



## Post-colectomy IBD pathology

Professor Neil A Shepherd  
Gloucester & Cheltenham

**BDIAP/BSG Lower GI Pathology Symposium**  
**RIBA, London: 23 November 2018**



Gloucestershire Cellular Pathology Laboratory



# Speaker Declarations

Name of Speaker: Professor Neil A Shepherd

**This presenter has the following declarations of relationship with industry: NONE**

20 November 2018



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# The big issues

- total (procto)colectomy for IBD – UC, IC, some cases of CD

**is it UC, CD or IC?**

**it's all about whether or not to undertake ileal pouch surgery**

- pathology of the ileal pouch and its environs

**adaptive changes, pouchitis, cuffitis and pre-pouch ileitis**



# Types of ileal pouch surgery

- three stage:

total colectomy, mucus fistula and ileostomy  
proctectomy and ileal pouch construction  
ileostomy reversal

- two stage:

total proctocolectomy, ileal pouch formation and ileostomy  
ileostomy reversal

- one stage:

total proctocolectomy, ileal pouch formation and restoration of  
continuity

# What surgery for UC/IBDU?

- emergency/urgent presentation: bleeding, toxic megacolon, impending perforation, perforation
  - three stage pouch surgery
  - most cases of IC
- failed medical treatment
  - certain diagnosis – one or two stage pouch surgery (usually)
  - uncertain diagnosis (some cases of IC) – three stage pouch surgery
- neoplasia



# Colectomy from a surgeon's perspective

The difference in colectomy



Non oncologic resection



Oncologic lymphadenectomy

So, apart from cases of suspected malignancy, same operation for

CD

UC

IBDU

*Spinelli, 2018*



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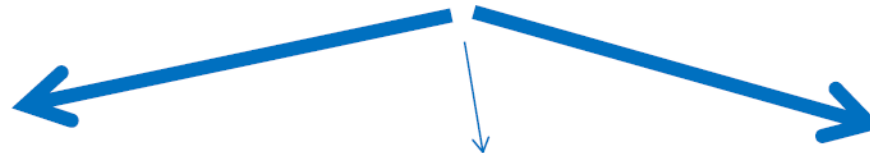


## 2 pathologists + GE + Surgeon = IBD MDT

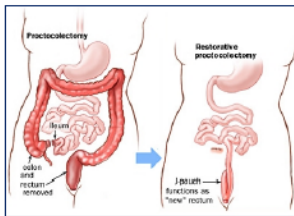
If struggle with diagnosis

Go for subtotal colectomy first

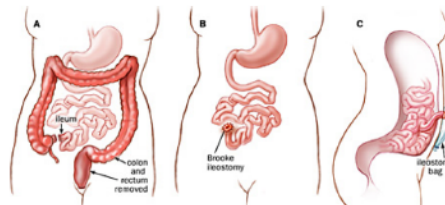
If still struggling



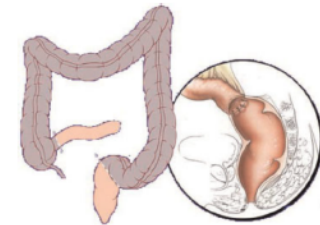
RP with IPAA



RP without reconstruction



Ileorectal anastomosis







## European evidence based consensus on surgery for ulcerative colitis

Tom Øresland\*, Willem A. Bemelman, Gianluca M. Sampietro, Antonino Spinelli, Alastair Windsor, Marc Ferrante, Philippe Marteau, Oded Zmora, Paulo Gustavo Kotze, Eloy Espin-Basany, Emmanuel Tiret, Giuseppe Sica, Yves Panis, Arne E. Faerden, Livia Biancone, Imerio Angriman, Zuzana Serclova, Anthony de Buck van Overstraeten, Paolo Gionchetti, Laurents Stassen, Janindra Warusavitame Michel Adamina, Axel Dignass, Rami Eliakim, Fernando Magro, André D'Hoore, On behalf of the European Crohn's and Colitis Organisation (ECCO)

*Journal of Crohn's and Colitis, 2015, 4–25*

### 2.2.1.2. ECCO Statement 4B

Patients within inflammatory bowel disease type unclassified are potential candidates for proctocolectomy and ileoanal pouch surgery. However, a subtotal colectomy with ileostomy is recommended to allow proper histological evaluation of the colectomy specimen (EL5). Completion proctectomy with a pouch is standard in patients with ulcerative colitis, and could be considered in selected patients with Crohn's disease, well informed of a higher failure rate

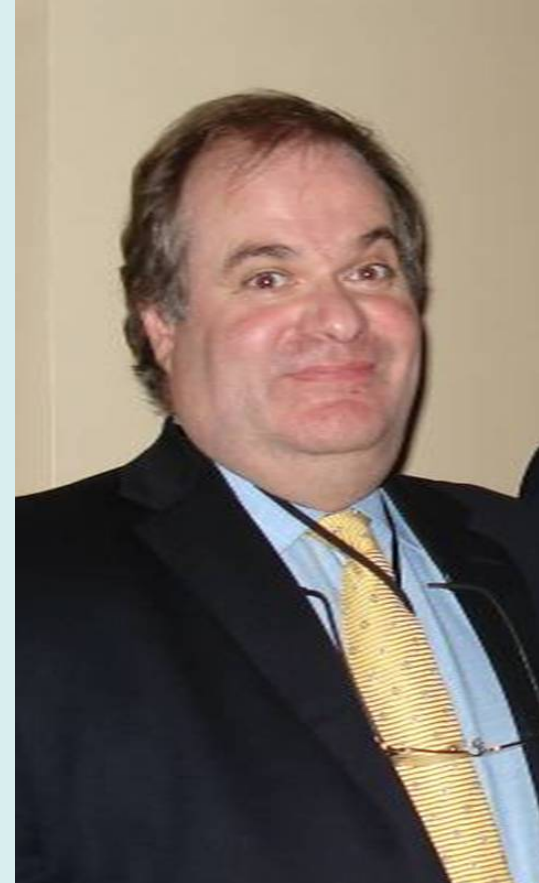
### 2.8.5.3. ECCO Statement 5I

Under optimal circumstances ileorectal anastomosis is a reasonable alternative to IPAA. Outcome advantages such as lower morbidity, preserved female fecundity need to be weighed against the need for rectal surveillance and subsequent proctectomy in 50% of cases (EL 3)





# Classical UC



Professor Bryan Warren (1958-2012)

“Ulcerative colitis goes up to where it stops”

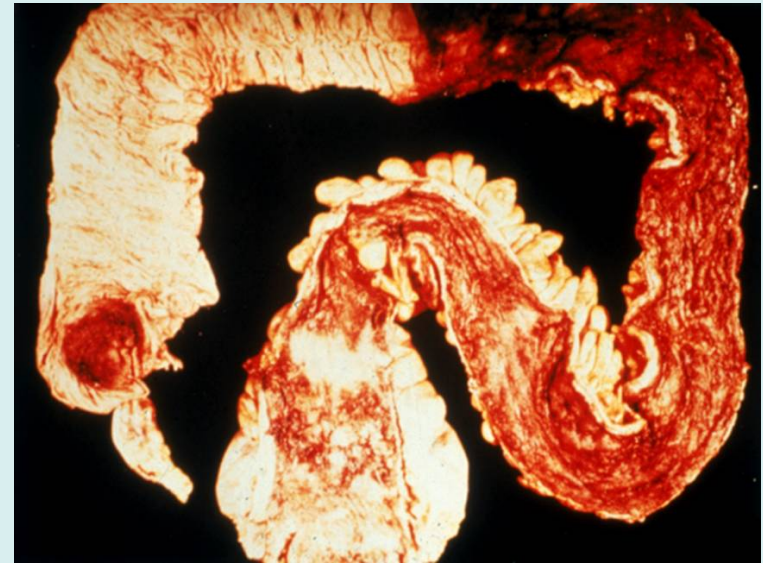
# Classical Crohn's disease



# When does ulcerative colitis mimic Crohn's disease?

- patchiness of disease after treatment
- resolution of histological changes after treatment
- fulminant colitis
- diversion proctitis in UC
- SKIP LESIONS
  - caecal patch lesion
  - appendix
  - sigmoid colonic diverticulosis

