IBD Cases Workshop

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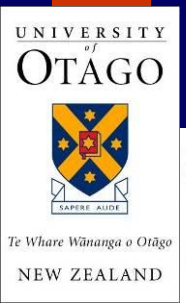
Gastroenterology and Endoscopy Specialists



Gastroenterology and Endoscopy Specialists

Conflicts of Interest

- I am an advisor, have received travel assistance or unrestricted research grants from the following companies

  - Abbott
  - MSD
  - Ferring
  - Olympus
  - Given imaging
  - PFK
  - Orphan
  - Astra Zeneca
  - Roche

Petra, 22 year old student

- 6 weeks of intermittent abdominal pain
  - Lower abdomen
  - Present every day
  - Mild nausea
  - Poor apetite, 3kg weight loss
- Bowel motions 1 → 2-3X/day
  - Soft but no blood or urgency
- No new rashes, joint pain, red eyes

Petra, 22 year old student

- Meds
  - OCP
  - OTC diclofenac for back pain
- FHx
  - Mother / sister diagnosed with IBS
- SHx
  - Smoker 5 cigarettes per day
  - Broke up with boyfriend 3 months ago, struggling at university

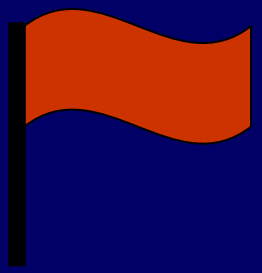
Petra, 22 year old student

- Examination
  - Mild non-specific abdominal tenderness
- Petra wants to know what is going on and how she can get better

Petra, 22 year old student

- What is your next step?

- Blood tests
  - FBC Hb 110, MCV 81, N WCC / diff
  - tTG Ab 3 (normal IgA)
  - B12 / folate normal
  - CRP 5
  - TFT normal

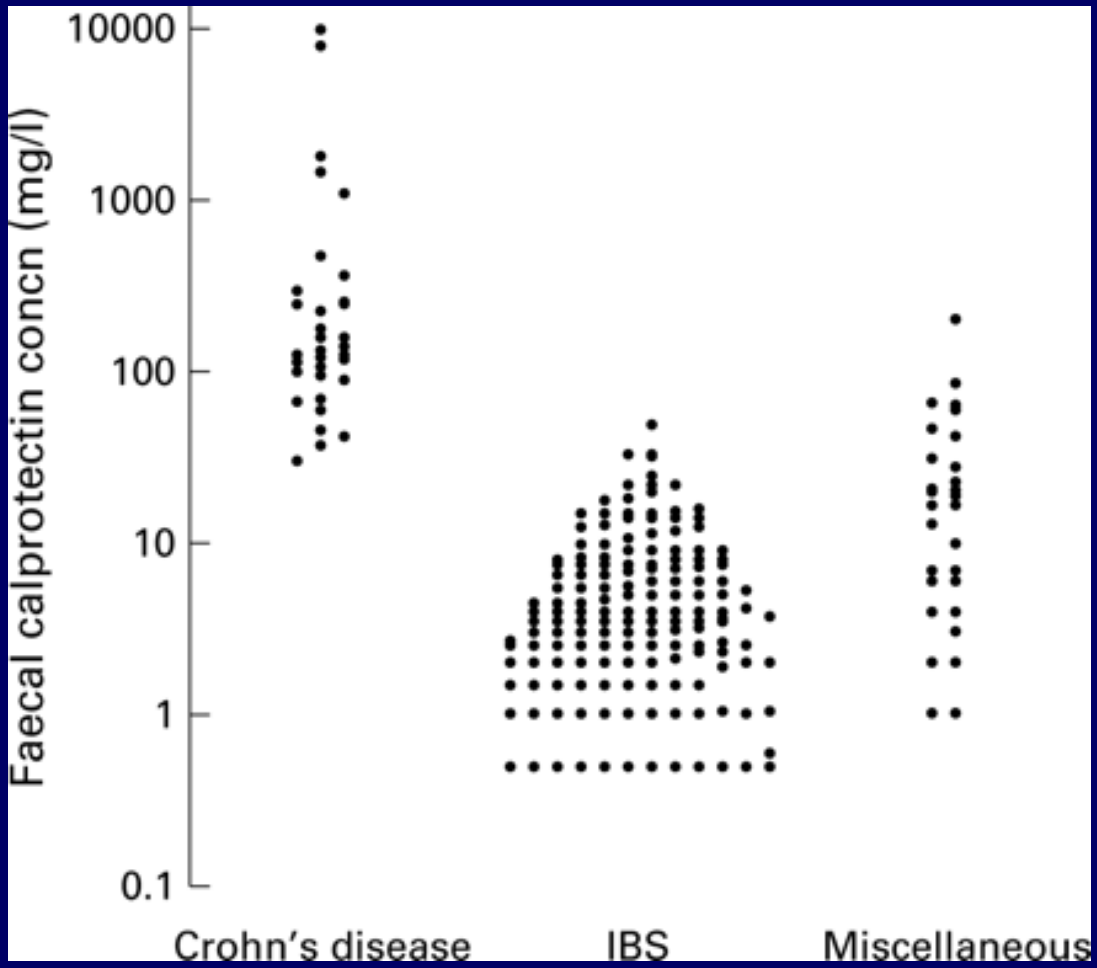


Petra, 22 year old student

- What is your next step?
- Faecal culture and parasites
  - normal
- Faecal calprotectin
  - 250 (normal <50)

A simple method for assessing intestinal inflammation in Crohn's disease.

Tibble et al. Gut 2000



Petra, 22 year old student

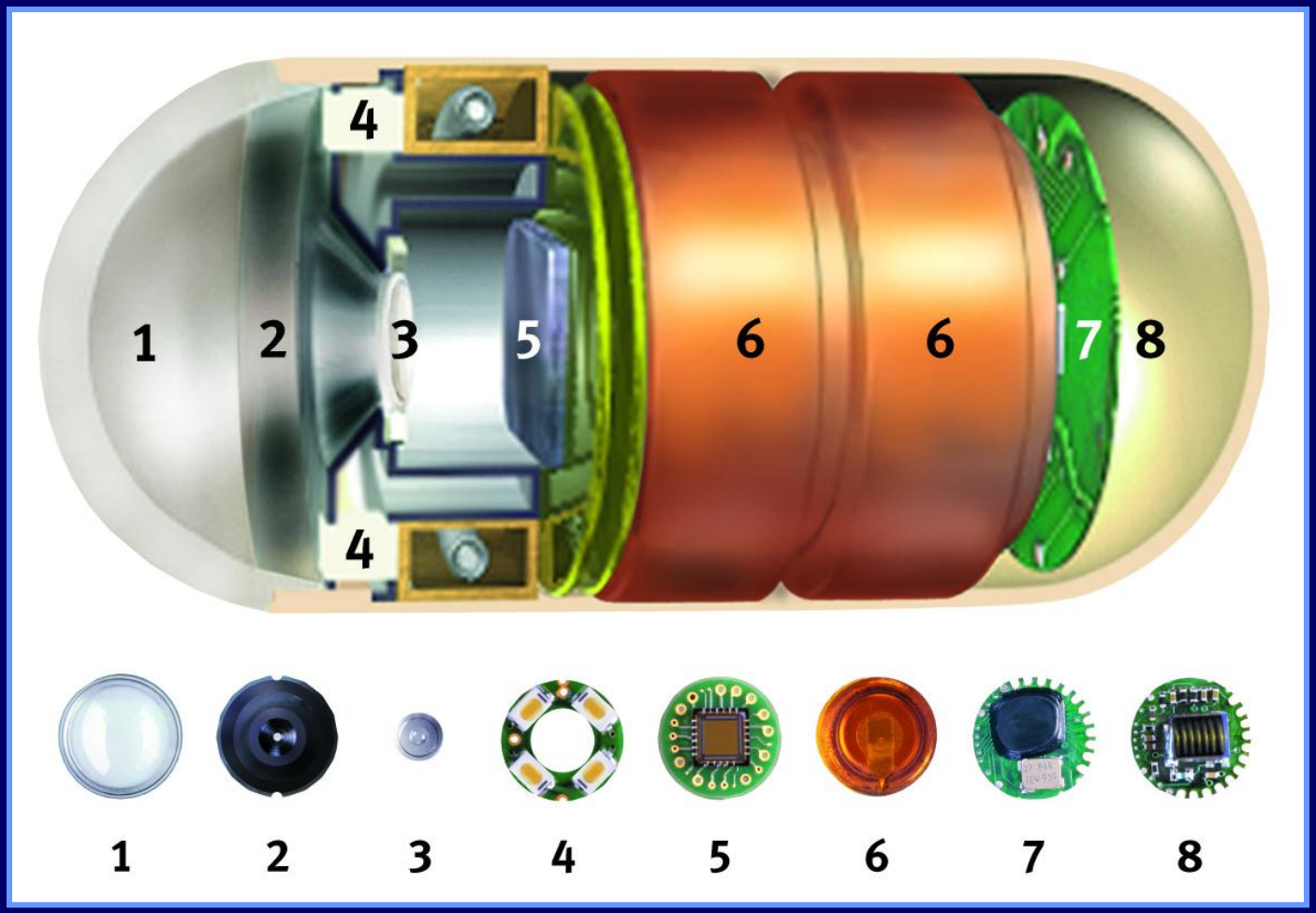
- What is your next step?
- Colonoscopy
  - normal
- Ongoing suspicion of Crohn's disease
  - Small bowel imaging …

Considerations for small bowel imaging

- SBFT, CT or MR enterography, Capsule
- Availability
- Contraindications
- Cost
- Risk

Diagnostic Medical Radiation

Newnham, Gearry et al, 2007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INDICATIONS PILL CAM

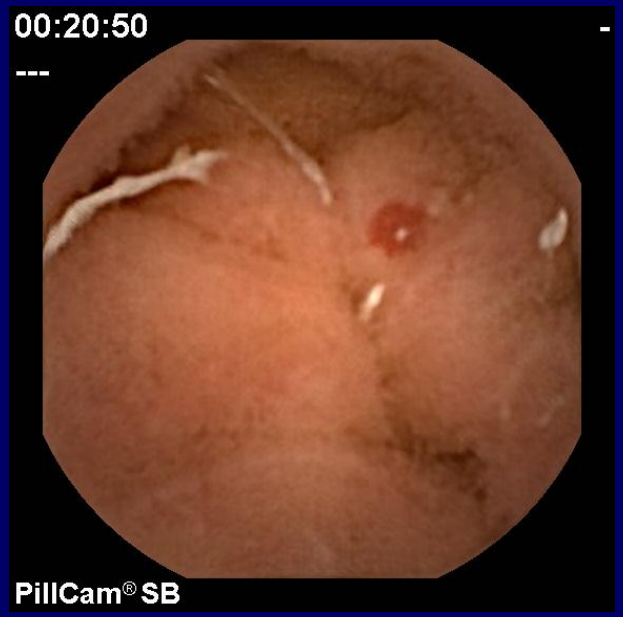
- Investigations Crohn's
- Obscure anaemia
- Peutz-Jeghers Syndrome
- Small intestinal tumours

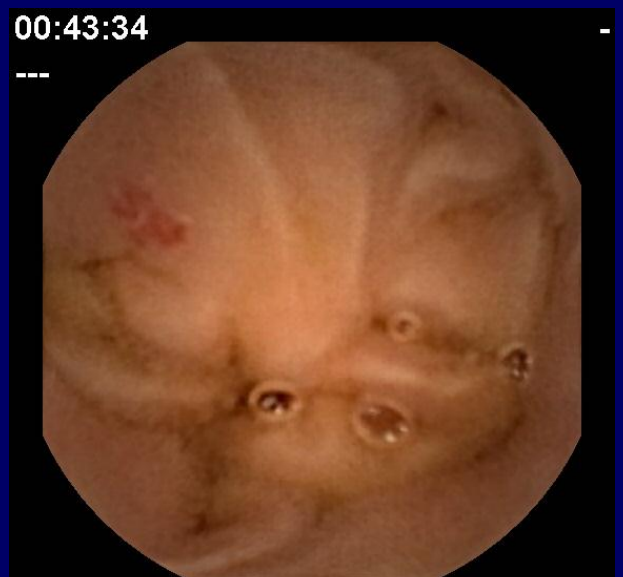
(GIST, Carcinoid, lymphoma, Adenocarcinoma)

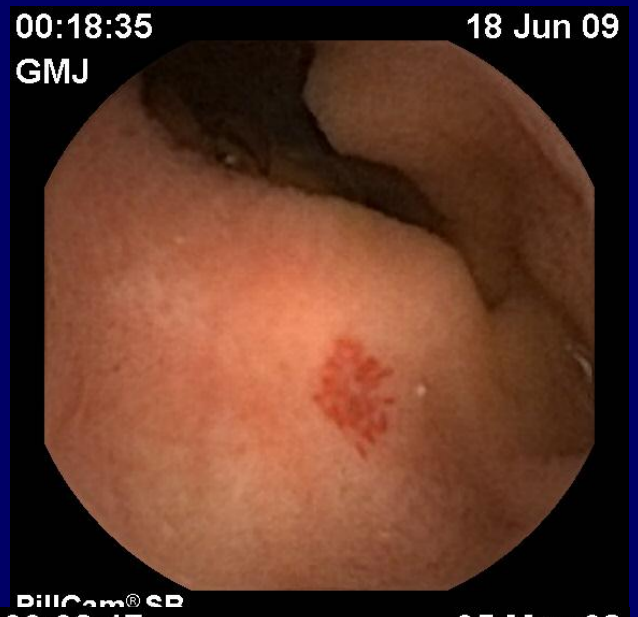
Not Abdominal pain!

