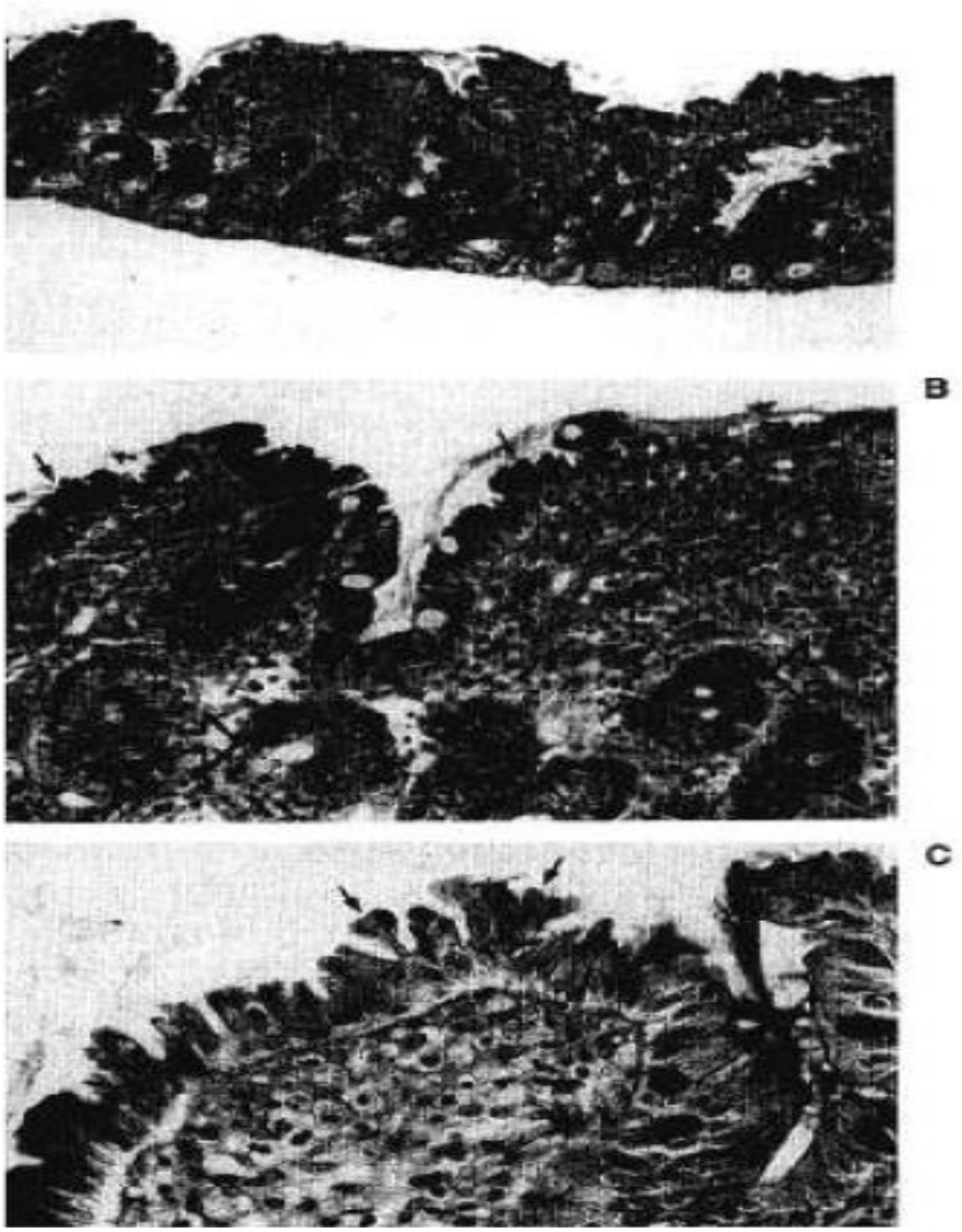
# Tufting Enteropathy: A Newly Recognized Clinicopathological Entity Associated with Refractory Diarrhea in Infants

*Ram M. Reifen, †Ernest Cutz, *‡Anne-Marie Griffiths, †§Bo Y. Ngan, and *‡Philip M. Sherman

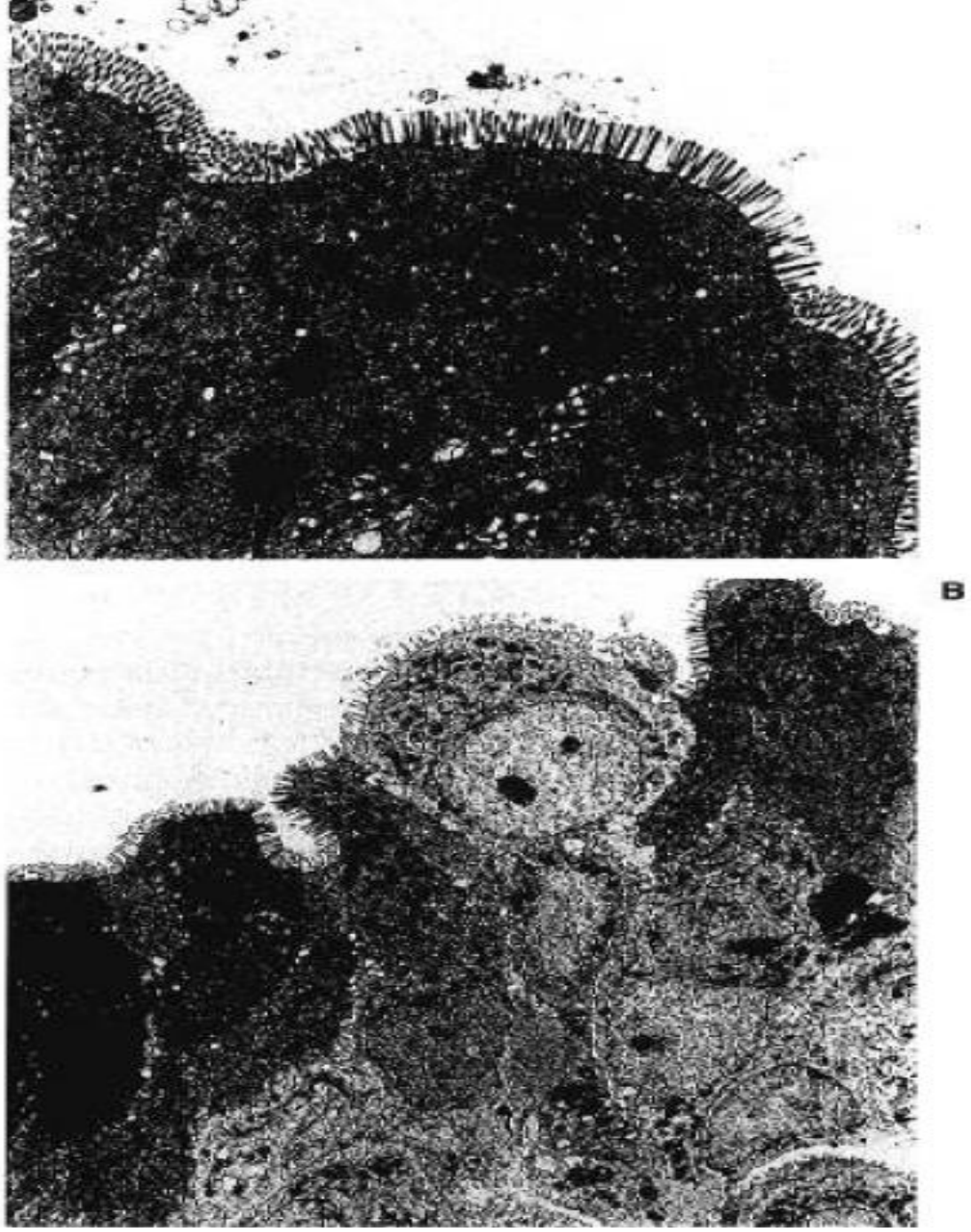
**Division of Gastroenterology, Research Institute, the Hospital for Sick Children; §Department of Pathology, Sunnybrook Health Sciences Center; Departments of ‡Pediatrics and †Pathology, University of Toronto, Toronto, Ontario, Canada*

# Congenital tufting enteropathy

- **3 patients with protracted diarrhea**
- **1 girl and 1 boy investigated for unexplained protracted diarrhea**
- **Re-evaluation of biopsies from patients with Dx of unclassified intractable diarrhea over previous 25 yrs**
- **Similar features to those seen in the biopsies of the 2 current patients were seen in one of the previously unclassified patients**




Reifen R, Cutz E. et al. J Pediatr Gastroenterol Nutr 1994;18:379-85.




Reifen R, Cutz E. et al. J Pediatr Gastroenterol Nutr 1994;18:379-85.

# What is CTE?

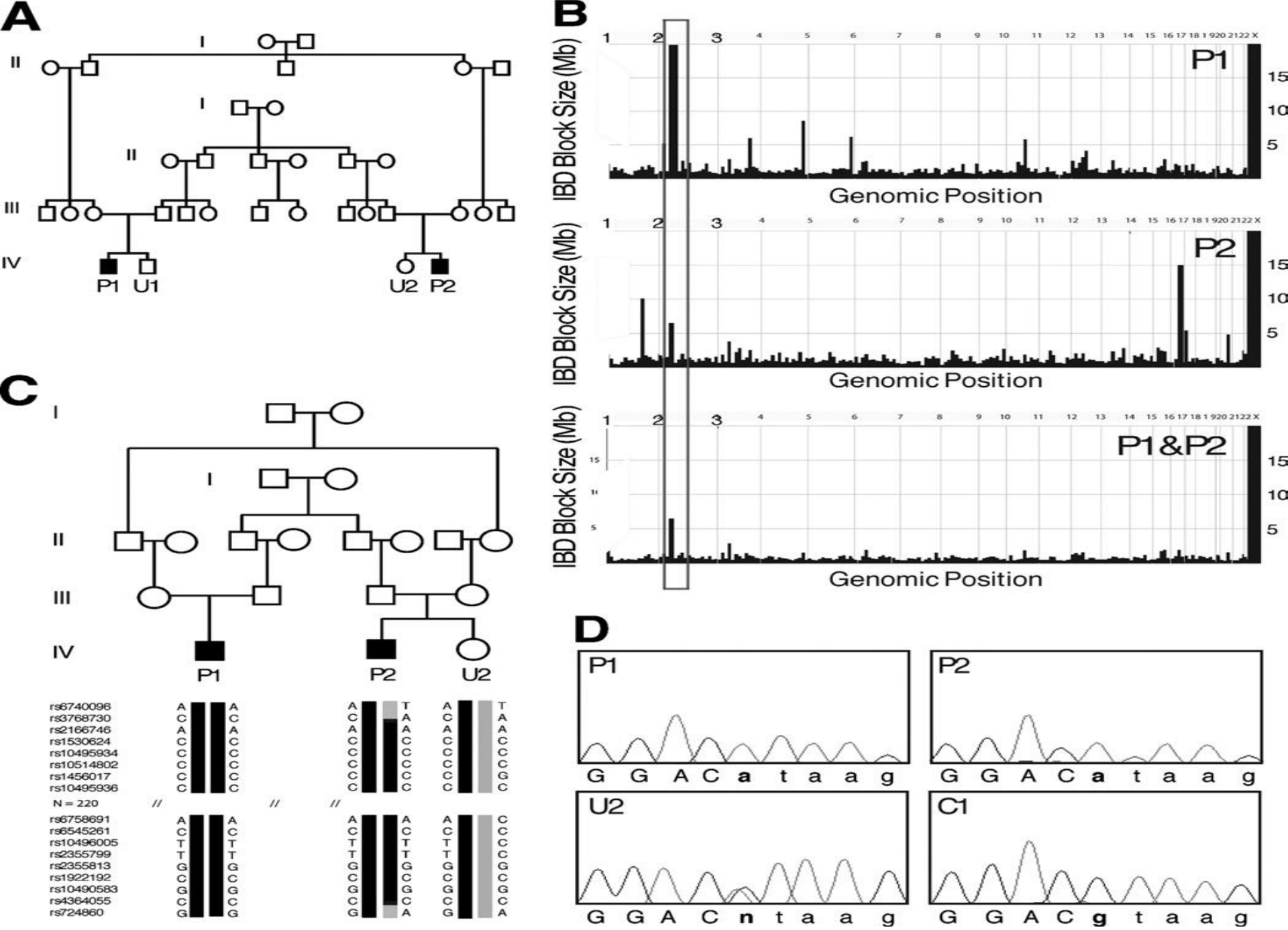
- Aka intestinal epithelial dysplasia
- Enteropathy presents in neonatal period
- Characterized by profuse watery diarrhea
- Uneventful prenatal history
- Appears to be inherited in an autosomal recessive fashion
- Increased incidence in siblings and with consanguinity

