INSELGRUPPE

Wednesday seminar: Pathophysiology of IBD

03-15-2023

Niklas Krupka

Early attempts to uncover Crohn's pathophysiology

REGIONAL ILEITIS

A PATHOLOGIC AND CLINICAL ENTITY

BURRILL B. CROHN, M.D.
LEON GINZBURG, M.D.
AND
GORDON D. OPPENHEIMER, M.D.
NEW YORK

DR. BURRILL B. CROHN, New York: In a disease of this type, in which an attempt is being made to establish the etiology of the disease, we have naturally taken great pains to exclude every known etiologic factor. Histologic sections were made of the tissues and stained with various types of stains. Cultures were made. Ground material was injected into guinea-pigs and fowl. Various types of laboratory animals were used to eliminate any possible form of tuberculosis. Löwenstein cultures were made. Dr. Klemperer, the pathologist, exhausted all the known possible scientific methods of finding an etiologic factor. I can say that no etiologic factor was found.

Today we know more

Crohn BB et al. 1932

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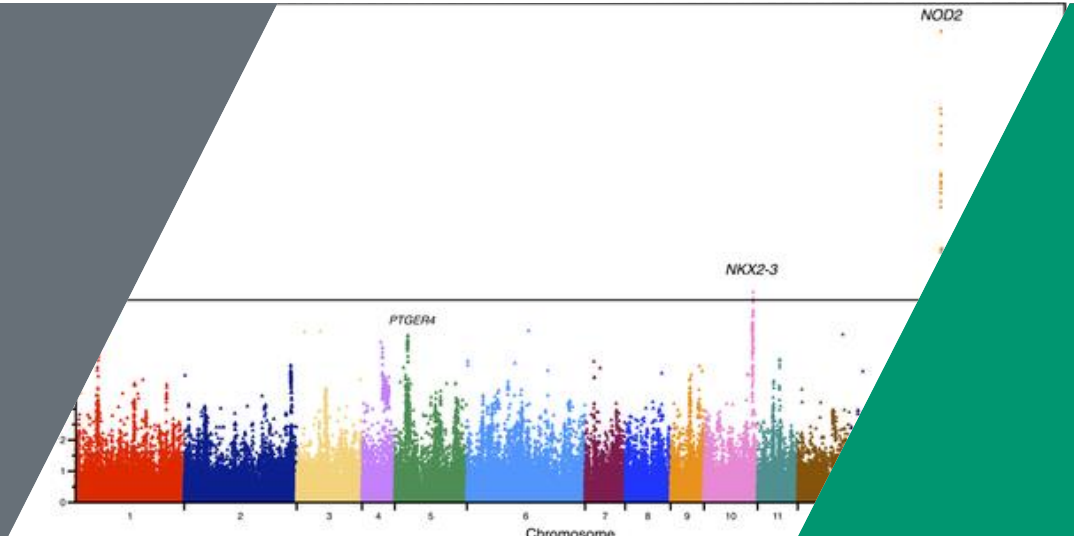
Genetic factors



Increased IBD risk in first-degree relatives of IBD patients

Table 3. Prevalence of Ulcerative Colitis and Crohn's Disease per 100,000 Persons among First- and Second-Degree Relatives.*

Disease in Proband	Prevalence among First-Degree Relatives		Prevalence among Second-Degree Relatives	
	Ulcerative colitis	Crohn's disease	Ulcerative colitis	Crohn's disease
Ulcerative colitis	1522 (1114, 2030)	99 (21, 288)	264 (165, 542)	12 (0, 67)
Crohn's disease	711 (230, 1660)	569 (155, 1457)	52 (1, 289)	156 (32, 455)

Conclusions. The 10-fold increase in the familial risk of ulcerative colitis and Crohn's disease strongly suggests that these disorders have a genetic cause. (N Engl J Med 1991; 324:84-8.)

Orholm M et al. N Engl J Med 1991; 324:84-88

Increased IBD risk in identical twins

Concordance for inflammatory bowel disease in twin pairs

	Identical twin		Non-identical twin	
Proband's diagnosis	**Disease**	**No disease**	**Disease**	**No disease**
Crohn's disease	5	20	3	43
Ulcerative colitis	6	32	1	33
Total	11	52	4	76

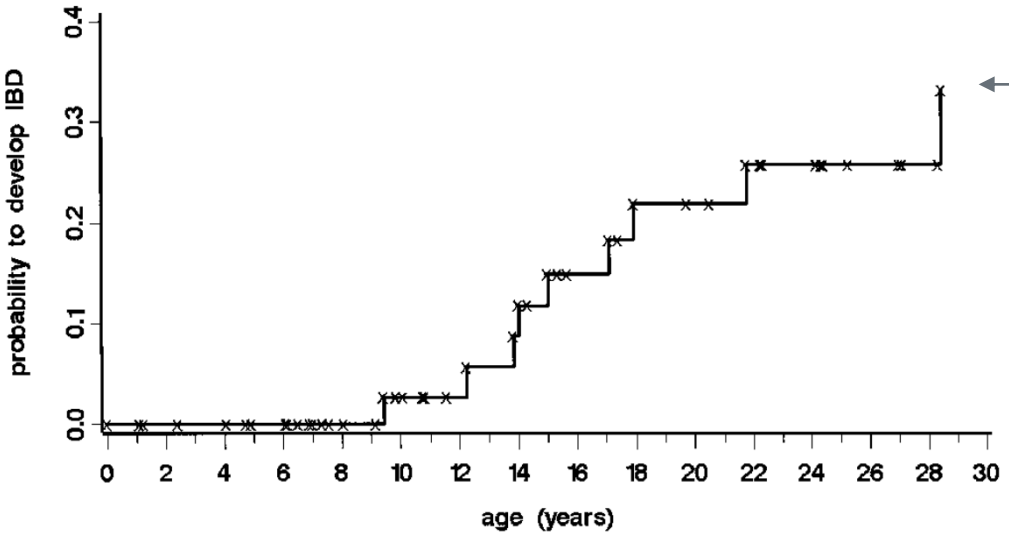
In twins of IBD patients:

- 17% IBD if monozygotic
- 5% IBD if dizygotic

→ Genetic factors are important but >83% of variance is unexplained by genetics

Thompson NP et al. BMJ. 1996;312(7023):95-6

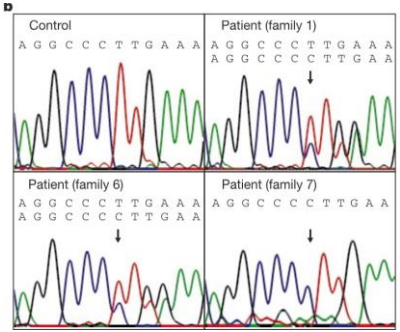
Increased risk of CD if both parents have CD