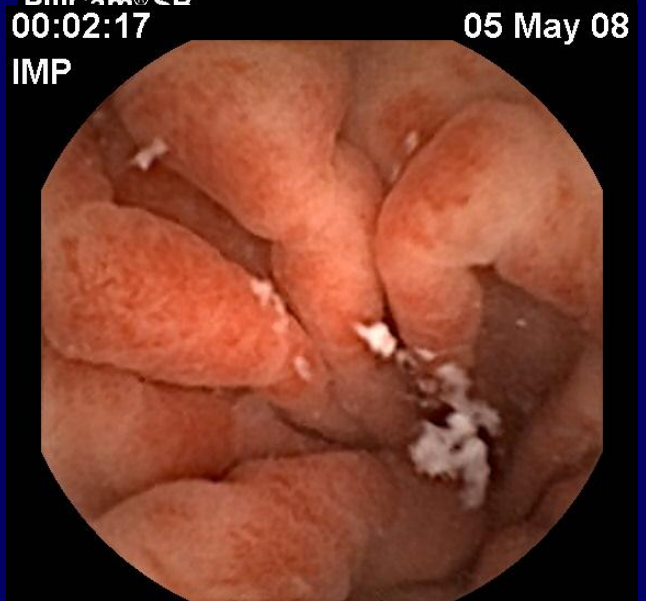
SensorBelt & DR Pouch

Small Bowel Capsule Findings

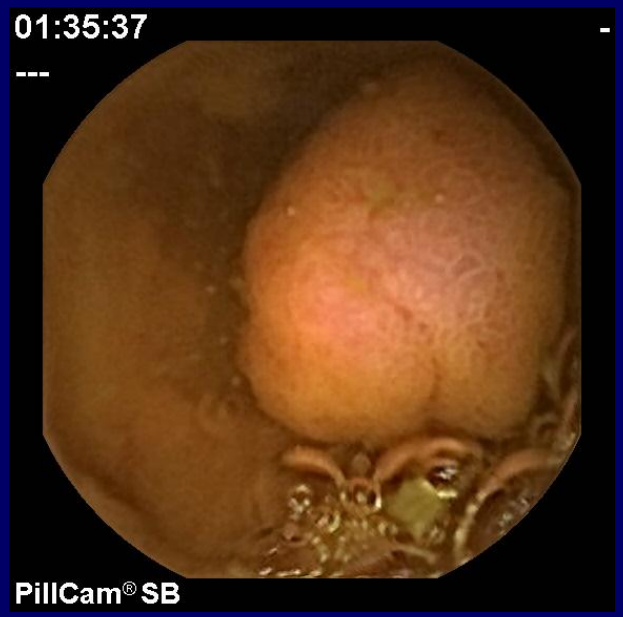


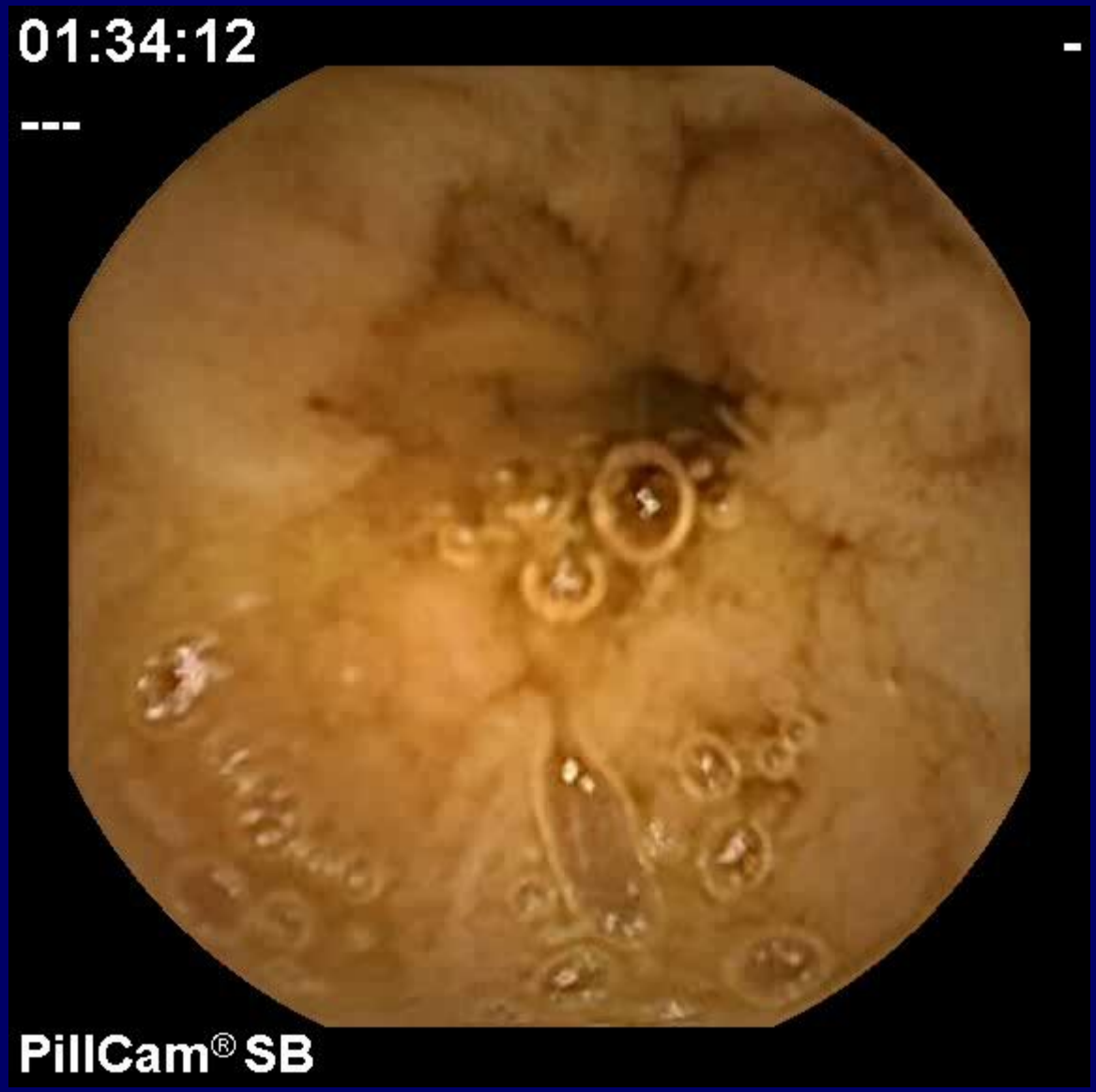






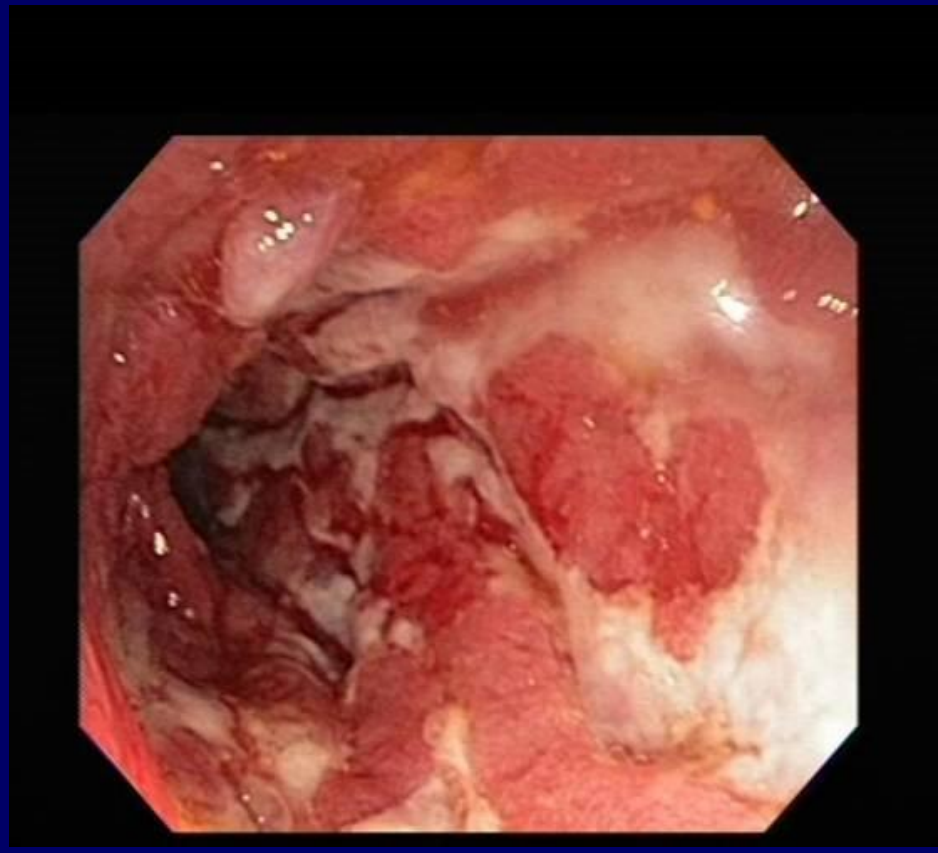
Peutz – Jeghers syndrome





Petra, 22 year old student

Small bowel
Crohn’s disease



Petra, 22 year old student

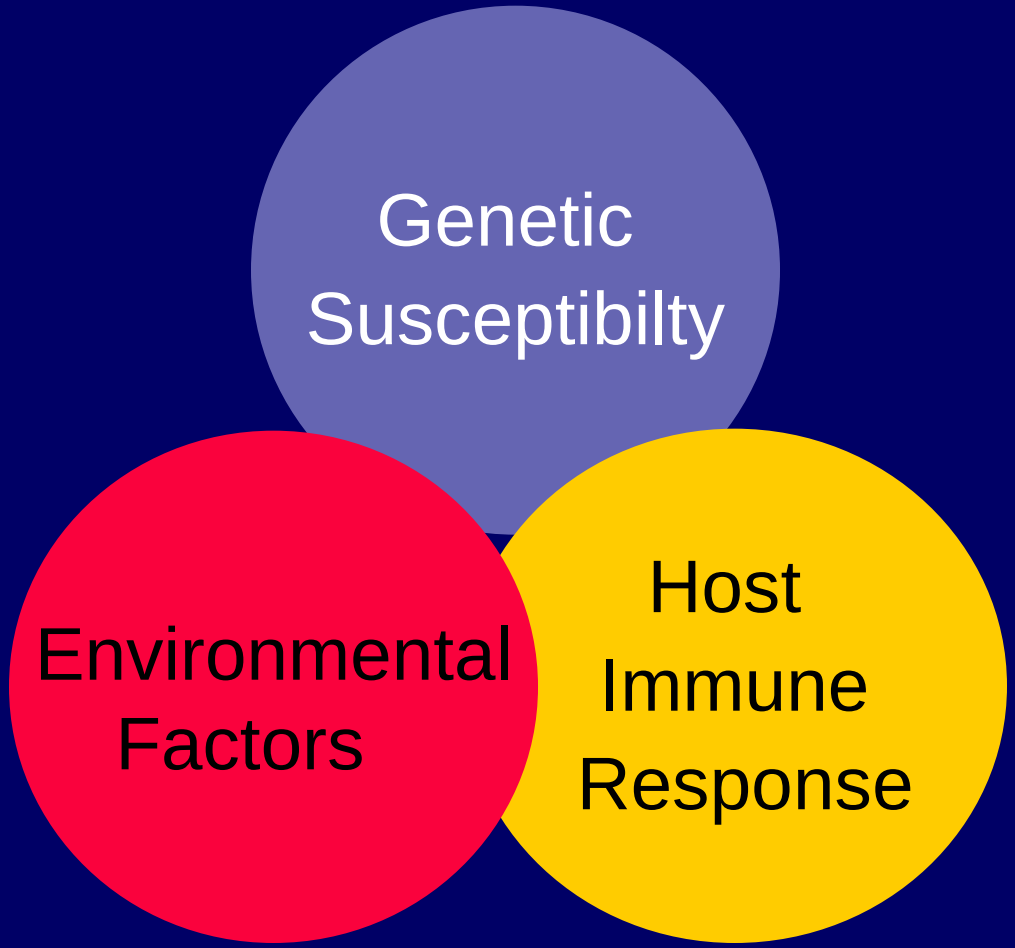
- Diagnosis Small bowel Crohn's disease

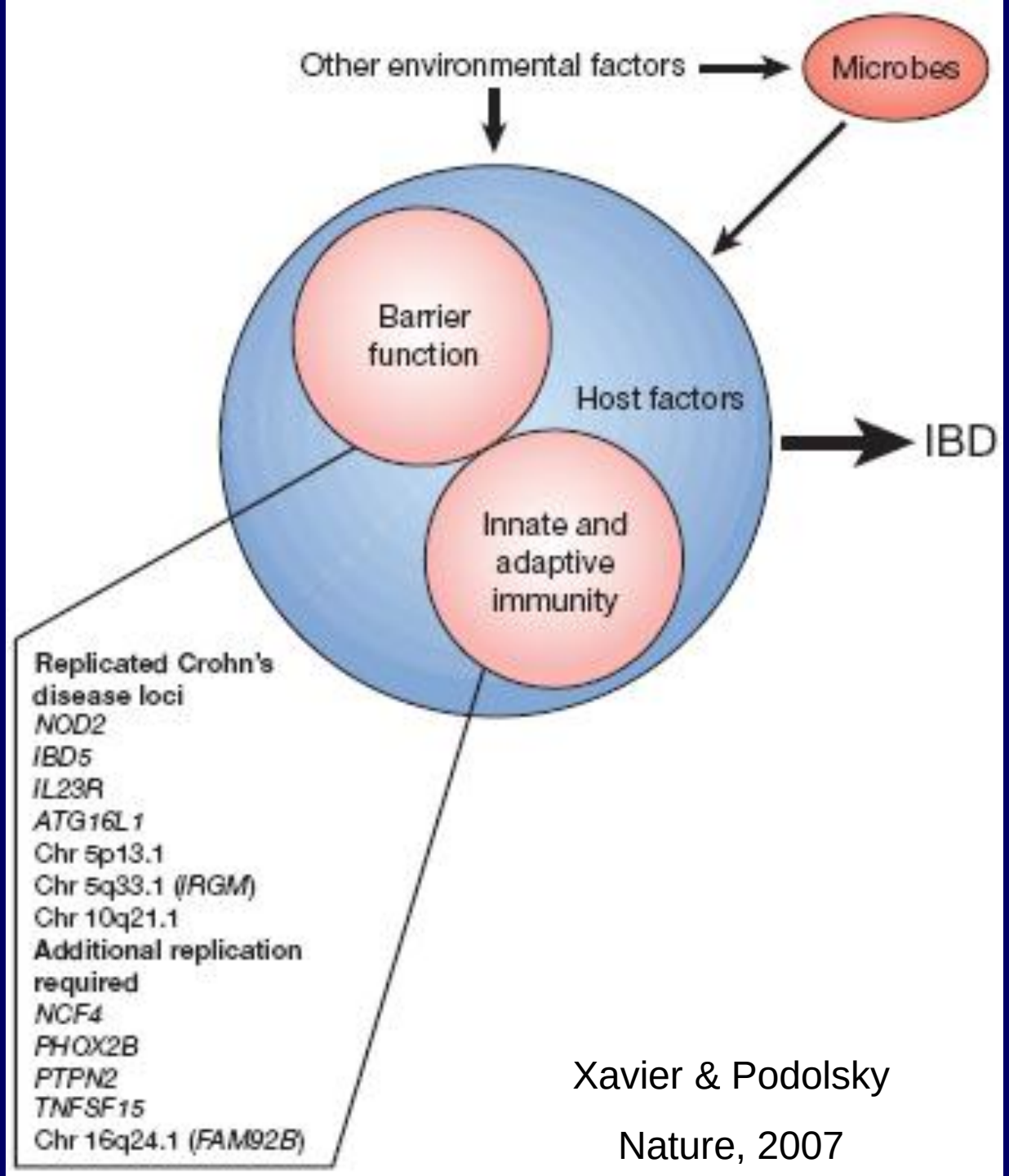
- What do patients want to / need to know?

