



A Diagnostic Close-Up: Microvillous Inclusion Disease (MVID) Under Electron Microscopy

Dr Hiba Issa
ST4 Histopathologist
Sheffield Teaching Hospitals NHS Foundation Trust

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Outline

-
- Case presentation
 - Clinical course
 - Microscopy findings (light and **electron**)
 - Diagnosis and differentials
 - What is MVID?
 - Conclusion
 - Acknowledgements
 - References

Case Presentation

—

Neonatal Period

-
- Uneventful intrauterine period, term birth, well, breastfed, discharge home within 24 hours.
 - D2 – readmitted, lethargic, treated for sepsis, discharged on D8
 - D21 – readmitted with 1 episode of bilious vomiting. Also had poor weight gain and slow feeding.
 - O/E – significantly distended abdomen
 - Initial investigations - metabolic acidosis
 - NGT (relieve distention and feeds)
 - Subsequently also developed ‘loose explosive stools’
 - Investigated by surgeons and medics (nephrologists initially) for possible causes including:
 - Hirschsprung enterocolitis
 - Metabolic diseases/ inborn errors of metabolism
 - Renal tubular acidosis
 - Infection/ sepsis
 - Congenital diarrhoeal diseases



Initial Investigations

-
- Blood investigations: urea and electrolytes - electrolytes imbalance, -ve blood culture
 - Urine investigations and culture – kidneys functioning well concentrating urine to preserve water, -ve culture
 - Stool testing for malabsorption screen and electrolyte testing - assess whether the intestines are properly absorbing nutrients using different parameters like stool PH, faecal fat ..etc, - consistent with secretory diarrhoea
 - Metabolic screen – No IEM found
 - Imaging: US abdomen + kidneys, AXR + contrast via NGT – dilated large bowel, excluded malrotation/volvulus
 - Differential diagnosis:
 - Hirschsprung enterocolitis
 - ~~Metabolic diseases/inborn errors of metabolism~~
 - ~~Renal tubular acidosis~~
 - ~~Infection/sepsis~~
 - Congenital diarrhoeal disease
 - MVID
 - Congenital Tufting Enteropathy
 - Enteroendocrine Cell Dysgenesis
 - Autoimmune Enteropathy

Further Investigations

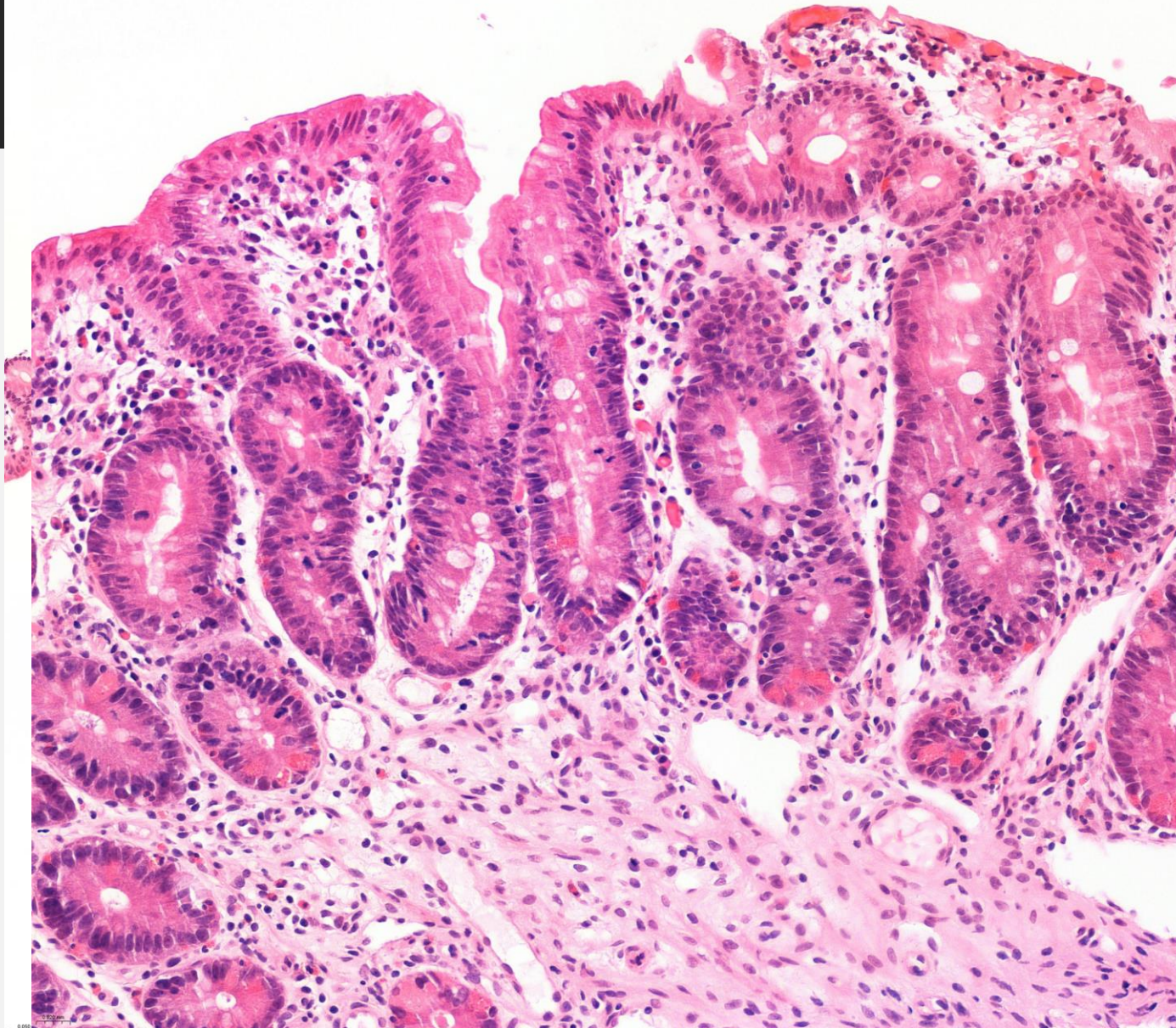
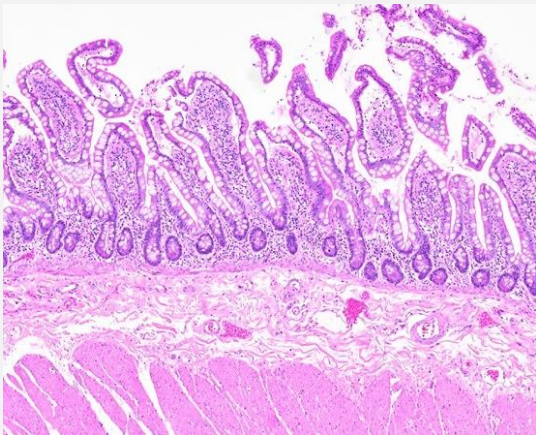
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- Oesophago-Gastro-Duodenoscopy (OGD) and sigmoidoscopy:
 - Gastric, sigmoid colon and rectal biopsies were WNL - Hirschsprung's disease excluded
 - **Duodenal biopsies clinched the diagnosis**
 - Genetic testing – confirmed the diagnosis
-
- Differential diagnosis:
 - ~~Hirschsprung enterocolitis~~
 - ~~Metabolic diseases/ inborn errors of metabolism~~
 - ~~Renal tubular acidosis~~
 - ~~Infection/ sepsis~~
 - Congenital diarrhoeal disease:
 - **MVID**
 - Congenital Tufting Enteropathy
 - Enteroendocrine Cell Dysgenesis
 - Autoimmune Enteropathy

Duodenal Biopsy

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Light Microscopy

H&E

- Villous blunting/ atrophy
- No epithelial tufting, increased IELs, or crypt hyperplasia
- No organisms seen



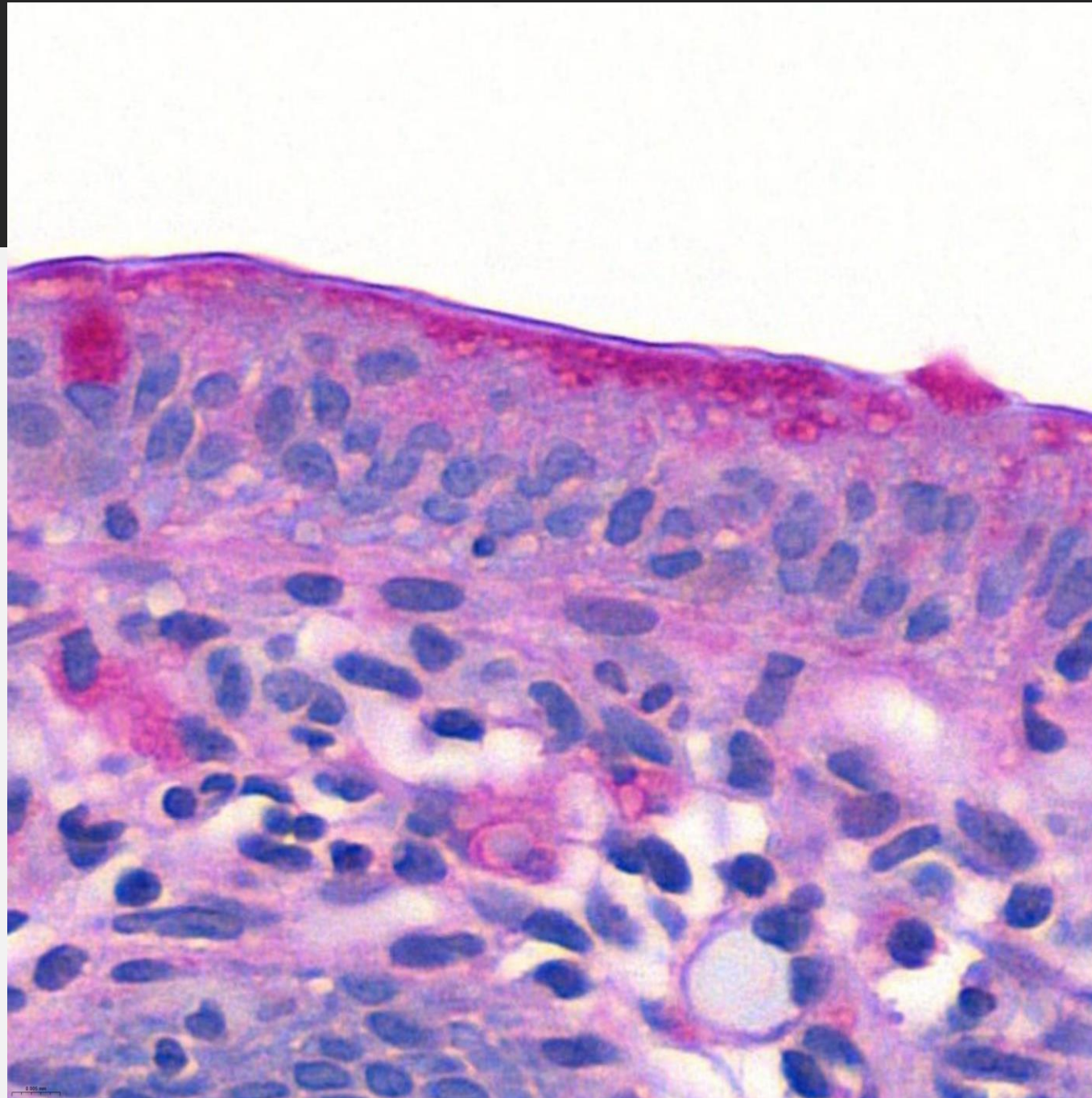
PAS

Normal:

- Periodic acid-Schiff
- Stains basement membrane, glycogen, some mucins and mucopolysaccharides
- Normally stains the brush border of enterocytes in a sharp continuous apical fashion
- Reflecting the glycoprotein-rich layer (glycocalyx) at the tips of microvilli



SMALL BOWEL | AbdominalKey



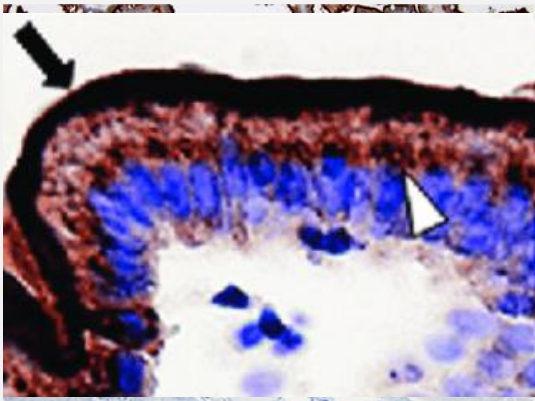
Our Case:

- **Abnormal intracytoplasmic apical band/blush (+ deeper)**
- Areas of staining loss