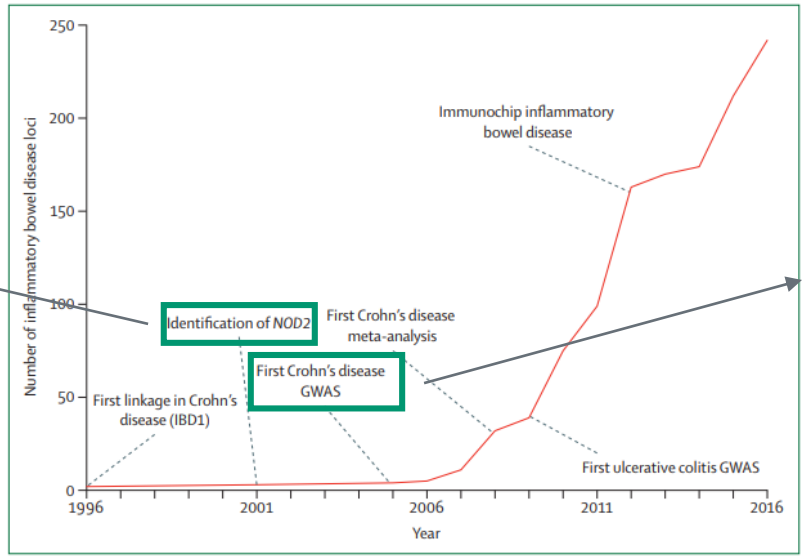


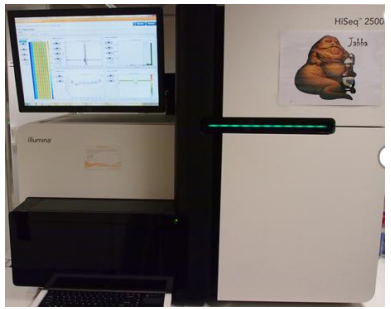
33% CD risk if both parents have CD

Laharie D et al. Gastroenterology. 2001;120(4):816-9

Identification of more IBD risk loci by high-throughput sequencing

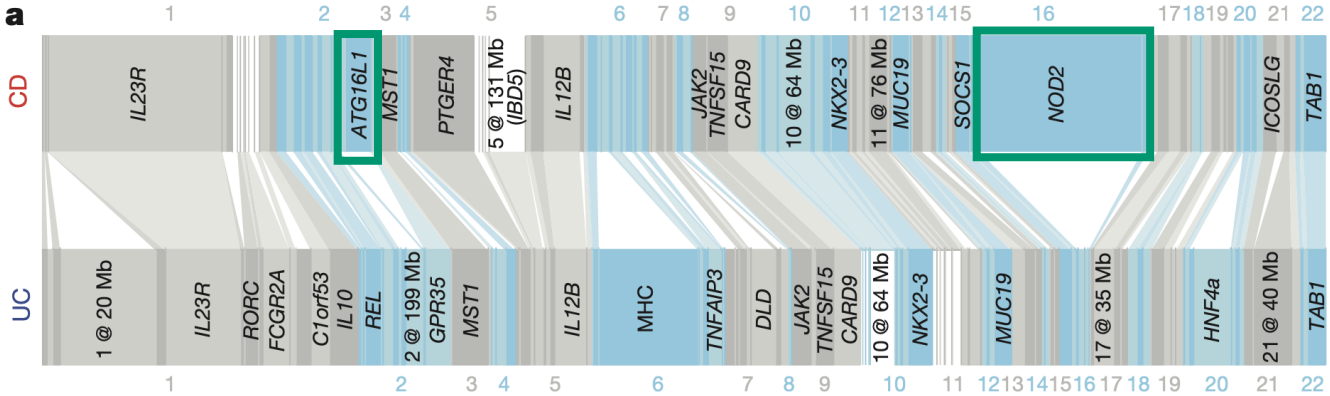






Ogura Y et al. Nature. 2001;411(6837):603-6
Irkov et al. Lancet Gastroenterol Hepatol 2017; 2: 224–34

Over 200 loci have been associated with IBD

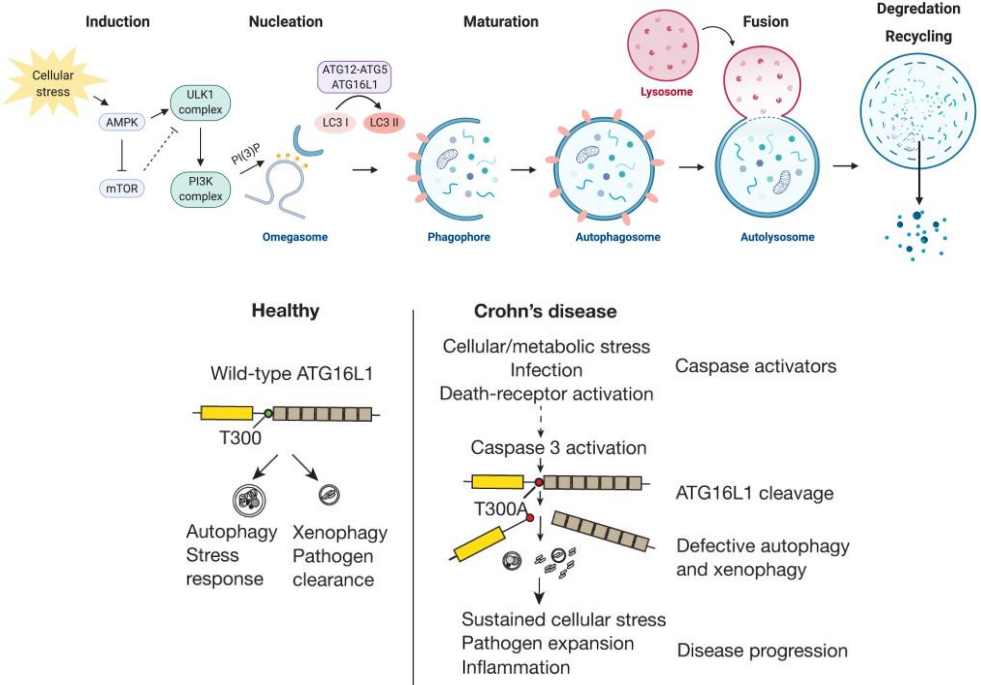


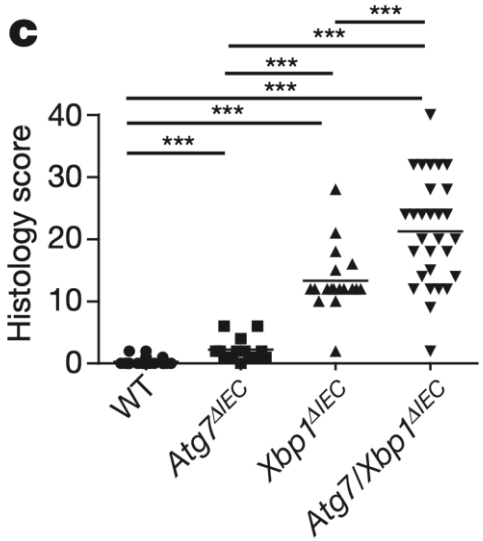
Most loci can be mapped to genes that are involved in:

- Epithelial barrier
- Mucosal immune function
- Basic cell functions (e.g. autophagy, ER stress)

Jostins L et al. Nature. 2012;491(7422):119-243

The T300A variant of ATG16L1 leads to impaired autophagy, cellular stress and inflammation





Murthy A et al. Nature. 2014;506(7489):456-62
Adolph TE et al. Nature. 2013;503(7475):272-6

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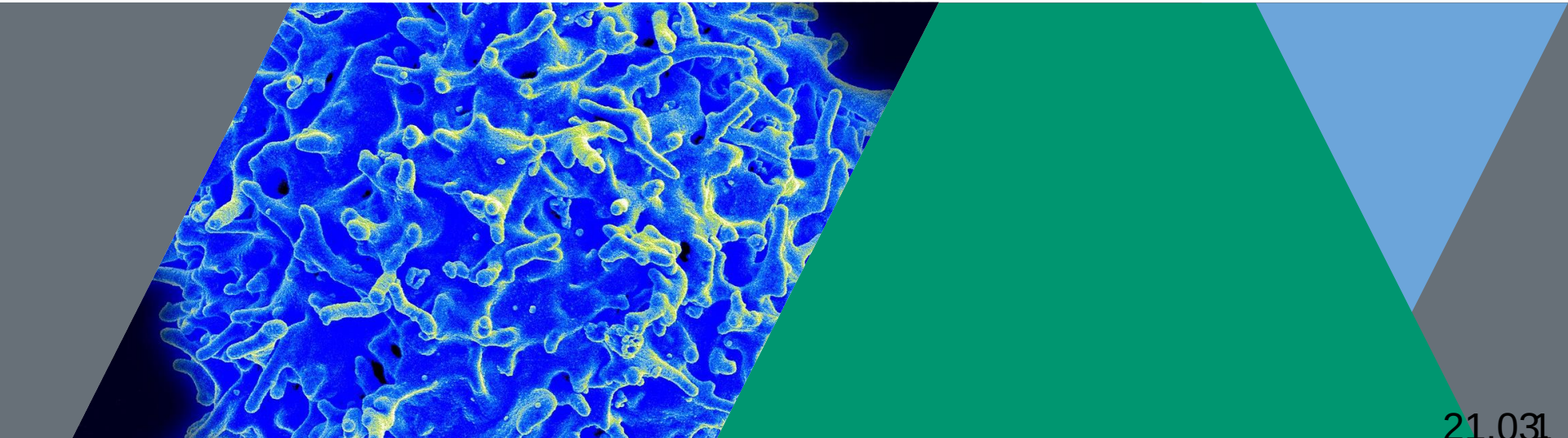
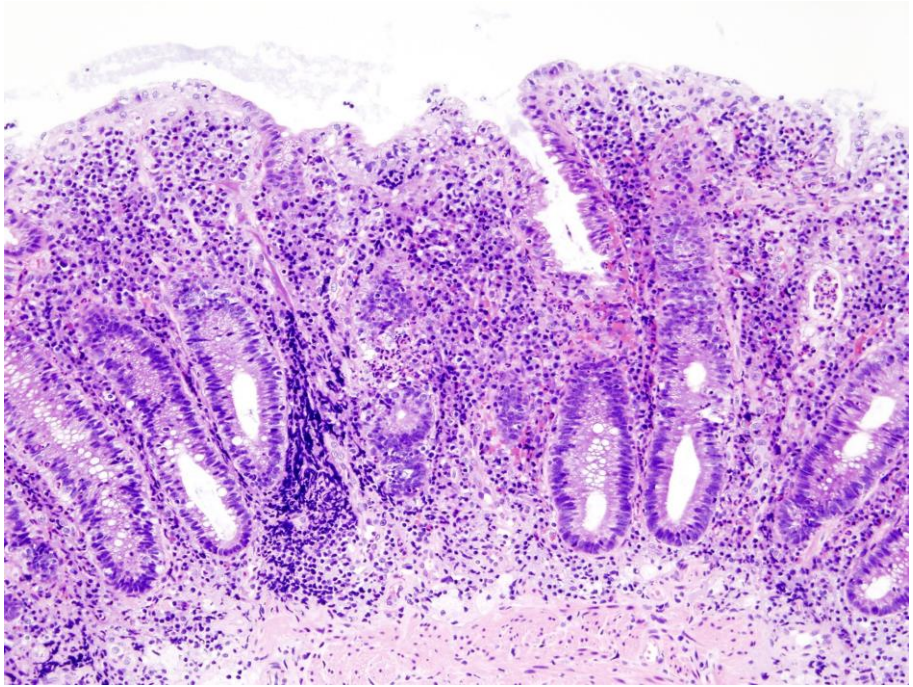
Mucosal immunity



