The ABCs of IBD

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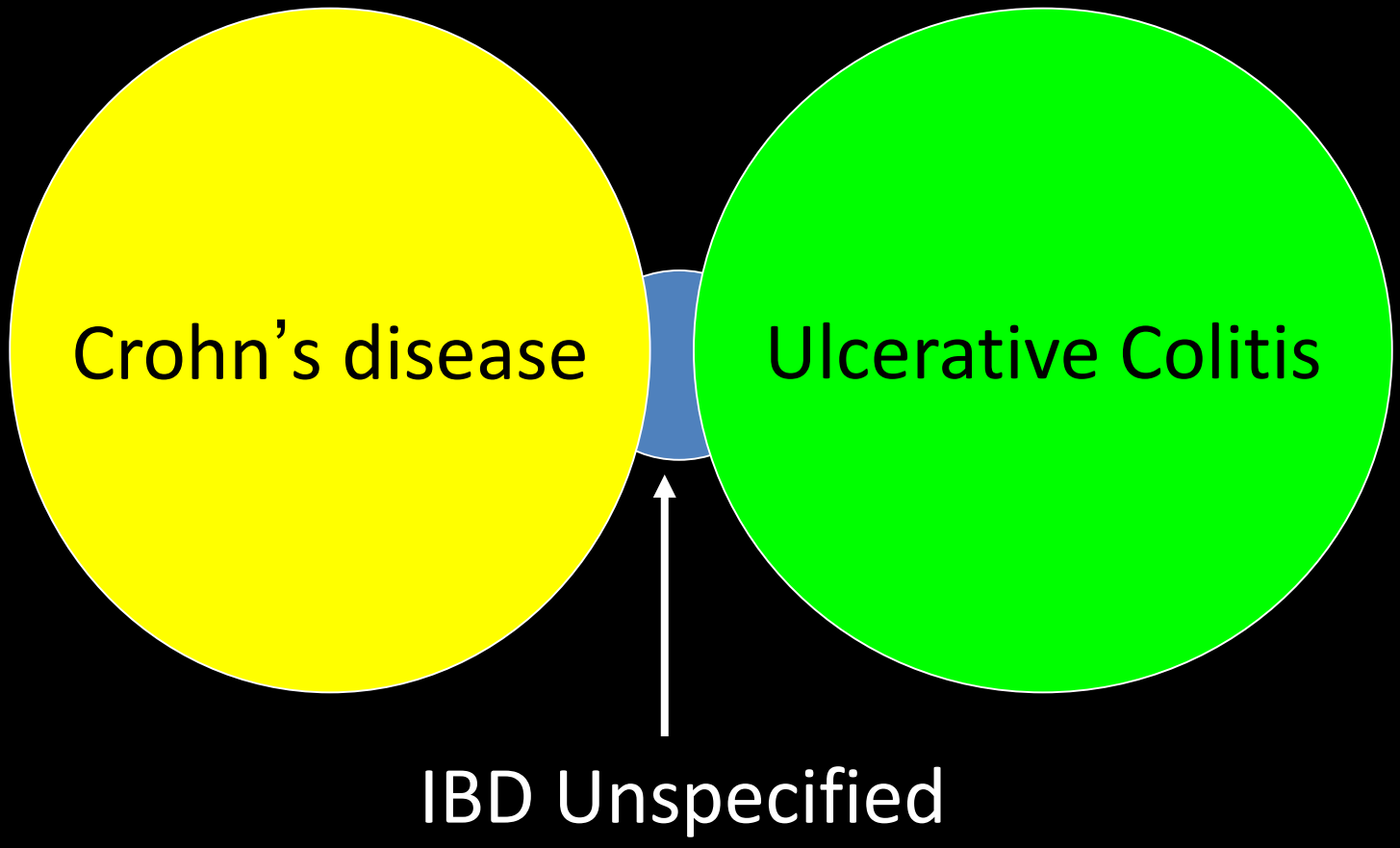
Professor of Medicine

Overview

- What is IBD?
- How common is IBD / who gets it?
- Why do people get IBD?
- How do we diagnose IBD?
- How do we treat IBD?
- What are the complications of IBD?
- What does the future hold?
- Areas of controversy

What is IBD?

Inflammatory Bowel Disease



The Gastrointestinal Tract

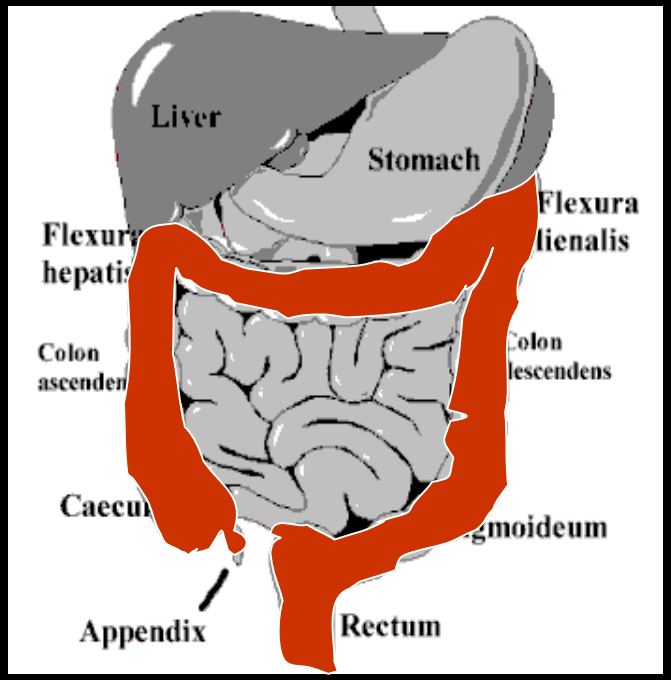
Crohn's disease

Any part of the GI tract

Patchy inflammation

Inflammation affects full thickness of intestine

Perianal disease



Ulcerative Colitis

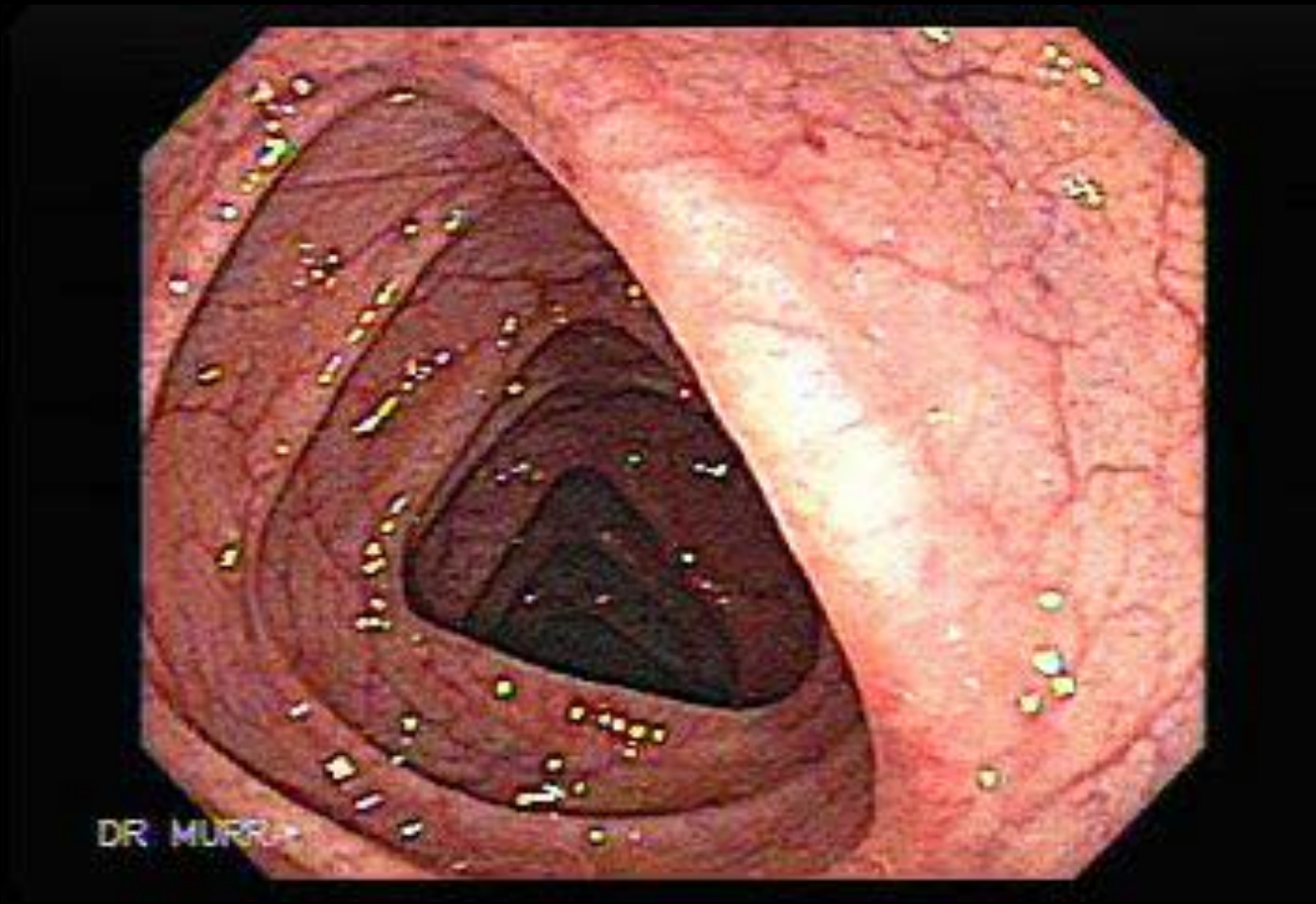
Colon only

Continuous inflammation

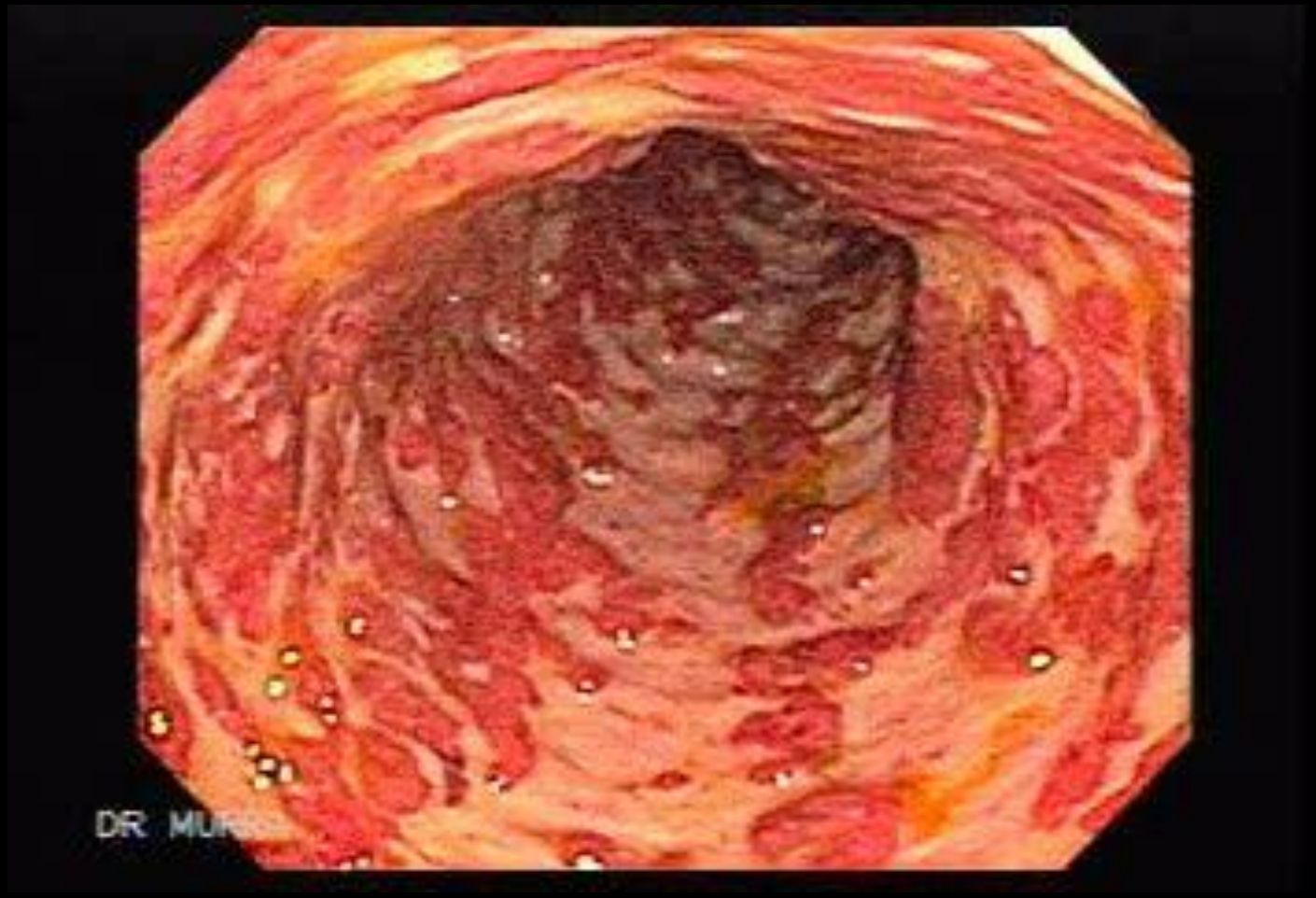
Inflammation starts at the bottom and moves proximally

Inflammation affects inner lining of bowel only (mucosa)