*Warren et al, 1993*





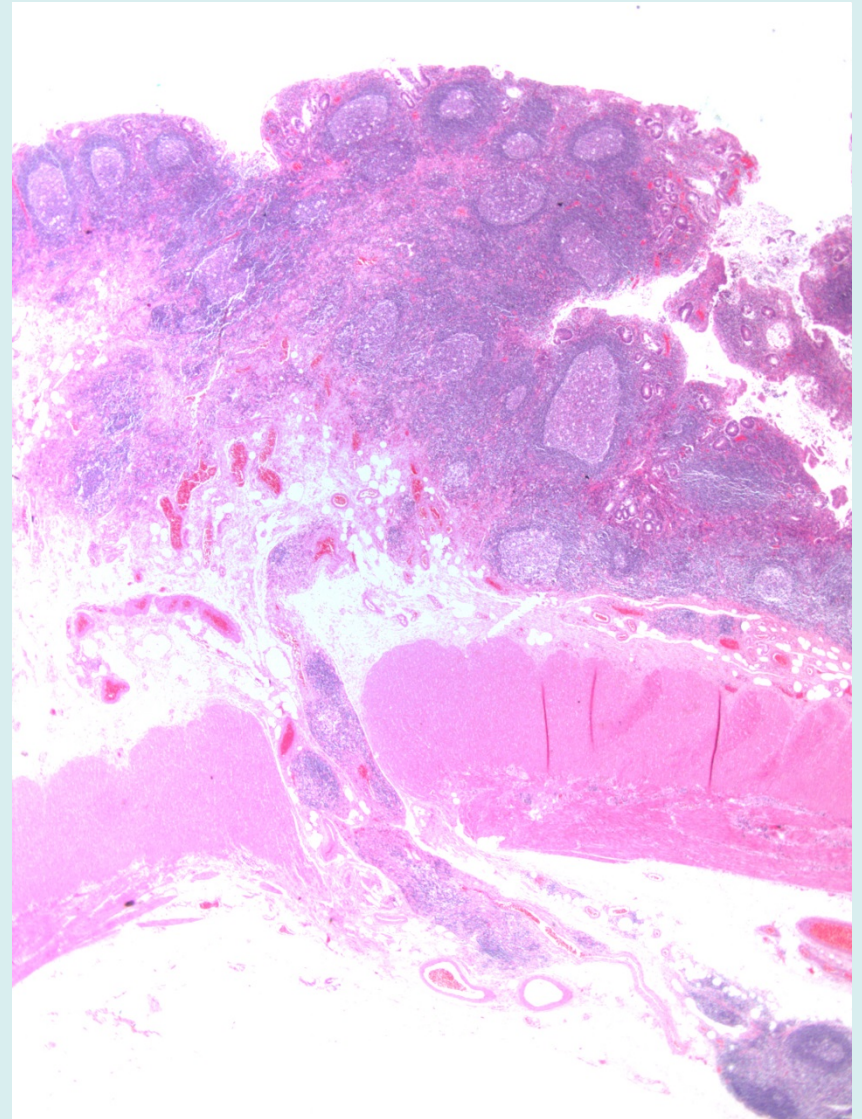
# Defunctioned rectum excised during 3-stage pouch surgery

- combination of UC and diversion changes, in the rectal stump, produces mimicry of CD
- transmural inflammation and granulomatous inflammation
- also PMC-like changes
- if uncertainty, crucial review of the colectomy specimen for a more accurate assessment of CIBD type

*Warren et al 1993;*

*Goldstein et al, 1997;*

*Loughrey & Shepherd, 2017*



# Discontinuous disease in UC

- appendix

*The appendix as a skip lesion in ulcerative colitis.  
Davison AM, Dixon MF. Histopathology, 1990.*

- caecal patch lesion
- sigmoid colon with diverticular disease
- 'rectum'
- what links these four sites of disease?

*Faecal stasis*



# The caecal patch lesion of ulcerative colitis

- first defined in 1958: eight cases of UC as ‘an island’ in normal caecal mucosa, with a tendency to occur in the lower caecum opposite the ileocaecal valve

*Lumb & Protheroe, 1958*

- classic description by d’Haens and colleagues

*d’Haens et al, 1997*

- more severe distal disease but better response to therapy

*Matsumoto et al, 2002*

- commoner in younger male patients and pronounced symptomatology, especially abdominal pain, rectal bleeding and diarrhoea

*Yamagishi et al, 2002; Nevin et al, 2012*

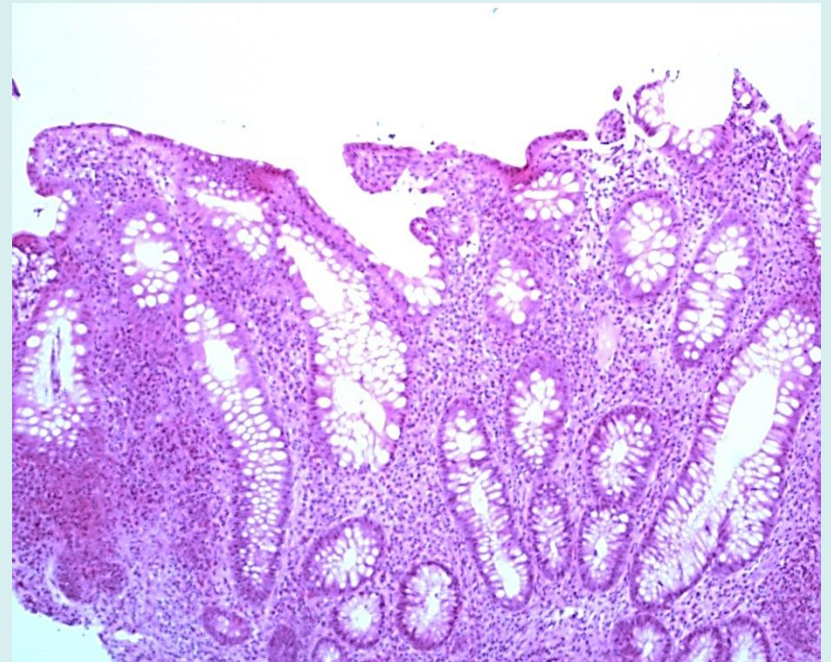
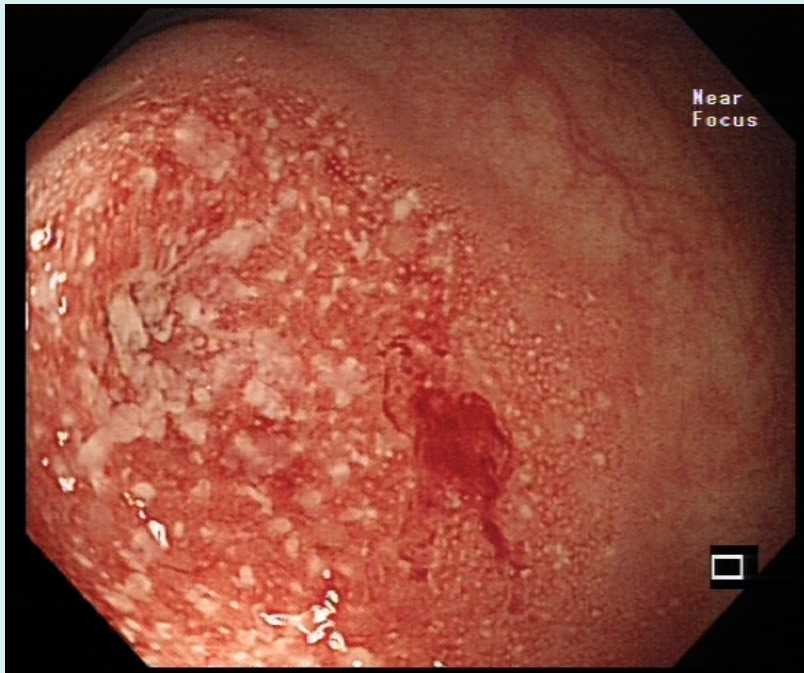
- does not predict prognosis of UC, including remission rate, relapse rate, proximal disease extension and the need for proctocolectomy

*Byeon et al, 2005; Bakman et al, 2011; Park et al, 2014*

# The isolated caecal patch lesion: a clinical, endoscopic and pathological study

criteria:

normal colonoscopy apart from CPL;  
biopsies of CPL show active IBD features;  
colonic & rectal biopsies normal





# The caecal patch lesion of ulcerative colitis

- important to recognise as one of the skip lesions of ulcerative colitis
- major differential diagnosis will always be Crohn's disease
- reflects more severe distal disease in UC
- but in some studies not predictive of any known prognostic parameter in UC
- can rarely occur in isolation but then may represent other diseases, especially NSAID colopathy



# Indeterminate colitis

*Journal of Clinical Pathology*, 1978, 31, 567-577

## Overlap in the spectrum of non-specific inflammatory bowel disease—‘colitis indeterminate’

ASHLEY B. PRICE

*From Northwick Park Hospital and CRC, Harrow, Middlesex (work carried out at St. Mark's Hospital, City Road, London EC1)*



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# Indeterminate colitis

- diagnosis made only in resection specimens
- 10-20% of colectomies, especially 'fulminant' colitis
- some features of UC and Crohn's
- generally behave as UC
- cautious positive approach to pouch surgery



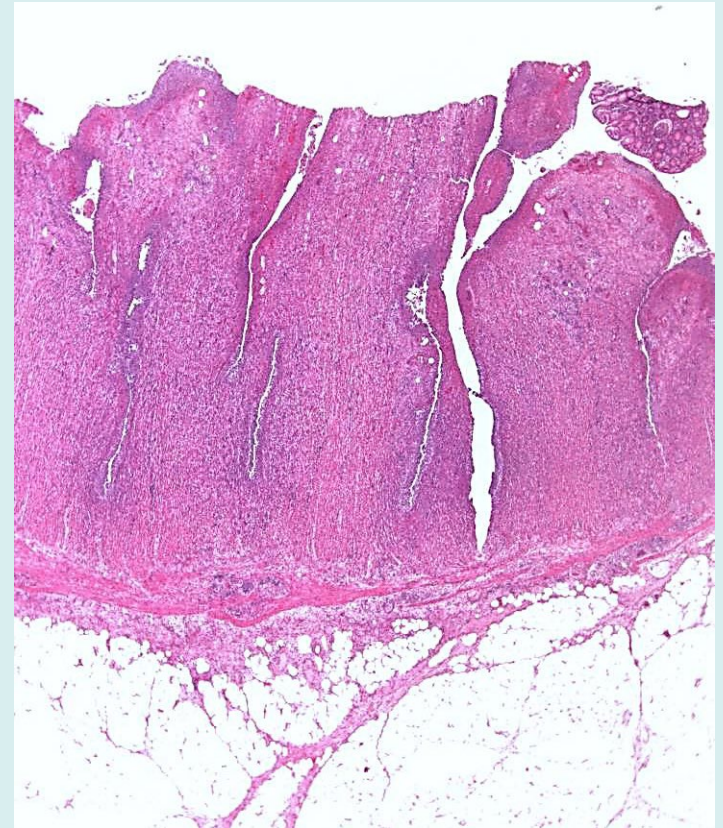
# Indeterminate colitis: importance of macroscopic pathology