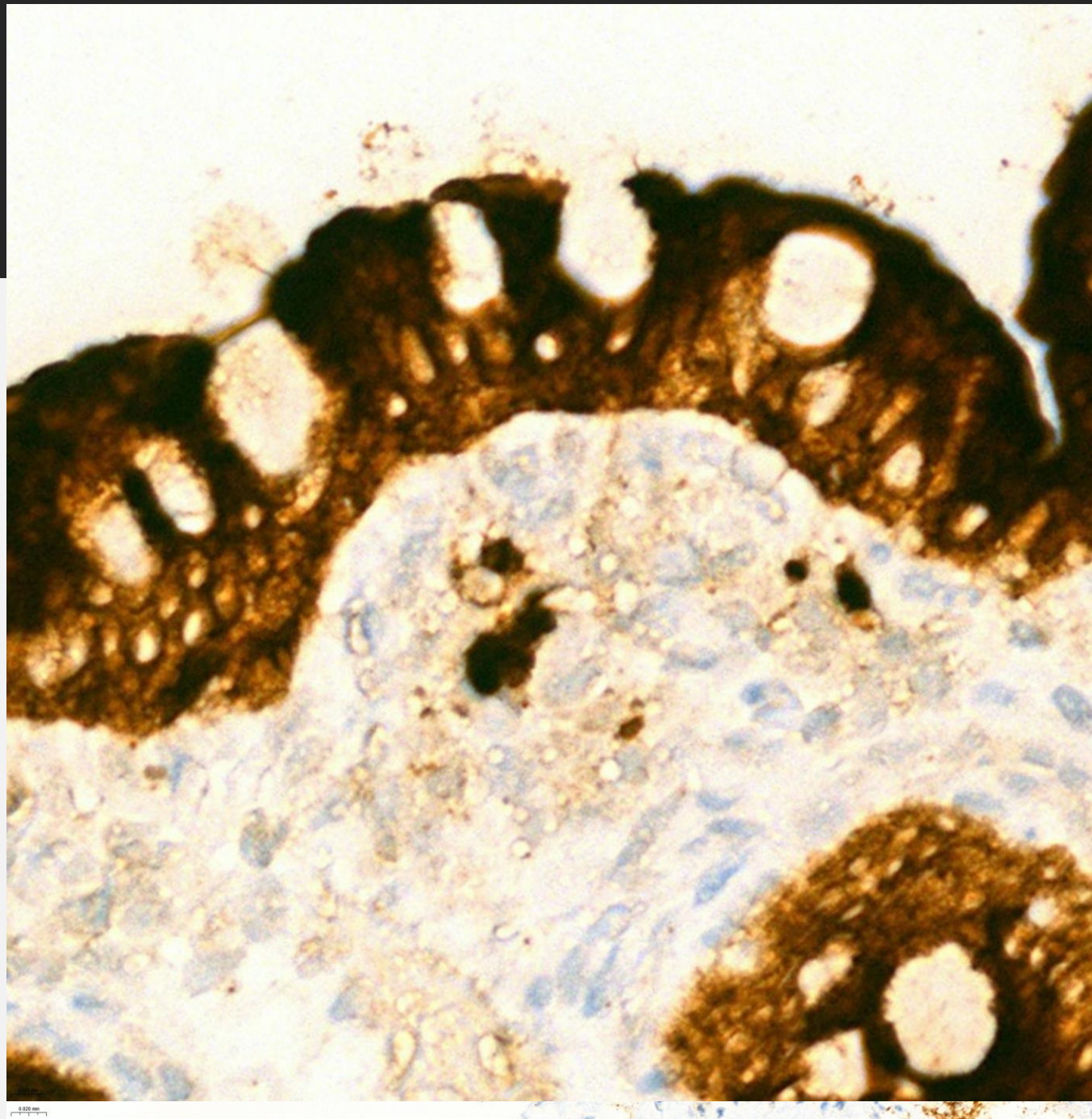
CD10

Normal:

- CD10 is a membrane-associated neutral peptidase (enzyme), present in the brush border
- Continuous strong positivity of the luminal surface of the epithelium



CD10 staining along the horizontal axis of the intestine of 2 patients... [Download Figure from Modern Pathology]



Our Case:

- Intense apical cytoplasmic staining
- May have areas of loss and cytoplasmic accumulation in vacuoles

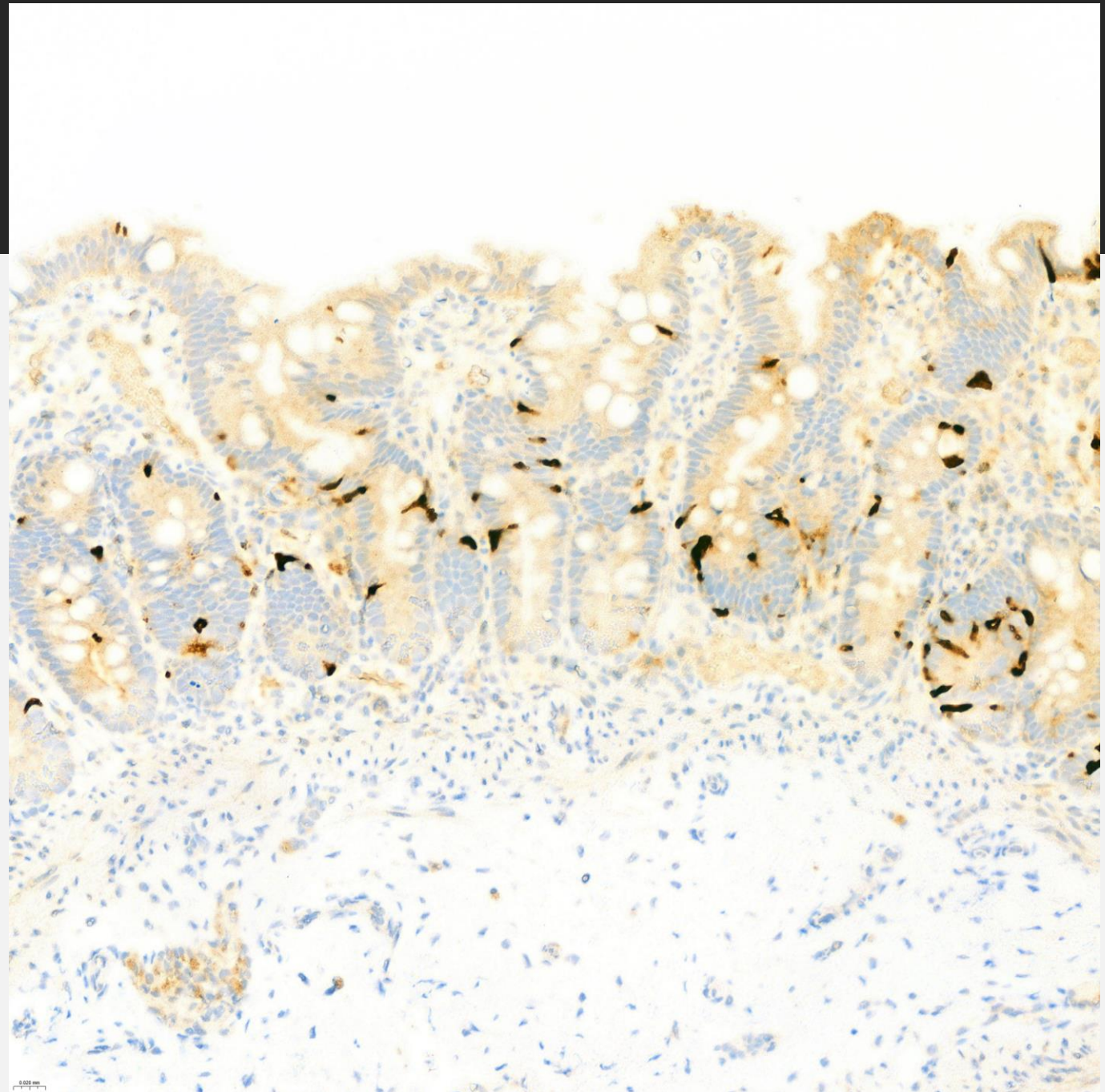
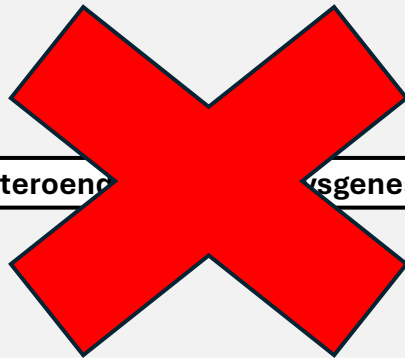
Chromogranin

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Neuroendocrine cells

Enteroendocrine

genesis



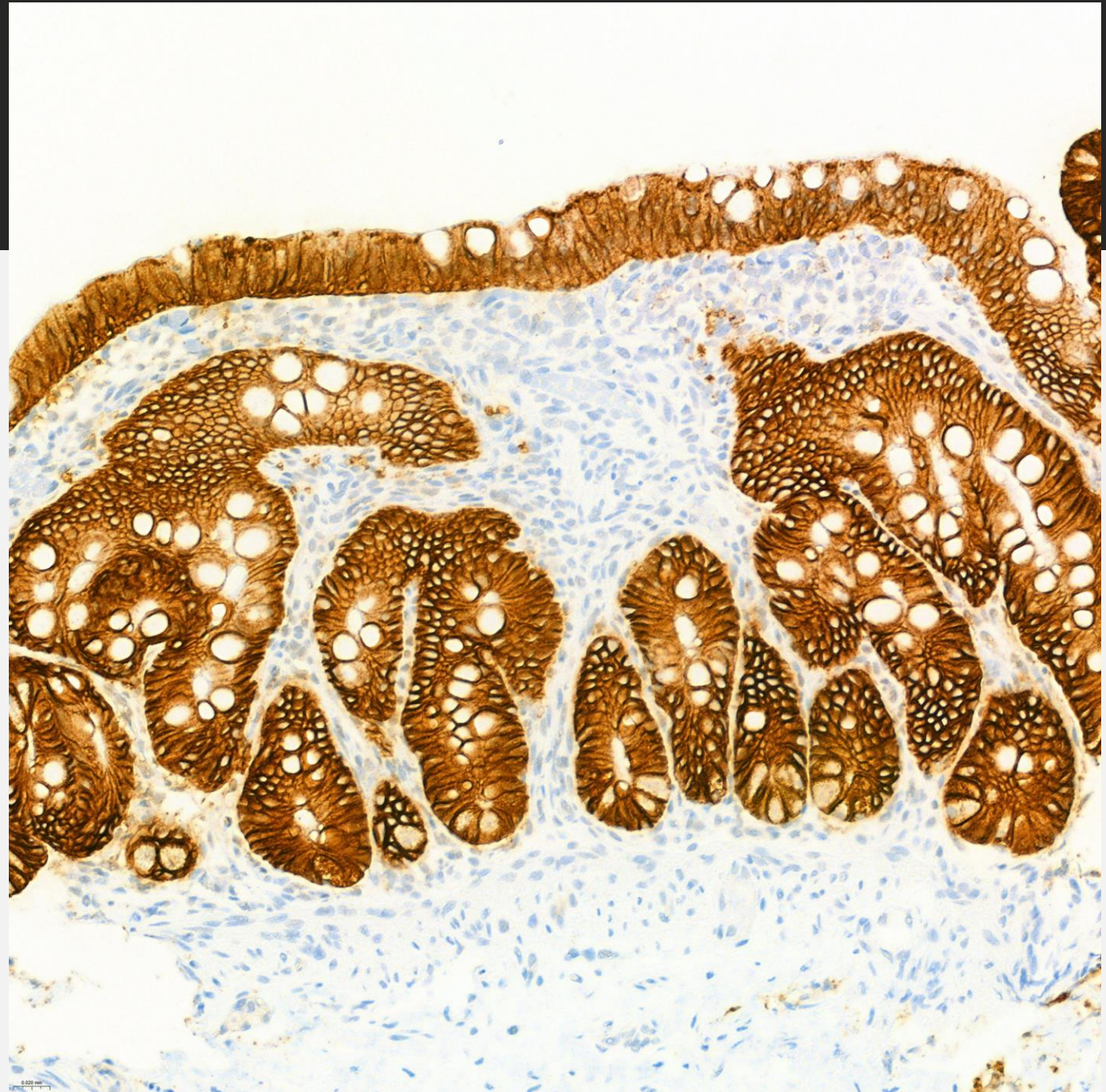
MOC31

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Binds to EpCAM (cell membrane glycoprotein) – strong membranous staining