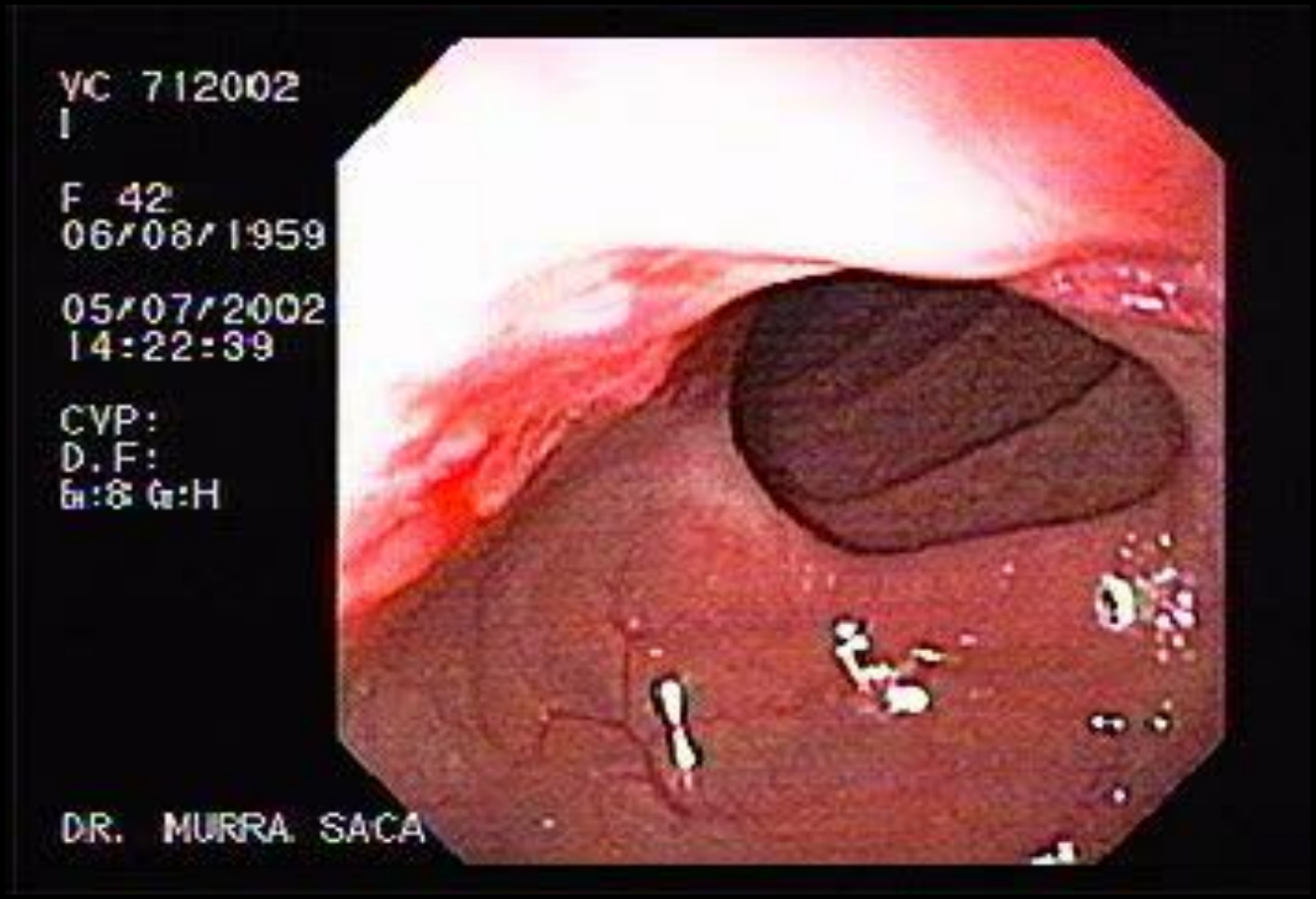
Normal colonoscopy



Severe ulcerative colitis



Crohn’s disease

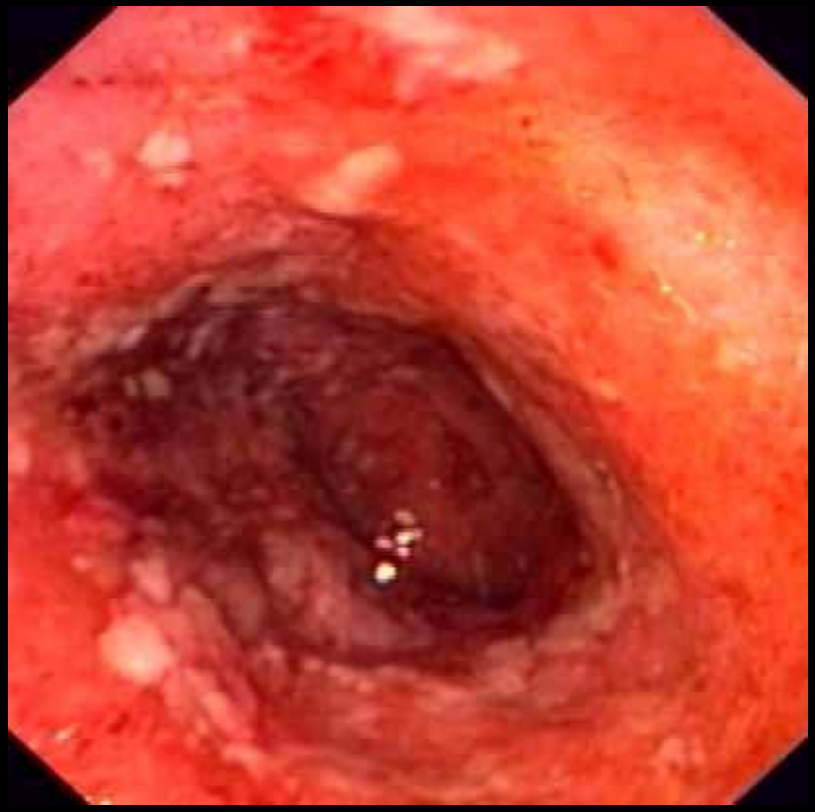


Inflammatory Bowel Disease

Abdominal Pain

Diarrhoea

Rectal Bleeding



Weight Loss

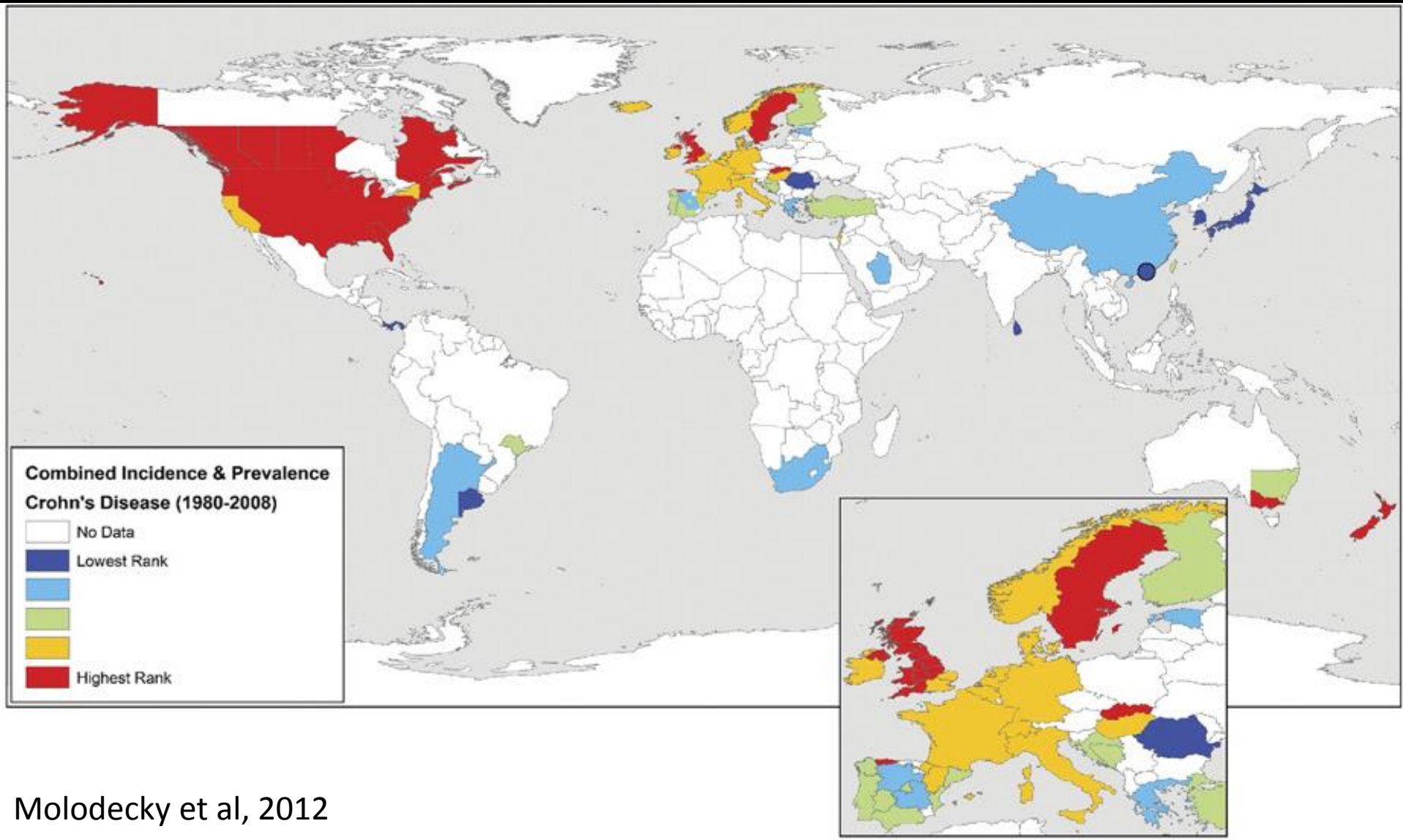
Medication/ Surgery

Colorectal Cancer

Normal v IBD

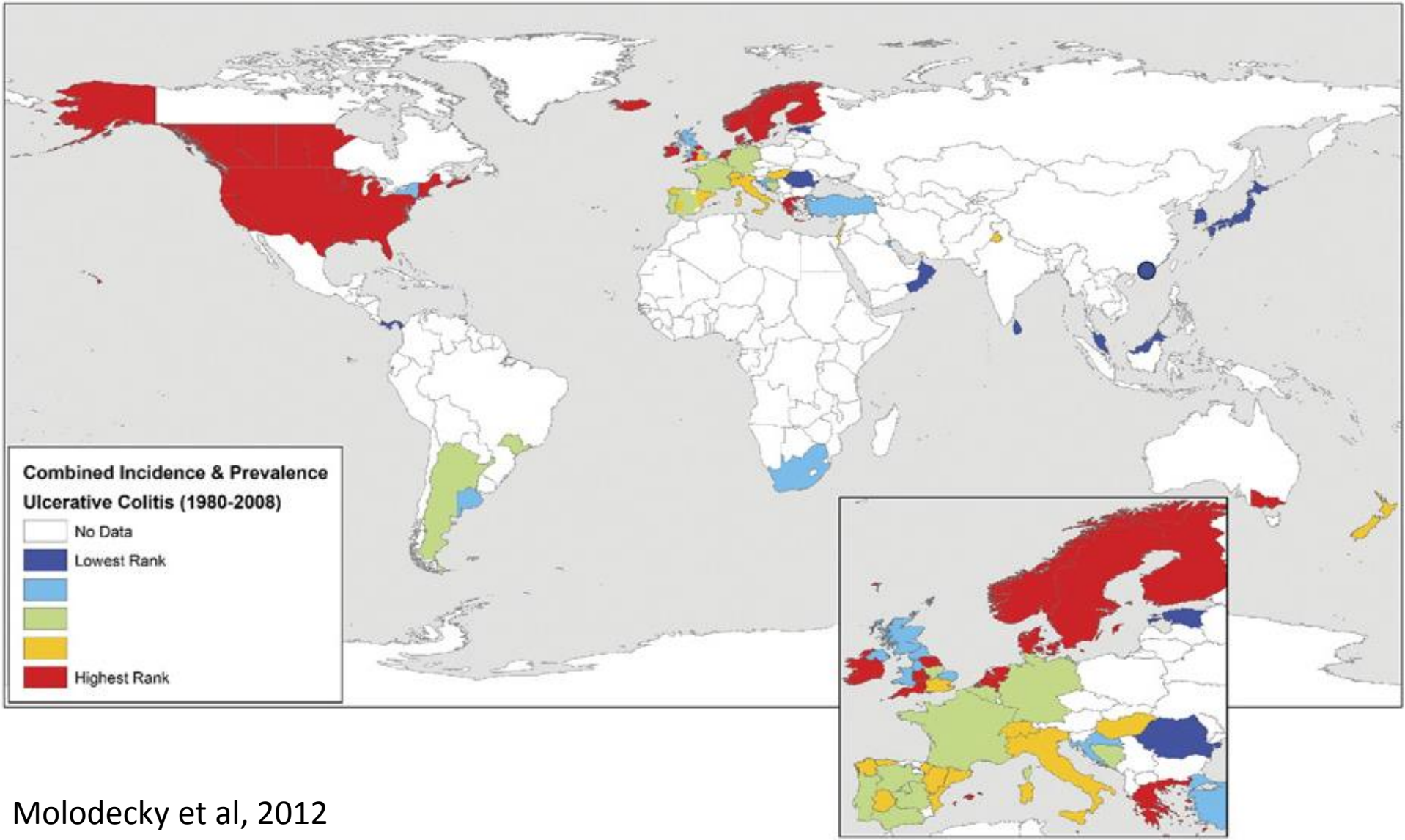
How common is IBD and who gets it?

IBD – a global problem?



Molodecky et al, 2012

IBD – a global problem?



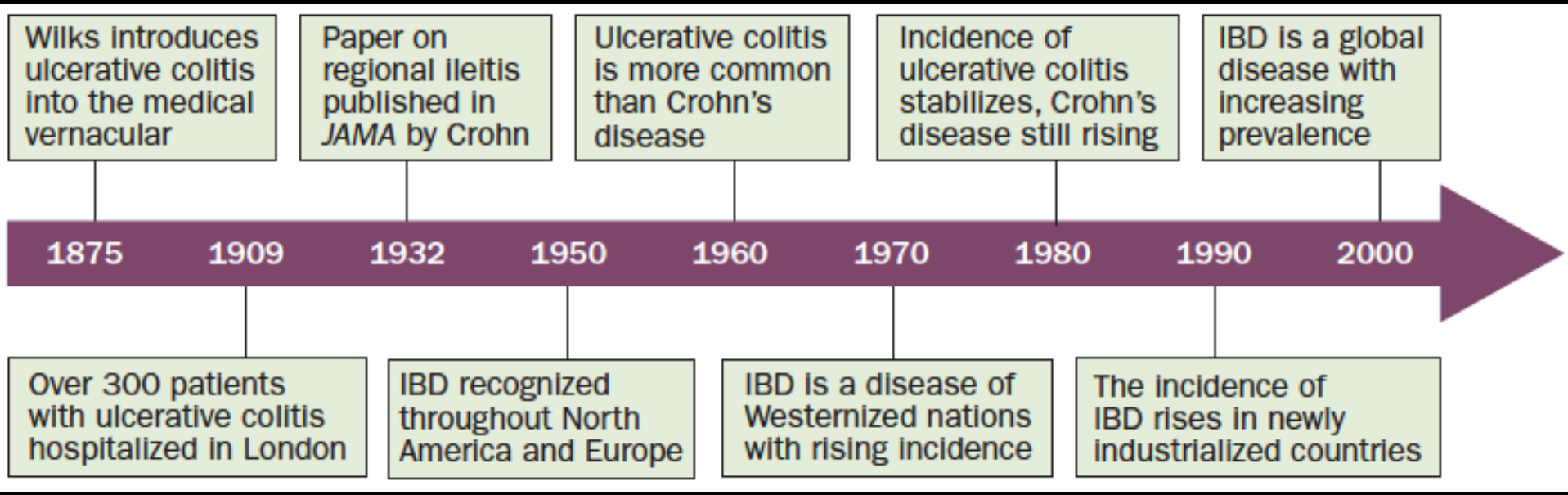
Molodecky et al, 2012

IBD Prevalence – the basic facts

- ~5 million people affected worldwide
- 0.5% of population in the highest prevalence regions
- Compound prevalence
  - cumulative addition of incident cases in a chronic disease with young age of onset and low mortality

Patterns of disease spread

Historical worldwide timeline of IBD



Kaplan et al, 2015

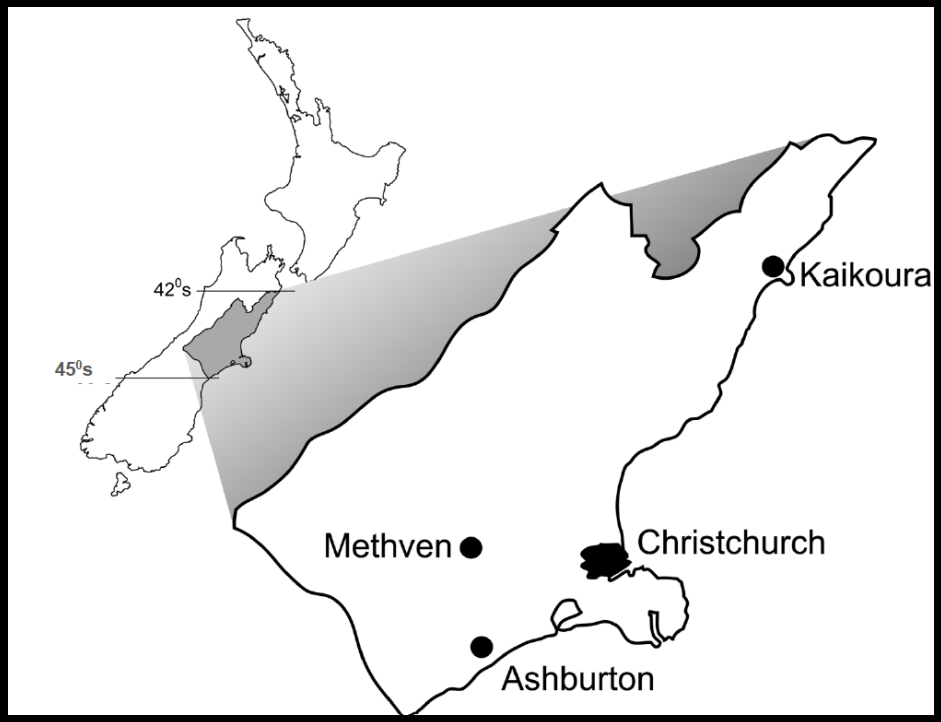
Similarities in epidemiology

- UC emerges first, followed by CD
- North America / Europe

  Australasia

  Asia
- CD incidence eventually surpasses UC incidence
- IBD incidence plateauing in the West?

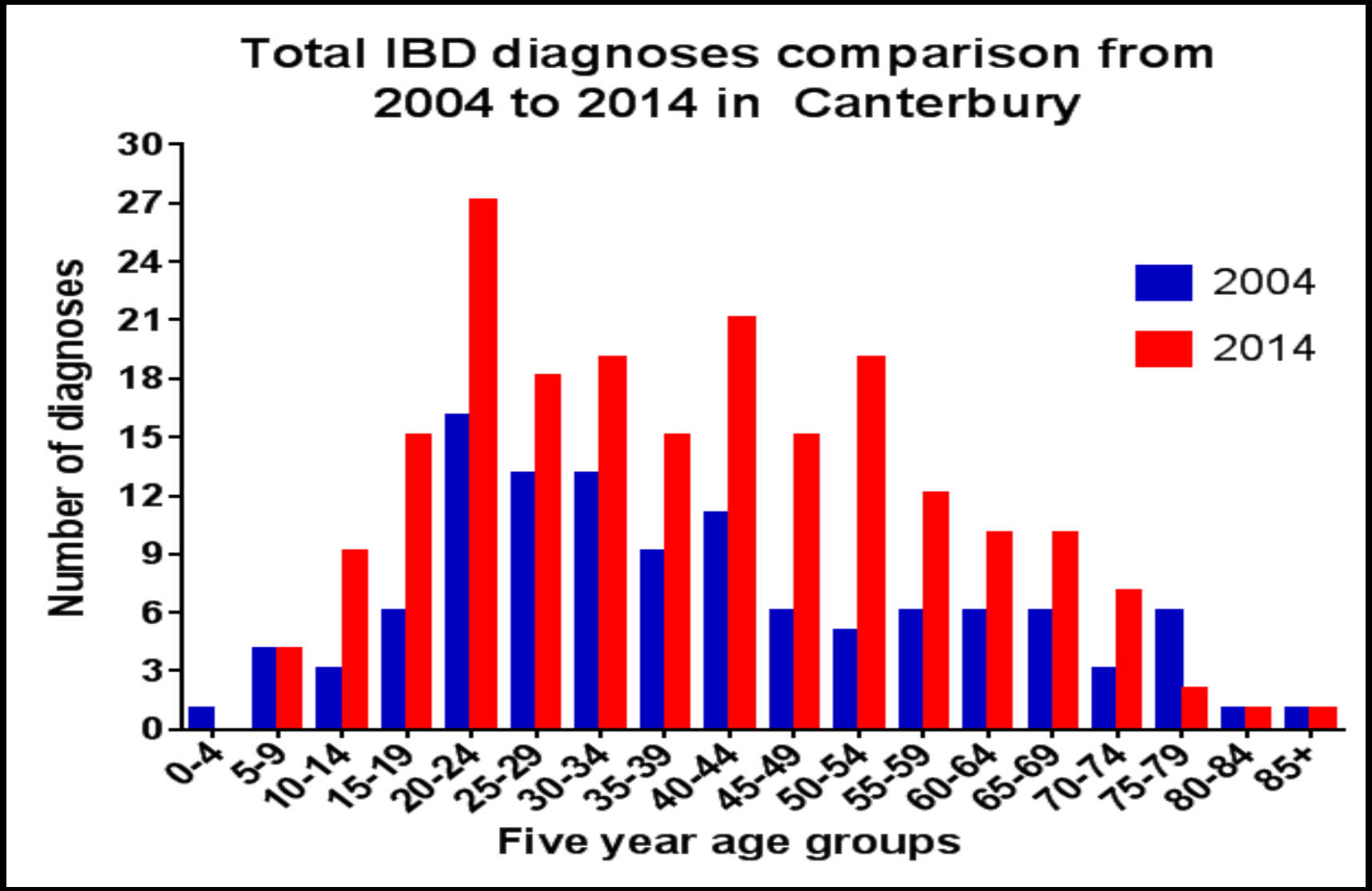
The Canterbury IBD Study, 10 years on …



	2004
Total Population	460680
New CD cases	76
Incidence /100000	16.5
New UC cases	35
Incidence /100000	7.6
New IBD cases	116
Incidence /100000	25.2

