Medical and Nutritional Management of Inflammatory Bowel Disease

David G. Binion, M.D.

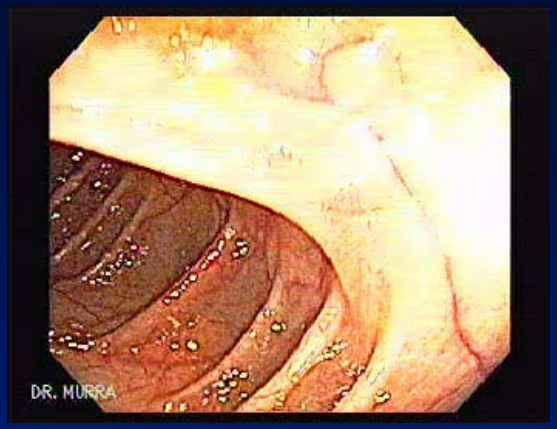
Co-Director, IBD Center – Translational Research
Director, Nutrition Support Service
Professor of Medicine, Clinical and Translational Science
Division of Gastroenterology, Hepatology and Nutrition
University of Pittsburgh School of Medicine
UPMC Presbyterian Hospital
Pittsburgh, PA, USA

Overview:

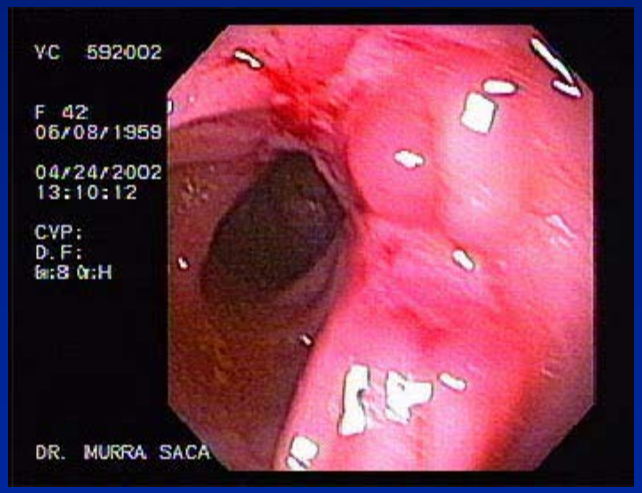
- I. Advances in IBD 2013: Pathogenesis and treatment
- II. Medical treatment goals in IBD
  - Personalizing therapy
  - Healing inflammation
- II. Nutritional management of IBD
  - Vitamin B12
  - Vitamin D
- IV. Summary

