

# Coeliac Disease (CD)

## Pathological mimics and complications

Dr. Shaun Walsh  
Dept of Pathology  
Ninewells Hospital, Dundee

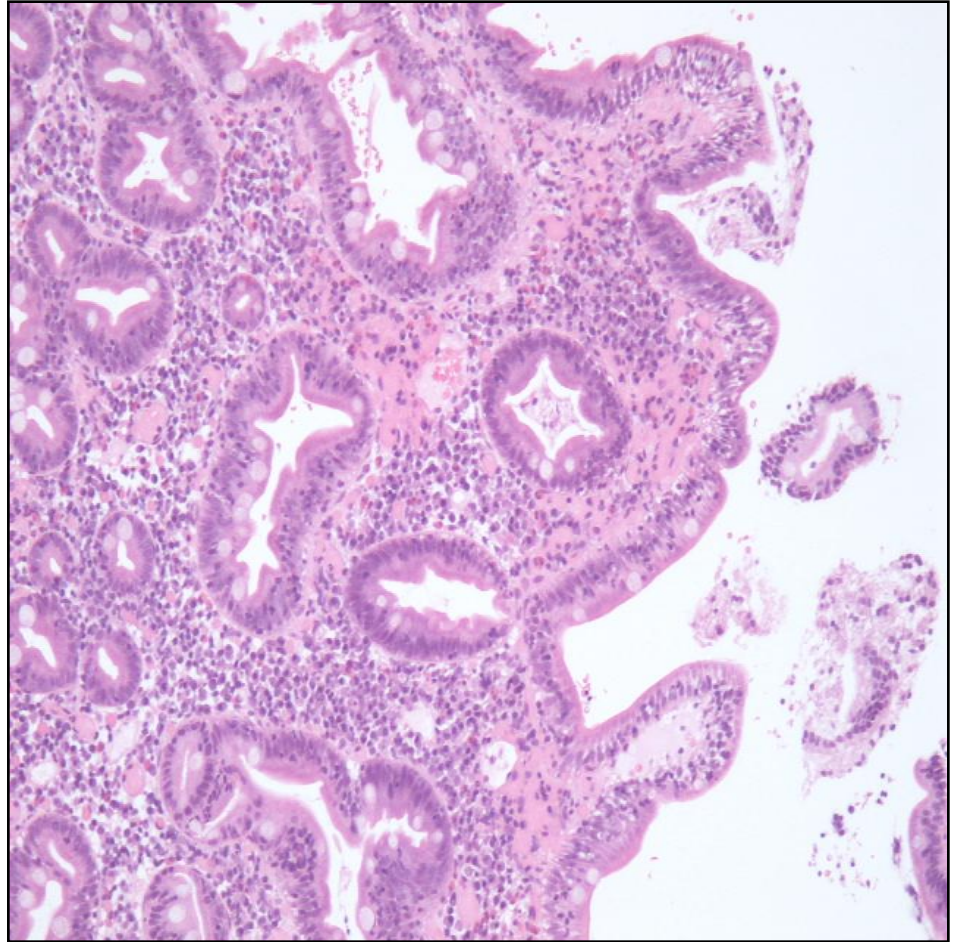
# Pathological mimics and complications

## 25 minutes

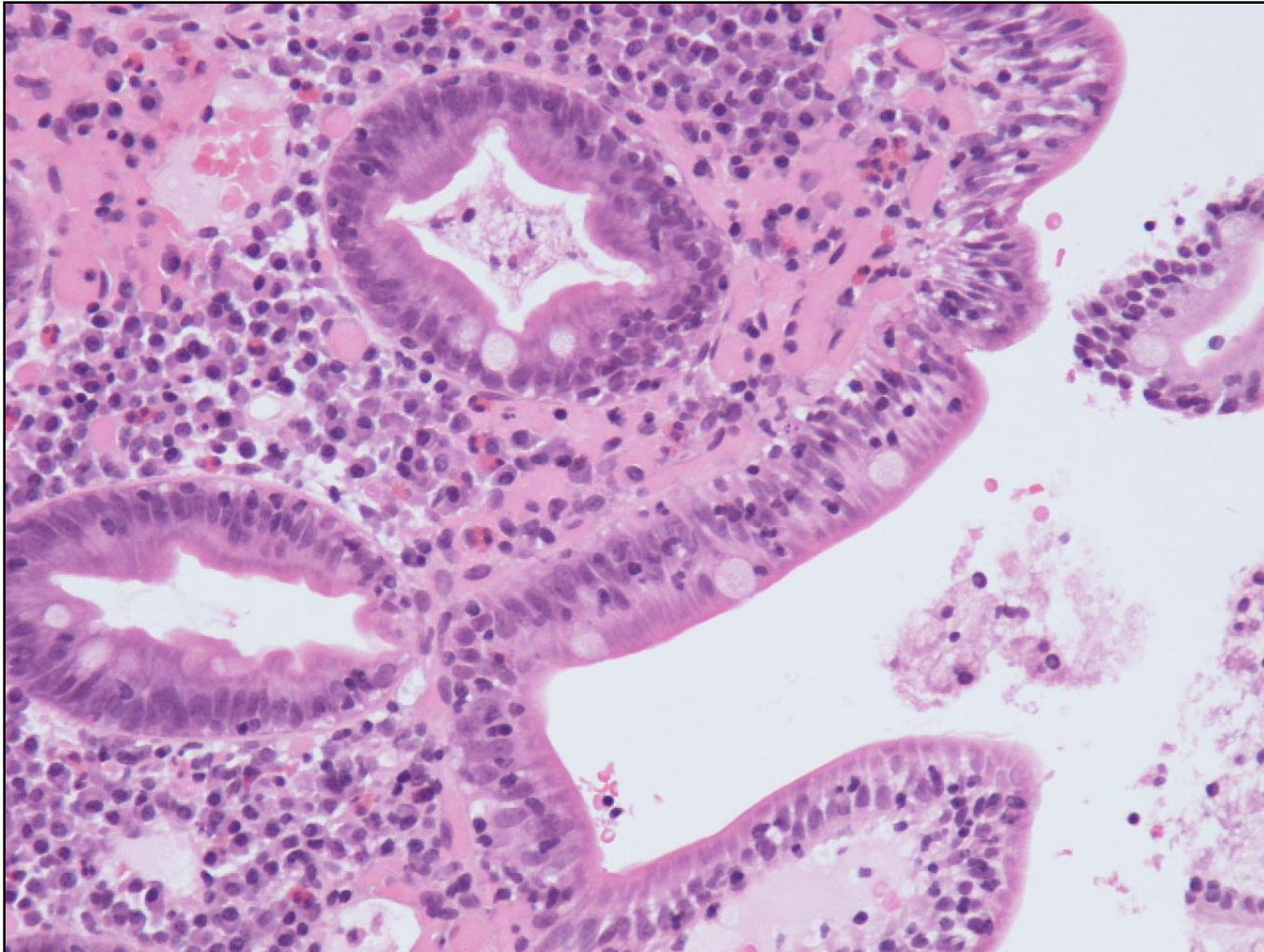
- Recent challenging case
- Place of histopath. in investigating CD
- Common mimics of CD
- Refractory CD

## A recent case

- 7 year old boy
- c/o Abdo pain
- Type 1 DM, TTG 52
- D2 biopsies under GA
- Villous blunting, crypt hyperplasia



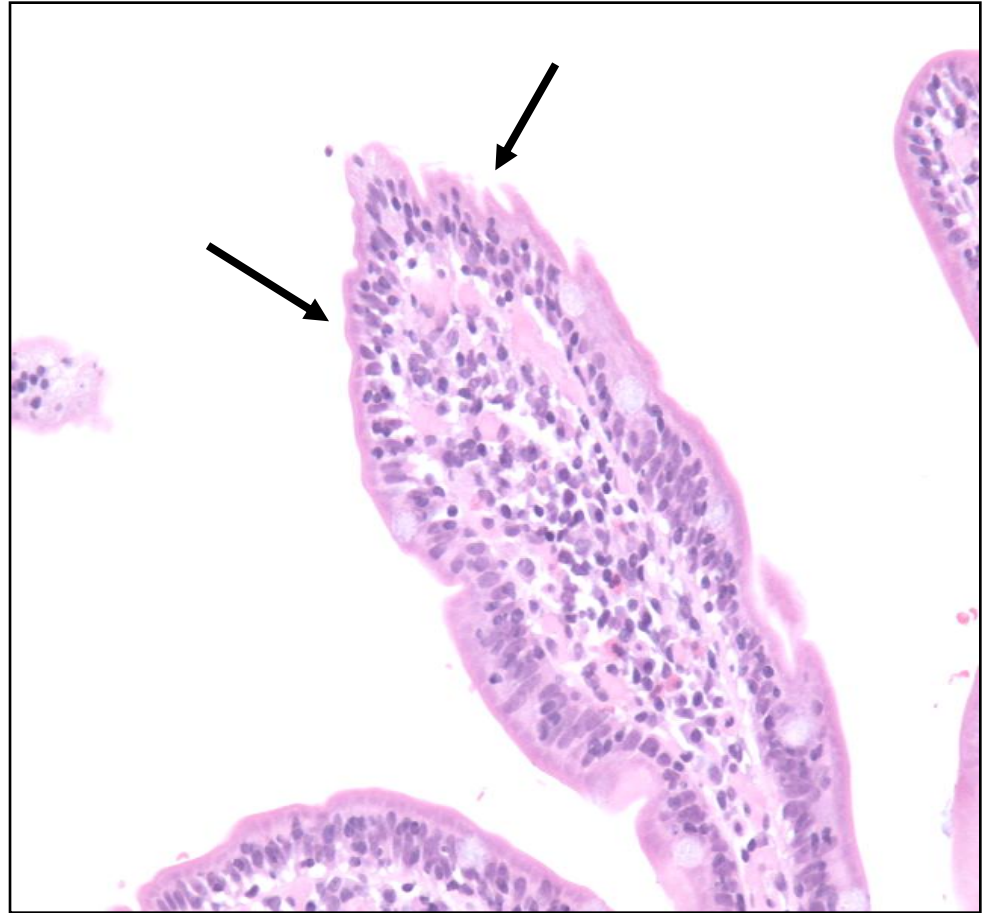
# Raised intraepithelial lymphocytes (IELs)



➤ 40/100 Ecs

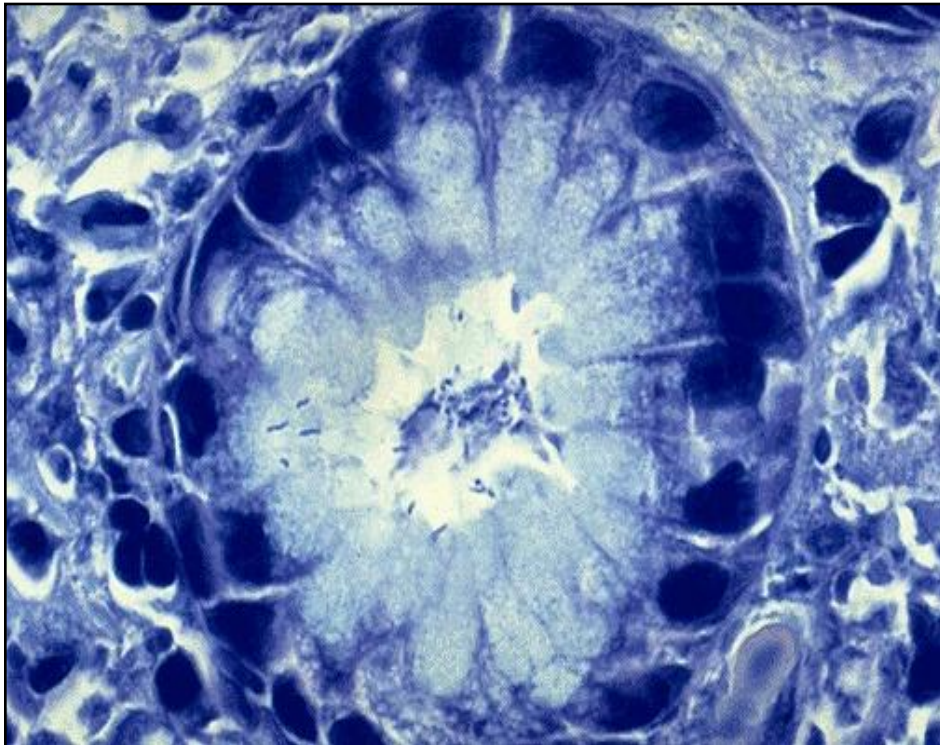
## One bx normal villi ... but increased IELs

- Loss of the decrescendo pattern of IELS
- $>23$  IELS/20  $\times 5$  tip ECs
- The stomach was also biopsied .....



# Gastric antral biopsy

- Chronic active inflammation
- Abundant *Helicobacter*

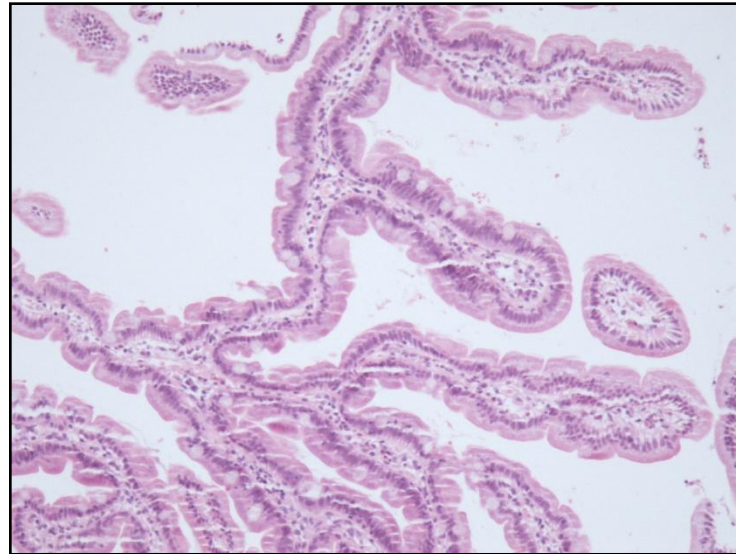


# Report and MDT

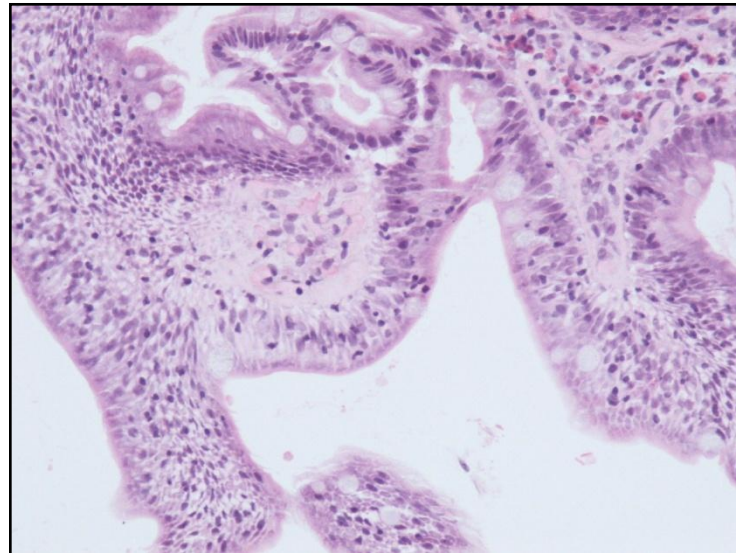
- Features in keeping with CD present however.....
- H.Pylori gastritis also present which can be associated with duodenal changes in children
- Clinical correlation and discussion at MDTM is required
- CD clinically/serologically but family very reluctant for GFD
- Decision: Treat H.pylori first and rebiopsy

# 6 months later ... H.Pylori eradicated

- Pt asymptomatic, TTG 15
- Second GA and endoscopy (Stomach normal)
- Path report: .... could represent CD but not specific
- Paediatricians feel he may have latent CD
- Family very unhappy, feel it is all due to H.Pylori. Patient not on GFD
- **Who is right?**
- **How much weight should we give to biopsy findings?**



Normal villi



Raised IELs

# BSPGHAN 2005 guidelines

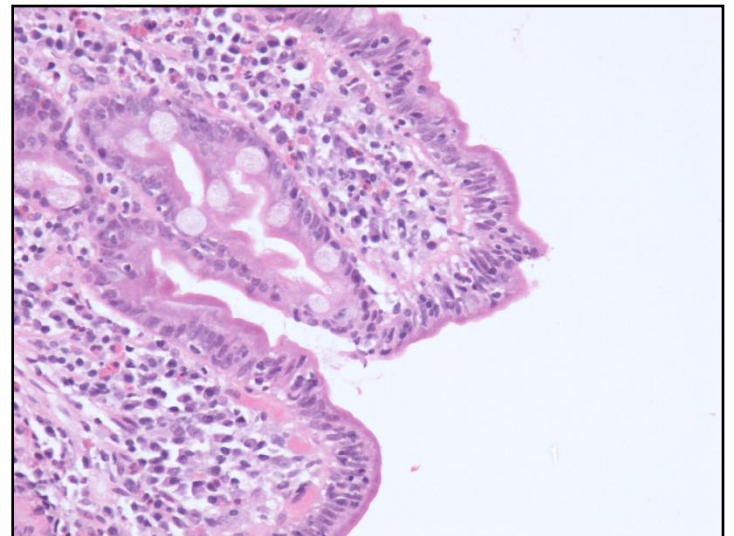
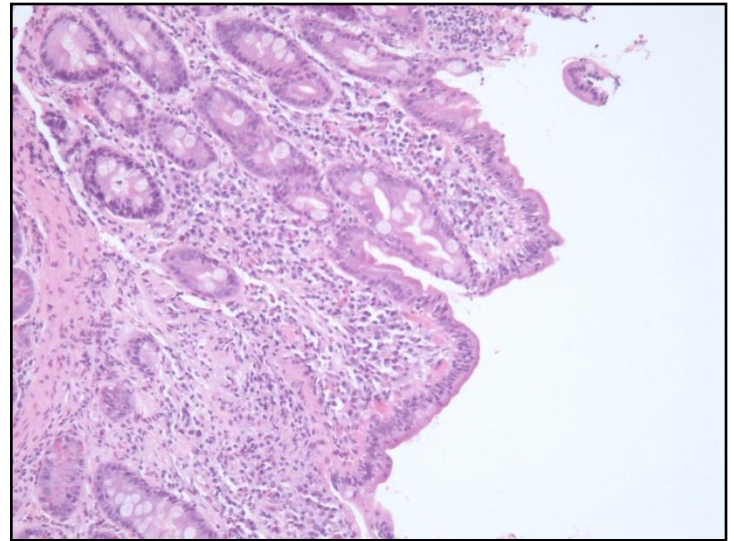
## Investigation of CD

- Clinical investigation pt on gluten
- Serology (TTG)
- Duodenal biopsy required for confirmation of dx
- Must have villous atrophy (VA) and increased IELs
- Increased IELs (Marsh 1) alone not specific
- Response to GFD to be documented

# BSG Guidelines Adults 2010

CD is commonest cause of enteropathy in UK by some margin

- Duodenal biopsy is the **mandatory gold standard**
- Serology has false negatives (IgA defic) and there is a need for certainty
- If Pt. on gluten and has Villous atrophy (VA) and raised IELs ... confident



# BSG/AGA: Qualifiers

## BSG

- Site , number, orientation of biopsies
- Confident description/experienced pathologist
- 'where possible histology should be reviewed in the **clinical context ..diet, serology, symptoms**
- 'VA and increased IELs are not exclusive to CD'

## AGA

- ' a small bowel biopsy is the **current gold standard...**'  
  
Three paragraphs later
- ' small bowel biopsy in itself is not a perfect gold standard ...
- 'Histologic features are not unique to coeliac disease'.

# Summary of all guidelines until 2011:

- Duodenal biopsies **are required** to investigate CD
- Villous flattening and increased IELs on duodenal biopsy **nearly** always means coeliac disease in the correct

## CONTEXT

**Pathologists do not diagnose CD by themselves**

# Consensus never lasts long



Not the Irish football team trying new tactics ....  
... These are Paediatric Gastroenterologist

# Investigation of CD in children is changing

- BSPGHAN May 2012 (ESPGHAN)
- Children with clinical evidence of CD
- IgA Anti-TTG > 10 times normal
- (Pref. With EMA Ab+, HLA-DQ2,DQ8+)
- **No duodenal biopsy (No GA, no delay)**
- Diagnosed with probable CD
- Straight to GFD



Arch Dis Child May 2012 Vol 97; 393-394

J Pediatr Gastroent Nutr 2012 Jan 54: 136-60

J Pediatr Gastroenterol Nutr 2012 Oct 29 Epub

# Investigation of CD in children is changing

## Paediatricians

- Biopsy if asymptomatic
- Biopsy only when no response to GFD
- Our patient would probably not be biopsied at first!

## Pathologists

- New case mix
- Typical histology will be relatively rarer
- Tricky cases: Latent CD, compliance issues, and **mimics** will appear more commonplace

# Pathological Mimics of CD

- Tropical sprue
- Bacterial overgrowth
- Blind loop syndrome
- CVID, IPEX
- AIDS enteropathy
- Graft v's Host dse
- Malnutrition
- Zollinger Ellison
- Ischaemia
- Radiation
- MVID
- Viral enteritis
- Giardiasis
- Acid-peptic injury
- Helicobacter pylori
- Drugs/immunosuppression
- Crohns disease
- Collagenous sprue
- Derm. herpetiformis
- RCD2/Lymphoma
- Autoimmune enteritis
- Allergic gastroenteritis

# RARE and not often biopsied mimics of CD

- Tropical sprue
- Bacterial overgrowth
- Blind loop syndrome
- CVID, IPEX
- AIDS enteropathy
- Graft v's Host dse
- Malnutrition (here)
- Zollinger Ellison
- Ischaemia
- Radiation
- MVID
- Viral enteritis
- Giardiasis
- Acid-peptic injury
- Helicobacter pylori
- Drugs/immunosuppression
- Crohn's disease
- Collagenous sprue
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# Commoner MIMICS OF CD

- Tropical sprue
- Bacterial overgrowth
- Blind loop syndrome
- CVID, IPEX
- AIDS enteropathy
- Graft v's Host dse
- Malnutrition
- Zollinger Ellison
- Ischaemia
- Radiation
- MVID
- Viral enteritis
- Giardiasis
- Acid-peptic injury
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# Self inflicted

- Biopsies must be correctly orientated
- Need 3 levels
- 3-5 reasonably parallel villi
- Tangential sections make villi look shorter

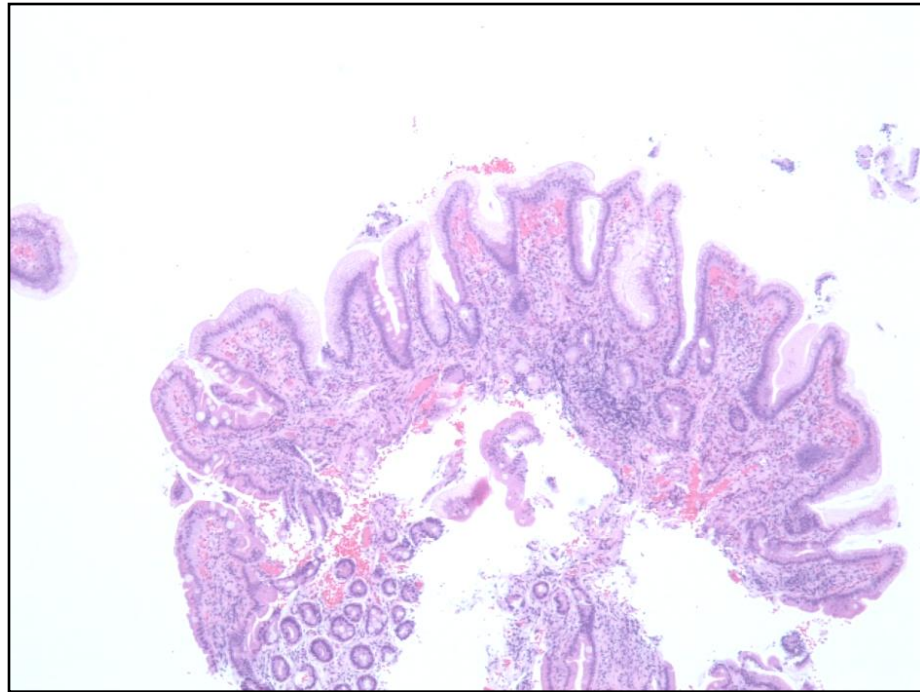
# I. Acid-peptic duodenal injury

- Very common duodenal pathology
- Associated with H.Pylori infection
- Direct effect of acid/enzymes on duodenal mucosa
- Commonest in D1 (physiological?)