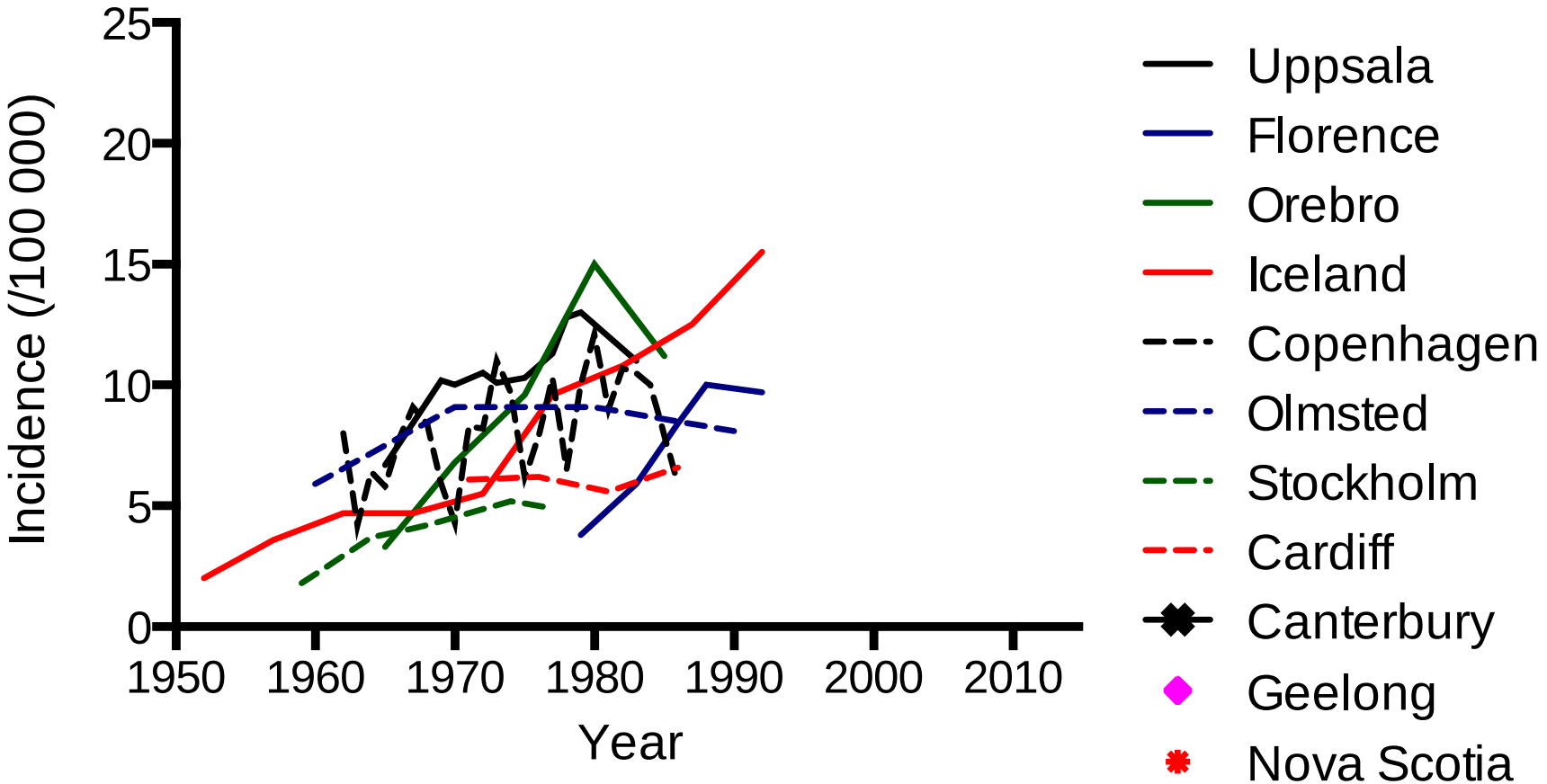
Gearry et al, 2006; Su et al, In Press

Age distribution of new IBD diagnoses in Canterbury



Su, Gupta, Day, Gearry, 2015

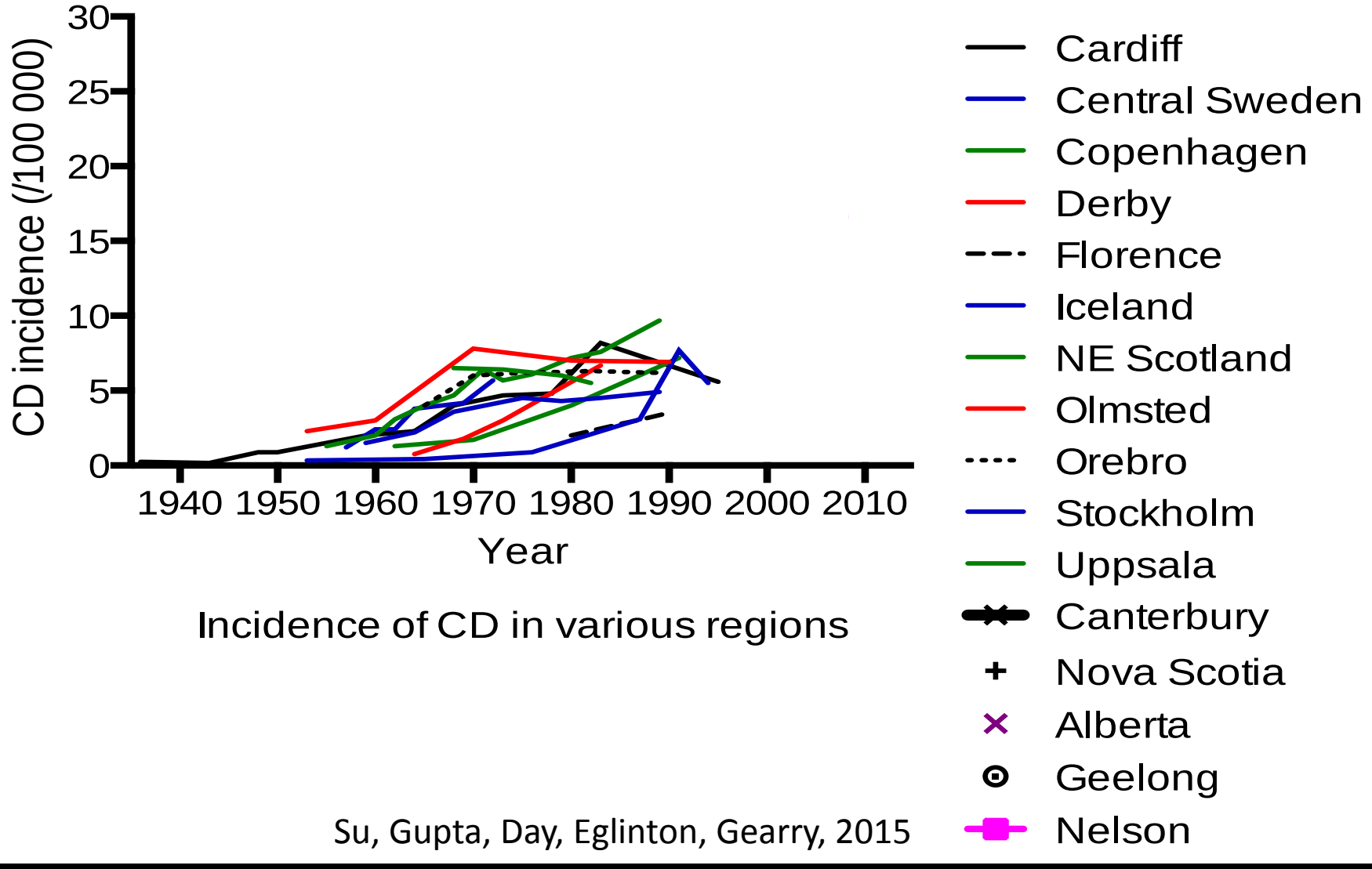
Worldwide ulcerative colitis incidence



Incidence of UC in various regions

Su, Gupta, Day, Eglinton, Gearry, 2015

Worldwide Crohn's disease incidence



Incidence of CD in various regions

Su, Gupta, Day, Eglinton, Gearry, 2015

CD age of diagnosis

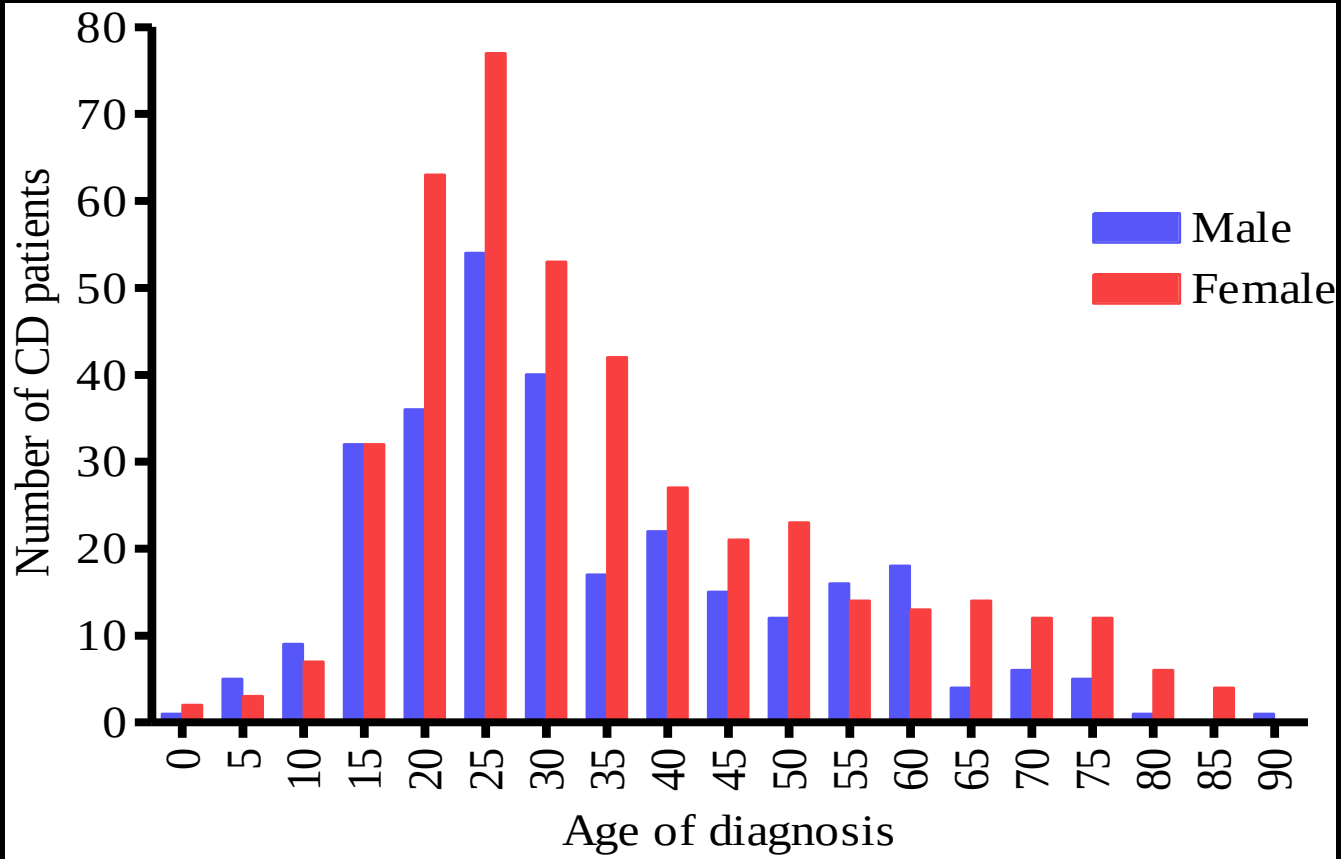


Figure 2.5A
CD age of diagnosis by sex

UC age of diagnosis

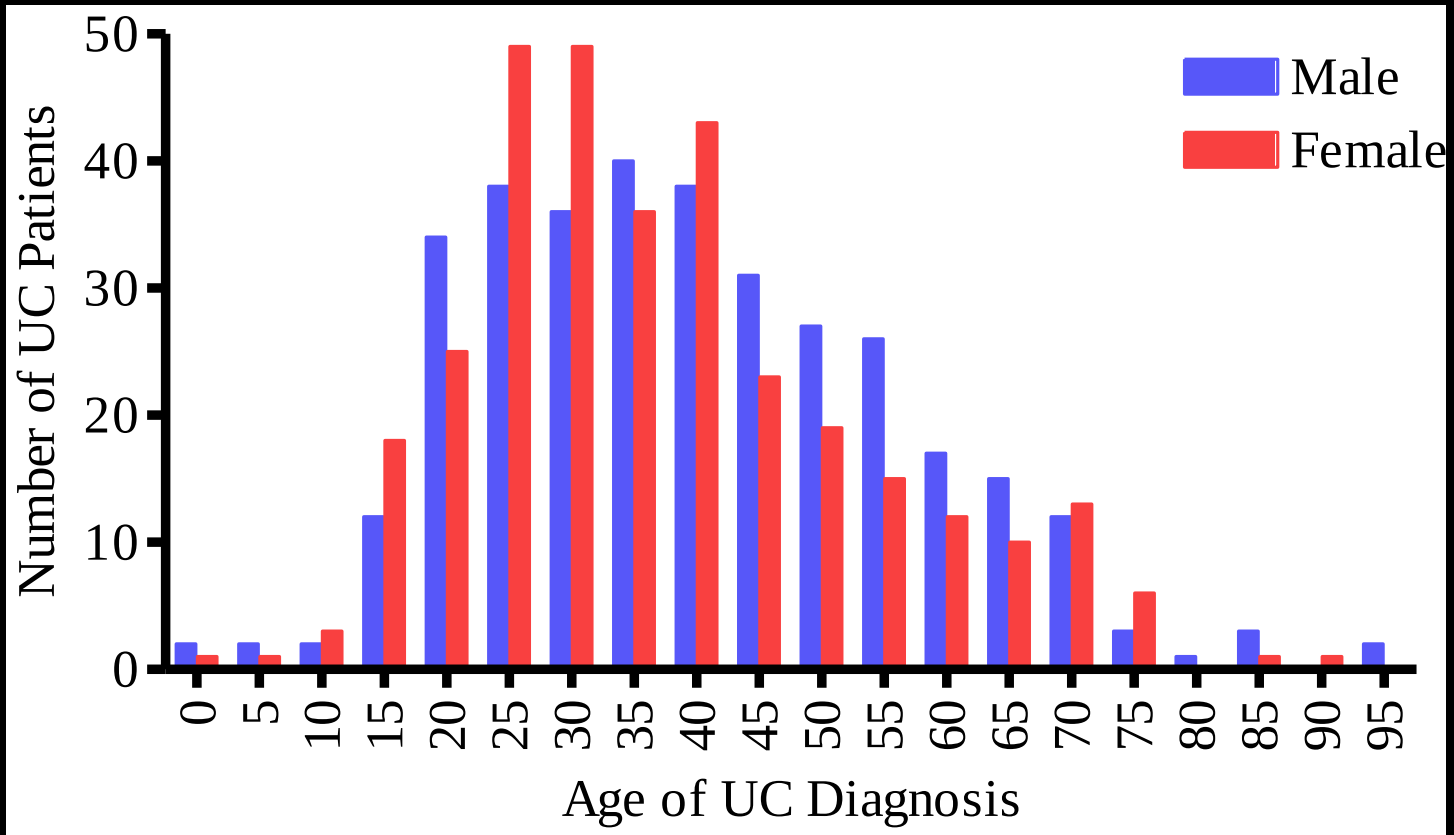
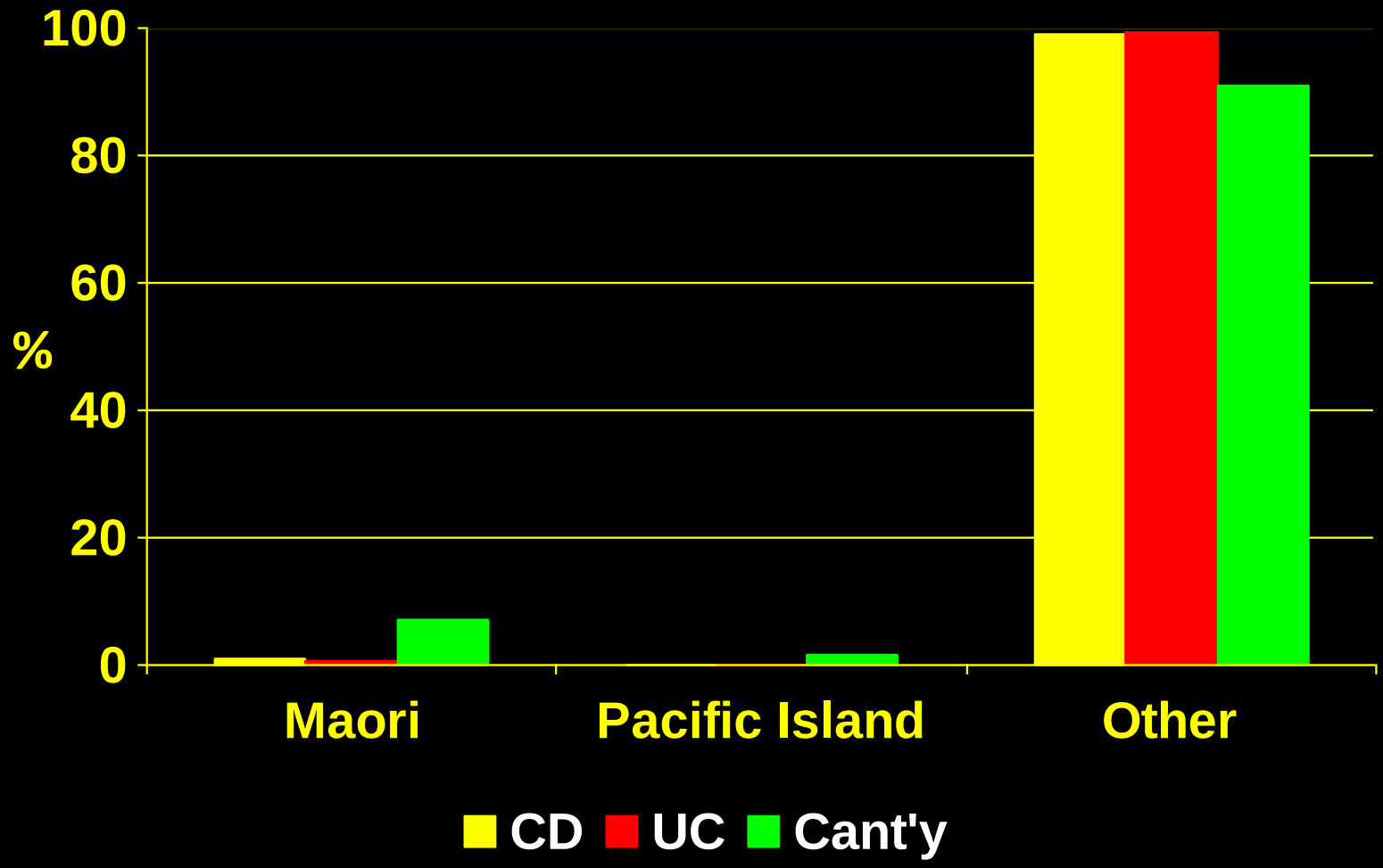


Figure 2.5B
UC Age of Diagnosis by Sex

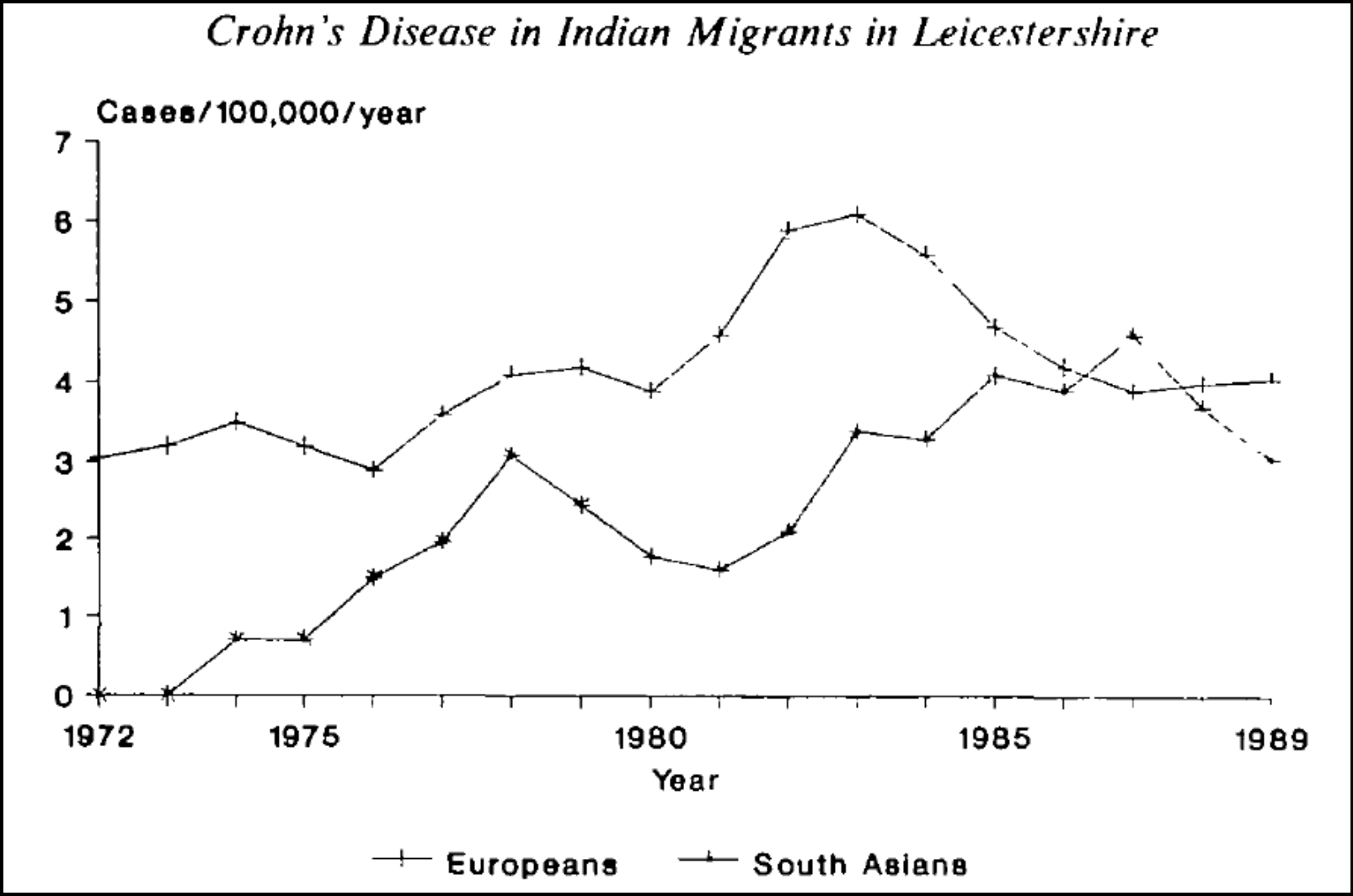
Canterbury IBD cohort ethnicity



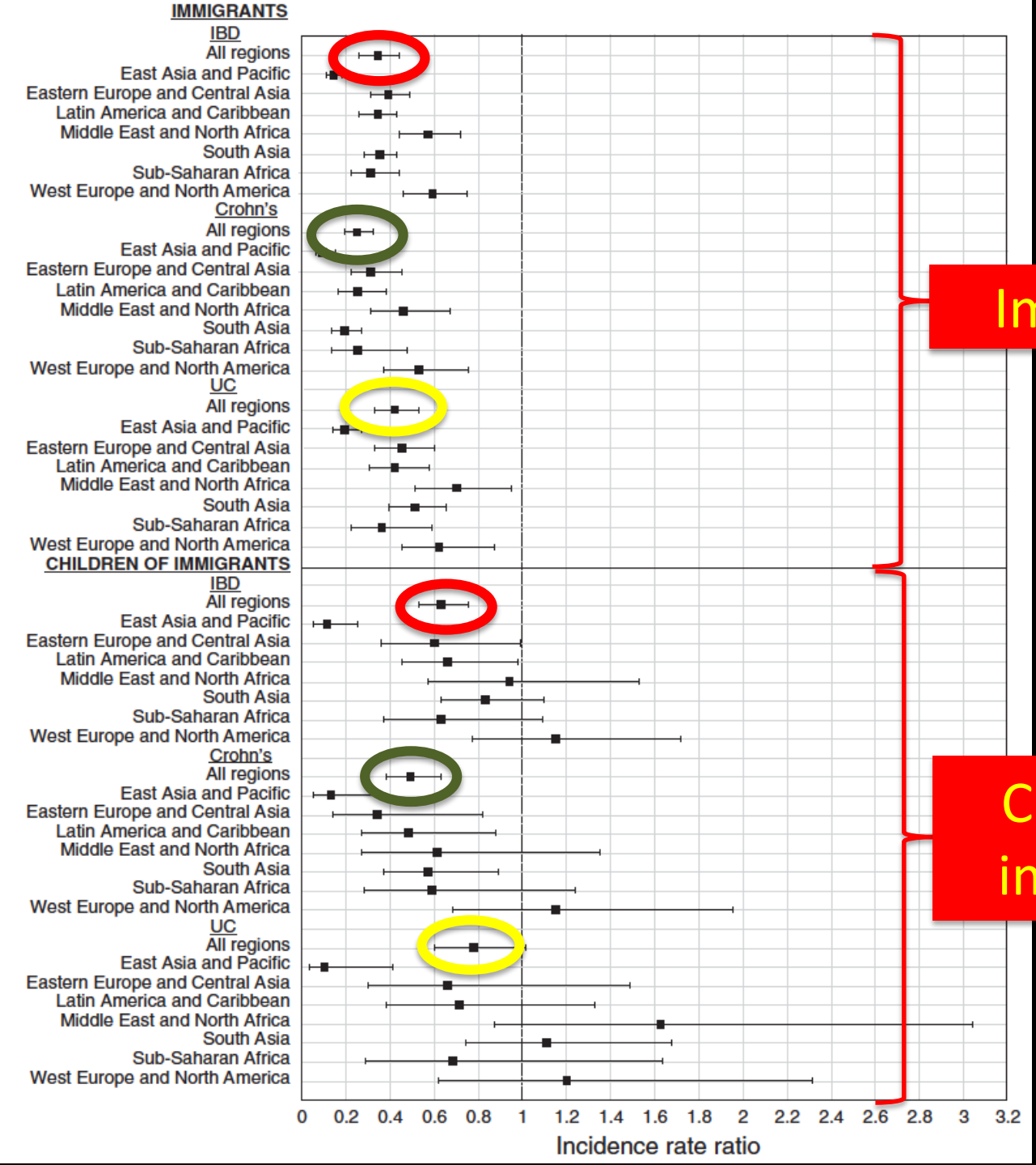
IBD is less common in Maori and Pacific Island people ($p<0.001$)

Gearry et al, *Inflammatory Bowel Diseases*, 2006

Clues from migrant studies



Jayanthi et al, 1992

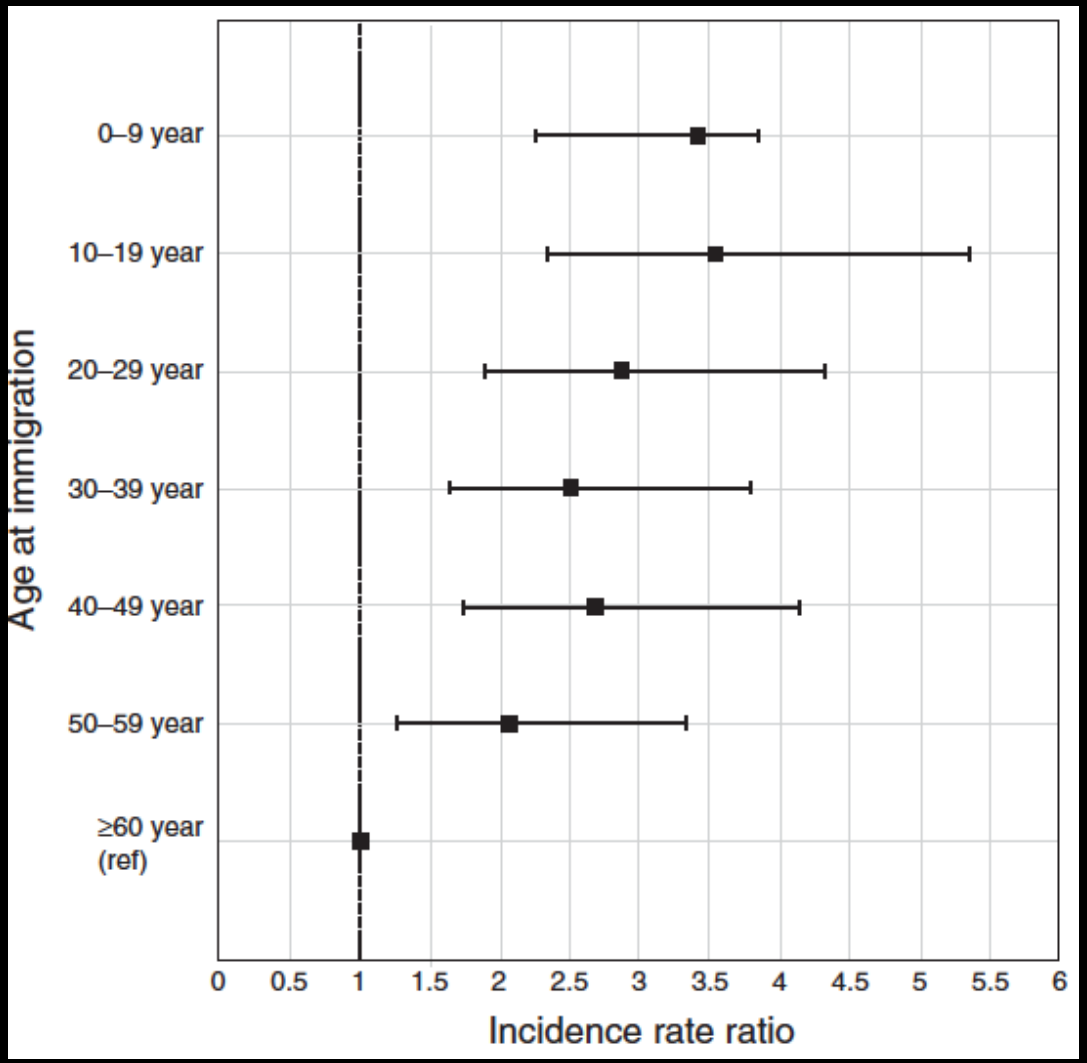


Immigrants

Children of immigrants

Benchimol et al, 2015

Clues from migrant studies



Benchimol et al, 2015

Clues from migration studies

- The incidence of IBD rose in North America / Europe well before New Zealand

- Canterbury IBD Study — OR
  - UC (born overseas) — 1.4 [1.14-2.01]
  - CD (born overseas) — 1.44 [1.03-2.02]

- Do those from high incidence regions bring their increased IBD risk with them?

Gearry et al, 2010

Does it all come down to your childhood environment?

Why do people get IBD?

The Gut in Health

- The most complex of the organs

- ~1200 bacterial species found in human gut
- ~160 in any given individual

- We are more bug than human!


Your body is
mostly microbes

100 TRILLION

The human microbiome is made up of more than 100 trillion bacteria, fungi, protozoa, and viruses that live on and inside the body.

10X

We have 10 times more microbial cells in our body than human cells and the majority live in our guts—especially the large intestine, or colon.