Congenital

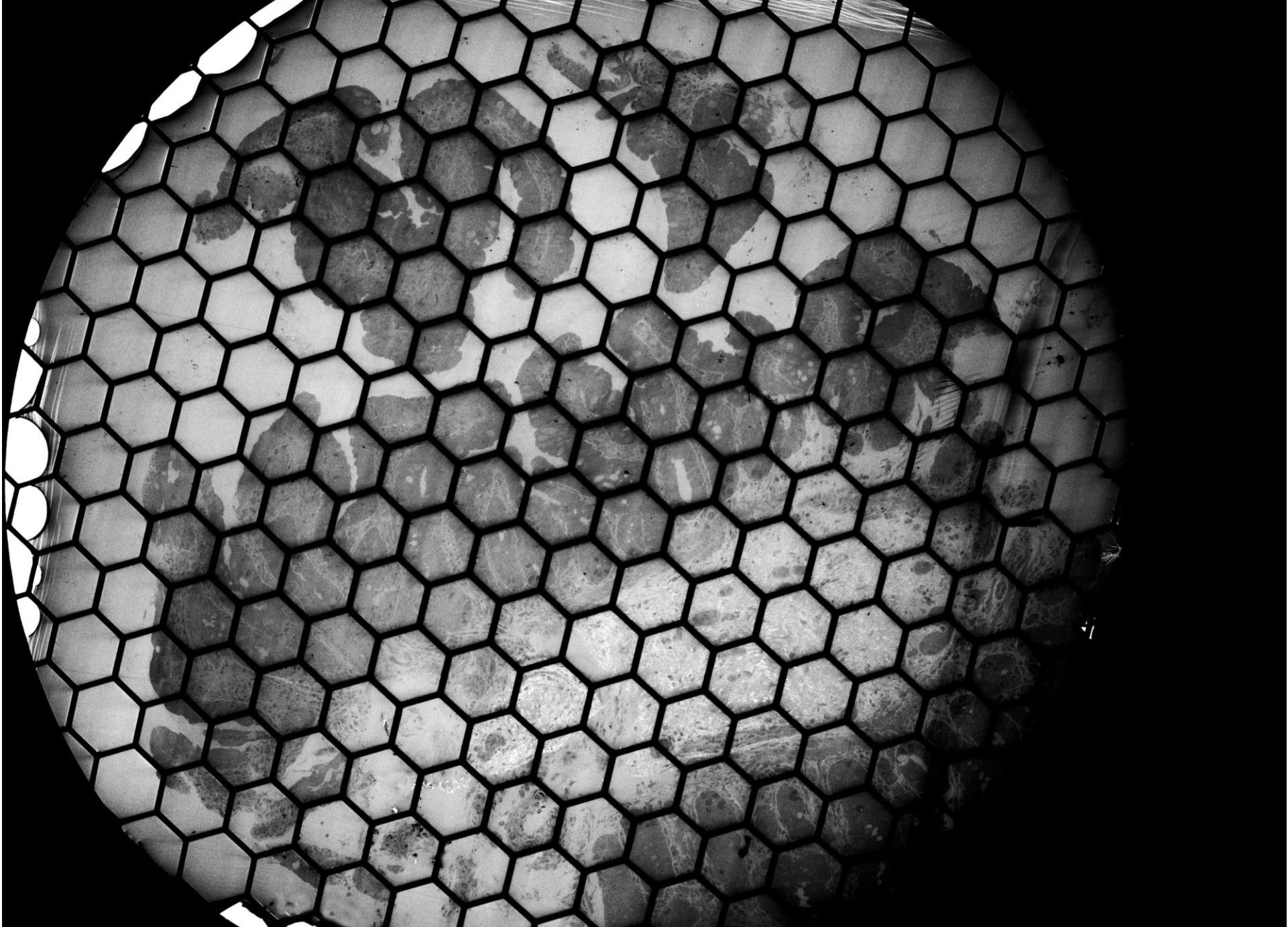
pathy (CTE)



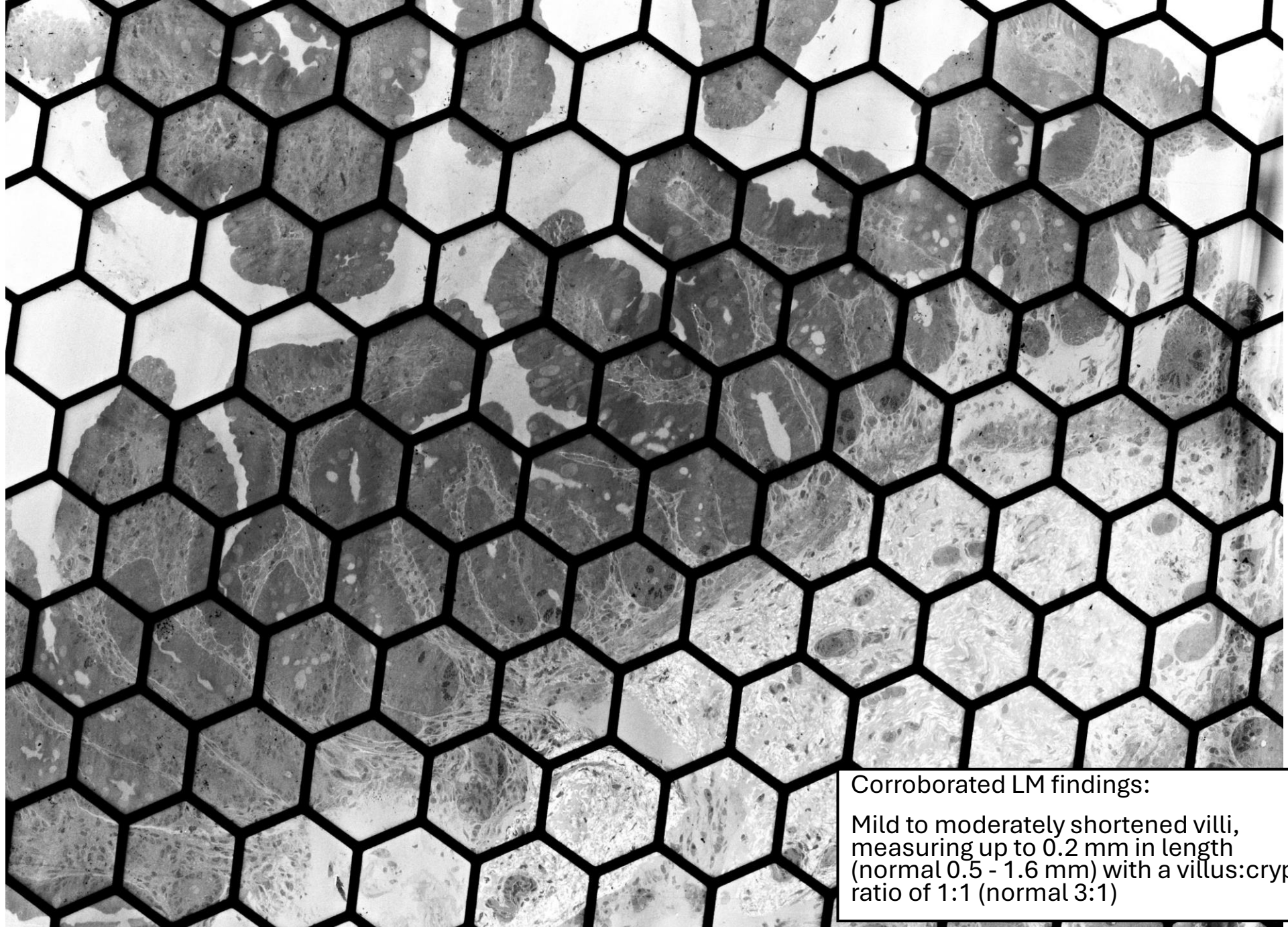
Duodenal Biopsy

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Electron Microscopy – Can you identify the findings?



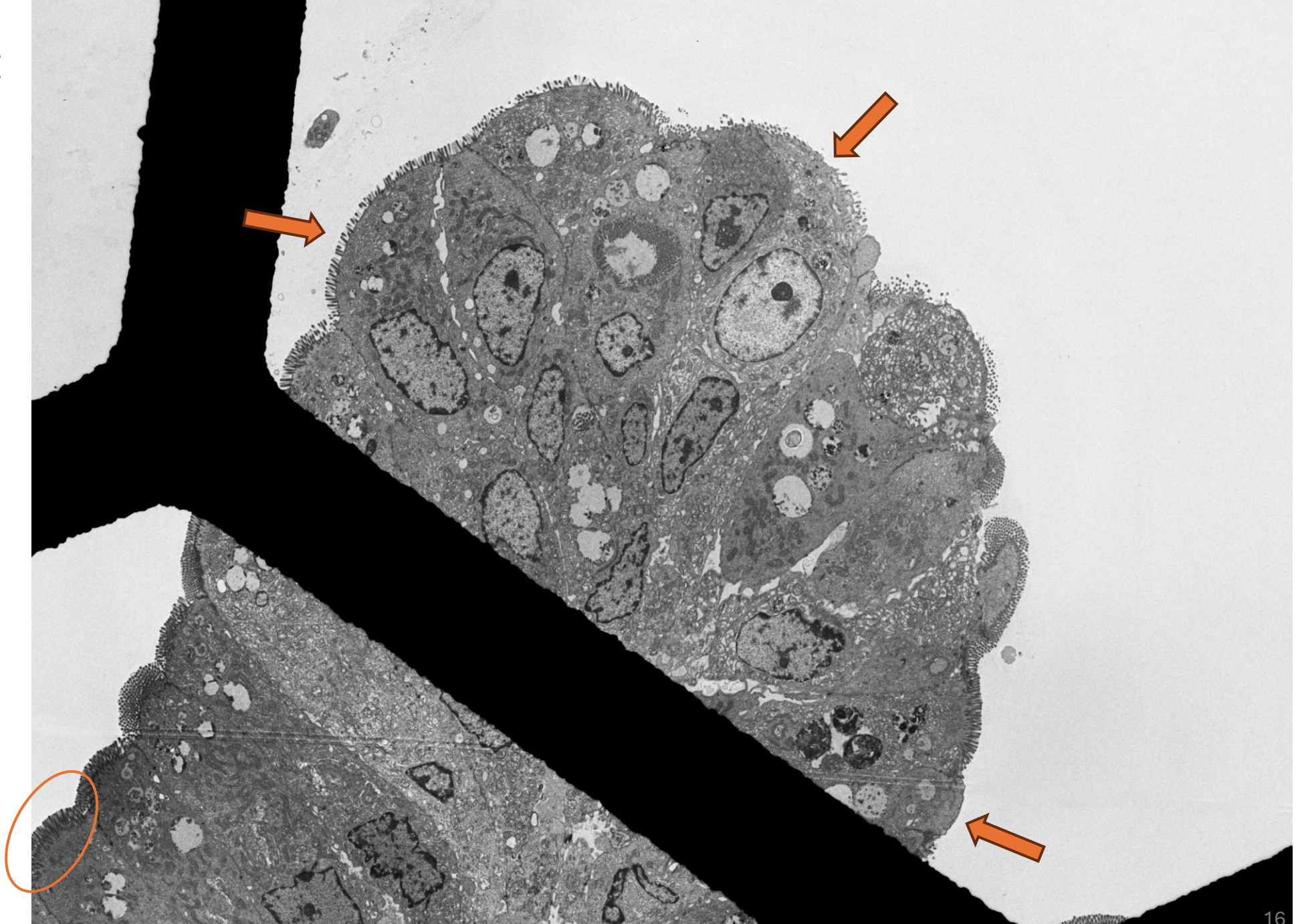
10 μ m
Direct Mag: 20 x



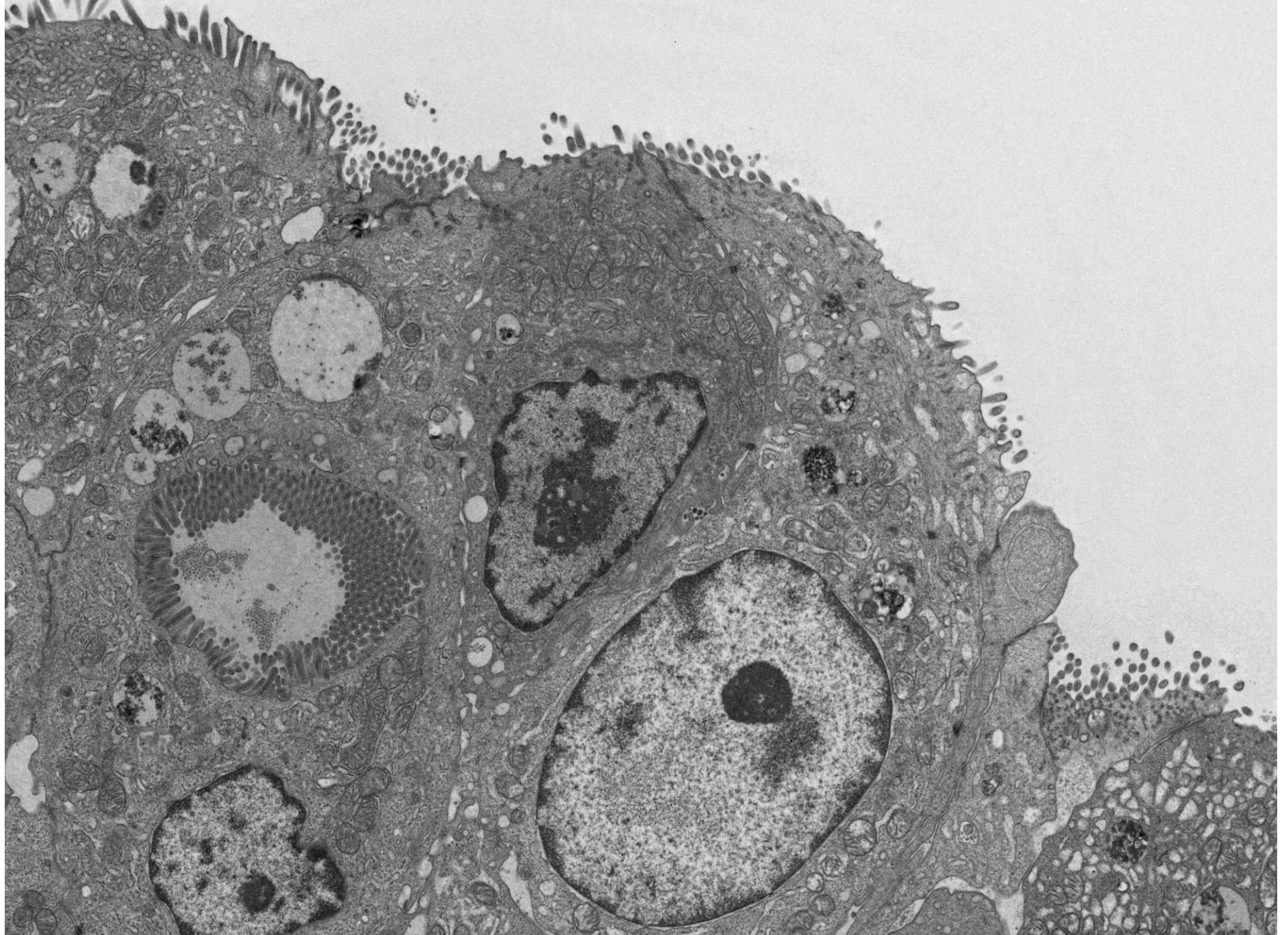
Corroborated LM findings:

Mild to moderately shortened villi, measuring up to 0.2 mm in length (normal 0.5 - 1.6 mm) with a villus:crypt ratio of 1:1 (normal 3:1)

Finding #1:



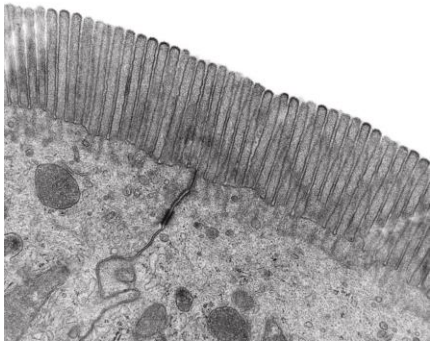
Finding #1:



Finding #1?