I. Advances in IBD 2013: Pathogenesis and Treatment

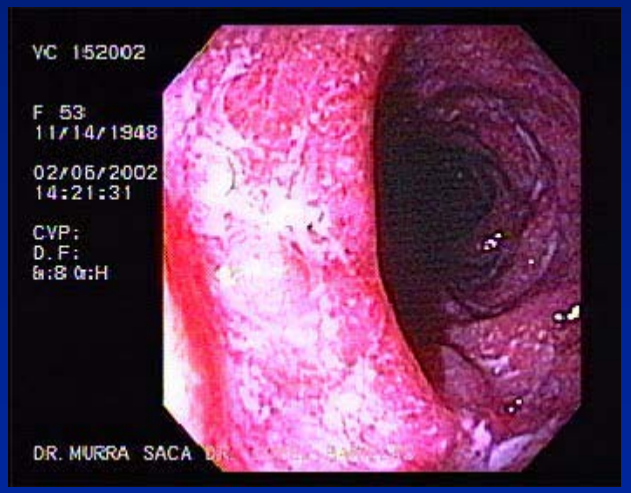
Normal colon



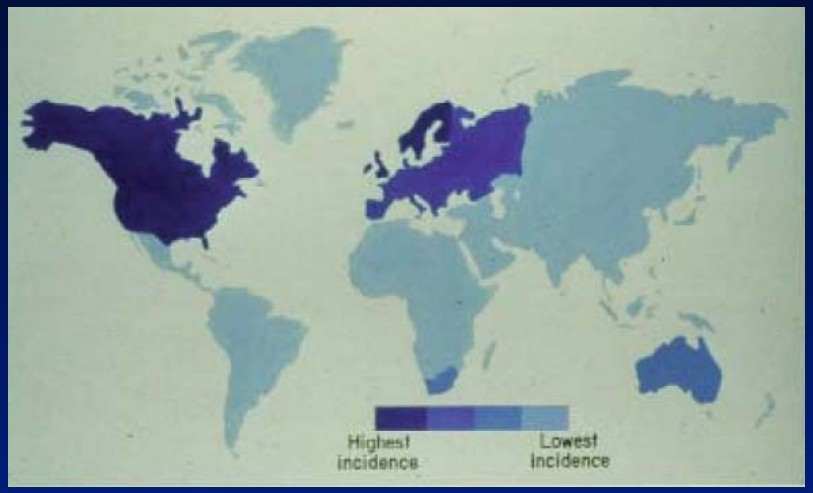
Crohn’s disease

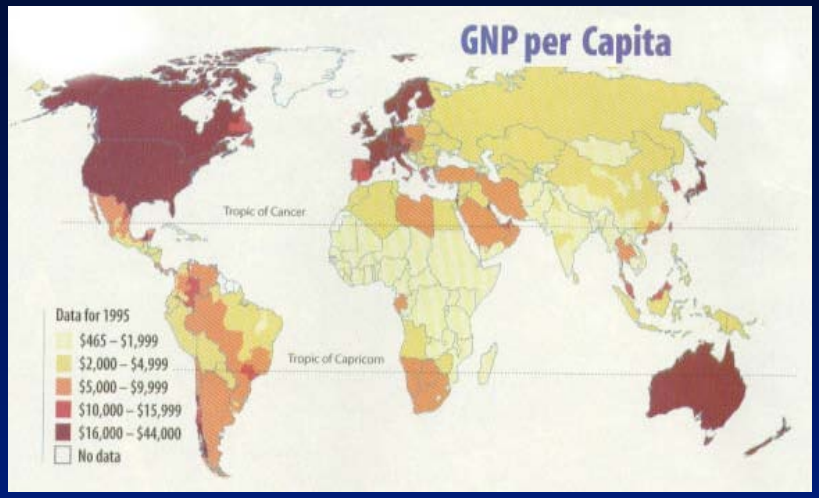


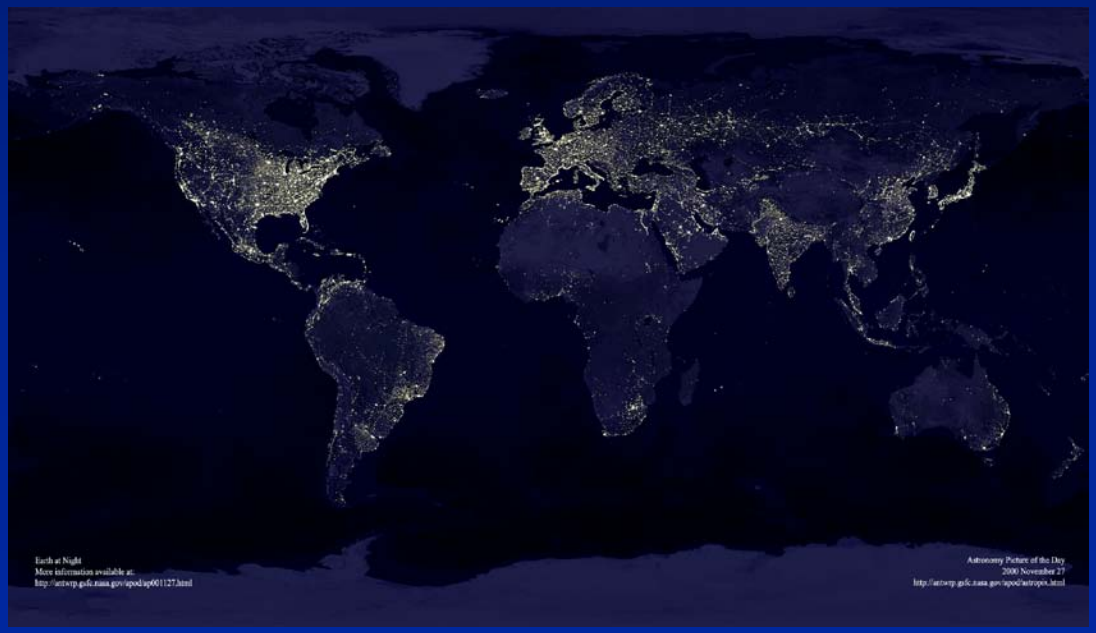