The bacteria in our microbiomes are essential to human health and aid in biological processes such as:

$E=mc^2$

Extracting energy from food

RETINOL
FOLATE
RIBOFLAVIN
BIOTIN
NIACIN

Producing essential vitamins

Regulating our immune system

Regulating our glucose levels and metabolism

Protecting us against disease-causing microbes

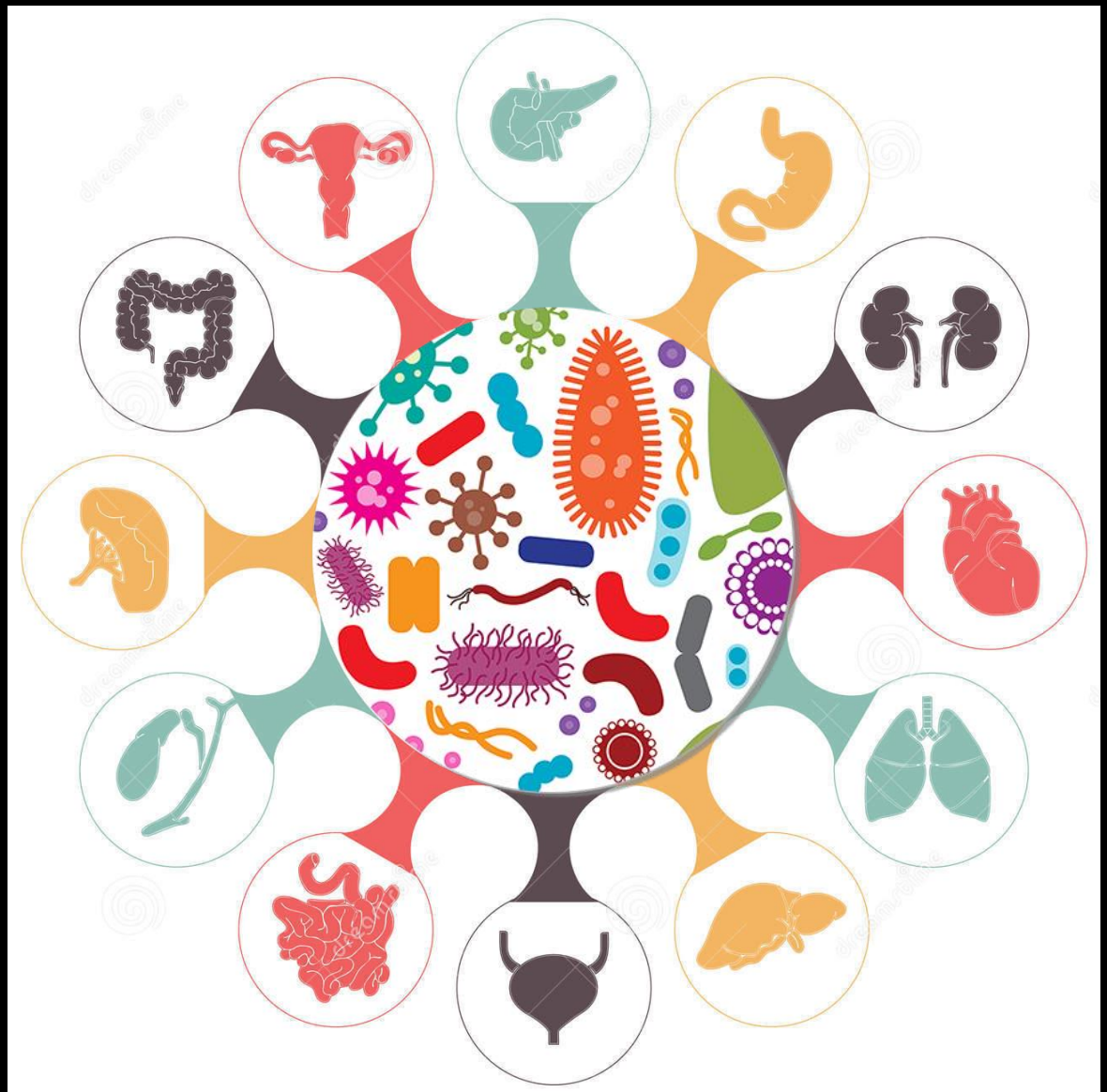
SYMBIOTIC

The beneficial and symbiotic relationship between humans and our microbiomes has likely evolved and changed throughout human development.

Personal microbial communities shift throughout a person's life and are influenced by diet, exercise, medications such as antibiotics, pathogens, and other environmental factors.

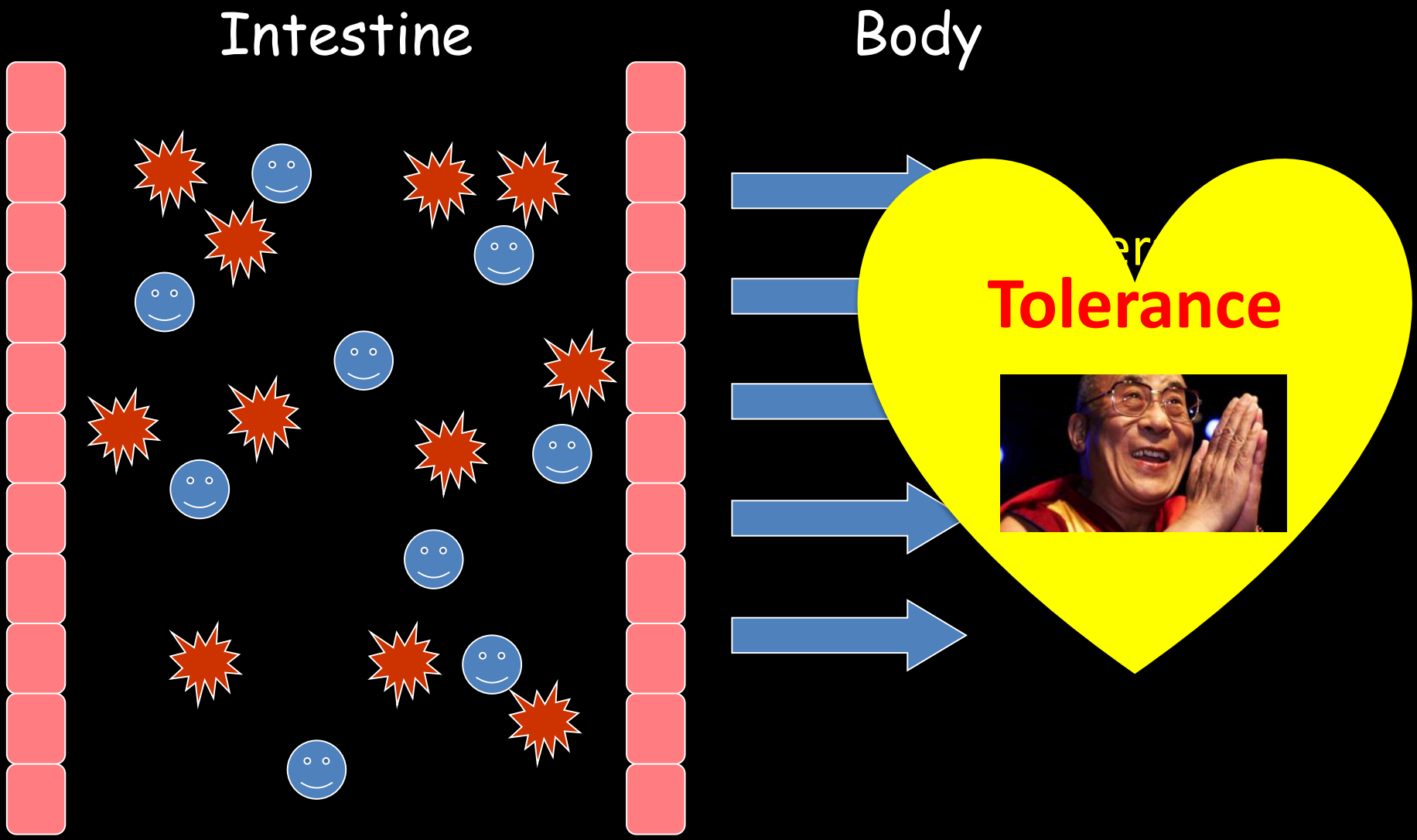
Each of us is unique on the inside

The last internal organ isn’t human



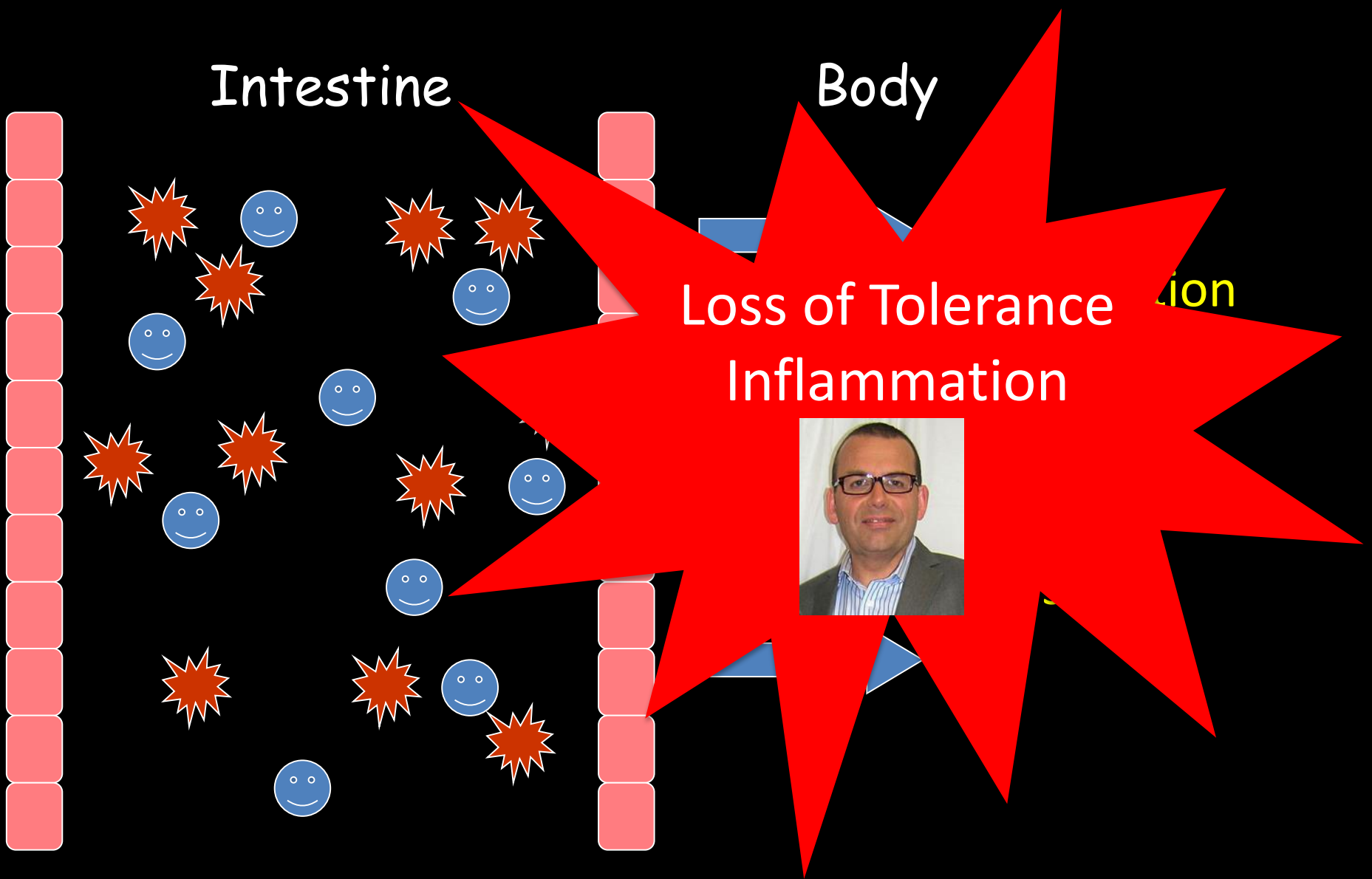
Why is the healthy gut like the Dalai Lama?

The Human Gut in Health

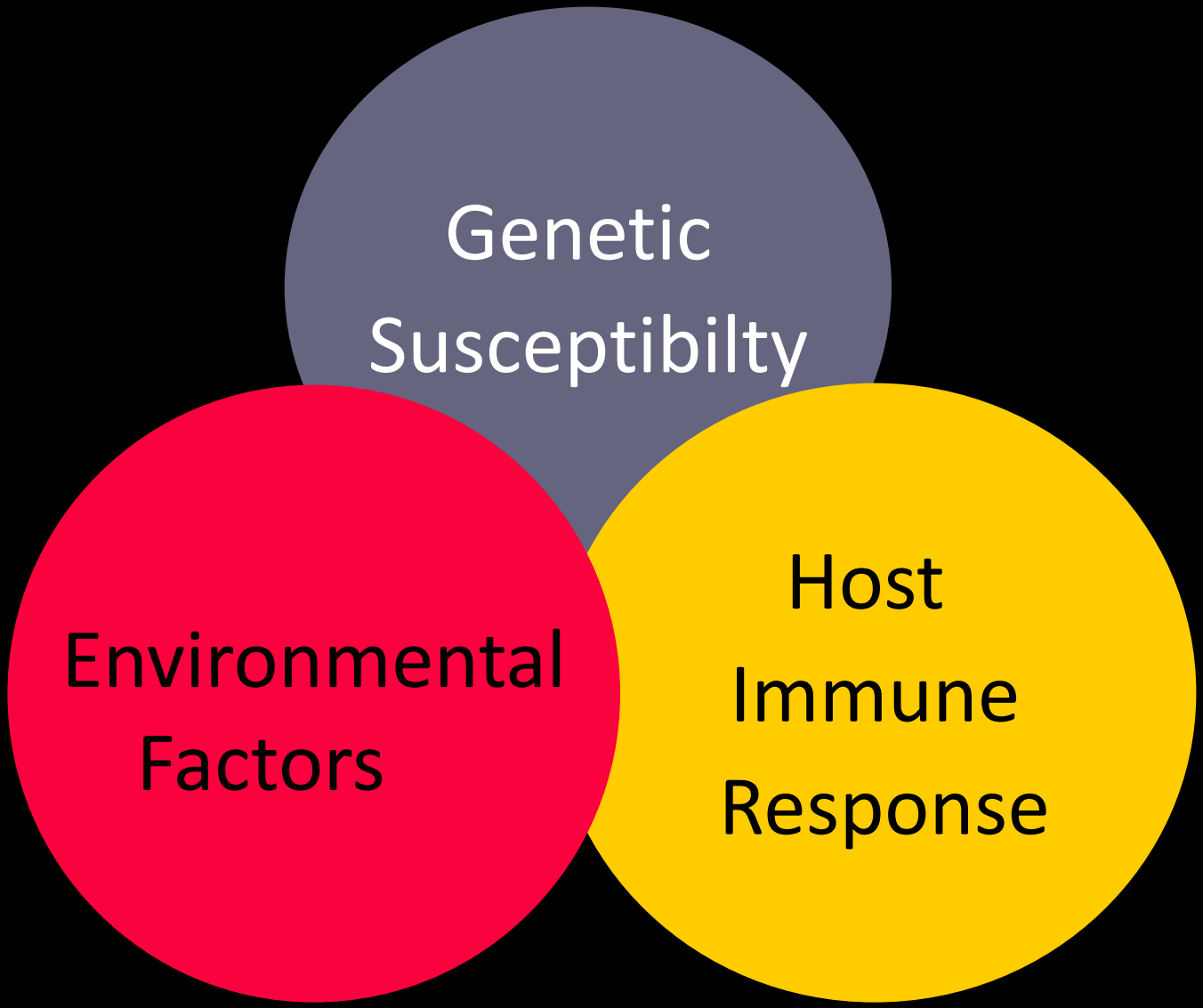


Why is the IBD gut like Paul Henry?

The Human Gut in IBD

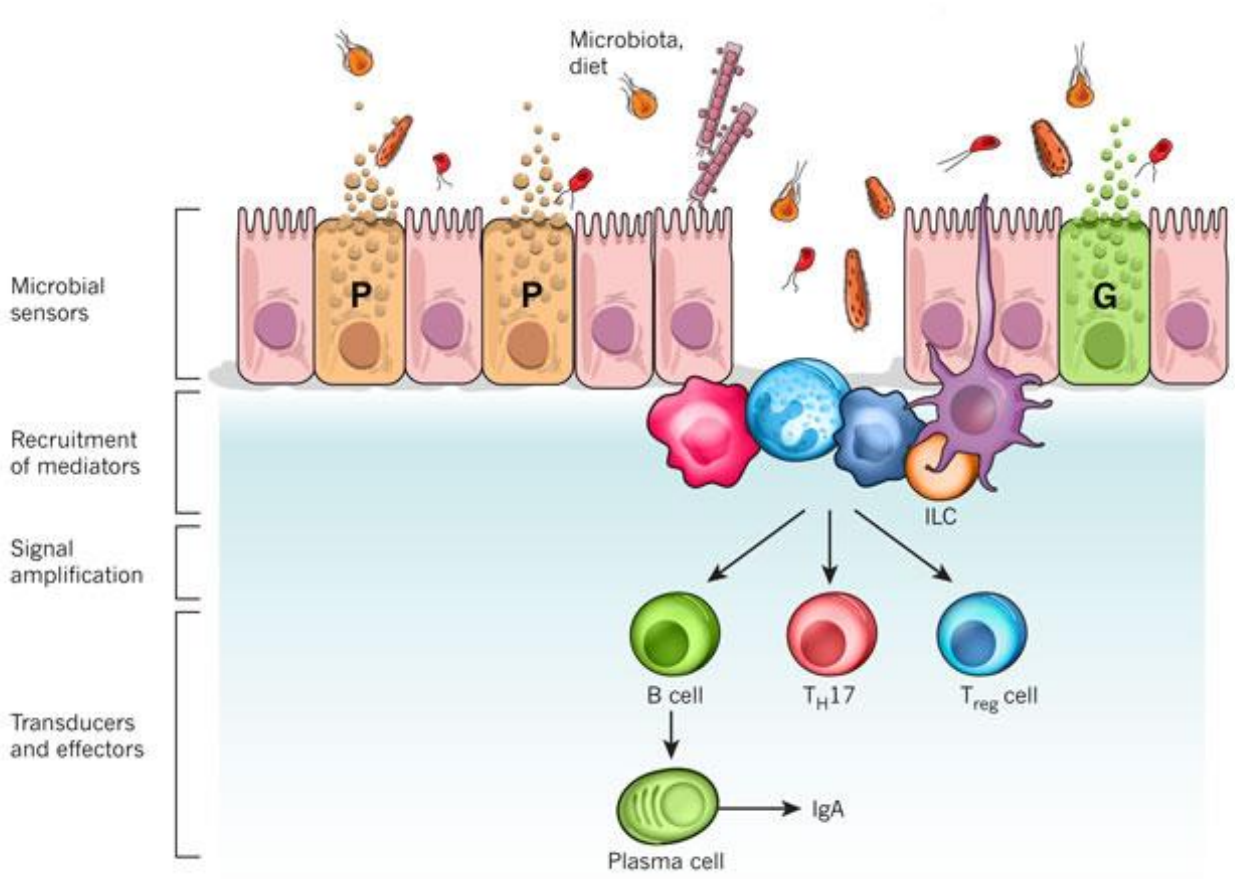


Why do people get IBD?



Genes and IBD

- Is IBD a genetic disease?
- A family history of IBD is the strongest known risk factor for IBD
- Most people with IBD do not have a relative with IBD



IBD-related processes

Epithelial barrier
GNA12*, HNF4A, CDH1, ERRFI1, MUC19, ITLN1*

Restitution
REL, PTGER4, NKX2-3, STAT3, ERRFI1, HNF4A, PLA2G2A/E

Solute transport
SLC9A4, SLC22A5, SLC22A4*, AQP12A/B, SLC9A3, SLC26A3

Paneth cells
ITLN1*, NOD2*, ATG16L1*, XBP1*

Innate mucosal defence
NOD2*, ITLN1*, CARD9*, REL, SLC11A1, FCGR2A*/B

Immune cell recruitment
CCL11/CCL2/CCL7/CCL8, CCR6, IL8RA/IL8RB, MST1*

Antigen presentation
ERAP2*, LNPEP, DENND1B

IL-23/T_H17
IL23R*, JAK2, TYK2*, STAT3, ICOSLG, IL21, TNFSF15

T-cell regulation
NDFIP1, TNFSF8, TAGAP, IL2, IL2RA, TNFRSF9, PIM3, IL7R*, IL12*, IL23R*, PRDM1, ICOSLG, TNFSF8, IFNG, IL21

B-cell regulation
IL5, IKZF1, BACH2, IL7R*, IRF5

Immune tolerance
IL10, IL27*, SBNO2, CREM, IL1R1/IL1R2, NOD2*

Cellular responses

Autophagy
ATG16L1*, IRGM, NOD2*, LRRK2, CUL2, PARK7, DAP

ER stress
CPEB4, ORMDL3, SERINC3, XBP1*

Intracellular logistics
VAMP3, KIF21B, TTLL8, FGFR1OP, CEP72, TPPP

Cell migration
ARPC2, LSP1, AAMP

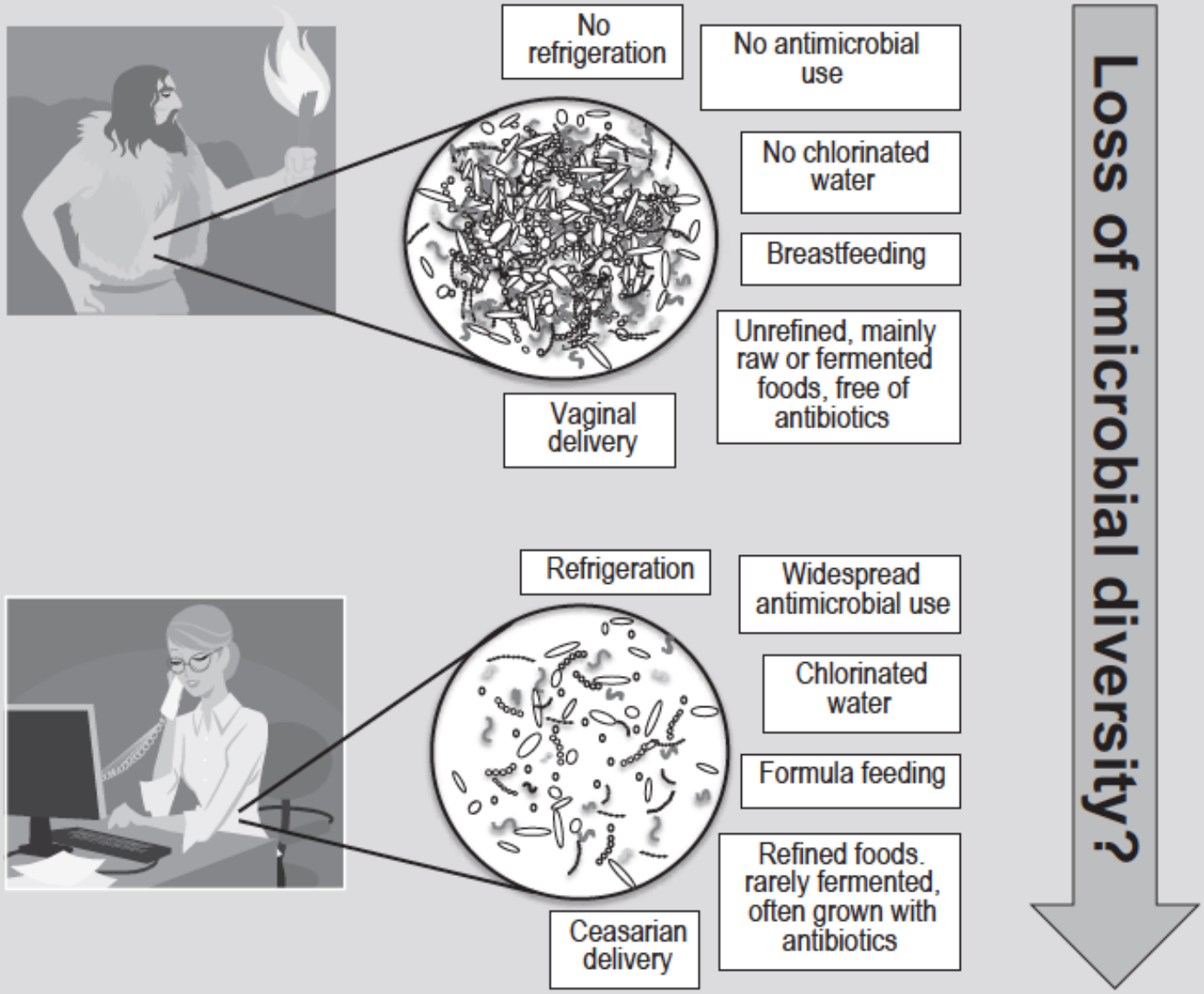
Apoptosis/necroptosis
FASLG, THADA*, DAP, PUS10, MST1*