# Pathophysiology

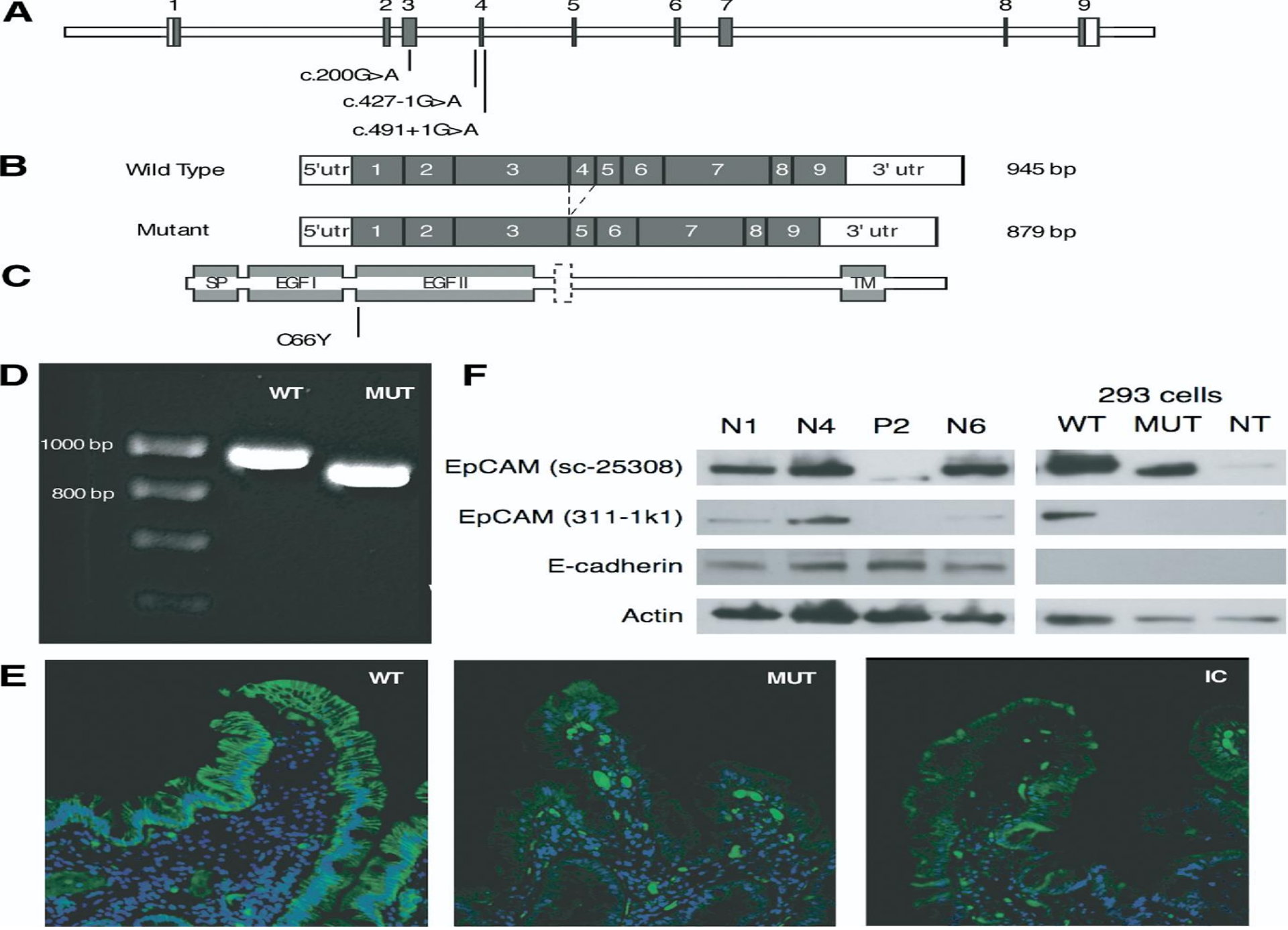
- Villous atrophy with tufted, rounded, teardrop-shaped enterocytes
- Shedding of enterocytes
- Mutation of EpCAM on chromosome 2p
- Pan-epithelial differentiation antigen and seen in all carcinomas
- Immunotherapeutic target in gastrointestinal and urologic carcinoma
- Linked to Cadherin-Catenin and WNT pathways

# Sivagnanam's Study

- One family with 2 affected children studied
- Subjects were doubled 2nd cousins
- Genotype performed on 2 affected children and 1 unaffected sibling using SNP chips
- DNA sequencing of EpCAM gene, reverse-transcription PCR, IHC and western blot on patients' and control samples
- Unique 6.5 Mbp haplotype of homozygous SNPs on 2p21, site of 40 genes




Sivagnanam M, Mueller JL, Lee H et al. Gastroenterology 2008; 135:429-37.




Sivagnanam M, Mueller JL, Lee H et al. Gastroenterology 2008; 135:429-37.

# Tufting Enteropathy Revisited

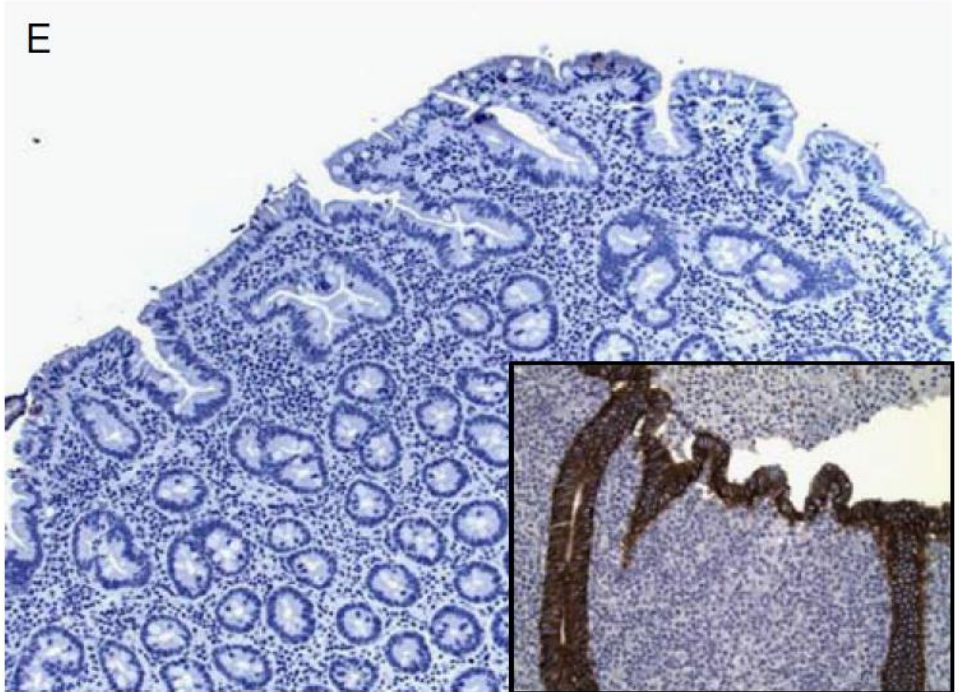
## *The Utility of MOC31 (EpCAM) Immunohistochemistry in Diagnosis*

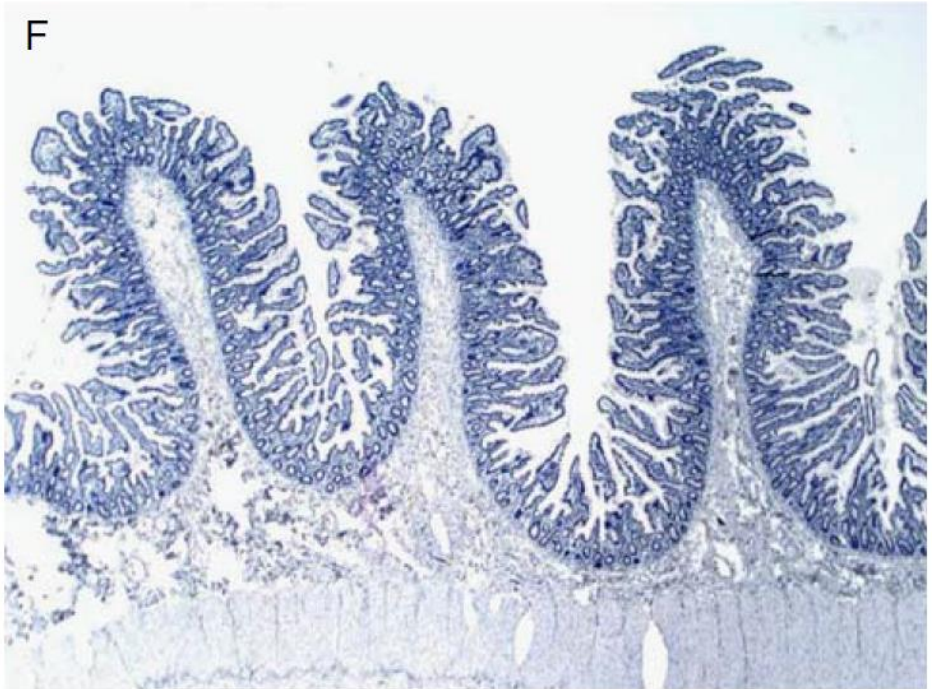
*Sarangarajan Ranganathan, MD,* Lori A. Schmitt, BS,* and Rakesh Sindhi, MD†*

**Am J Surg Pathol; 2014;38:265-272**

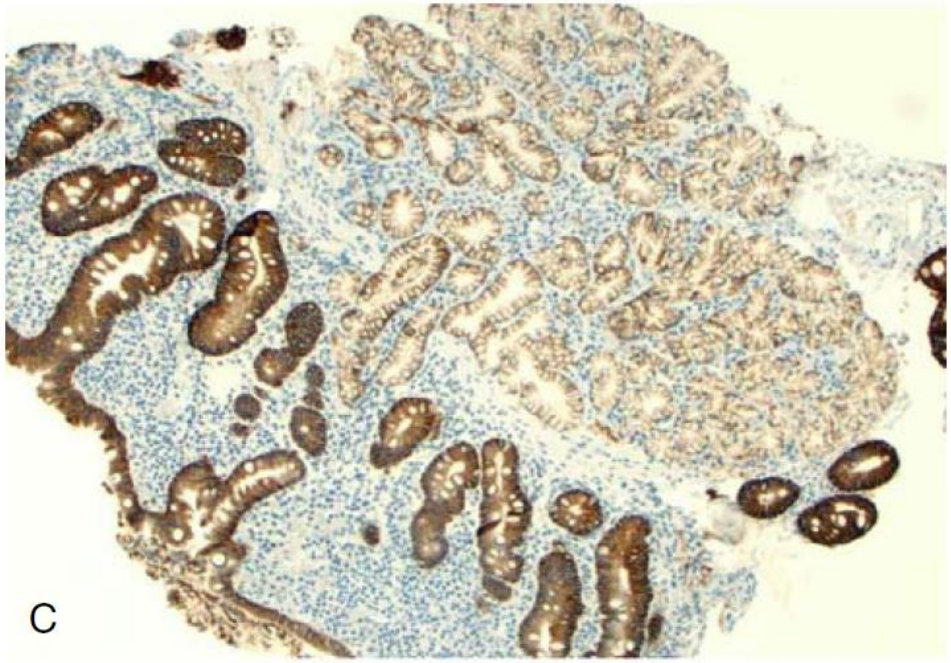
**Abstract:** Tufting enteropathy (TE) is an uncommon disease causing intractable diarrheas starting in early childhood and resulting in failure to thrive, dependence on total parenteral nutrition, and eventually requiring transplantation for treatment. The diagnosis has been based on histology showing the presence of epithelial "tufts" in the small bowel and colonic mucosa and variable villus alterations with mild to no in-

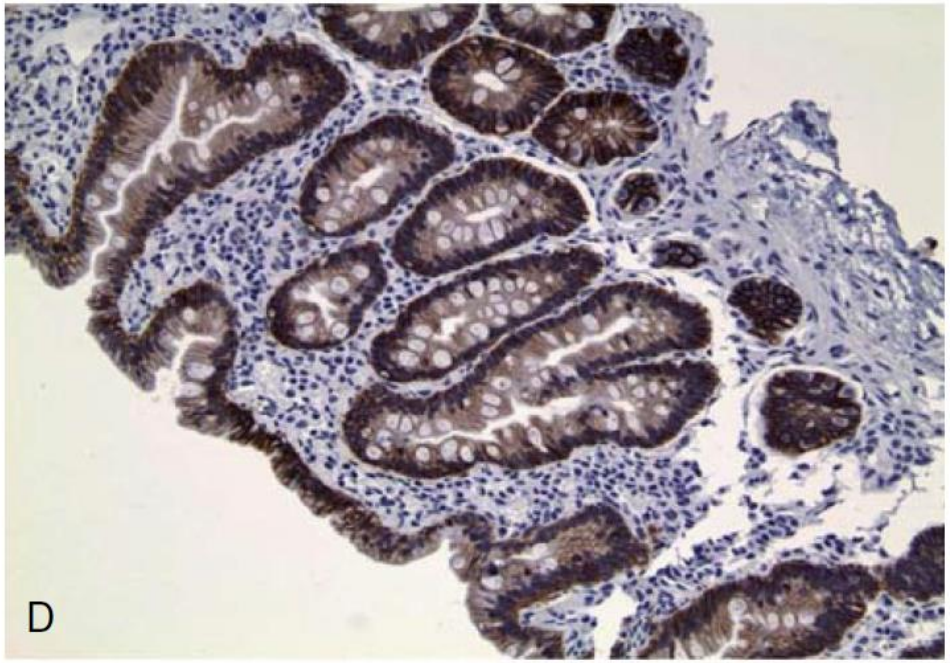
Intractable diarrhea of infancy can be defined as a group of disorders causing persistent diarrhea in early infancy, despite protracted bowel rest, requiring long-term parenteral nutrition for survival. The term was coined by Avery[1] to describe chronic, unexplained diarrhea in young infants. Over the years, the spectrum of diseases that could manifest with protracted infantile diarrhea has expanded and includes those that do not alter the villus/