Petra, 22 year old student

- No cure
- Aim is remission
  - Normal quality of life but will need some treatment
- Address concerns around surgery / stoma
- Discuss causes if patients bring it up

Current concepts of IBD





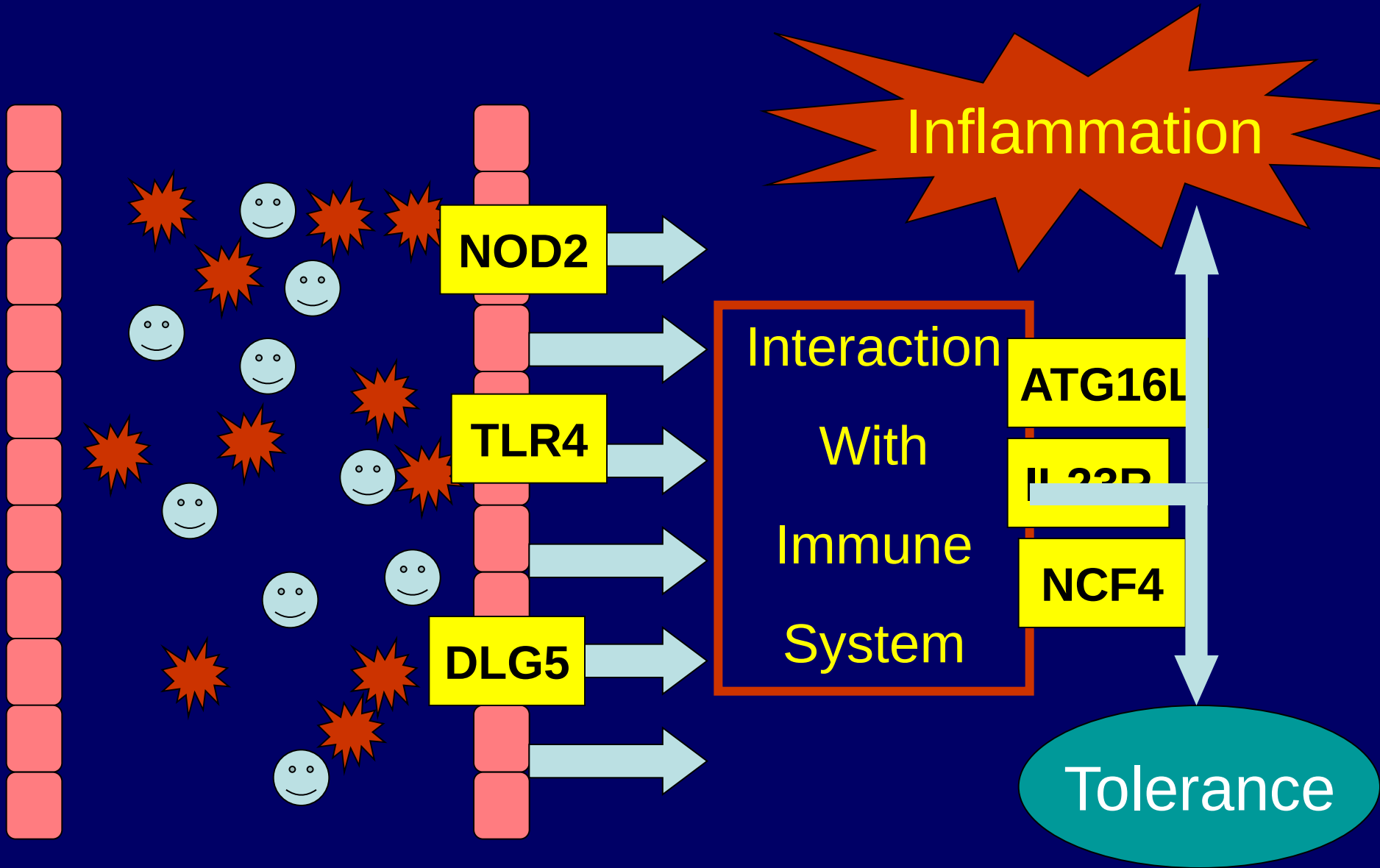
Xavier & Podolsky

Nature, 2007

IBD Genetics (briefly)

Gene	CD	UC	Paper
NOD2	✓	X	Gearry et al. *Inflamm Bowel Dis,*2006
DLG5	✓	X	Browning et al. *Inflamm Bowel Dis,*2007
TLR4	✓	X	Browning et al. *Am J Gastroenterol,*2007
ATG16L	✓	X	Roberts et al. *Am J Gastroenterol,*2007
IL23R	✓	✓	Roberts et al. *Am J Gastroenterol,*2007
DEFA	✓	X	Ferguson et al. *J Gastro Hepatol, 2008*
Gli1	X	X	Bentley et al, Genes Immunity, 2010
NCF4	✓	X	Roberts et al. Genes Immunity, *2009*
IRGM	✓	X	Roberts et al. *Genes Immunity, 2009*
KCNN4	✓	X	Simms et al, Am J Gastro, 2010
FcgR2a	✓	X	Weersma et al, Inflamm Bowel Dis
CARD8	✓	X	Roberts et al. Genes Immunity
NALP3	✓	X	Roberts et al. Genes Immunity
DEFB	✓	X	Bentley et al, Genes Immunity
GWAS X2	✓	✓	IIBDC Nature Genetics X 2

IBD Pathogenesis



Environmental risk factors & CD

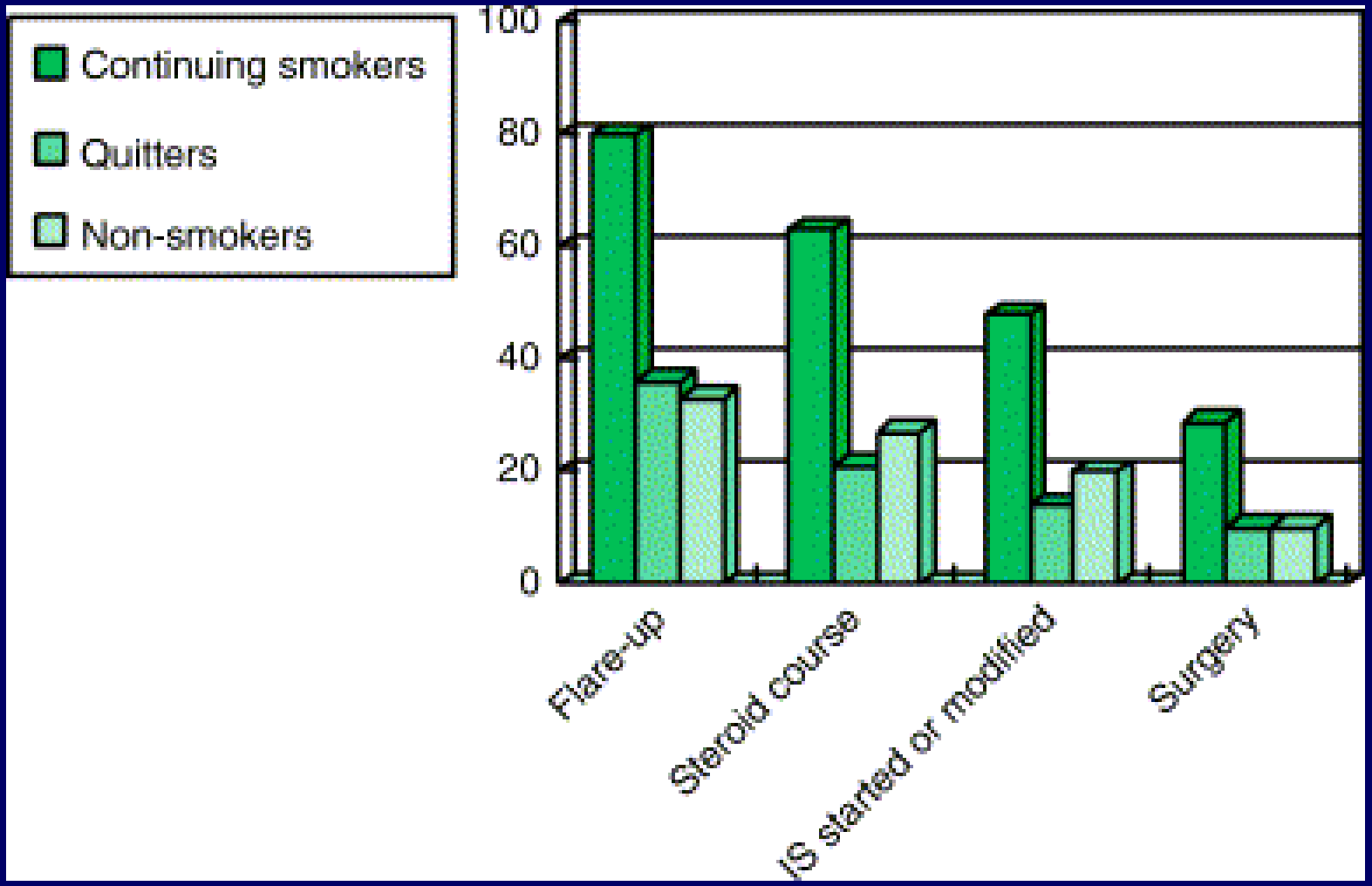
Risk Factor	OR	95%CI
One relative IBD	3.0	2.2-4.1
Two relatives IBD	7.0	3.3-15
Smoker at diagnosis	2.0	1.5-2.7
Maternal smoking	1.7	1.2-2.3
Appendicectomy	1.7	1.2-2.0
Tonsillectomy	1.5	1.1-2.0
Breastfed as infant	0.5	0.4-0.7
OCP use	1.8	1.1-3.1
High antibiotic use (adolescence)	2.1	1.3-3.3
Urban living	1.5	1.1-2.1
Childhood vegetable garden	0.5	0.4-0.7
High childhood SES	1.6	1.1-2.2
High recruitment SES	0.5	0.3-0.7

Gearry et al, 2010

Petra, 22 year old student

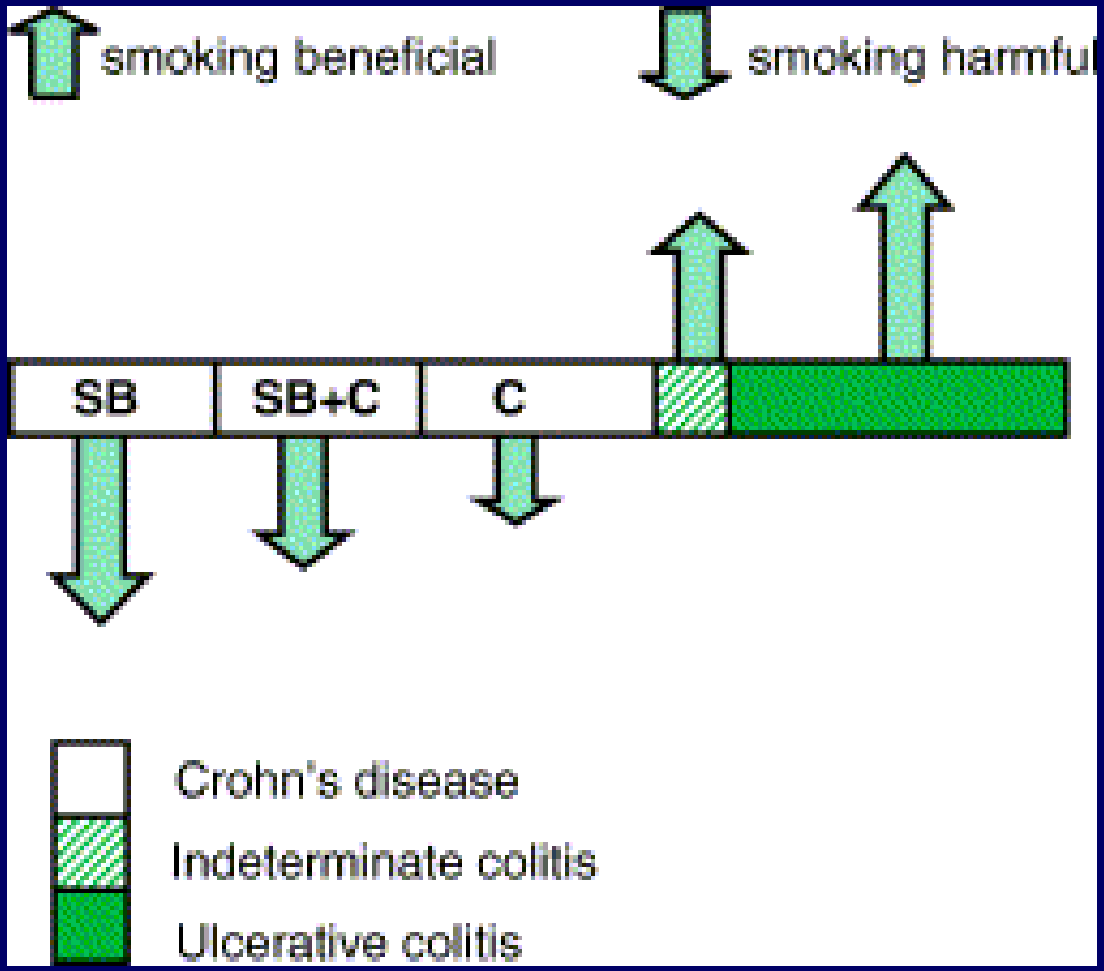
- Treatment
- Options
  - 5-ASA (Pentasa)
  - Steroids
  - Immunomodulators
  - Biologics
- Lifestyle options???

Effect of smoking on Crohn's disease course



Cosnes et al, 2001

Effect of smoking on course of IBD



Cosnes et al, 2001

Petra, 22 year old student

- Treatment

- Discussion around treatment options
  - Smoking cessation stressed – GP to
  - Pentasa commenced
  - Prednisone declined
  - Azathioprine commenced
  - Clinic review to follow

Diagnosis of IBD Questions?

Simon, 36 year old accountant

- 2 months diarrhoea
  - 5X/day plus 2X overnight
  - Bloody
  - Urgency ++ (no incontinence)
  - Poor appetite
  - Colicky lower abdominal pain prior to defecation
- No drugs (including OTC)

Simon, 36 year old accountant

- Diagnosed with left-sided ulcerative colitis 9 months ago – on Pentasa 1g bd
- Cousin with ulcerative colitis
- Examination
  - What do you want to know?

Simon, 36 year old accountant

- Examination
  - Not tachycardic 70/min
  - No peritonism
  - No signs of EIM IBD
- Where to now?

Simon, 36 year old accountant

- Management of a flare of UC
  - Optimise 5-ASA
    - Increase oral 5-ASA Pentasa 4g / day
    - Introduce rectal 5-ASA Pentasa enemas
  - Consider steroids
    - Discuss with patient
    - Use at full dose 40mg/day, reduce by 5mg/week
    - Have an exit plan
    - Remember the bones Vit D / Ca

Simon, 36 year old accountant

- Investigations
  - Faecal spec for culture / *Clostridium difficile*
  - FBC / CRP as biomarkers
  - AXR / admission if concerns about megacolon etc

Flare of UC

- 5-ASA is the core drug
  - Effective
  - Well-tolerated
  - Delivered multiple routes to optimise exposure to the colon
- Steroids work well but need to be given for long enough
- Recurrent steroids = immunomodulator

Simon, 36 year old accountant

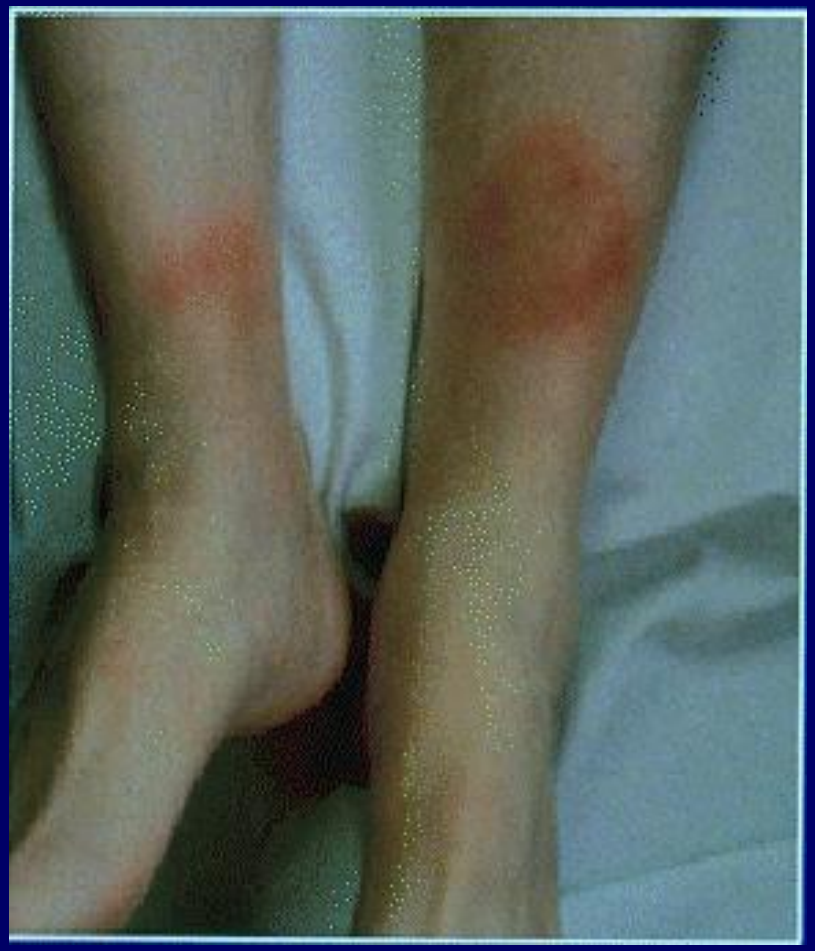
- Pentasa 4g / day
  - Can be taken all at once
- Pentasa enemas
  - Can be difficult to hold but need to persist
- Limited response after one week
  - Prednisone 40mg / day commenced
  - Remission achieved over 10 days