Carbohydrate metabolism
GCKR*, SLC2A4RG

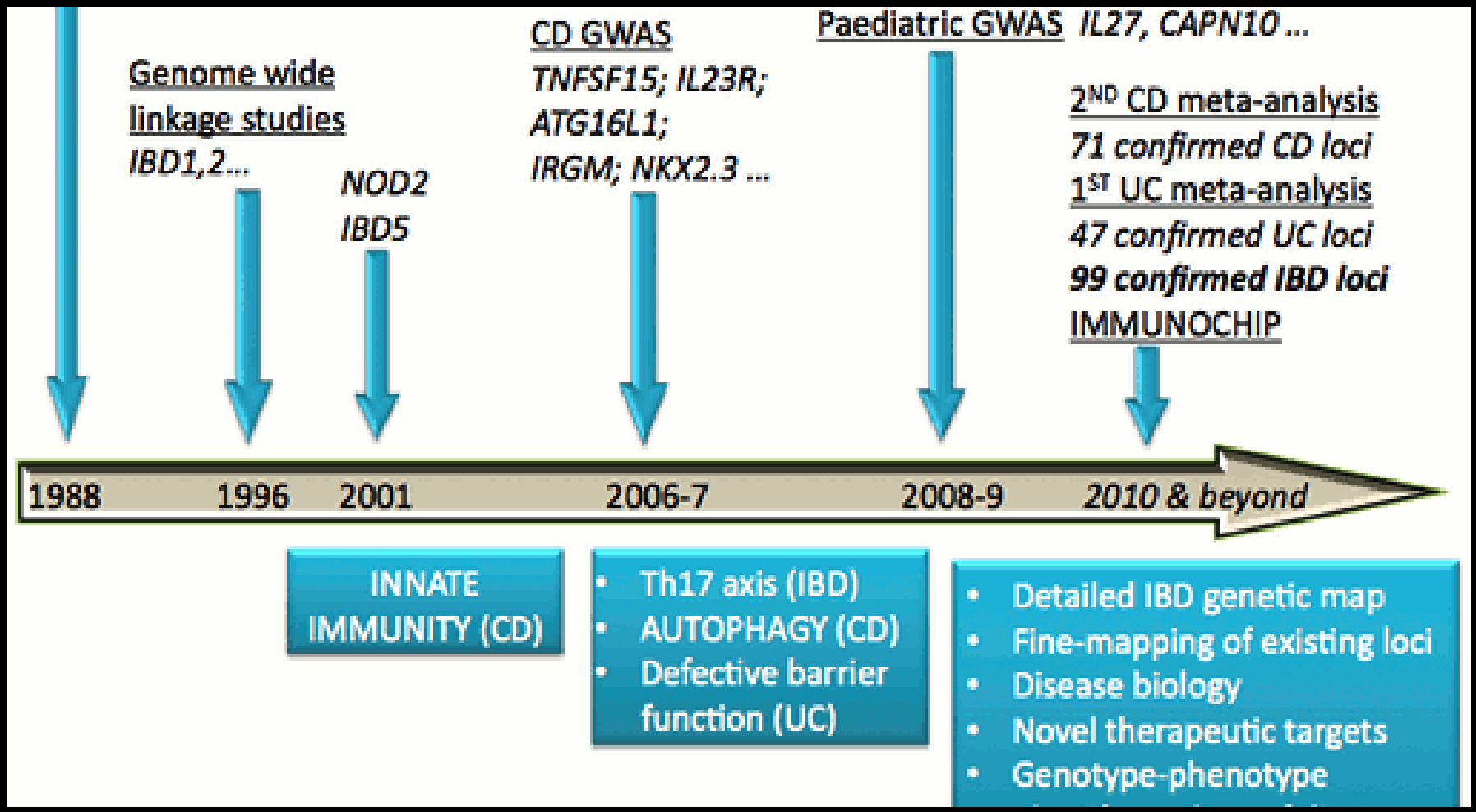
Oxidative stress
PRDX5, BACH2, ADO, GPX4, GPX1*, SLC22A4, LRRK2, NOD2*, CARD9*, HSPA6, DLD, PARK7, UTS2*, PEX13

UC
CD
UC/CD
cis-eQTL
*Coding mutation

Loss of microbial diversity



IBD Genetics



The environment and IBD

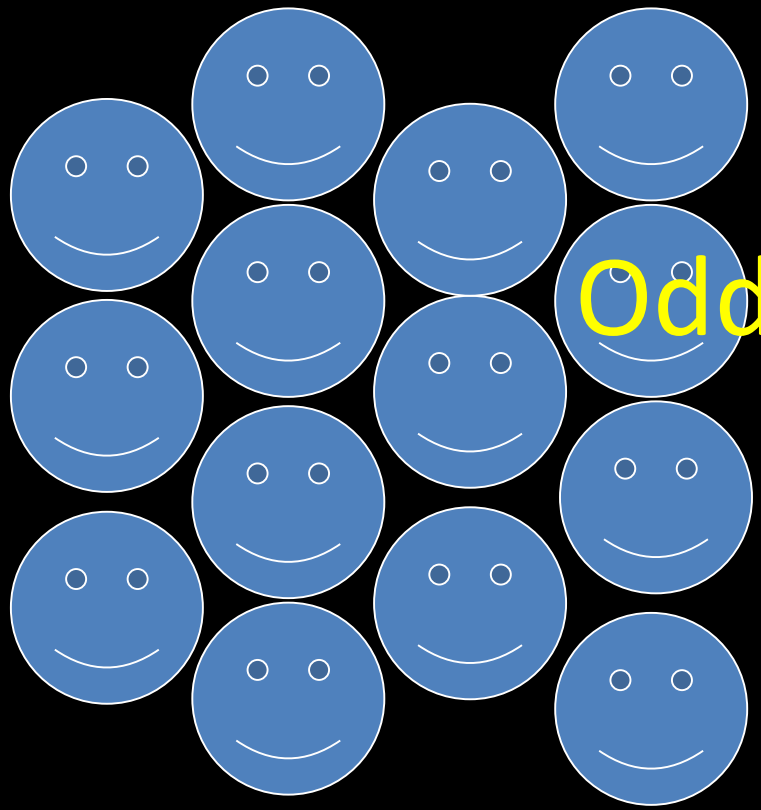
- Genes cannot explain the rapid increase in IBD
- Rapid changes in disease incidence

=

Changes in environmental factors

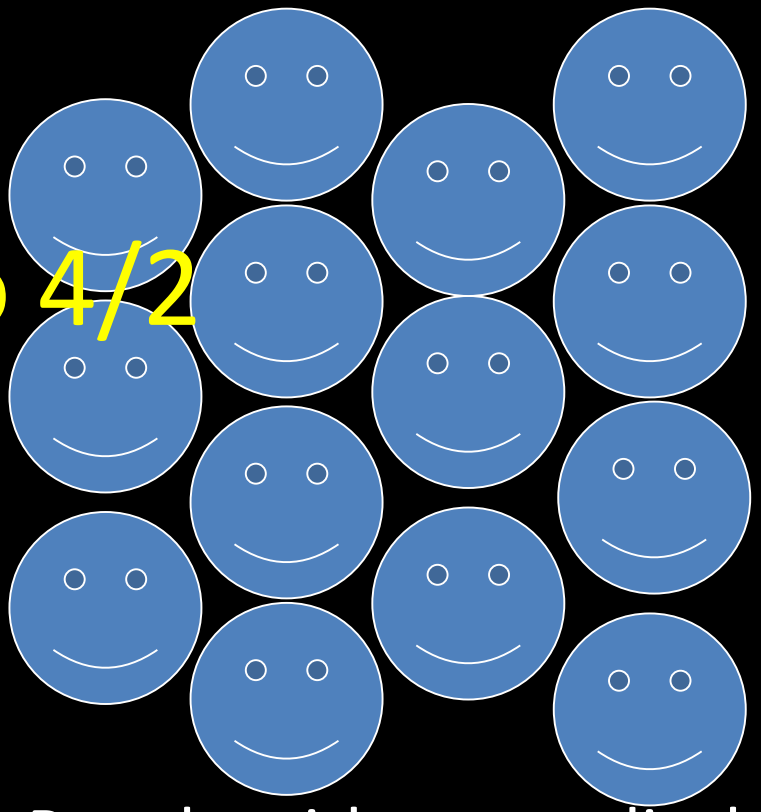
"Genes may load the gun, but the environment pulls the trigger"

Case-control study



Odds ratio 4/2

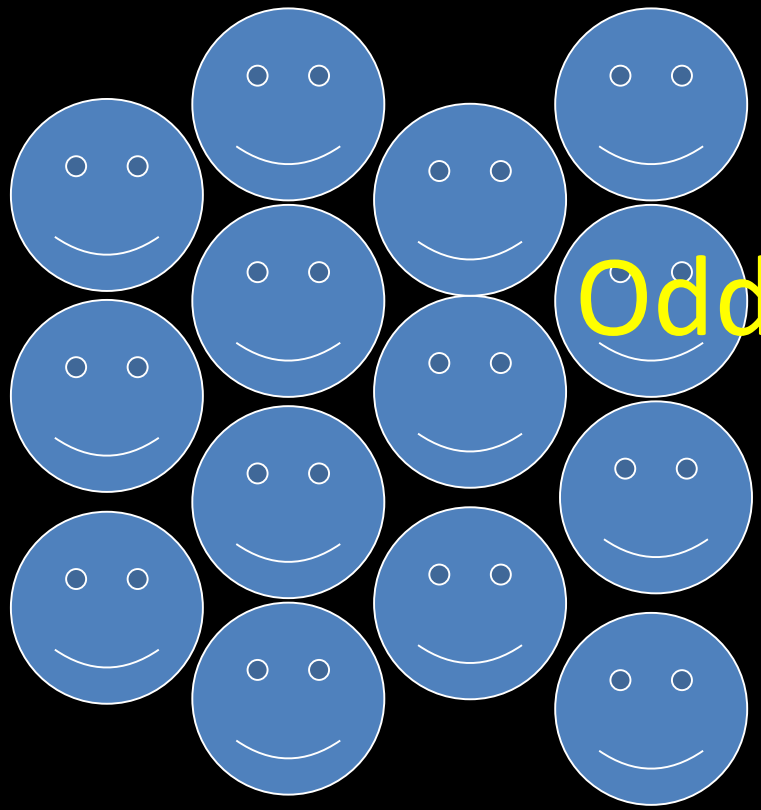
= 2.0



People with medical condition

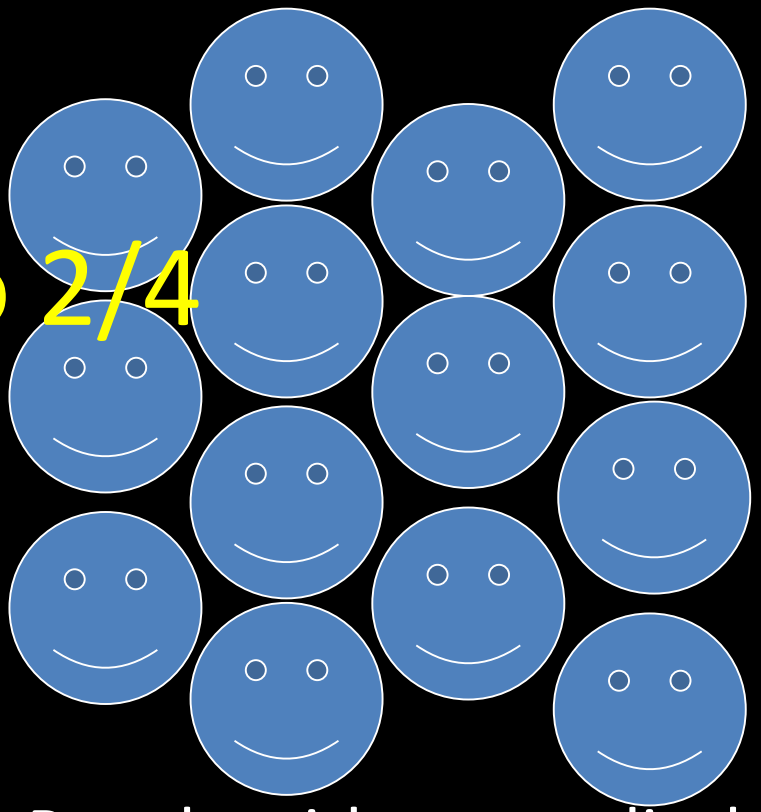
People without medical condition

Case-control study



Odds ratio 2/4

= 0.5



People with medical condition

People without medical condition

Environmental risk factors and IBD

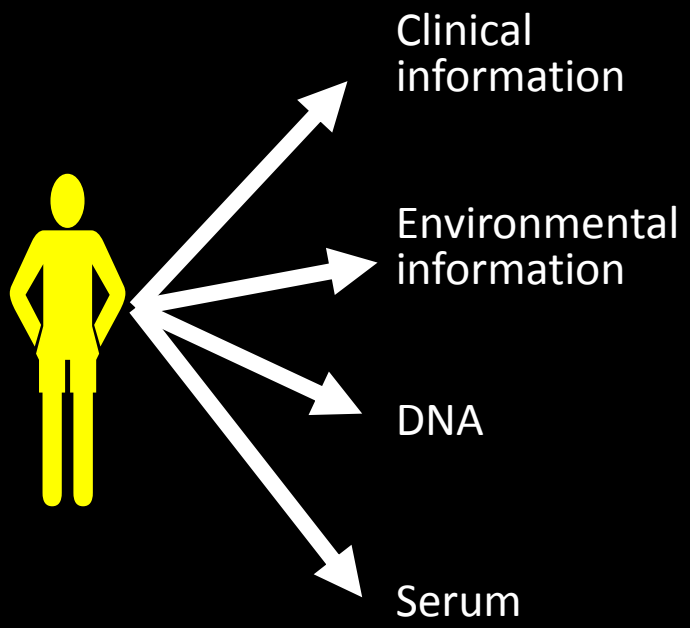
- Case-control studies
  - Compare the frequency of exposure to factors between those with IBD and matched controls without IBD

- The Canterbury IBD Study …

Methods

Case recruitment and prevalence study

- Outpatient clinics
- Inpatients
- Support Groups
- Advertising
- Direct Mail



The Canterbury IBD Study

Epidemiology

Genetic studies

Environmental risk factors

Drug studies

Role of microbes

Effect on people

Established risk factors for UC

Variable		Adjusted OR	95% CI
Family History of IBD	One relative	2.52	(1.90-3.54)
(vs no family history)	≥ two relatives	6.83	(3.13-14.9)
	First degree relative	2.19	(1.94-4.35)
	Other relative	3.17	(2.11-4.77)
Smoking (vs never)	Current	0.69	(0.50-0.95)
	Ex smoker	1.92	(1.40-2.37)
Appendicectomy	Yes	0.41	(0.27-0.63)

Gearry et al, J Gastro Hepatol, 2012

Established risk factors for Crohn's disease

Variable		Adjusted OR	95% CI
Family History of IBD	One relative	3.06	2.18-4.30
(vs no family history)	≥ two relatives	7.41	3.40-16.14
	First degree relative	3.21	2.13-4.84
	Other relative	3.34	2.23-5.81
Smoking (vs never)	Current	2.01	1.51-2.68
OCP use	Ever vs never	1.85	1.09-3.11
Place of birth	Town vs city	0.68	0.50-0.93
	Country vs city	0.64	0.46-0.88

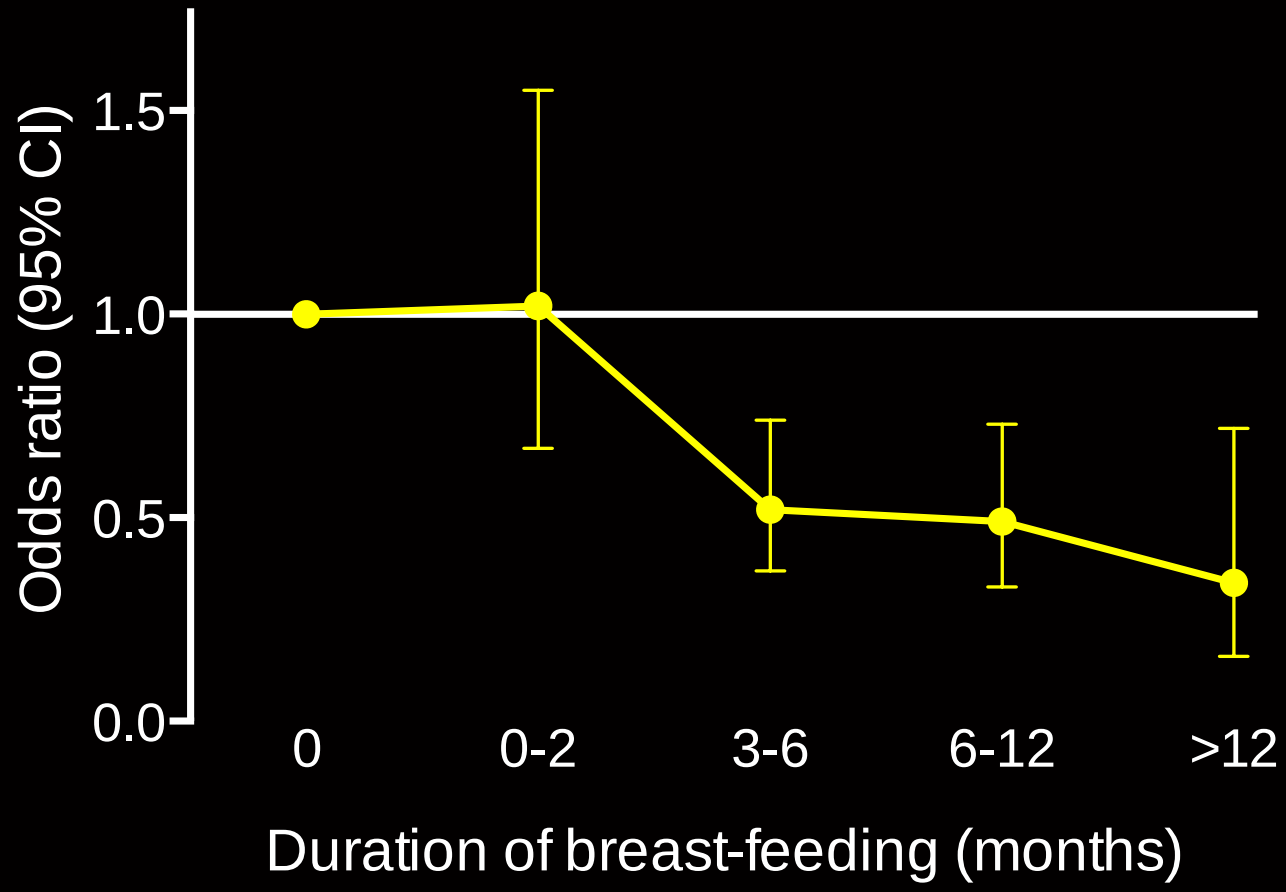
Gearry et al, J Gastro Hepatol, 2012

Novel Risk Factors for Crohn's disease

Variable		Adjusted OR	95% CI
Intra-uterine smoke		1.69	1.20-2.38
Antibiotic >4x/year		1.89	1.16-3.09
Vegetable garden	0-5y	0.49	0.34-0.69
	6-11y	0.52	0.36-0.76
	12-16y	0.64	0.47-0.88
Tonsillectomy		1.37	1.03-1.83
Glandular fever		1.64	1.11-2.43
Sharing bedroom	0-5y	0.76	0.58-0.99
Takeaway food 2x/week v never		2.09	1.13-3.89

Gearry et al, J Gastro Hepatol, 2012

Risk of Crohn's disease and duration of breast-feeding



Gearry et al, J Gastro Hepatol, 2012

Faecal microflora

- The final frontier
- Intimately linked to health and disease
- Science now allowing us to delve more deeply
- University of Otago well positioned

How do we diagnose IBD?

Clinical assessment

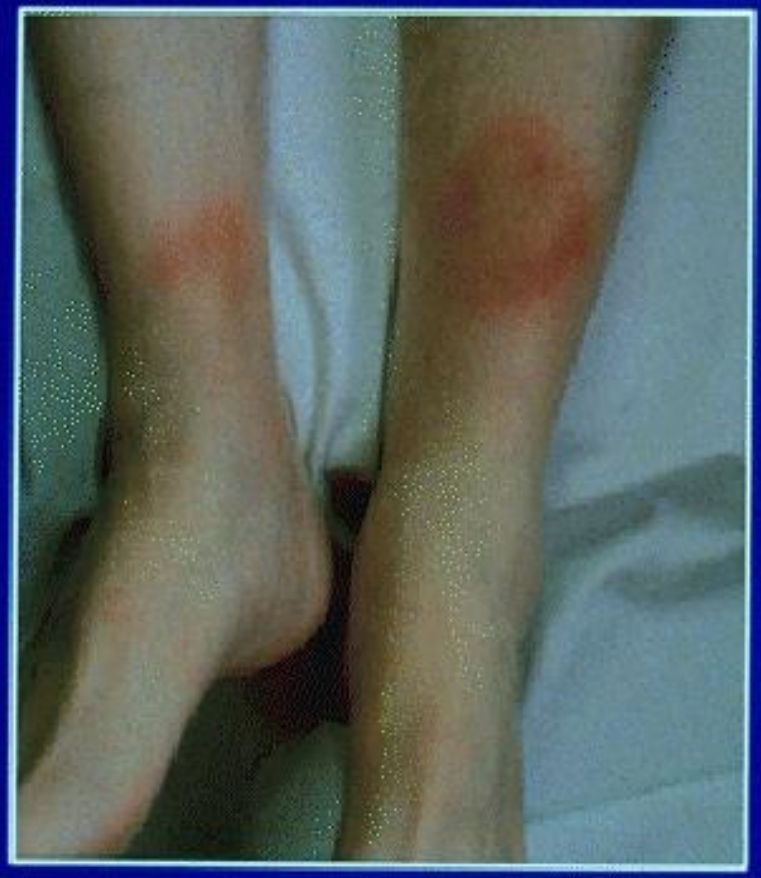
- History
  - types of symptoms over a timeframe
  - presence of non-GI symptoms (EIMs)
  - drugs recently used
  - family history of GI disease
  - smoking history
  - recent stresses

EIMs in Canterbury

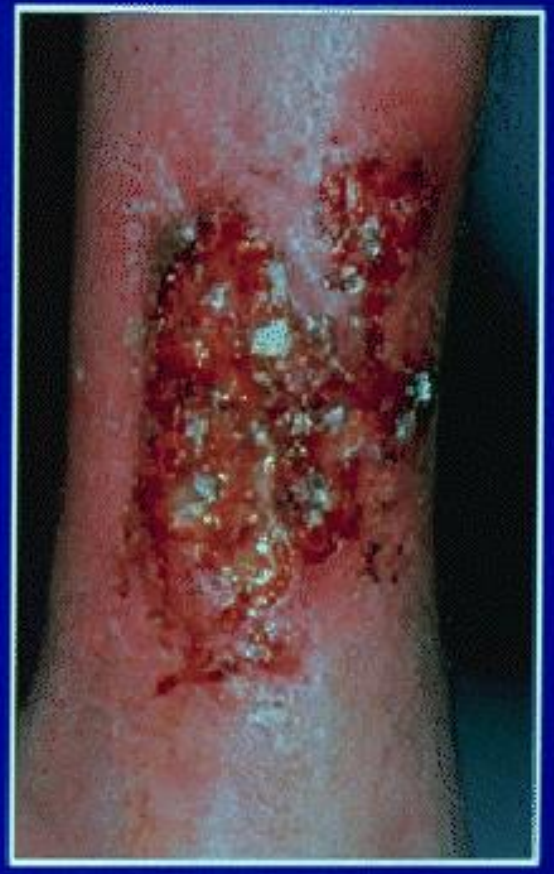
Extra-Intestinal Manifestation	CD (%)	UC (%)
Primary Sclerosing Cholangitis	9 (1.3)	21 (3.1)
Axial arthritis	15 (2.1)	16 (2.4)
Peripheral arthritis	56 (8.4)	56 (8.4)
Pyoderma gangrenosum	6 (0.9)	6 (0.9)
Erythema nodosum	32 (4.5)	7 (1.0)
Uveitis	4 (0.6)	0
Iritis	7 (1.0)	1 (0.3)
Episcleritis	6 (0.8)	0
Total	122 (17.1)	96 (14.4)