- extensive ulceration
- involvement of transverse and right colon (more severely than distal colon)
- involvement of more than 50% of the mucosal surface
- usually diffuse disease, but may show rectal sparing
- toxic dilatation may be present





# Indeterminate colitis: histology



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# Indeterminate colitis

- 9-20% of colectomy specimens

*Nicholls & Wells, 1992*

- 1.6 to 2.4 per 100,000

*Stewenius et al, 1995; Moum et al, 1996*

- equal sex distribution

*Wells et al, 1991*

- about 80-90% will behave like ulcerative colitis

*McIntyre et al, 1995; Meucci et al, 1999; Yu et al, 2000*

- 65% will be reclassified into UC or CD on further analysis of clinical, radiological and/or further histopathological evidence

*Wells et al 1991; Nicholls & Wells 1992*



# Indeterminate colitis & the natural history of the ileal reservoir

	IC v UC	% pouch failure IC v UC	% pelvic sepsis IC v UC
Atkinson et al 1994, Vancouver	16/158	19/5	25/1
Foley et al 1997, Lahey	42/499	12/2	44/23
Yu et al 2000, Mayo	82/1437	27/11	17/7
Delaney et al, 2002, Cleveland	115/1399	3.4/3.5	8.7/2.2





# After IPAA: IC vs UC

448 patients

Single-institution prospective study

1985-2014

Outcomes IPAA for IC vs UC

Follow-up 122.06 months (+/- 80.77 m)

- ✓ **no increased short term complications**
- ✓ **higher risk of long term fistulae and development of CD**

K. L. Jackson - J Gastrointest Surg 2017

**Table 2** Short-term post-operative complications in indeterminate colitis and ulcerative colitis patients undergoing IPAA

	Indeterminate colitis (n = 224) (%)	Ulcerative colitis (n = 224) (%)	p value
Anastomotic leak	7 (3.1)	9 (4.0)	0.61
Pelvic abscess	14 (6.2)	9 (4.0)	0.29
Pelvic sepsis	19 (8.5)	19 (8.5)	0.99

**Table 3** Long-term post-operative complications in indeterminate colitis and ulcerative colitis patients undergoing IPAA

	Indeterminate colitis (n = 224)	Ulcerative colitis (n = 224)	p value
Fistula	35 (15.6 %)	18 (8.0 %)	0.01
Crohn's disease of ileal pouch	15 (6.7 %)	6 (2.7 %)	0.04
Pouch failure	13 (5.8 %)	11 (4.9 %)	0.58
Happy to undergo IPAA again	94.8 %	94.5 %	0.90



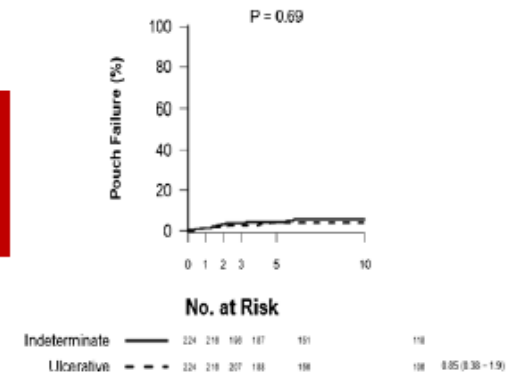
# After IPAA: IC vs UC

## Comparable functional outcomes

**Table 5** Quality of life in indeterminate colitis and ulcerative colitis patients undergoing IPAA

	Indeterminate colitis (n = 224)	Ulcerative colitis (n = 224)	p = value
Quality of life	7.86 ± 1.74	7.90 ± 1.97	0.36
Quality of health	7.82 ± 1.73	7.73 ± 1.85	0.80
Level of energy	7.00 ± 2.13	7.60 ± 2.08	0.85
CGQL score	0.76 ± 0.17	0.76 ± 1.80	0.94
Social restrictions	21.7 %	14.4 %	0.05
Work restrictions	20.4 %	15.4 %	0.19
Diet restrictions	31.9 %	31.6 %	0.95
Sexual restrictions	24.2 %	18.9 %	0.19

Comparable functional outcomes, quality of life scores and pouch failure.



K. L. Jackson - J Gastrointest Surg 2017

## Comparable rates of pouch retention

Review: pouch failure rates among IC, IBD-unclassified, and UC are similar

Chang, Gastroenterology & Hepatology 2017

Study	Year	N	Follow-Up (yrs)	Pouch Retention (%)
Brown et al <sup>15</sup>	2005	21	NS	90.0
Fazio et al <sup>19</sup>	1995	75	1.5	98.1
Gramlich et al <sup>102</sup>	2003	115	3.4	96.6
Jackson et al <sup>102</sup>	2017	224	10.2	94.2
Pezim et al <sup>103</sup>	1989	25	3.2	92.0
Lightner et al <sup>8</sup>	2017	76	30.0	90.0
Rudolph et al <sup>100</sup>	2002	35	NS	100.0
Pishori et al <sup>104</sup>	2004	13	4.0	100.0
Fazio et al <sup>18</sup>	2013	63	7.0	95.2
Delaney et al <sup>105</sup>	2002	115	3.4	98.3
Tekkis et al <sup>97</sup>	2005	26	1.8	89.5
Yu et al <sup>106</sup>	2000	82	10.0	73.0
Marcello et al <sup>107</sup>	1997	53	NS	75.0



# Indeterminate colitis

- we must restrict this term to the middle ground of colectomy CIBD specimens

*WCOG Montreal IBD guidelines, 2005*

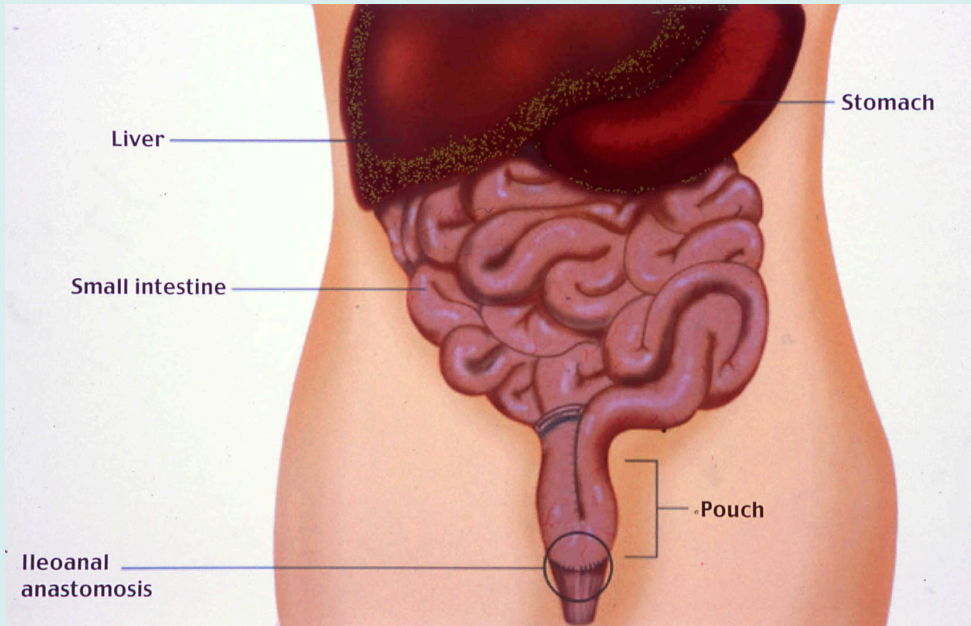
*Martland & Shepherd, 2007*

*Langner et al, ECCO guidance, 2014*

- when so restricted, it defines a group, seemingly, that mainly reflects fulminant UC
- although a small proportion will eventually be shown to have CD
- some may represent fulminant infective colitis, especially campylobacter colitis
- pouch surgery is not contraindicated (it may be too late, anyway!) but there is an increased rate of pouch failure and pelvic sepsis
- a cautious 'yes' to pouch surgery for IC



# The pelvic ileal reservoir/pouch



***Parks AG, Nicholls RJ.***

***Proctocolectomy without ileostomy for ulcerative colitis.***

***Br Med J 1978; ii: 85-88.***



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# Which patients get ileo-anal pouches?