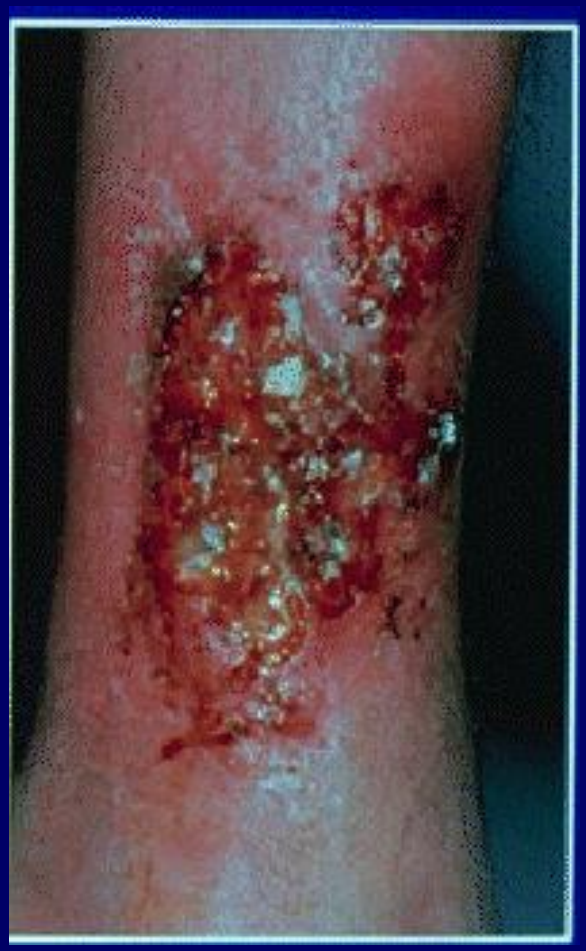
Flare of known UC Questions?

Rachel, 39 year old hairdresser

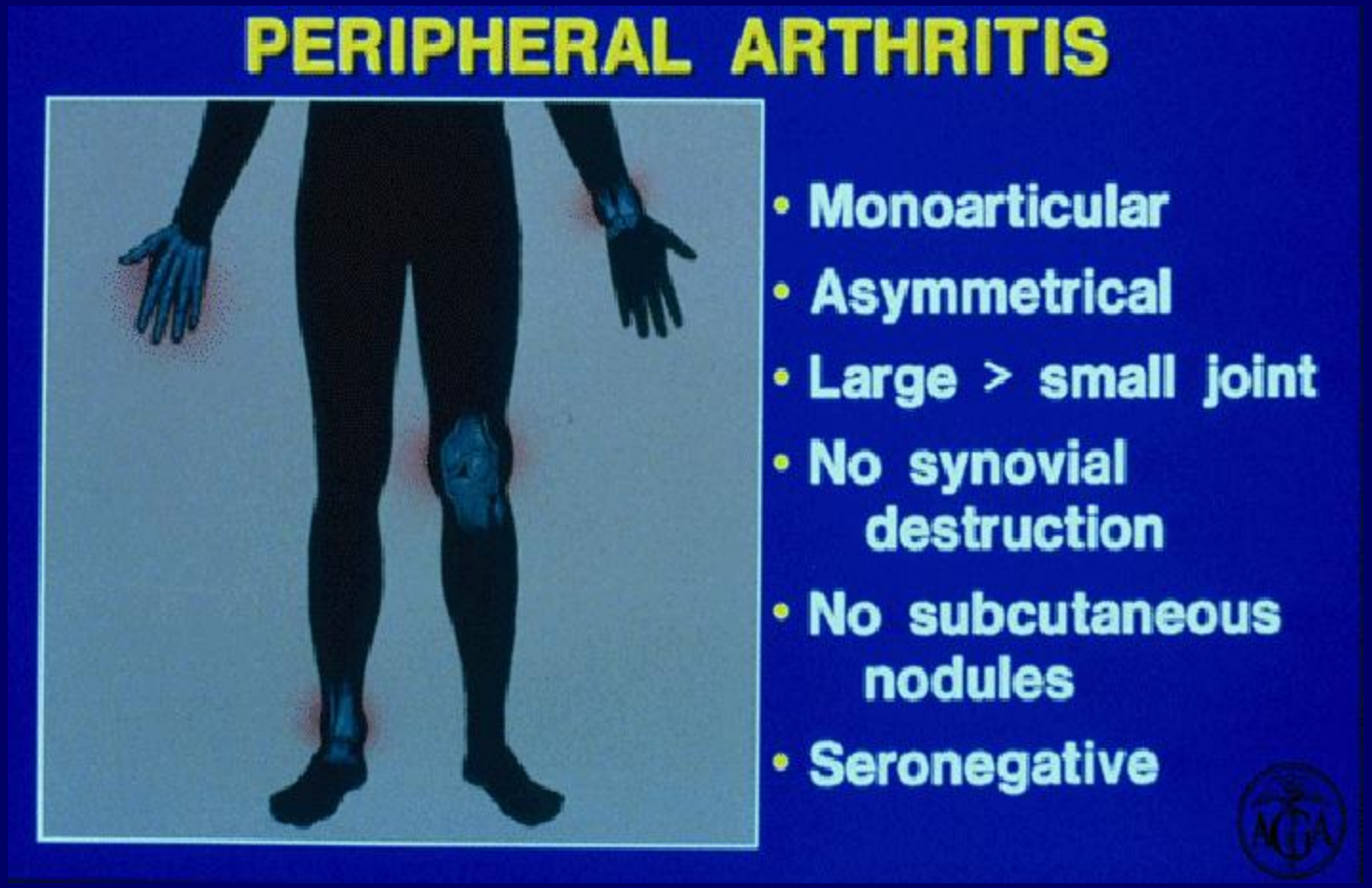
- 2 weeks
  - intermittent abdominal pain / vomiting
  - diarrhoea up to 12 times per day
  - weight loss and a skin rash over her shins
  - difficulty in walking due to a swollen knee

Rachel, 39 year old hairdresser





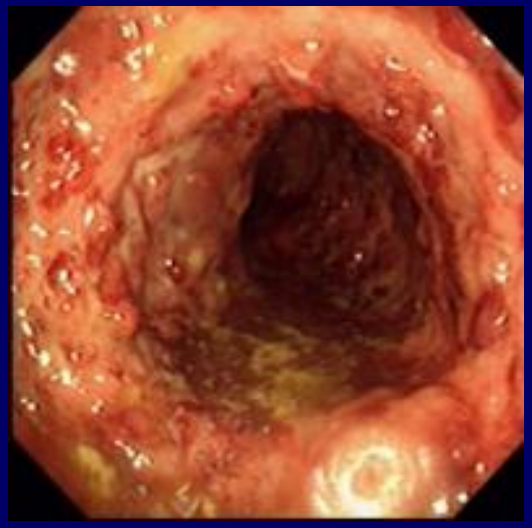
Rachel, 39 year old hairdresser

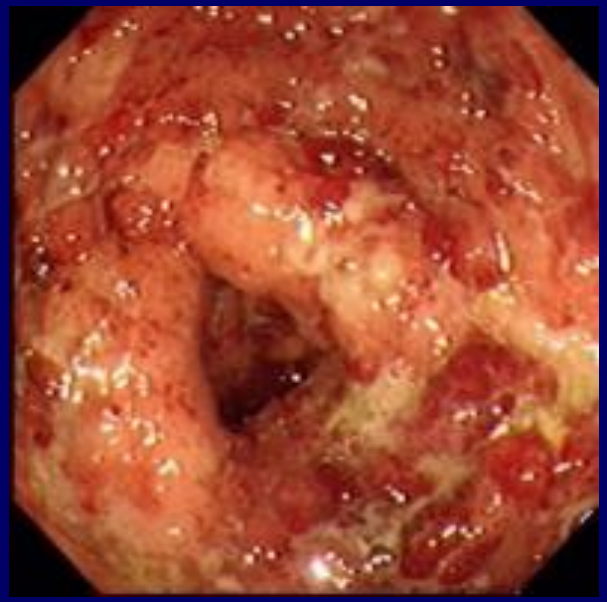


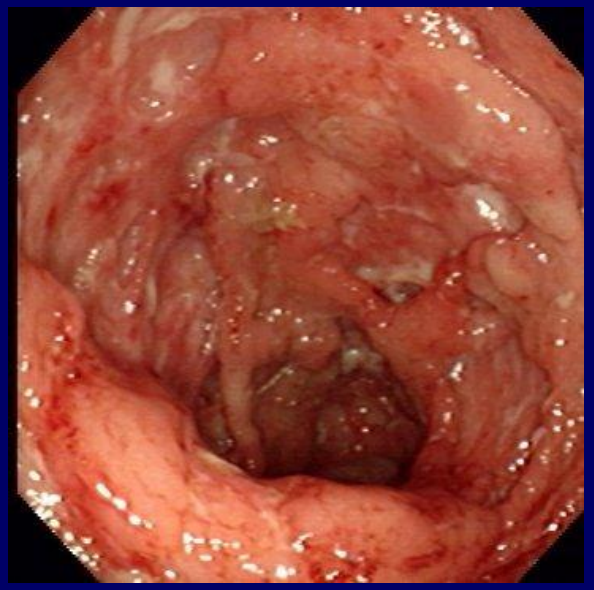
Rachel, 39 year old hairdresser

- 2 weeks
  - intermittent abdominal pain / vomiting
  - diarrhoea up to 12 times per day
  - weight loss and a skin rash over her shins
  - difficulty in walking due to a swollen knee
- Crohn's ileocolitis 6 months earlier
  - Pentasa and one course of steroids

Rachel, 39 year old hairdresser







Rachel, 39 year old hairdresser

- Flare of known ileocolitis
- What do you do next?

Rachel, 39 year old hairdresser

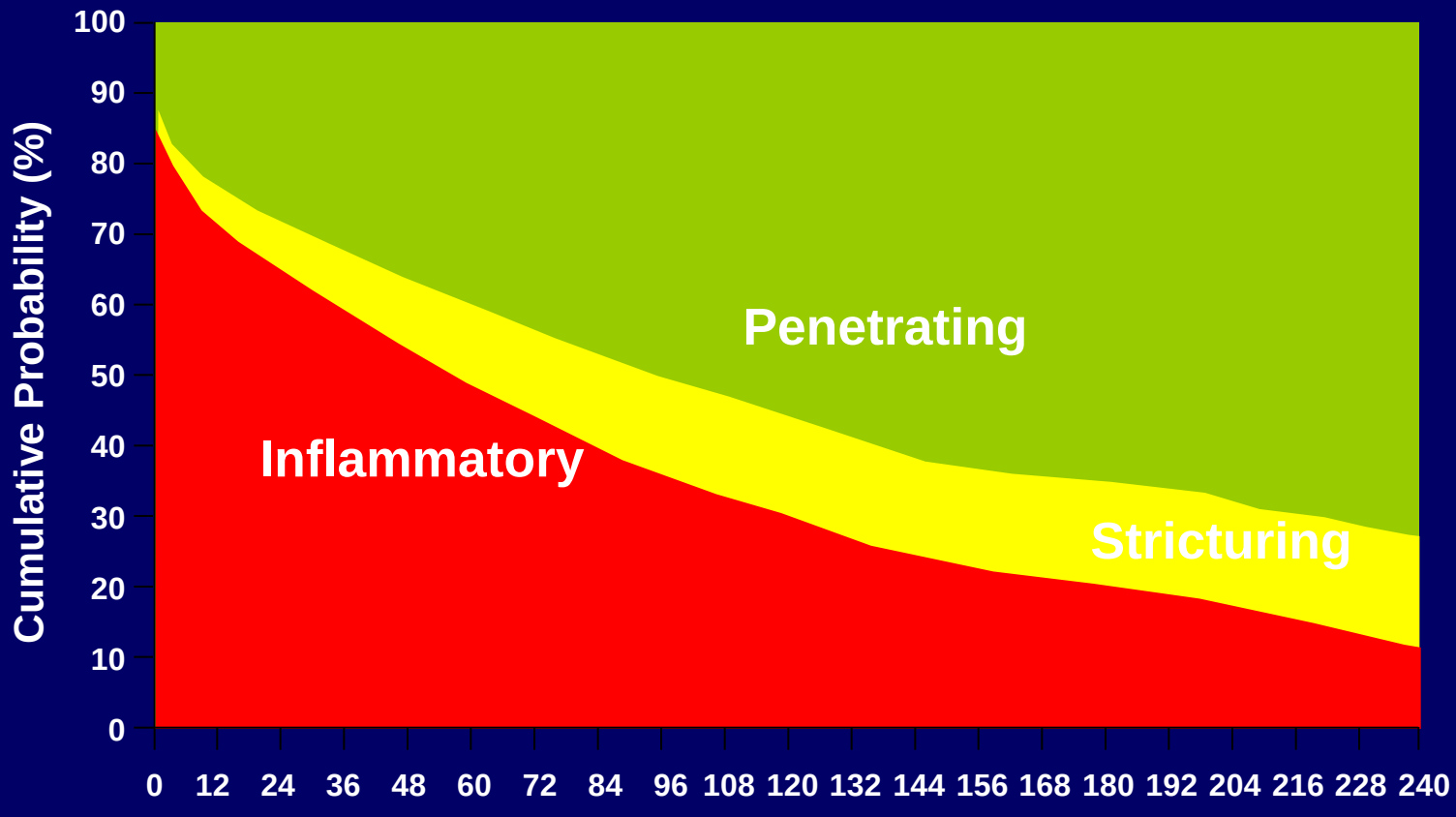
- Flare of known ileocolitis
- What do you do next?
- Investigations
  - Hb 105, MCV 84, Plat 557, CRP 78, Alb 33
  - Faecal culture negative
- Treatment
  - Prednisone started / refer to Gastroenterology

Rachel, 39 year old hairdresser

- Gastroenterology OP one week later
- Symptoms improving on Prednisone
- Discussion - ↑ maintenance treatment
- Azathioprine discussed …

Rachel, 39 year old hairdresser

- Why do we want to prevent flares?