Systemic Complications In Ulcerative Colitis

SKIN



Erythema Nodosum

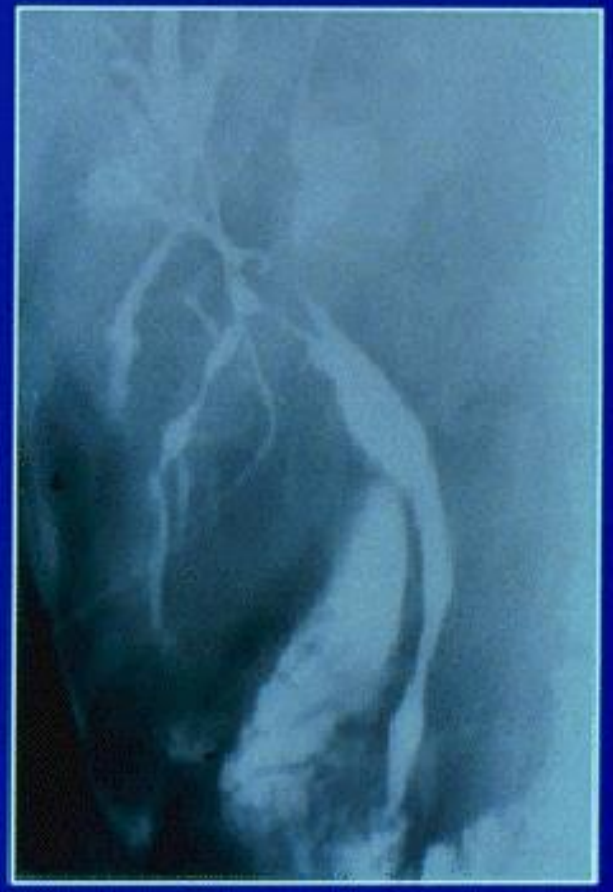


Pyoderma Gangrenosum

Systemic Complications Of Ulcerative Colitis

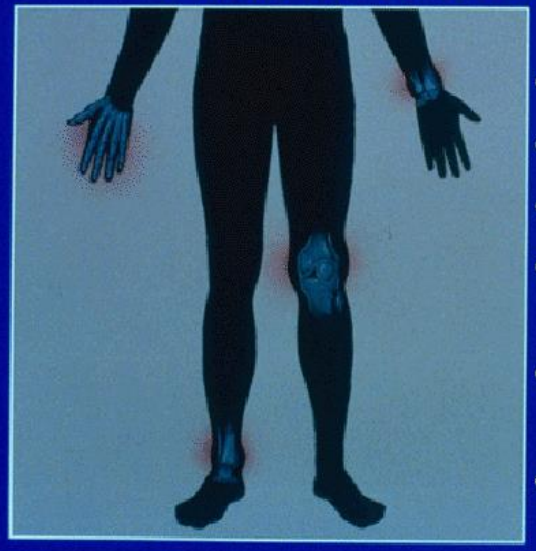
BILE DUCT LESIONS

Sclerosing Cholangitis



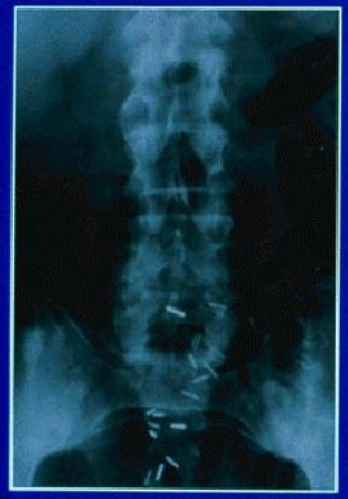
Cholangiocarcinoma

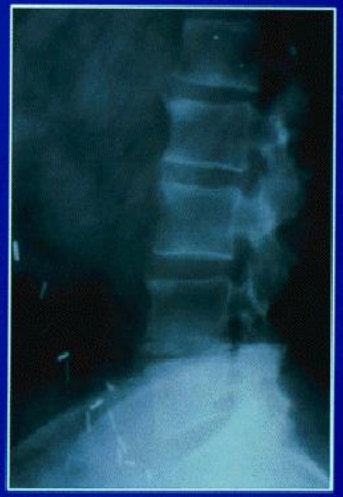
Systemic Complications Of Ulcerative Colitis
PERIPHERAL ARTHRITIS



- Monoarticular
- Asymmetrical
- Large > small joint
- No synovial destruction
- No subcutaneous nodules
- Seronegative

Systemic Complications Of Ulcerative Colitis
CENTRAL (AXIAL) ARTHRITIS

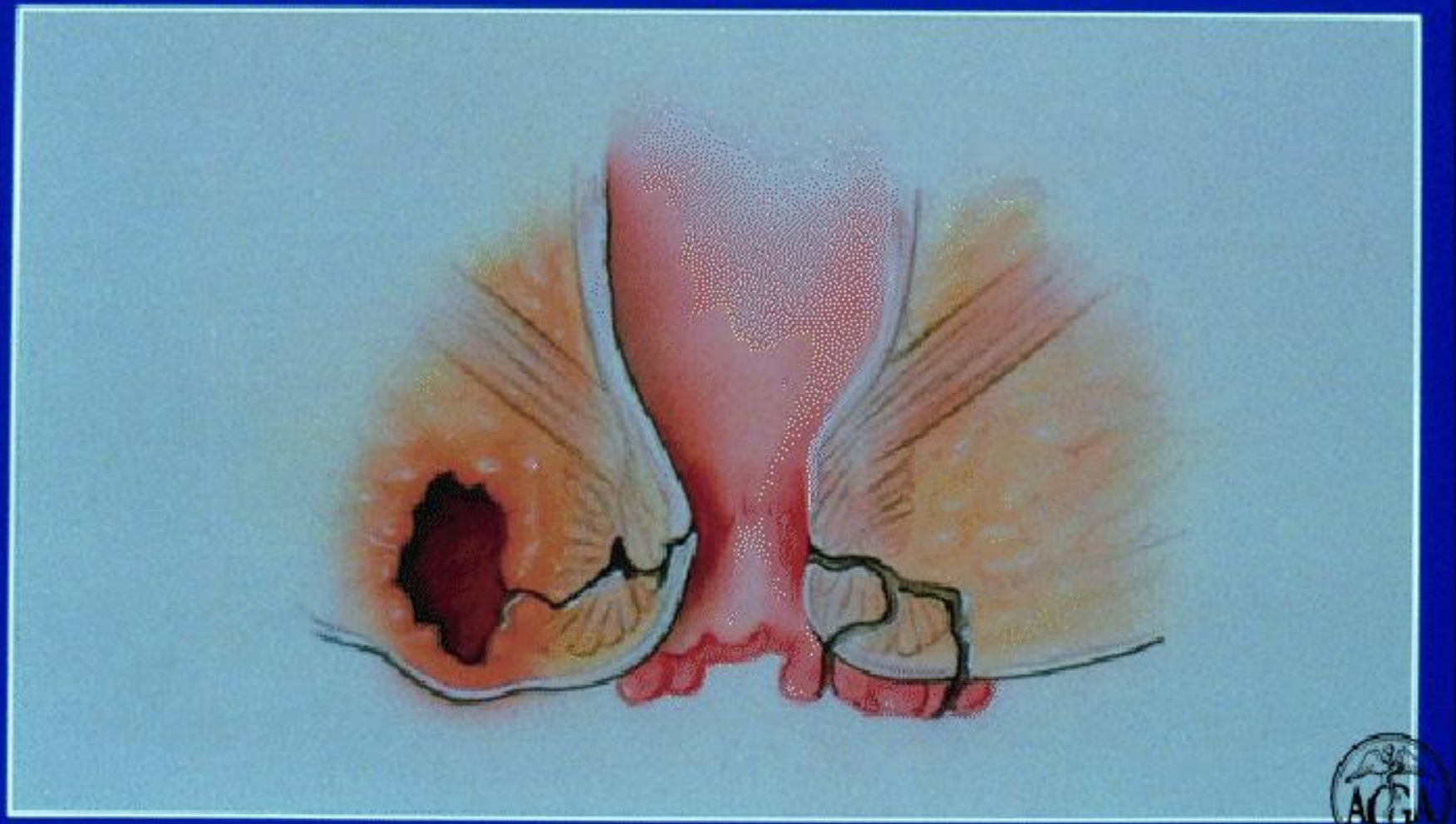




Ankylosing Spondylitis and Sacro-iliitis

Perineal Complications Of Crohn's Disease

PERIANAL FISTULAE and ABSCESS



Lab tests

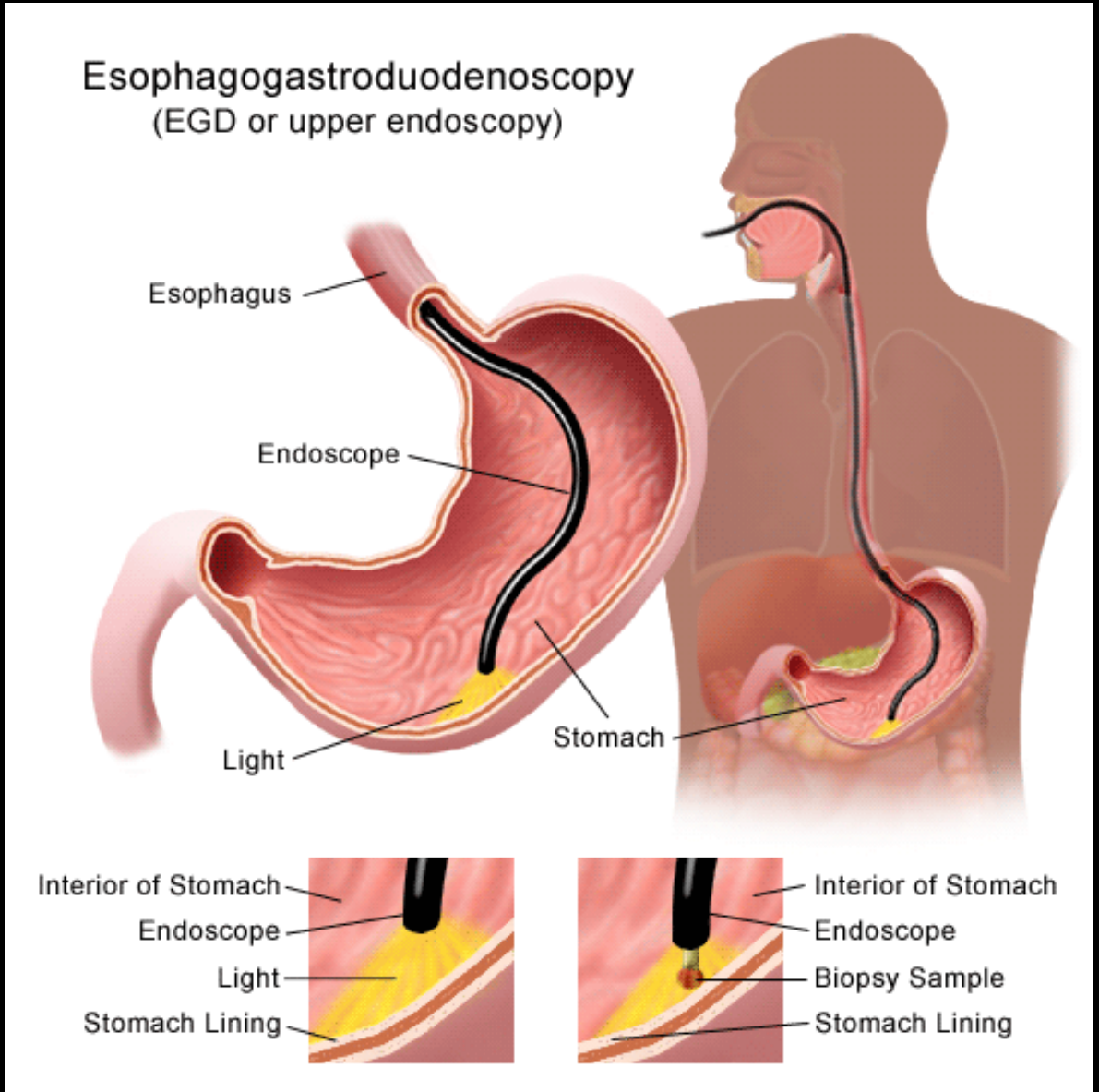
- Blood
  - Full blood count
  - C-reactive protein
  - Liver function tests
  - Absorptive markers (Iron, B12, folate, Vit D …)
- Faeces tests
  - microbiology
  - (calprotectin)

Endoscopy

- Upper GI endoscopy (Gastroscopy)
- Colonoscopy
- Capsule endoscopy
- Balloon enteroscopy

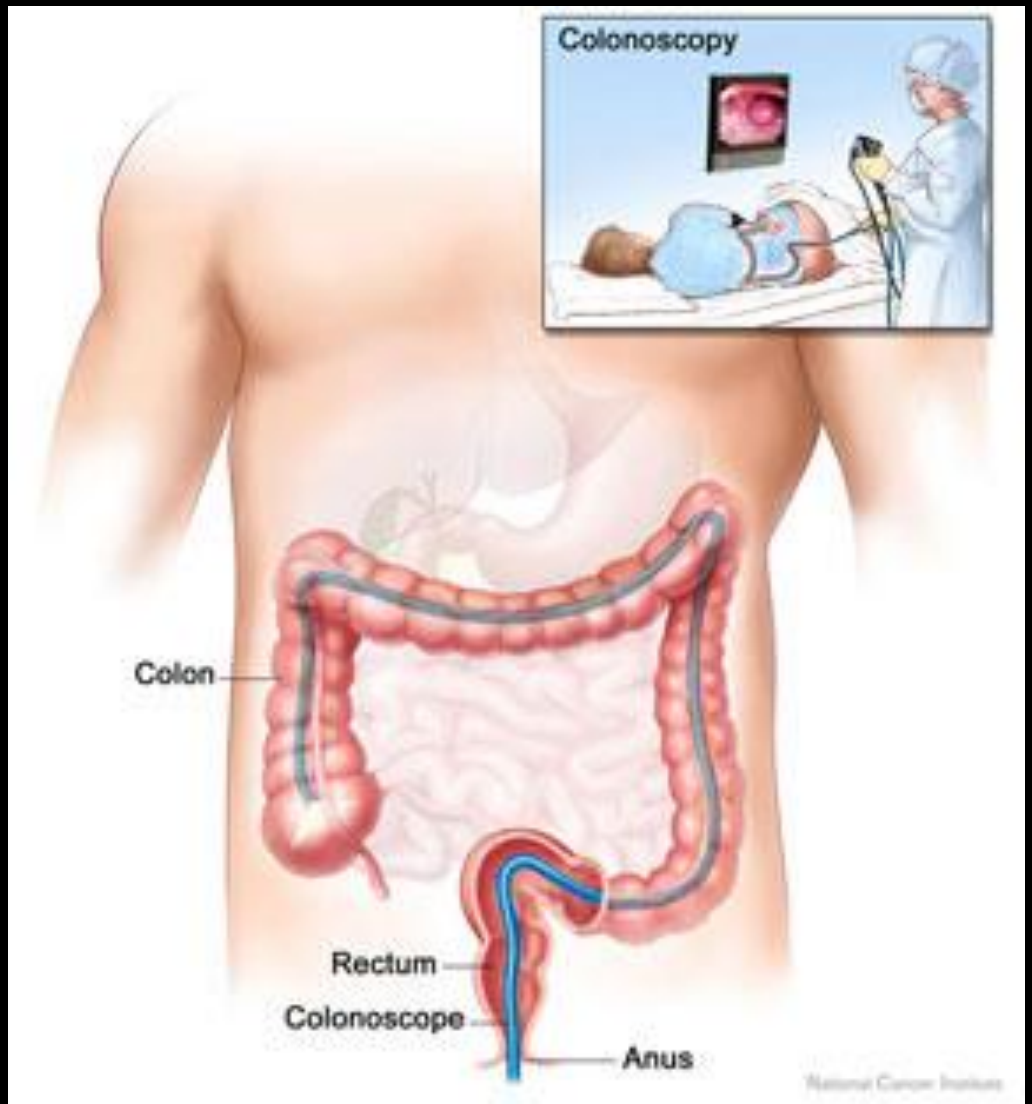
Investigation of the Upper Gut

Endoscopy



Investigation of the colon

- Colonoscopy



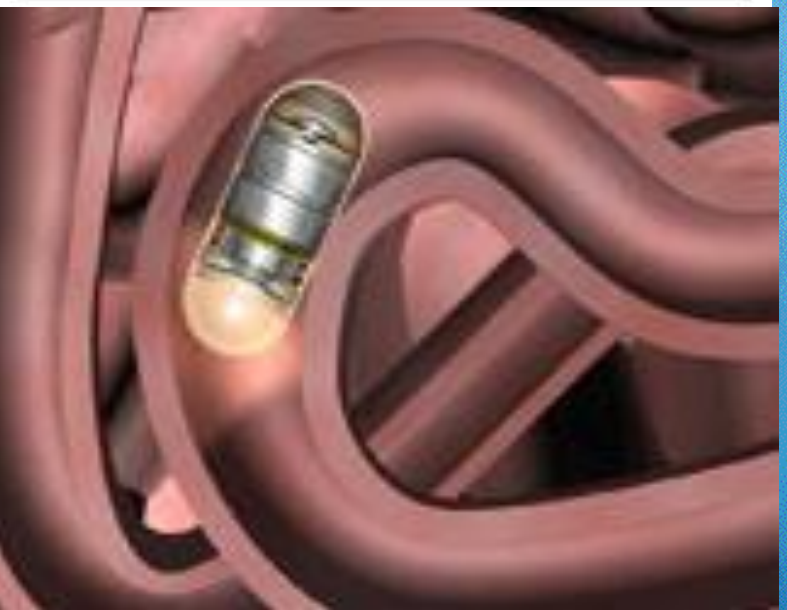
Investigation of the small intestine

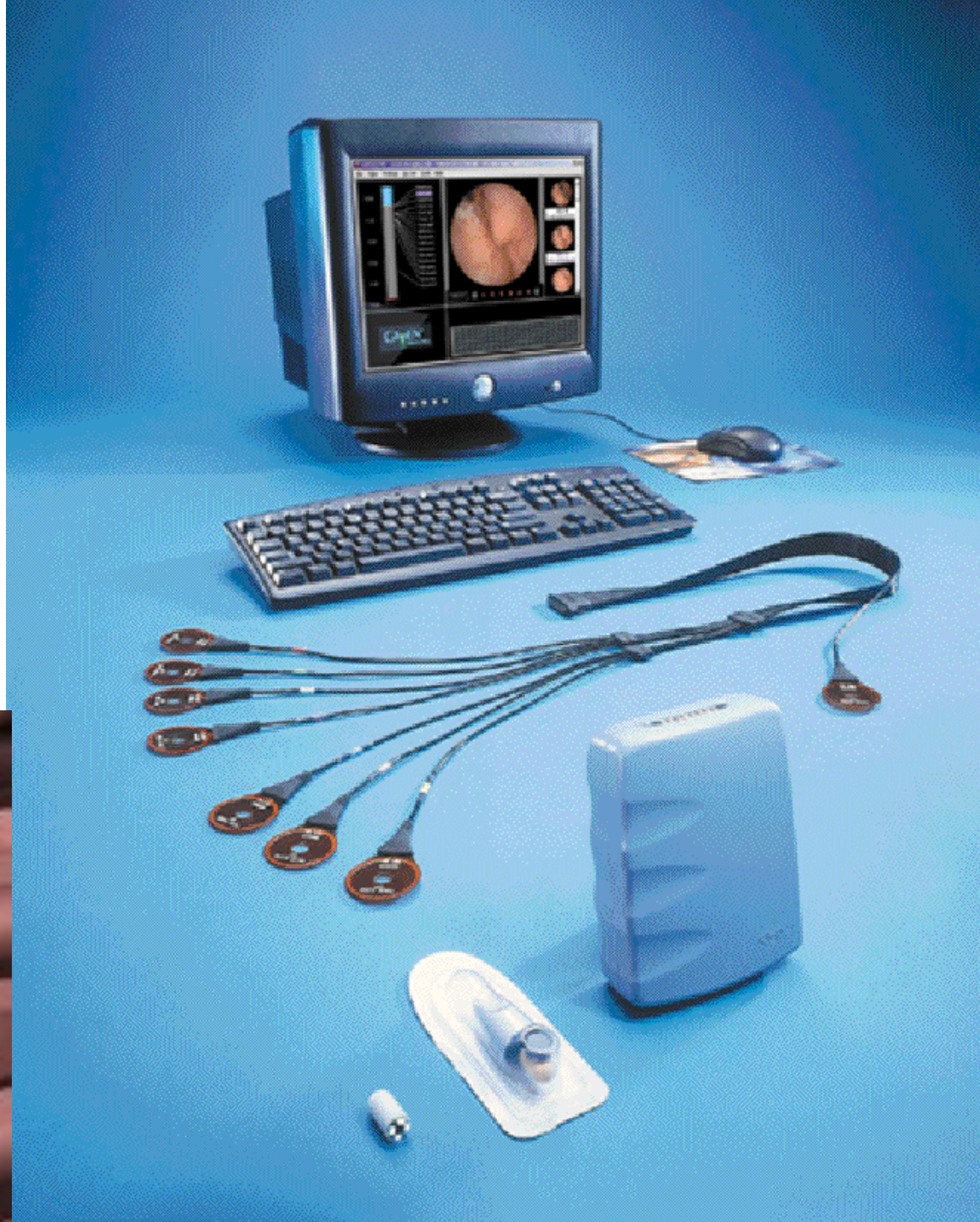
- (Gastroscopy and colonoscopy)