**Sarangarajan Ranganathan, Lori Schmitt, Rakesh Sindhi. Am J Surg Pathol 2014;38:265-272**

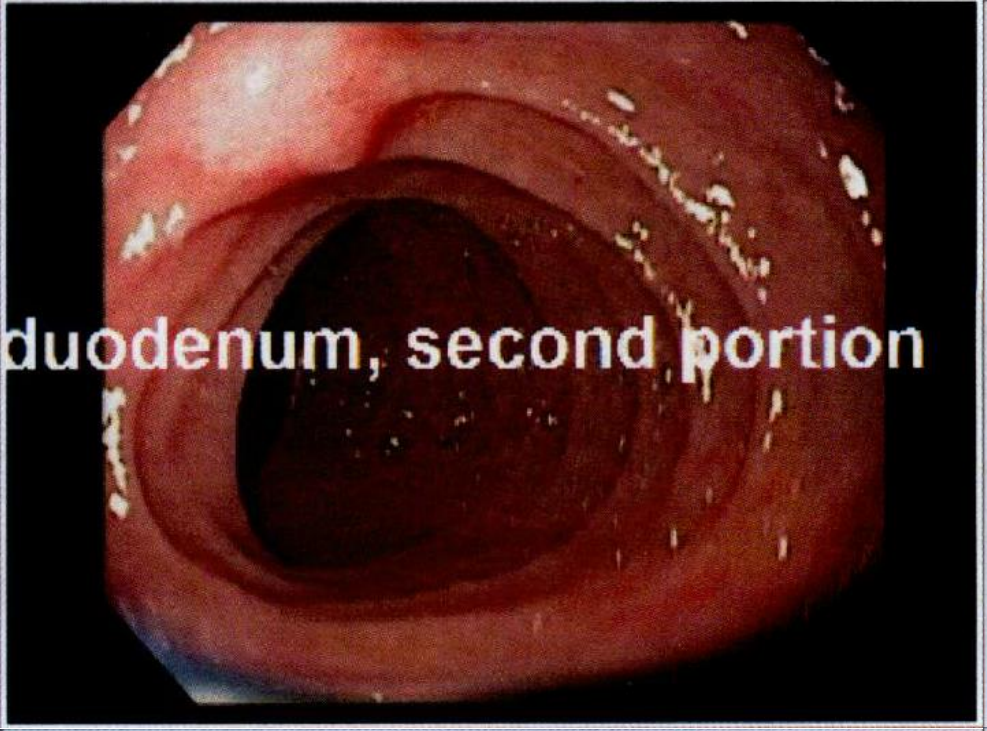


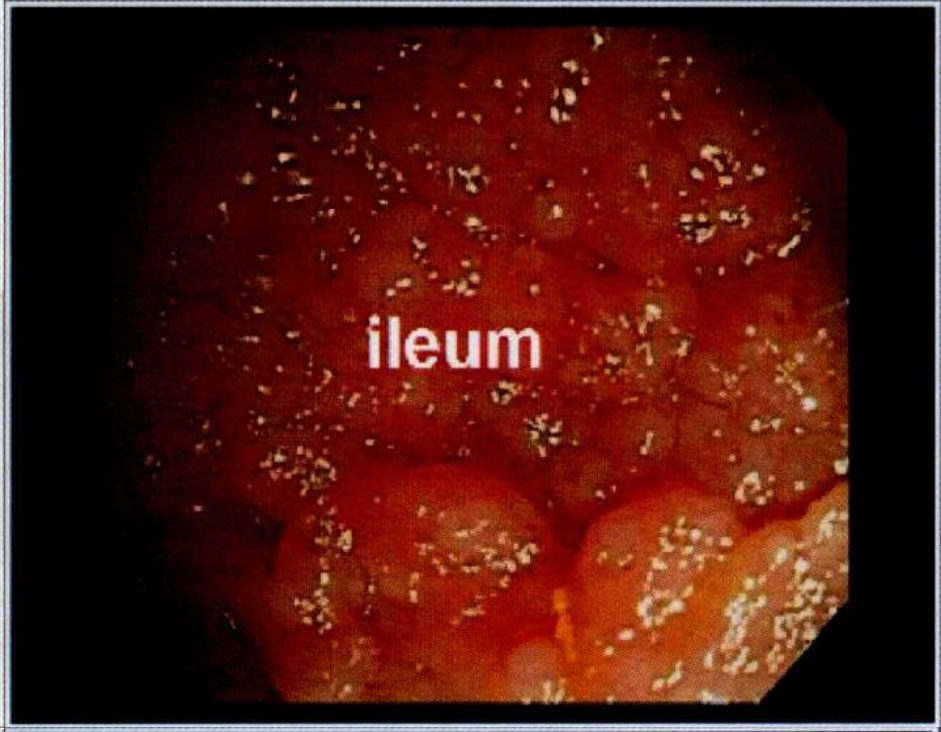



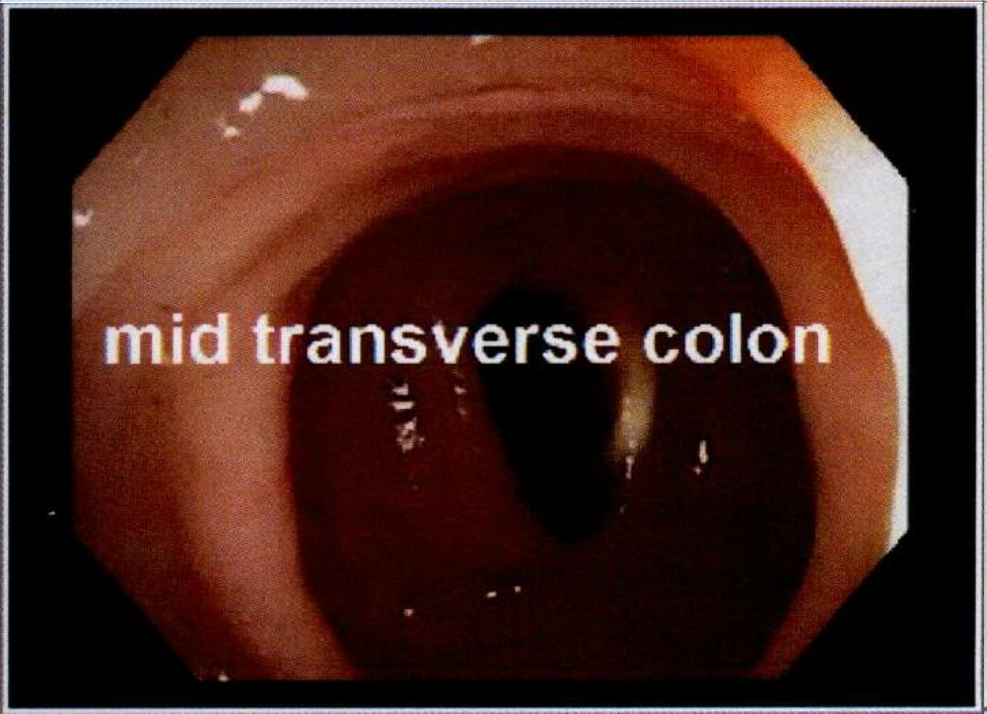

**Sarangarajan Ranganathan, Lori Schmitt, Rakesh Sindhi. Am J Surg Pathol 2014;38:265-272**

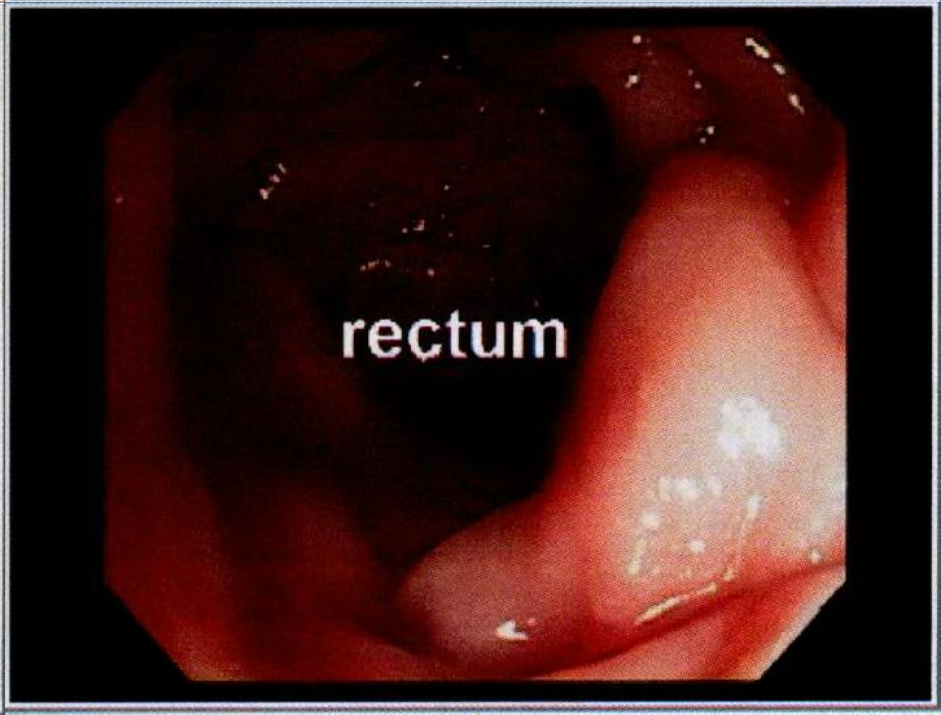
# Case 2

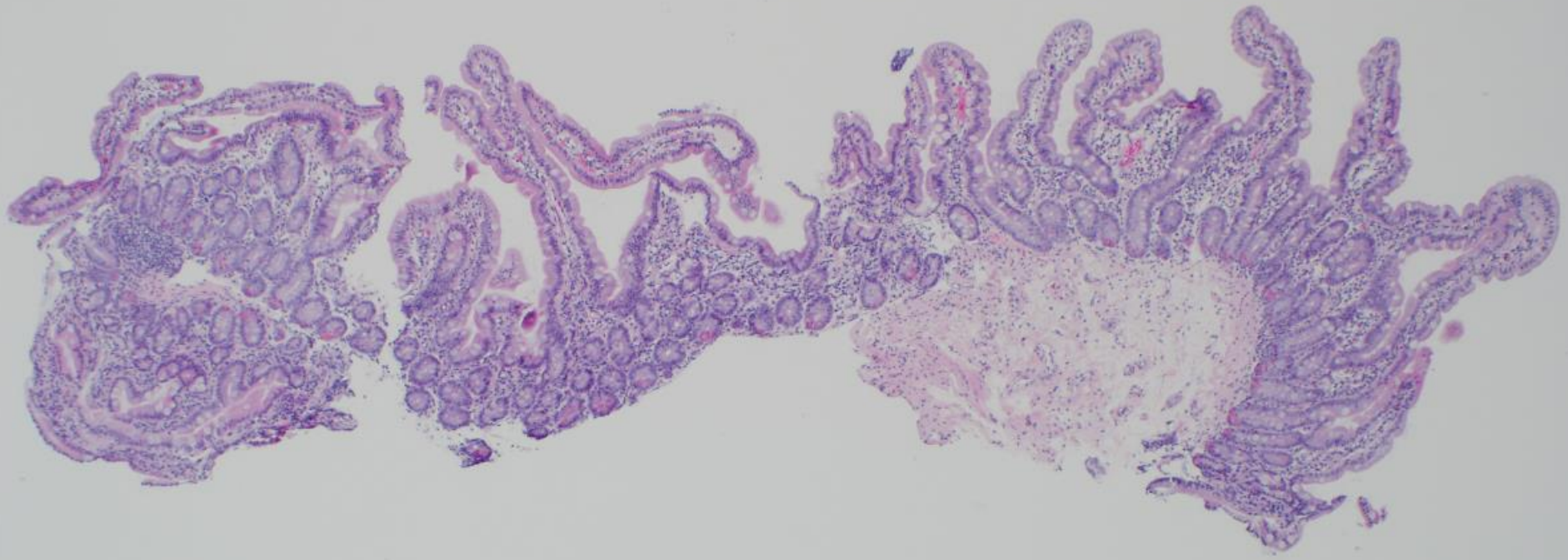
- 9 month old female infant of Mexican parentage is brought to medical attention because of profuse watery diarrhea
- Careful interrogation by the medical student reveals that the diarrhea is brought on by oral feeding of any type
- She has no symptomatology after drinking water
- Mom claims that stool output ceases once oral feeding is stopped
- On physical examination the child appears malnourished
- Parameters of infant wellbeing show that the child is at the $15^{th}$ percentile for body length and at the $10^{th}$ percentile for weight
- She was referred to the gastroenterology service where she had endoscopic studies performed