The mucosal immune system separates the inner from the outer world

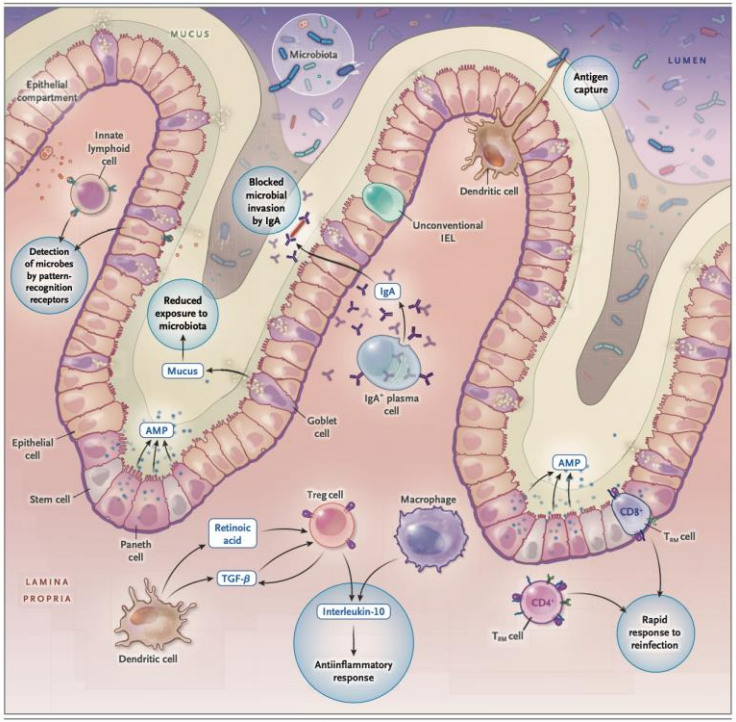


Not everything that is “foreign” needs a strong immune response (e.g. food antigens, microbiota)

Dysregulation
→ Inflammation

Image: Wikipedia

Intestinal immunity in IBD



Impaired in IBD:

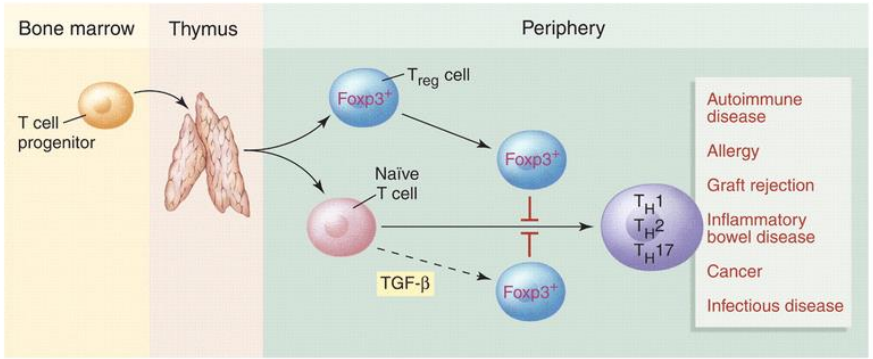
- Mucin
- Tight junctions
- Paneth cell function

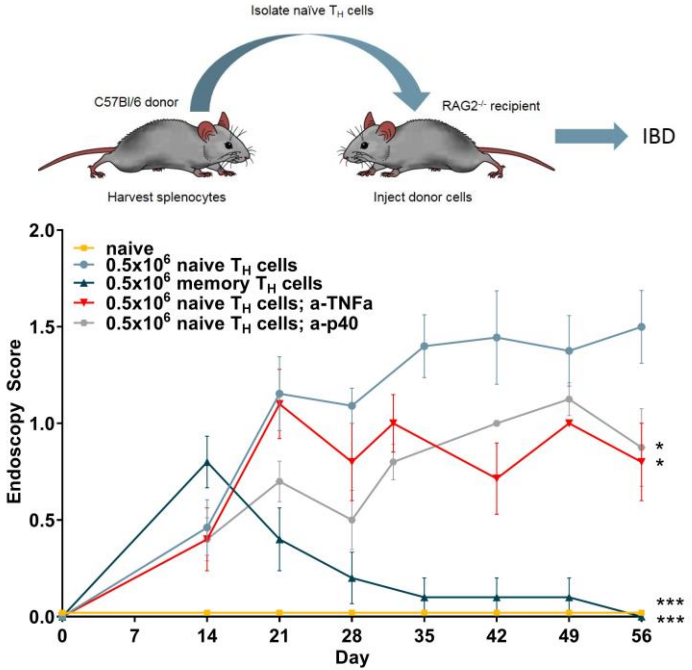
- Balance of cytokines
- Balance of Th_1 /Th_{17}/T_{reg}

And many more…

Chang JT. N Engl J Med. 2020;383(27):2652-2664

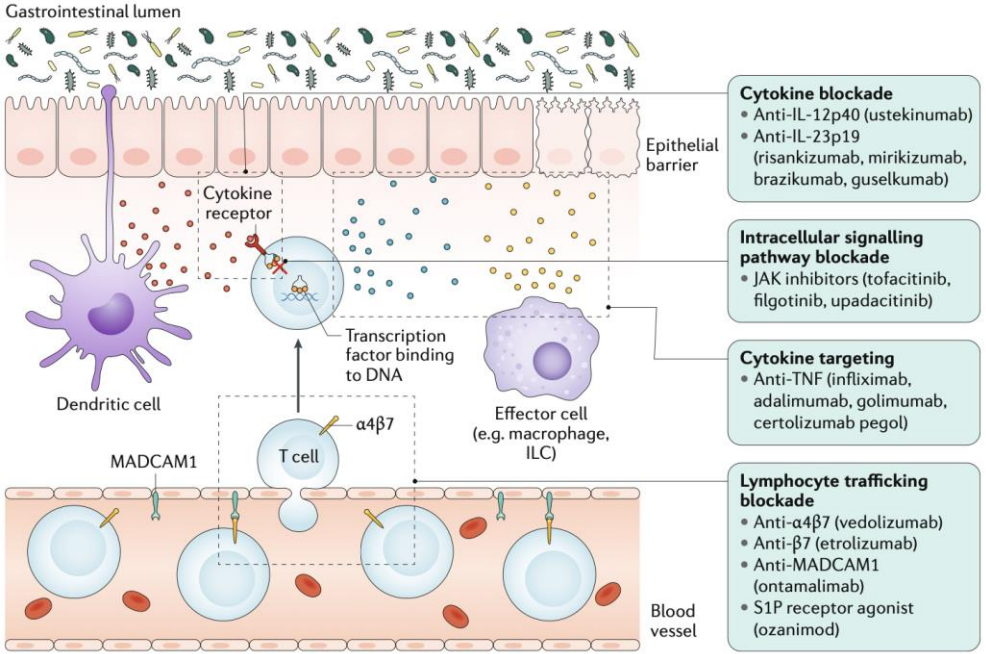
Disturbed T cell homeostasis can lead to intestinal inflammation





Images: Biomodels.com
Model: Powrie F et al. Int Immunol. 1993;5(11):1461-71
Sakaguchi S et al. Science. 2007;317(5838):627-9