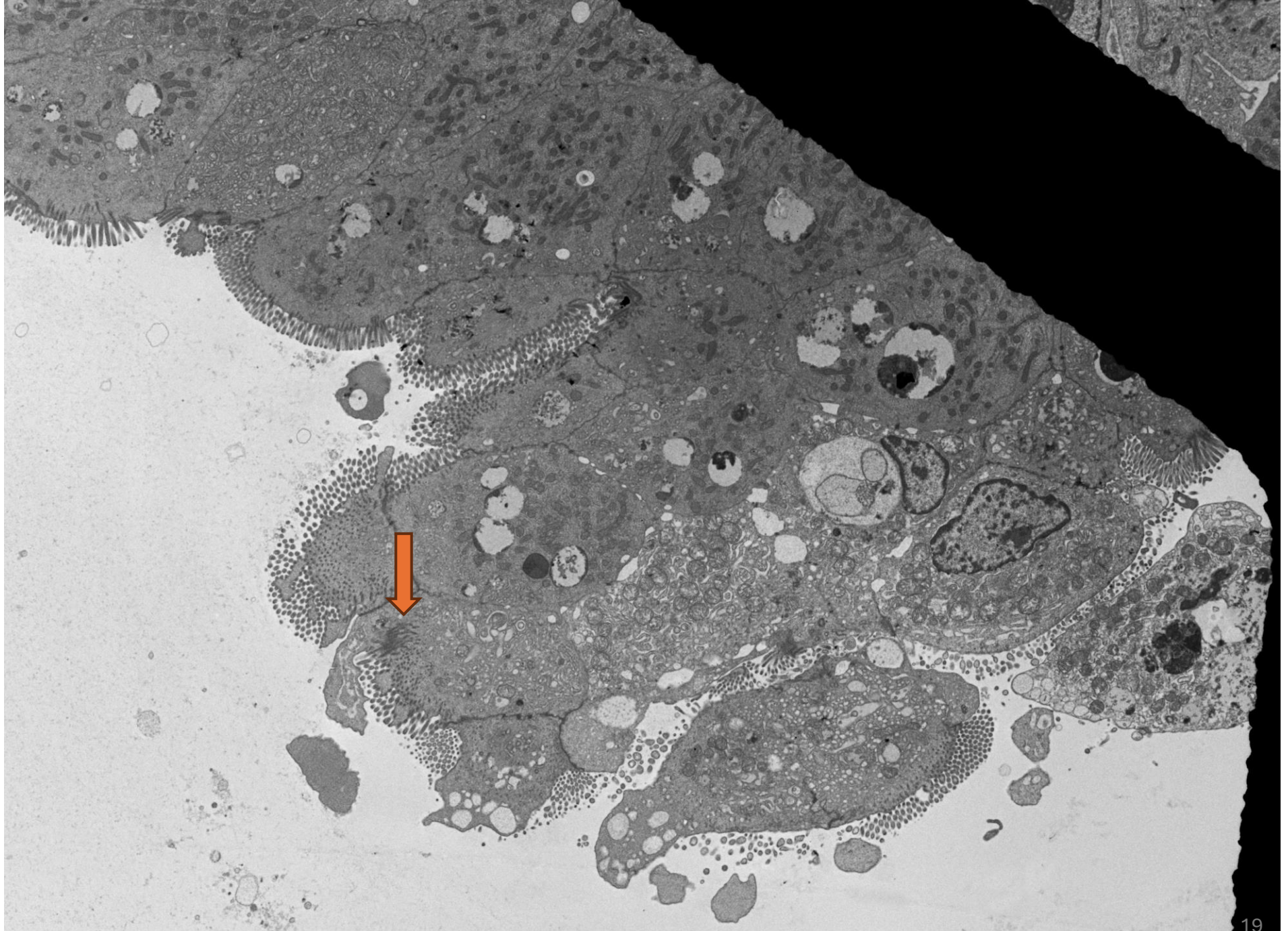


Normal enterocytes for comparison:

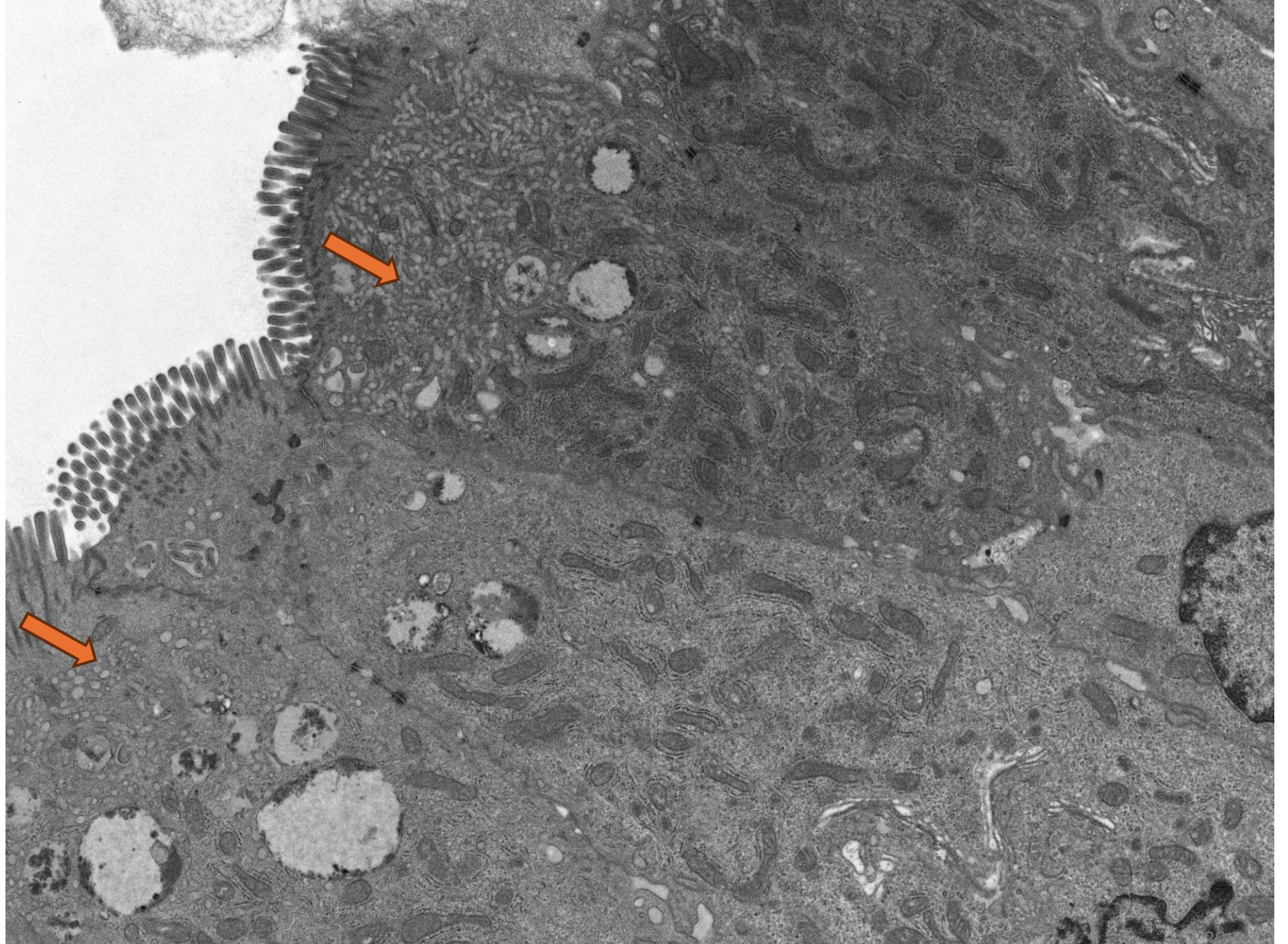


Microvilli Of The Small Intestine Photograph by Science Photo Library - Pixels

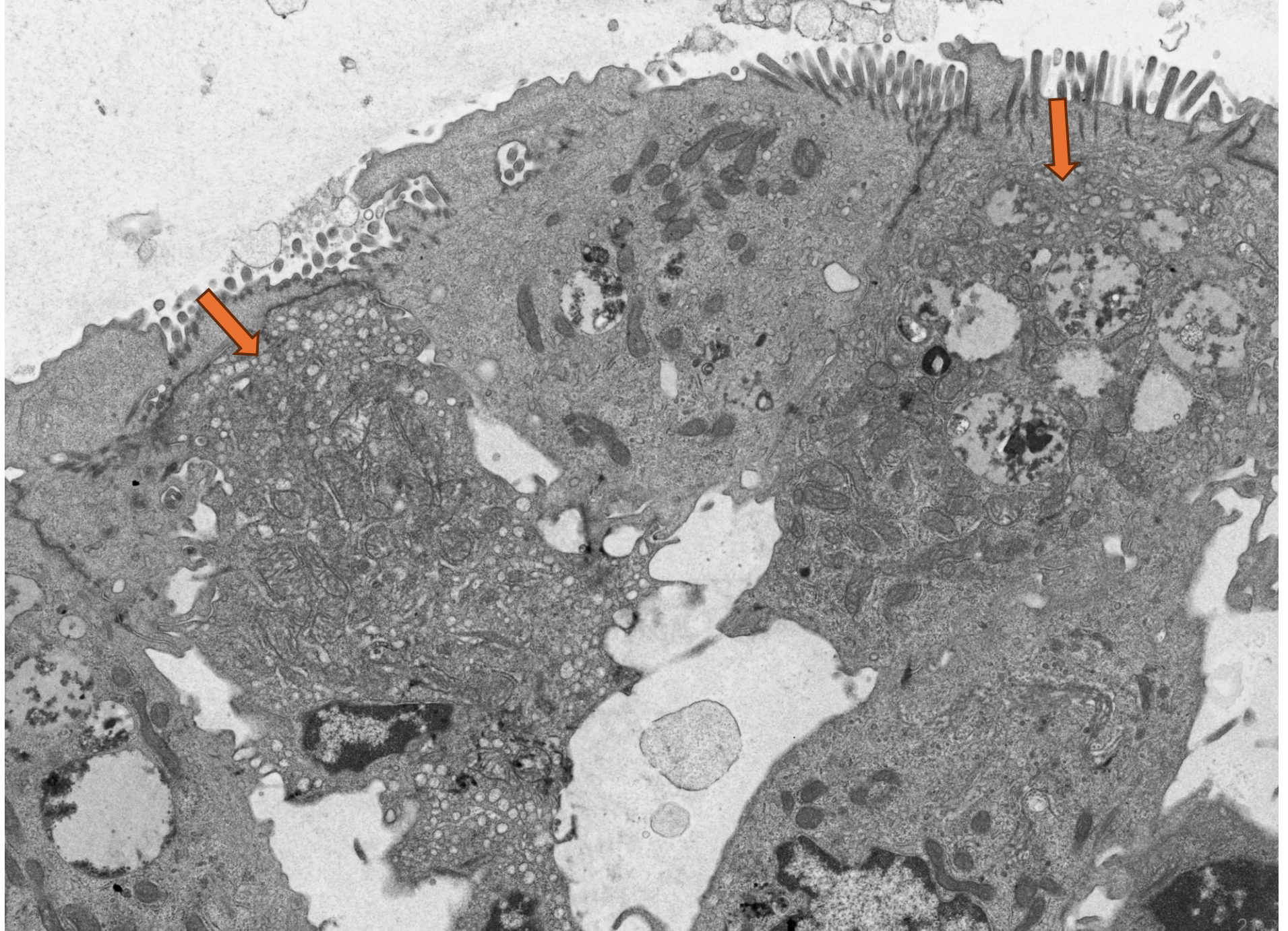
Finding #2:



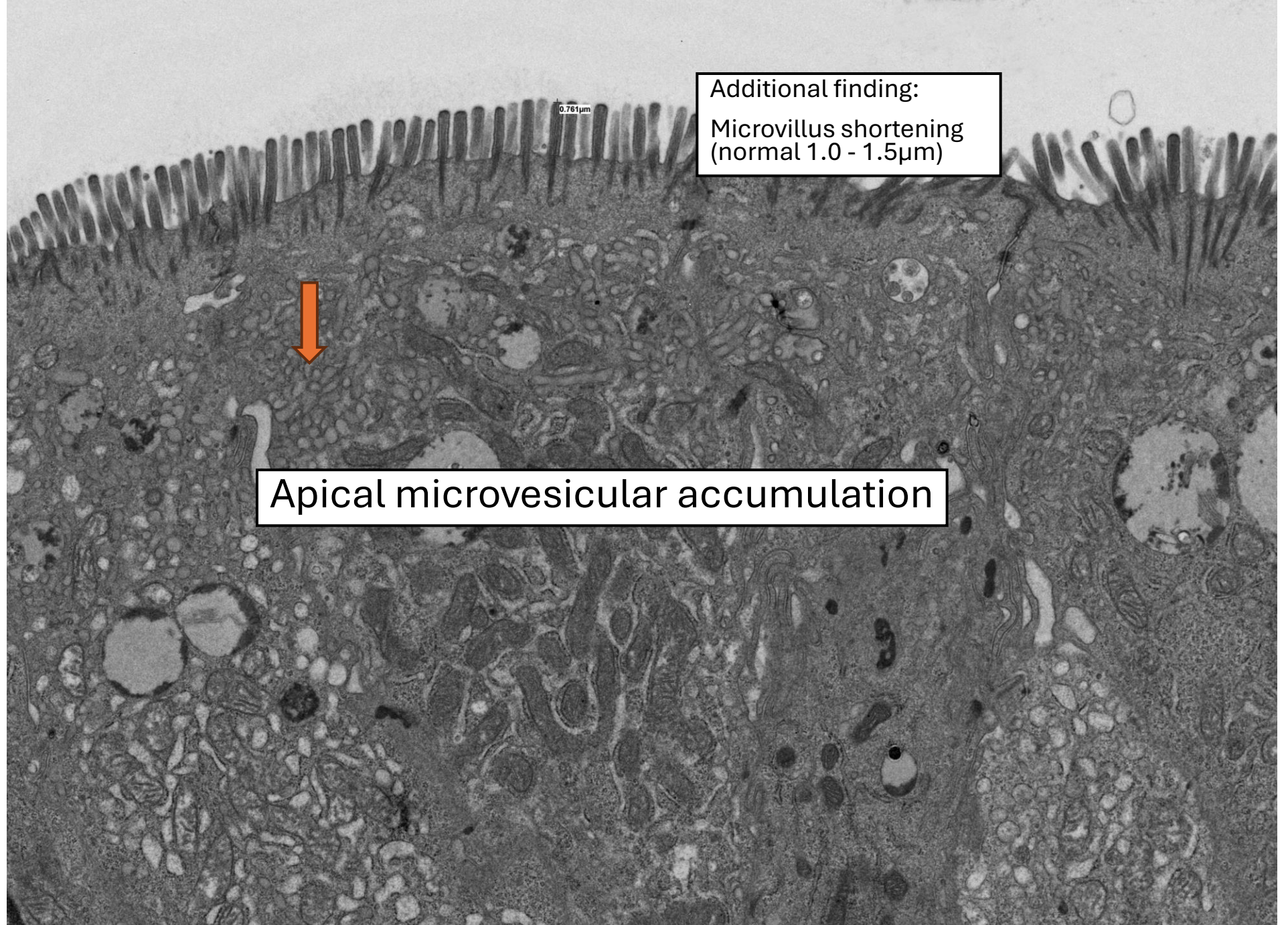
Finding #2:



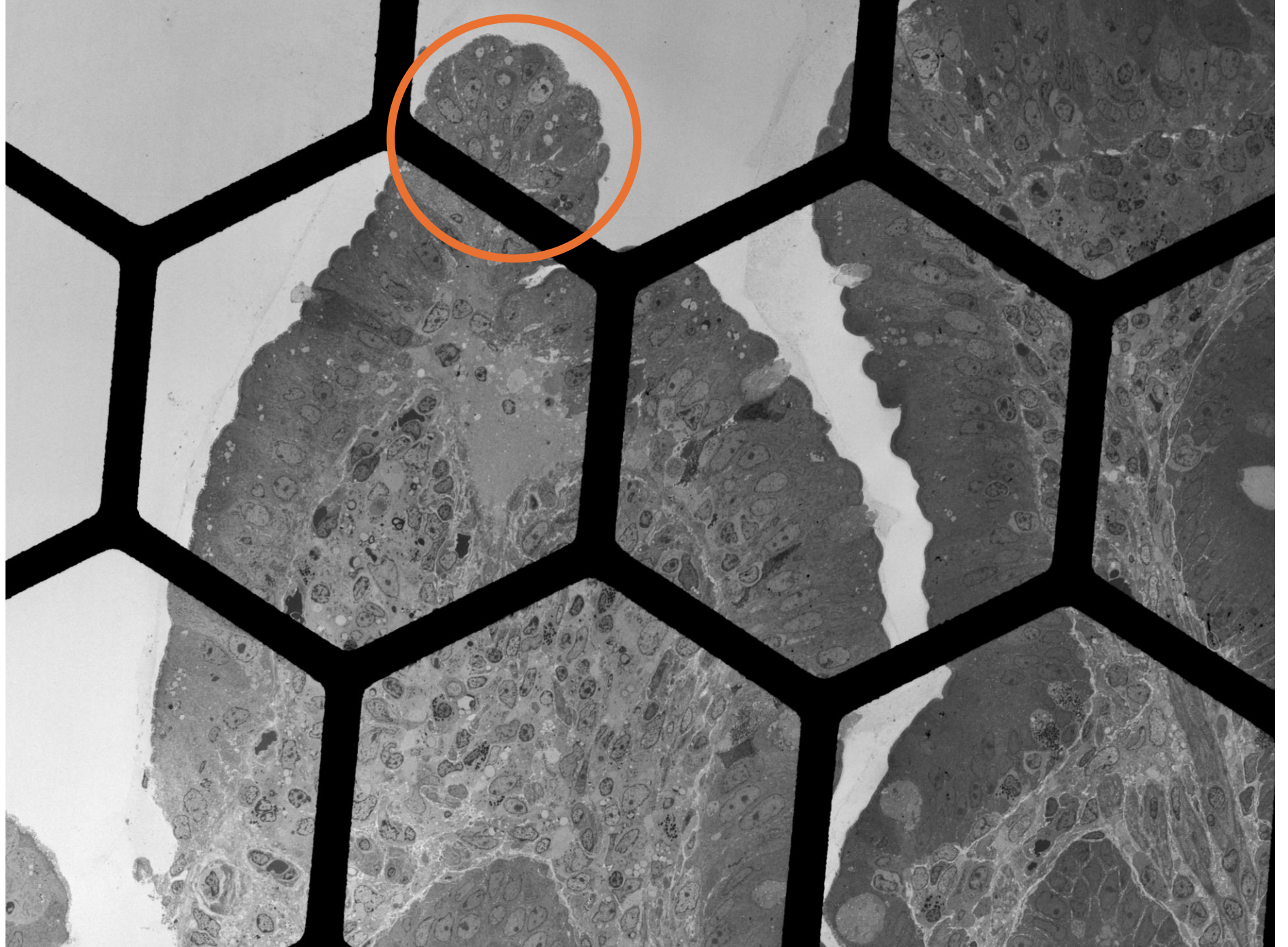
Finding #2:



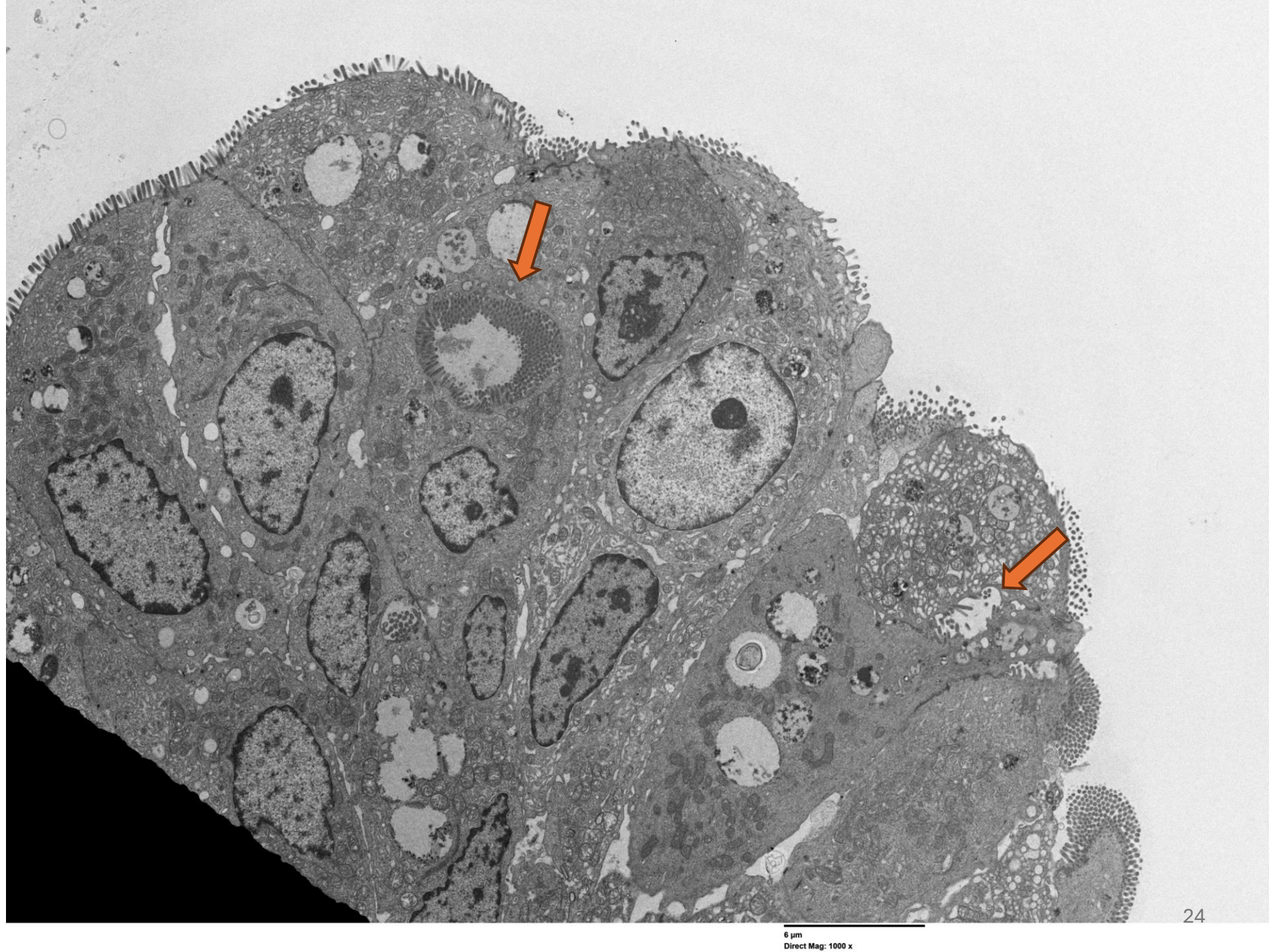
Finding #2?
+ bonus



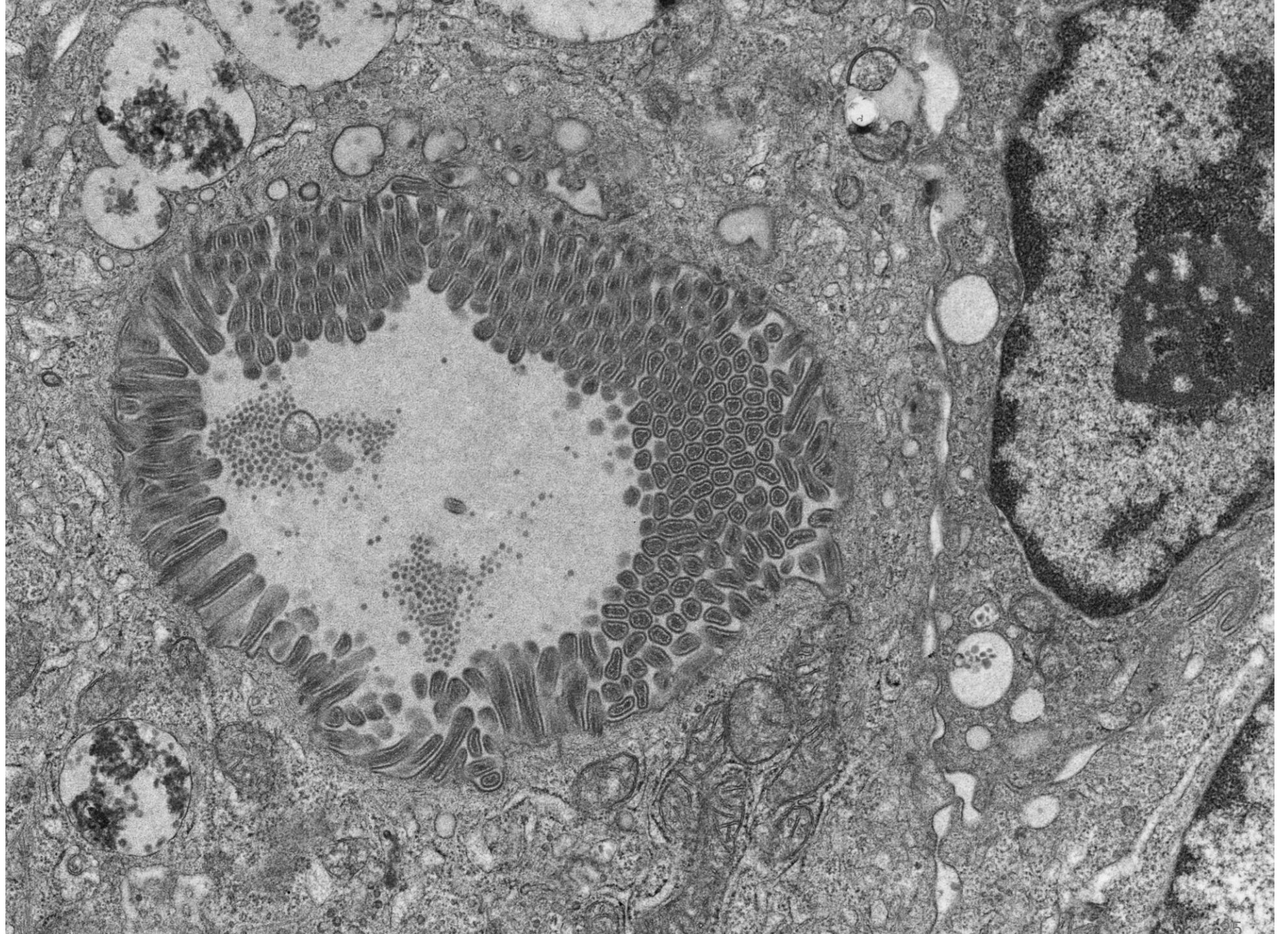
Finding #3:



Finding #3:



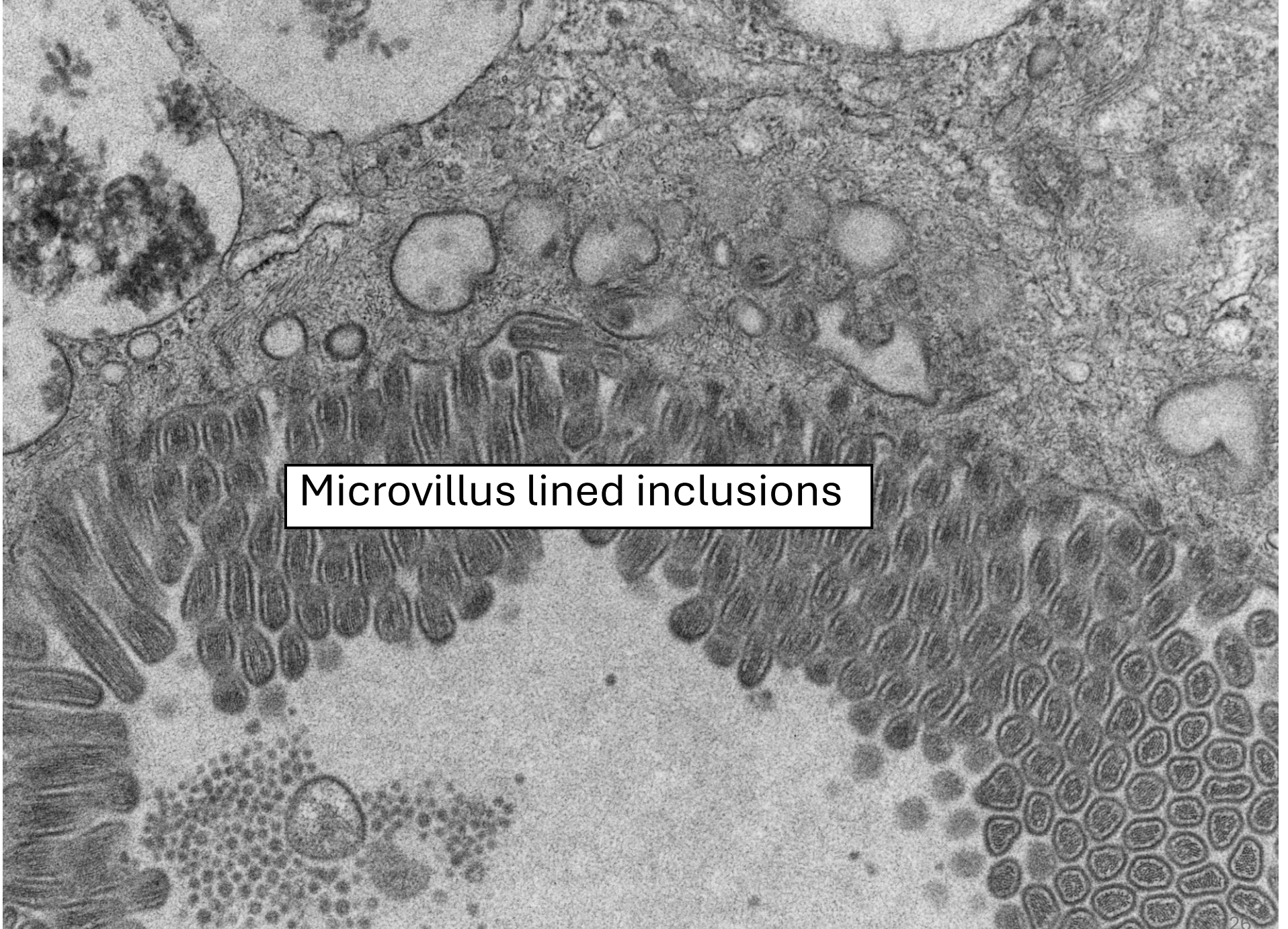
Finding #3:



Finding #3?

Characteristic finding

Microvillus lined inclusions



Important negatives:

-
- No excess inflammatory cells – infection, autoimmune enteropathy (AIE), celiac, inflammatory bowel disease (IBD)
 - No microorganisms - infections
 - No villus tufting – congenital tufting enteropathy (CTE)
 - No crypt hyperplasia - infection, autoimmune enteropathy, celiac disease

Genetics Testing

- Identification of pathogenic mutations in the MYO5B gene confirmed the diagnosis
 - Heterozygous for 2 pathologic variants



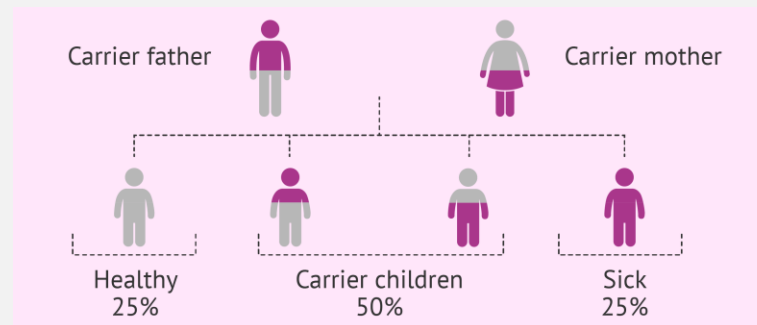
Microvillous Inclusion Disease (MVID)

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A quick run-through

What is MVID

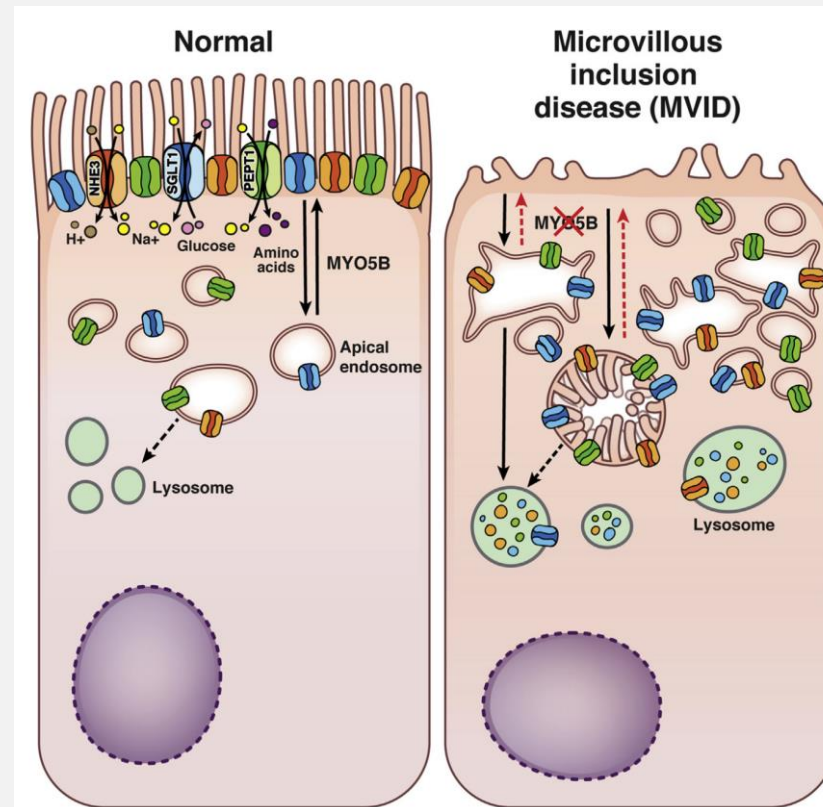
- Also referred to as Microvillous Atrophy (MVA)
- Rare, congenital disorder of enterocytes
- Inherited AR disorder (require 2 defective copies of the gene to manifest it)
- Slight male predominance (1.5:1)
- Persistent life-threatening watery diarrhoea during the neonatal period (usually within the first days of life)
- The diagnosis relies on a holistic approach, integrating clinical presentation, microscopic findings, and genetic analysis.
 - But identifying characteristic morphological enterocyte abnormalities by LM and EM on a small bowel biopsy is KEY



Aetiology and Pathophysiology

- MYO5B encodes myosin Vb, a motor protein involved in intracellular trafficking and recycling.
- It helps transport endosomes carrying apical membrane components (enzymes, transporters, glyocalyx proteins..) to the apical surface of epithelial cells.

Note: other MVID variants may have **STX3** and **STXBP2** mutations which code for proteins which control **apical plasma membrane fusion**. When defective: **inhibition of vesicle fusion with the apical membrane** resulting in the intracellular retention of apical proteins, and similar consequences.



- Defective myosin Vb and MYO5B-dependent trafficking.
- Disruption in the delivery of membrane components to the apical surface and brush border assembly
- Normal microvilli fail to form properly, which leads to their shortening and loss impairing absorption
- Apical components are therefore mislocalised and trapped in the cytoplasm – apical vesicles on microscopy
- Cell also redirects them to **lysosomes** for degradation as mislocalised
- Some microvilli may be aberrantly internalised forming inclusion bodies (vs. assembled in the wrong compartment)
- This damaged brush border impairs fluid and nutrient absorption leading to severe diarrhoea

CLINICAL PUZZLE

The role of enterocyte defects in the pathogenesis of congenital diarrheal disorders

Arend W. Overeem¹, Carsten Posovszky², Edmond H. M. M. Rings^{3,4}, Ben N. G. Giepmans¹ and Sven C. D. van IJzendoorn^{1,*}

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Exploiting Alternative Brush Border Trafficking Routes to Treat Microvillous Inclusion Disease

Shobnam Abtahi¹, Jerrold R. Turner²

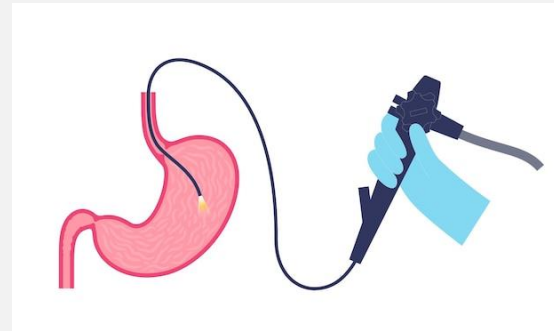
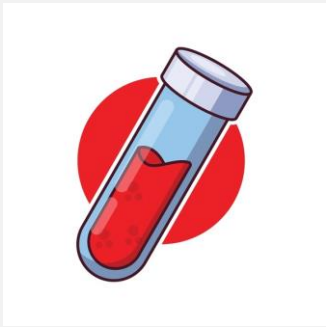


Clinical presentation

-
- Uneventful intrauterine course and delivery
 - Early onset vs late onset
 - Severe watery diarrhoea begins within the first days of life
 - Severe dehydration
 - Severe metabolic acidosis
 - Can lose up to 30% of body weight
 - Life-threatening
 - No involvement of other organs, no malformations
 - Examination reveals abdominal distension with fluid-filled intestinal and colonic loops (massive secretory diarrhoea and defective absorption = massive intraluminal fluid buildup)