# Six features of acid-peptic injury

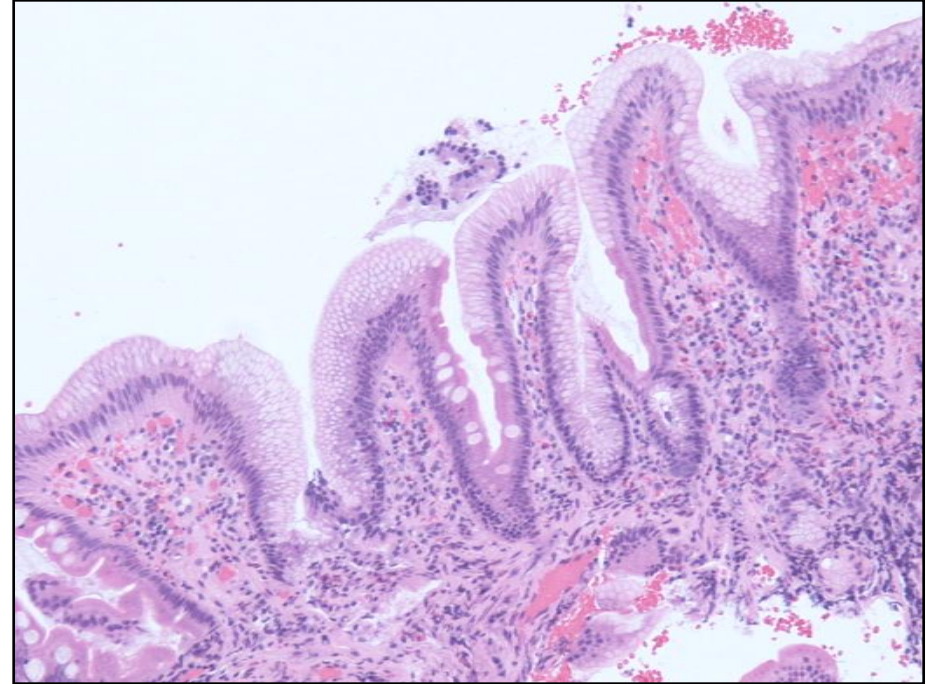
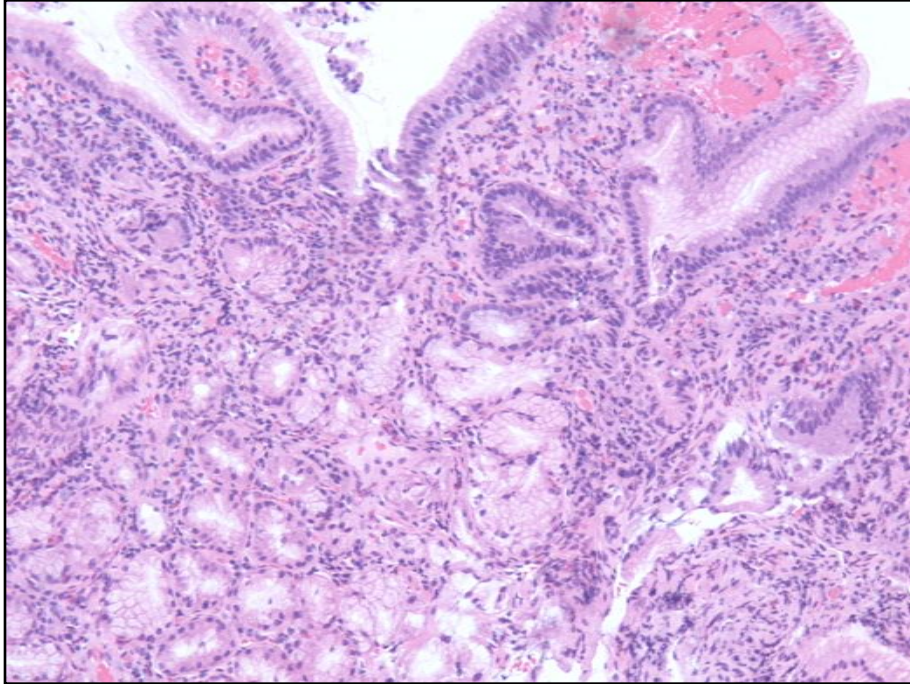
1. Variable villous flattening

2. Crypt hyperplasia



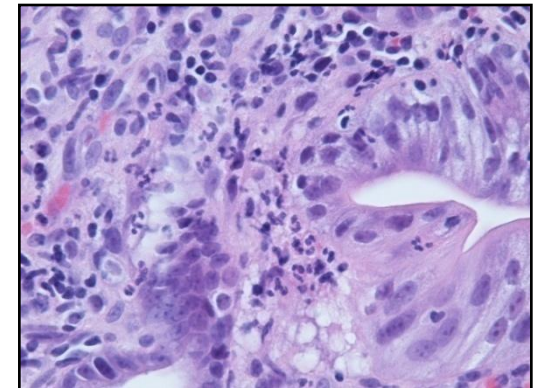
# Features of acid-peptic injury

3. Brunner gland hyperplasia    4. Gastric metaplasia (HP+/-)



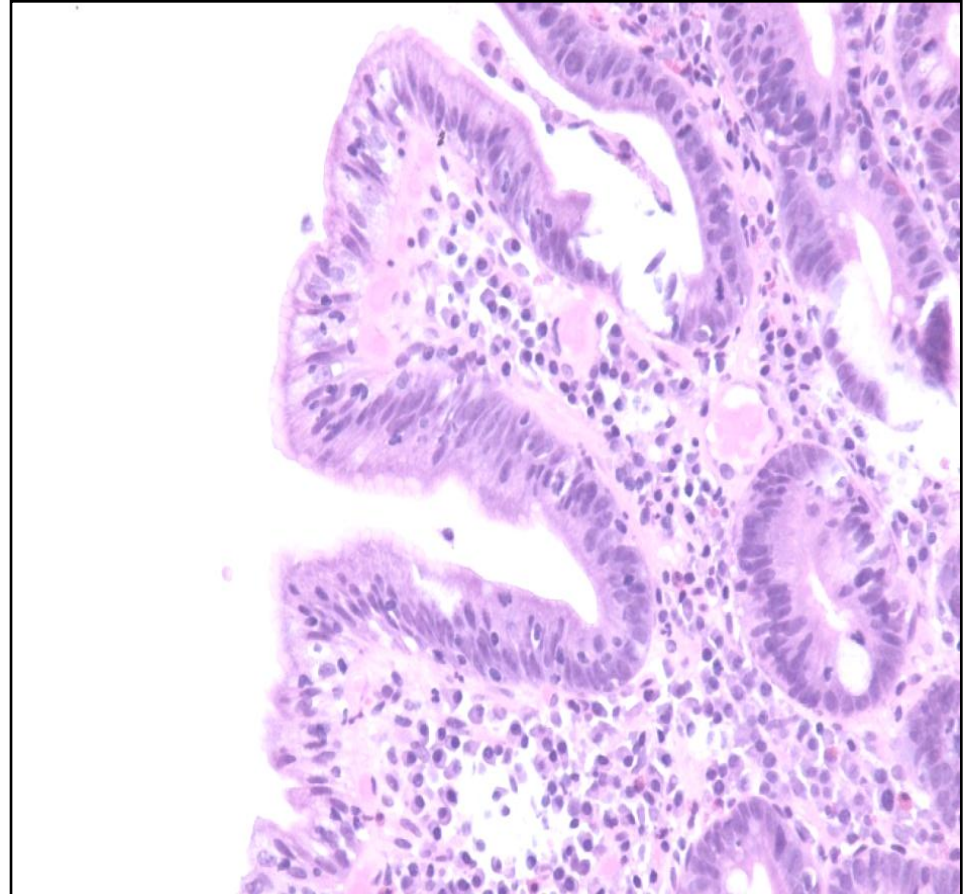
5. Variable amounts of acute and chronic inflammation ....

6. Normal numbers of IELs



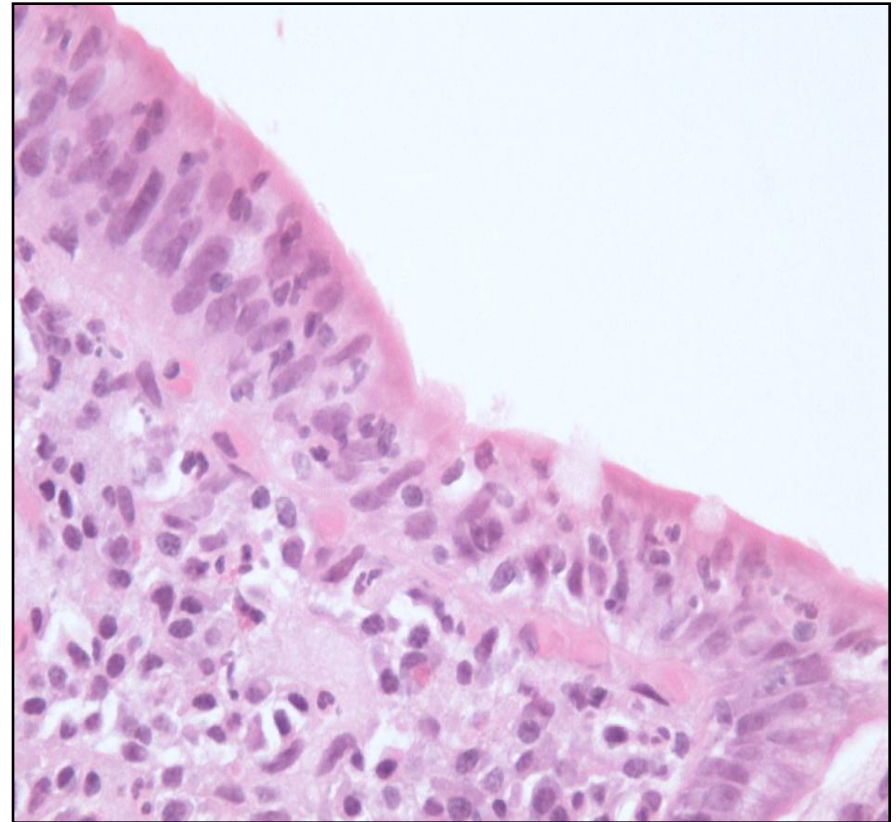
## Pitfall: Gastric metaplasia can be seen in CD and Crohn's dse!

- Present in 66% of CD biopsies from D2
- In CD and Crohn's it is more focal and less well developed



# Pitfall: Neutrophils can be seen in CD and Crohn's dse.!

- 28-56% of CD biopsies from D2
- Commoner in children
- May relate to severity of disease



*Am J Clin Pathol 2012 138:42-9*  
*Am J Surg Pathol 2012 36:1339-45*

# Overlapping features of acid-peptic injury and CD

## Acid-peptic injury

- Villous flattening
- Crypt hyperplasia
- Gastric metaplasia
- Brunner gland hyper
- Acute inflammation
- Chronic inflammation
- Normal IEL's

## Coeliac disease

- Villous flattening
- Crypt hyperplasia
- Focal gastric metaplasia
- Acute inflammation
- Chronic inflammation
- Abnormal brush border
- Raised IELs

Traditionally D2 is biopsied to avoid D1 acid-peptic injury .....

# Update: D1 (bulb) bx's for CD

- CD involves bulb in the vast majority (cranio-caudal)
- Recent studies .. 6-18% of CD missed if only D2 biopsied
- D1 biopsies should come from 9-12 o' clock position
- D1 x2 and D2 x4 biopsies are now proposed for adults (already std for paediatricians)

*J Pediatr Gast Nutr 2008 47: 618-622*

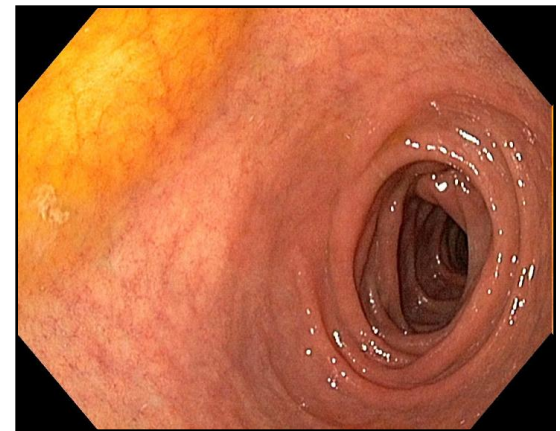
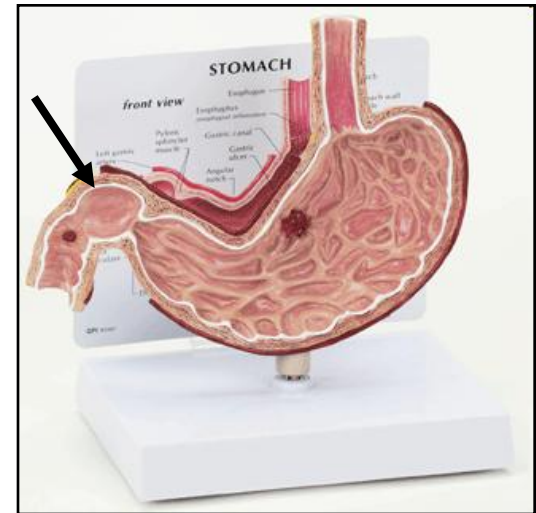
*J Clin pathol 2012 65:791-4*

*Am J Gastroenterol 2011 106: 1837-742*

*Gastrointest Endosc 2012 75: 1190-6*

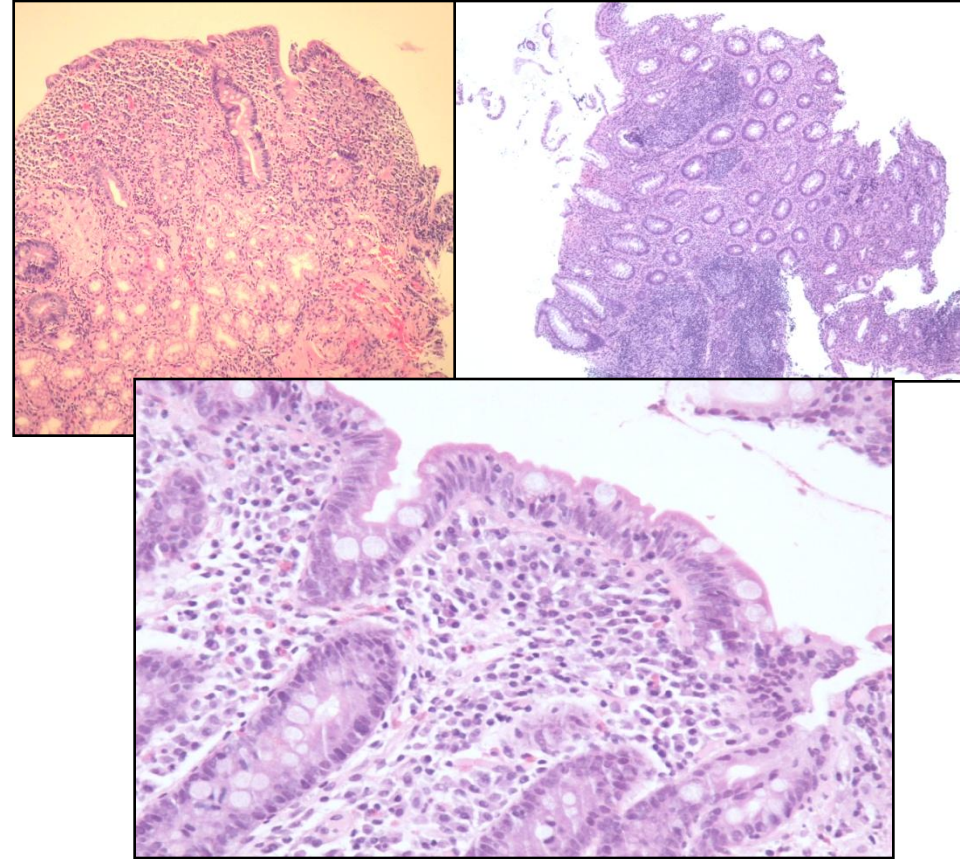
# Problems with bulb biopsies:

- Acid-peptic injury
- Aware D1 villi are usually shorter than D2
- Brunner gland hyperplasia and lymphoid aggregates distort/flatten villi
- Scrappy bx's are harder to orientate and assess (3-4 parallel villi)



# What are the features of Coeliac dse in D1?

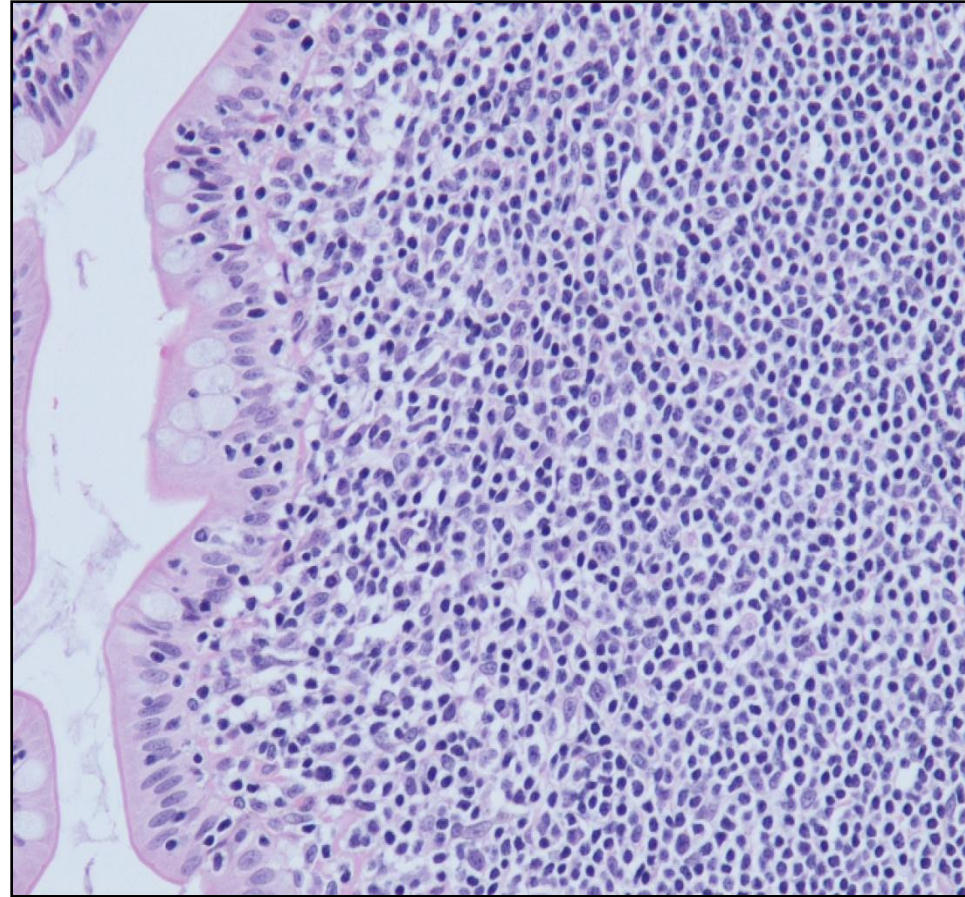
- Same as for traditional D2 biopsies
- **Raised IELs** and villous flattening
- Similar IEL counts in CD bxs from D1 and D2
- May be more severe lesions in D1 than D2



Gastroent 2010 139: 112-119  
Am J Gastro 2011 10:1837-742  
BMC Gastroenterol 2009 9:78-85

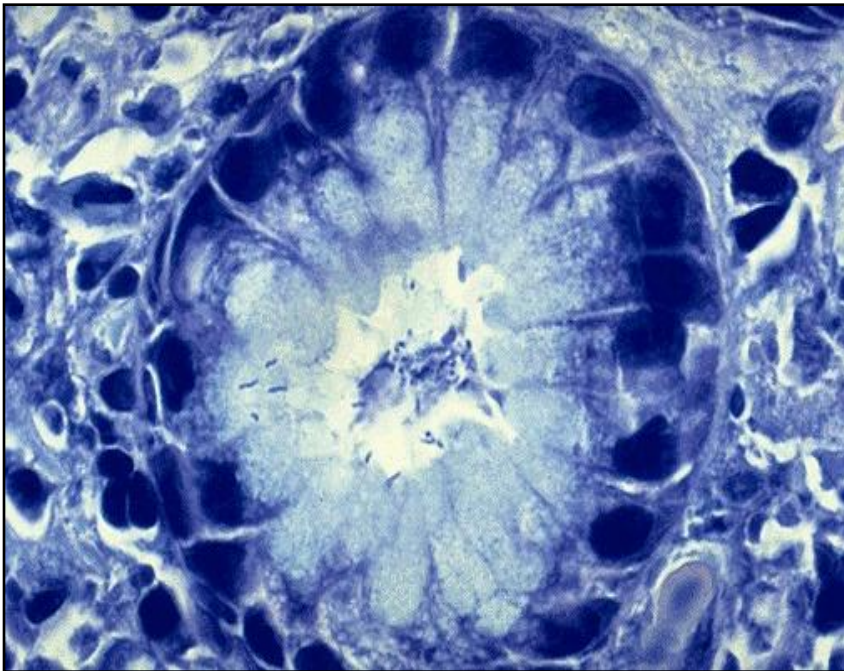
# Pitfall: Lymphoid aggregates in bulb bx's

- IELs are always increased over lymphoid aggregates
- Even in normal biopsies
- If considering counting IELs .. Count somewhere else



# H.Pylori Gastritis

- May cause 2-3% of Marsh 1 lesions in Children
- Also associated with lymphocytic gastritis



Gut 1999 45:495-498  
J Pediat Gastro Nutr Epub 2012

# Lessons

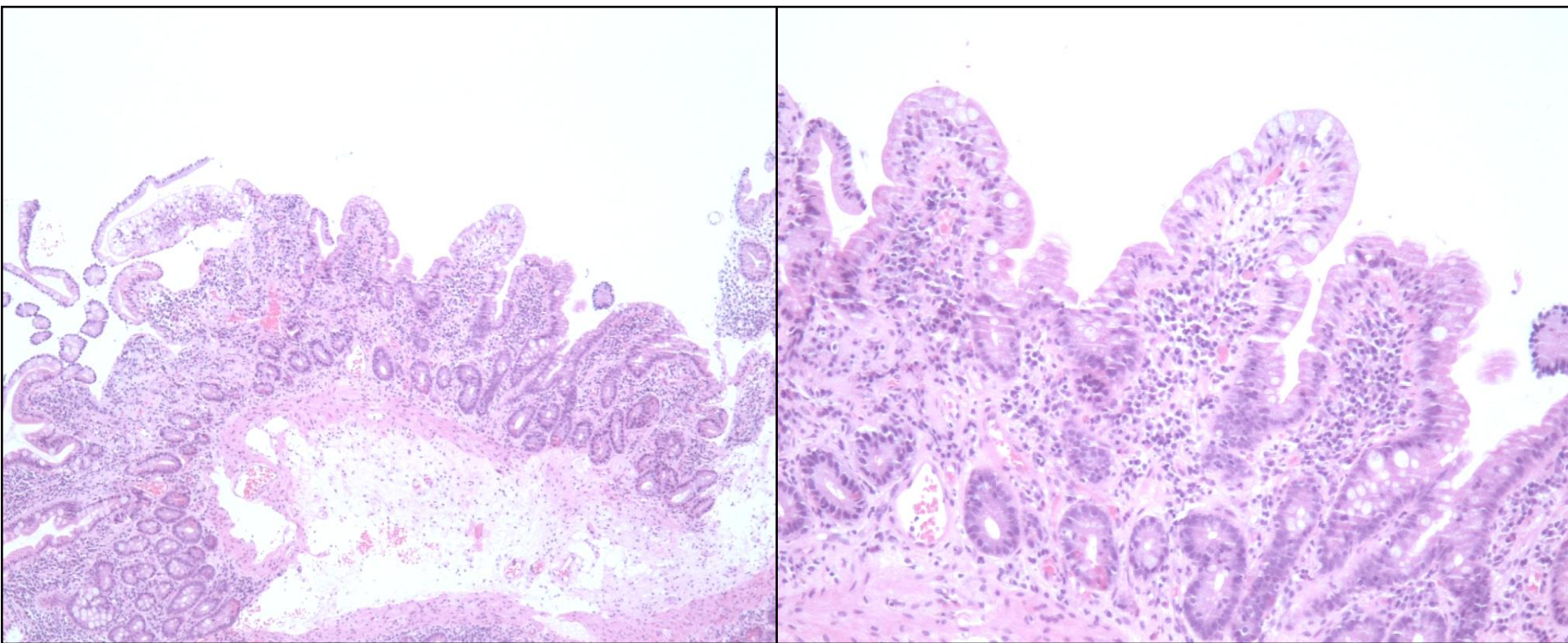
- Acid peptic injury and CD share some features
- Raised IELs most helpful for recognising CD but watch out for H.Pylori
- CD can involve the bulb
- Caution reporting CD in bulb biopsies alone
- Always demand separate pots for D1 and D2 or multiwell cassettes

## II. Drugs

- A growing problem
- List is getting longer
- Rarely get history/context!