Mucosal immune cells and their cytokines are drug targets in IBD



Digby-Bell JL et al. Nat Rev Gastroenterol Hepatol. 2020;17(1):9-20

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Microbiota

High exposure of the GI tract to microbiota

Location	Typical concentration of bacteria [1] (number/mL content)	Volume (mL)	Order of magnitude bound for bacteria number
Colon (large intestine)	10^{11}	400 [2]	10^{14}
Dental plaque	10^{11}	<10	10^{12}
Ileum (lower small intestine)	10^{8}	400 [5]	10^{11}
Saliva	10^{9}	<100	10^{11}
Skin	$<10^{11}$ per m^2 [3]	1.8 m^2 [4]	10^{11}
Stomach	10^{3}–10^{4}	250 [5]–900 [6]	10^{7}
Duodenum and Jejunum (upper small intestine)	10^{3}–10^{4}	400 [5]	10^{7}

Sender R et al. PLoS Biol. 2016;14(8):e1002533

Intestinal contents trigger recurrence of CD

TABLE II—ENDOSCOPIC AND HISTOLOGICAL DATA

	During exclusion		After reanastomosis		
Patient	Ileocolonoscopy	Histology	Ileocolonoscopy score*	Extent of disease (cm)	Histology
1	Normal	No visible lesions	i_4	20	Severe inflammation
2	Normal	No visible lesions	i_3–i_4	25	Severe inflammation; microgranulomas
3	Normal	No visible lesions	i_2	5	Severe inflammation; microgranulomas
4	Normal	No visible lesions	i_2	10	Severe inflammation
5	Normal	No visible lesions	i_3	30	Severe inflammation

*See text for details of scoring system

Rutgeerts P et al. Lancet. 1991;338(8770):771-4

Intestinal contents trigger postoperative recurrence of CD

Table 1. Patient Characteristics

Patient	Sex	Age (*yr*)	Age at diagnosis (*yr*)	Involvement	Indication for surgery	Indication for loop ileostomy	Clinical recurrence
1 (D.M.)	M	29	20	Ileum + cecum + rectosigmoid colon	Ileal perforation	Fistulizing rectal disease	3 mo after reanastomosis
2 (M.V.)	F	38	19	Ileum + asc + rectosigmoid colon	Fistulization, ileum-sigmoid colon, sacral bone	Inflammation around colorectal anastomosis	6 wk after reanastomosis
3 (N.W.)	F	51	27	Ileum + anus + rectosigmoid colon	Stenotic ileitis, stenosis sigmoid colon, anorectal fistulas	Fistulizing rectal disease	—

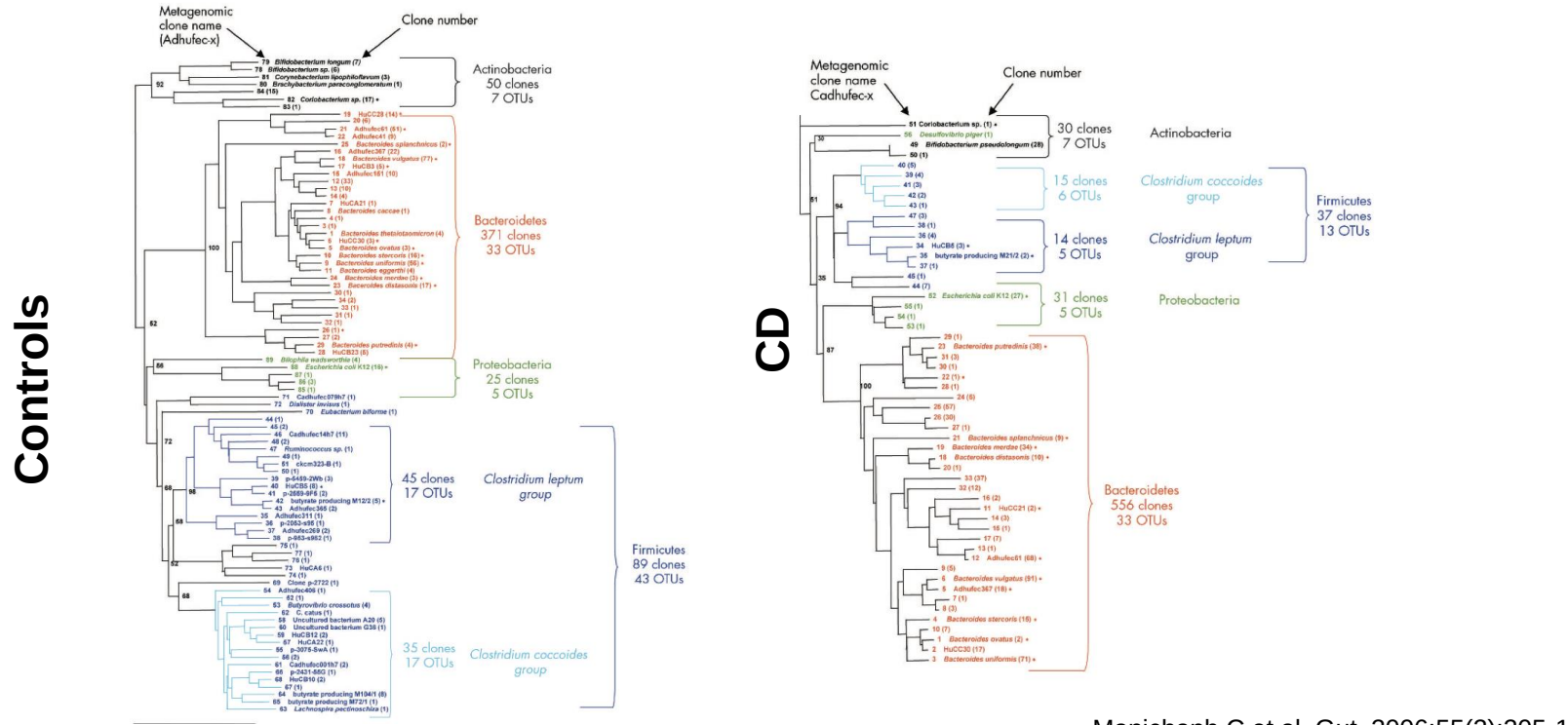
Table 3. H&E Biopsy Specimen Score and Immunohistochemical Features of Normal Ileal Biopsy Specimens and Crohn's Disease Ileal Biopsy Specimens in the Distal Loop Before and After Reinfusion

	Normal ileum (controls)	Proximal ileum			Distal ileum before infusion			Distal ileum after infusion		
		Pt 1	Pt 2	Pt 3	Pt 1	Pt 2	Pt 3	Pt 1	Pt 2	Pt 3
H&E (CD biopsy score)	0	0	0	0	0	0	0	5	6	8
HLA-DR epithelium	0/+	0/+	+	0/+	+	0	+	++	+++	+++
CD68 (KP-1)	0/+	0/+	0	0/+	0/+	0/+	0	+++	+++	+++
RFD-7	+	+	0	+	+	+	+	++	++	++
RFD-9	0	0	0	0	+	0	+	++	++	++
B7-1	0/+	0	0	0/+	+	0/+	0	+	+	+
ICAM-1 endothelium	+	+	+	0	++	+	++	+++	+++	+++
ICAM-1 monocytes	0	0	0	0	0/+	0	0/+	+	++	+
LFA-1	++	+	++	+	+	++	+	++	++	++

NOTE. For patient characteristics, see Table 1. Staining positivity was assessed semiquantitatively as follows: 0, entirely negative; 0/+, <10% positive cells; +, 10%–33% positive cells; ++, 33%–66% positive cells; and +++, >66% positive cells.
CD, Crohn's disease; Pt, patient.