- MRI
- CT
- Capsule
- Balloon enteroscopy

Inside the M2A™ Capsule

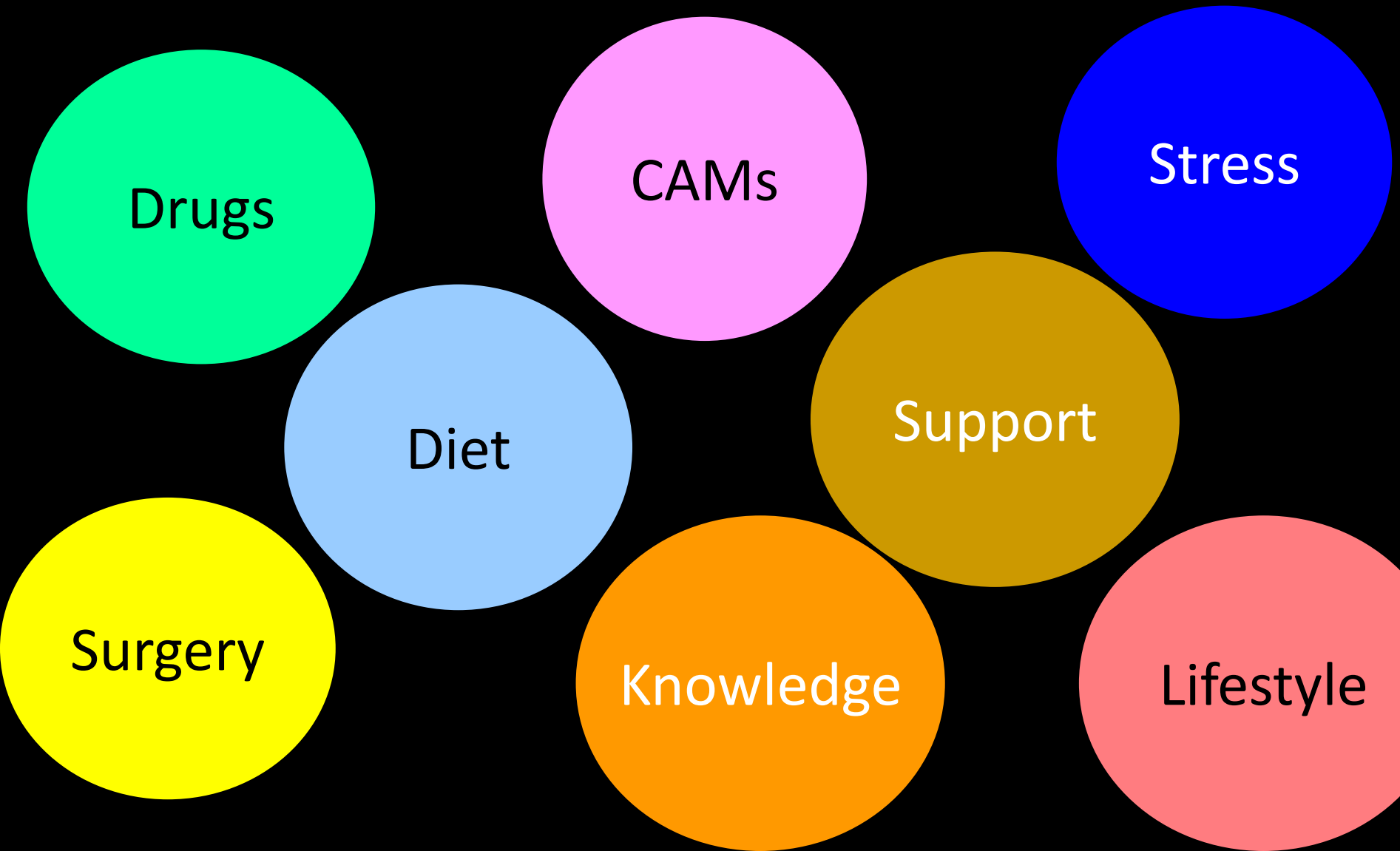
1. Optical dome
2. Lens holder
3. Lens
4. Illuminating LEDs (Light Emitting Diode)
5. CMOS (Complementary Metal Oxide Semiconductor) imager
6. Battery
7. ASIC (Application Specific Integrated Circuit) transmitter
8. Antenna





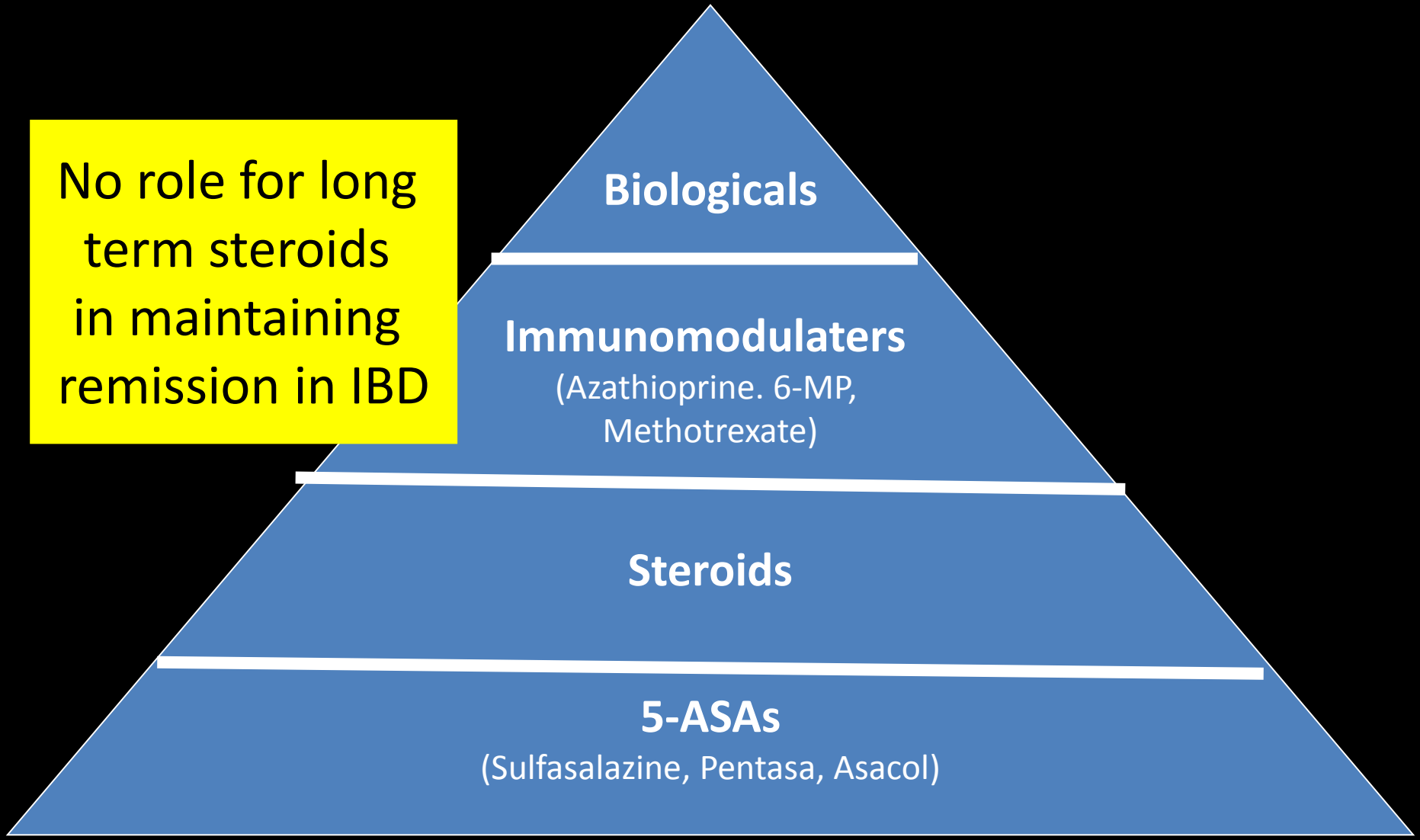
How do we treat IBD?

Treatment for IBD



Medical Treatment for IBD

No role for long term steroids in maintaining remission in IBD



5-ASA Drugs

- Pentasa / asacol / asamax
- Mostly for ulcerative colitis
- Delayed release oral drug
- Rectal preparation (enema / suppository)
- Generally safe but less effective than others

Corticosteroids

- Intravenous (Hydrocortisone)
- Oral (Prednisone / budesonide)
- Rectal (Colifoam)

- Highly effective at inducing remission
- No role in maintaining remission

- Multiple side effects

Azathioprine / 6MP

- Immunomodulators

- Slow onset – used to maintain remission
- “anchor drug” for Crohn’s disease

- Early and late side effects for some
  - a few of these may be predictable

- Regular blood testing required

Anti-TNF drugs (Biologics)

- Infliximab (Remicade) – IV infusions
- Adalimumab (Humira) – SC injections

- Newer / more expensive, limited access
- Gastroenterologist only to initiate

- Work better with an immunomodulator

Antibiotics

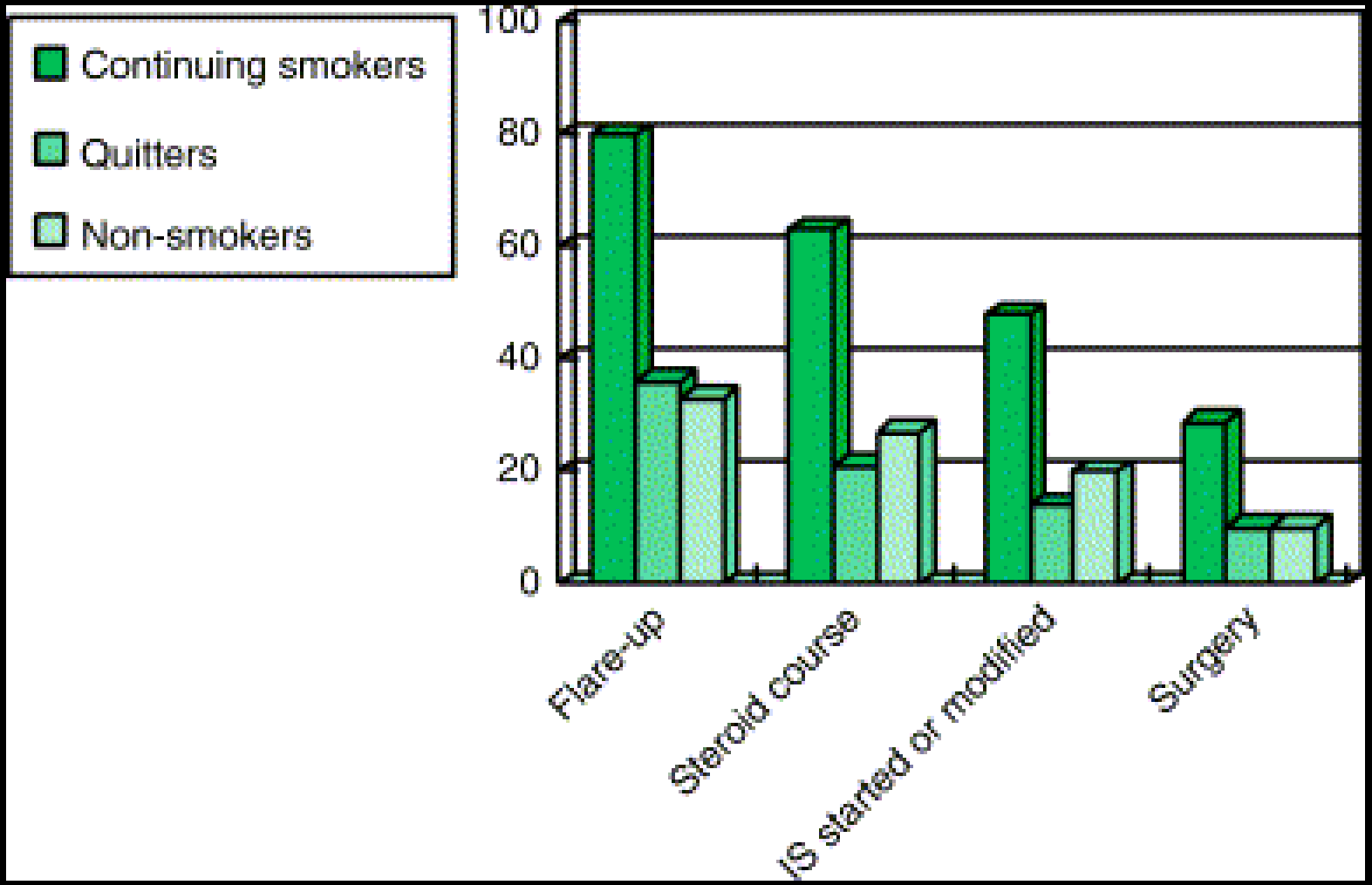
- No role in UC

- Can control infection in perianal CD
- Can have limited effect in colonic CD

Nutrition

- Exclusive enteral nutrition (EEN)
  - all nutrition provided by formula for a given period
  - = steroids for children, may be effective in adults
- Partial / supplemental nutrition
  - improves nutrition and health
- Micronutrient replacement
  - Fe, B12, Folate, Vit D ….

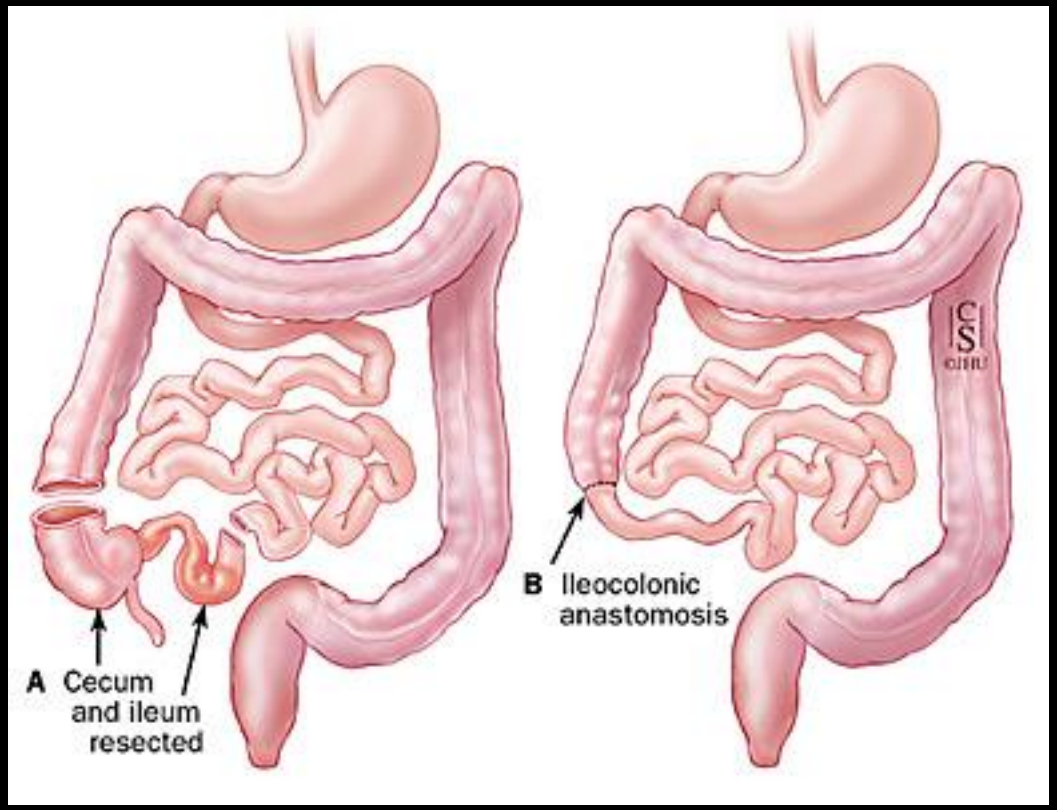
Effect of smoking on Crohn's disease course



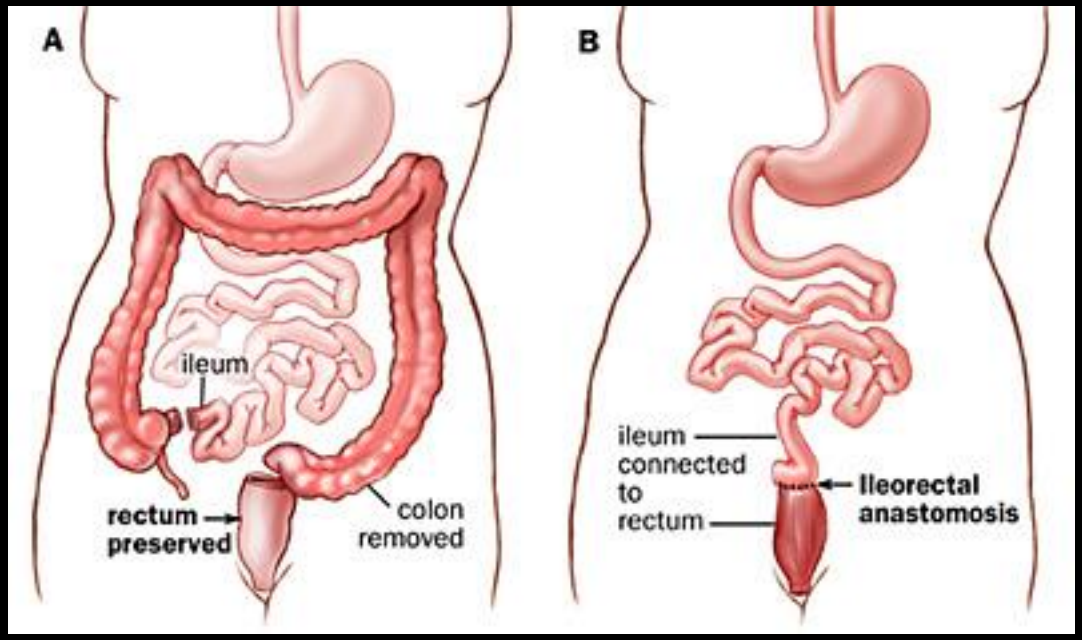
Surgery

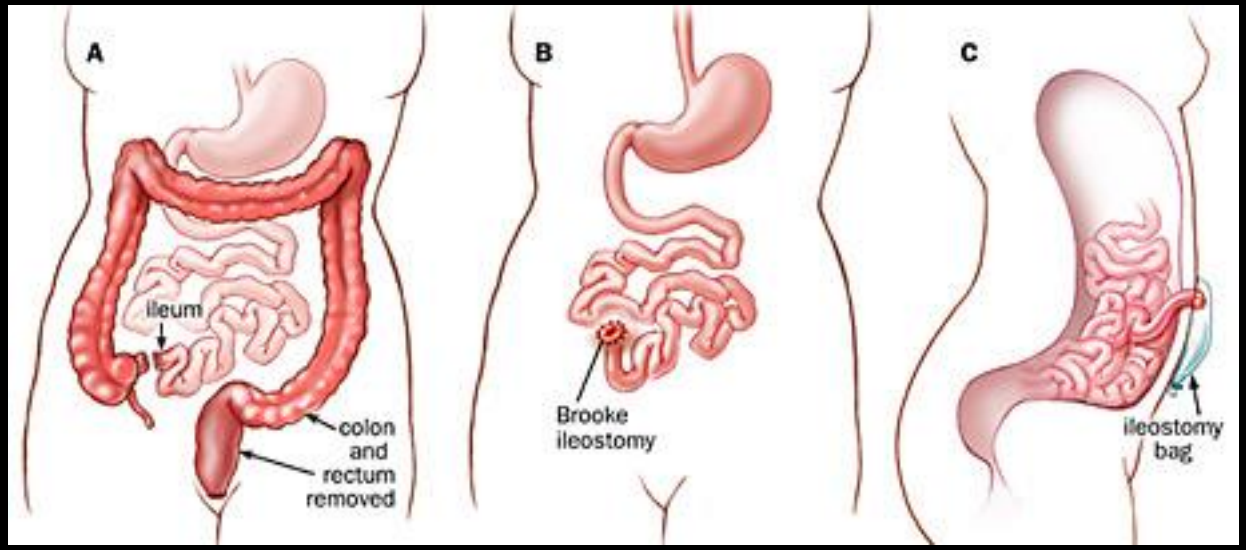
- Indications
  - Complications
  - Failure of medical therapy

Ileocolic resection

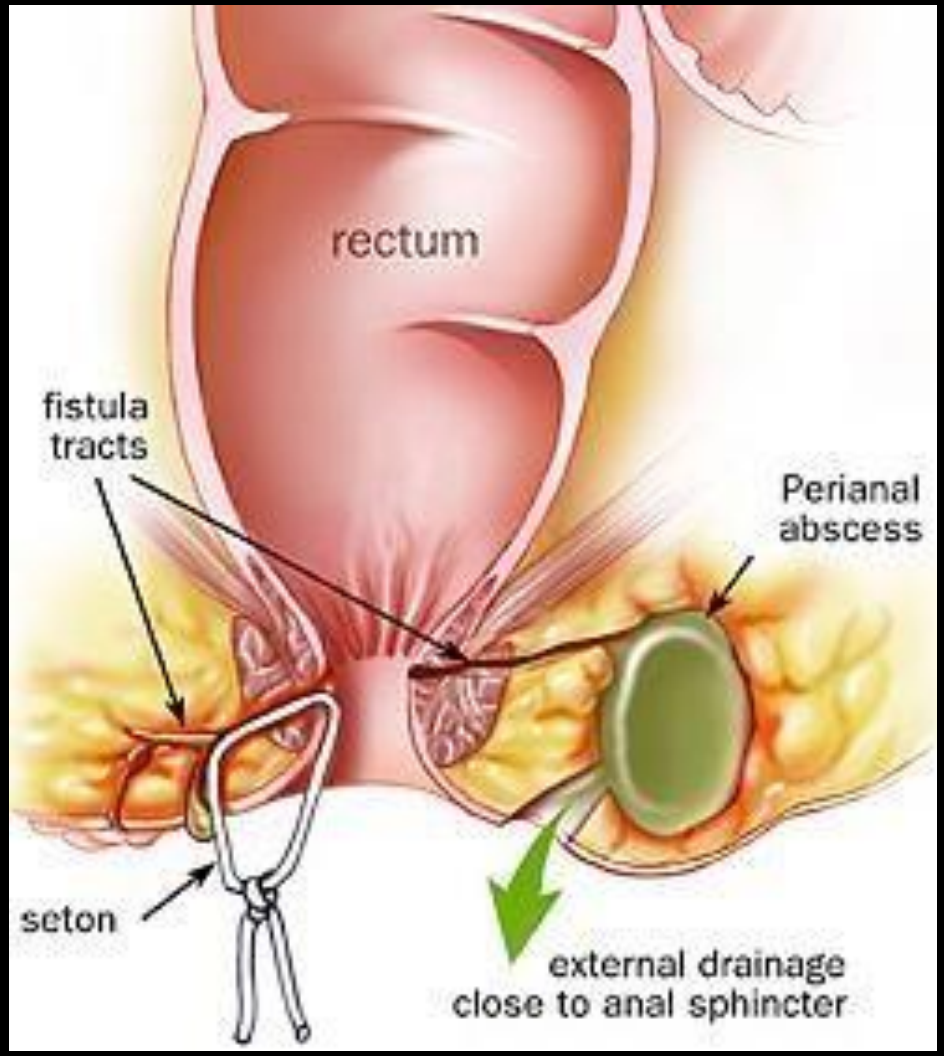


Total colectomy





Perianal Crohn's disease surgery



Other aspects

- Psychological support
- Management of stress
- Management of coexisting IBS
- Workplace support
- Family support

Complications of IBD

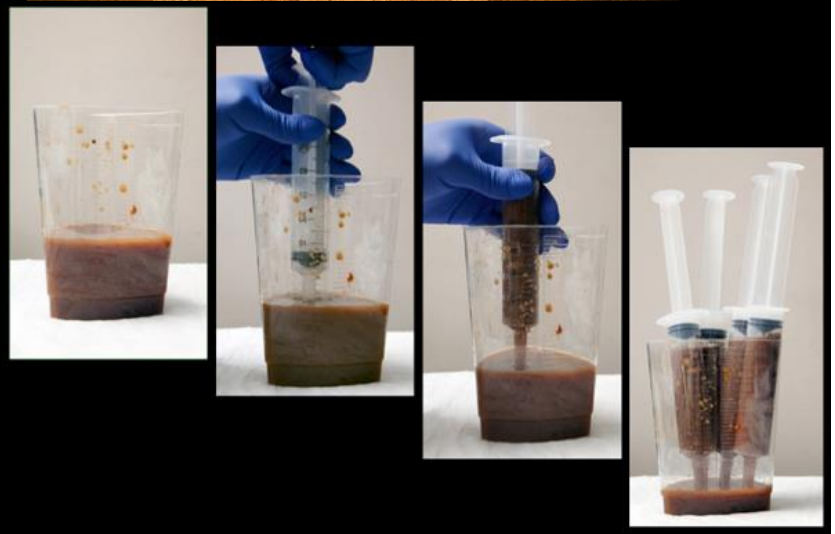
- Complications of disease
  - nutrition
  - cancer
  - clots
  - infection