Ulcerative colitis



IBD Incidence: Environmental Factors





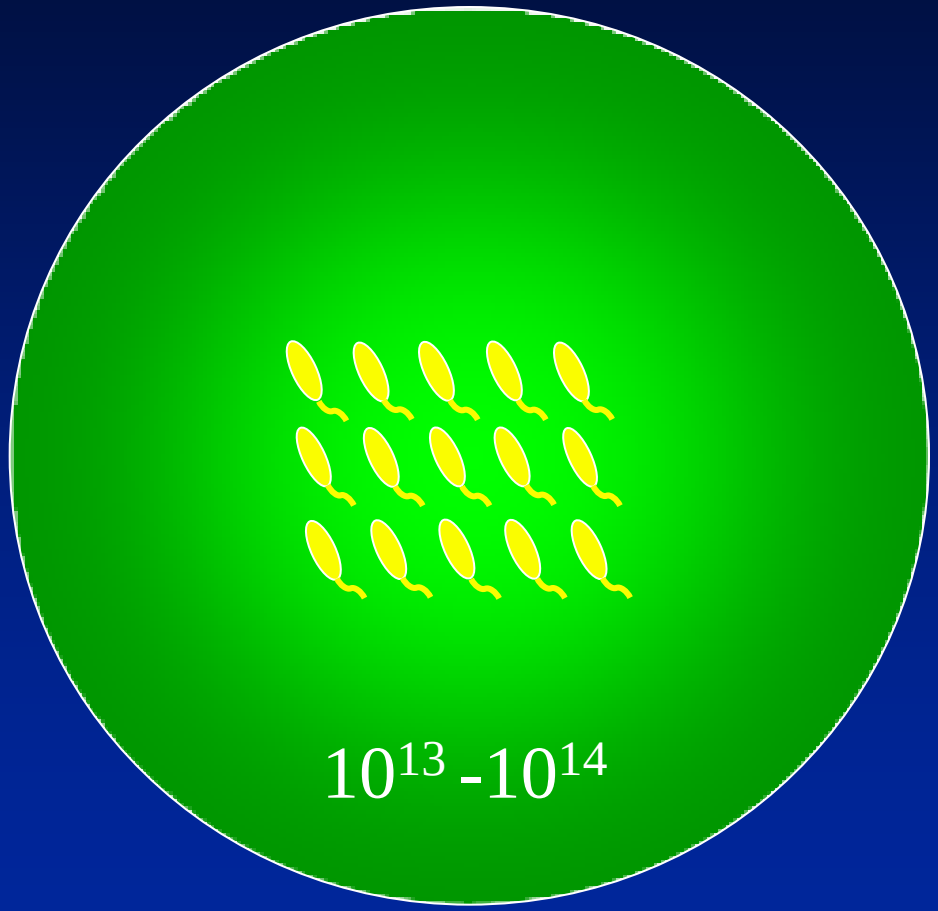


You are only 10% Human

Lots of bacteria
- 50% of fecal solids
- >400 species
- Most non-culturable
- 1-2 kg of body weight