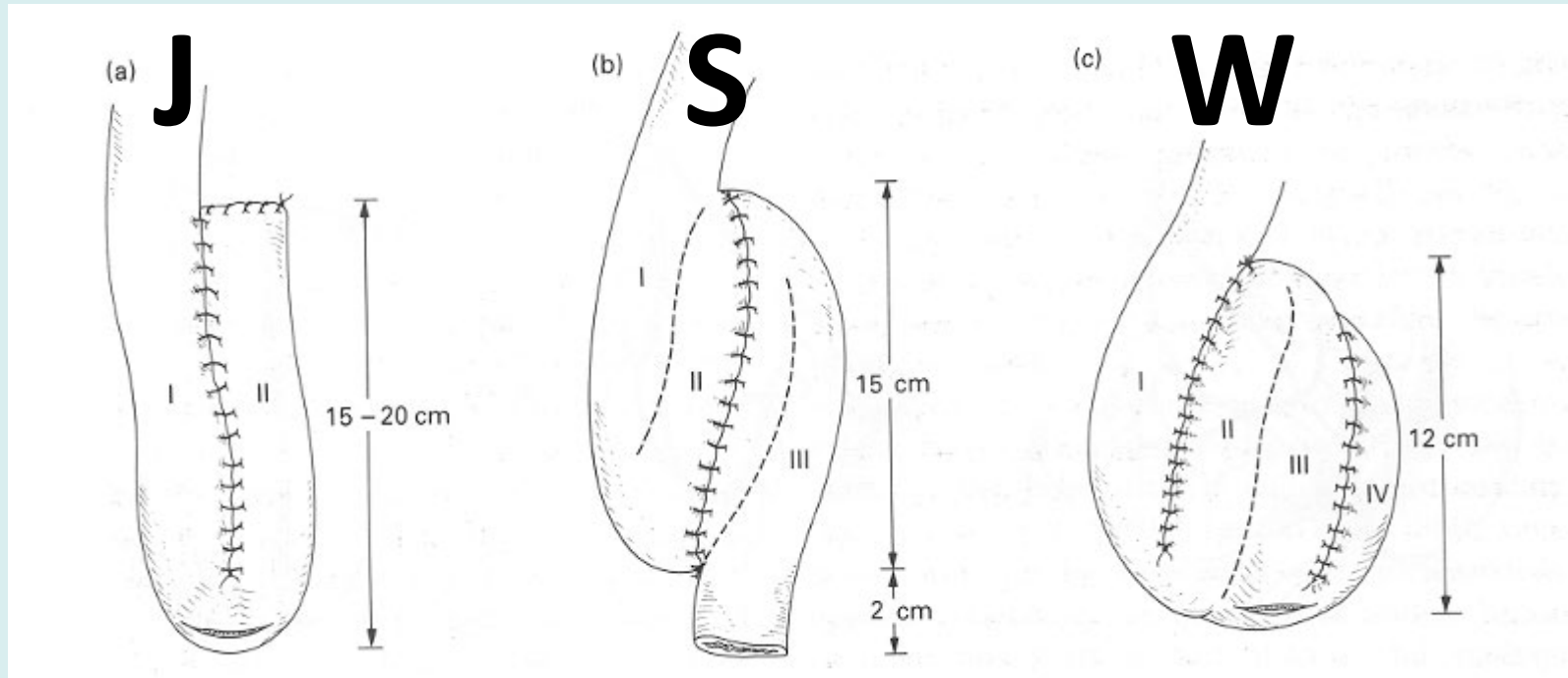
- ulcerative colitis
- indeterminate colitis
- familial adenomatous polyposis and other polyposis syndromes
- Crohn's disease
- colonic myopathy/neuropathy





# Restorative proctocolectomy

## Pouch configuration

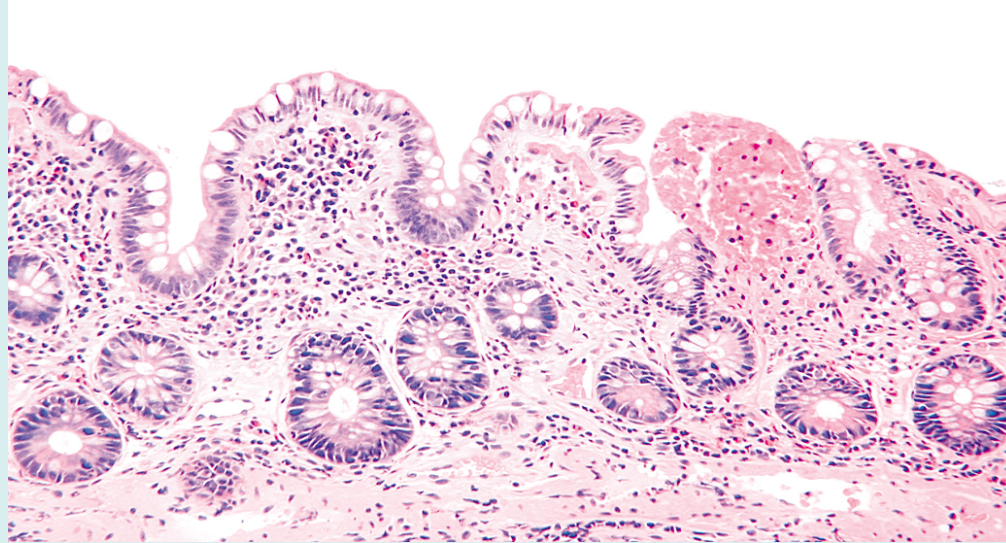


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# The ileal pouch

Mucosal adaptation



*Shepherd, Jass, Duval, Moskowitz, Nicholls & Morson, 1987;  
de Silva et al 1990; Veress et al 1990;  
Setti Carraro, Talbot & Nicholls, 1994 & 1998*

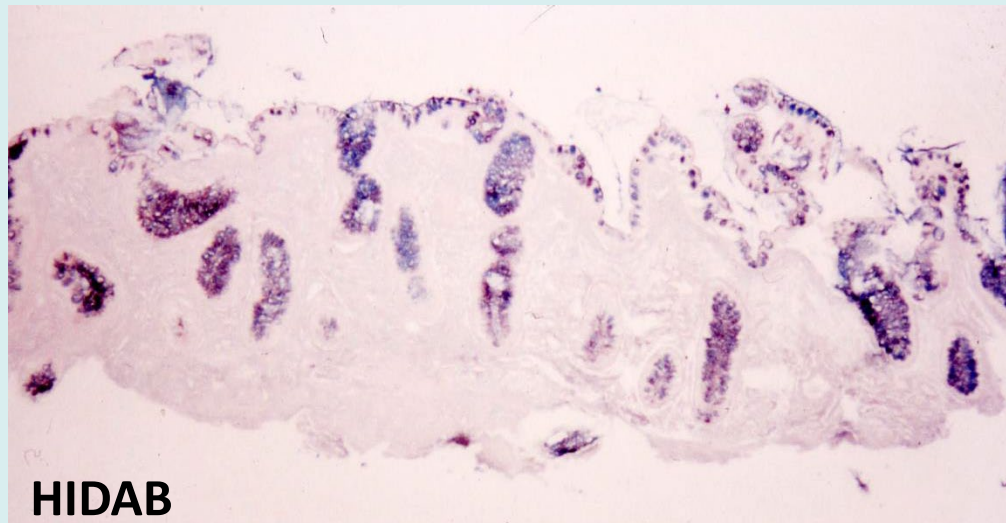
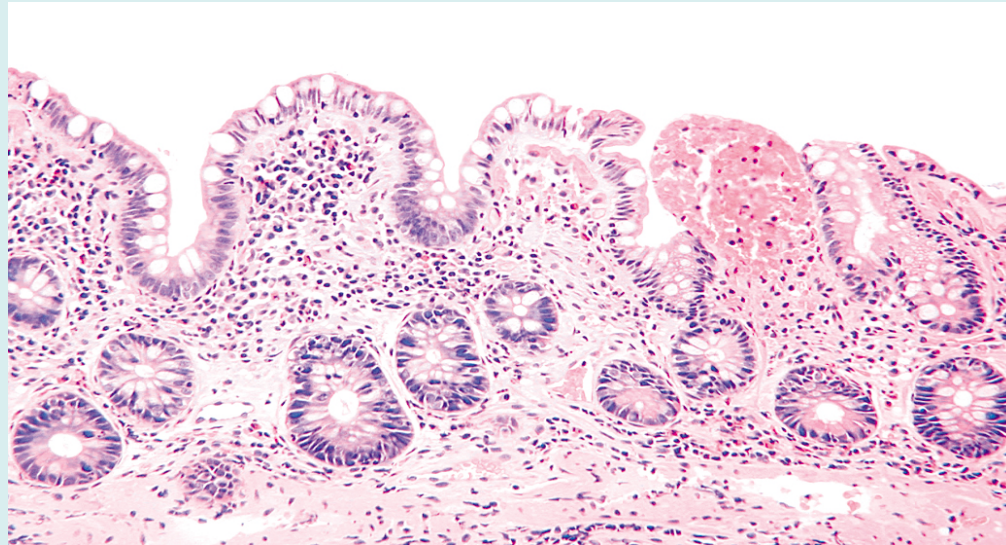


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# The mucosal pathology of the pouch



# Colonic phenotypic change, colonic metaplasia or colonisation?

- morphology
- mucin and lectin histochemistry and immunohistochemistry
- electron microscopy

BUT

- disaccharidase activity and enteric supramucosal defence barrier maintained
- not all pouches, and not all mucosa in pouches, show colonic phenotypic change

*Shepherd et al, 1987 & 1993; de Silva et al, 1990; Sylvester et al, 2000*

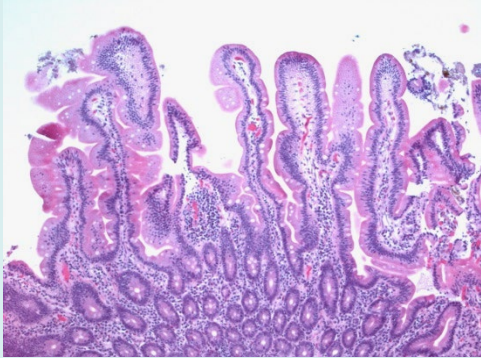


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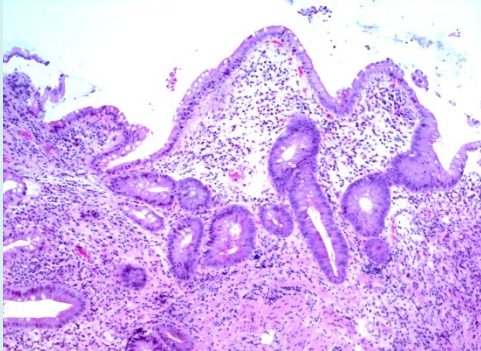