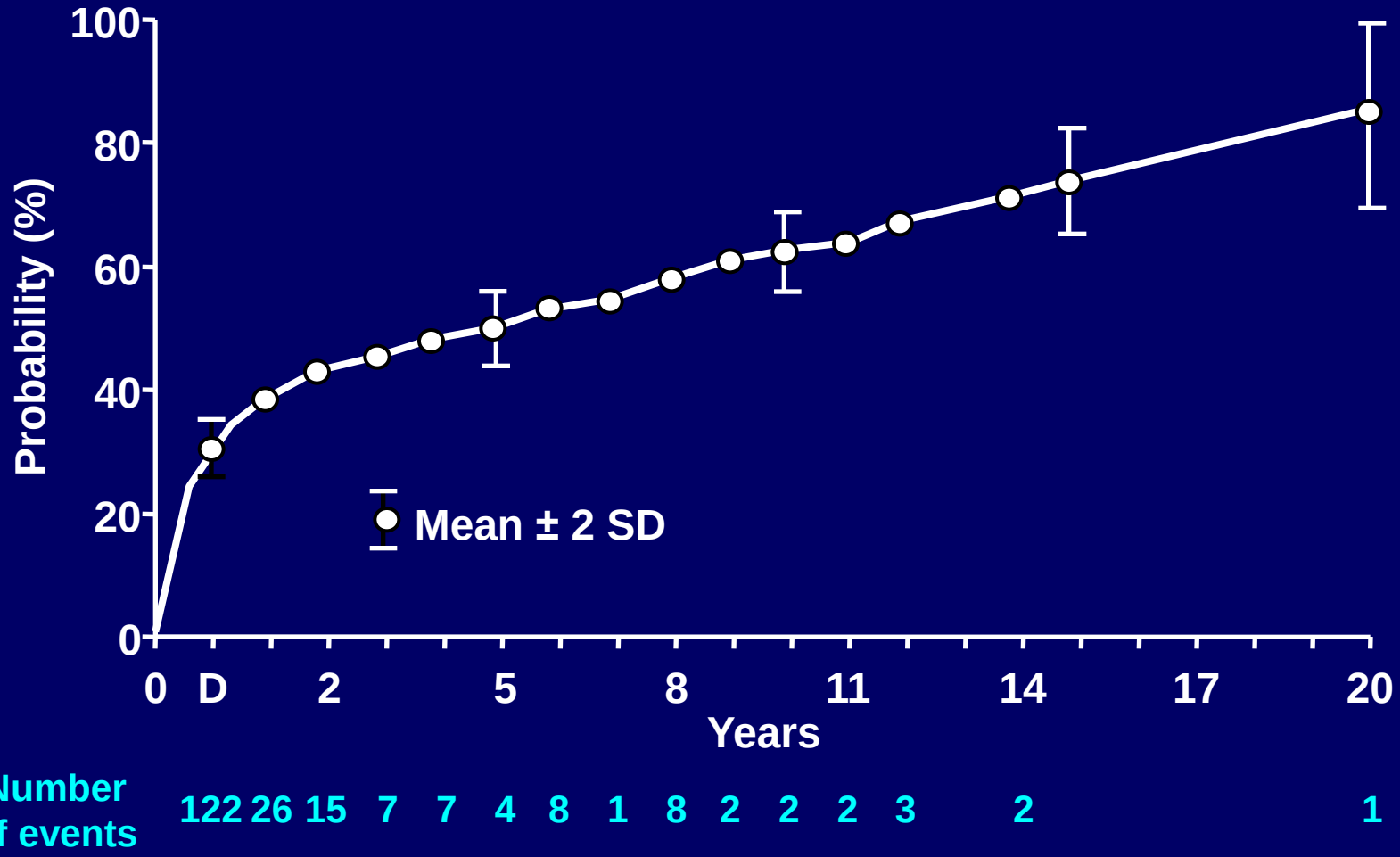


Patients at risk:

N=	**2002**	**552**	**229**	**95**	**37**

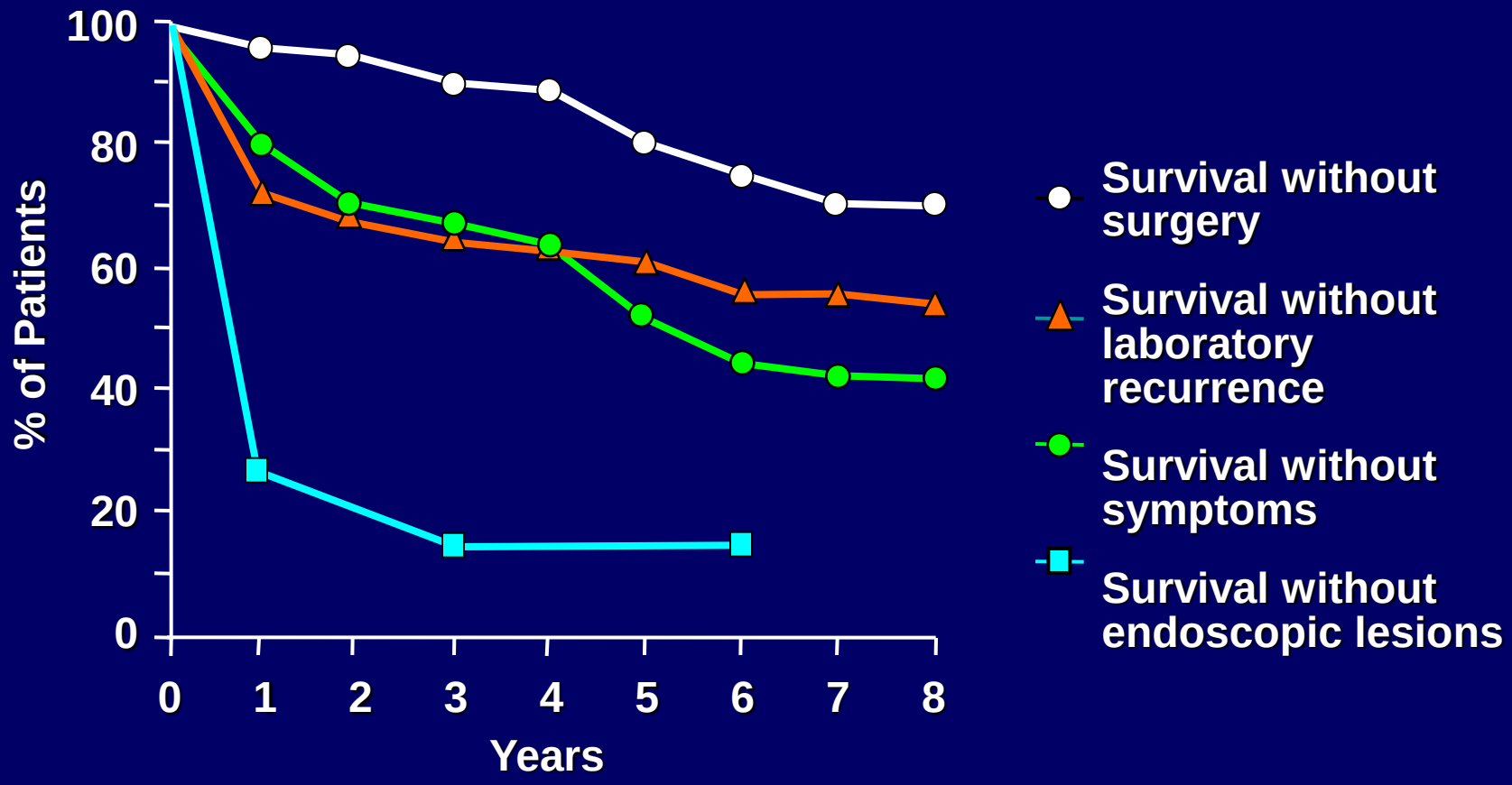
Cosnes et al. Inflamm Bowel Dis. 2002;8:244-250

Surgery is required in up to 80% of people with Crohn's



Munkholm et al. Gastroenterology. 1993;105:1716–1723.

Crohn's disease recurs after surgery



Rutgeerts et al. Gastroenterology. 1990;99:956–963

Rachel, 39 year old hairdresser

- Azathioprine for IBD
  - 2/3 of patients will respond
  - 3-6 months for full effect
  - ¼ patients will get a side effect → cessation
    - Nausea / vomiting
    - Abnormal LFTs
    - Bone marrow suppression
    - Rash
    - Arthralgia
  - Long term risks of skin cancer/lymphoma (rare)

Weekly FBC/LFTs for 1 month
Then three-monthly

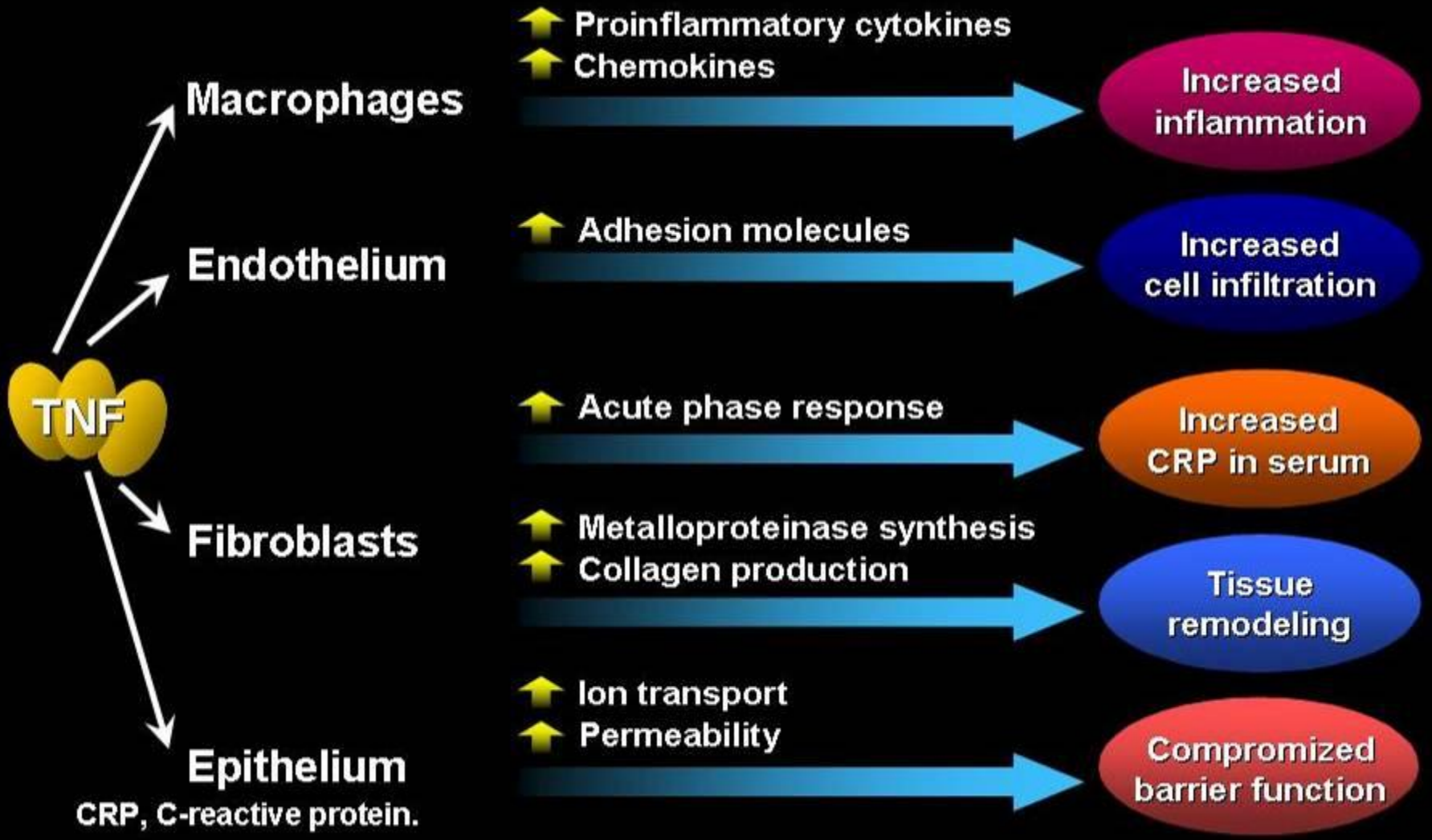
Rachel, 39 year old hairdresser

- Flare at Prednisone 10mg
- Further course of prednisone
- Flare at Prednisone 15mg

- Azathioprine metabolites measured
  - [6-TGN] 350 (therapeutic)

- Discussion regarding biologic therapy

Actions of TNF-α



CRP, C-reactive protein.

Anti-TNF-α Crohn's disease drugs

Chimeric monoclonal antibody

Infliximab

Human monoclonal antibody

Adalimumab

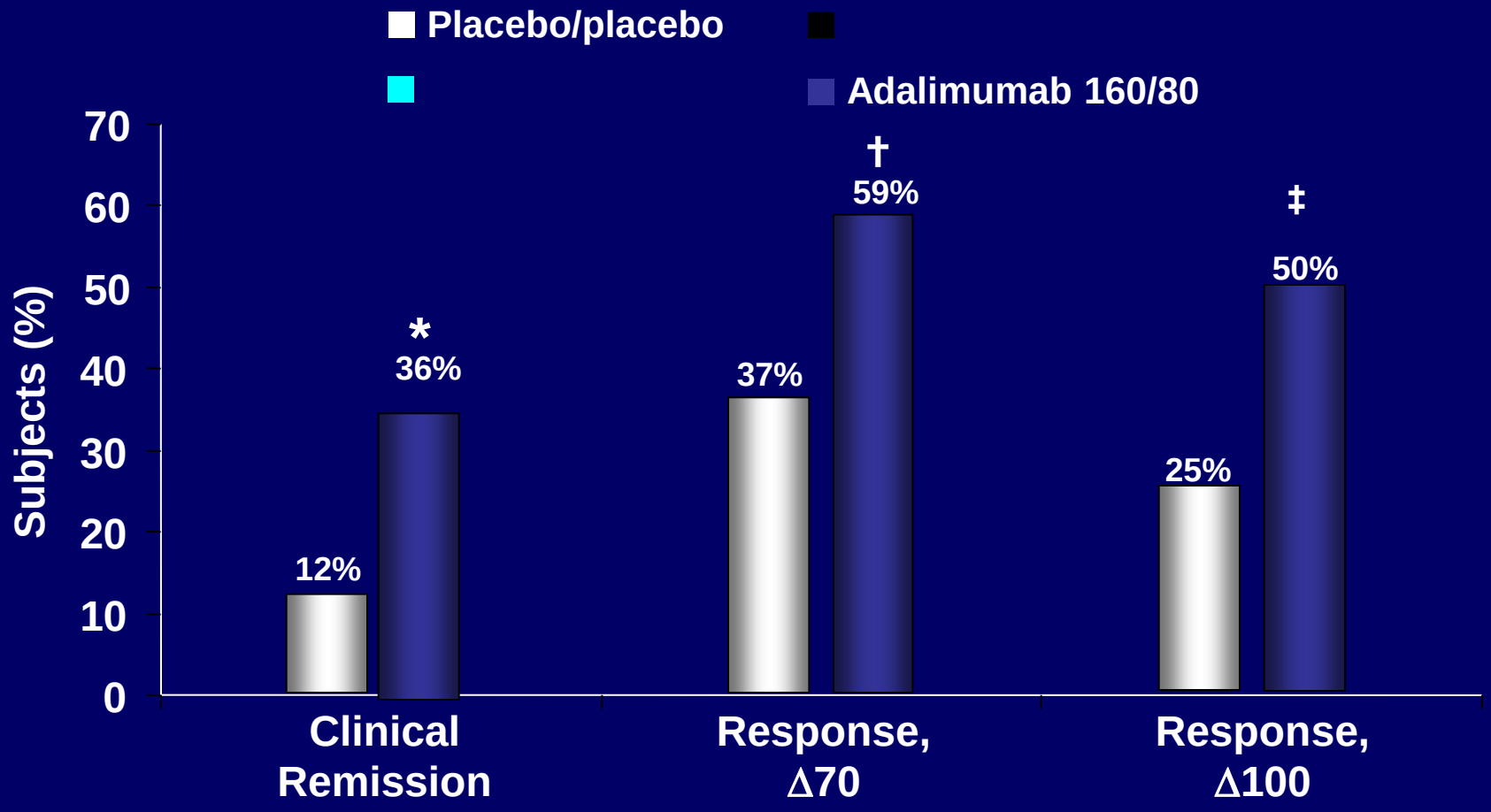
Humanized Fab′ fragment

Certolizumab pegol

Characteristics of anti-TNF-α drugs

	Infliximab	Adalimumab
Construction	25% murine	100% human
T1/2	7-10 days	12-14 days
Administration	IV infusion (2 hours)	Sub-cutaneous injection
Induction	5mg/kg weeks 0, 2, 6	160mg week 0, 80mg week 2
Maintenance	5mg/kg 8 weekly	40mg 2 weekly