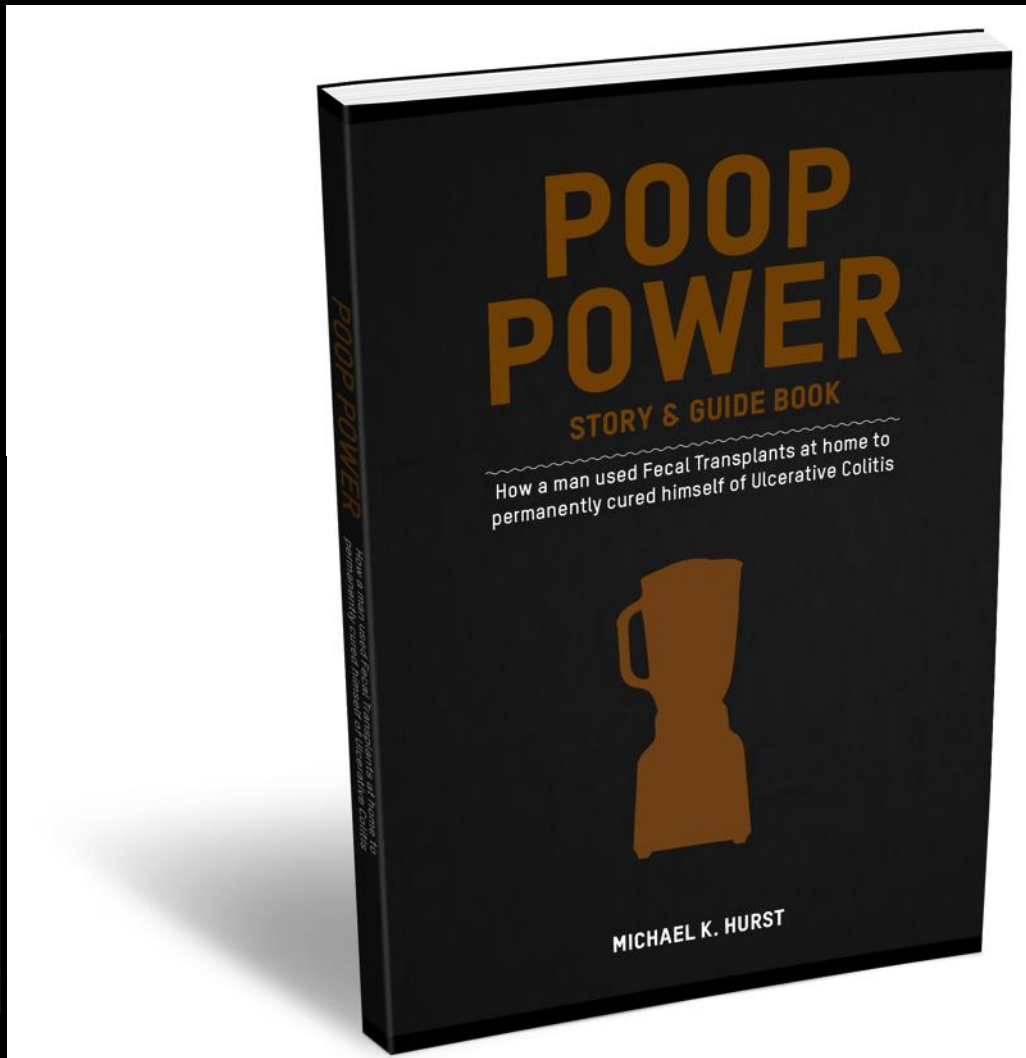
Areas of Controversy

Anti-MAP therapy

- Mycobacterium avium ssp paratuberculosis
- Variable evidence to support an association (no evidence to support causation)
- One negative randomised controlled trial
- Second RCT currently recruiting

Faecal transplant



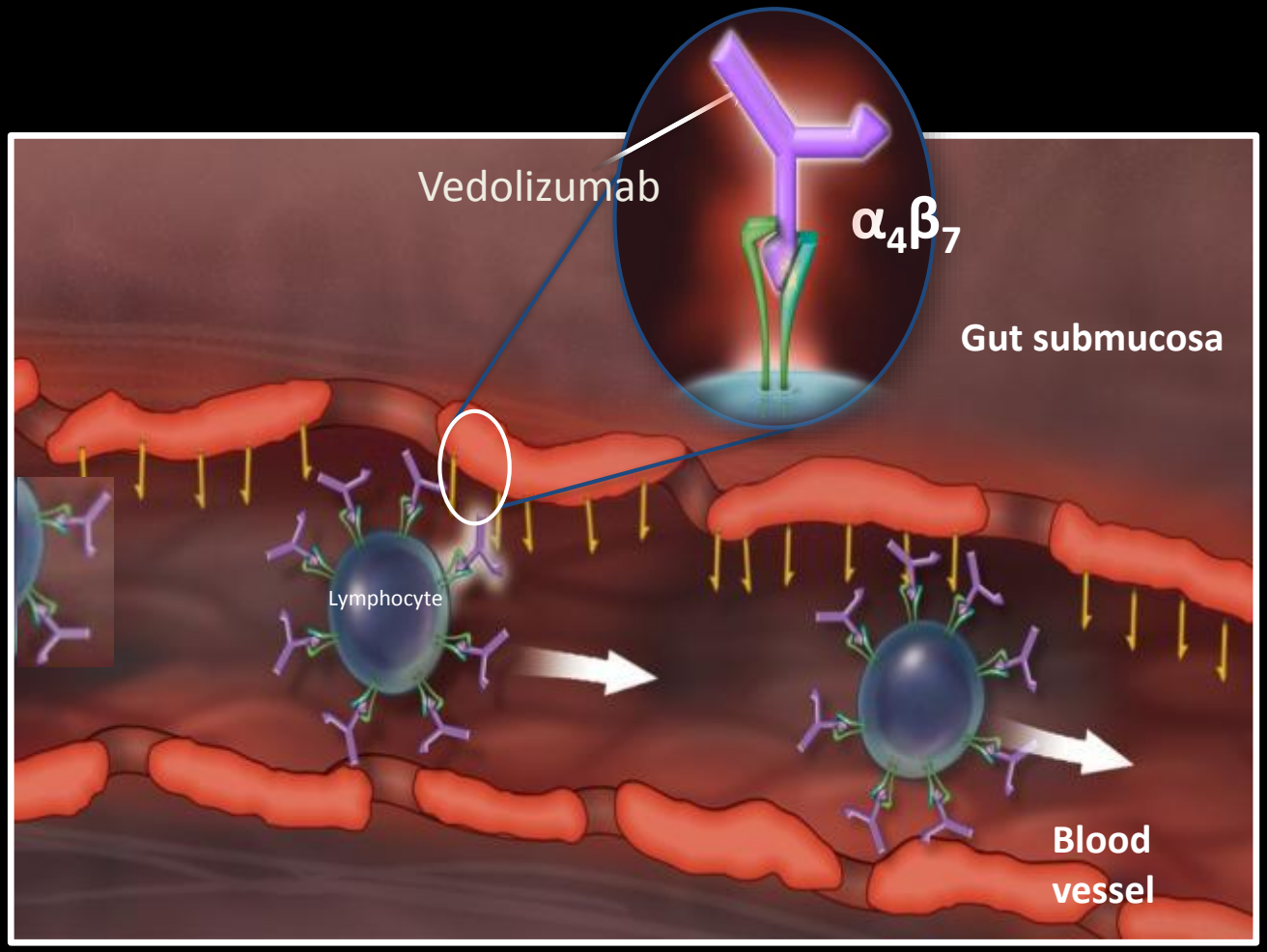


Future directions

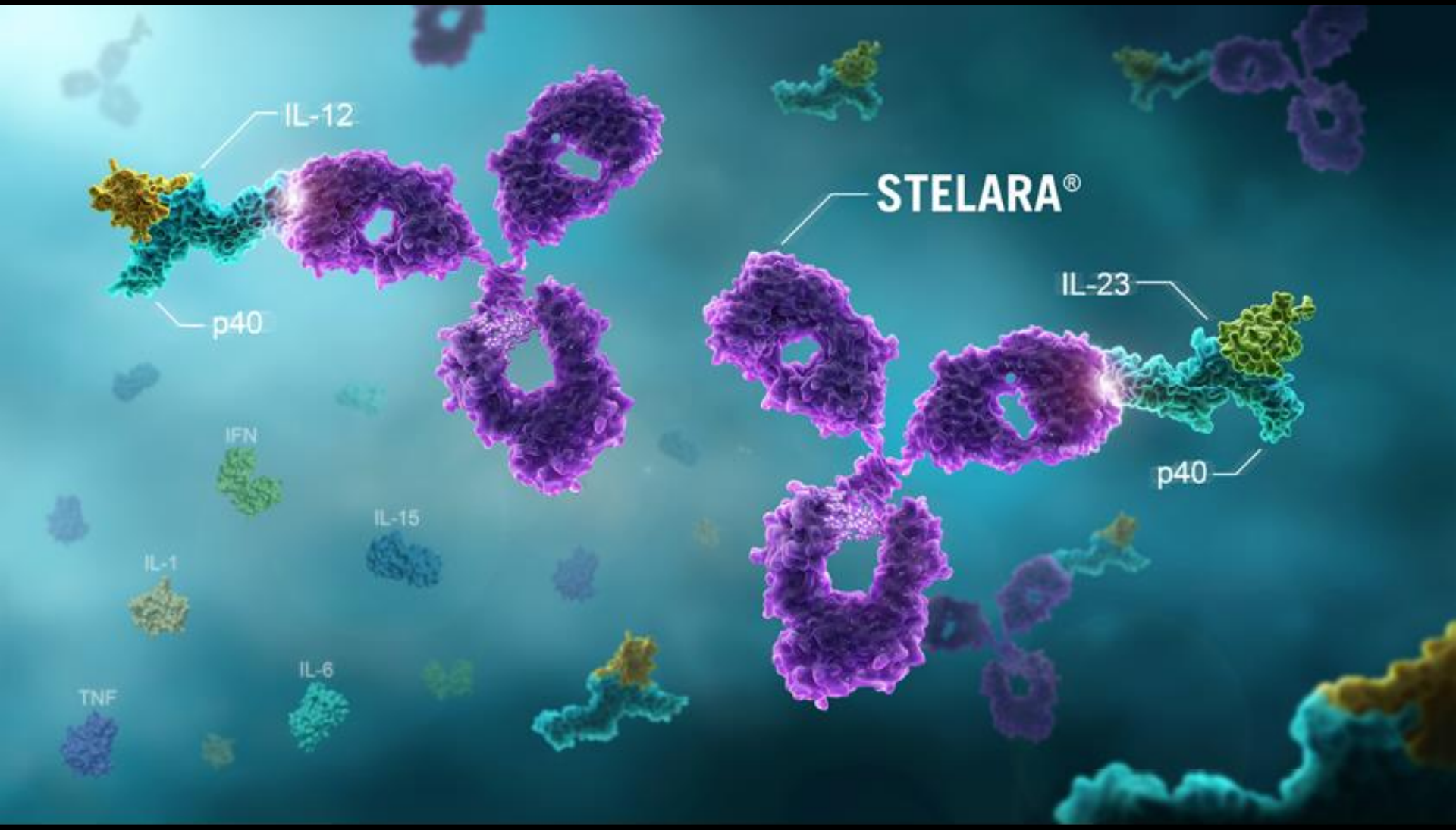
New Drugs

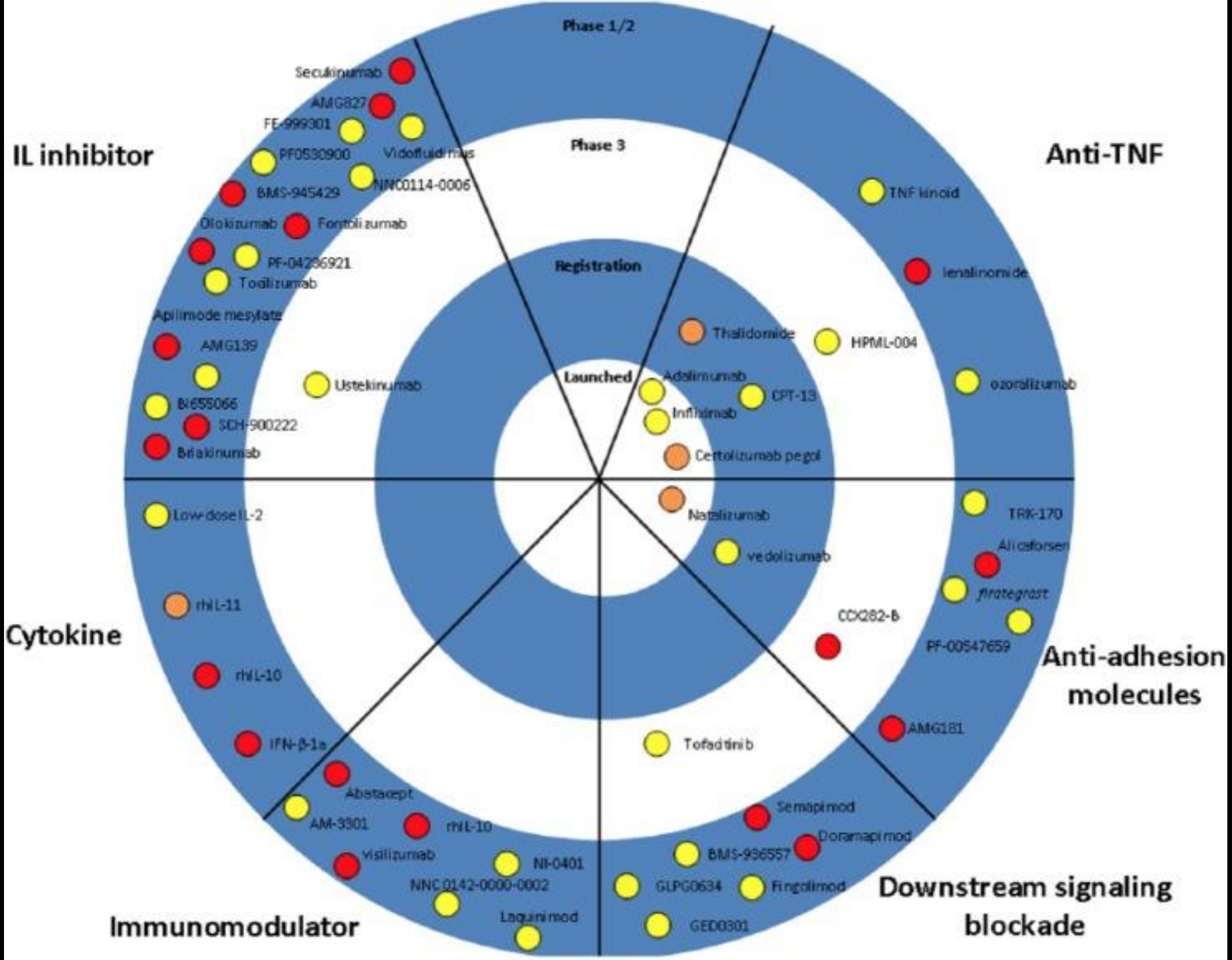
- Understanding the inflammation behind IBD has given us more targets for drugs – these are now coming to market

Vedolizumab

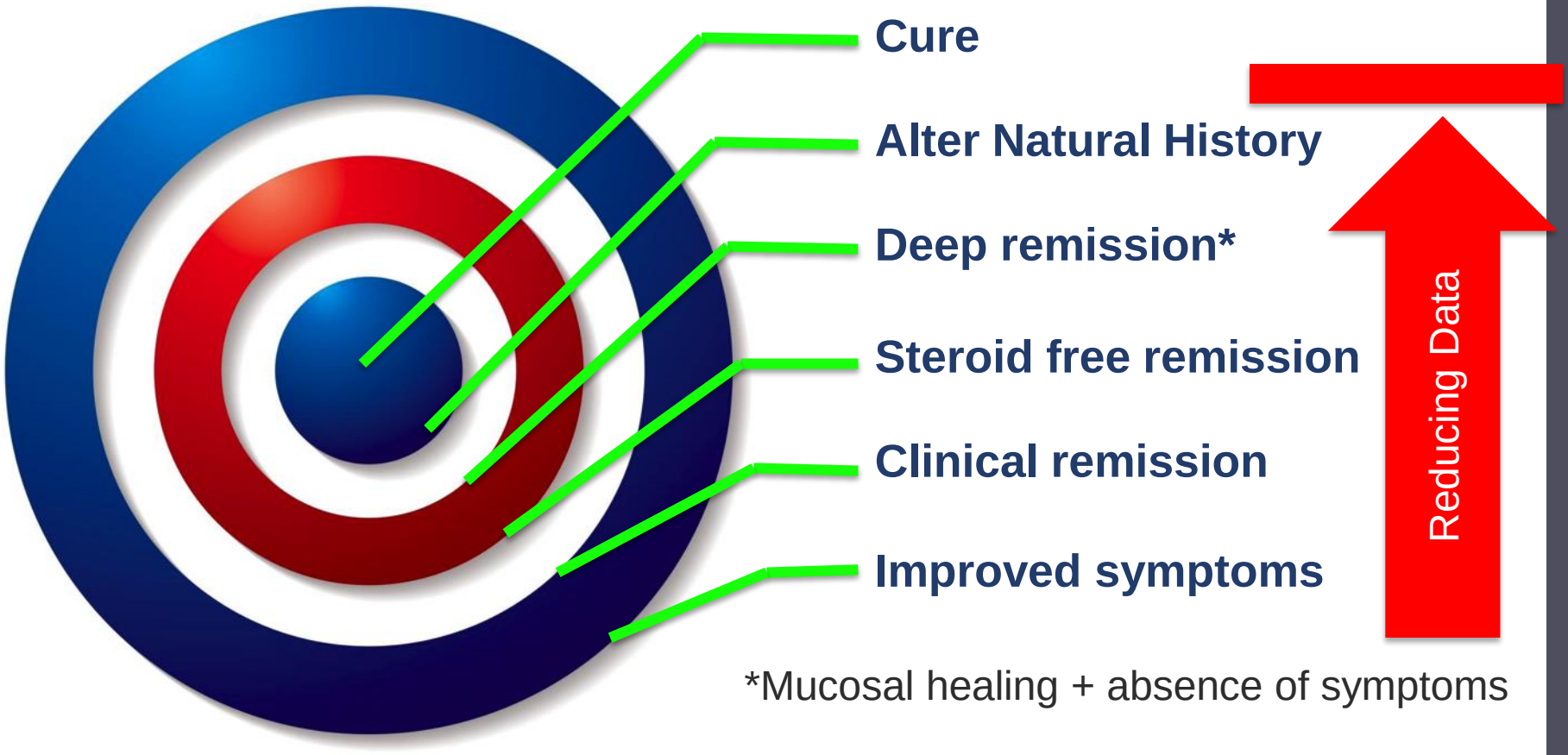


Ustekinumab




Phase 1/2
Phase 3
Registration
Launched
IL inhibitor
Anti-TNF
Cytokine
Anti-adhesion molecules
Immunomodulator
Downstream signaling blockade
Secukinumab
AMG827
FE-999301
PF0530900
Vidofludimus
BMS-945429
NNC0114-0006
Olokizumab
Fontolizumab
PF-04236921
Tocilizumab
Apilimode mesylate
AMG139
BI655066
SCH-900222
Briakinumab
Ustekinumab
Low-dose IL-2
rhIL-11
rhIL-10
IFN-β-1a
Abatacept
AM-3901
rhIL-10
Visilizumab
NI-0401
NNC 0142-0000-0002
Laquinimod
Thalidomide
HPML-004
Adalimumab
CPT-13
Infliximab
Certolizumab pegol
Natalizumab
vedolizumab
Tofacitinib
TNF kinoid
lenalinomide
ozoralizumab
TRK-170
Alicaforsen
fingolimod
PF-00547659
CCX282-B
AMG181
Semapimod
Doramapimod
BMS-936557
GLPG0634
Fingolimod
GED0301

What is acceptable in 2016?



*Mucosal healing + absence of symptoms

What we can achieve determines what is acceptable

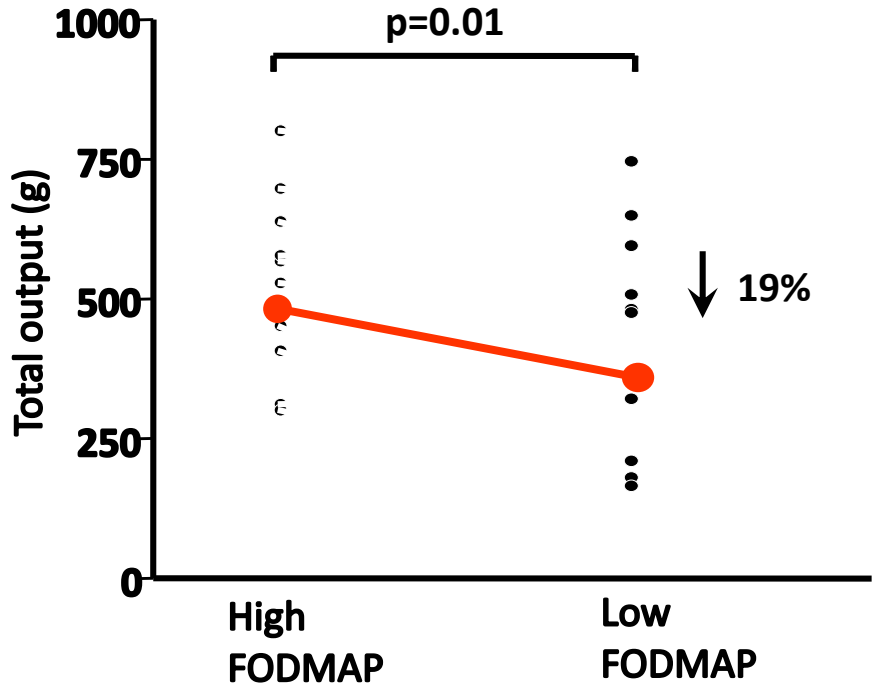
Canterbury Ileostomate Opportunities for research

- People with ileostomies can give us a unique into how food can have an effect on the gut

- If we want to know the effect of food / food components on the small intestine, we need to know what is present at the end of the small intestine

Ileostomates help us to understand the gut

- 10 ileostomates 3 days low or high FODMAP diet



Reduction in dry weight and water content

Reduction in all FODMAPs recovered, especially fructans

Patients described a subjective change in the ileostomy effluent

Barrett, Gearry et al, Aliment Pharmacol Ther., 2009

Conclusions

- IBD incidence appears to still be increasing
  - IBD patients need a voice
- The causes of IBD are becoming clearer (slowly)
- We have many drugs and should use them appropriately
- New drugs will be different and probably better
- We need randomised controlled trials before we support new treatments