# The mucosal pathology of the pouch

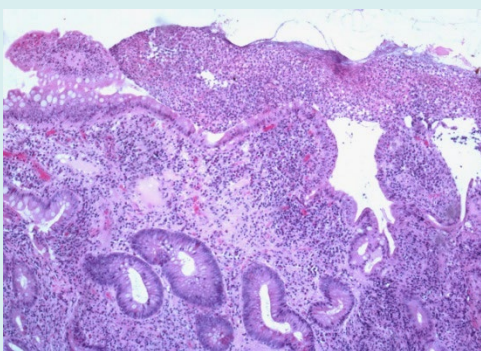
Three groups:



A: 45%: UC and FAP: no active inflammation: normal or mild chronic changes/villous abnormalities



B: 42%: mainly UC but occasional FAP: chronic changes but transient active inflammation



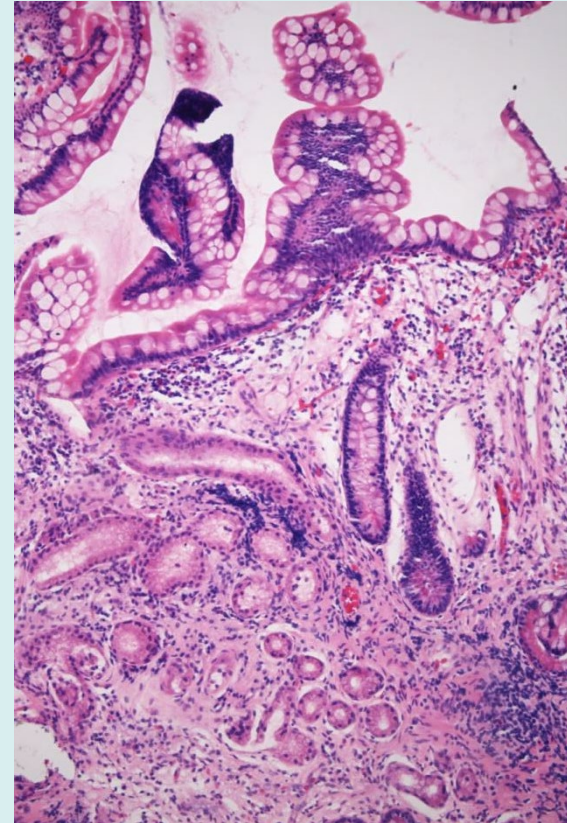
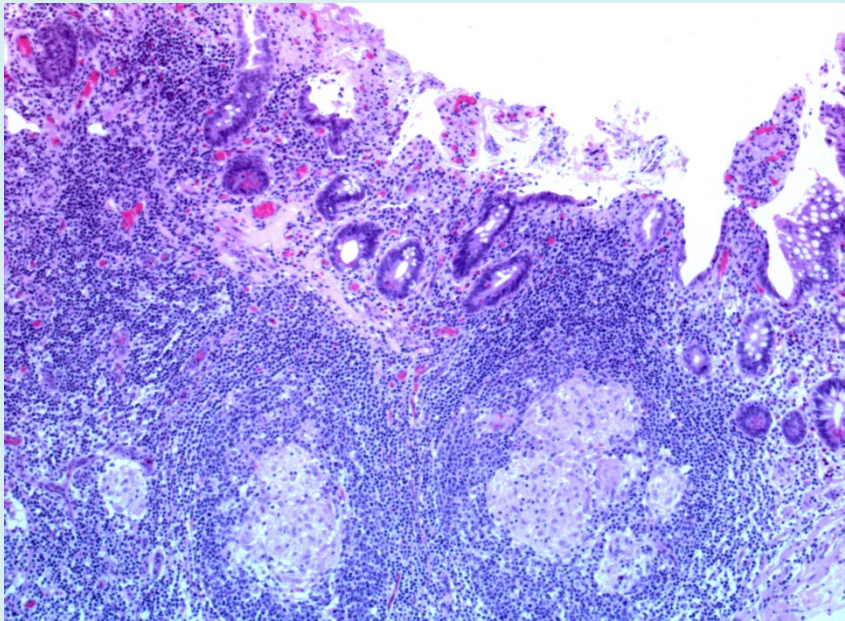
C: 13%: always UC: severe chronic active inflammation: chronic changes constant: (chronic relapsing) pouchitis

*Veress et al, 1990;*

*Setti Carraro, Talbot & Nicholls, 1994 & 1998*



# Pouch pathology: is this Crohn's disease?

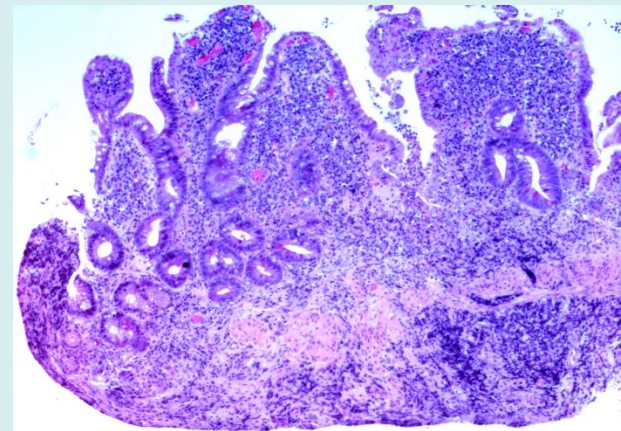
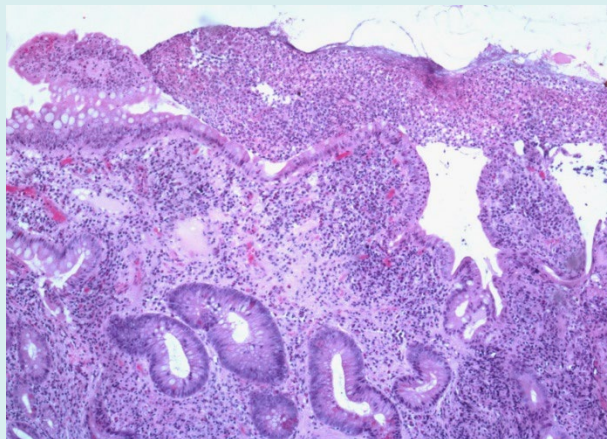
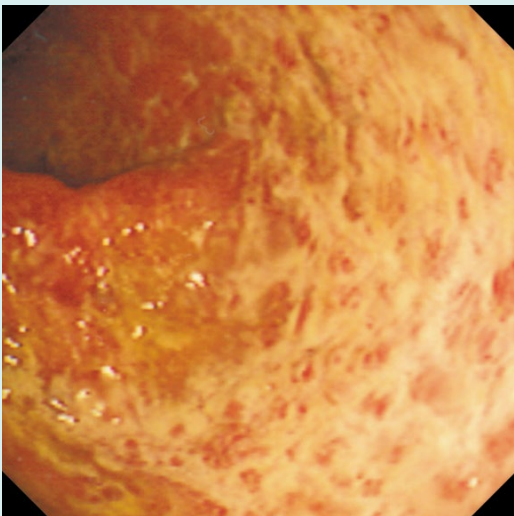


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# Pouchitis

- better termed 'chronic relapsing pouchitis'
- it is NOT just any old inflammation in the pouch
- 10-20% but very variable (definitions)
- defined by clinical (diarrhoea/discharge, systemic symptoms, like UC), endoscopic and histopathological criteria/scoring





## Scoring system for pathological changes in the ileal reservoir mucosa

(Shepherd et al 1987)

	score
<b>acute changes</b>	
acute inflammatory cell infiltrate	
none	0
mild and patchy infiltrate in the surface epithelium	1
moderate with crypt abscesses	2
severe with crypt abscesses	3
ulceration	
none	0
mild superficial	1
moderate	2
extensive	3
maximum	6
<b>chronic changes</b>	
chronic inflammatory cell infiltrate	
none	0
mild and patchy	1
moderate	2
severe	3
villous atrophy	
none	0
minor abnormality of villous architecture	1
partial villous atrophy	2
subtotal villous atrophy	3
maximum	6

# Questionnaire on activity scoring in routine GI pathology practice

- sent to UK pathologists, half specialist and half non-specialist
- 50 returns

No activity scoring system used at all	74%
pouchitis scoring	24%
coeliac disease	8%
inflammatory bowel disease	6%
reflux oesophagitis	2%
gastritis (Sydney, OLGA, etc)	0%