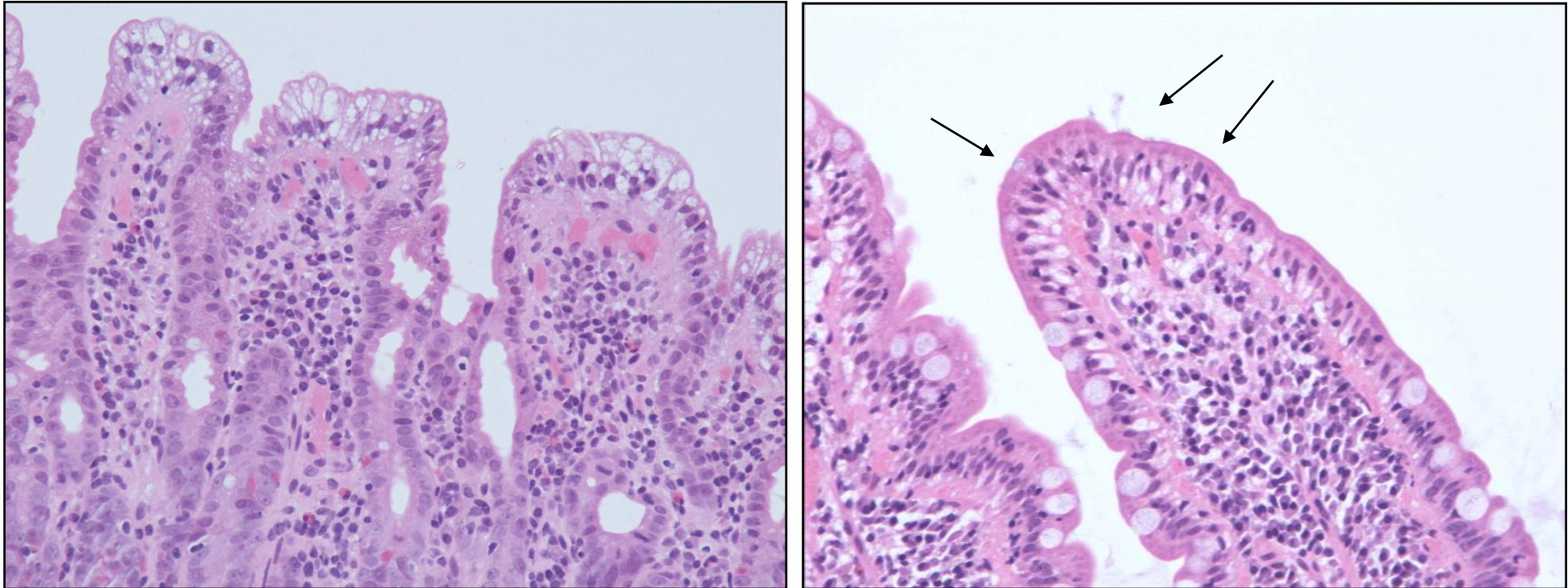


42 yr old lady: Hx of diarrhoea and renal failure



Partial villous flattening and mild increase in IELs

# Very abnormal villous tips



Loss of decrescendo of IELs but overall number not increased

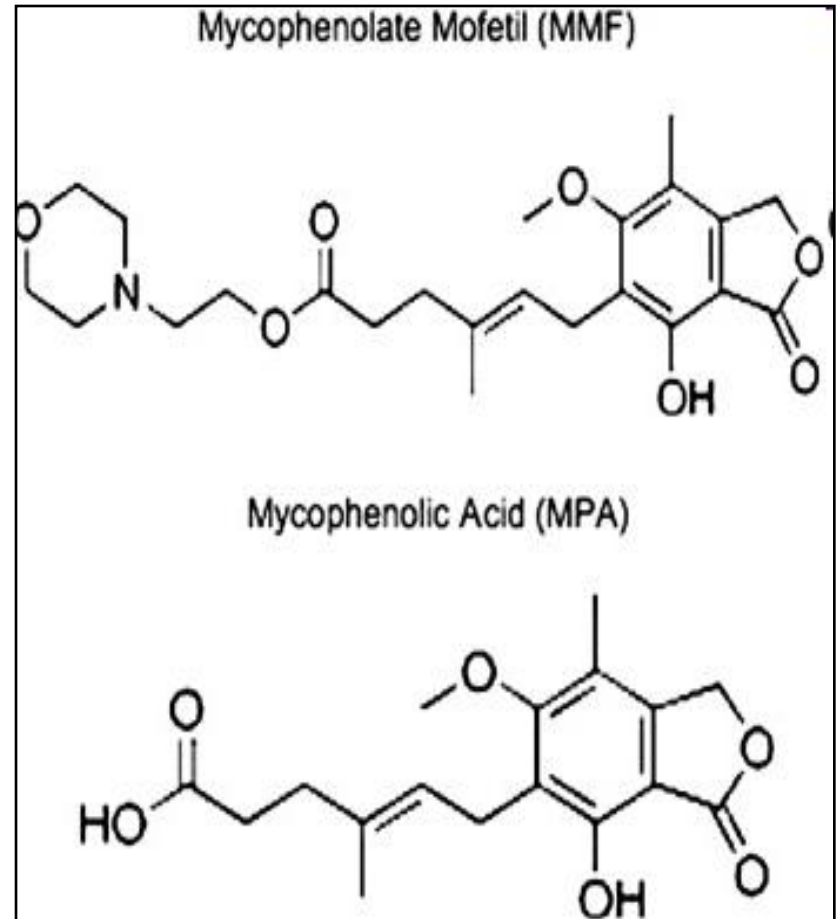
Abnormal vacuolisation in enterocytes

Context: Pt actually had a renal transplant

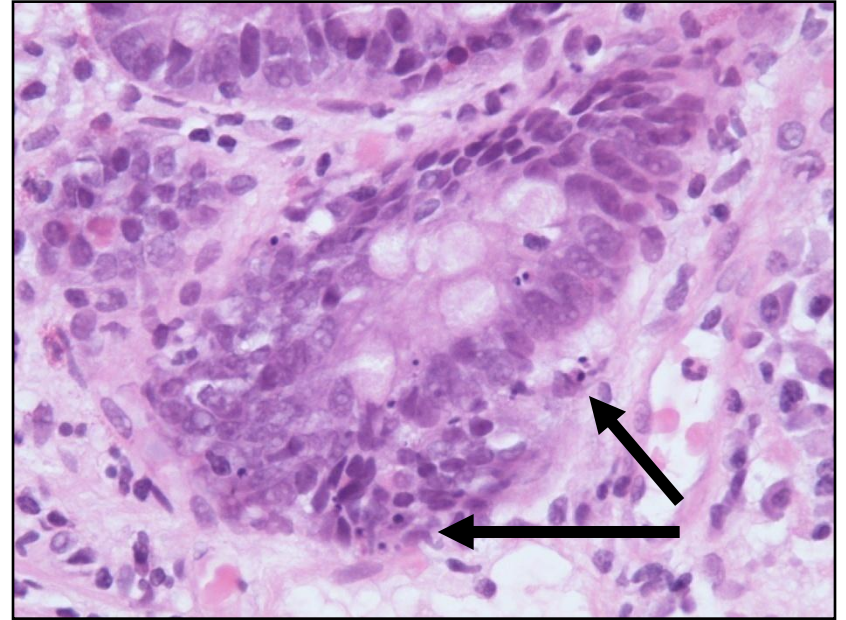
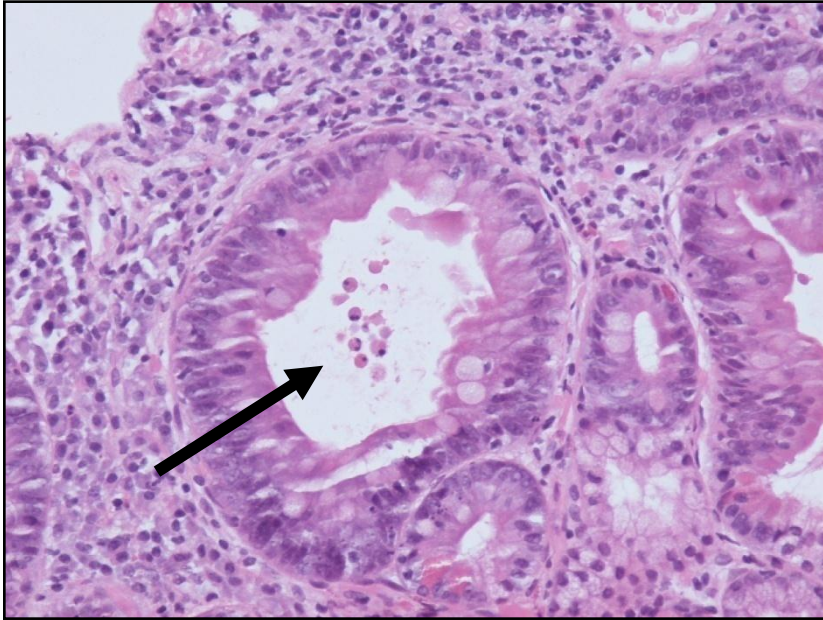
- And was taking

# Mycophenylate

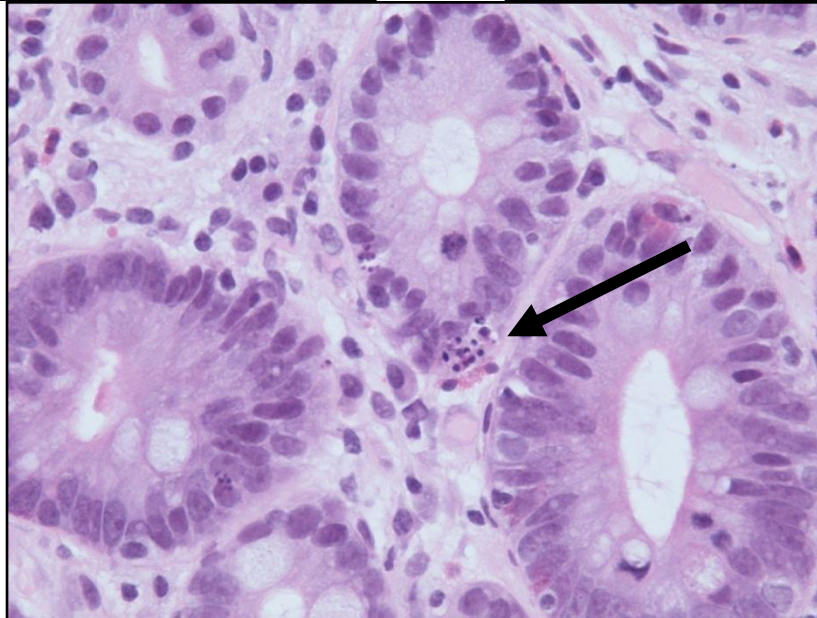
- Immunosuppressive drug ..
- Known GI toxicity
- Increasingly used transplants/vasculitis
- Also causes colonic damage



# Mycophenylate clue: Apoptosis in crypts



RARE  
in this case!



RARE  
In this case!

## Other drugs can cause villous flattening and/or increased IELs

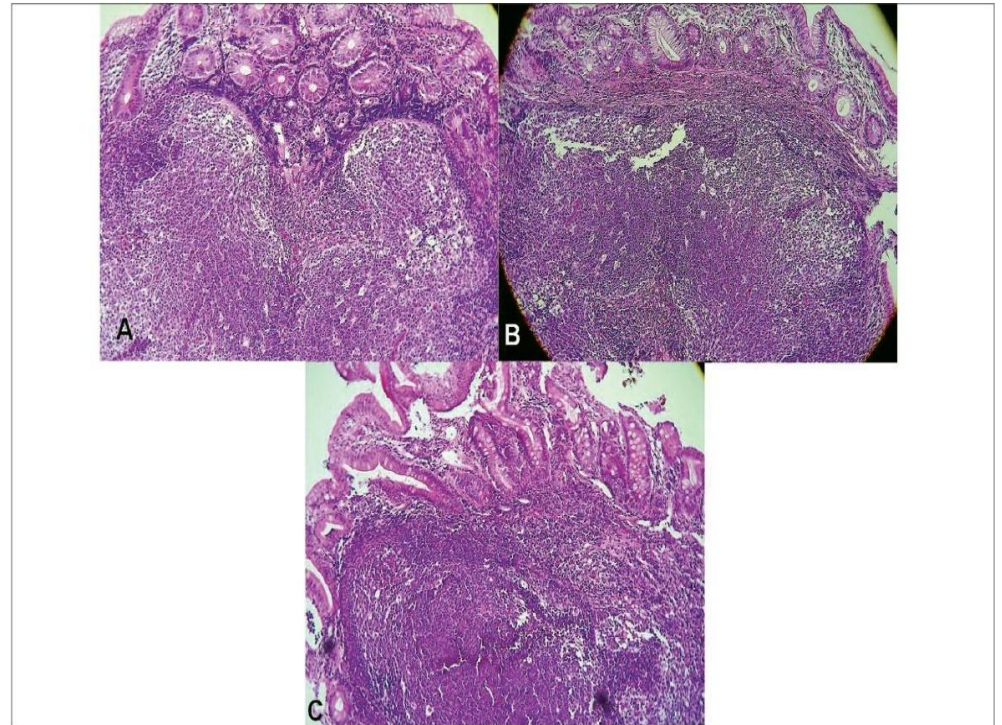
- Azothioprine (transplant setting)
- Conventional chemotherapy
- HAART
- Triparanol
- ACE inhibitor Olmesartan (Olmotec)
  
- Context is crucial

# III. Immunocompromise

- AIDS enteropathy
- Hypogammaglobulinemia
- T cell disorders e.g. IPEX syndrome
- Rarely IgA deficiency
  
- Rare, mostly children but some adults

# CVID Common variable immunodeficiency

- Abnormality throughout GI tract
- Lymphocytic gastritis
- 60% increase IELs in duod
- 80% villous blunting
- Lymphoid nodules

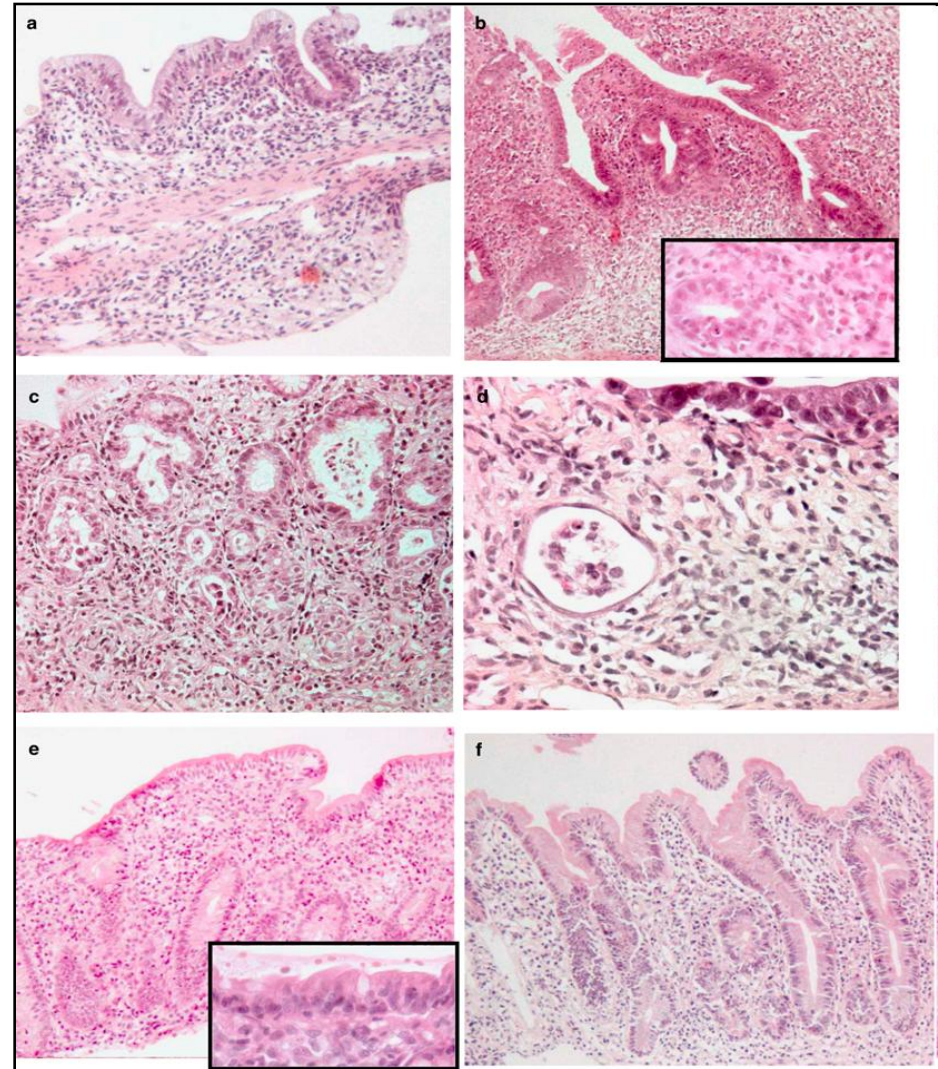


Am J Surg Path 2007 31: 1800-12  
Am J Gastroent 2003 98: 118-21

# IPEX

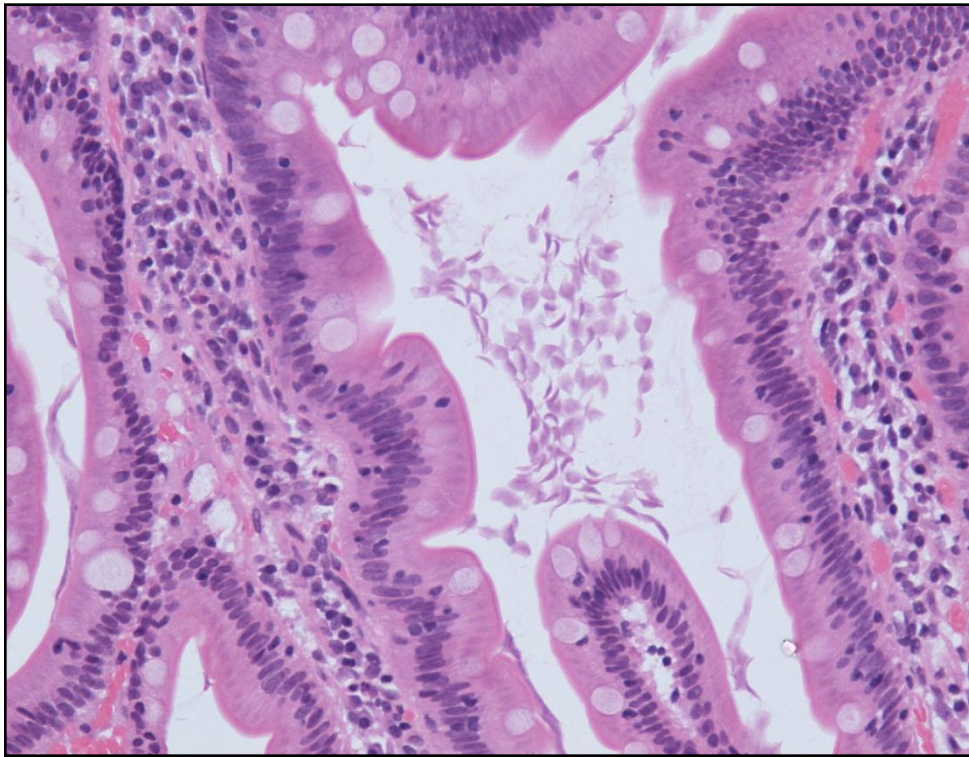
## Immunodysregulation polyendocrinopathy enteropathy X linked inheritance

- FOX P3 mutation
- Deficient Treg cells
- Numerous infections
- Can mimic CD, GVHD or produce goblet cell depletion