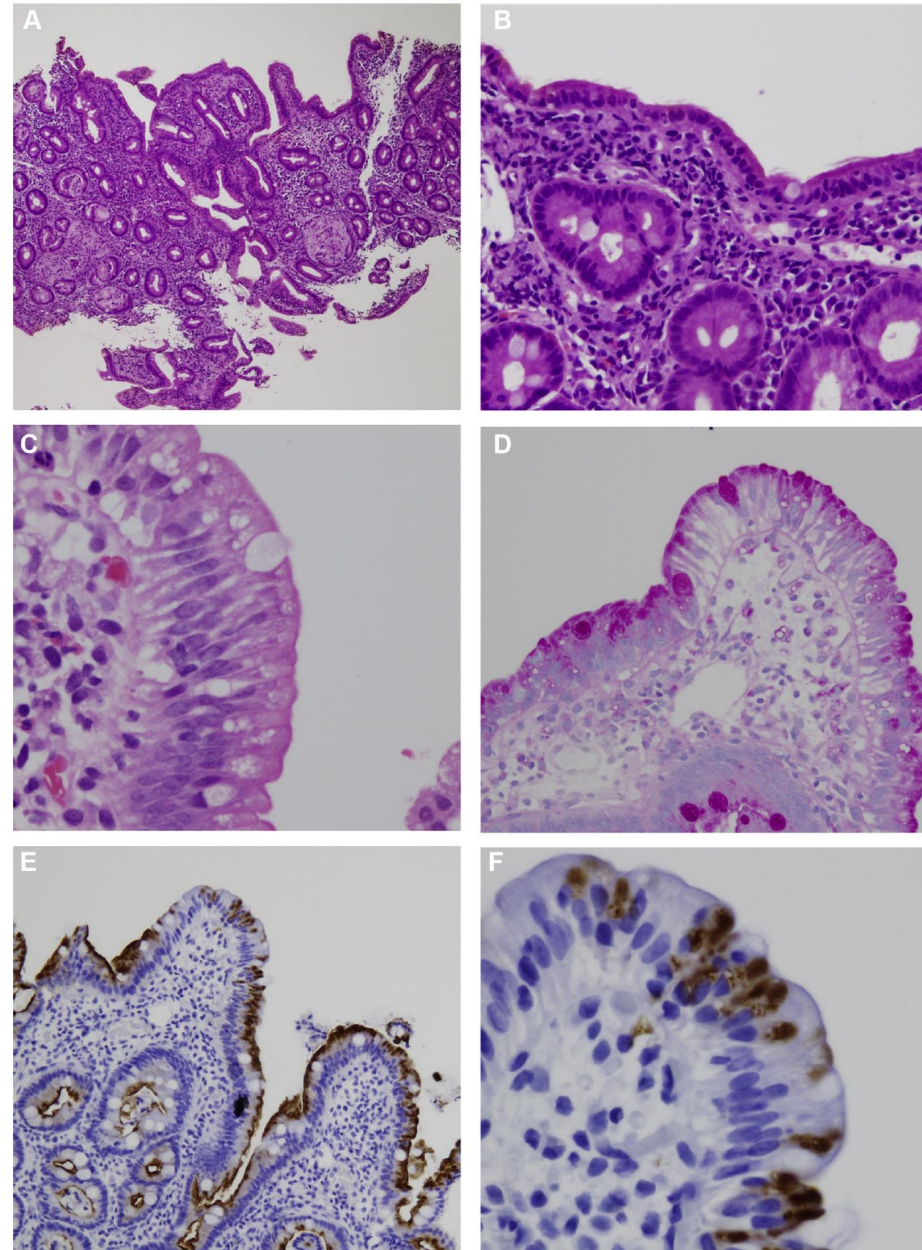
Diagnostic Workup

- Blood investigations: Metabolic acidosis and signs of dehydration
- Stool examination: faecal sodium concentrations between 100 and 130 mmol/L - secretory diarrhoea, losing Na and H₂O
- Endoscopy and biopsies: combined light/electron microscopic histological analysis of small bowel biopsies– GOLD STANDARD
- Others: to rule out differentials



Light Microscopy

- A: moderate **villous blunting** with no significant crypt hyperplasia or increased inflammatory cells
- B: No intraepithelial lymphocytosis
- C: **subtle vacuolization** of their apical cytoplasm
- D: PAS, absence of the sharp linear brush border which is replaced by **apical cytoplasmic blush** & few **PAS+ secretory granules** in the apical cytoplasm
- E: CD10, **patchy absence** of the linear brush border
- F: CD10, **apical cytoplasmic vacuoles**



Contents lists available at ScienceDirect

Journal of Microscopy and Ultrastructure

journal homepage: www.elsevier.com/locate/jmau



Original Article

Microvillus inclusion disease: A clinicopathological study from western region of Saudi Arabia

Omar I. Saadah^{a,*}, Rana Y. Bokhary^b, Sawzan M. Jalalah^b, Yagoub Y. Bin-Taleb^a

^a Department of Pediatrics, Division of Pediatric Gastroenterology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

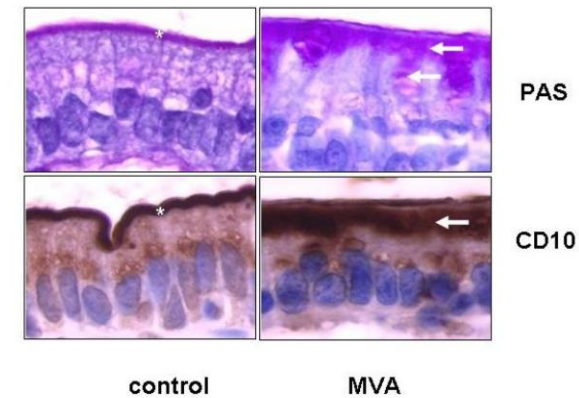
^b Department of Pathology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Light Microscopy

- Enlarged intracytoplasmic band (arrow) along the apical pole of enterocytes
- Others: **CEA** (glycoprotein), **alkaline phosphatase** (enzyme) stains – both also proteins found in the brush border
- Paper noted that MV inclusions also reported in colon, gallbladder and renal tubular epithelium

Orphanet Journal of Rare Diseases 2006, 1:22

<http://www.OJRD.com/content/1/1/22>



Microvillous inclusion disease (microvillous atrophy)

Frank M Ruemmele*, Jacques Schmitz and Olivier Goulet

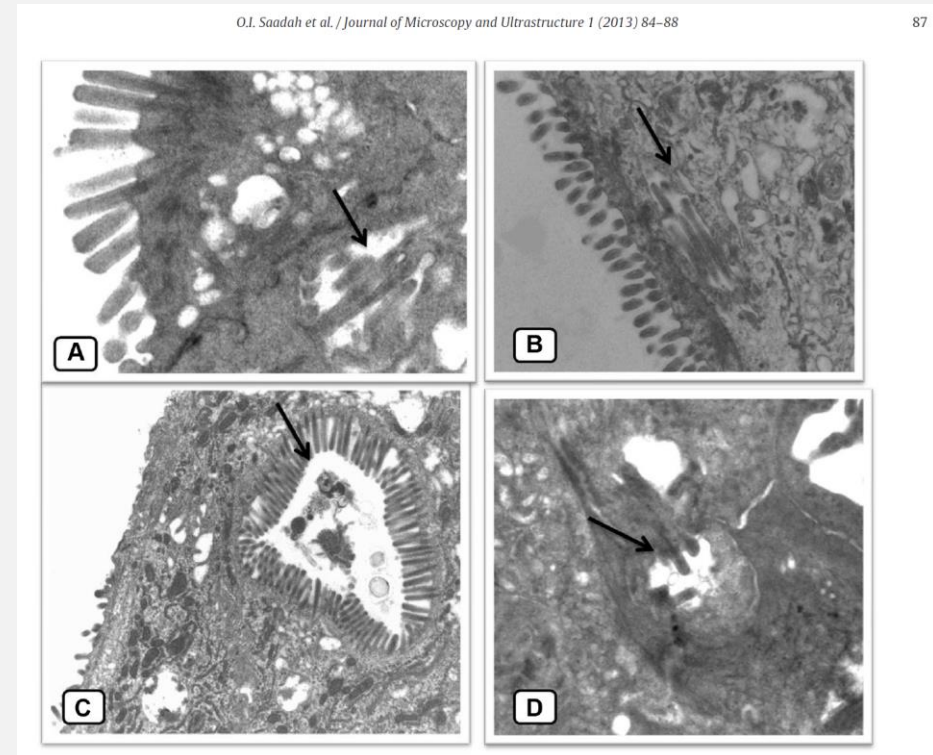
Address: INSERM EMI 0212, Pediatric Gastroenterology, Hepatology and Nutrition, Hôpital Necker-Enfants Malades, 149 Rue de Sévres, 75743 Paris Cedex 15, France

Email: Frank M Ruemmele* - frank.ruemmele@nck.ap-hop-paris.fr; Jacques Schmitz - jacques.schmitz@nck.aphp.fr; Olivier Goulet - olivier.goulet@nck.ap-hop-paris.fr

* Corresponding author

Electron Microscopy

- Shortened and absent microvilli
- Microvillous inclusion bodies (diagnostic and characteristic, but might be low in frequency)

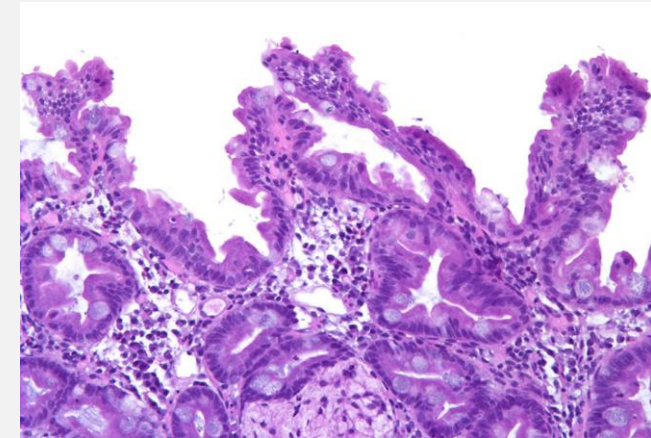


Differential Diagnosis

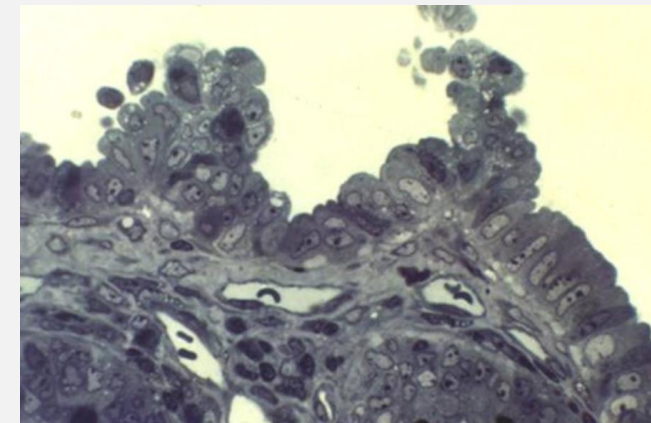


Differential Diagnosis SEVERE DIARRHEA OF EARLY INFANCY

	Microvillous Inclusion Disease	Tufting Enteropathy	Enteroendocrine Cell Dysgenesis	Autoimmune Enteropathy
Presentation	First 2 weeks	First 2 weeks	First 2 weeks	After 1 month
Gene defect	<i>MYO5b</i> (18q21) <i>RAB11</i> (10q26)	<i>EpCAM</i> (2p21)	<i>NEUROG 3</i> (10q21.3)	<i>FOXP3</i> (Xp11.23) in IPEX syndrome
Extraintestinal disease	Low serum γ -glutamyl transferase cholestasis after bowel transplantation	Dysmorphism; autoimmune diseases (arthritis)	Insulin- dependent diabetes	Polyendocrinopathies
Anti-enterocyte antibodies	No	No	No	Yes
Villous atrophy	Yes	Variable	Variable	Variable
Surface epithelium	Absent brush border	Tufting and desquamation	Normal	Normal or atrophic
Lamina propria inflammation	Minimal	Variable	Minimal	Usually increased