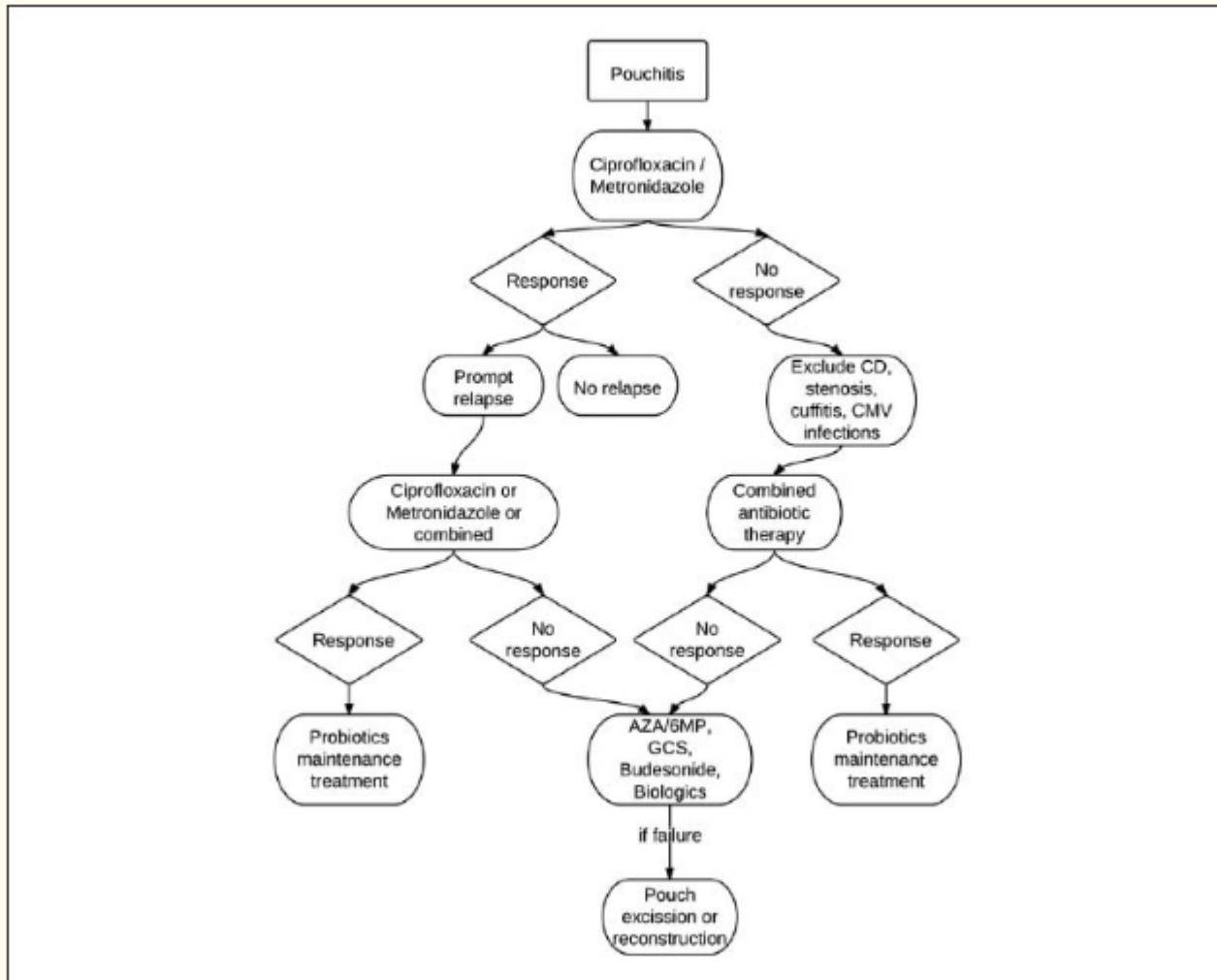
# Pouchitis

- fascinating clinical, pathological and immunological relationships with UC and with its extra-intestinal manifestations (very rare in FAP)
- role of colonic phenotypic change – is this UC in metaplastic colonic mucosa?
- BUT good remission rates with metronidazole and ciprofloxacin, maintained with probiotics, argues for a bacterial aetiology

***Mimura et al, 2004; Gionchetti et al, 2012***

- microbiological research disappointing – role of anaerobes, sulphate-reducing anaerobes, etc





***Gionchetti P, et al. The role of antibiotics and probiotics in pouchitis.  
Ann Gastroenterol 2012; 25: 100-5.***



# Apocalypse Now

## **The pelvic ileal reservoir: apocalypse later?**

*Patients need monitoring for the long term  
effects of reservoir construction*



# Long term natural history of the pouch mucosa

- does the combination of chronic active inflammation and colonic phenotypic change predispose to an increased neoplastic risk?
- yes – in the rectal cuff with cuffitis (especially stapled anastomoses) ; cases of dysplasia and cancer reported
- yes – modest risk in FAP – adenomas and cancers  
*Nugent et al, 1993; von Herbay et al, 1996; Thompson-Fawcett et al, 2001*
- probably not much – in the ileal mucosa of the pouch itself
- earlier worries from Huddinge, Sweden  
*Veress et al, 1995; Gullberg et al, 1997*
- but large reviews have shown very low rates of dysplasia: only very occasional case reports of cancer



# The natural history of the pouch mucosa and surveillance

- the rectal cuff with cuffitis probably does require surveillance
- patients with type C pathology/pouchitis merit surveillance
- can we leave the others alone?





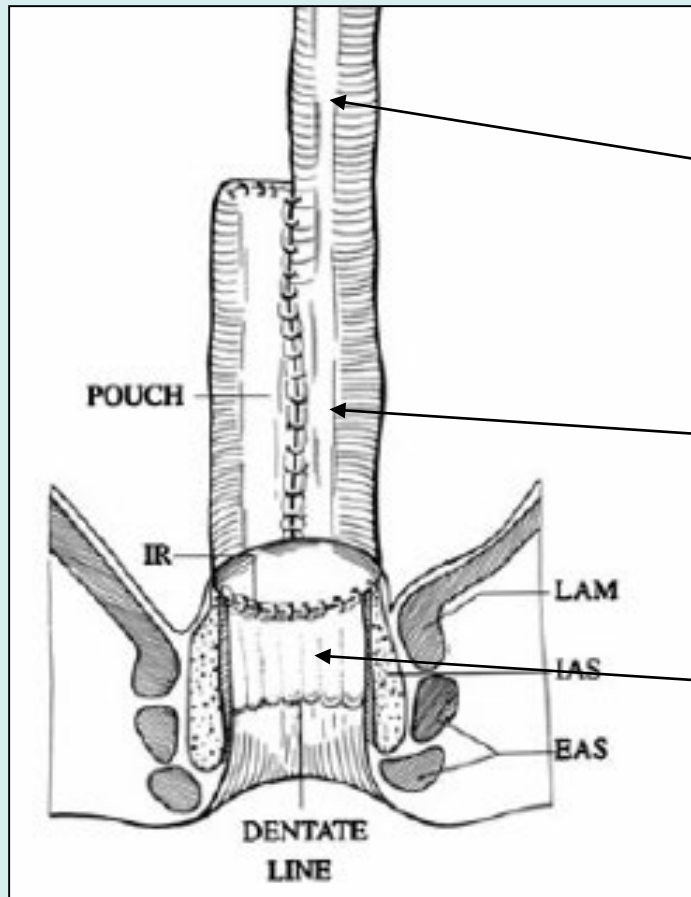
**All looks fairly simple so what is the problem?**



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# Site of biopsies



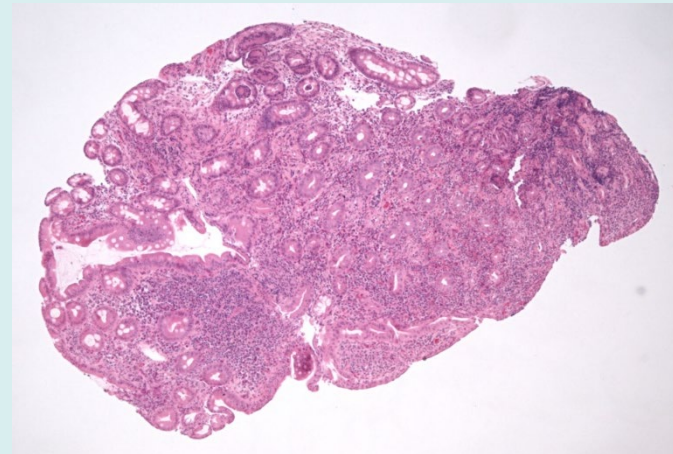
pre-pouch

pouch

anal cuff

# Pre-pouch ileitis

- enigmatic and rare disease
- some cases represent Crohn's disease (and likely that intestinal pathology was always Crohn's disease) (3/19) and NSAID enteropathy (1/19)
- most a non-specific small intestinal inflammatory and ulcerative complication of UC (15/19)
- pathology similar to pouchitis, with colonic phenotypic change: 47% also had pouchitis
- many cases respond well to biologic therapy