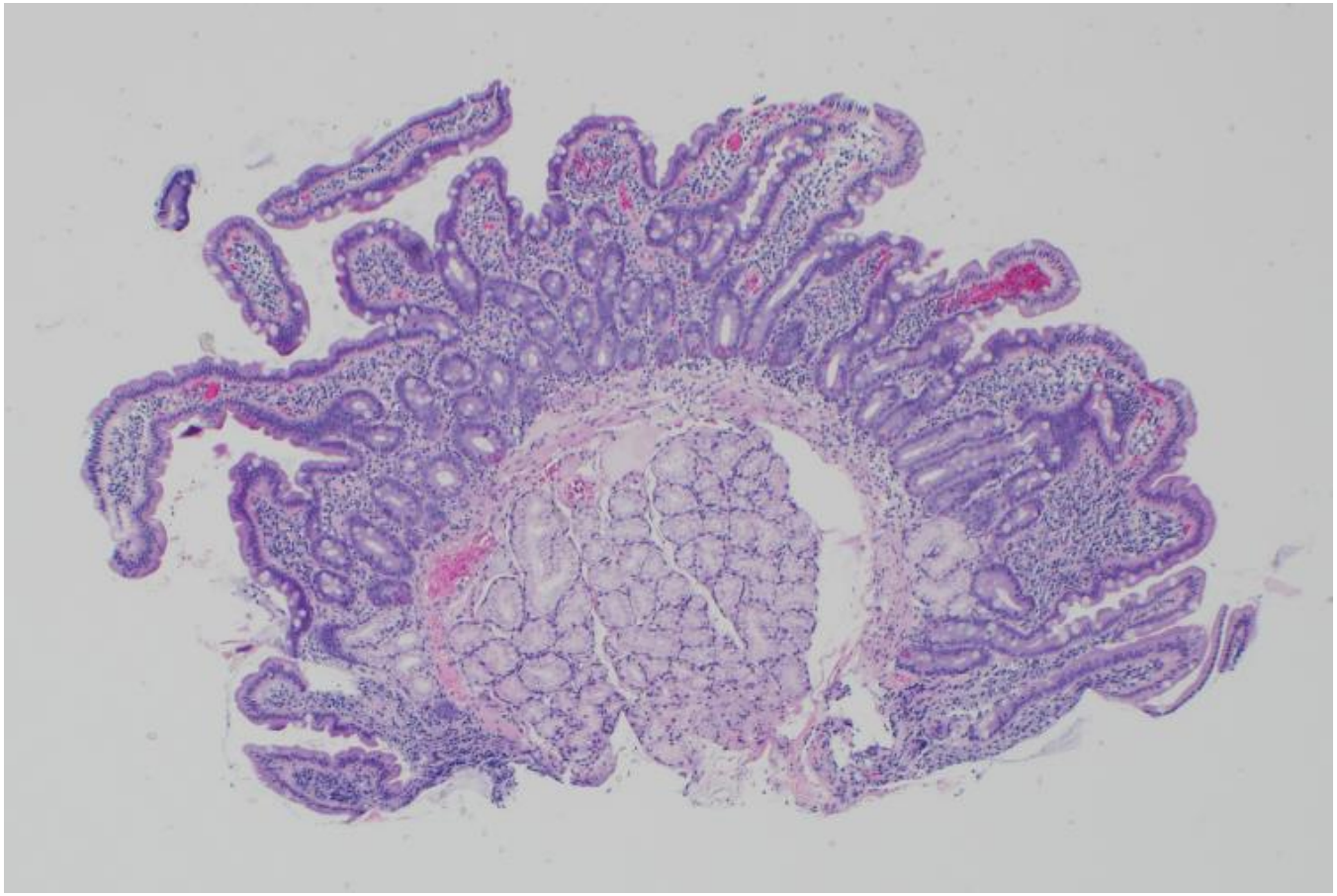

duodenum, second portion

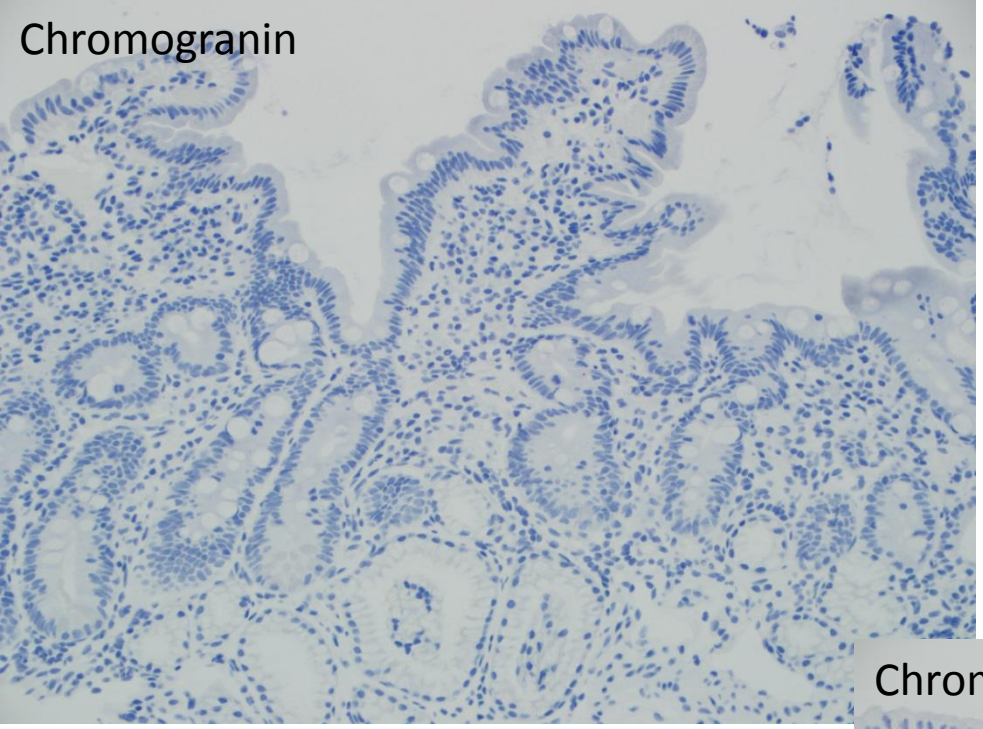

ileum

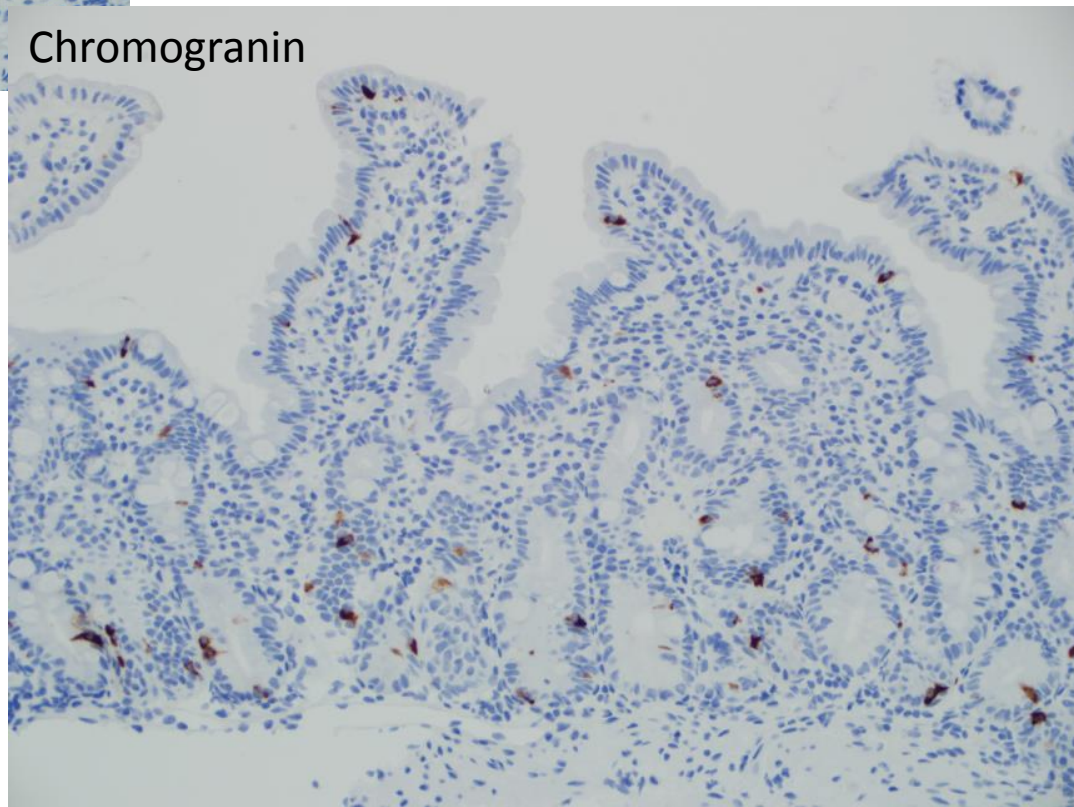

mid transverse colon


rectum






Chromogranin


Chromogranin

# Diagnosis

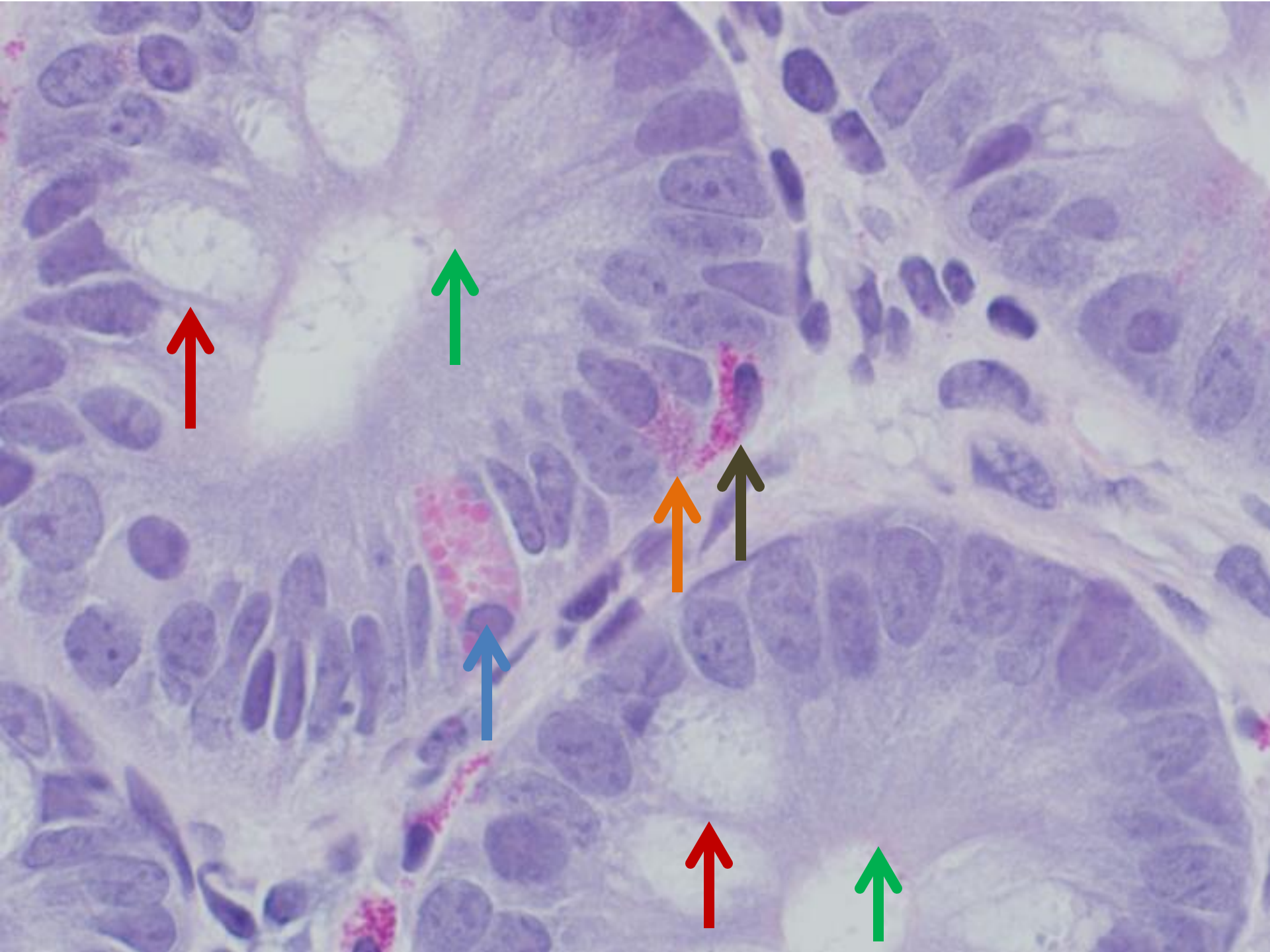
- Microvillus inclusion disease
- Congenital tufting enteropathy
- α6β4 integrin defect
- Enteroendocrine cell dysgenesis
- IPEX syndrome

# Enteroendocrine cell dysgenesis

- Rare congenital disorder, recently recognized
- Life threatening intestinal malabsorption early in life
- Water is absorbed normally
- Dehydration, metabolic acidosis, malnutrition of all nutrients
- Most patients are of Mexican origin

# Pathophysiology and Pathology

- **Arrest in endocrine cell development in small intestine and colon**
- **Biopsies may appear normal or show nonspecific changes on H&E**
- **Absence of enteroendocrine cells revealed by chromogranin IHC**
- **Normal compliment of Paneth, goblet and absorptive cells**
- **Autoimmune enteropathy may also show loss of enteroendocrine cells along with loss of Paneth and Goblet cells**



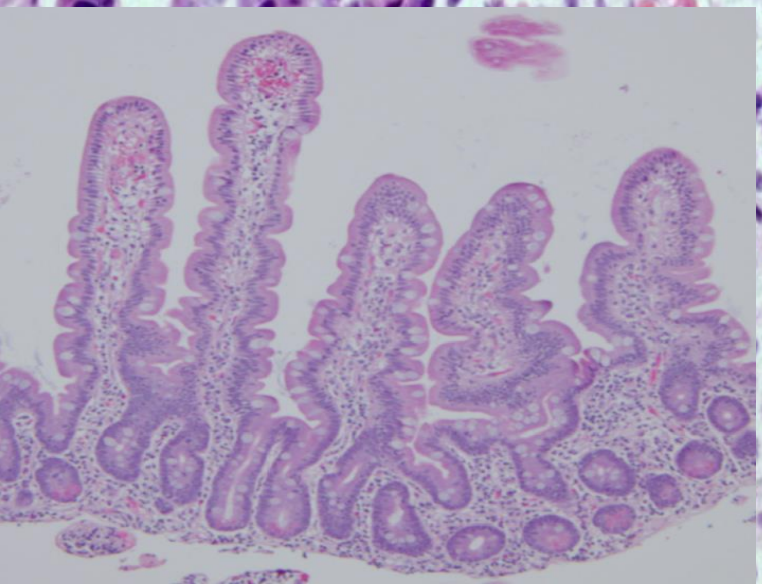
# Mutant Neurogenin-3 in Congenital Malabsorptive Diarrhea

Jiafang Wang, B.S., Galen Cortina, M.D., Ph.D., S. Vincent Wu, Ph.D., Robert Tran, M.D., Jang-Hyeon Cho, Ph.D., Ming-Jer Tsai, Ph.D., Travis J. Bailey, Ph.D., Milan Jamrich, Ph.D., Marvin E. Ament, M.D., William R. Treem, M.D., Ivor D. Hill, M.D., Jorge H. Vargas, M.D., George Gershman, M.D., Douglas G. Farmer, M.D., Laurie Reyen, M.N., and Martín G. Martín, M.D.