Other life forms undefined
- Archaea
- Fungi
- Protists
- Viruses

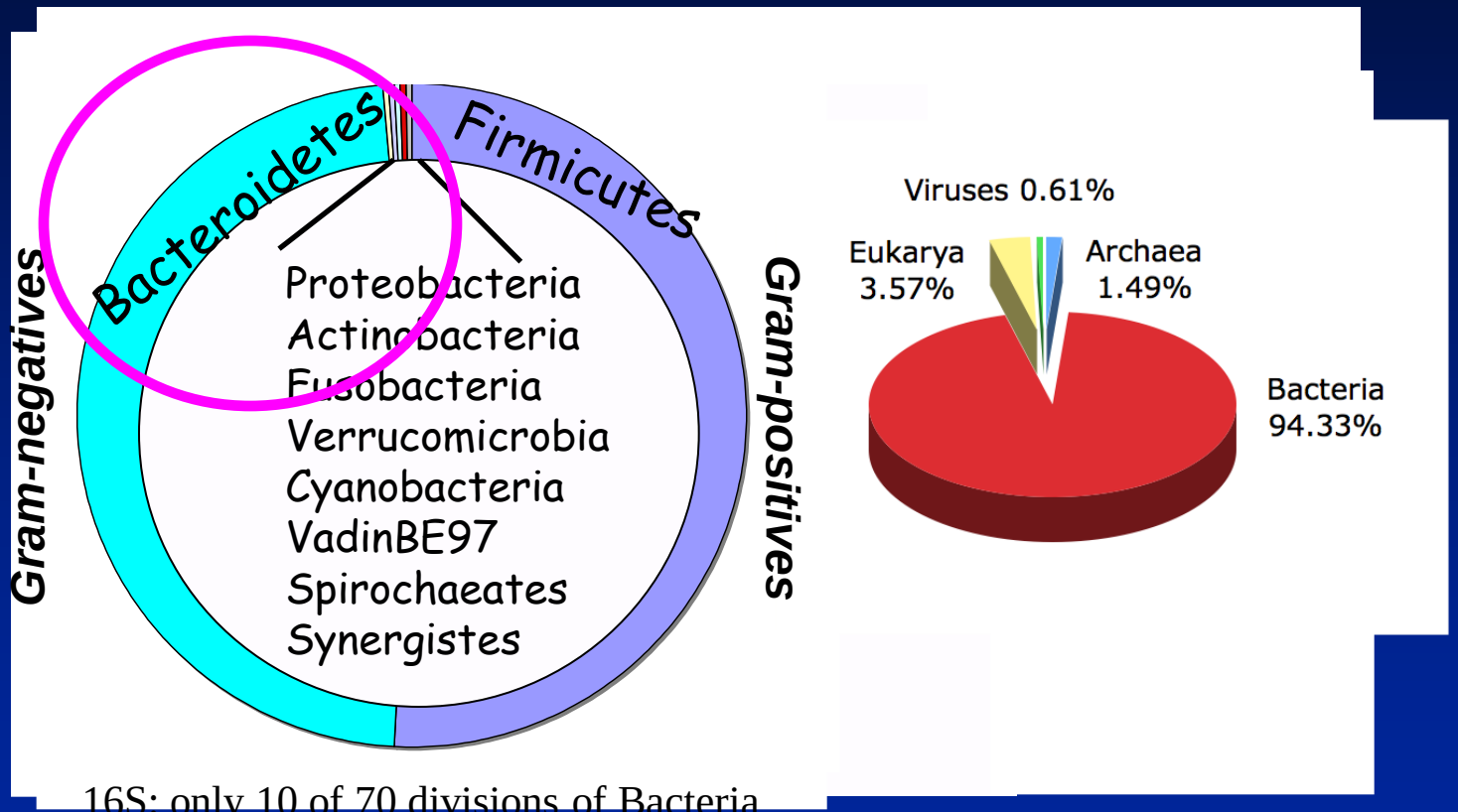
Total human cells in the body



Your Intestinal Bacteria

Kindly provided by Dr. Jon Braun

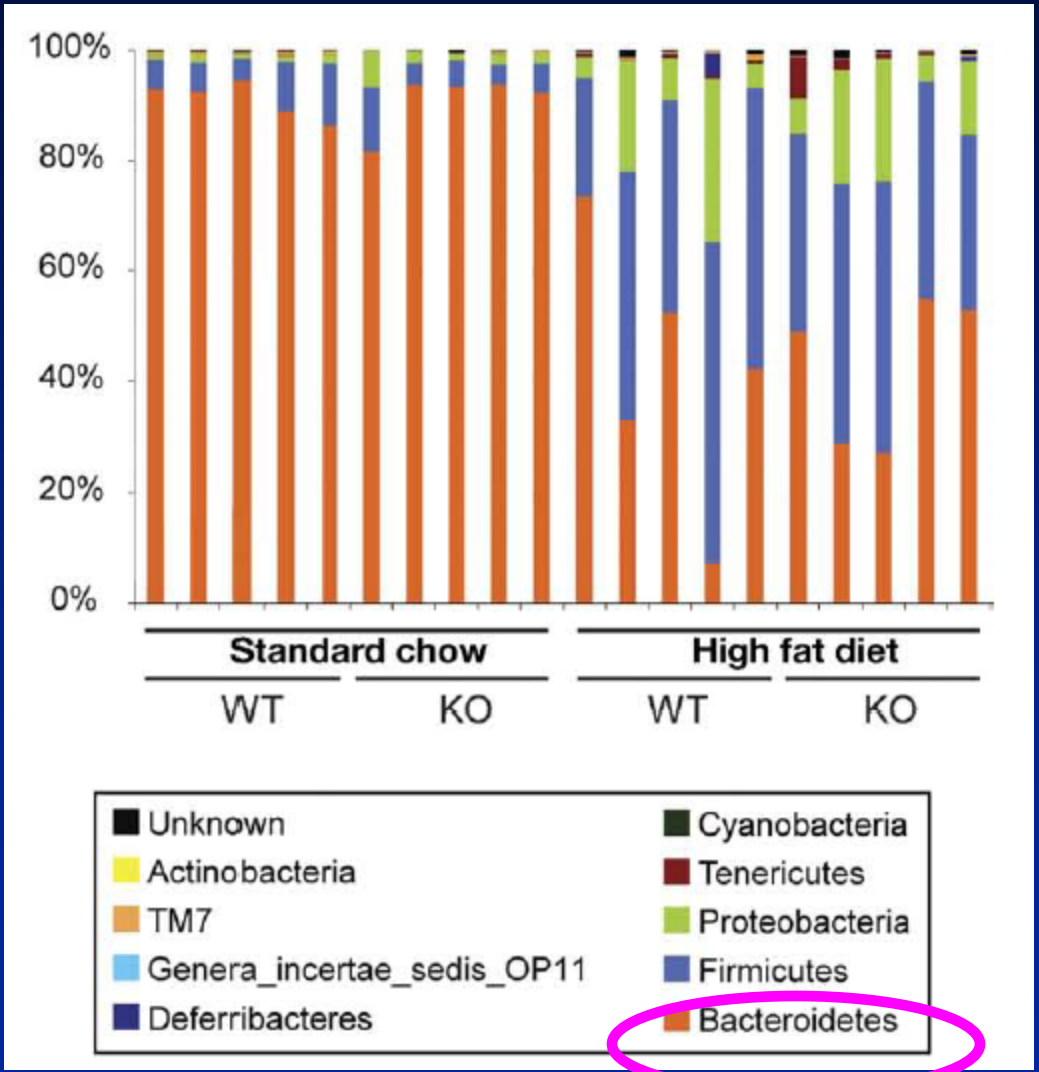
Microbial makeup of the human colon