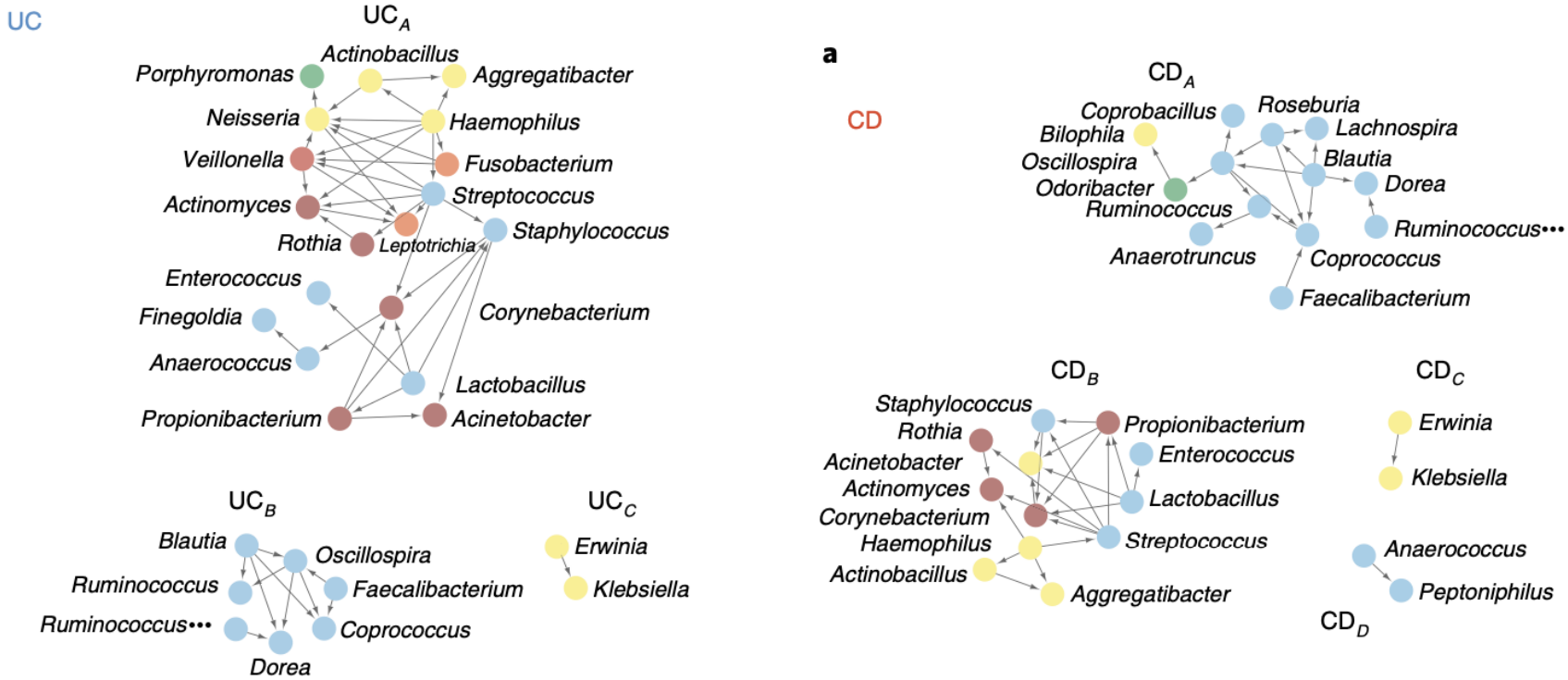
D'Haens GR et al. Gastroenterology. 1998;114(2):262-7

IBD is associated with reduced diversity in fecal microbiota



Manichanh C et al. Gut. 2006;55(2):205-11

IBD is associated with changes of the intestinal microbiota



Yilmaz B. et al. Nature Medicine volume 25, 323–336 (2019)

Arguments in favor of the involvement of microbiota in IBD

Data highlighting the involvement of intestinal microbiota in IBD	Disease
Fecal stream diversion prevents recurrence of Crohn's disease in the neoterminal ileum	CD
Reinfusion of luminal contents into bypassed colonic segments rapidly results in recurrent disease	CD
Antibiotic therapy with metronidazole, ciprofloxacin, or rifaximin were associated with clinical improvement in patients with IBD	CD (including perianal or fistulous disease), UC, and pouchitis
Higher level of serum reactivity toward microbial antigens	CD
Mucosal barrier defects	CD
Increased bacterial translocation	CD
Altered intestinal mucus barrier	UC
Increased number of colon-associated mucolytic bacteria (*Ruminococcus gnavus* and *torques*)	CD and UC
Higher concentrations of mucus- or mucosal-associated bacteria (γ-proteobacteria, actinobacteria, and bifidobacteria)	CD and UC
Higher concentrations of mucosal- and intraepithelial-associated bacteria	CD
Decrease in microbiota biodiversity observable in mucosa-assosiated microbiota and/or in feces	CD and UC
Decrease in Feacalibacteria (*Feacalibacterium prausnitzii*) in mucosa-assosiated microbiota or fecal samples	CD and UC
Decreased antimicrobial peptides secretion leading to overgrowth, increased mucosal adherence, and translocation of commensal bacteria.	UC and CD
Polymorphisms of CD-susceptibility genes involved in the killing of intracellular bacteria and/or antimicrobial peptide secretion by Paneth cells (*NOD2*, *ATG16L1*, *IRGM*)	CD
Polymorphism of the IBD-susceptibility gene Xbp1 involved in ER stress and antimicrobial peptides secretion by Paneth cells	CD and UC