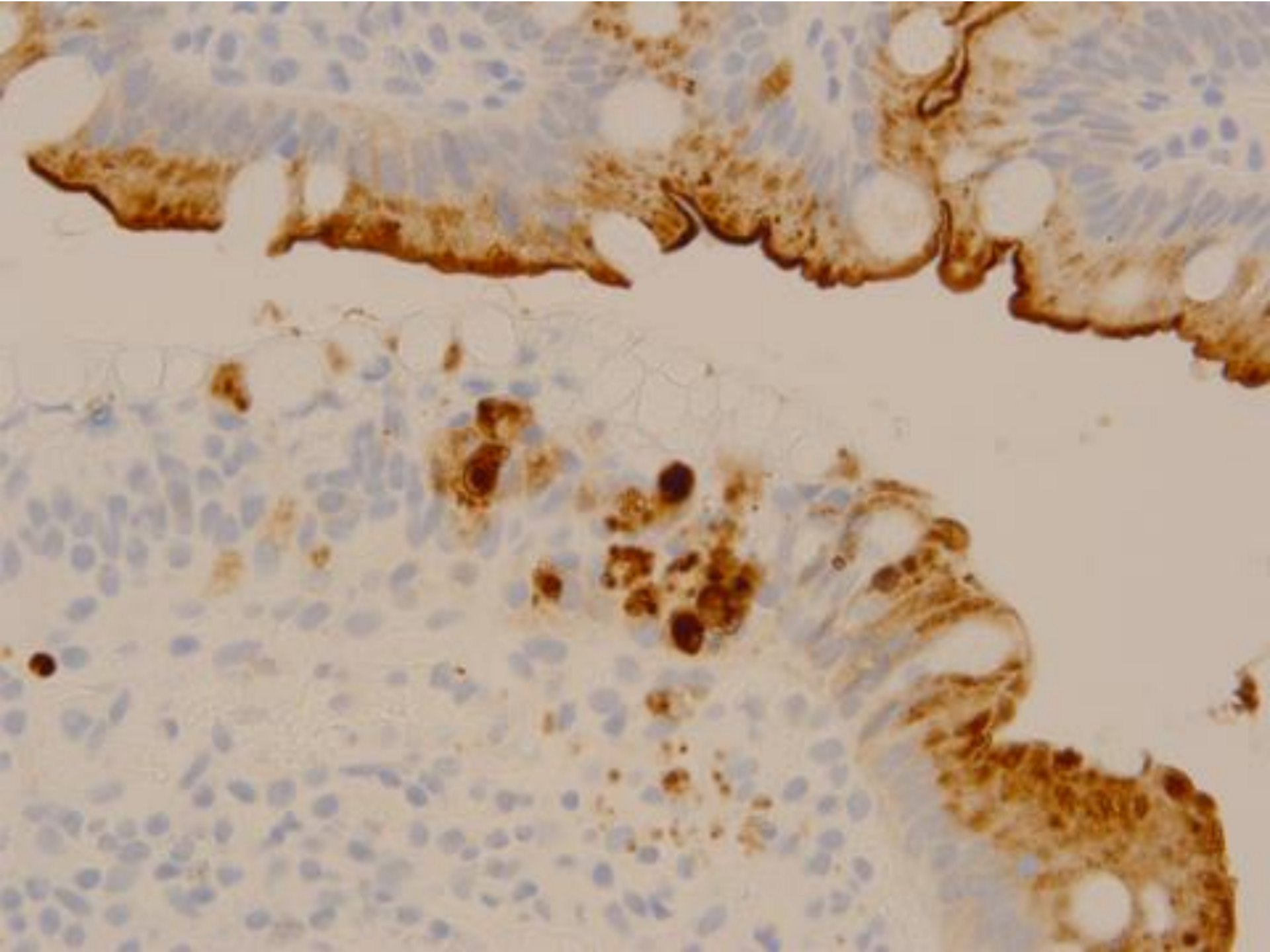
N Engl J Med 2006;355:270-80.

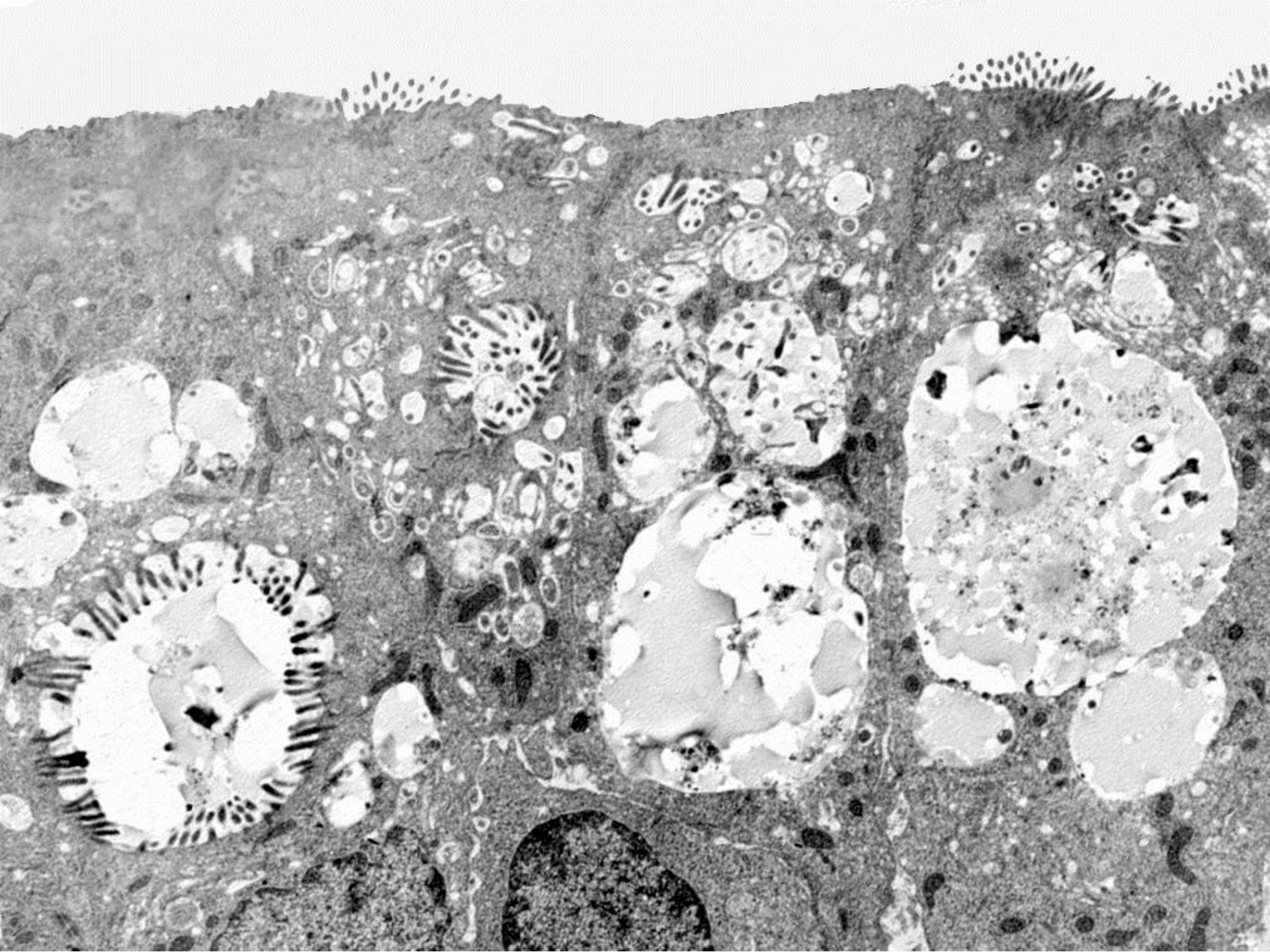
# Case 3

- **46 day old boy from the Four Corners region of the United States**
- **Has been having severe bouts of watery diarrhea that started mere days after birth**
- **Parents mention a similar history in a paternal cousin**
- **The infant appears lethargic**
- **He is at the 10$^{th}$ percentile for both body length and weight**
- **A biopsy showed villous blunting with no significant increase in intraepithelial lymphocytes**



# Diagnostic considerations





# Diagnosis

## Microvillus inclusion disease

# WHAT DO WE KNOW ABOUT MVID?

- Rare congenital, autosomal recessive disorder
- First described by Davidson
- Presents within first days of life with protracted diarrhea
- Due to an enterocyte defect
- Initial survival depends on early recognition and institution of TPN
- Intestinal transplant is necessary for long term survival

Gastroenterology. 1978 Nov;75(5):783-90.

# Familial enteropathy: a syndrome of protracted diarrhea from birth, failure to thrive, and hypoplastic villus atrophy.

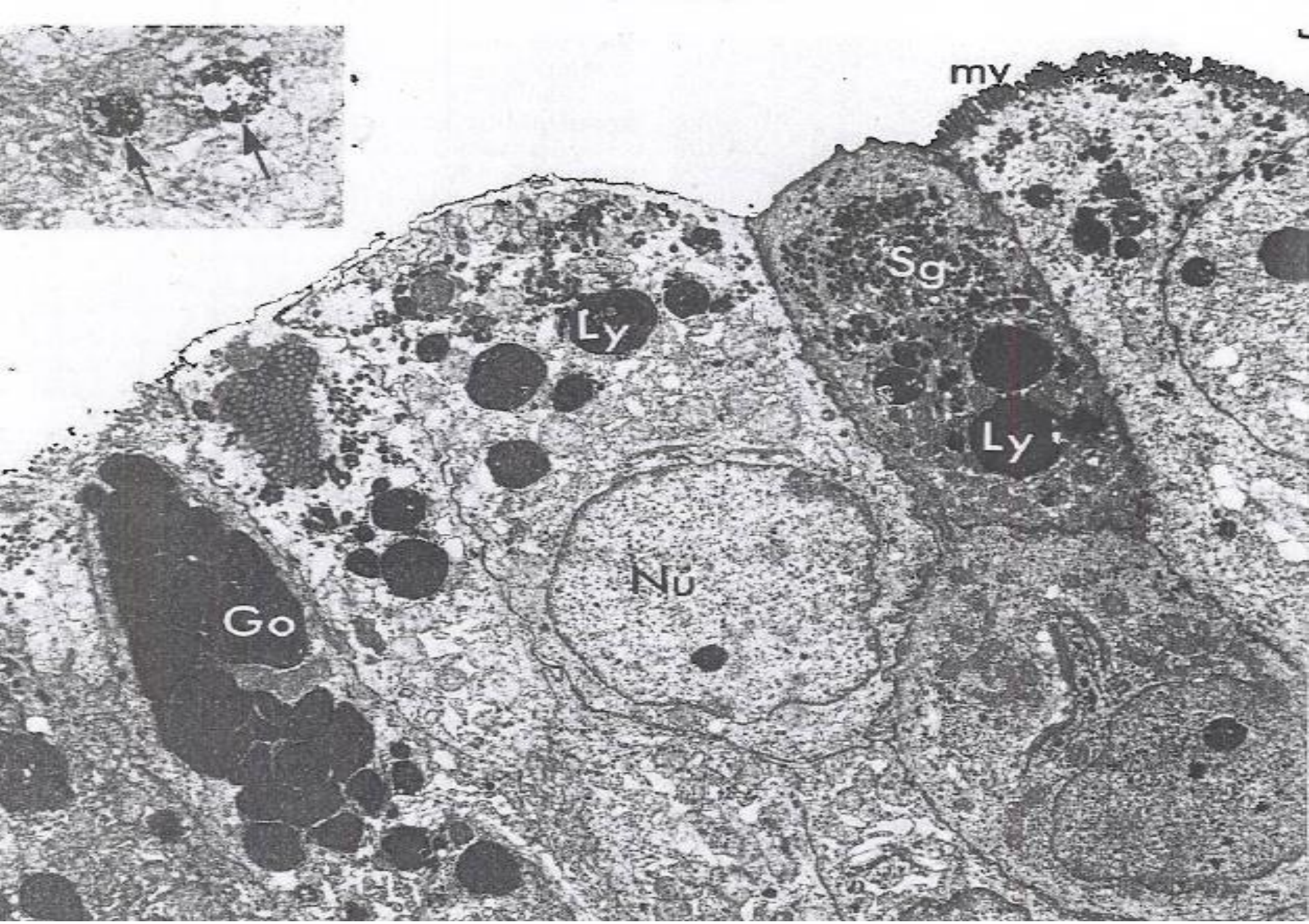
Davidson GP, Cutz E, Hamilton JR, Gall DG.