*Bell et al, 2006*

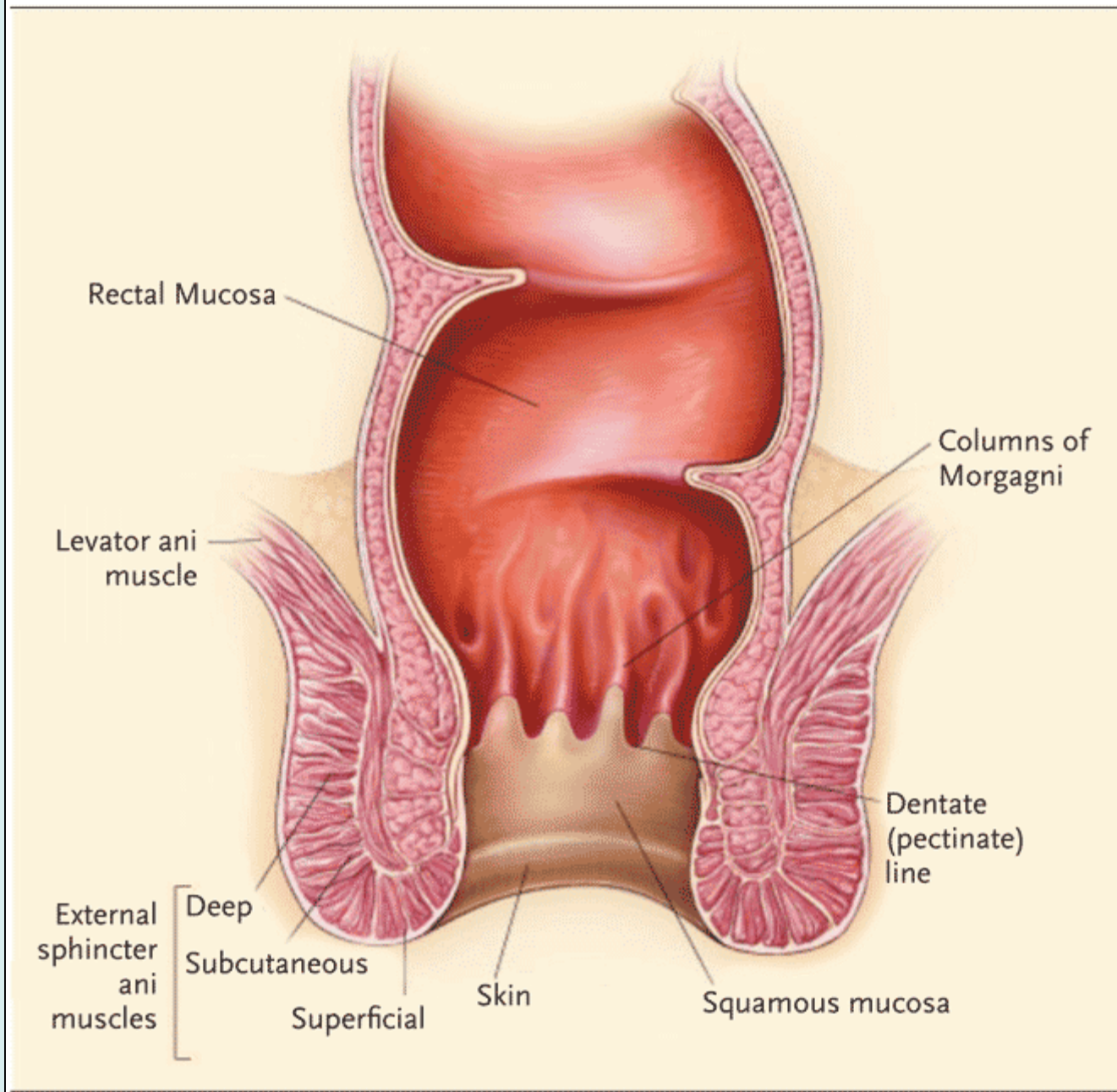
# Pre-stomal ileitis

- another enigmatic and rare disease
- occurs after total colectomy and ileostomy for UC
- long segment disease with dilatation and extensive ulceration
- poor prognosis (three patients died)
- another small bowel manifestation of UC

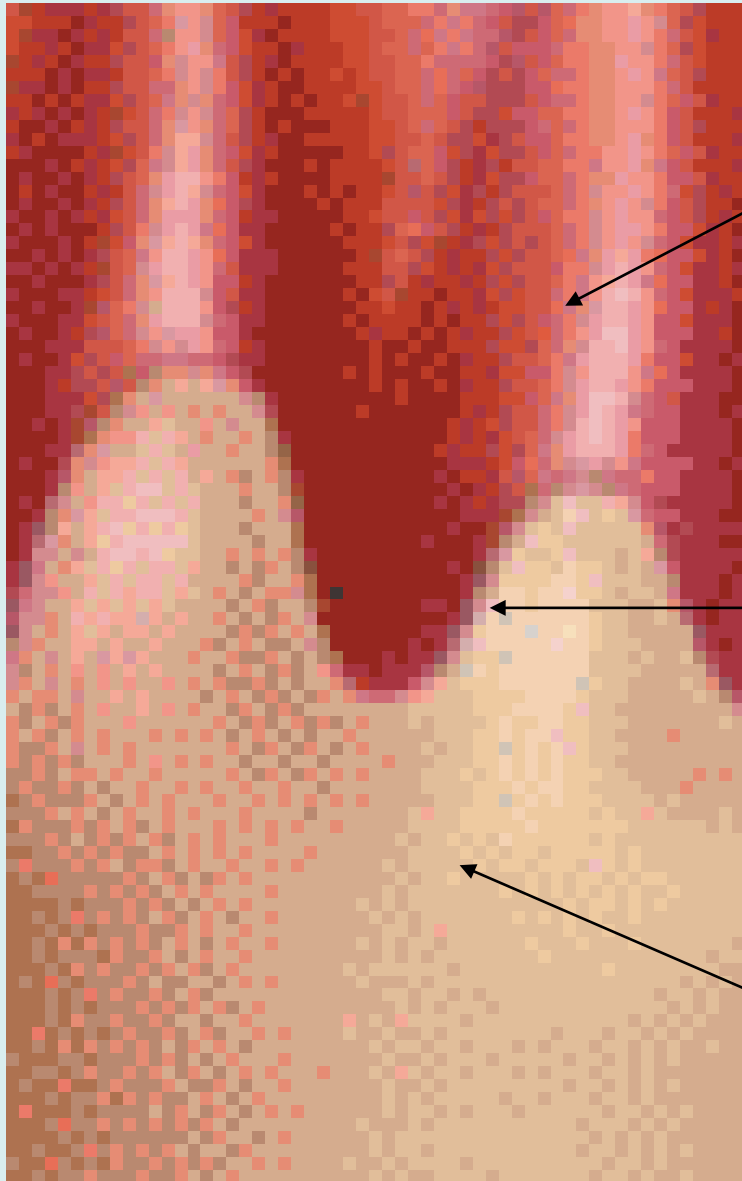
***Knill-Jones RP, Morson B, Williams R.  
Prestomal ileitis: clinical and pathological findings in five cases.  
Quart J Med 1970; 39: 287-97.***



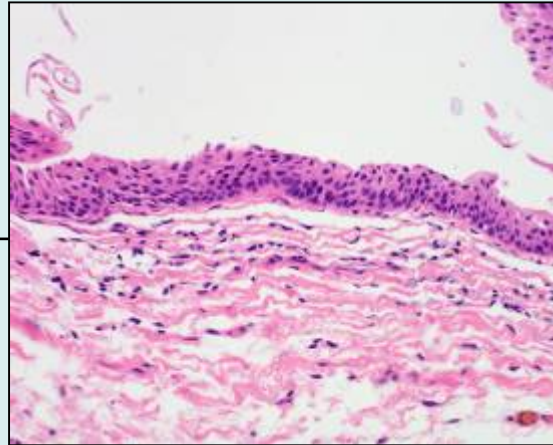
**Figure 4. Anatomy of the Anus**



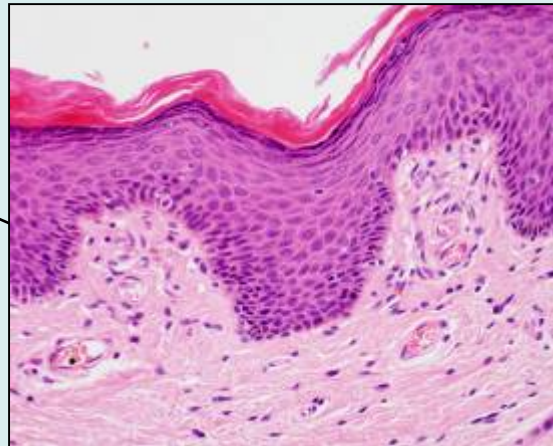




colorectal  
zone  
(anal cuff)