16S: only 10 of 70 divisions of Bacteria

P. B. Eckburg. Science 308, 1635 (2005)
R. E. Ley. Proc.Natl Acad.Sci U.S.A 102, 11070 (2005)

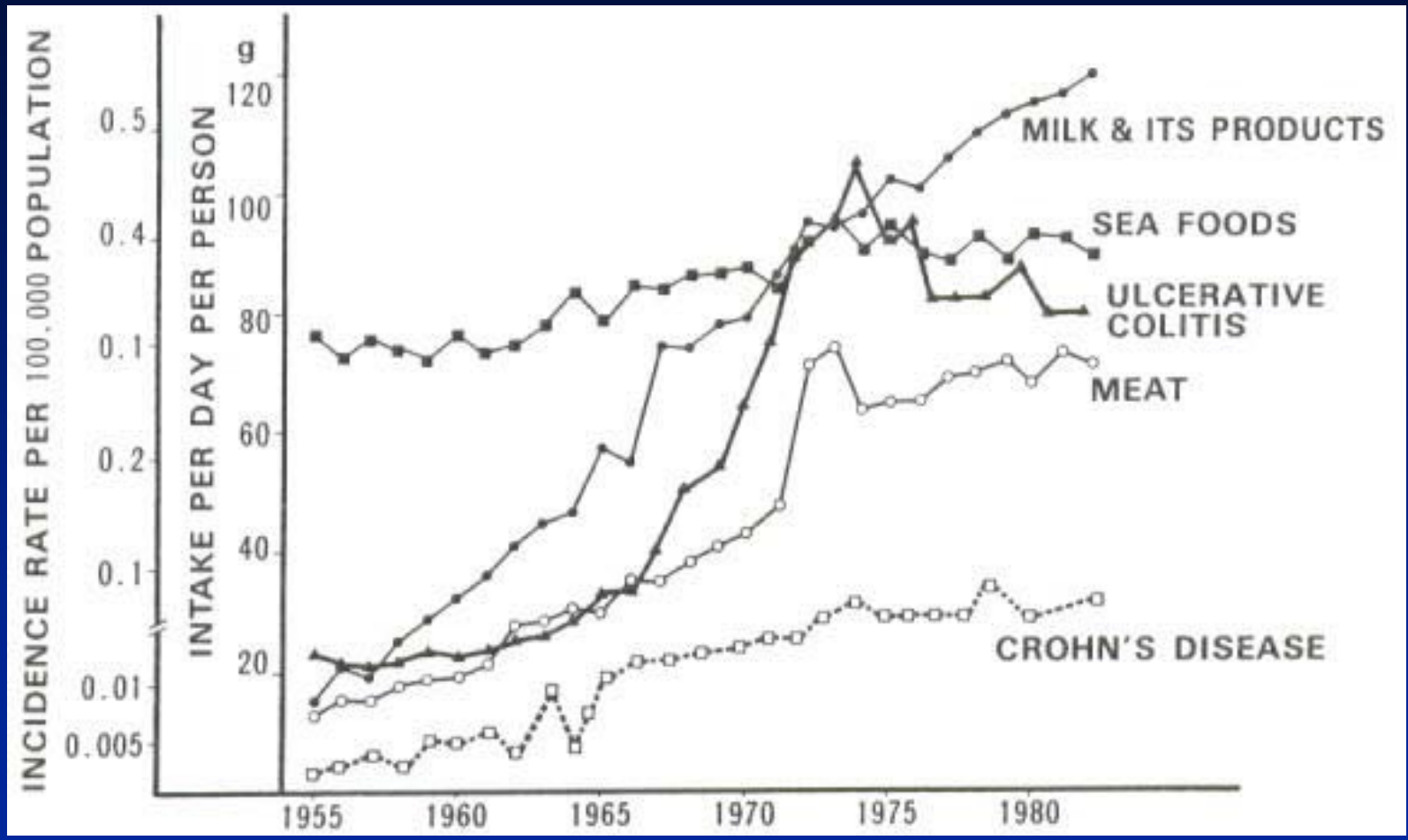
High-fat diet determines the composition of the microbiome independently of obesity