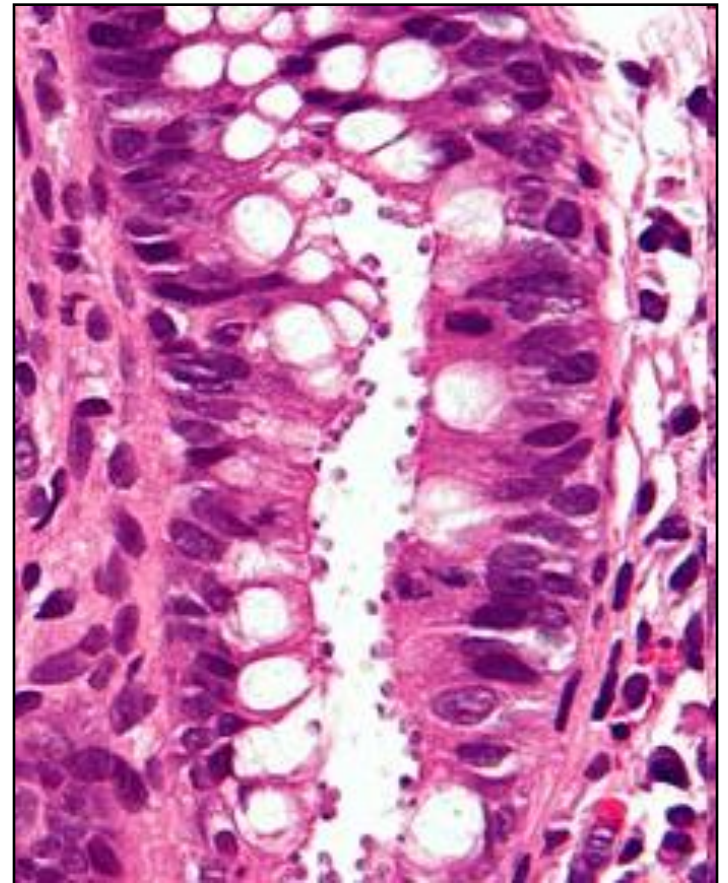


# Clues to immunodeficiency

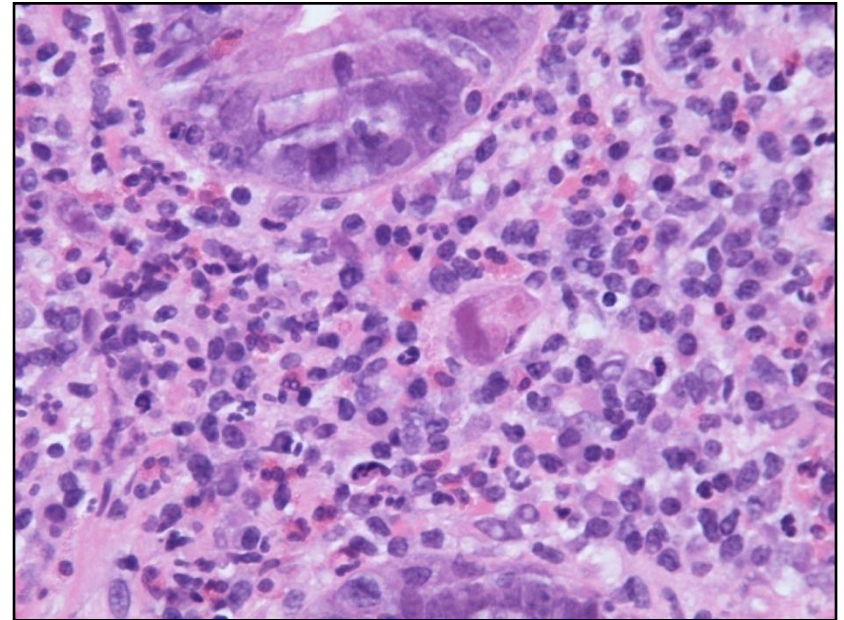
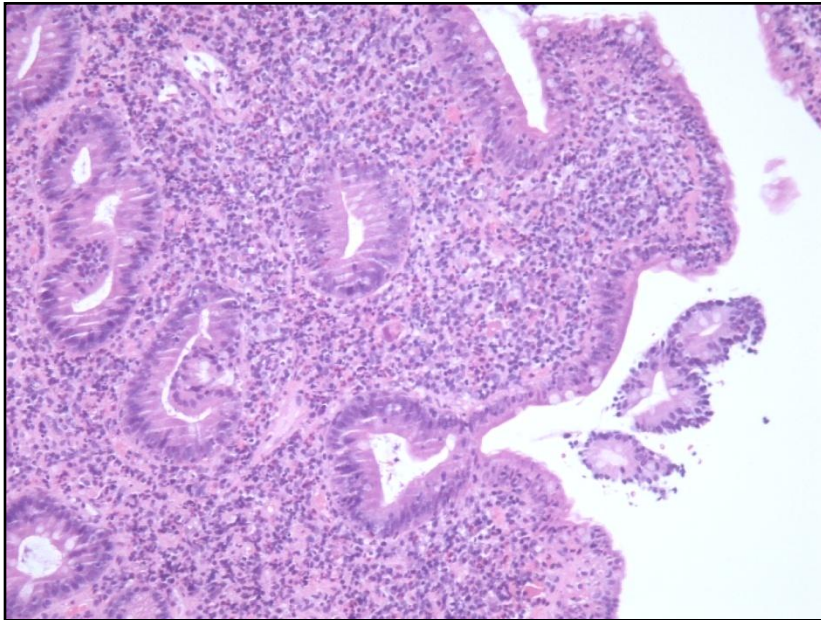
- *Giardia*



- *Cryptosporidium*

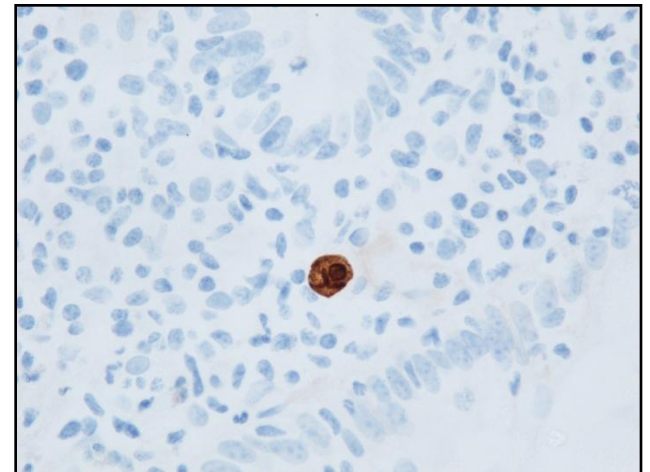


# Clues to immunodeficiency: CMV

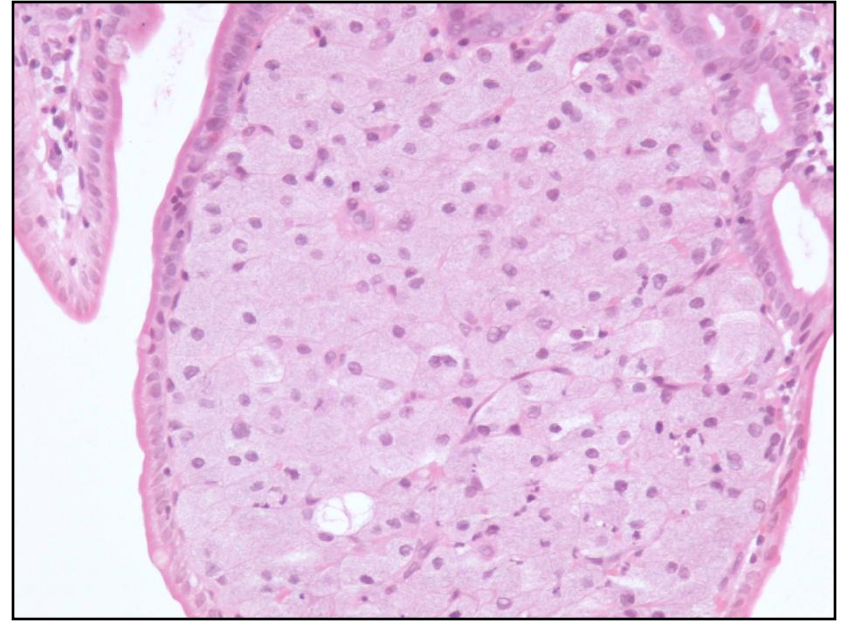
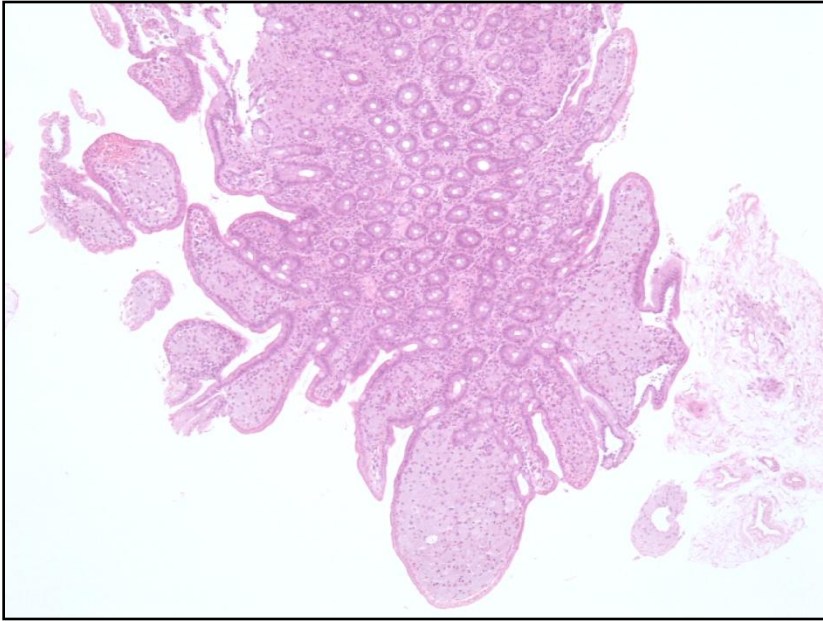


More commonly seen in iatrogenic  
Immunosuppression

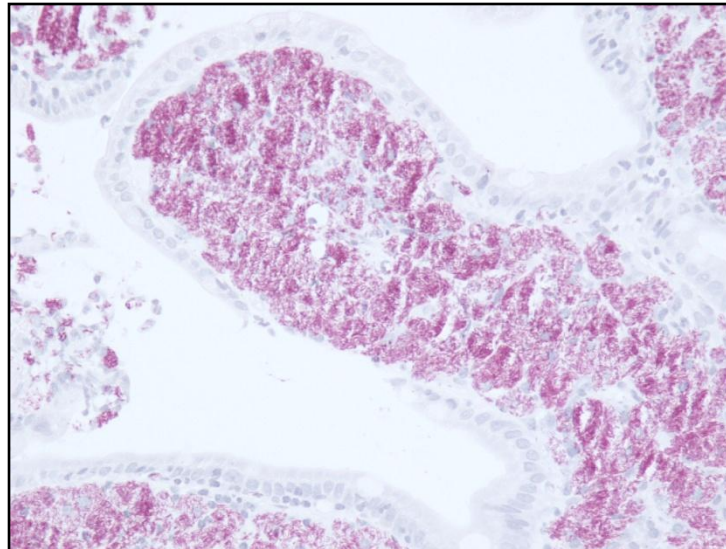
Immunohistochemistry is helpful



# Clues to immunodeficiency: MAI



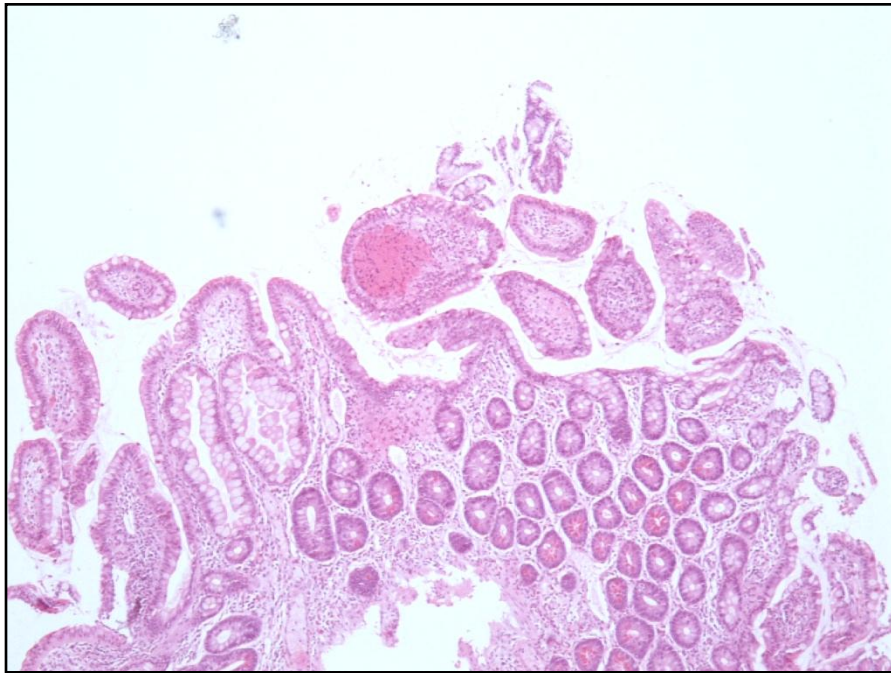
ZN and PAS positive



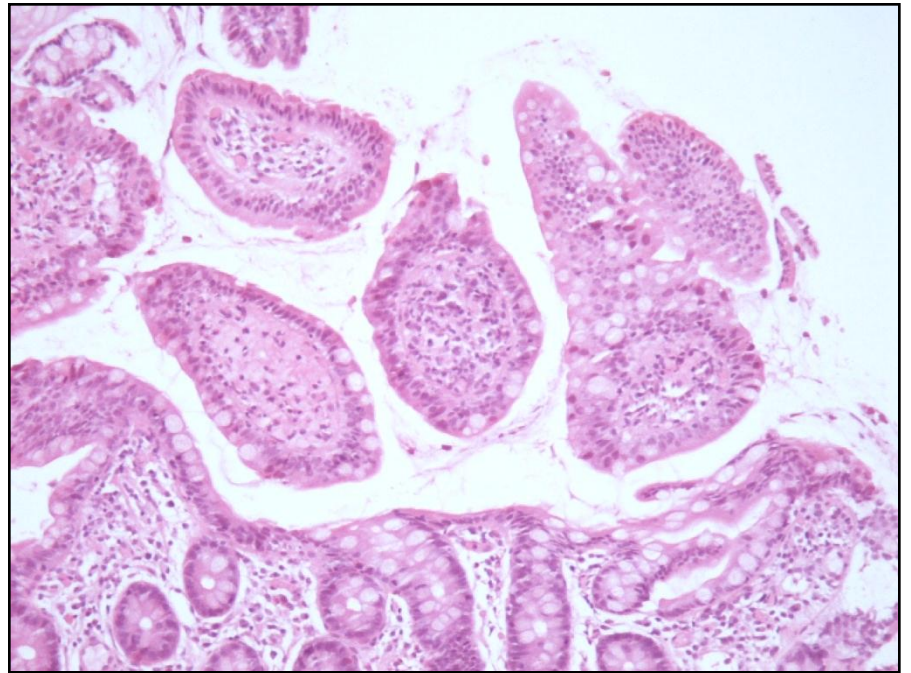
DDx is Whipples disease

When we have context path can be very useful!

7 year old girl post small bowel transplant

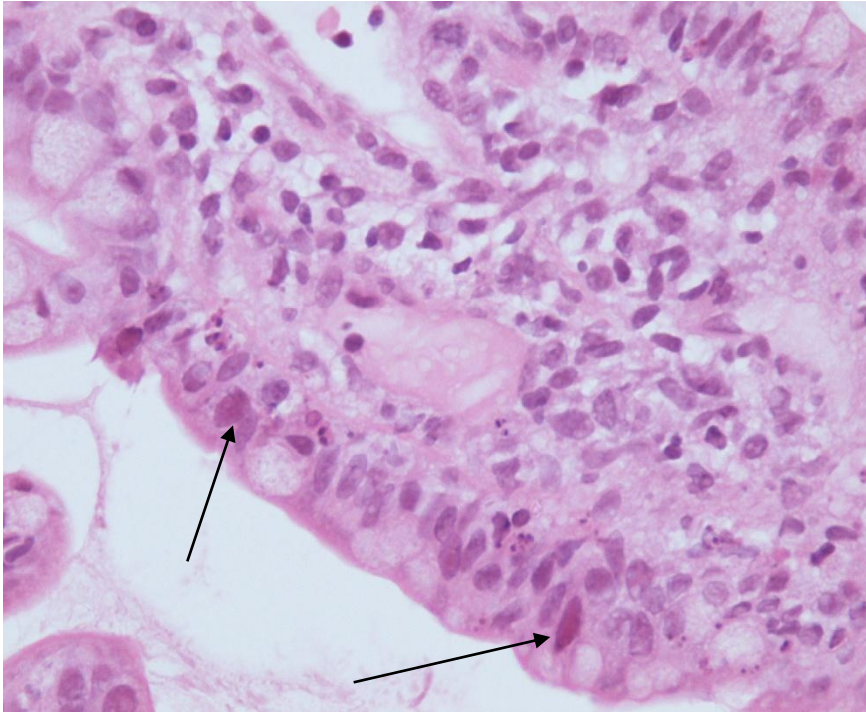


Distorted mucosa

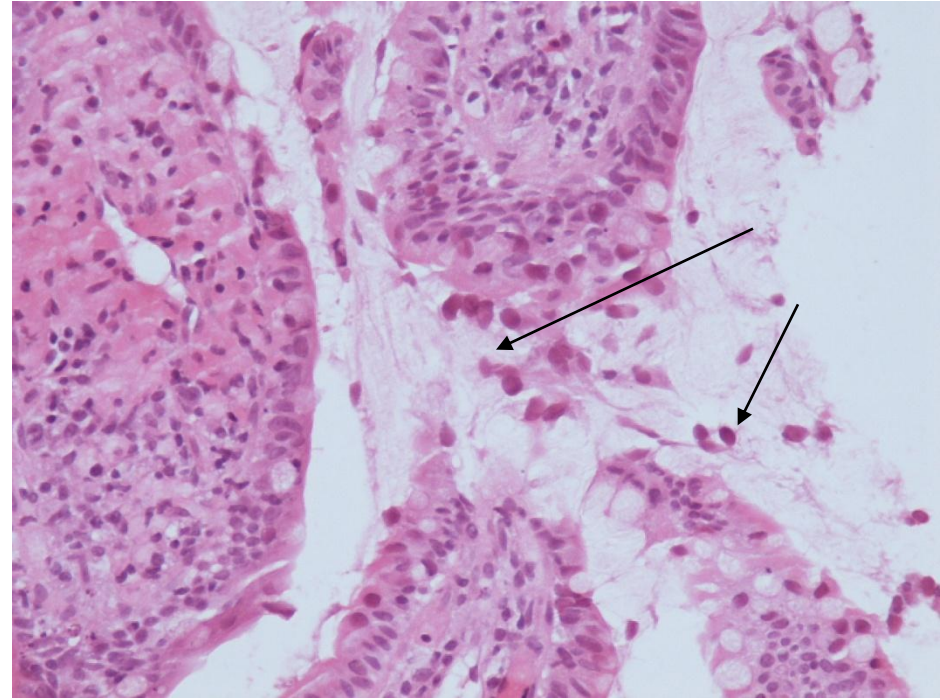


Something in the intervillous space

# Adenovirus



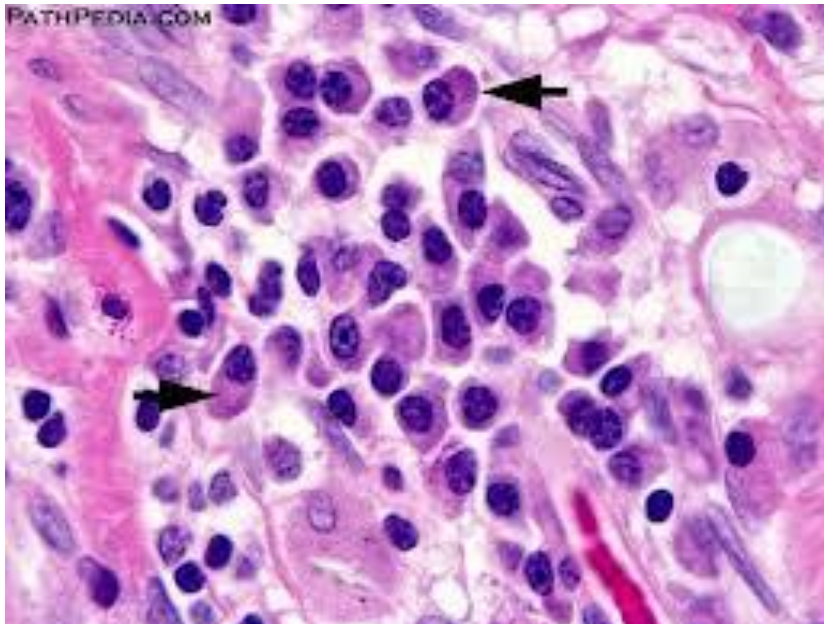
Smudged cells (viral purple)



Sloughed off ECs

# Best clue to immunodeficiency

- No plasma cells in lamina propria
- Always check for them when thinking of CD



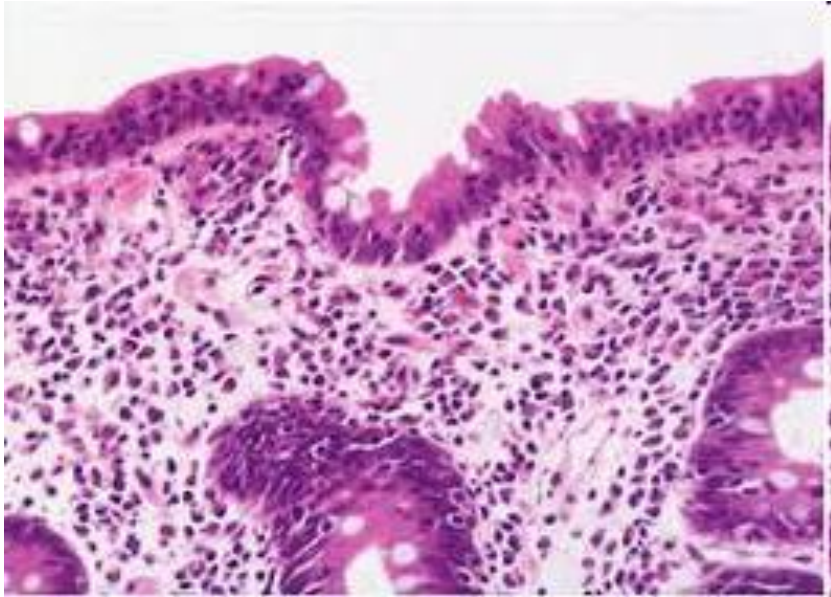
# Other infections: Tropical sprue

- Perfect mimic
- Need history of travel to endemic regions
- Biopsy features identical to CD
- Rarely biopsied