CLASSIC I Trial: Results at Week 4

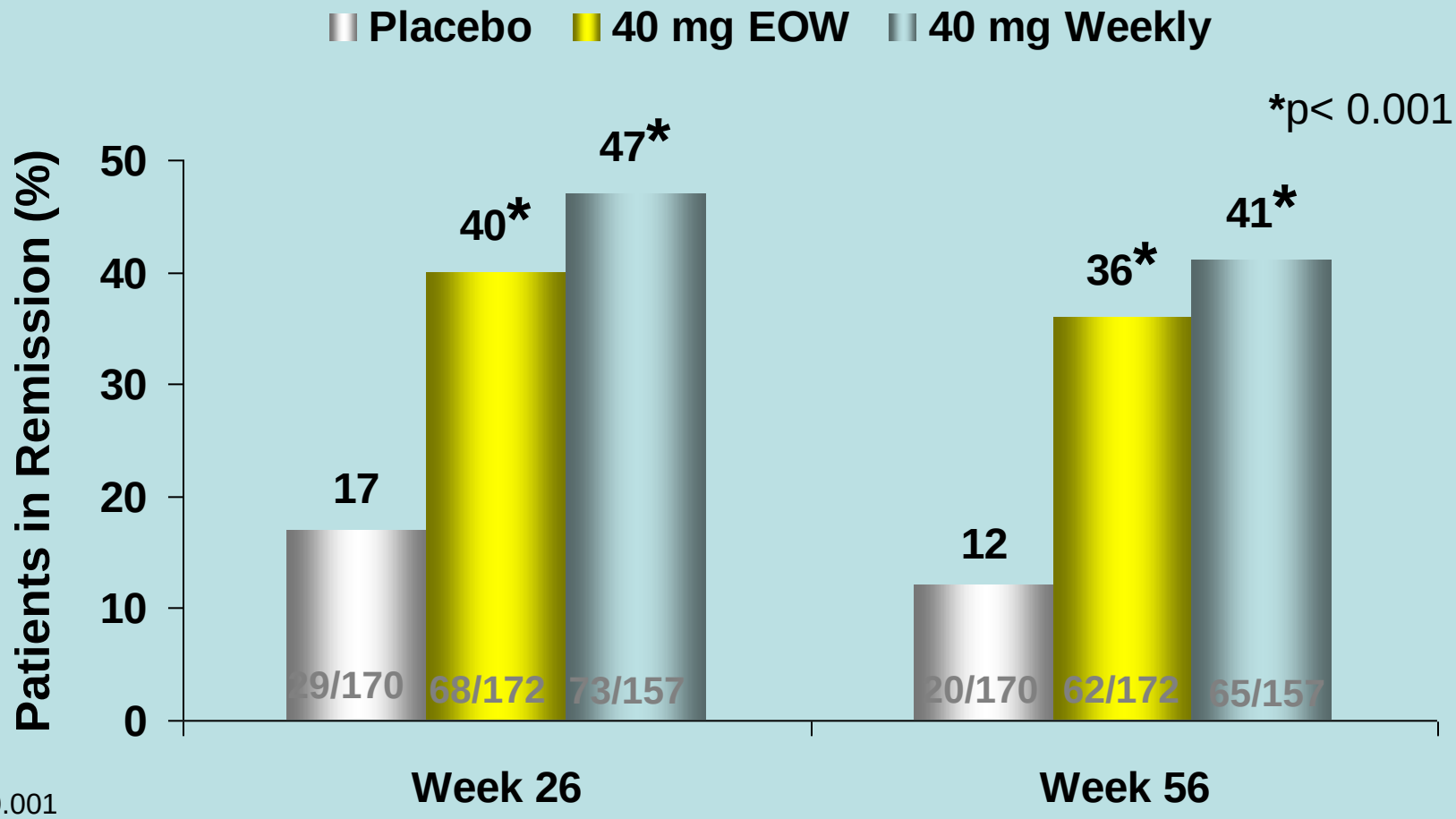


•p<0.05; † p=0.003; ‡ p=0.002

Clinical remission=CDAI<150

Hanauer et al, 2006

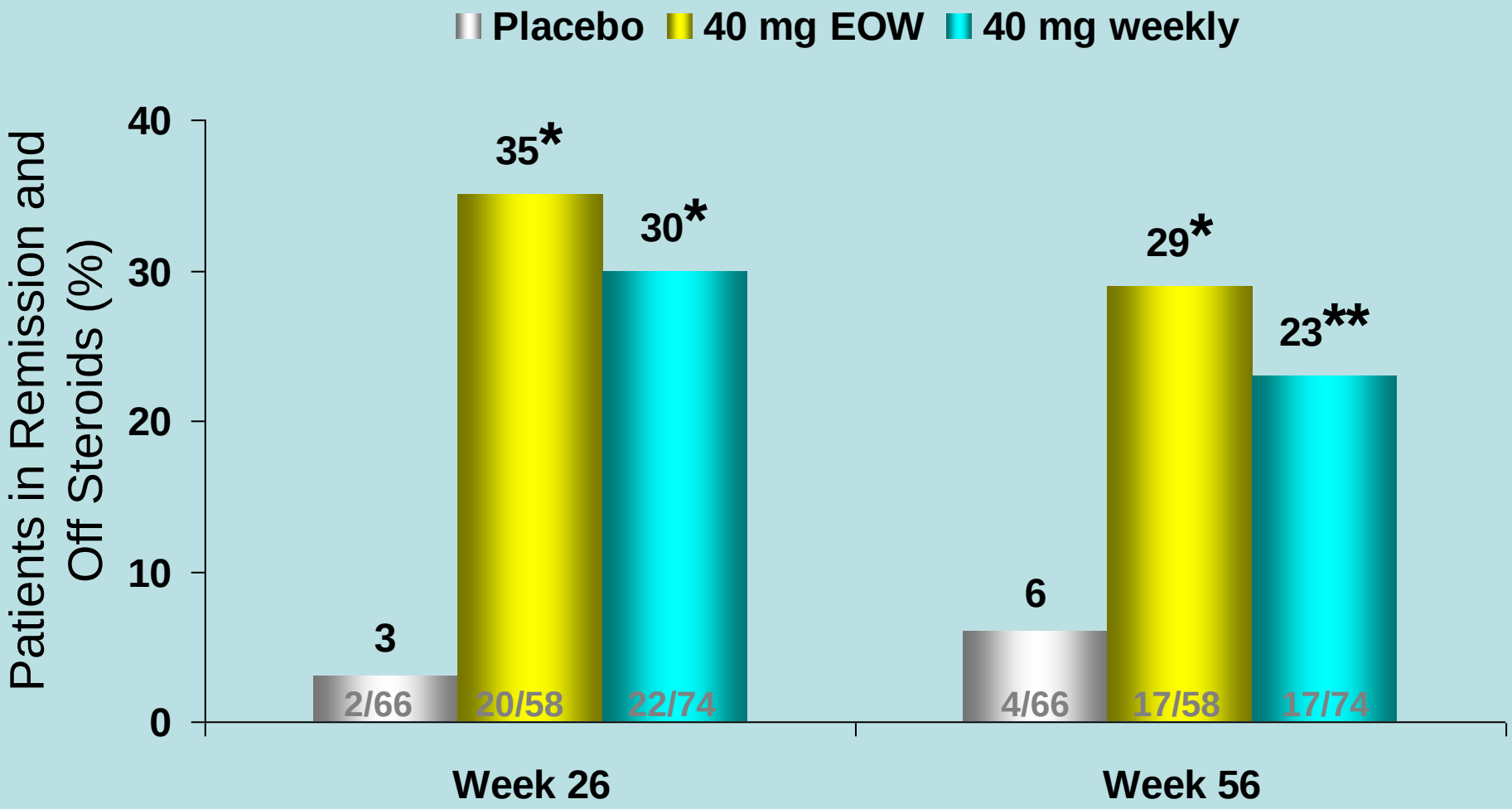
Clinical Remission at Weeks 26 and 56 Randomized Responders



*p<0.001

Colombel JF, et al. *Gastroenterol.* 2007;132 (1):52-65

90 Day Steroid-Free Remission at Weeks 26 and 56



*p<0.001; **p=0.008

Colombel JF, et al. *Gastroenterol.* 2007;132 (1):52-65

Access to biologic drugs in NZ

- Infliximab (Remicade)
  - DHB dependent → postcode prescribing
- Adalimumab (Humira)
  - PHARMAC criteria
  - Severe disease (CDAI >300)
  - Intolerant of / resistant to aza /mtx
  - Surgery is inappropriate
  - Reassess at 6 months to confirm response
  - Specialist only for first prescription / GP thereafter

Biologic Safety
Infections

- Increasing immunosuppression = increasing risks
- Tb
  - 2001 / USA 70 cases reported to FDA
  - 2003 / Spain 50-90X ↑ risk
  - 2005 / Sweden 4X ↑ risk
  - 2004 / USA 8X ↑ risk
  - Most cases occur in countries of low Tb incidence
- Quantiferon gold / CXR before commencing

Risk of serious infections

TREAT Registry

	OR	95% CI
Current use of narcotic analgesics	2.38	1.56–3.63***
Current use of corticosteroids	2.21	1.46–3.34***
Current use of infliximab	0.979	0.619–1.547
Current use of 6-MP / AZA / MTX	0.780	0.507–1.198

***p<0.001

Lichtenstein et al, Clin Gastroenterol Hepatol 2006; 4: 621

Increasing immunosuppression and infections

- 100 cases IBD + opportunistic infection
- 200 controls IBD

Table 4. Association Between Use of Specific Medications and Odds for Opportunistic Infection

Medication	OR (95% CI)[a]	*P* value[b]
Any medication[c]	3.9 (2.2–6.9)	<.001
No medications	1.0 (reference)	
Mesalamine	1.0 (0.6–1.6)	.94
No mesalamine	1.0 (reference)	
Corticosteroids	3.3 (1.8–6.1)	<.001
No corticosteroids	1.0 (reference)	
AZA/6MP	3.8 (2.0–7.0)	<.001
No AZA/6MP	1.0 (reference)	
Methotrexate	4.0 (0.4–45)	.26
No methotrexate	1.0 (reference)	
Infliximab	4.4 (1.1–17)	.03
No infliximab	1.0 (reference)	

Increasing immunosuppression & infections

- 100 cases IBD + opportunistic infection
- 200 controls IBD

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Any medication[c]	3.9 (2.2–6.9)	<.001
No medications	1.0 (reference)	
Mesalamine	1.0 (0.6–1.6)	.94
No mesalamine	1.0 (reference)	
Corticosteroids	3.3 (1.8–6.1)	<.001
No corticosteroids	1.0 (reference)	
AZA/6MP	3.8 (2.0–7.0)	<.001
No AZA/6MP	1.0 (reference)	
Methotrexate	4.0 (0.4–45)	.26
No methotrexate	1.0 (reference)	
Infliximab	4.4 (1.1–17)	.03
No infliximab	1.0 (reference)	

Toruner et al. Gastroenterology 2008;134:929-936

Increasing immunosuppression and infections

- 100 cases IBD + opportunistic infection
- 200 controls IBD

	Odds Ratio (95% CI)	p value
1 medication	2.9 (1.5–5.3)	0.001
2-3 medications	14.5 (4.9-43)	<0.001

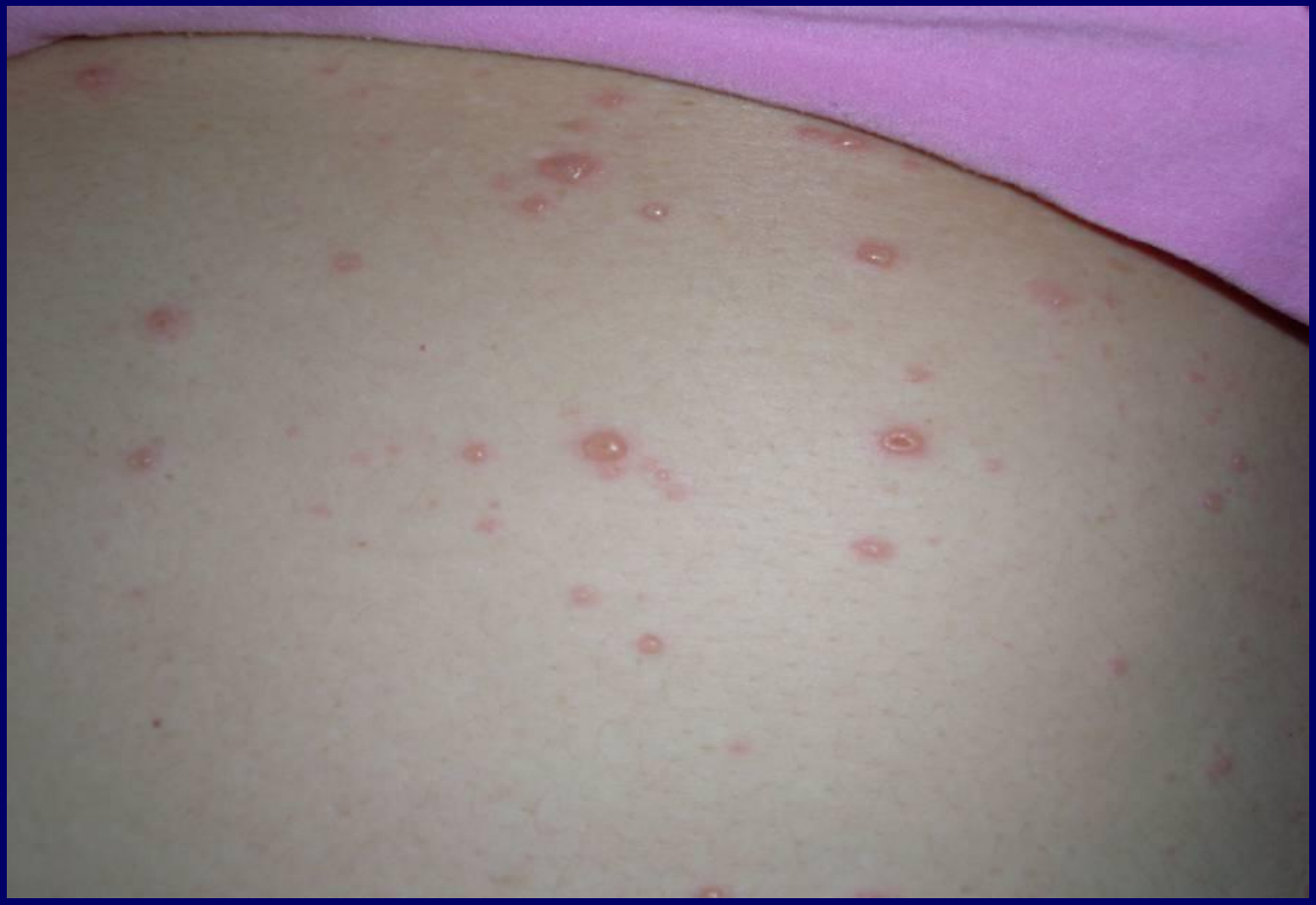
Toruner et al. Gastroenterology 2008;134:929-936

Local experience

- 6 Australian / NZ IBD clinics
  - 5613 patients
  - 600 exposed to biologics
- 9 serious infections (all receiving IM)
  - 2X primary Varicella infections
  - 1X pneumocystis pneumonia
  - 1X enterobacteraerogenes UTI
  - 5X no organism found
- All successfully treated

Lawrance, Gearry et al, 2010

Primary Varicella Infection



CD patients failing therapy

- Repeated courses of steroids are unacceptable
  - Halt the progression to strictures / fistulae / surgery
  - Refer for immunomodulators / biologics
- Patients on immunomodulators / biologics are at an increased risk of infections but not that much

CD Failing Treatment Questions?