Chassaing B , Darfeuille-Michaud A. Gastroenterology. 2011;140(6):1720-28

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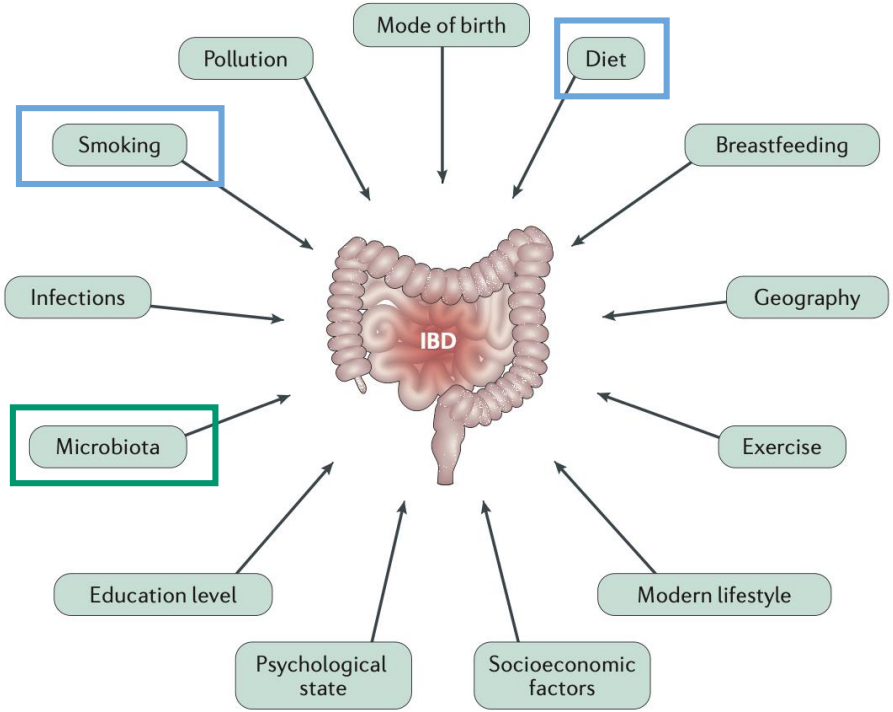
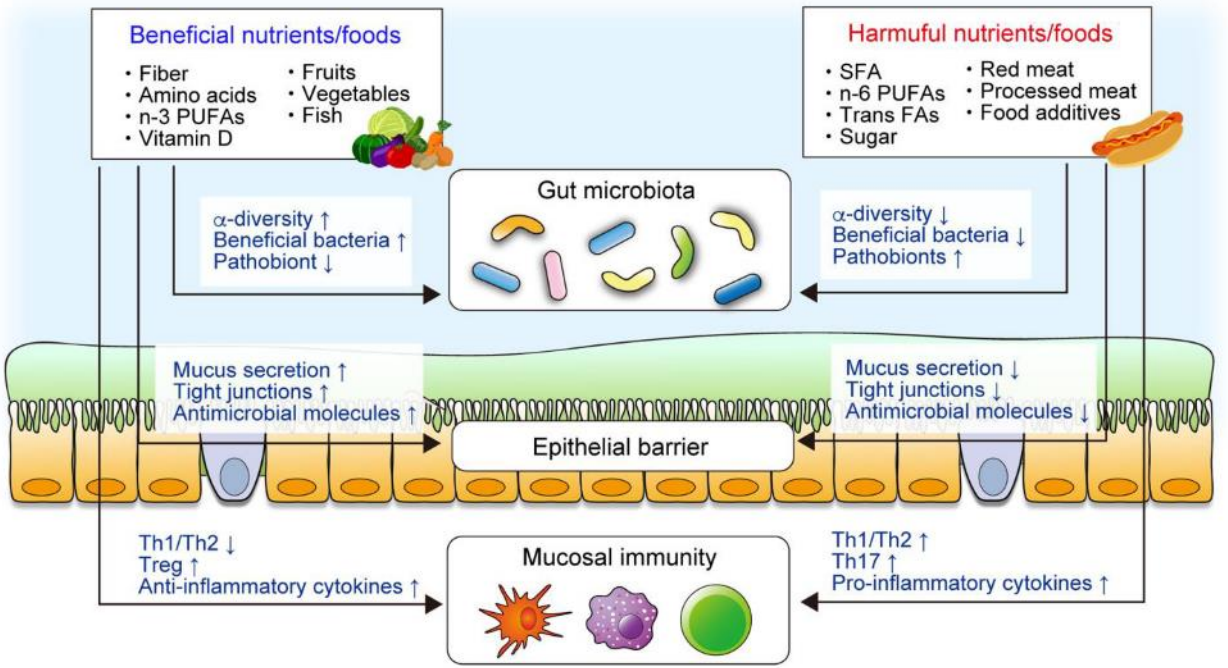
Other environmental factors

Other environmental factors are associated with IBD



Ananthakrishnan AN et al, Nat Rev Gastroenterol Hepatol. 2018;15(1):39-49

Effects of nutrition



Nutrition affects

- Microbiota composition
- Epithelial barrier
- Mucosal immunity

Sugihara et al. Nutrients 2021, 13(5), 1533

Nutrition – EEN or CDED are effective in CD

Avoid:

- Red meat
- Processed meat
- Saturated fatty acids
- Trans-fatty acids
- Artificial sweeteners
- Food additives