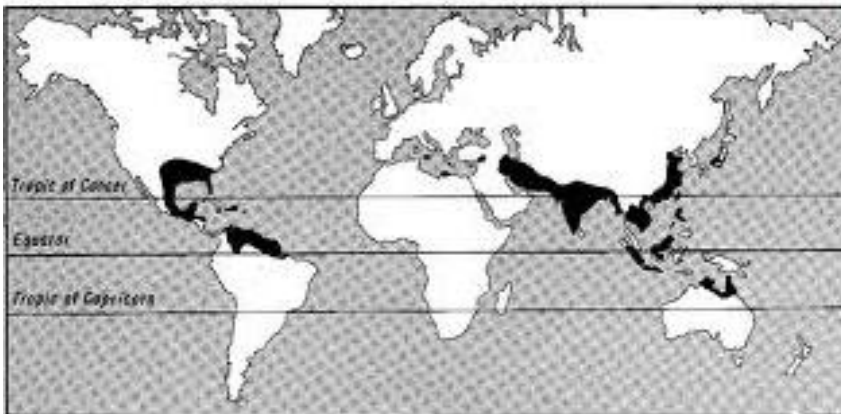
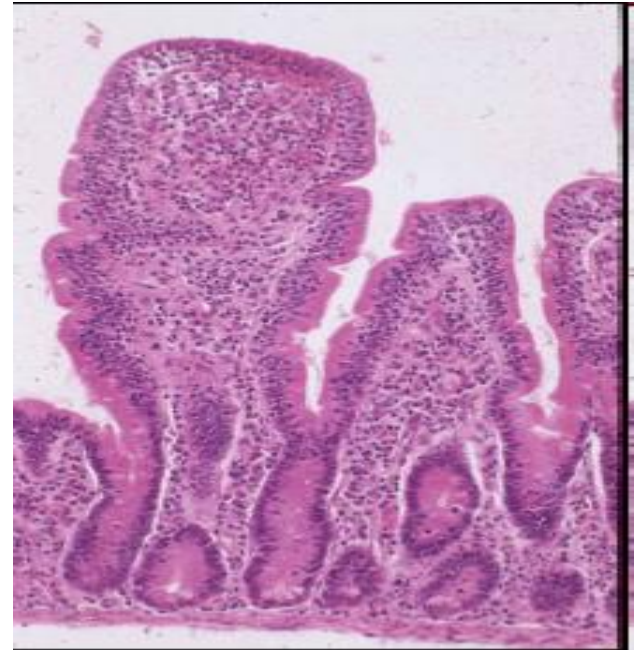


# Tropical Sprue

Villous flattening



Raised IELs



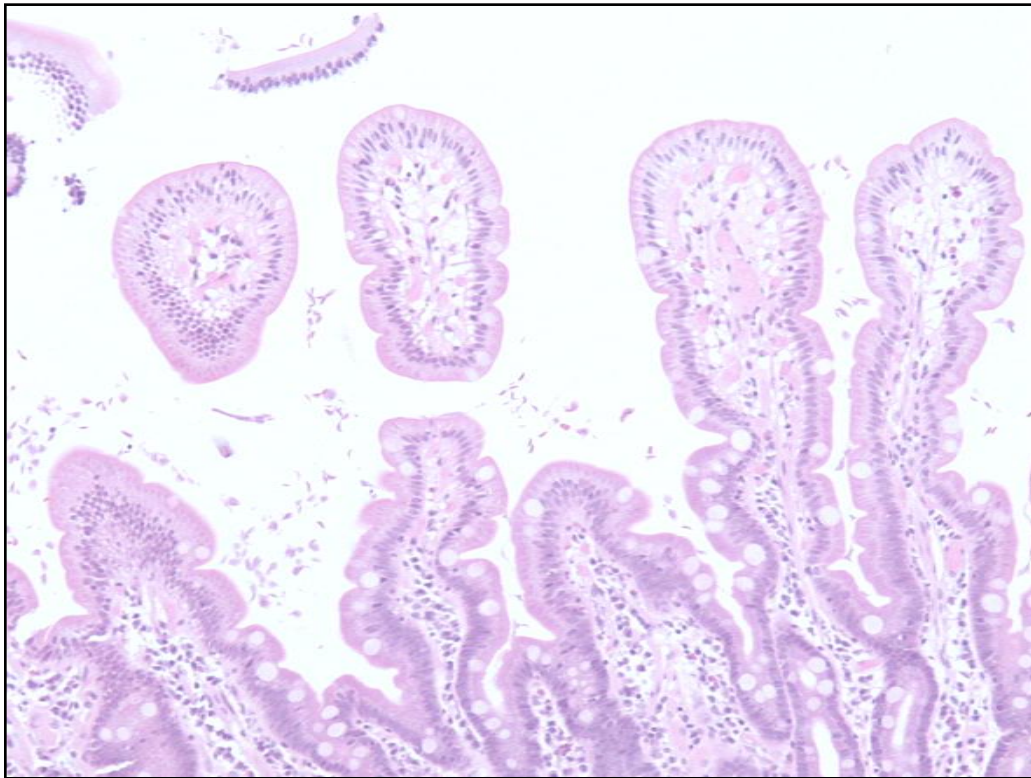
← Not just 'tropical'

# Pathological Mimics of CD

- Tropical sprue
- Bacterial overgrowth
- Blind loop syndrome
- CVID, IPEX
- AIDS enteropathy
- Graft v's Host dse
- Malnutrition
- Zollinger Ellison
- Ischaemia
- Radiation
- MVID
- Viral enteritis
- **Giardiasis**
- Acid-peptic injury
- Helicobacter pylori
- Drugs/immunosuppression
- Crohns disease
- Collagenous sprue
- Derm. herpetiformis
- RCD2/Lymphoma
- Autoimmune enteritis
- Allergic gastroenteritis

# Giardiasis in Immunocompetent patients

- Rarely see flat villi



Aonach Eagach ridge

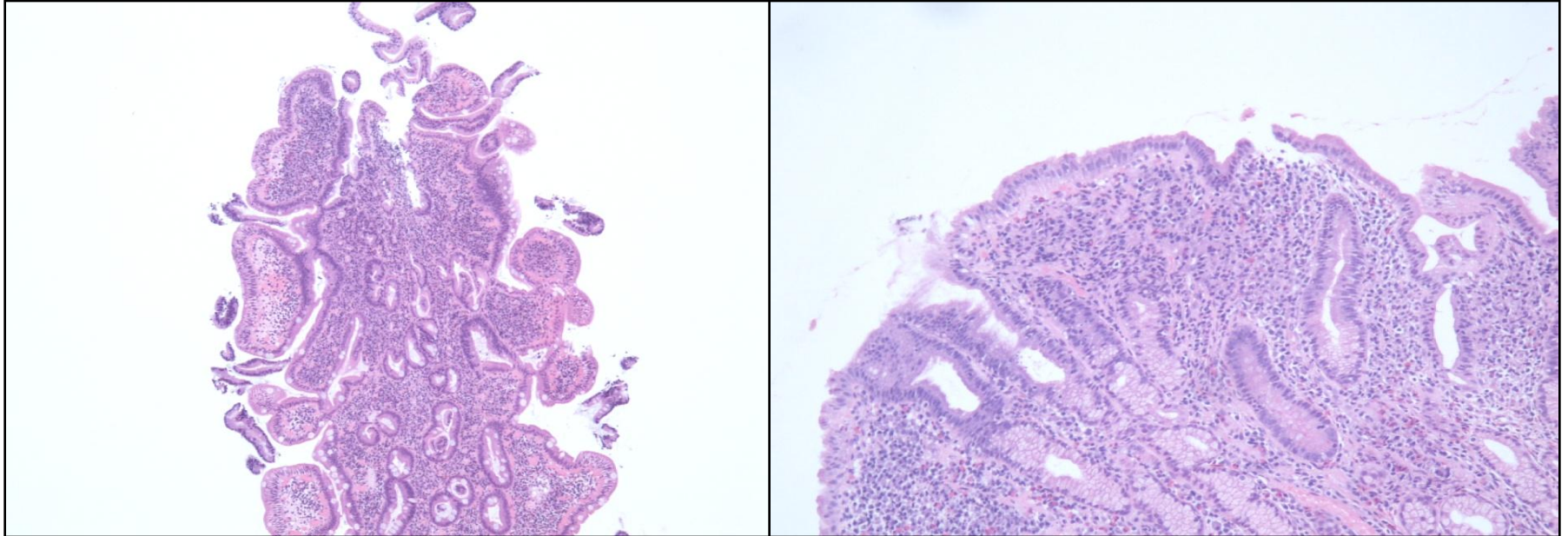
# IV. Autoimmune and Allergic diseases

- Crohn's disease
- Autoimmune enteropathy
- Collagenous sprue

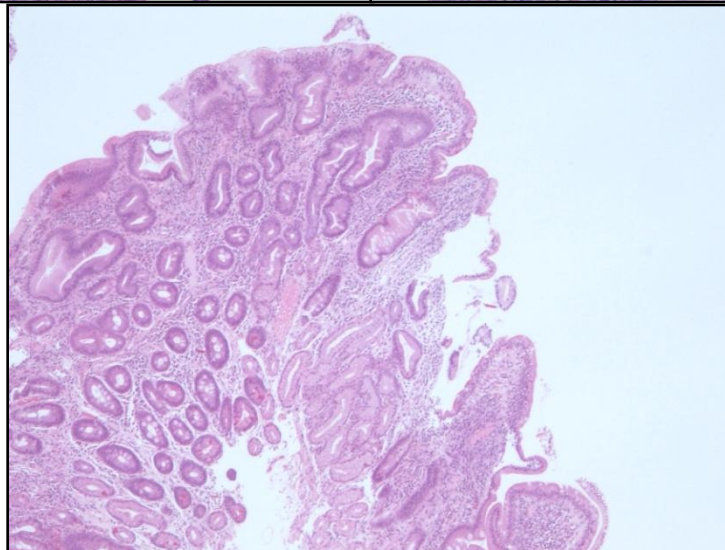
# Crohn's disease

- Good pathological mimic of Coeliac disease
- Can rarely coexist with CD
- TTG can be raised
- Essential to have clinical information e.g mouth ulcers, colonic disease
- Examine other biopsies from colon or stomach if available

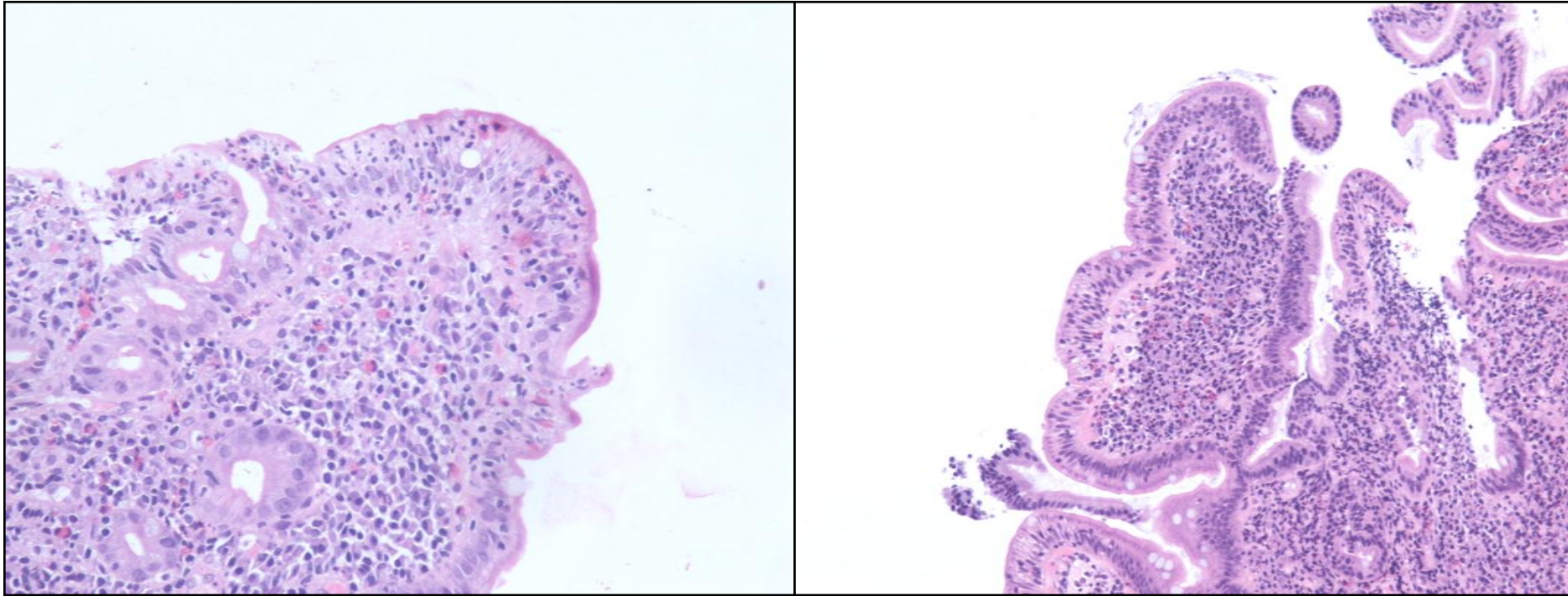
# Crohn's disease: Villous flattening and crypt hyperplasia



Tendency for  
more crypt  
distortion

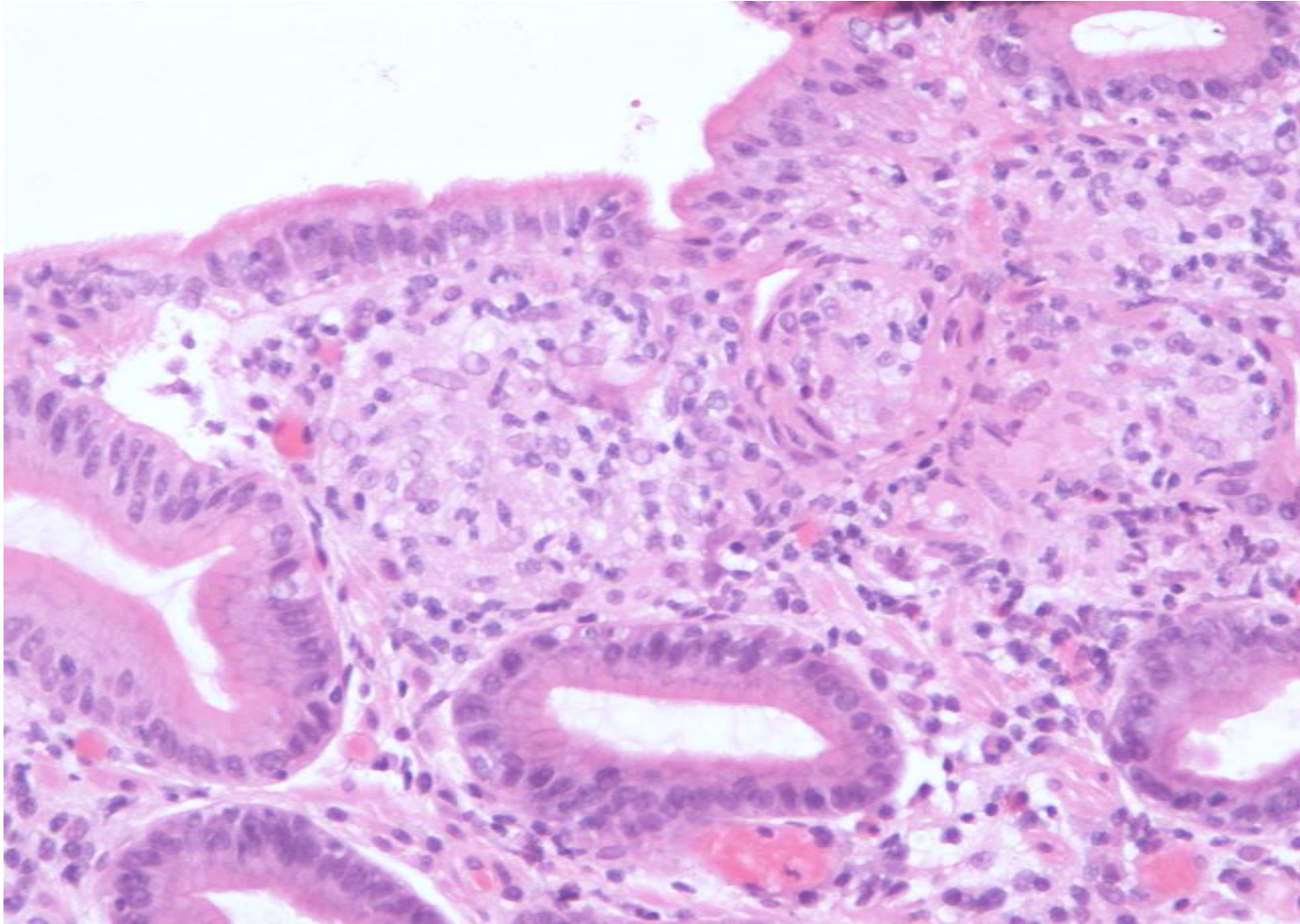


# Crohn's disease: Increased IELs



Often intraepithelial component is more polymorphous than Coeliac dse.

# Crohn's: Granulomas



So helpful (50%) of cases

NOT seen in Coeliac disease

If in doubt get some levels

# Autoimmune Enteropathy

- Rare: Adults and children
- Villous flattening and increased IELs
- Anti-enterocyte Ab's
- No Coeliac autoantibodies
- Other autoimmune diseases

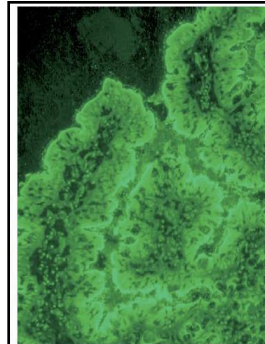
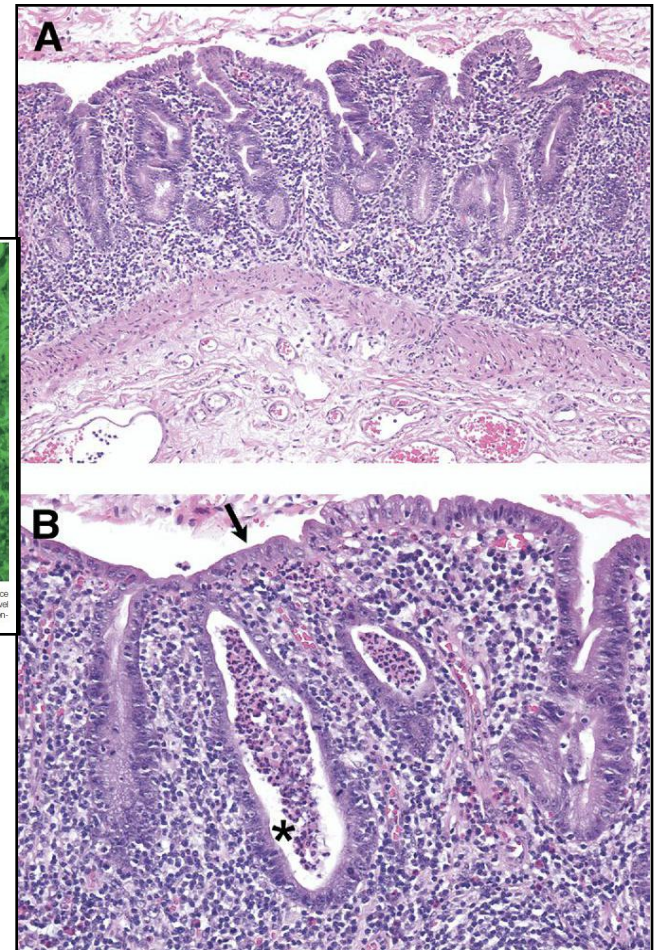
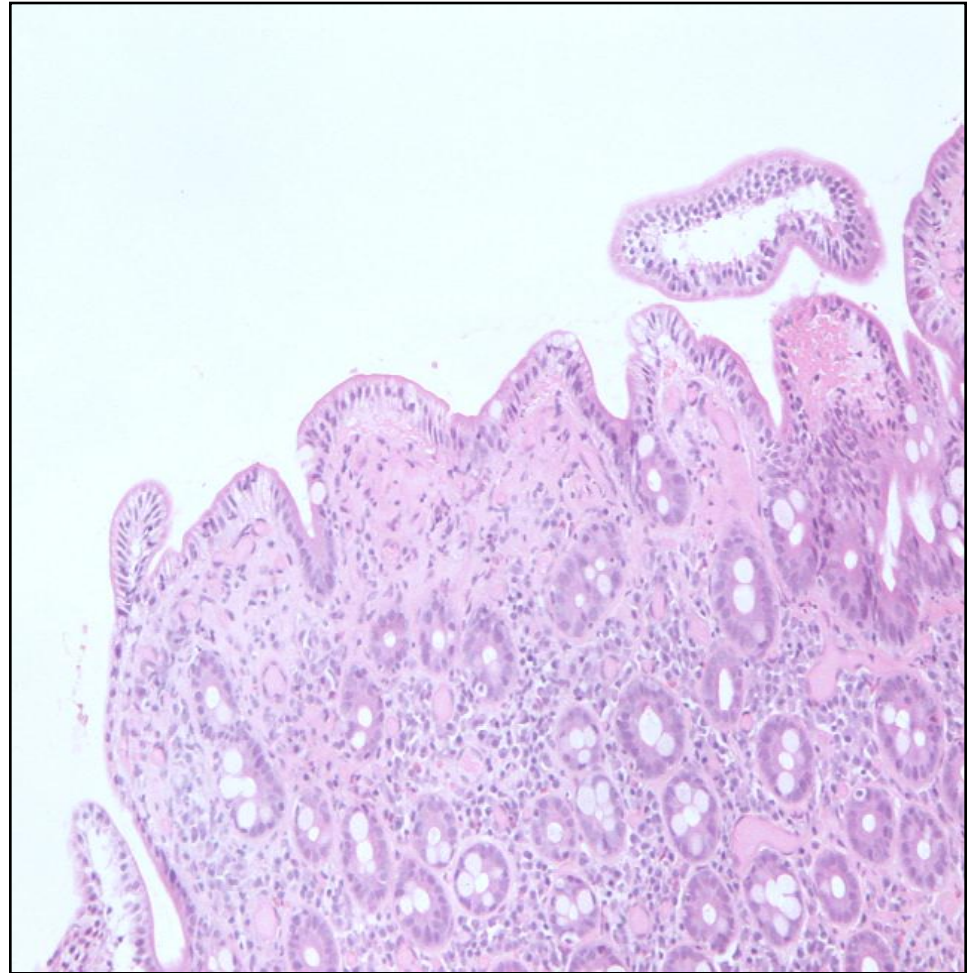


Figure 1. Anti-enterocyte antibodies. Indirect immunofluorescence with the patient's serum on frozen section of normal human small bowel shows a linear fluorescence pattern along the brush border of the enterocytes (original magnification, 300 $\times$ ).