John – 53 year old carpenter

- Diagnosed with UC 23 years ago
- Chronic poorly controlled symptoms
  - Diarrhoea 3-4X/day
- Recently found to have abnormal LFTs
- Presents with rectal bleeding

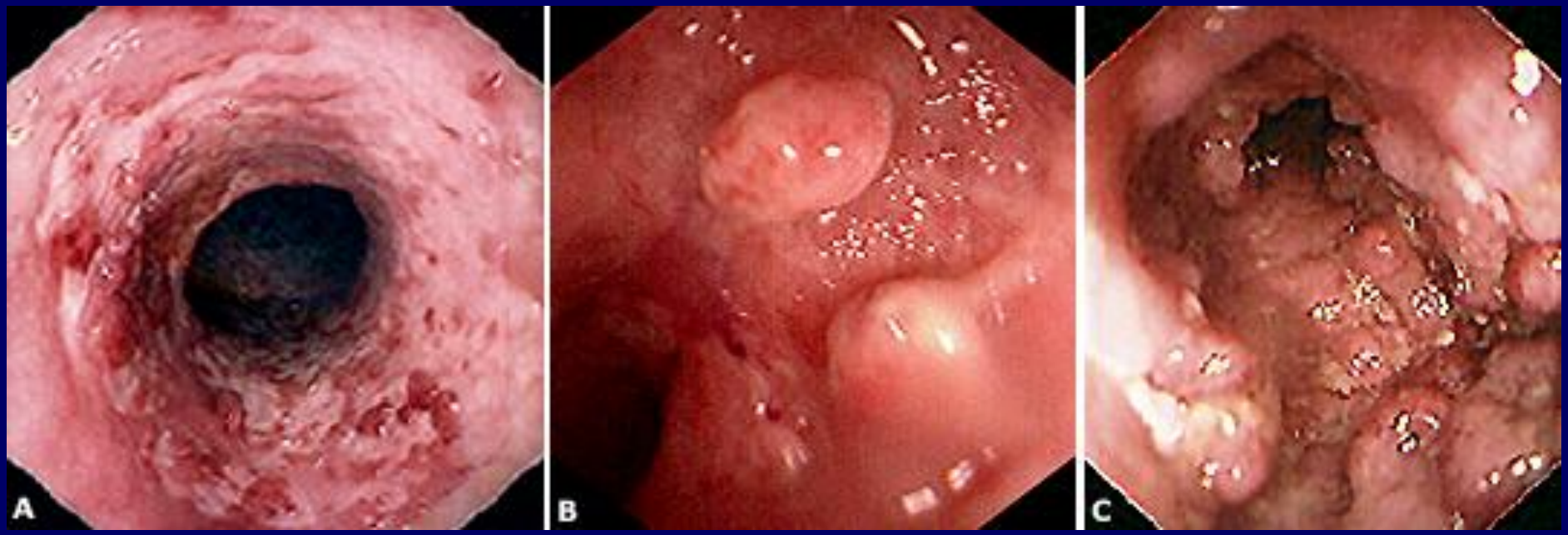
John – 53 year old carpenter

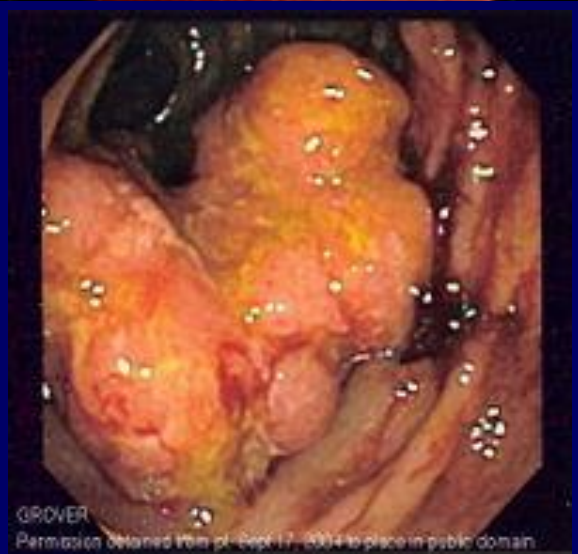
- What are the potential causes of this man's symptoms?
  - Flare of UC
  - Intercurrent infection
  - Colorectal cancer

John – 53 year old carpenter

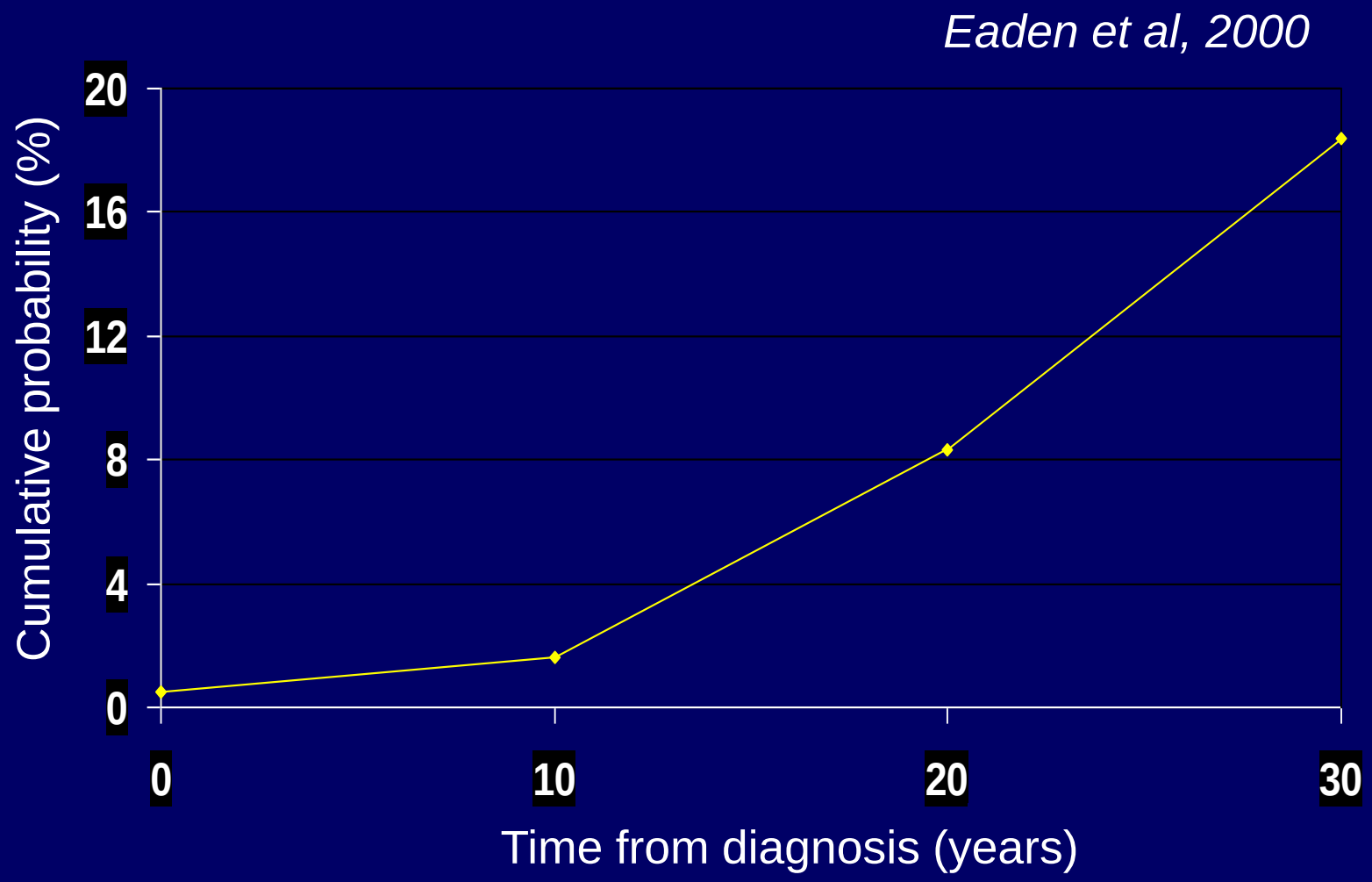
- How would you investigate this further?
  - Faecal specimen (M/C/S)
  - FBC, CRP, LFTs
  - Biliary imaging
  - Colonoscopy

John – 53 year old carpenter





Cumulative probability of developing CRC for UC patient



Strategies to reduce colorectal cancer

- Controlling disease activity
- Surveillance colonoscopy
- Increased risk
  - Primary sclerosing cholangitis
  - Family history of colorectal cancer
  - Yound diagnosis age
  - Pancolitis v proctitis

Sean – 22 year old lawyer

- 4/12 non specific abdominal pain
  - Increasing severity
  - Localising to right iliac fossa
  - 4 loose bowel motions/day
  - Associated nausea and anorexia
  - 2/52 off work
- Smoker 12 cigarettes / day
- Childhood asthma

Sean – 22 year old lawyer

- What could be causing this man's symptoms?
  - Appendicitis
  - Mesenteric adenitis
  - Crohn's disease
  - Irritable bowel syndrome
  - Infectious diarrhoea
  - Drugs (eg NSAIDs)
  - Ischaemia (if older)

Sean – 22 year old lawyer

- What other history would you ask about?
  - HPC
    - Fever, skin / eye / joint problems, perianal dis / mouth ulcers
  - Drugs
    - NSAIDs, antibiotics
  - PMedHX
    - Perianal abscesses
  - FamHX
    - IBD, colorectal cancer, coeliac disease, autoimmune disease

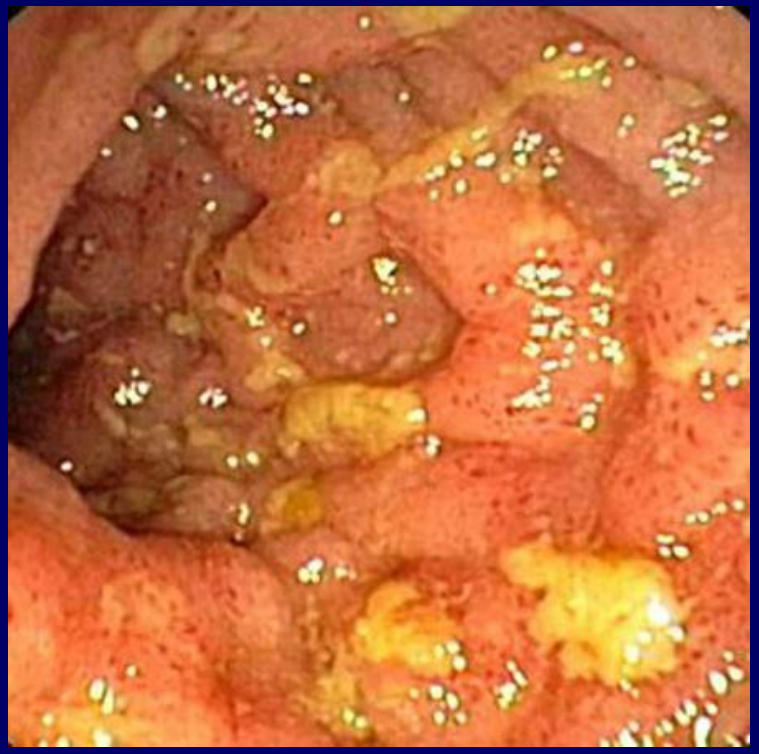
Sean – 22 year old lawyer

- What basic tests would you request?
  - Faecal sample
    - M/C/S, C diff toxin, parasites (if at risk)
    - Negative
  - Bloods
    - FBC — Hb 118, MCV 81, WCC 13 (N ↑)
    - CRP — 65
    - Electrolytes — Normal
    - LFTs — Albumin 31, otherwise normal

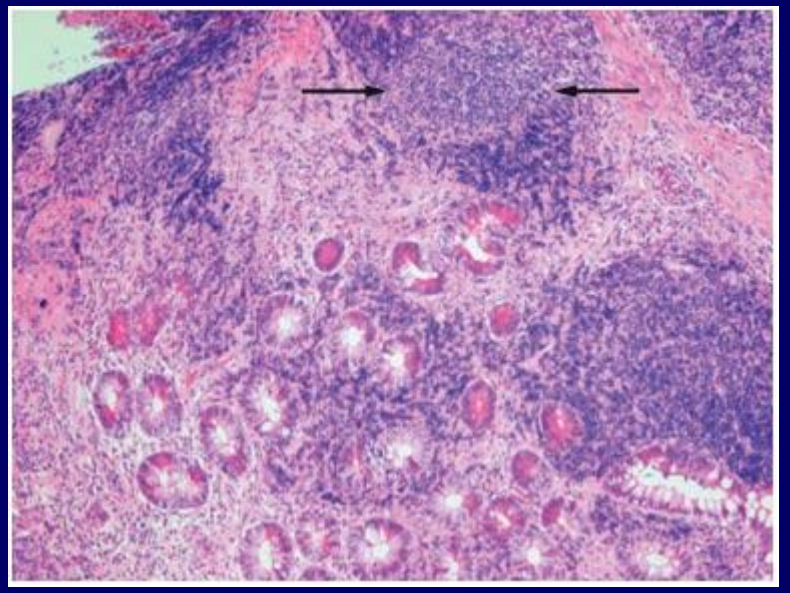
Sean – 22 year old lawyer

- Sean is referred to a Gastroenterologist who performs a colonoscopy
- Mild inflammation in the colon, more severe inflammation and ulceration in the TI
- Histology is consistent with Crohn's disease
- Further tests
  - Ferritin 24, Fe 4, Transferrin Saturation 23%
  - Red cell folate 180, B12 90

Sean – 22 year old lawyer



Ileal biopsy (H&E stain)