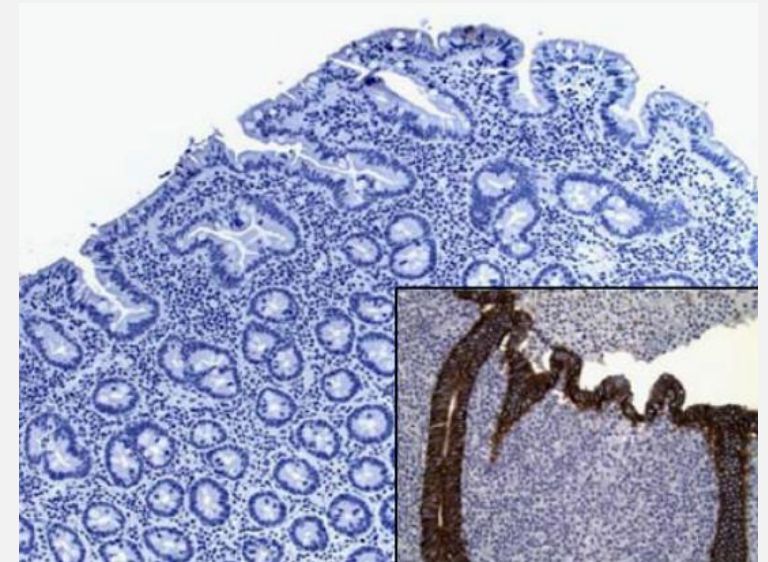
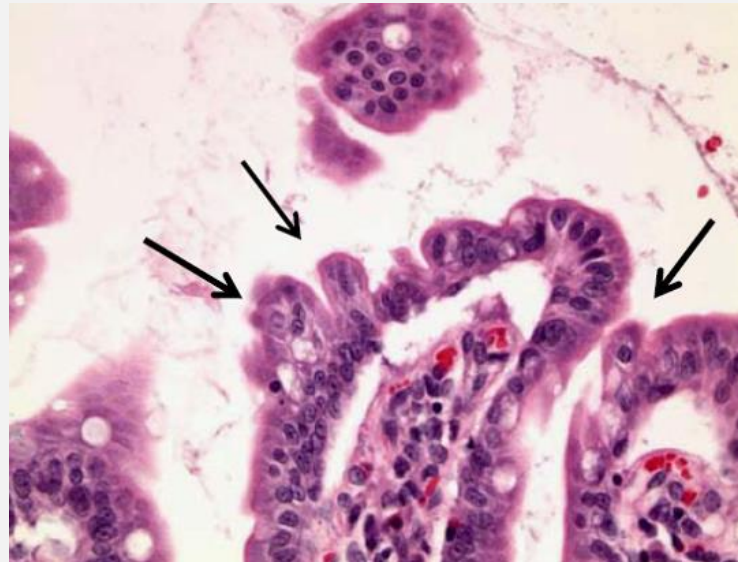
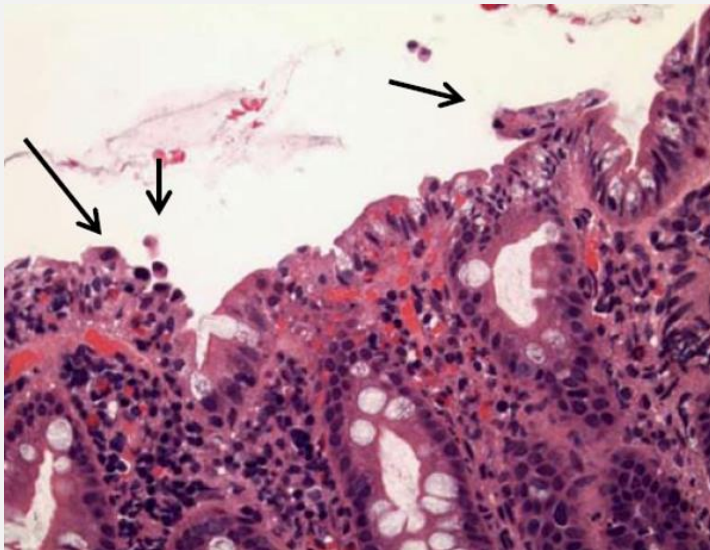


Enteropathies of infancy and childhood - PubMed



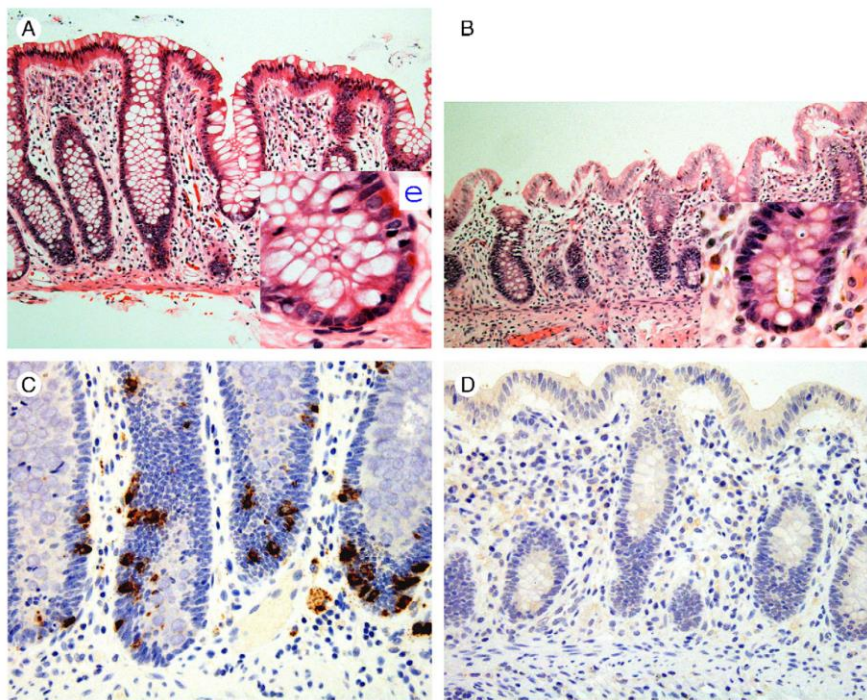
Intestinal epithelial dysplasia (tufting enteropathy) - PMC

Differential Diagnosis

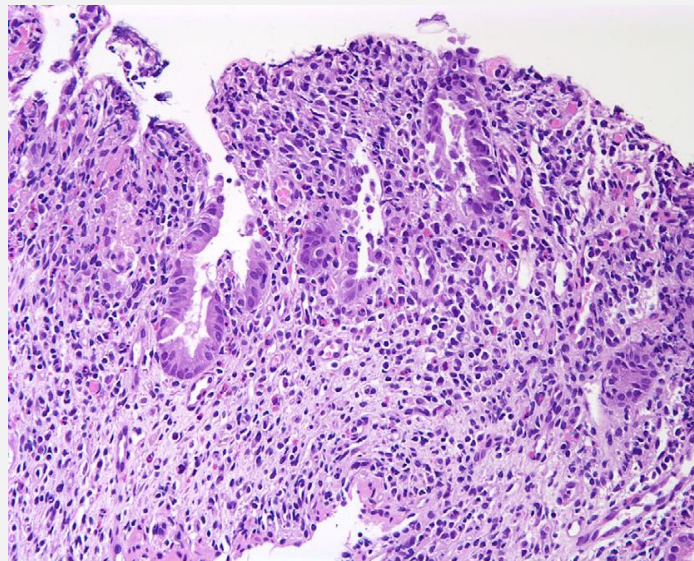


CTE: Tufting enteropathy revisited: the utility of MOC31 (EpCAM) immunohistochemistry in diagnosis - PubMed

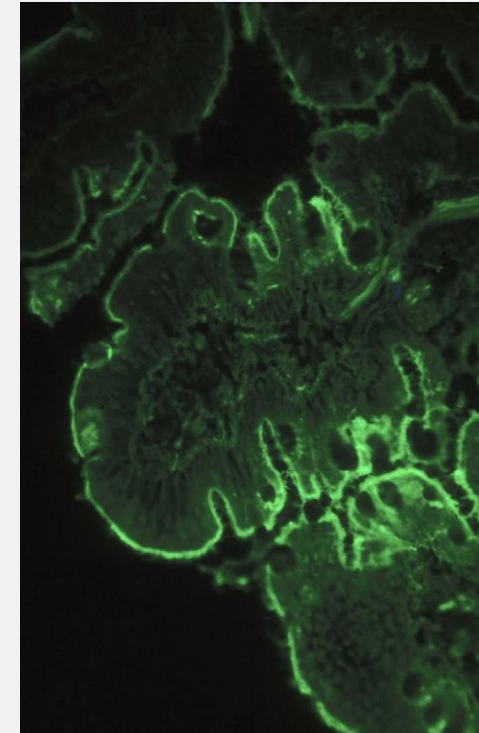
Differential Diagnosis



EED: Enteroendocrine cell dysgenesis and malabsorption, a histopathologic and immunohistochemical characterization – PubMed

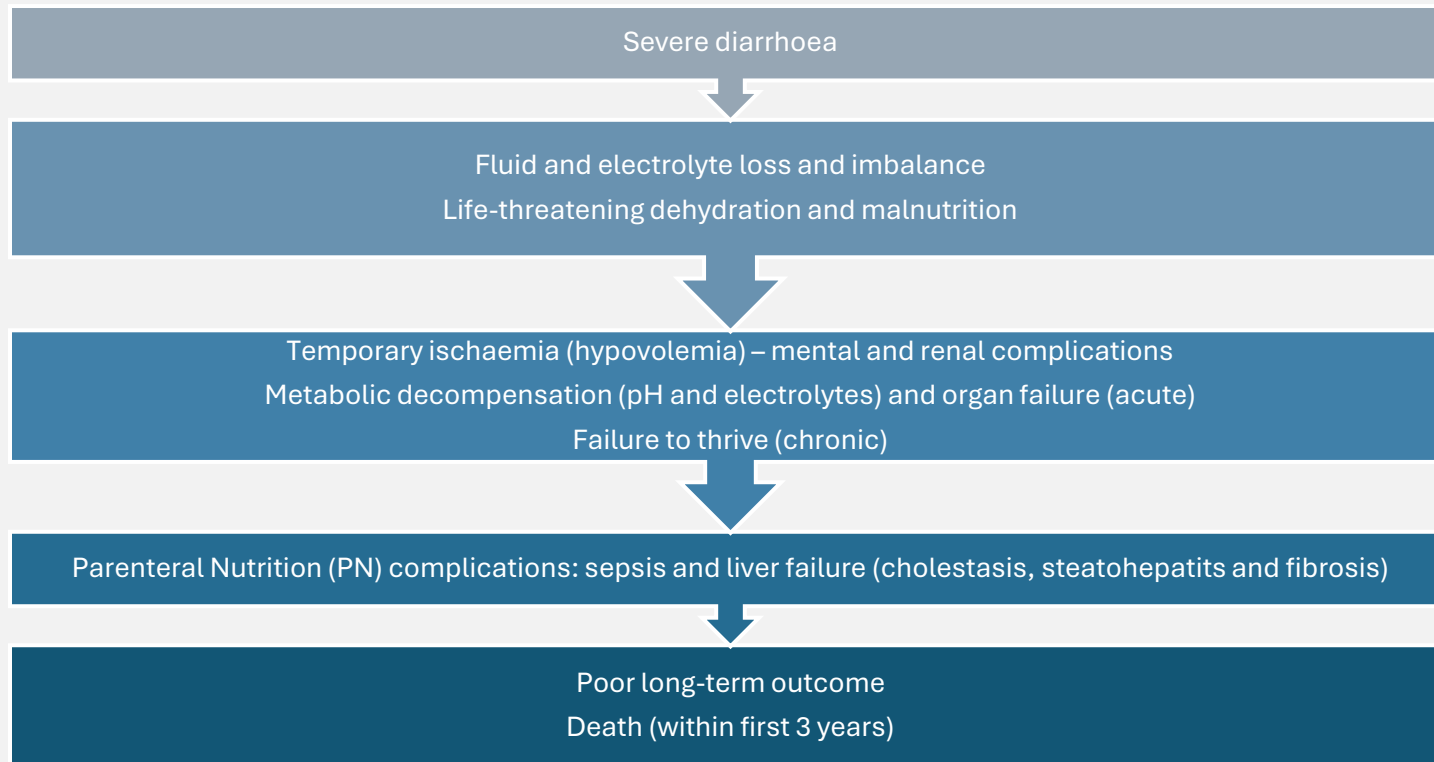


AIE: Enteropathies of infancy and childhood - PubMed



AIE: Enteropathies of infancy and childhood - PubMed

Complications



Management

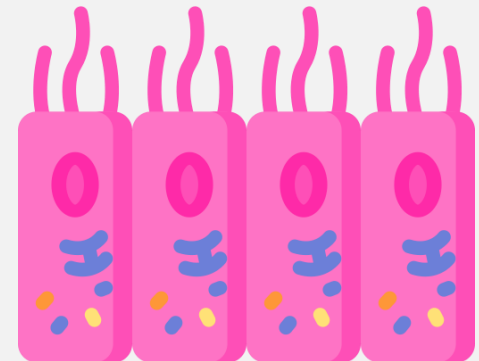
- Managed at highly specialized paediatric gastroenterology centres
- Oral caloric intake alone is impossible due to intestinal failure (especially in early-onset MVID)
- Dependent on exclusive Parenteral Nutrition (PN) – lifelong nutritional support
- Partial intestinal autonomy (late-onset MVID)
- Intestinal transplantation - ?curative



- Our patient:
 - Discharged on HPN (Home Parenteral Nutrition), and some enteral feeding (minimal sips orally - not enough for any nutritional value) – care of dieticians.
 - Regular outpatient reviews. Gaining weight.
 - Discussions with transplant centre – SB transplant reserved for:
 - Failure to manage fluid status
 - Loss of central line access
 - Significant liver disease
 - Parental/MDT discussion, risks vs benefits

Conclusion - MVID

-
- Severe congenital enteropathy that presents early in life with intractable **life-threatening diarrhoea**
 - Diagnosis requires a **high index of suspicion**
 - LM + EM are the **gold standard**, genetic testing helps confirm it
 - Management is mostly **supportive**
 - A deeper understanding of the **molecular pathways** may lead to the development of **targeted therapies**
- which may improve **patient management and outcomes**

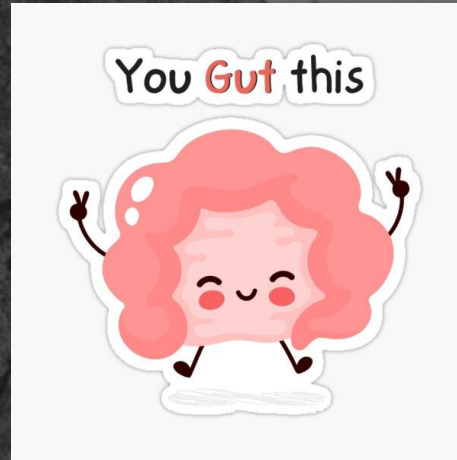


Acknowledgements

-
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 - Dr Arun Urs
 - Dr Rayna Alamurova

References

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Thank you for listening!