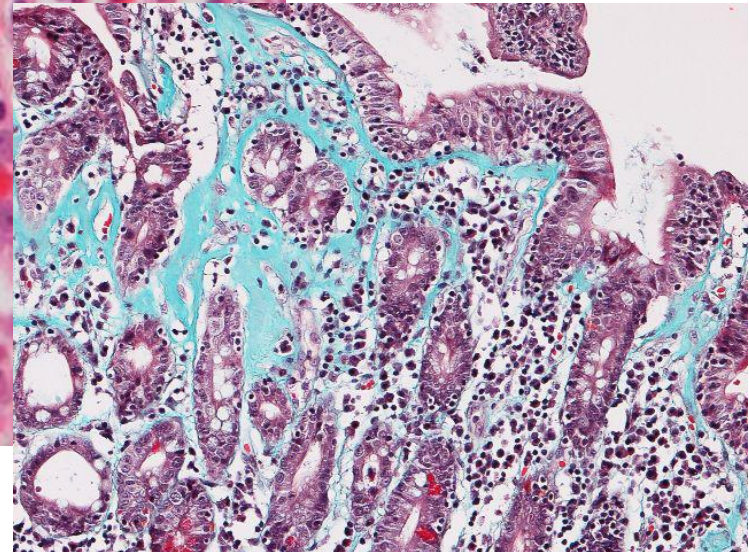
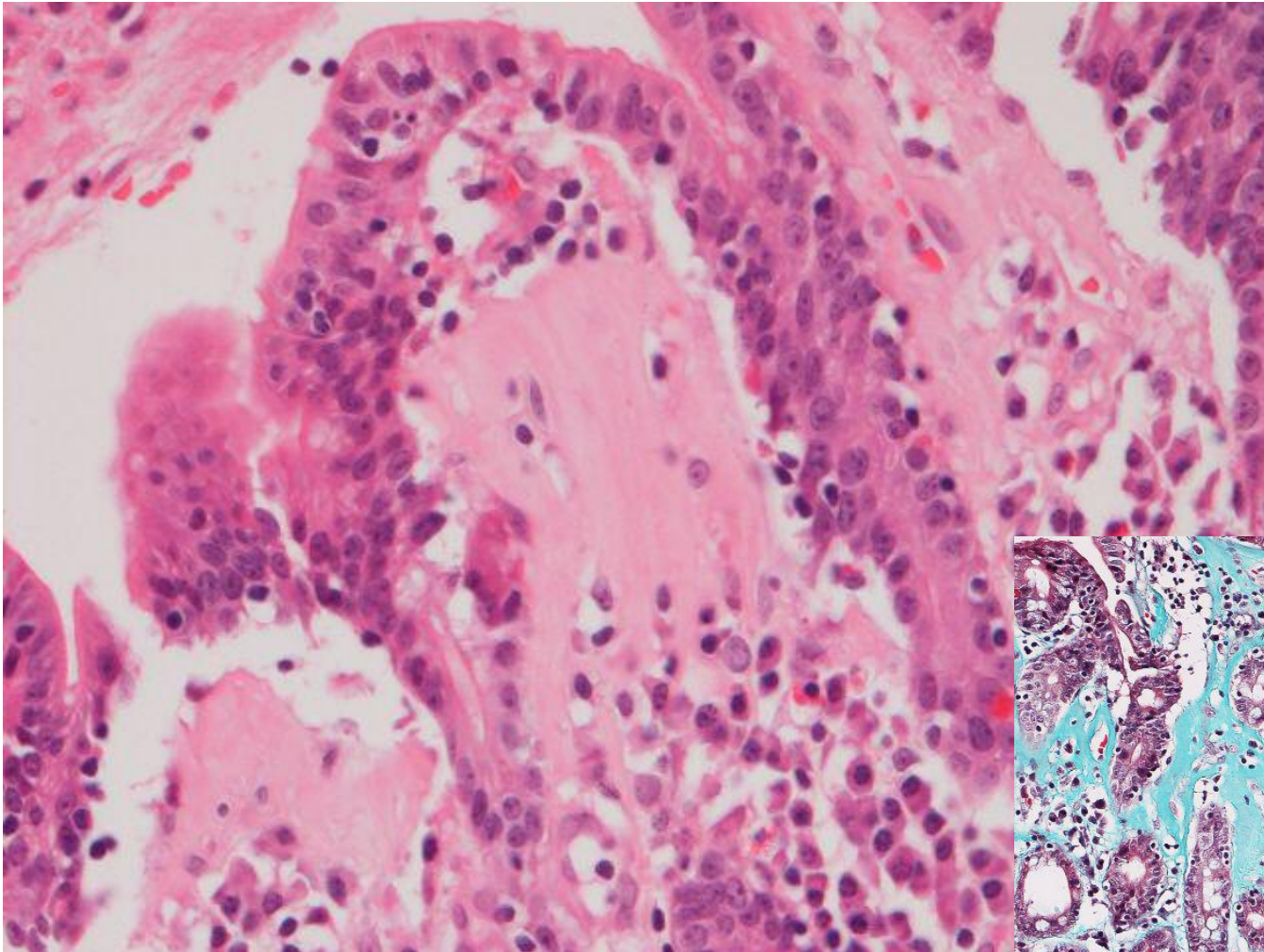


# Collagenous sprue

- Rare
- Deposition of subepithelial collagen
- Variable villous atrophy
- In the past associated with a poor prognosis
- Now GFD and immunosuppression effective treatment in most

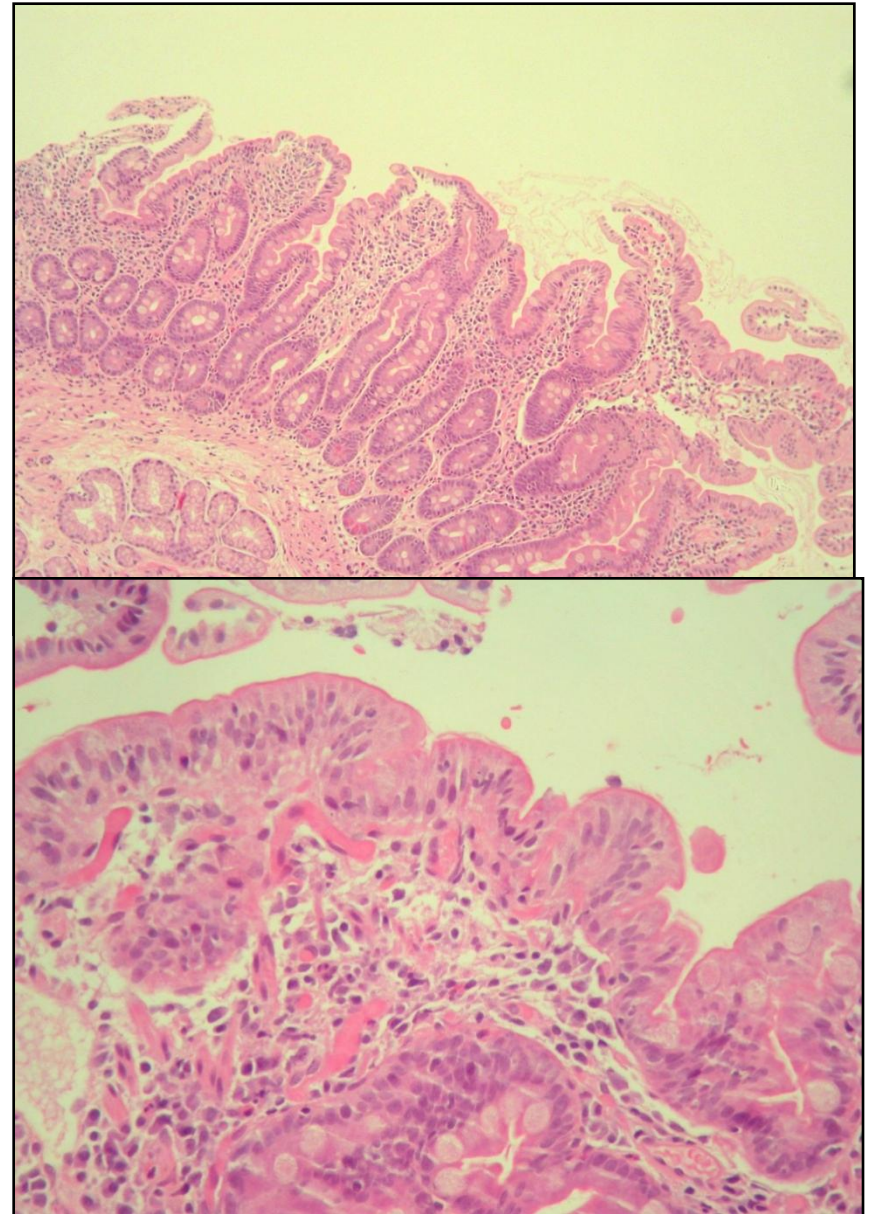


# Collagenous Sprue: collagen entrapping immune cells

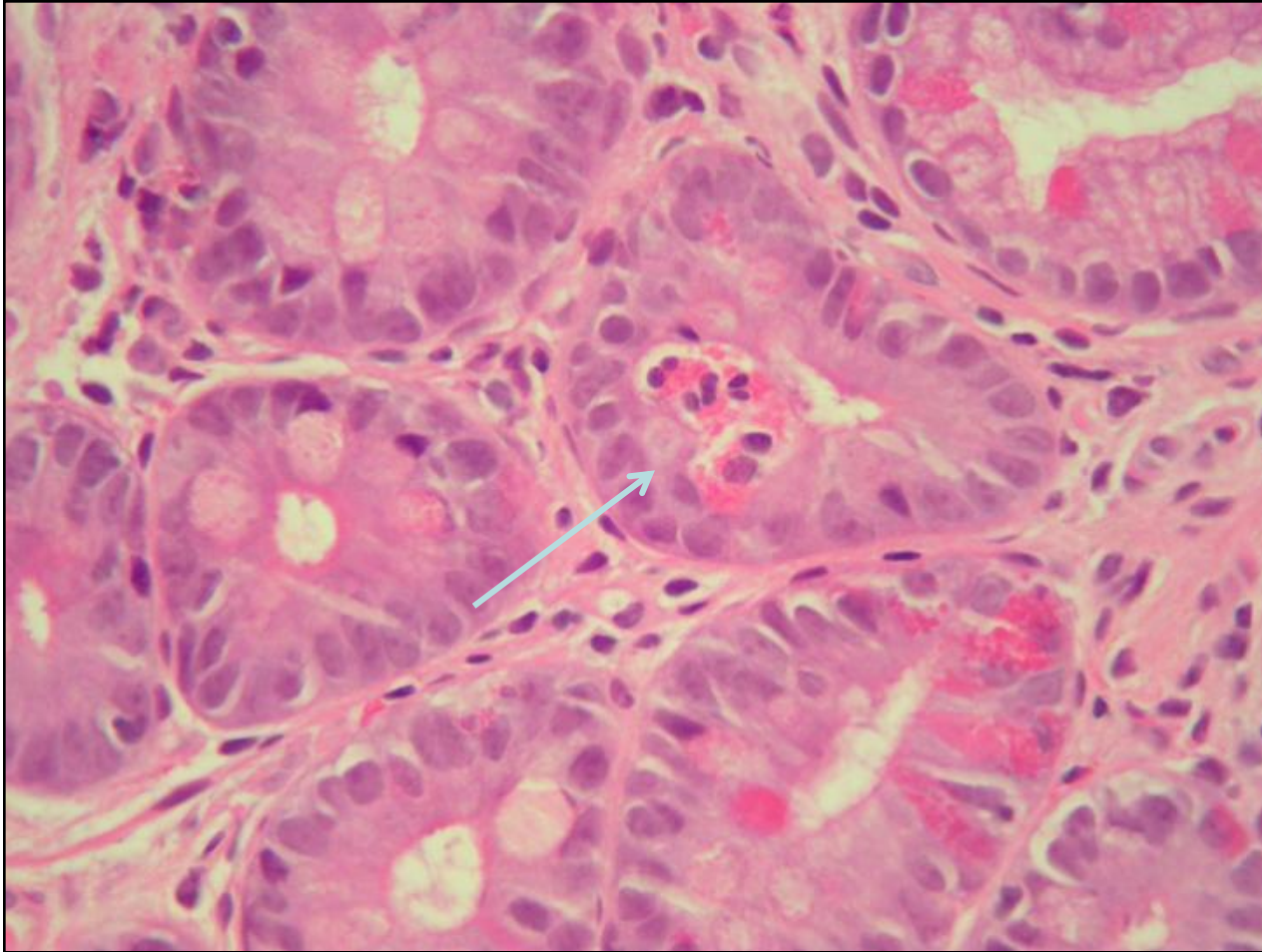


# Allergy

- Common in children but rarely biopsied
- Clinically diagnosed/tx by exclusion diet
- Cows milk/  
Eggs/**Wheat**
- Confusion with CD  
VA and Inc IEL's



# Clue to allergy: Eosinophils



Eosinophilic Cryptitis

or

Eosinophilic crypt  
Abscess

or

Large aggregates in LP

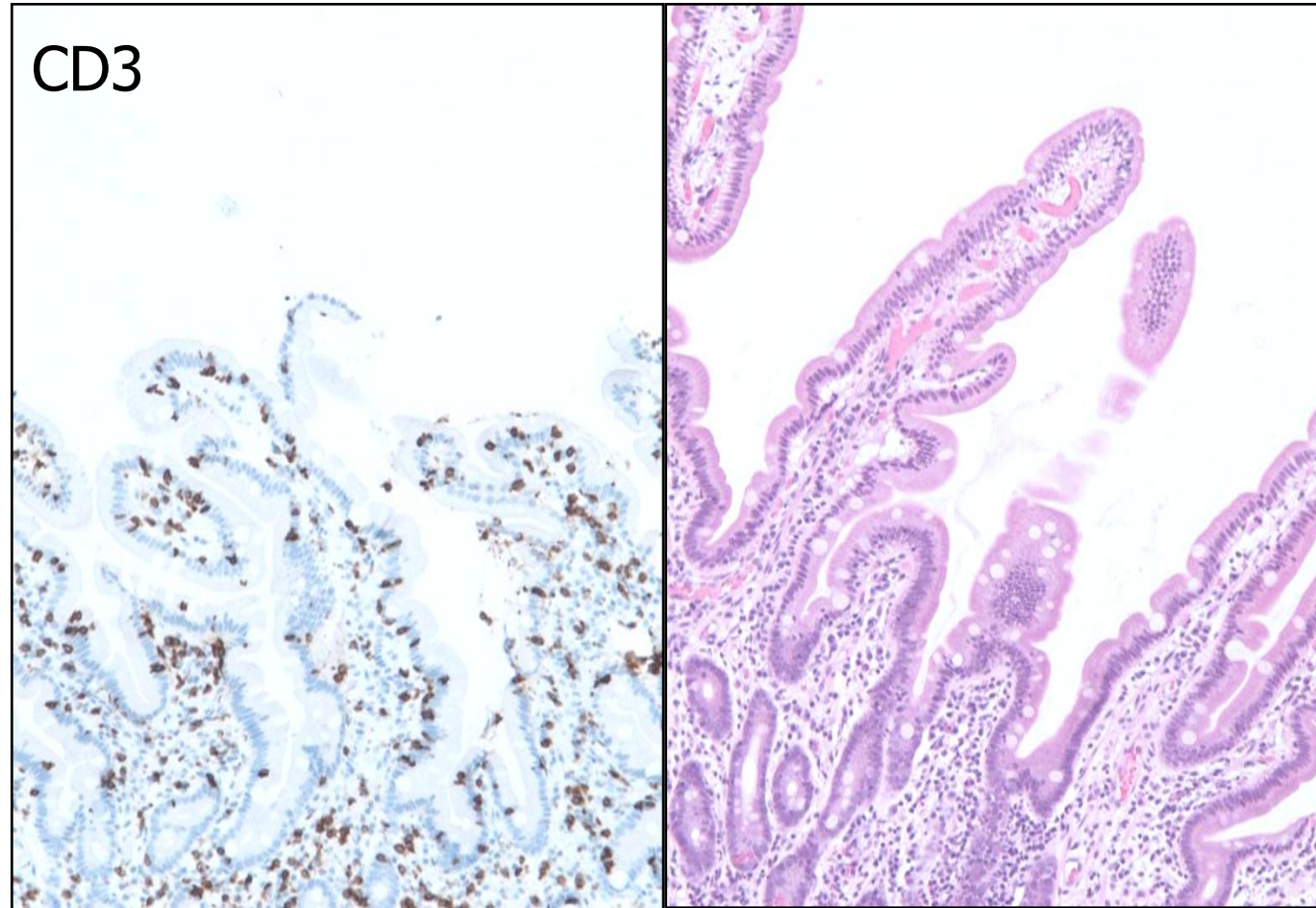
Pitfall: Eosinophils need to be doing something. Eosinophils in the lamina propria are a non specific finding and can be seen in CD

# How should we report CD biopsies?

- ...the findings are in keeping with CD in the correct clinical context...
- ..... in keeping with CD and serology should confirm the dx whilst the patient is on a GFD...
- ..... in keeping with CD. Clinical and serological correlation is urged.

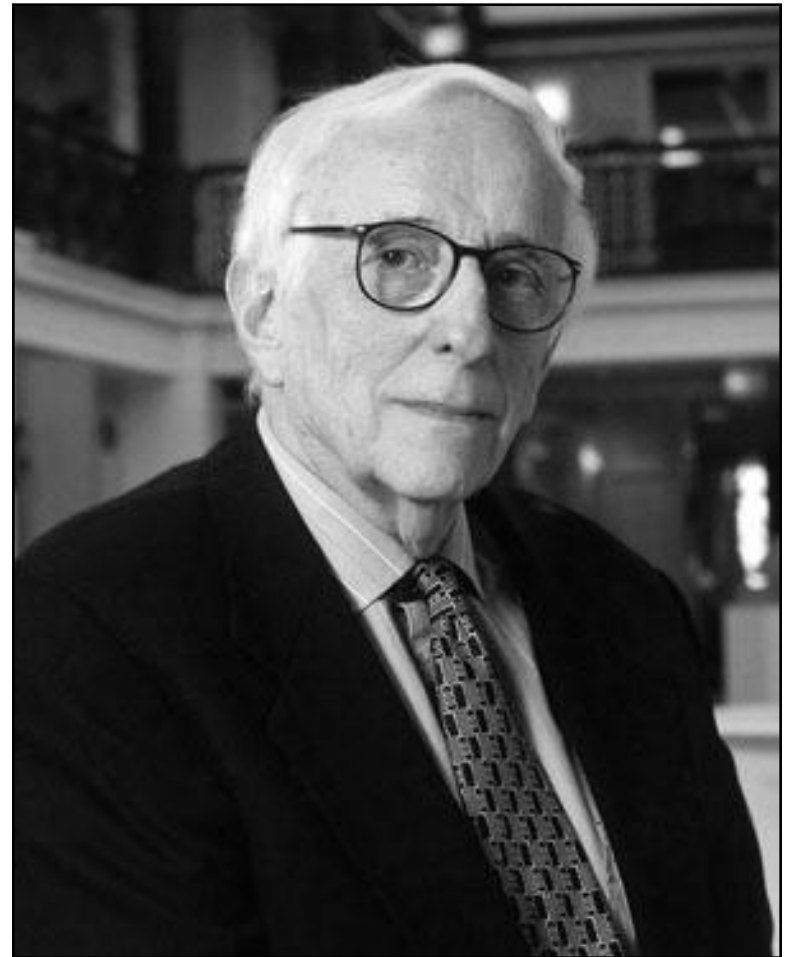
# Immunohistochemistry?

- No role in routine diagnosis
- Not useful for counting
- Not useful for spotting mimics



# Dr Goldman on CD

- ' The histopathologic features are non-specific in nature and can be seen in many other conditions.'
- CONTEXT



# Complications of CD

- Refractory CD
- Lymphoma (GI and elsewhere)
- Carcinoma
- Liver cancer (Sweden)
- Other AI disease (thyroid)
- Malnutrition
- Others

# Refractory Coeliac Disease (RCD)

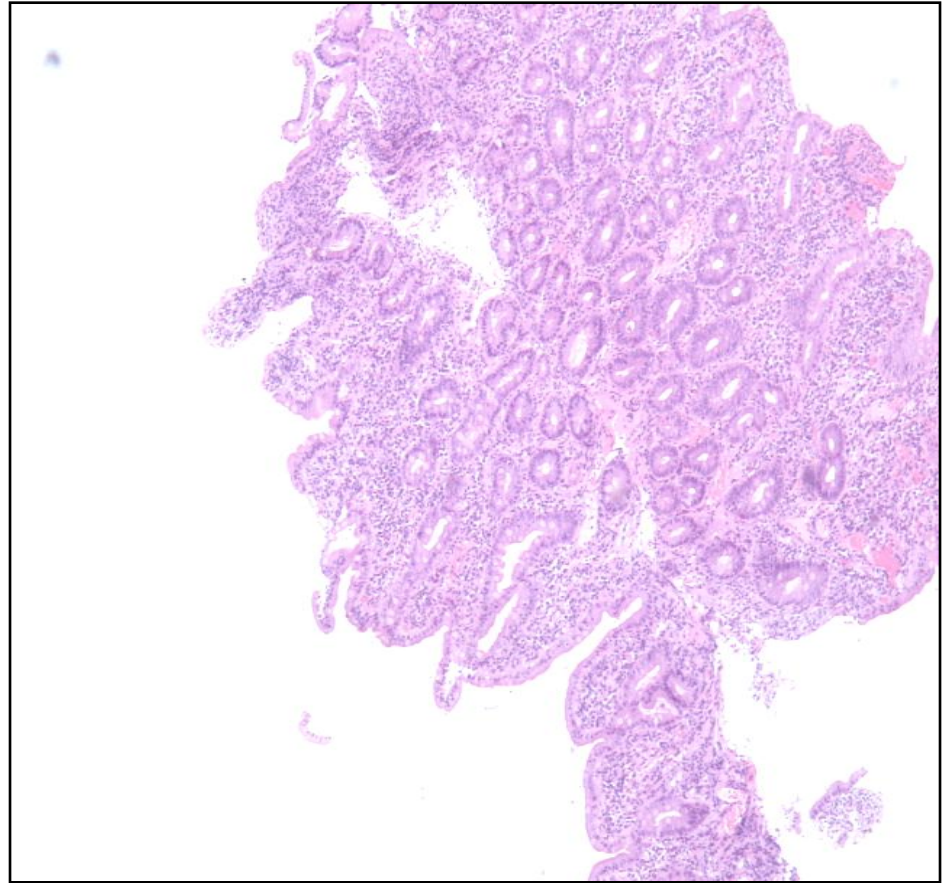
- RCD may be defined as persistent or refractory symptomatic malabsorption together with villous atrophy which persists despite adherence to a gluten free diet.
- 6/12, EATL excluded
- Combined clinical, pathological and molecular approach is necessary
- A real case