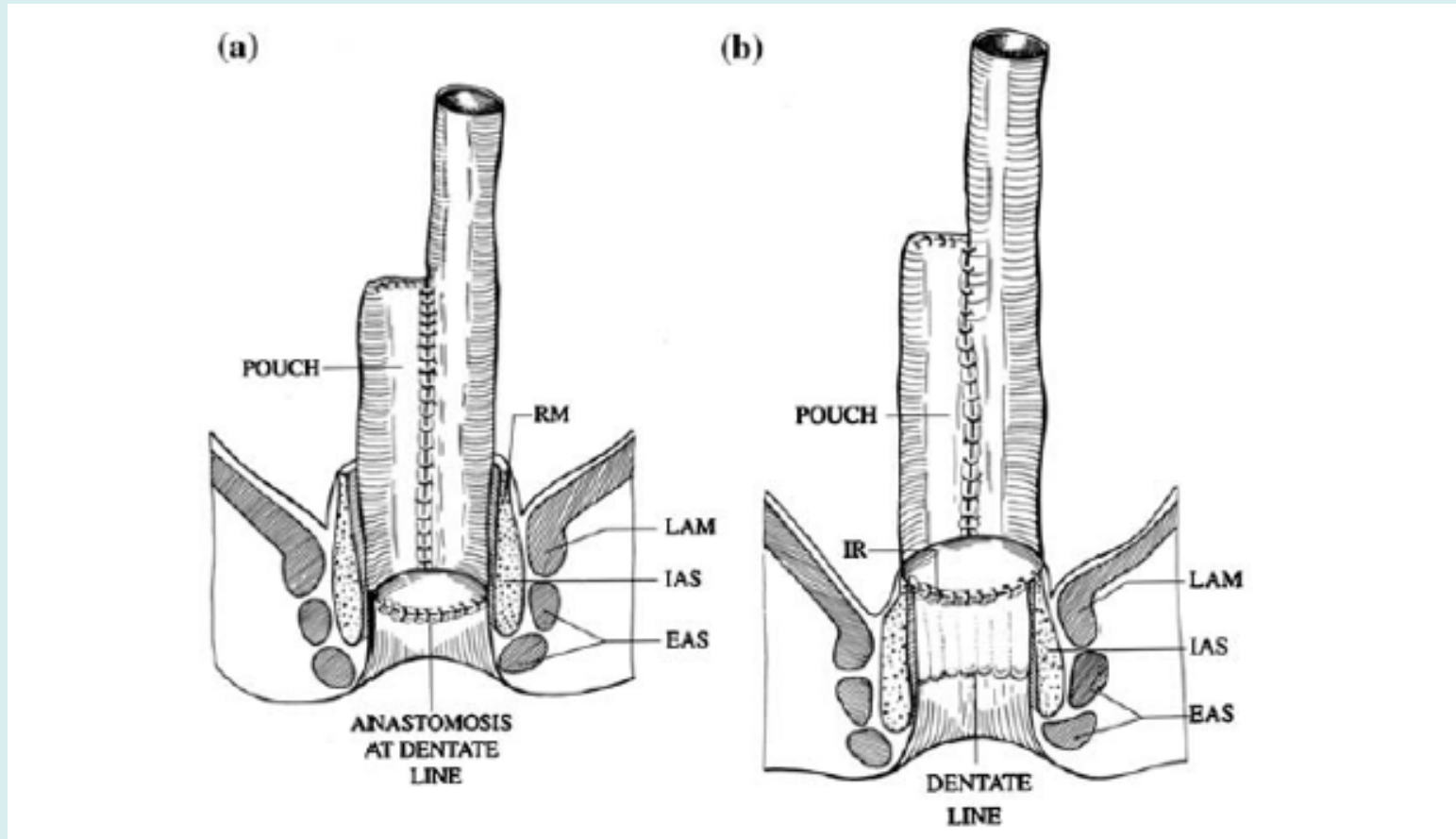
transitional  
zone

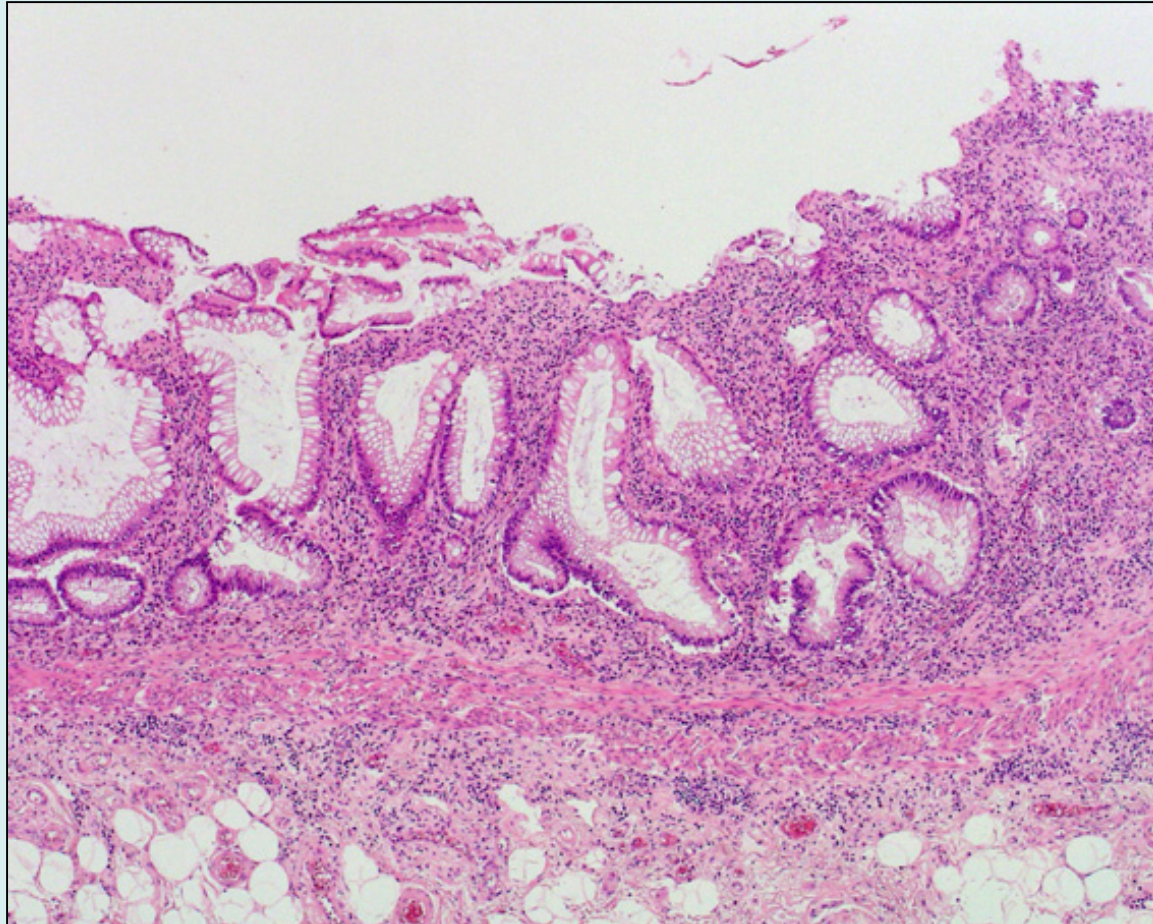


squamous  
zone

# Restorative proctocolectomy

## Hand-sewn versus stapled anastomosis





Cuffitis (UC involving the anal cuff)



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# Pouchitis vs cuffitis

- Symptoms

- frequency & urgency
- incontinence
- anorexia / fever
- extra-intestinal manifestations

- Diagnosis

- symptoms
- endoscopic findings: site
- histopathology

- Symptoms

- pain
- bleeding

- Diagnosis

- symptoms
- endoscopic findings; site
- histopathology

***Thompson-Fawcett M, Mortensen NJMcC, Warren BF.  
“Cuffitis” and inflammatory changes in the columnar  
cuff, anal transitional zone, and ileal reservoir after  
stapled pouch-anal anastomosis.  
Dis Colon Rectum 1999; 42: 348-355.***

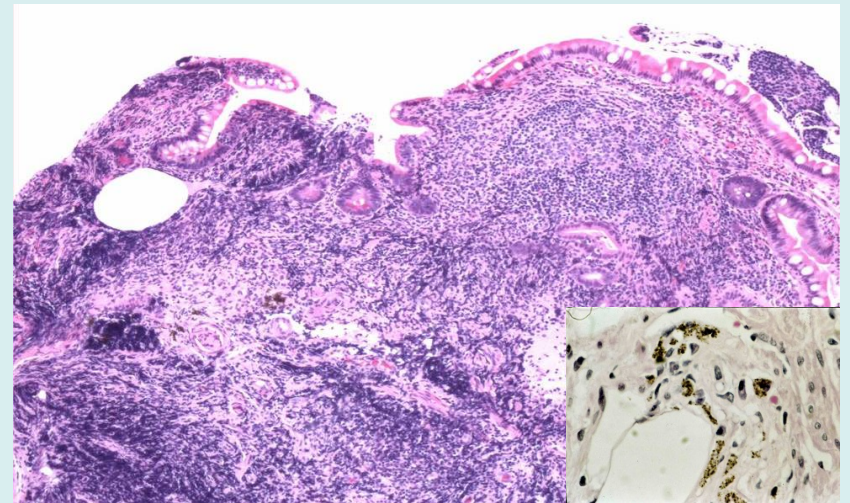


# Differentiating inflamed ileal pouch mucosa from inflamed cuff: any features that can help?

## Relative parameters

- UACL much more common in the small intestine
- crypt architectural distortion tends to be more severe in cuffitis
- Paneth cells tend to be more plentiful in the small intestine

## 'Peyer's patch pigment'



*Shepherd et al, 1987*



# Differential diagnosis of acute inflammation/ulceration in the pouch

- Crohn's disease

**NEVER MAKE A DIAGNOSIS OF CROHN'S DISEASE BASED ON POUCH PATHOLOGY ALONE**

- superinfection
- trauma
- intra-abdominal sepsis
- mucosal prolapse
- ischaemia

# Take home messages

- indeterminate colitis is a clinically and pathologically useful diagnosis when applied to colectomy specimens
- indeterminate colitis means the surgical pathology is indeterminate, not the pathologist.....
- cases of CIBD, on biopsy, with unclassifiable pathology should be termed IBDU, never mind what endoscopy reporting systems call it.....
- most cases of indeterminate colitis will act like UC but with increased complications. Only a small proportion will act like Crohn's disease



# Take home messages

- pouchitis is defined by clinical, endoscopic and pathological criteria – not just a bit of chronic inflammation and villous atrophy
- there are important mimics of Crohn's disease in UC surgery, especially the diverted rectum and pouch granulomas and UACL
- we still don't know the cause of pouchitis but it has important links to ulcerative colitis
- there is little evidence, currently, for significant neoplasia in the pouch mucosa but more in the anal cuff





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