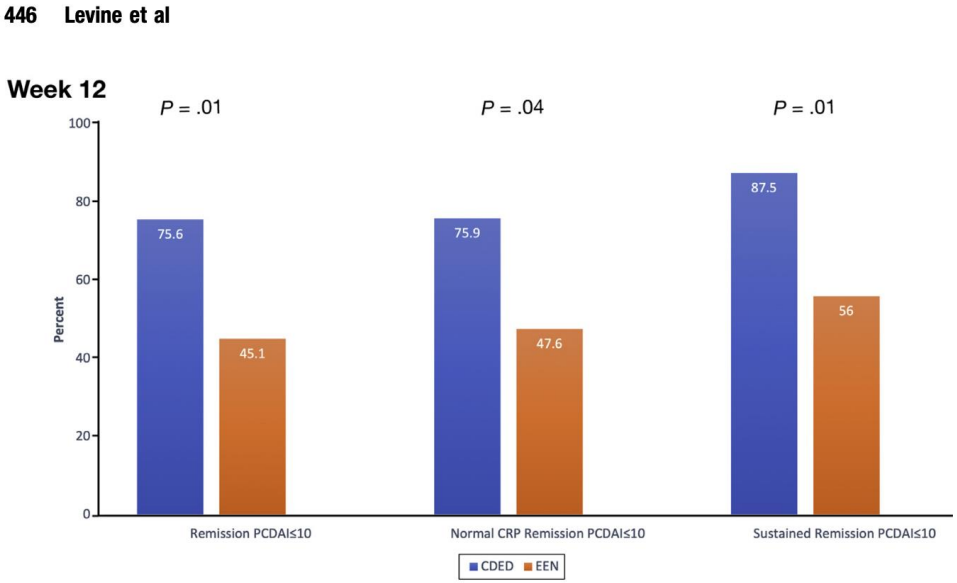
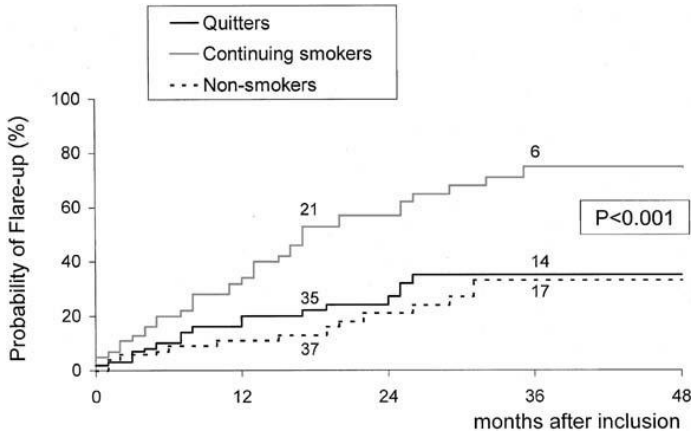


Image: Nestle

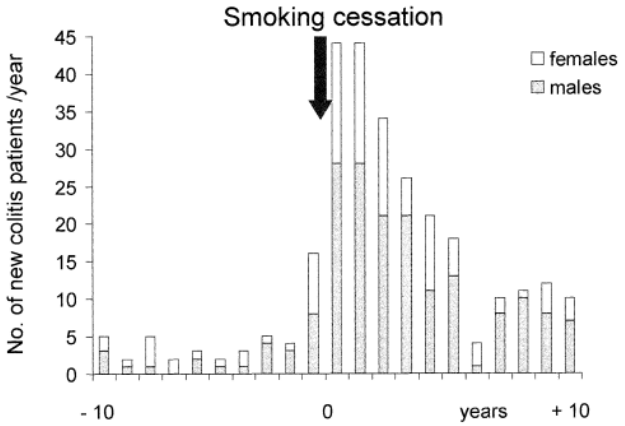
Levine A et al. Gastroenterology. 2019;157(2):440-450

Smoking

CD



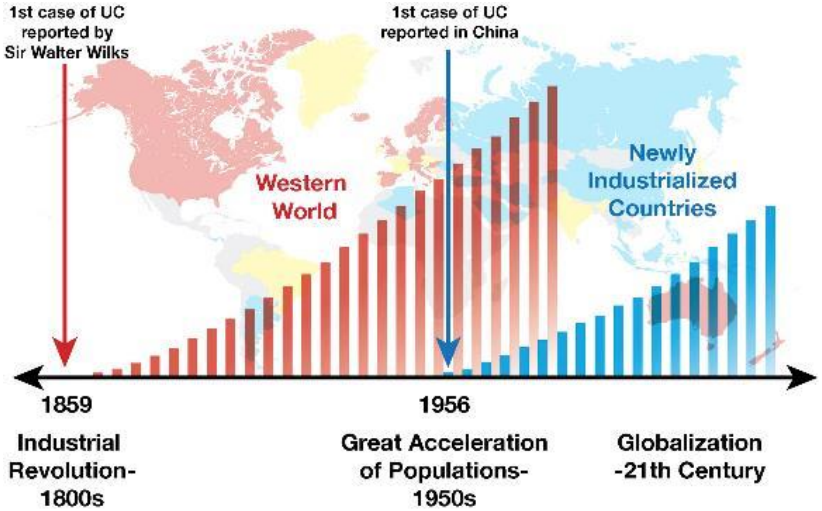
UC



Smoking is the most important modifiable environmental factor

Cosnes J. et al. Gastroenterology 2001;120:1093–1099
Cosnes J. et al. CGH 2004;2:41–48

More environmental factors…

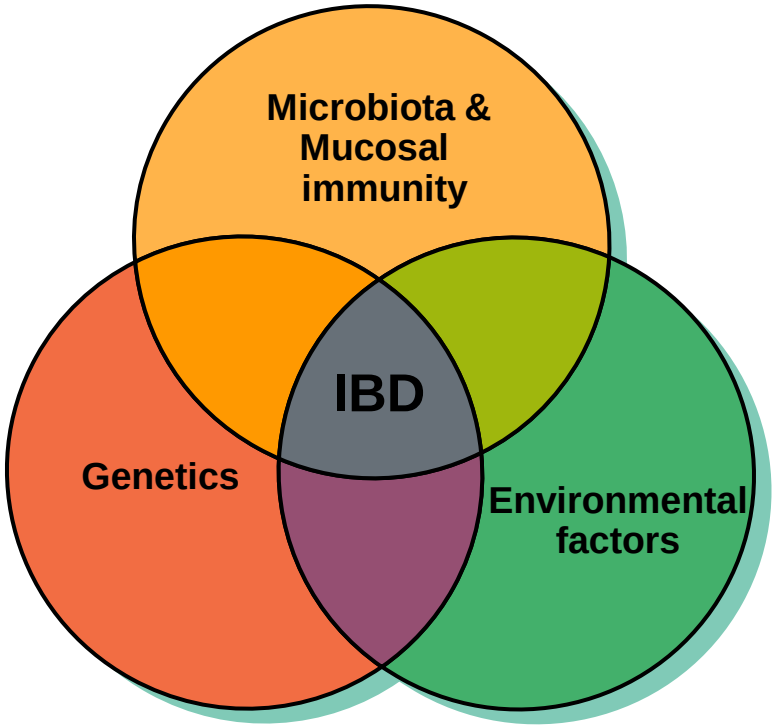


- Socioeconomic state
- Drugs (NSAIDS, estrogen)
- Exercise
- Psychological factors
- Appendectomy
- Birth mode, early life nutrition

Kaplan GG et al. Gastroenterology. 2017 Feb;152(2):313-321.e2

Summary

- There is no single cause of IBD
- The exact pathomechanisms of IBD are still largely unknown
- Complex interplay: genetics, mucosal immunity / microbiome and environmental factors



"Hey, Sisyphus, when you've got a minute I'd like to discuss this progress report with you."

Image: The New Yorker