*Walker and Murray Histopath 2011; 59; 166-179.*

*Ho-Yen et al Histopathology 2009; 54; 783-795.*

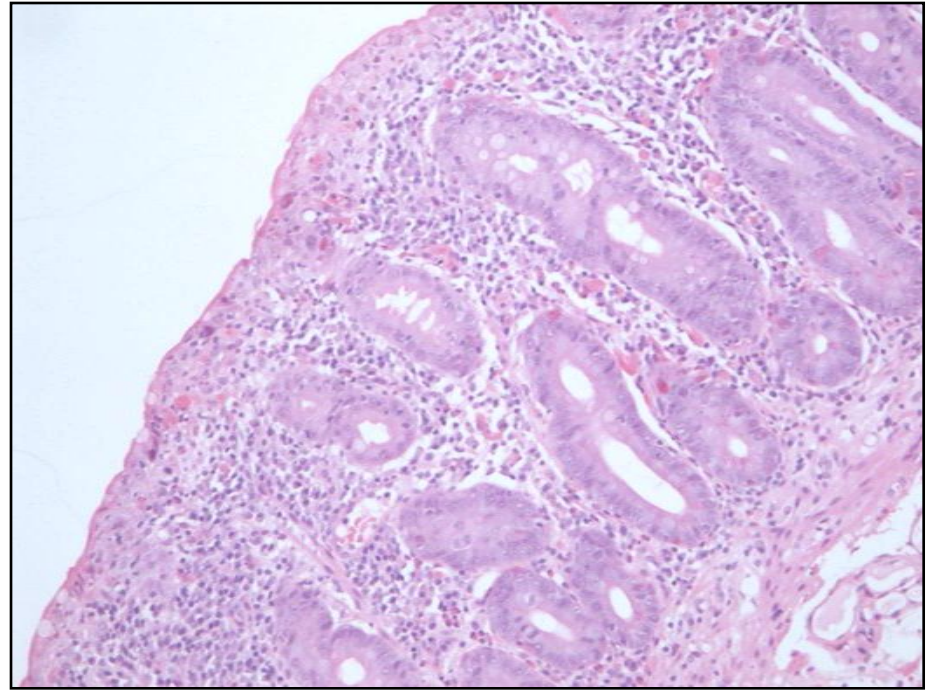
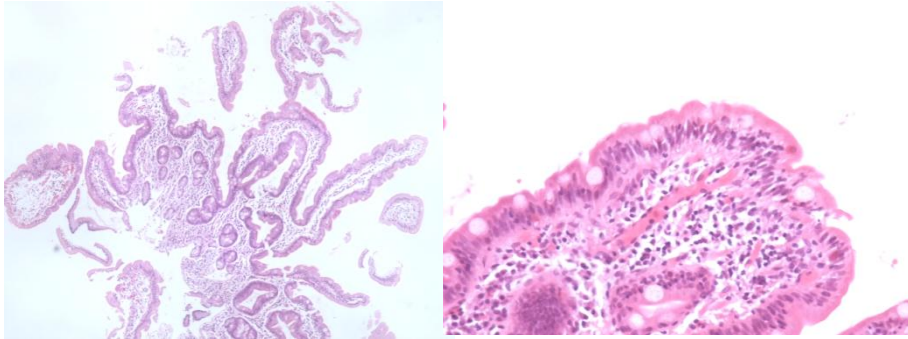
# A case of RCD

- 2006/7
- Pt had weight loss and diarrhoea
- Flat biopsy with IELs



# Pathological Diagnosis of RCD

- First review the previous biopsy and make sure it is Coeliac disease and not a mimic
- Pt presented 2001



Recovered on GFD a few IELs 2002

# Follow up: Pt treated with immunosuppressive drugs

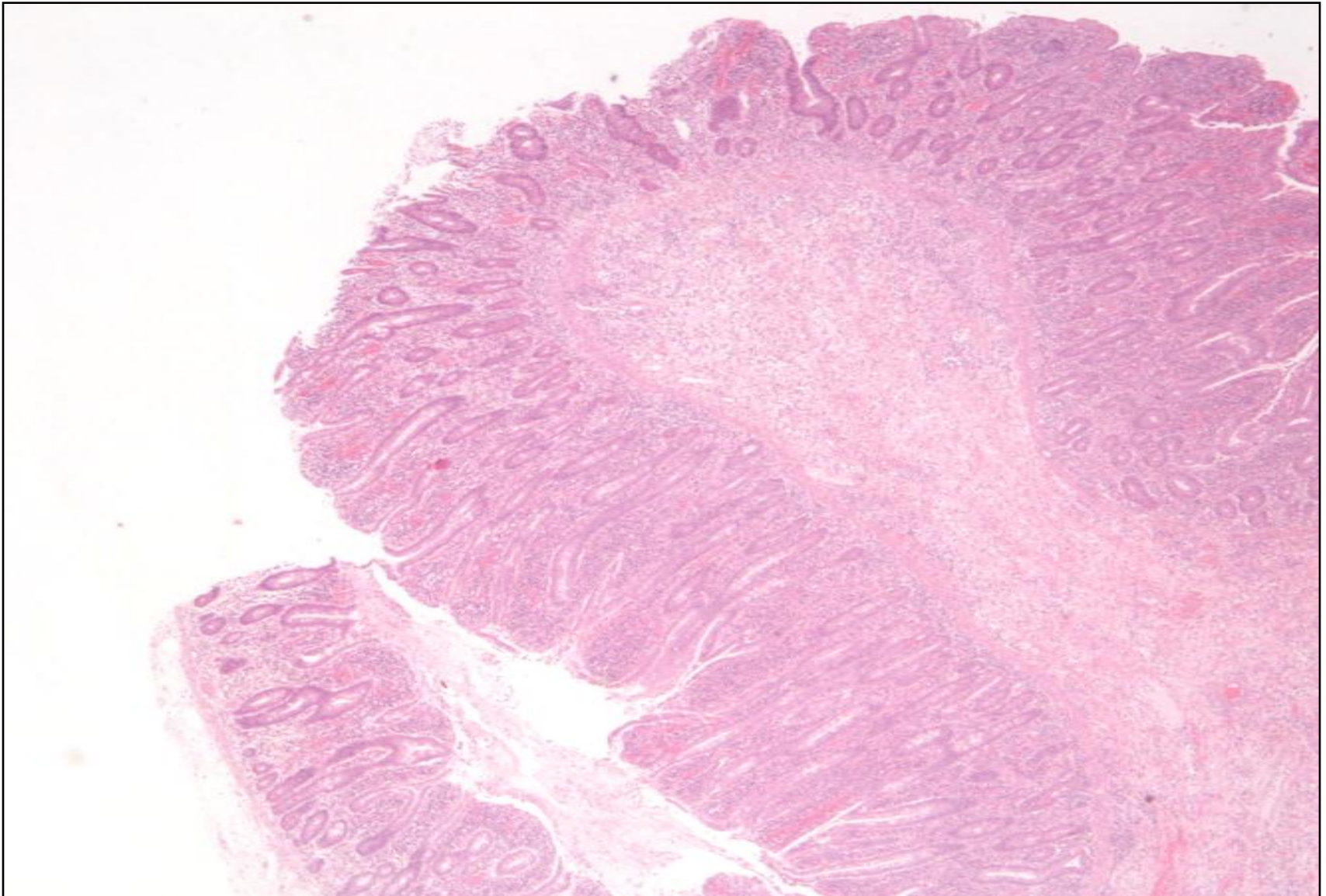
- Recovered for about a year
- Then fell apart
- Developed Acute abdomen
- Surgery revealed multiple perforations

# Ulcerative jejuno-ileitis

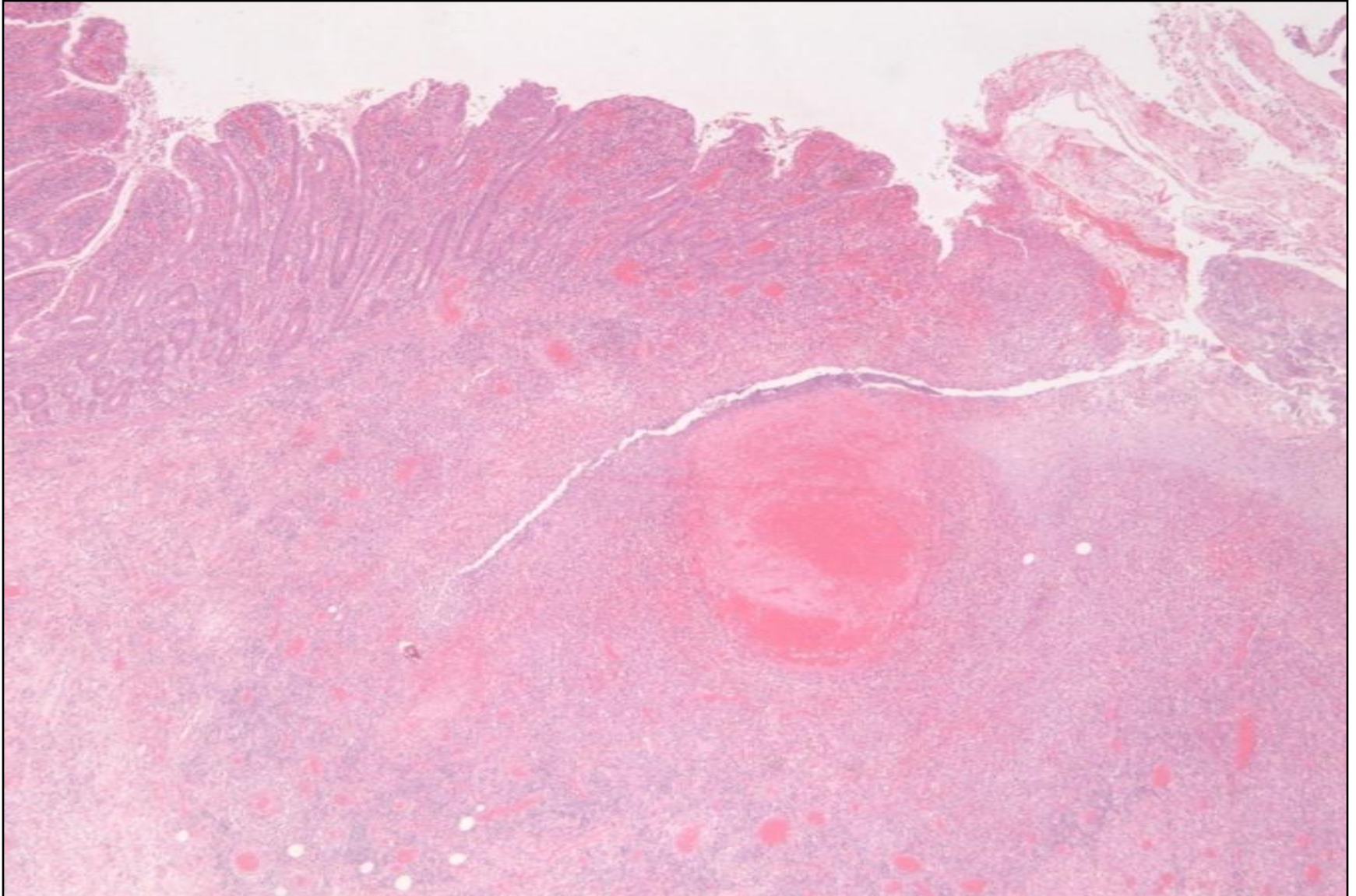


Multiple discrete ulcers without tumour mass

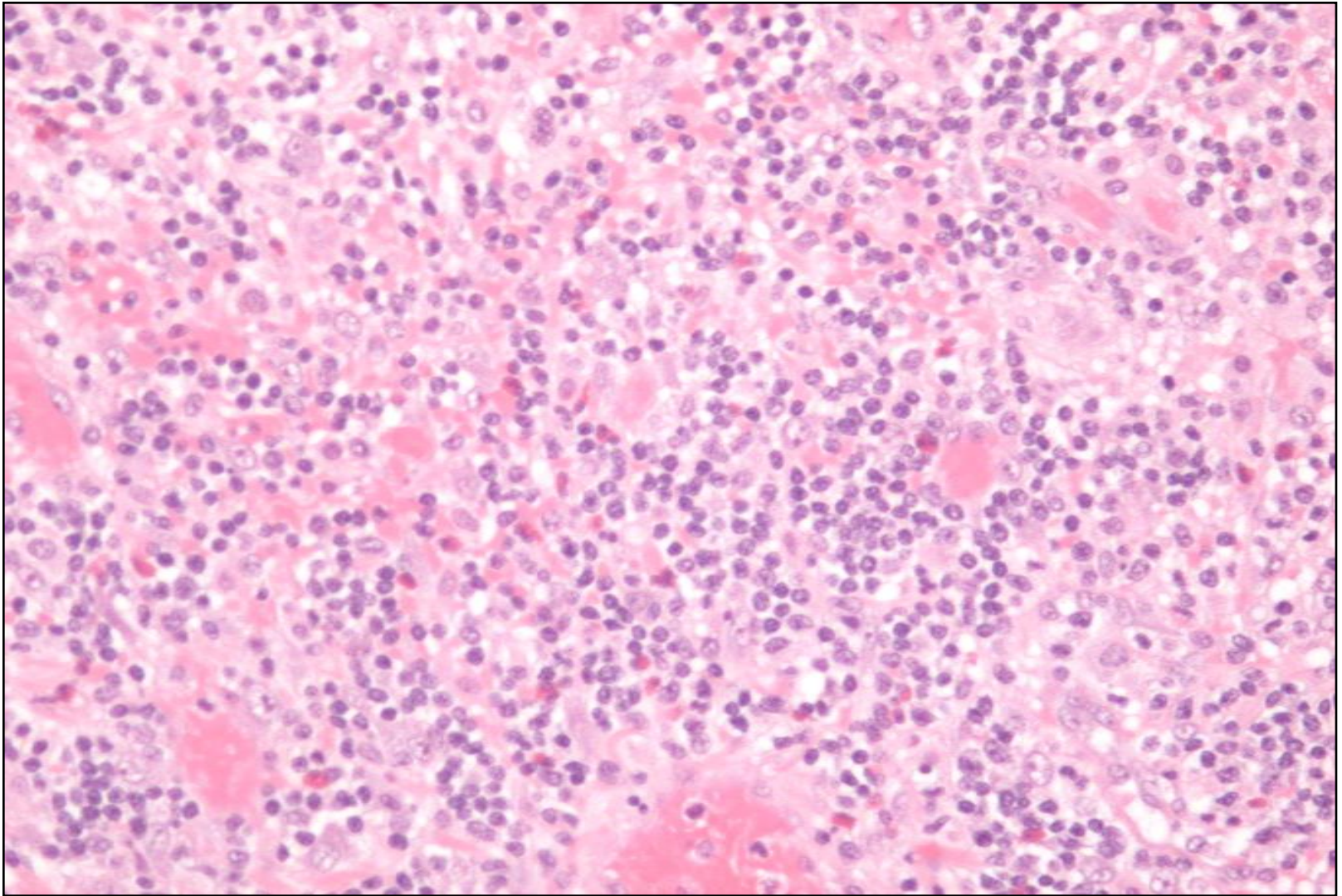
# Flattened inflamed mucosa



# Ulcers and severe inflammation



# Base of ulcers

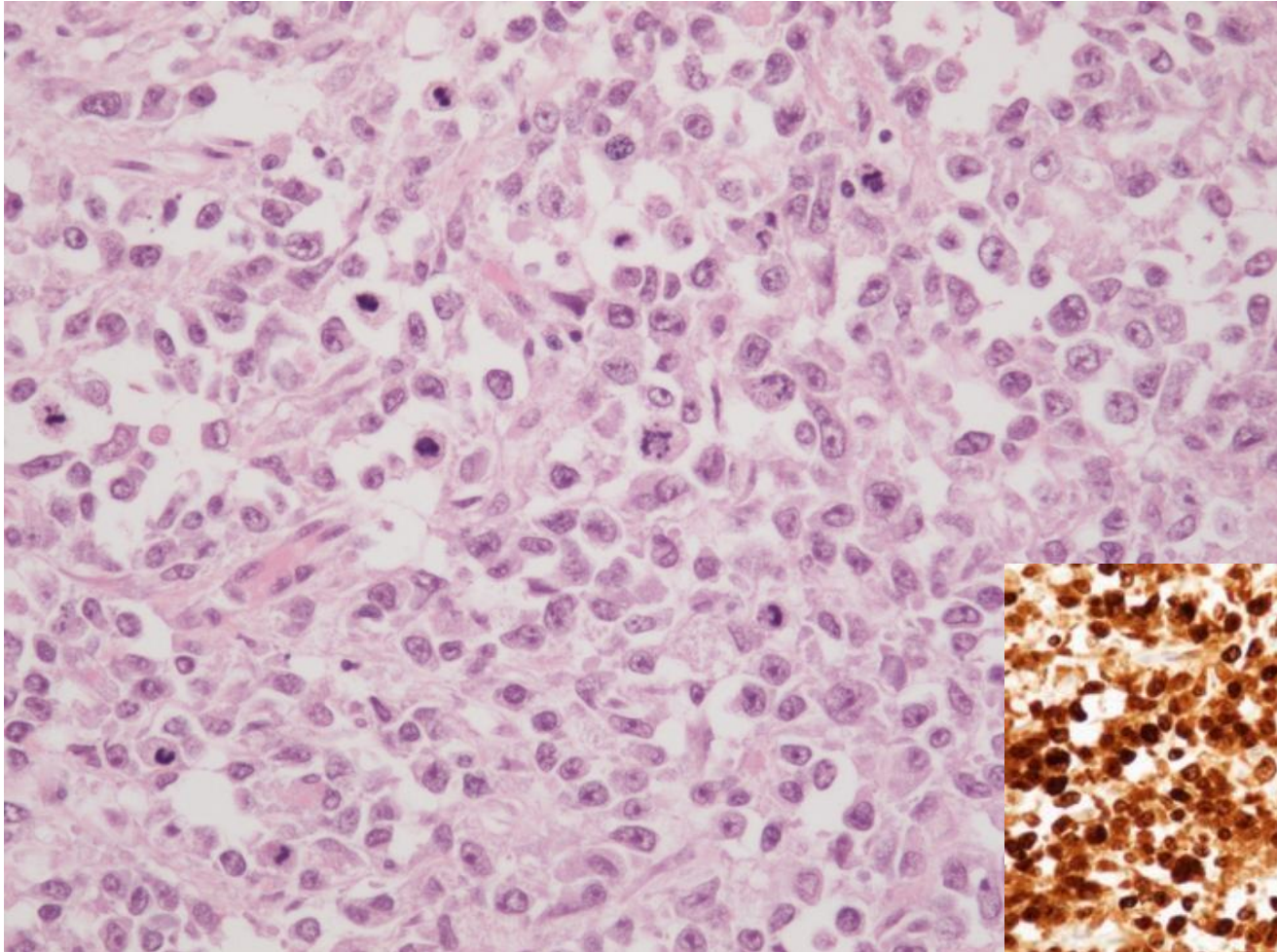


Polyclonal by IHC and TCR

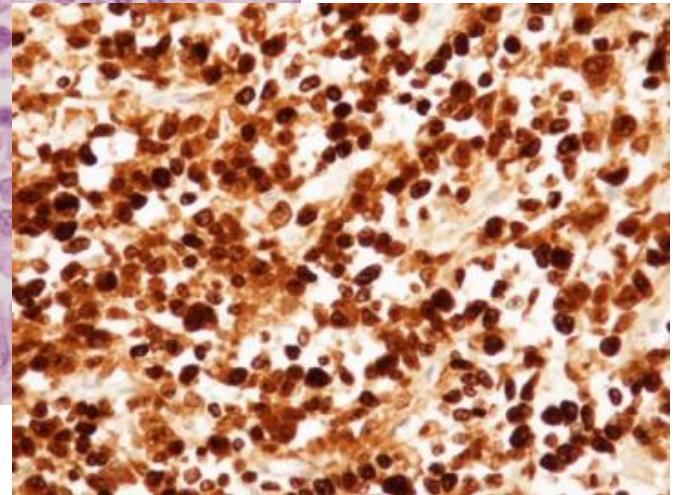
# EATL: Post mortem



# EATL: High grade lymphoma



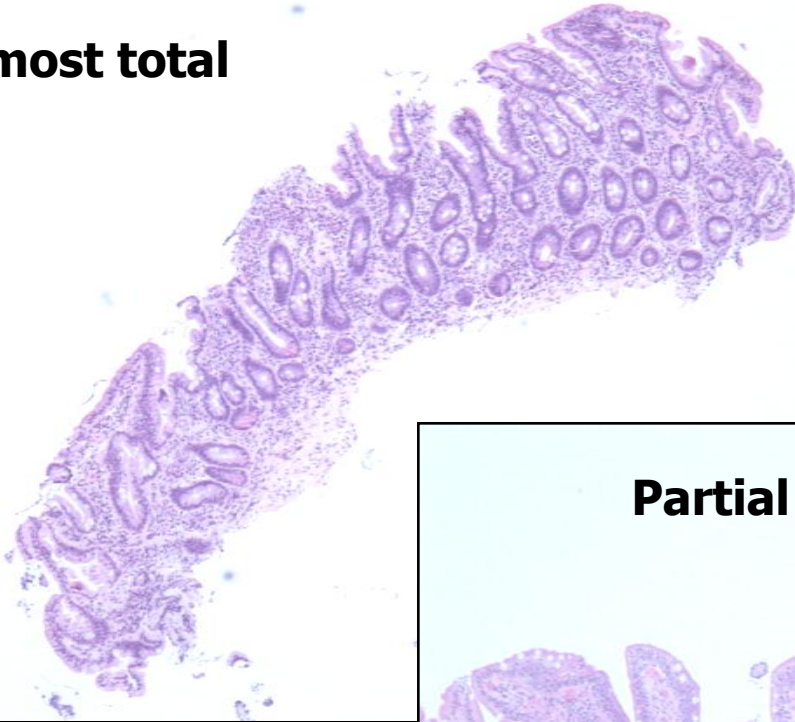
CD3 +  
CD8 -



MIB

# Biopsy features of RCD

**Almost total**



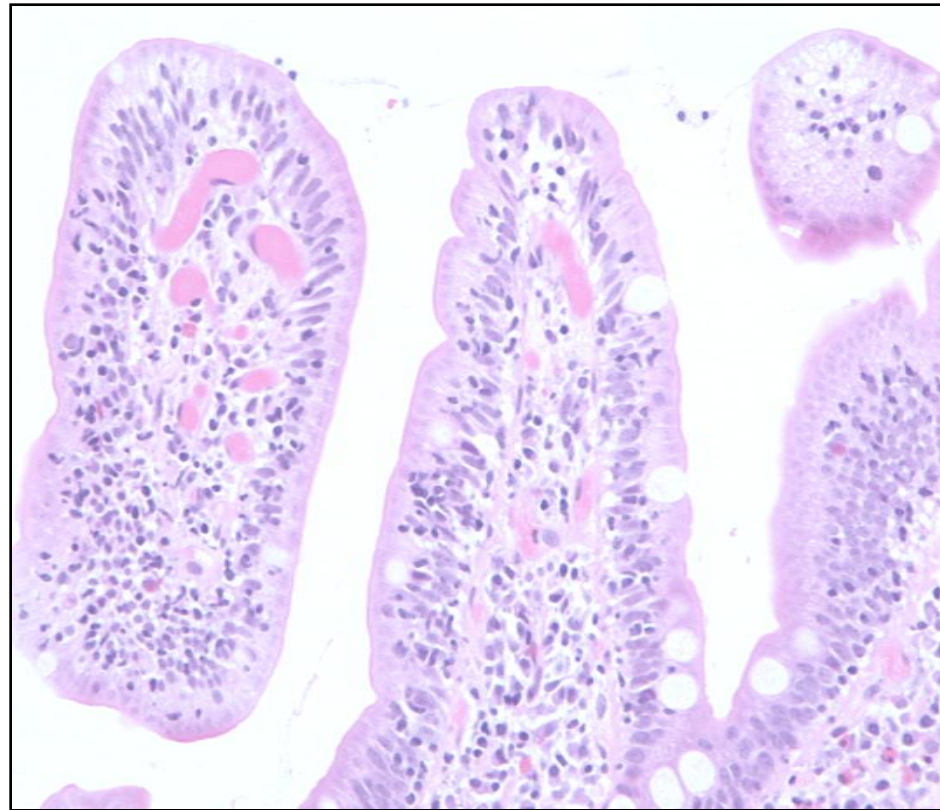
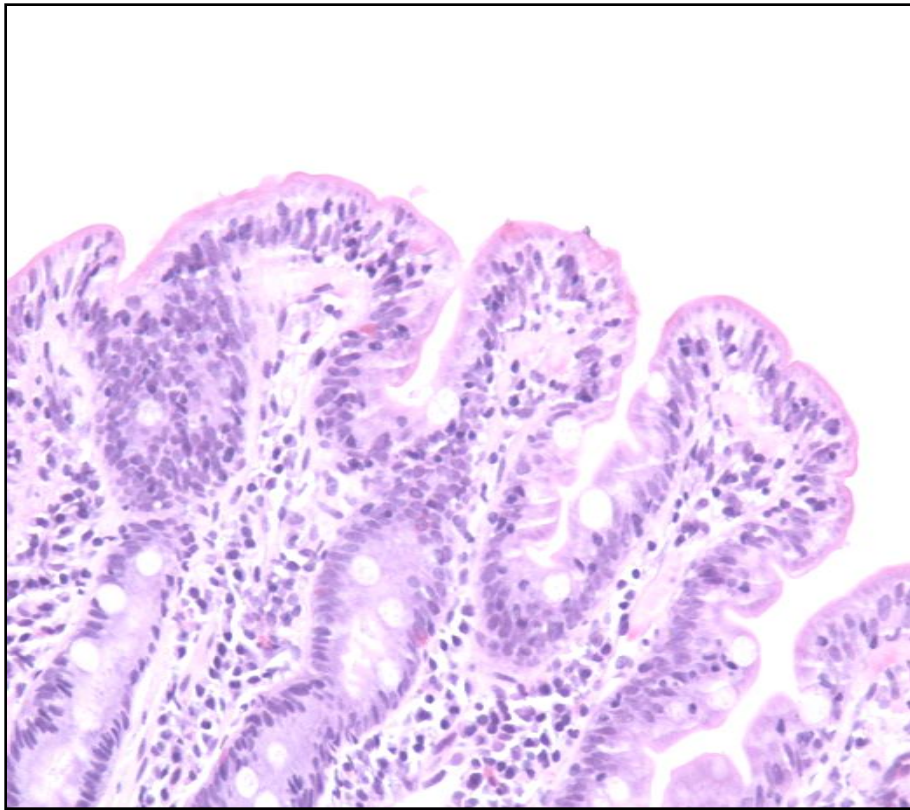
**Degree of villous flattening varies!**