## Abstract

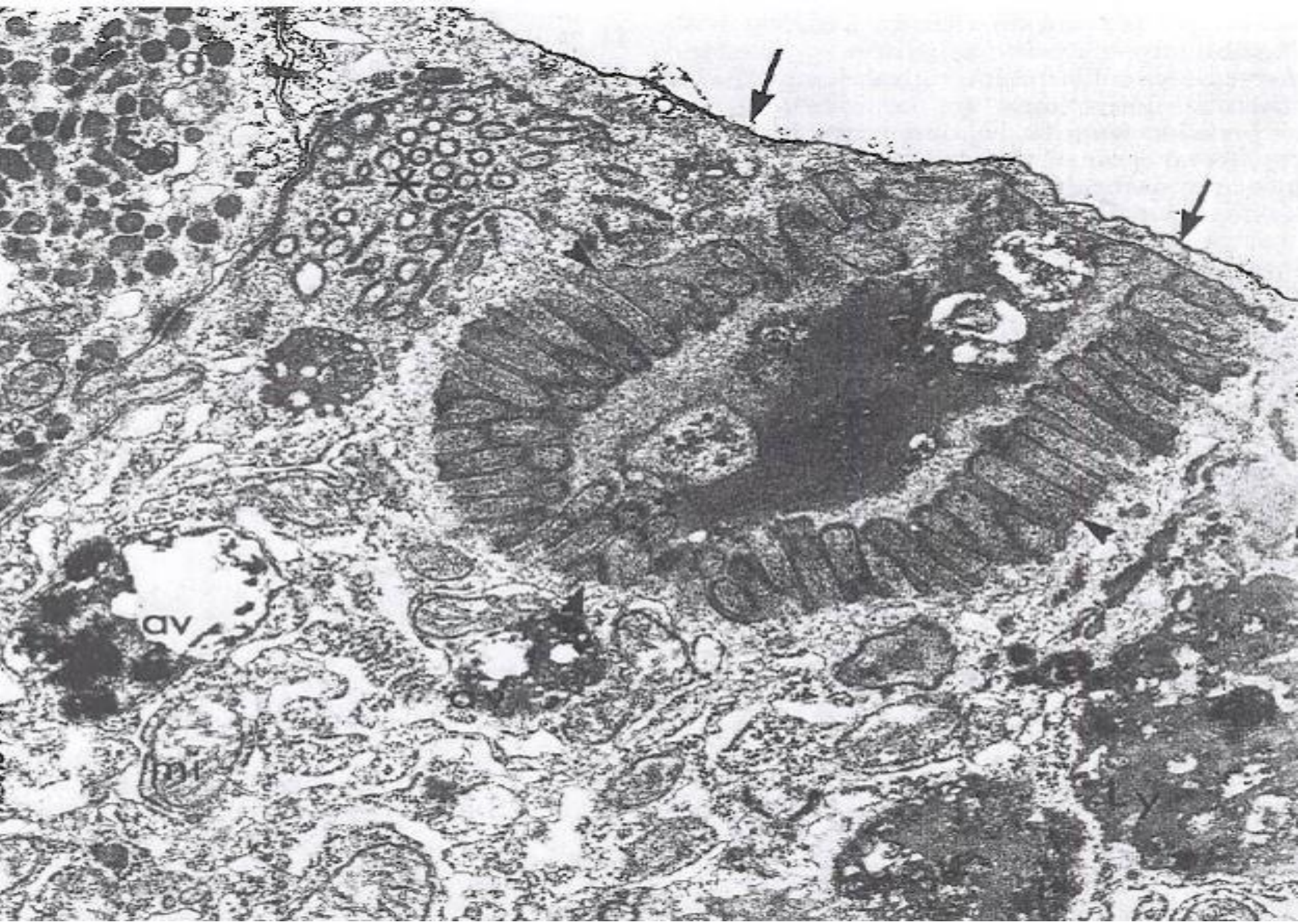
We have studied 5 infants with persistent severe diarrhea from birth and marked abnormalities of absorption associated with failure to thrive leading to death in 4 infants. Three had siblings who died and a sibling of a 4th is ill at present, all with a similar illness; 2 were the products of consanguinous marriages. Exhaustive investigation failed to identify a recognized disease entity in any patient. Steatorrhea, sugar malabsorption, dehydration, and acidosis were severe in all patients, whatever the diet fed. Total parenteral nutrition was used, but excessive stool water and electrolyte losses persisted even when nothing was fed by mouth. There was no evidence of a hematological or consistent immunological defect in any infant and no abnormalities of intestinal hormones were noted. In the duodenal mucosa of all infants we saw similar abnormalities characterized by villus atrophy, crypt hypoplasia without an increase in mitoses or inflammatory cell infiltrate in the lamina propria and in villus enterocytes absence of a brush border, increase in lysosome-like inclusions, and autophagocytosis. In 3 infants studied by marker perfusion of the proximal jejunum we found abnormal glucose absorption and a blunted response of Na+ absorption to actively transported nonelectrolytes; in 2 there was net secretion of Na+ and H2O in the basal state. Our patients evidently suffered from a congenital enteropathy which caused profound defects in their capacity to assimilate nutrients. The similar structural lesion seen in the small intestinal epithelium of all of our cases undoubtedly contributed to their compromised intestinal function, but the pathogenesis of this disorder, if indeed it is a single disease, remains obscure.

# History

- 5 infants with persistent severe diarrhea and failure to thrive
- 3 had siblings who died and 1 with a severely ill sibling
- 2 were products of consanguineous marriages
- No recognizable disease entity even after exhaustive investigation




Davidson GP et al. Gastroenterology 1978; 75:783-90.




Davidson GP et al. Gastroenterology 1978;75:783-90.

# MICROVILLUS INCLUSION DISEASE



## MEDICAL INTELLIGENCE

### MICROVILLUS INCLUSION DISEASE: AN INHERITED DEFECT OF BRUSH-BORDER ASSEMBLY AND DIFFERENTIATION

ERNEST CUTZ, M.D., J. MARC RHOADS, M.D.,
BRENDAN DRUMM, M.B., B.CH.,
PHILIP M. SHERMAN, M.D.,
PETER R. DURIE, M.D.,
AND GORDON G. FORSTNER, M.D.

transport, leading to aberrant assembly of the components of the enterocyte surface membrane.

## METHODS

### Patients

The general clinical features of our nine patients with microvillus inclusion disease are summarized in Table 1. Patients 1, 2, and 3 were from our original group of five infants with familial enteropathy described in 1978.[1] The disease was diagnosed retrospectively in Patients 2 and 3 after a review of jejunal biopsy material preserved for electron microscopy demonstrated typical intracytoplasmic brush-border inclusions in surface enterocytes.[1,2] The disease in the other six patients was diagnosed and treated at our institution after 1980. Five of the nine patients were girls, and four were boys. Eight were born after at least 36 weeks of gestation. One patient had a low birth weight (Patient 9), and one (Patient 6) was moderately premature. In all cases, pregnancy and delivery were uneventful. Hydramnios was not observed in any of our patients, in contrast to congenital chloride diarrhea and diarrhea due to deficient sodium–hydrogen exchange, both of which are invariably associated with hydramnios.[5,6] Three sets of siblings were represented among the patients. Patients 2 and 3 were siblings, as were Patients 4 and 5. Patient 1 had an older brother who died at four months of age with a

- **Nine cases were studied**
- **An autosomal recessive pattern of inheritance was suspected**
- **They speculated that the cause was an inborn error of intracellular transport**
- **8 of 9 died by age 18 months**

# GENETICS

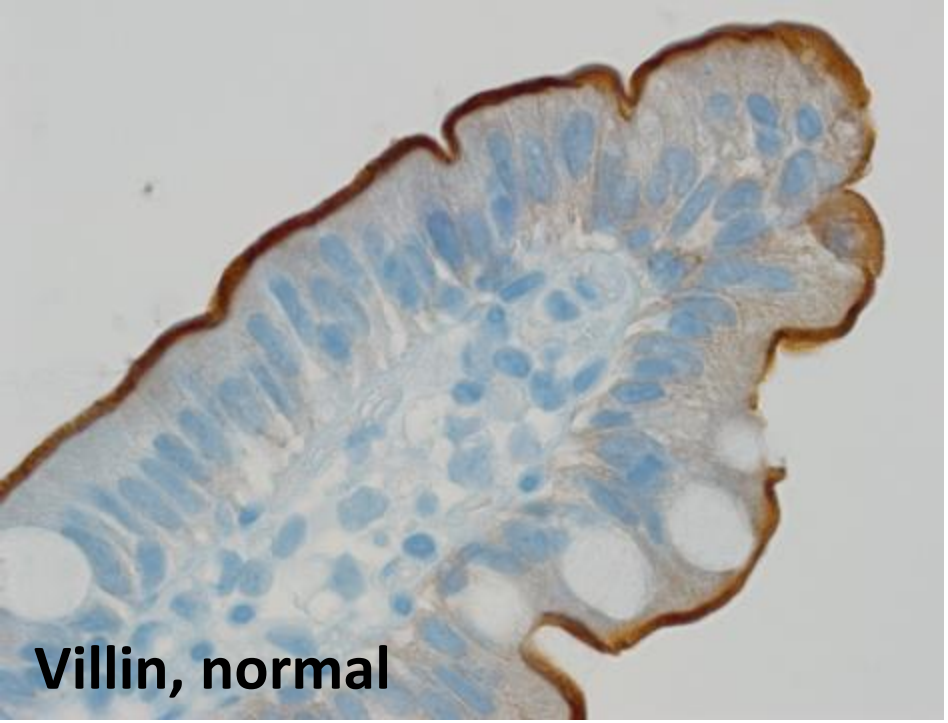
- In 1999 Pohl et al. described 5 unrelated cases of MVID among the Navajo people and suggested a founder effect
- Erickson et al. in 2008, identified a shared homozygous mutation in MYO5B
- Muller et al. reported similar findings in Turkish families in 2008
- Earlier studies by Caruthers et al. using protein electrophoresis implicated myosin

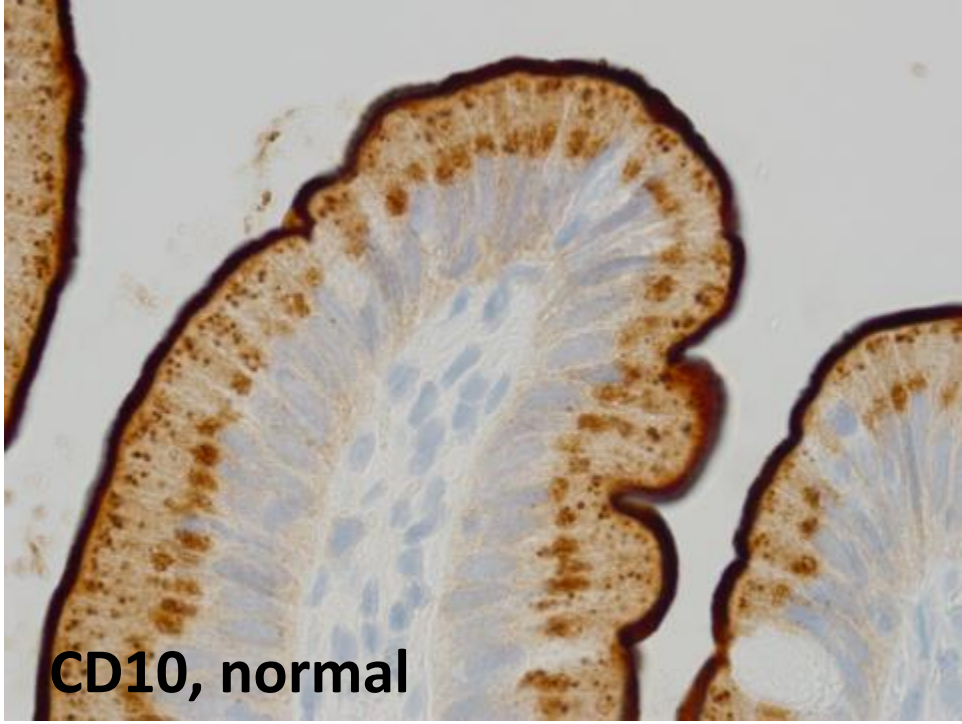
# DIAGNOSTIC TOOLS: HISTORY

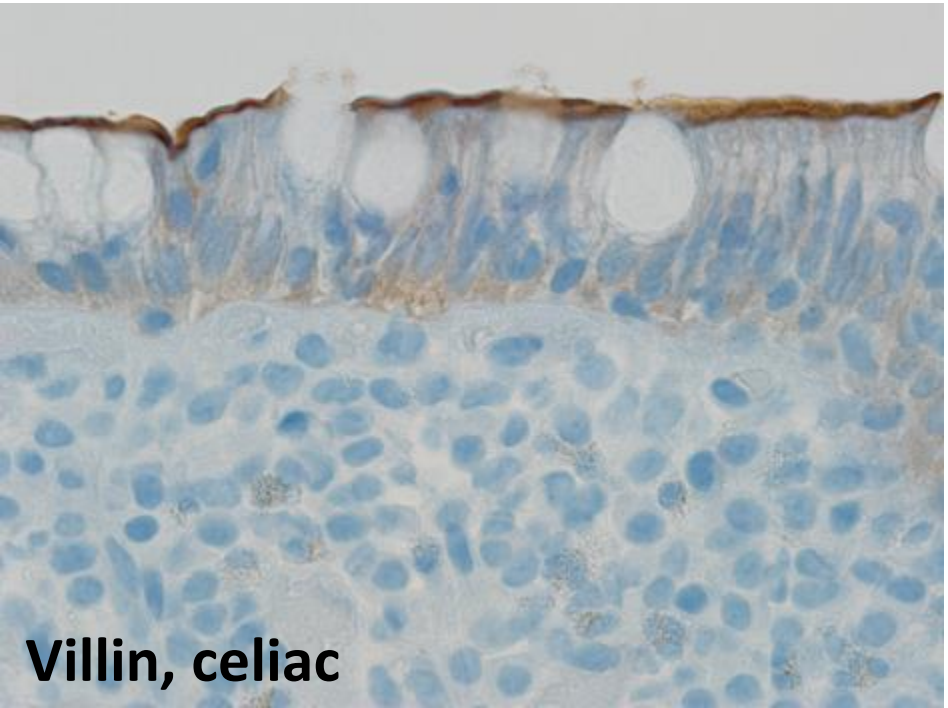
- Light and electron microscopy, Davidson et al., 1978
- PAS, Schmitz et al., 1982
- Alkaline phosphatase histochemistry, Lake, 1988
- Polyclonal CEA IHC, Groisman et al., 1993
- CD10 IHC, Groisman et al., 2002
- Rab 11 IHC, Talmon et al., 2012
- We decided to try a new marker, villin immunohistochemistry, as an adjunct in the diagnosis of MVID