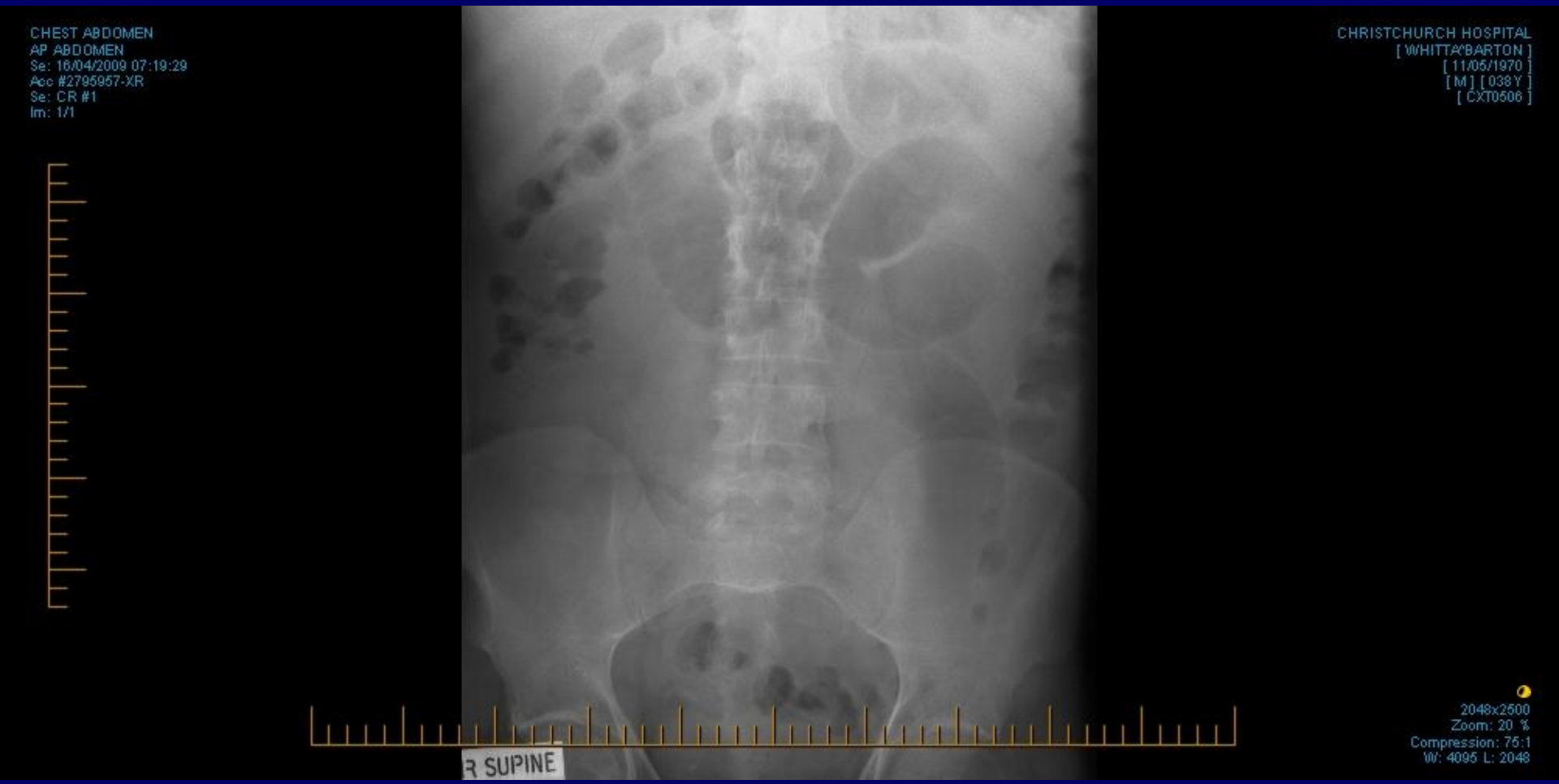
Sean – 22 year old lawyer

- Crohn's ileocolitis
- Smoker
  - Iron, B12, Folate deficient
- Treatment
  - Smoking cessation
  - Replace Fe, B12, Folate
  - Induce remission – prednisone / 5-ASA
  - Maintain remission – consider azathioprine

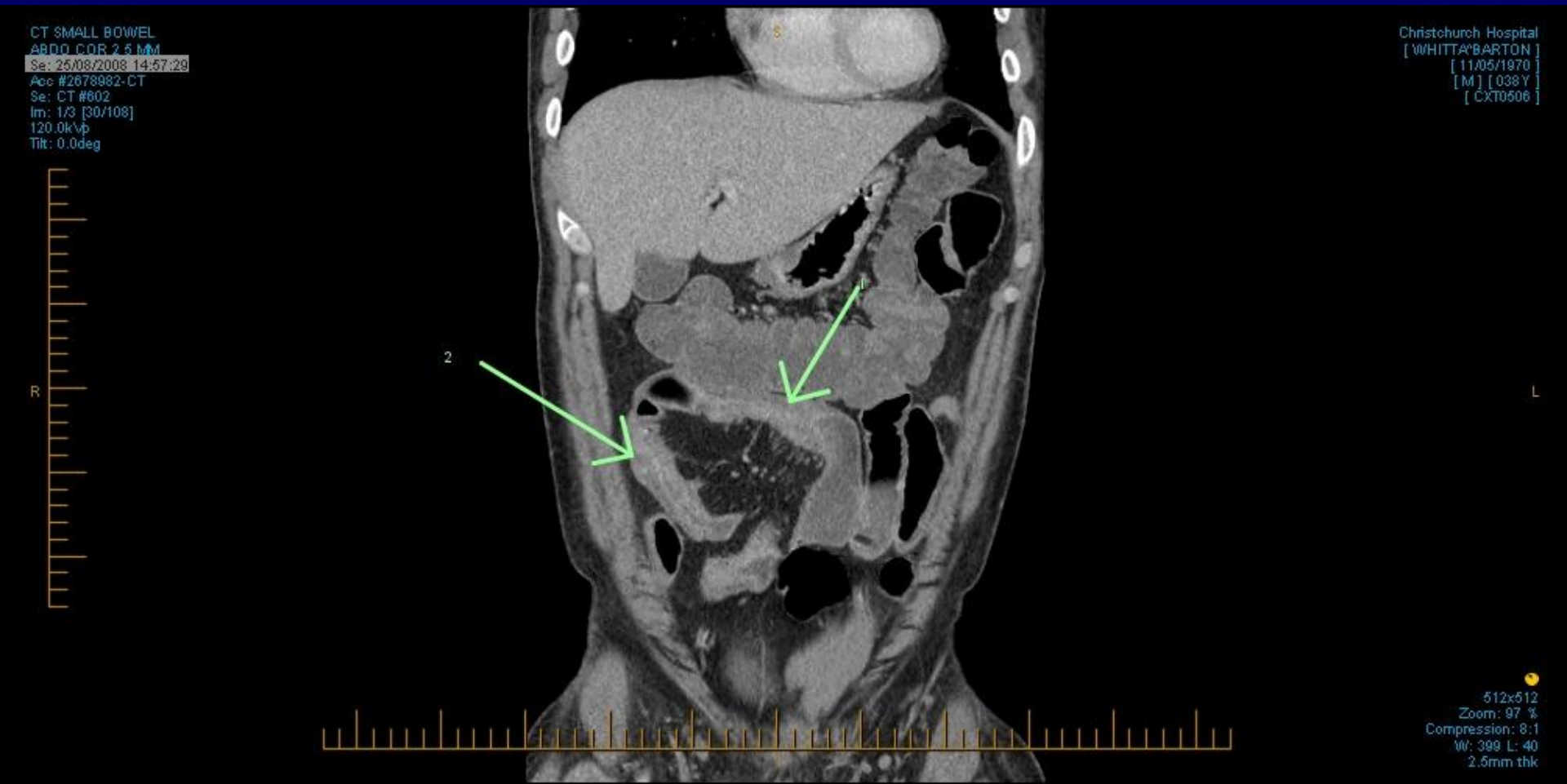
Sean – 22 year old lawyer

- 3 months later
  - ↑ abdominal pain, nausea and vomiting
- Plain abdominal Xray
- CT scan

Plain Abdominal Xray



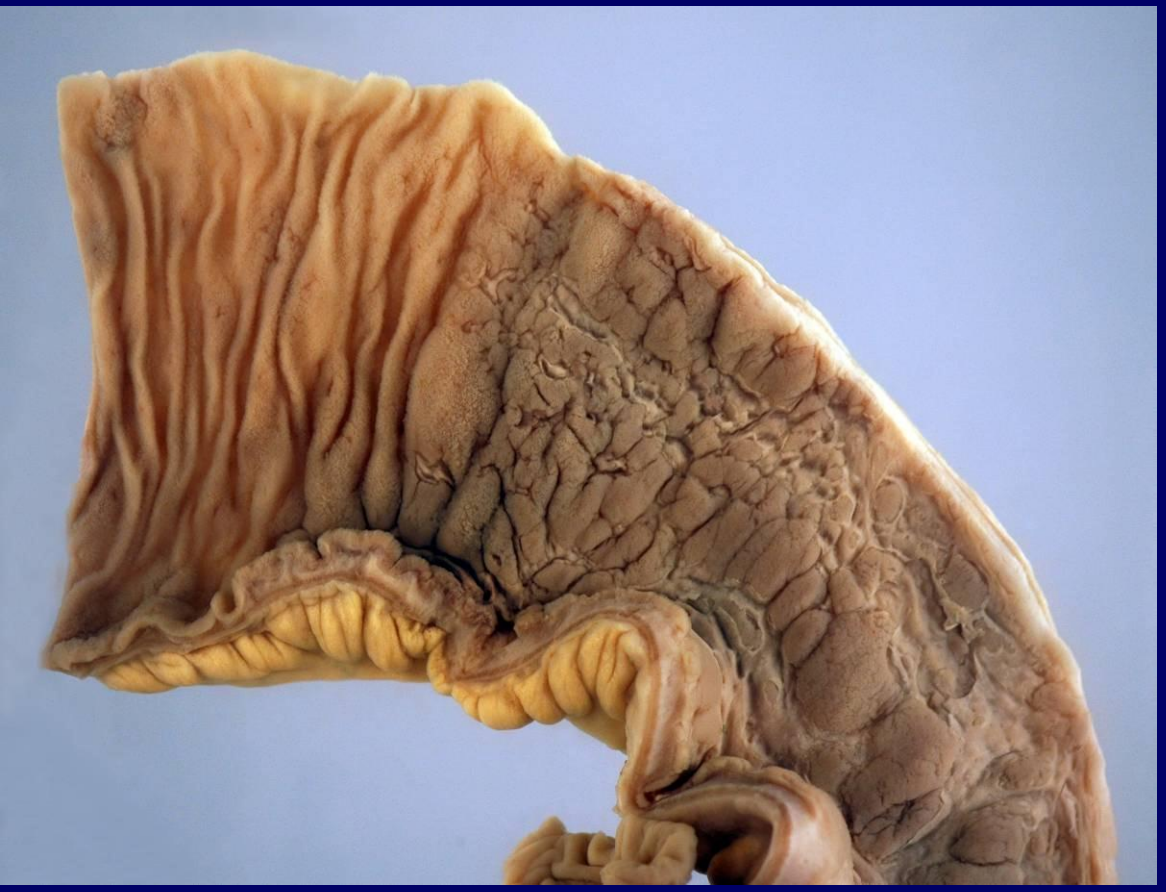
CT Small Intestine

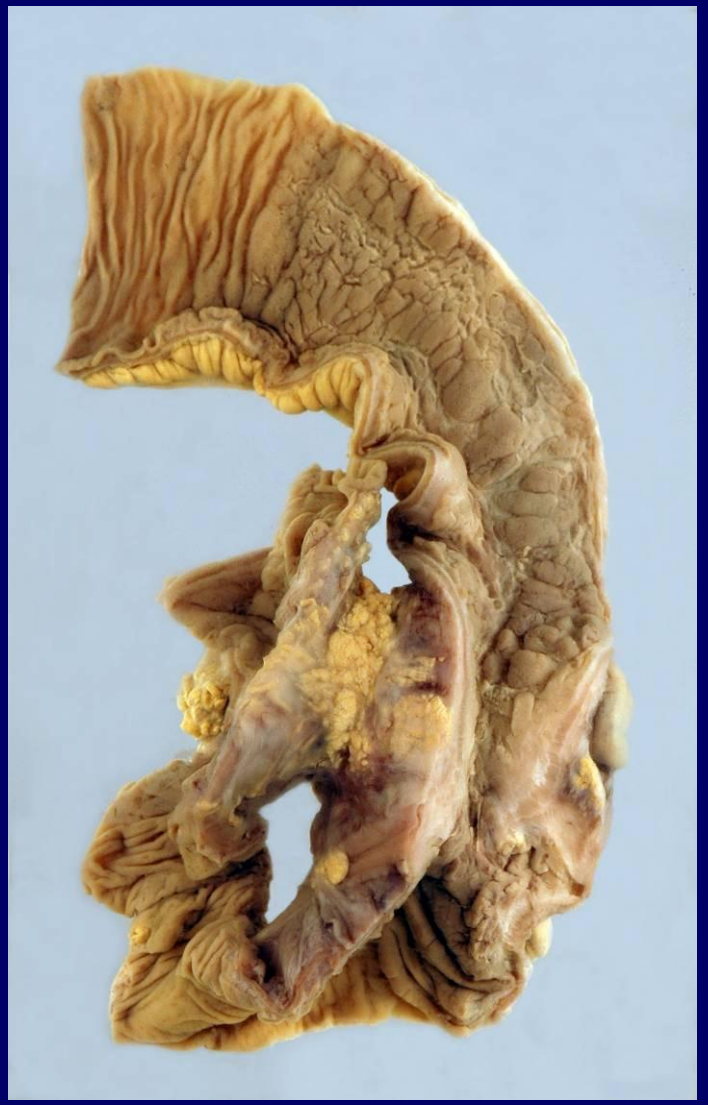


Operation

- Right hemicolectomy / stricturoplasties
- Surgical specimen
- Histology

Surgical specimen

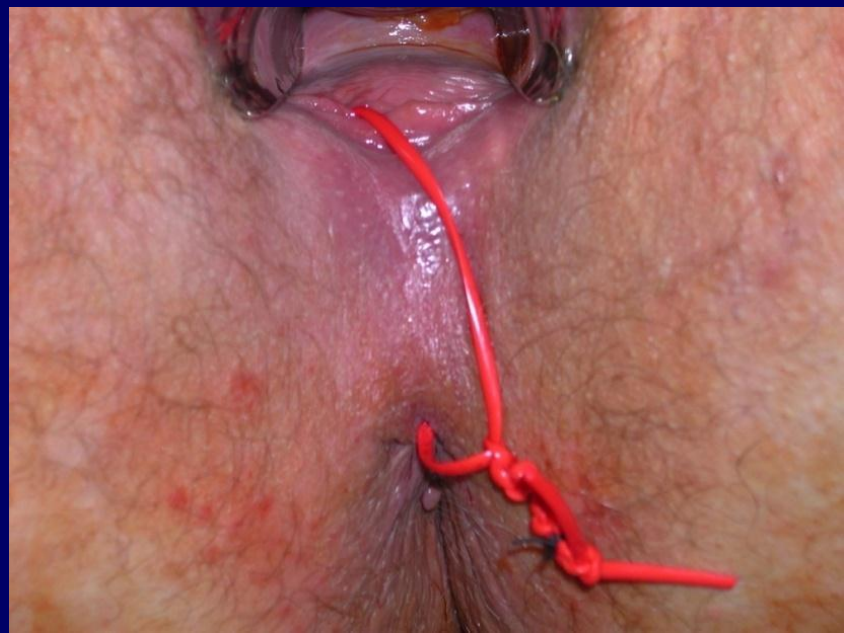




Random Practice Points

Perianal Crohn's disease

- Affects ~20% of CD patients
- May occur before CD diagnosed
- Flagyl/ciprofloxacin for minor infection
- Surgeons needed to drain infection
- IM may help but biologics best for healing



Monitoring IBD Drugs

Drug	Test	Frequency
5-ASA	Cr, Dipstick	6 monthly
Aza / 6MP / MTX	FBC / LFT	3 monthly
Steroids	Bone Min Dens	Don’t forget!

Long term complications