**Partial**



# Biopsy features of RCD

But increased Intraepithelial lymphocytes (IELs) are always a feature



# Recent advance : RCD split into two types on basis of finding aberrant T-cell clone

- Type 1

Polyclonal T cell IELs with a typical Coeliac immunophenotype CD3+CD8+

- Type 2

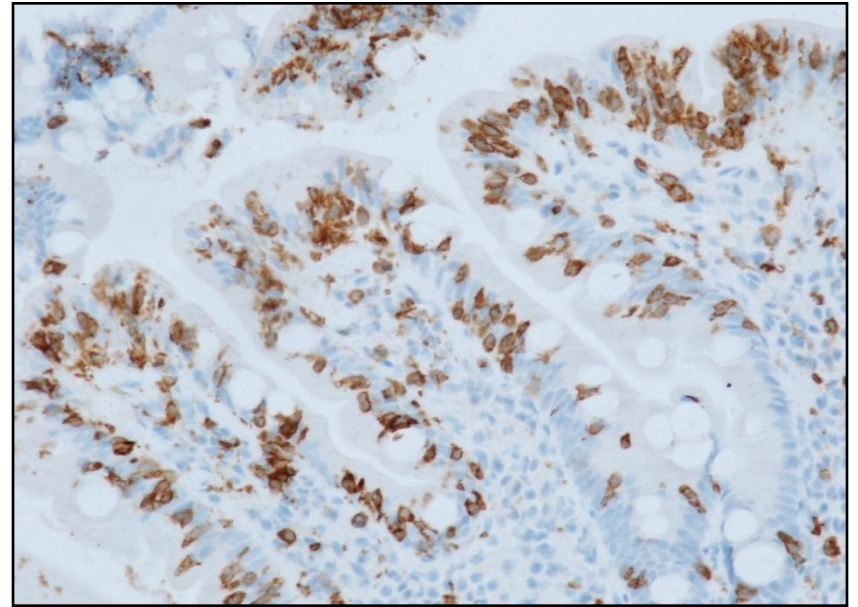
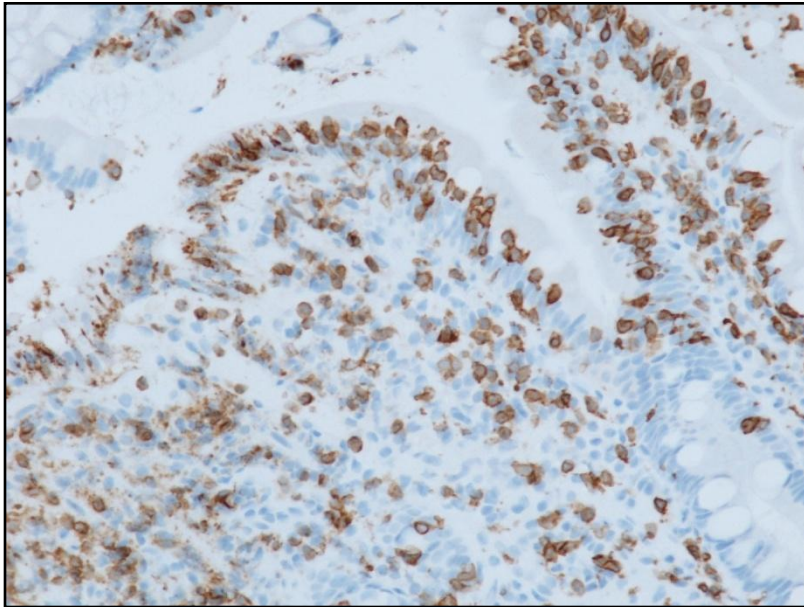
Clonal T cell IELs (TCR gamma or beta chain gene rearrangements) with loss of CD8 and cytoplasmic expression of CD3 instead of membranous localisation

**Time to involve Haematopathologist**

# RCD Type 1

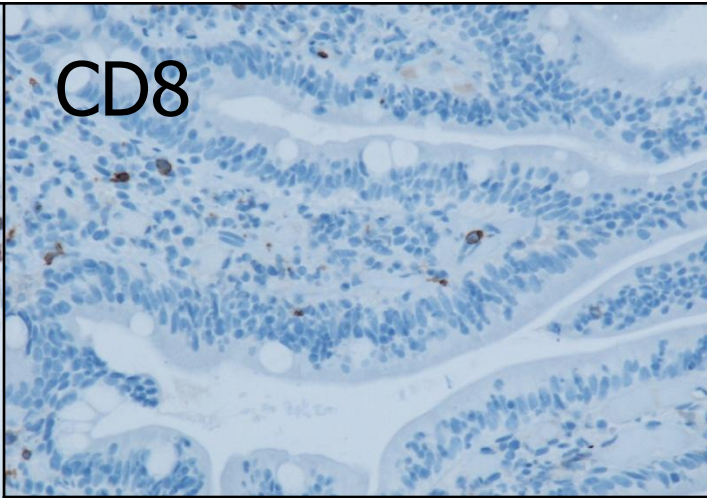
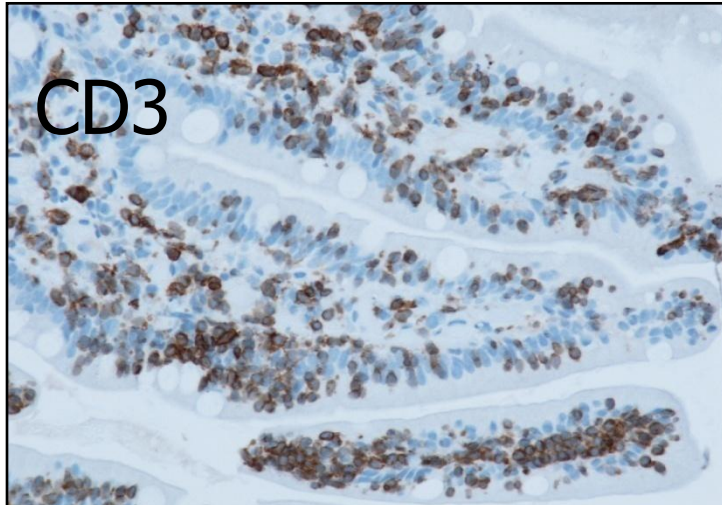
CD3

CD8

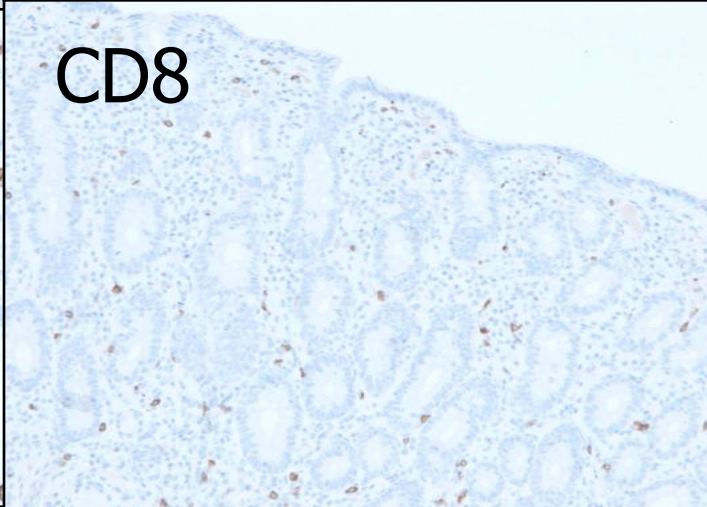
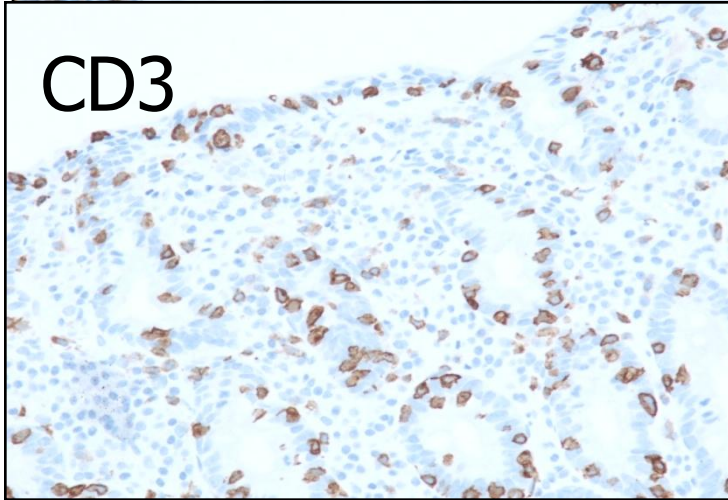


Quick and dirty alternative to double staining!

# RCD Type 2



Patient 1



Patient 2

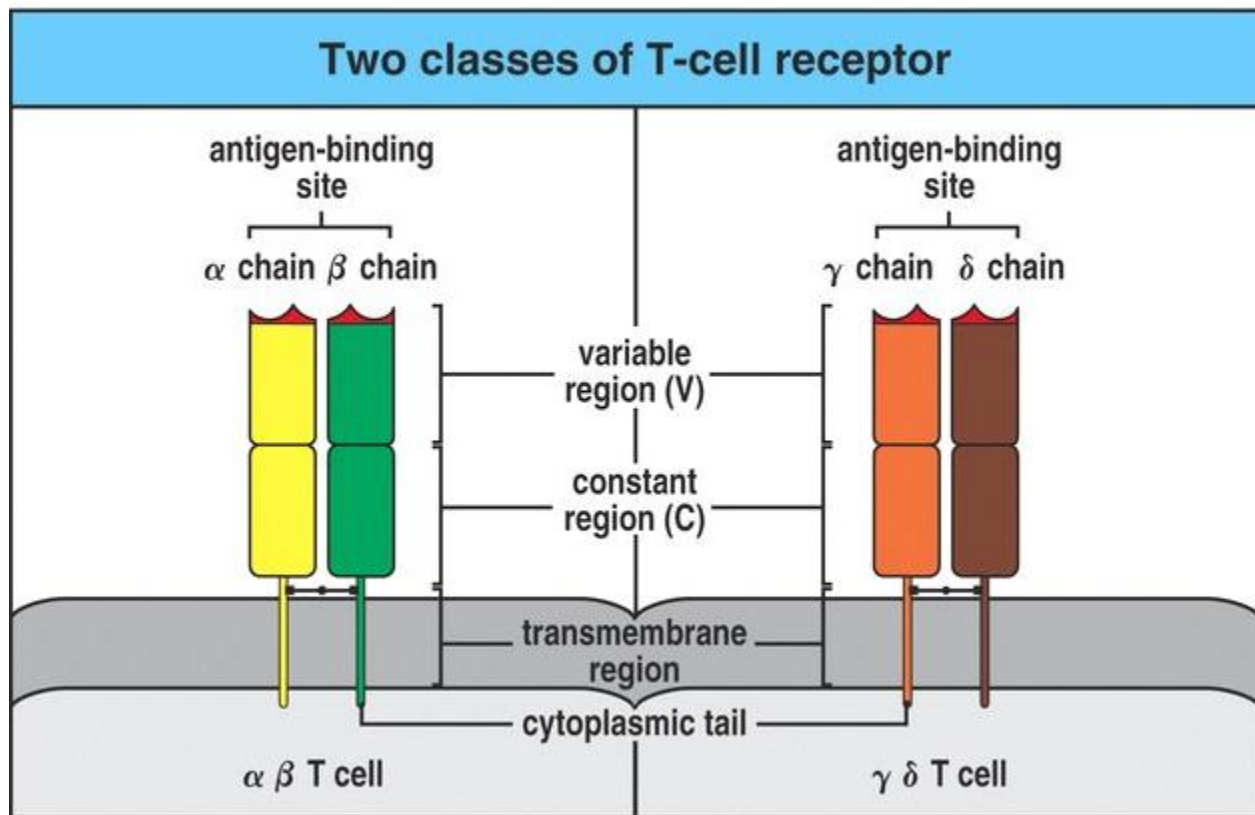
Cytoplasmic

Almost entirely lost

# RCD: IHC issues

- Double staining may be more sensitive
- **Thresholds**  
RCD if >50% of IELs have abnormal phenotype
- Flow cytometry  
RCD if >20%

# T cell receptor rearrangements



90% of IELs  
in normal  
mucosa

70% of IELs  
in CD

10% of IELs  
in normal  
mucosa

30% of IELs  
in CD

Figure 3-7 The Immune System, 2/e (© Garland Science 2005)

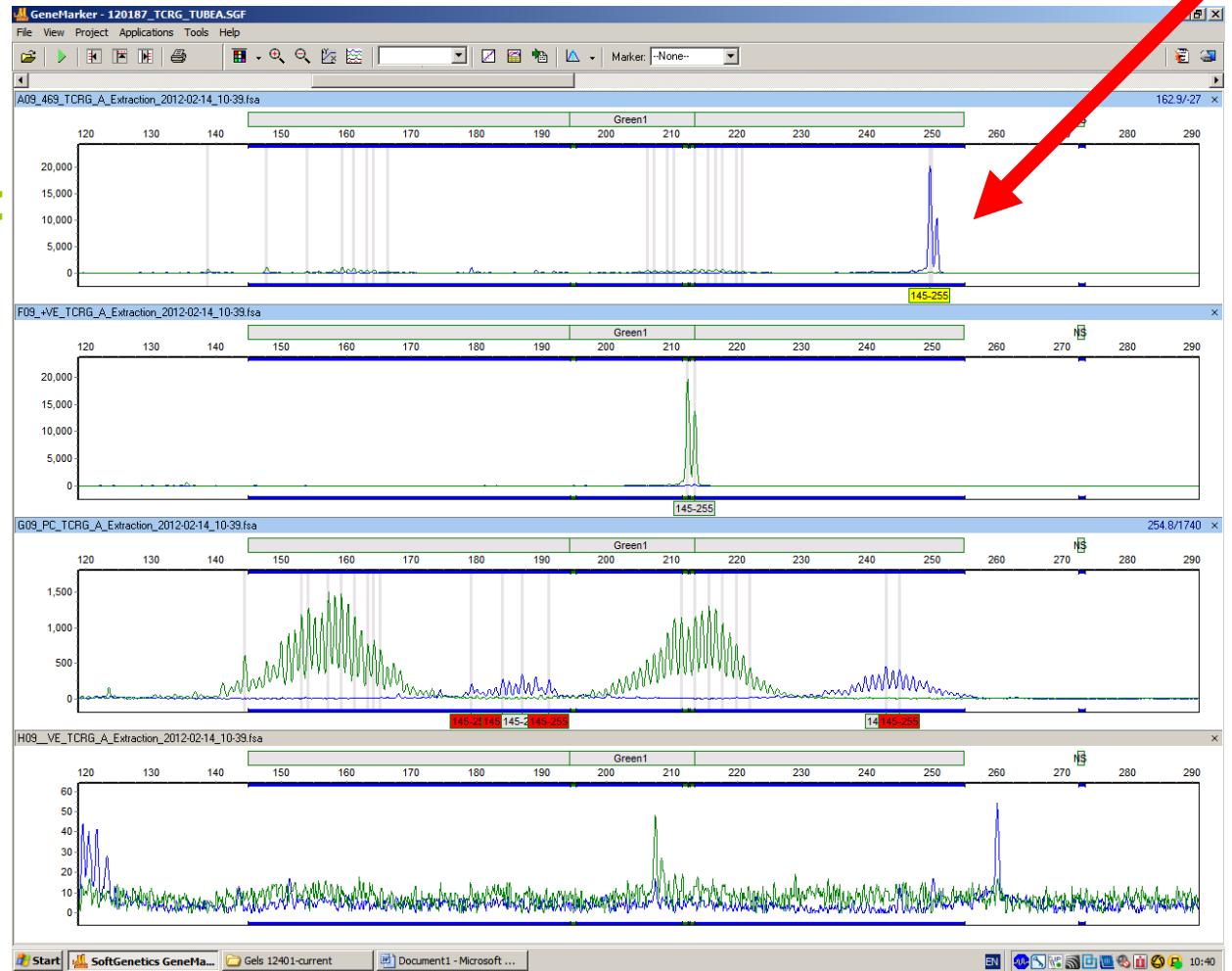
# RCD Type 2

## T cell receptor gamma clonality assay

RCD Type 2 patient

Positive control

Negative control



# Pitfalls

- TCR studies are not perfect
- Small biopsies with small numbers of T cells can yield false positives
- Poor quality DNA can yield false negatives
- Some RCD patients may have unusual T-cell clones

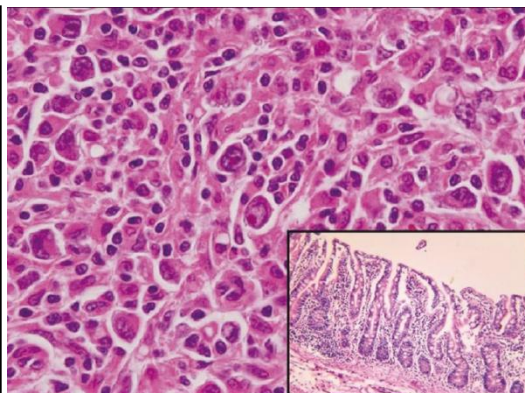
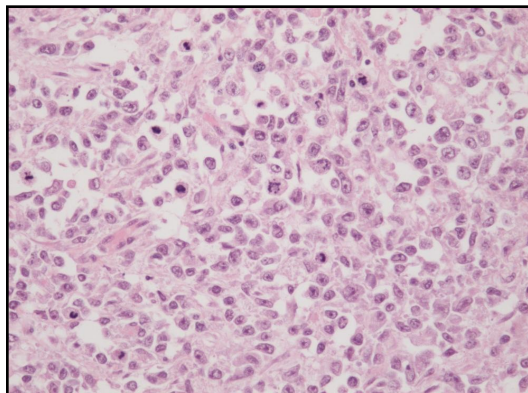
# Warning!

- Patients who are not compliant with their GFD may develop abnormal clones of IELs by IHC/TCR rearrangement .....
- **But they can regress when back on a GFD!**
- Continuously monitoring in patients suspected of RCD may be better than snapshot analysis
- Persistence of abnormal clone is most concerning

# Importance of RCD

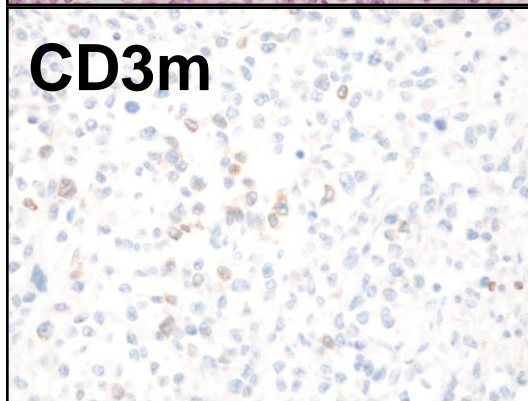
- Persistent Type 2 RCD at **greater risk** of developing Ulcerative Jejenitis and EATL (same immunophenotype)
- 5 year survival for type 2 RCD < 44%
- **Change treatment:** Many clinicians will treat RCD 2 patients with immunosuppression

# EATL

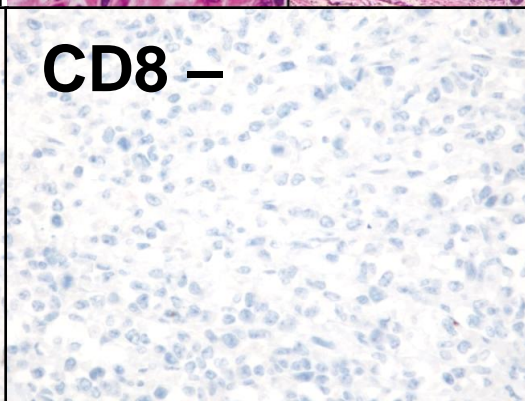


**Type I**

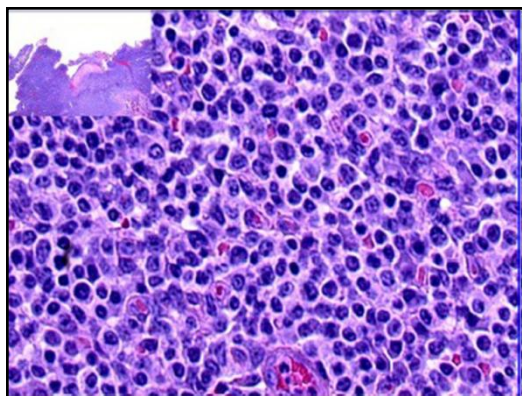
**CD3m**



**CD8 -**



**CD7, CD103+  
Granzyme, Perforin+  
TCR clonal by PCR**



**Type II (CD3+, CD8+)**

Ind J Cancer 2011; 48:124  
J Gastro Oncol 2012 3: 209-225

# RCD Pathology Conclusions

- **Clinical context is VITAL**
- Pt must be on a strict GFD
- Immunohistochemistry and molecular genetic analysis needed to subtype RCD
- Development of EATL almost always fatal

# Thanks

- Prof D Sanders
- Dr Nigel Reynolds
- Dr Mike Bisset
- Dr Dagmar Karstner
- Dr Aoife Maguire