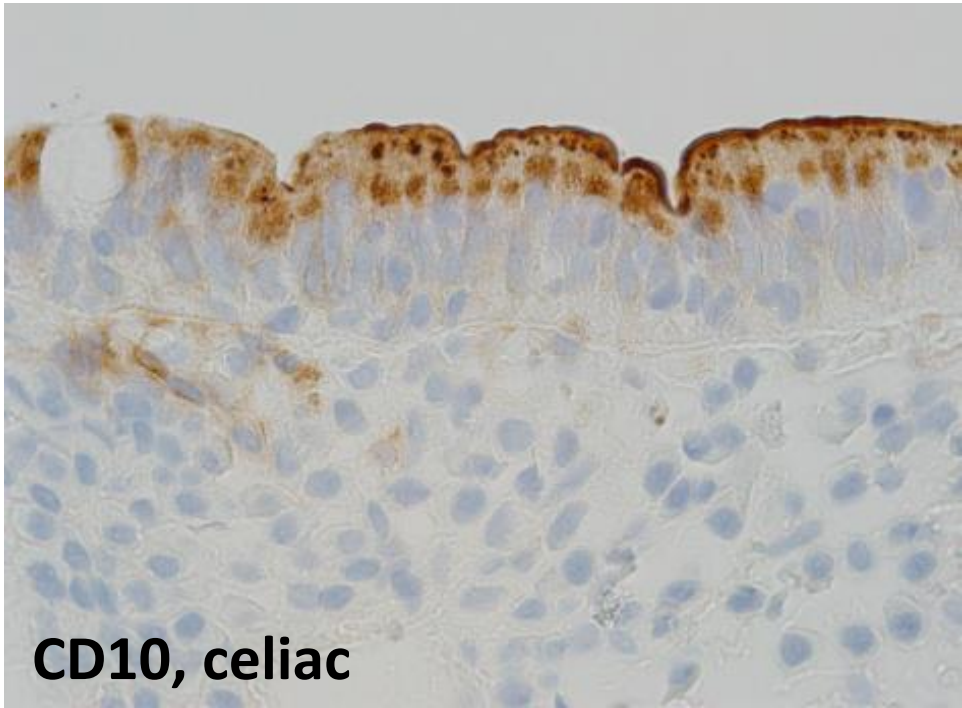
# Materials

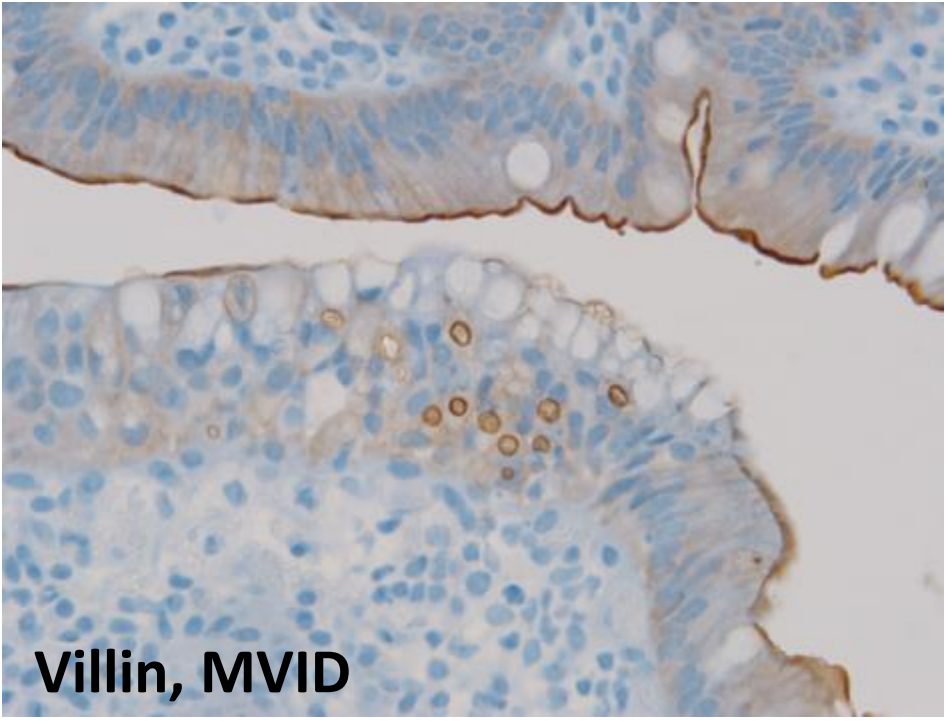
- 6 patients with a diagnosis of MVID since 1993
  - ✓ 7 duodenal
  - ✓ 5 gastric
  - ✓ 4 colonic
  - ✓ 1 terminal ileum
- 5 patients with a diagnosis of celiac disease
  - ✓ All duodenal biopsies
- 16 normal controls
  - ✓ 16 duodenal
  - ✓ 6 gastric
  - ✓ 5 colonic
  - ✓ 5 terminal ileum

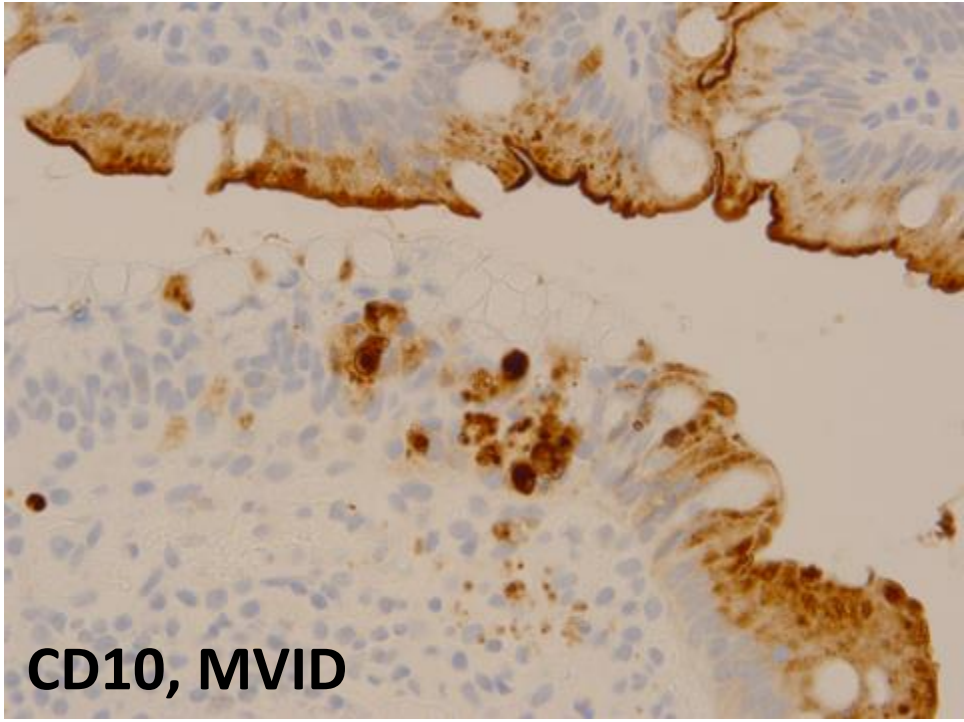

Villin, normal

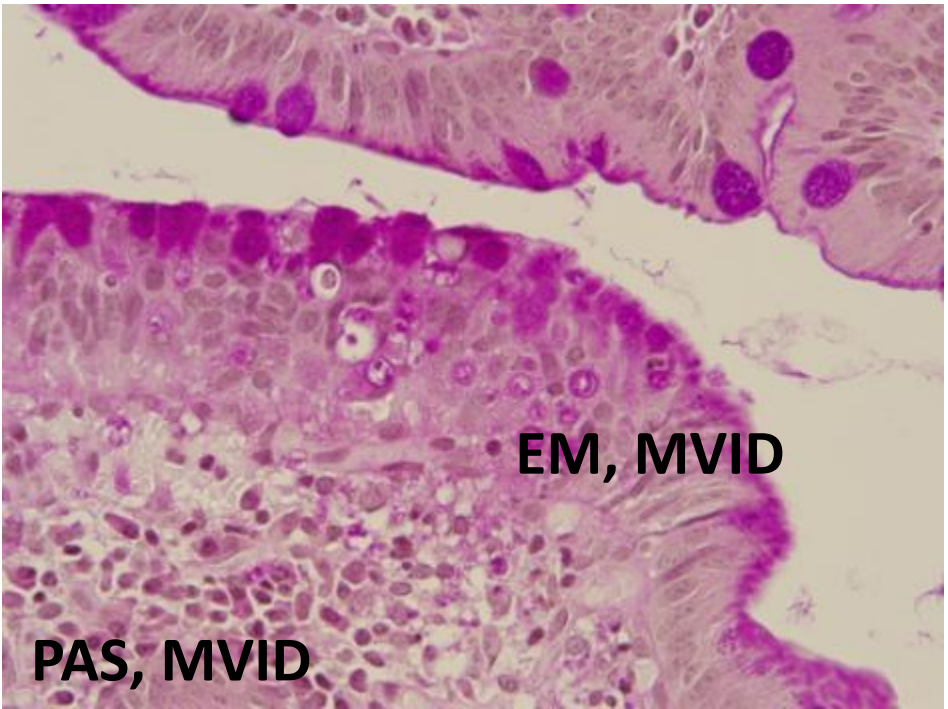

CD10, normal

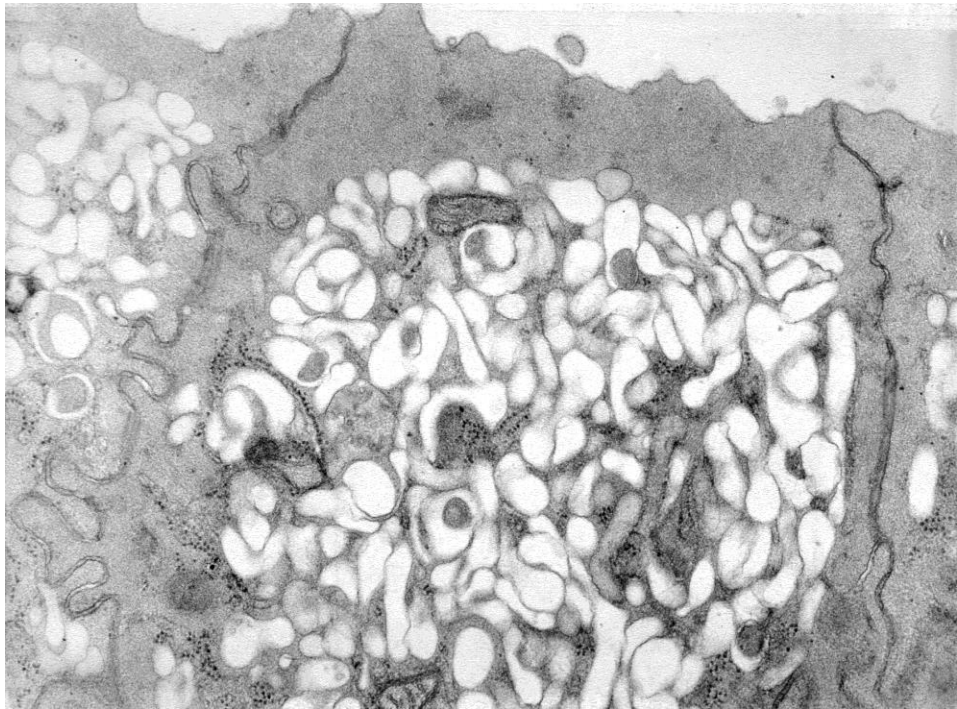

Villin, celiac

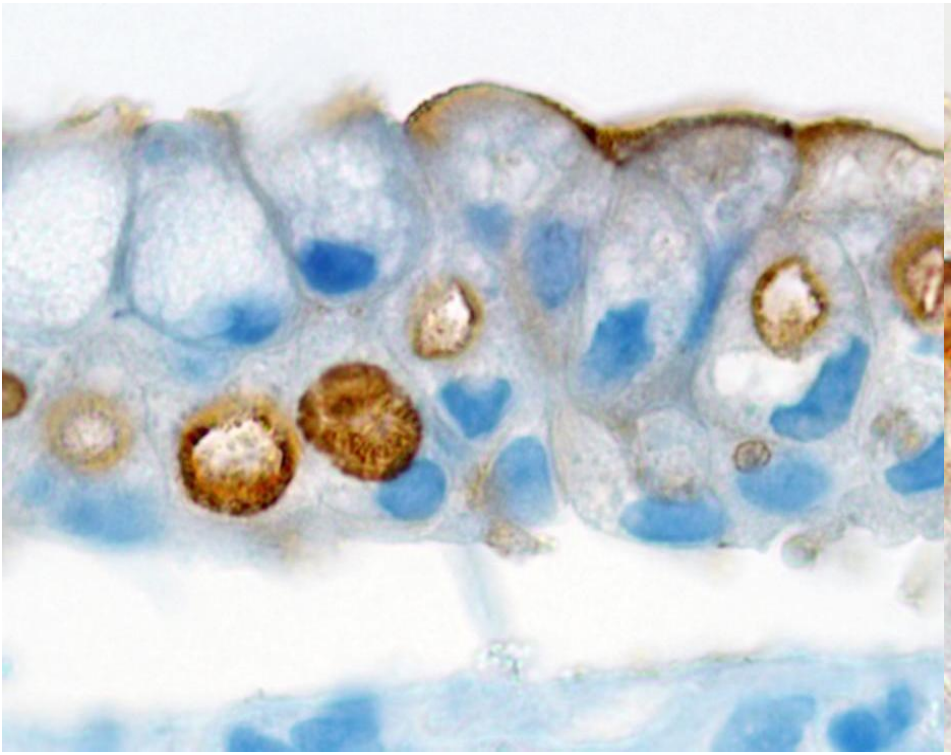

CD10, celiac


Villin, MVID

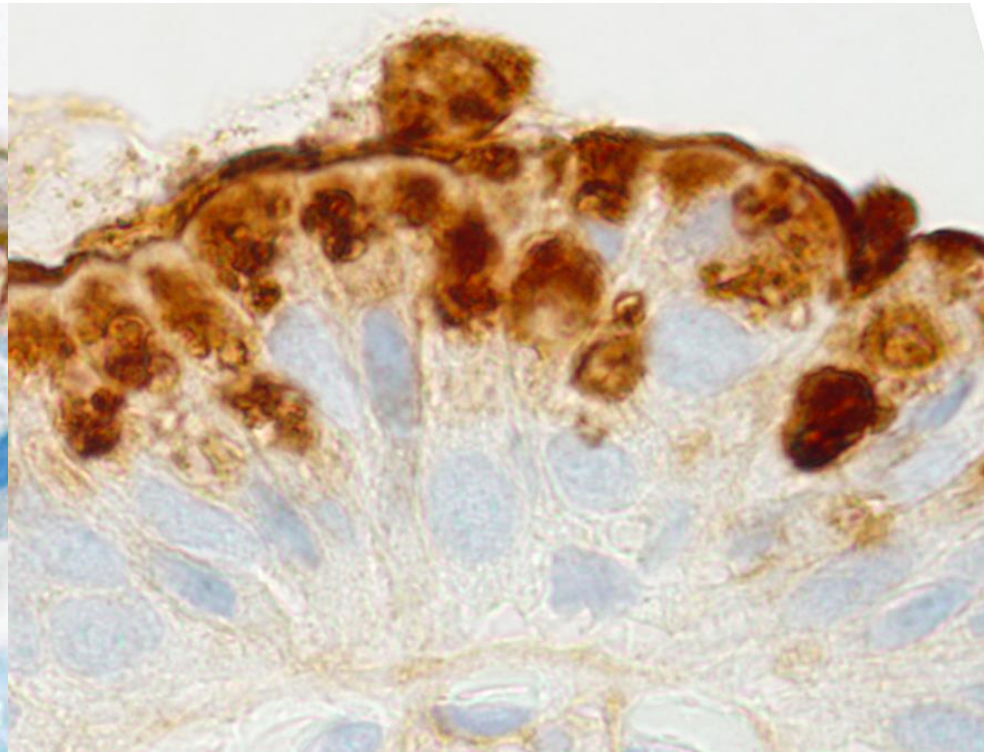

CD10, MVID


EM, MVID
PAS, MVID

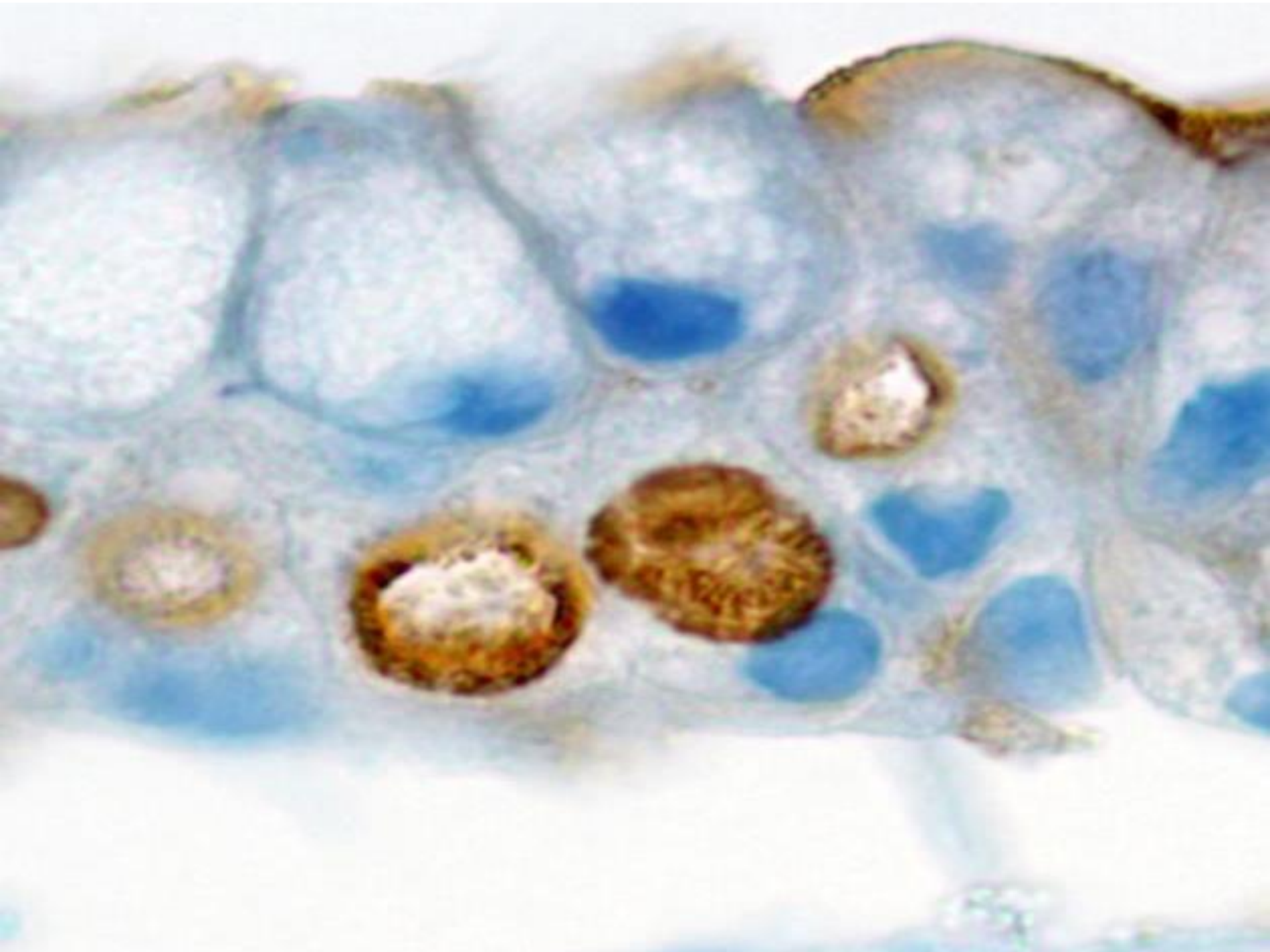




Villin, MVID



CD10, MVID



# Villin Immunohistochemistry Is a Reliable Method for Diagnosing Microvillus Inclusion Disease

*Nick M. Shillingford, MD,* Monica L. Calicchio, MS,* Lisa A. Teot, MD,* Theonia Boyd, MD,* Kyle C. Kurek, MD,* Jeffrey D. Goldsmith, MD,* Athos Bousvaros, MD,† Antonio R. Perez-Atayde, MD,* and Harry P.W. Kozakewich, MD**

***Am J Surg Pathol 2015;39:245-250***

**Abstract:** Microvillus inclusion disease (MVID) is a rare congenital disorder that manifests early in infancy as intractable watery diarrhea. The entity is characterized morphologically by a deficient brush border and apical cytoplasmic inclusions within absorptive cells (enterocytes) due to misplaced assembly of brush border proteins. The diagnosis is based upon histopathology, special stains, immunohistochemistry (IHC), and ultimately upon electron microscopy. Currently, the periodic acid-Schiff stain (PAS) and CD10 IHC are commonly used as adjuncts, but in addition to brush border structures, they stain a

Microvillus inclusion disease (MVID) is a rare autosomal recessive disorder characterized by profuse watery diarrhea beginning shortly after birth. The disease is progressive and fatal unless intestinal transplantation is performed. Intestinal biopsies show villous atrophy with variable absence of the brush border of enterocytes, increase in lysosome-like inclusions, and characteristic microvillus inclusions containing misplaced brush border structures. The extensive absence or misplacement of surface microvilli leads to the inability to absorb even the simplest of nutrients.[1,2]






# Differential diagnosis for enteroendocrine cell dysgenesis

| Enteroendocrine Cell Dysgenesis | Microvillus Inclusion Disease |
|---|---|
| Normal villi | Severe villus atrophy |
| Intestinal endocrine cells markedly decreased or absent | Normal intestinal endocrine cells |
| Normal enterocyte cytoplasm | PASd positive apical cytoplasmic inclusions (microlumena) |
| Normal brush border | Loss of brush border |
| Markedly decreased or absent endocrine cells | Endocrine cells present |

Both present with neonatal diarrhea and lack significant inflammation

| Enteroendocrine Cell Dysgenesis | Tufting Enteropathy |
|---|---|
| Normal villi | Variable villus atrophy |
| No enterocyte disorder or tufting | Surface epithelial crowding and tufting at villus tips |
| Markedly decreased or absent endocrine cells | Endocrine cells present |

Both present with neonatal diarrhea and lack significant inflammation

| Enteroendocrine Cell Dysgenesis | Abetalipoproteinemia |
|---|---|
| Normal enterocyte cytoplasm | Foamy cytoplasm filled with fat vacuoles |

Both present with neonatal diarrhea, essentially normal villus length and lack significant inflammation

| Enteroendocrine Cell Dysgenesis | Autoimmune Polyglandular Syndrome Type 1 |
|---|---|
| Congenital onset | Childhood or older onset |
| Unremitting diarrhea following feeding | Transient diarrhea |
| No associated abnormalities | Multiple endocrine organ failure, ectodermal dystrophy |

Both have essentially normal histology, without villus atrophy and decreased endocrine cells may be seen in both

| Enteroendocrine Cell Dysgenesis | Autoimmune Enteropathy |
|---|---|
| Normal villi | Partial to complete villus atrophy |
| No inflammation | Increased lamina propria and intraepithelial lymphocytes |
| Normal goblet cells | Goblet cells may be lost |
| Congenital | May present after neonatal period |
| Responds to total parenteral nutrition | Does not respond to parenteral feeding |

Endocrine cells may be depleted in autoimmune enteropathy

**Cortina et al. Human Pathology 2007;38:570–580**

# REFERENCES


- Tang W, Huang T, Xu Z, Huang Y. Novel Mutations in EpCAM Cause Congenital Tufting Enteropathy. J Clin Gastroenterol. 2016;00:000-000
- Shillingford N, Calicchio M, Teot L, Boyd T, Kurek K, Goldsmith J, Bousvaros A, Perez-Atayde A, Kozakewich H. Villin Immunohistochemistry is a Reliable Method for Diagnosing Microvillous Inclusion Disease. Am J Surg Pathol 2015;39:245-250
- Ranganathan S, Scmitt L, Sindhi R. Tufting Enteropathy Revisited. The Utility of MOC31 (EpCAM). Immunohistochemistry in Diagnosis. Am J Surg Pathol 2014;38:265-272
- Davidson GP, et al. Familial enteropathy. A syndrome of protracted diarrhea from birth, failure to thrive, and hypoplastic villus atrophy. Gastroenterology 1978;75:783-90.
- Cutz E, et al. Microvillous Inclusion Disease: An inherited defect of brush-border assembly and differentiation. N Eng J Med. 1989;320:646-651.
- Panebra A, et al. Regulation of phospholipase C-γ1 by the actin regulatory protein villin. Am. J. Physiol., Cell Physiol. 2007; 281 (3):C1046-58.
- Russo P, Parham D, Goldblum J, et al. Current Concepts in Pediatric Pathology. Surgical Pathology Clinics. Saunders 2010;vol 3:603-604.
- Erickson RP, Larson-Thome K, Valenzuelaa RK, et al. Navajo Microvillus inclusion disease is due to a mutation in MYO5B. Am J Med Genet A 2008;146:3117-9.
- Caruthers L, Phillips AD, Dourmashkin R, Walker-Smith JA. Biochemical Abnormality in Brush Border Membrane Protein of a Patient with Congenital Microvillus Atrophy. Journal of Pediatric Gastroenterology and Nutrition. 1985;(4):902-907.

# REFERENCES


- Lake BD. Microvillus inclusion disease: specific diagnostic features shown by alkaline phosphatase histochemistry. Journal of clinical Pathology 1988;41:880-882.
- Groisman GM, Ben-Izhak O, Schwersenz A, et al. The value of polyclonal carcinoembryonic antigen immunostaining in the diagnosis of microvillous inclusion disease. Human Pathology 1993;24:1232-1237.
- Groisman GM, Amar M, Livine E. CD10: a valuable tool for the light microscopic diagnosis of microvillous inclusion disease (familial microvillous atrophy). American Journal of Surgical Pathology 2002;26:902-907.
- Talmon G, Holzapfel M, DiMaio DJ, Muirhead D. Rab 11 Is a Useful Tool for the Diagnosis of Microvillous Inclusion Disease. International Journal of Surgical Pathology 2012;20(3):252-256.
- Khurana S, George S. Regulation of cell structure and function by actin-binding proteins: Villin's perspective. Federation of European Biochemical Societies. Elsevier 2008;dio:10.1016.
- Avery GB, Villavicencio O, Lilly JR, Randolph JG. Intractable diarrhea in early infancy. Pediatrics 1968;41:712-22
- Cortina G, Smart C, Farmer D, Bhuta S, Trim W, Hill I, Martin M. Enteroendocrine cell dysgenesis and malabsorption, a histopathologic and immunohistochemical characterization. Human Pathology 2007;38:570-580
- Sivagnanam M, Mueller JL, Lee H, et al. Identification of EpCAM as the gene for congenital tufting enteropathy. Gastroenterology 2008;135:429-37.

# REFERENCES


- Ram Reifen, Ernest Cutz, Anne-Marie Griffiths, Bo Ngan, Philip Sherman. Tufting Enteropathy: A newly recognized clinicopathological entity associated with refractory diarrhea in infants. Journal of Pediatric Gastroenterology and Nutrition 1994; 18:379-85.
- NG AY, Waring P, Ristevski S, et al. Inactivation of the transcription factor ELF# in mice results in dysmorphogenesis and altered differentiation of intestinal epithelium. Gastroenterology 2002;122:1455-66.
- Wang J, Cortina G, Wu SV, et al. Mutant Neurogenin-3 in congenital malabsorptive diarrhea. New England Journal of Medicine 2006;355:270-4.
- Lachaux A, Bouvier R, Loras-Duclaux I, et al. Isolated deficient alpha6beta4 integrin expression in the gut associated with intractable diarrhea. J Pediatr Gastroenerol Nutr 1999;29:395-401.
- Korber JS, Glasson MJ. Pyloric atresia associated with epidermolysis bullosa . J Pediatr 1997;90:600-601.
- Gerbe F, Legraverend C, Jay Philippe. The intestinal epithelium tuft cells: specification and function. Cellular and Molecular Life Sciences 2012. doi 10.1007/s00018-012-0984-7.
- Muller T, Hess MW, Schiefermeier N, et al. MYO5B mutations cause microvillus inclusion disease and disrupt epithelial cell polarity. Nat Genet 2008;40:1163-1165.


MY AUNT'S

# THANK YOU!