- Decrease in *Bacteroidetes*
- Increase in *Firmicutes* and *Proteobacteria*
- Microbiome displays increase in genes associated with nutrient transport, bacterial chemotaxis and flagellar assembly

Hildebrandt MA et al, Gastroenterology 2009;137:1716

IBD incidence in Japan



Evolution of Enteric Flora

- Mummy coprolites—paleofeces
- PCR of colonic DNA
- Electron microscopy
- Less *Bifidobacteria*, more *Bacteroides* in English flora vs. rural African flora

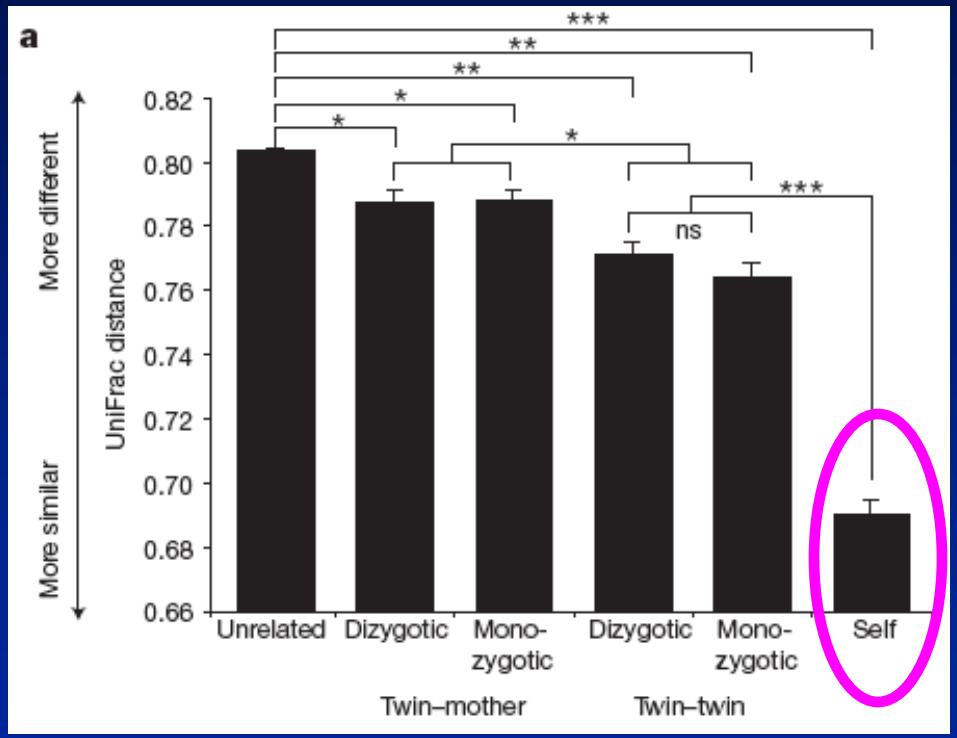
Fricker, Spigelman, and Fricker. (1997) *Letters in Applied Microbiology* 24: 351-354

Hidalgo-Arguello et al. J Parasitol. 2003 89:738-43

Tomkins, *J Hygiene, 1981*

Rotstein, *Infect Immun, 1989;*

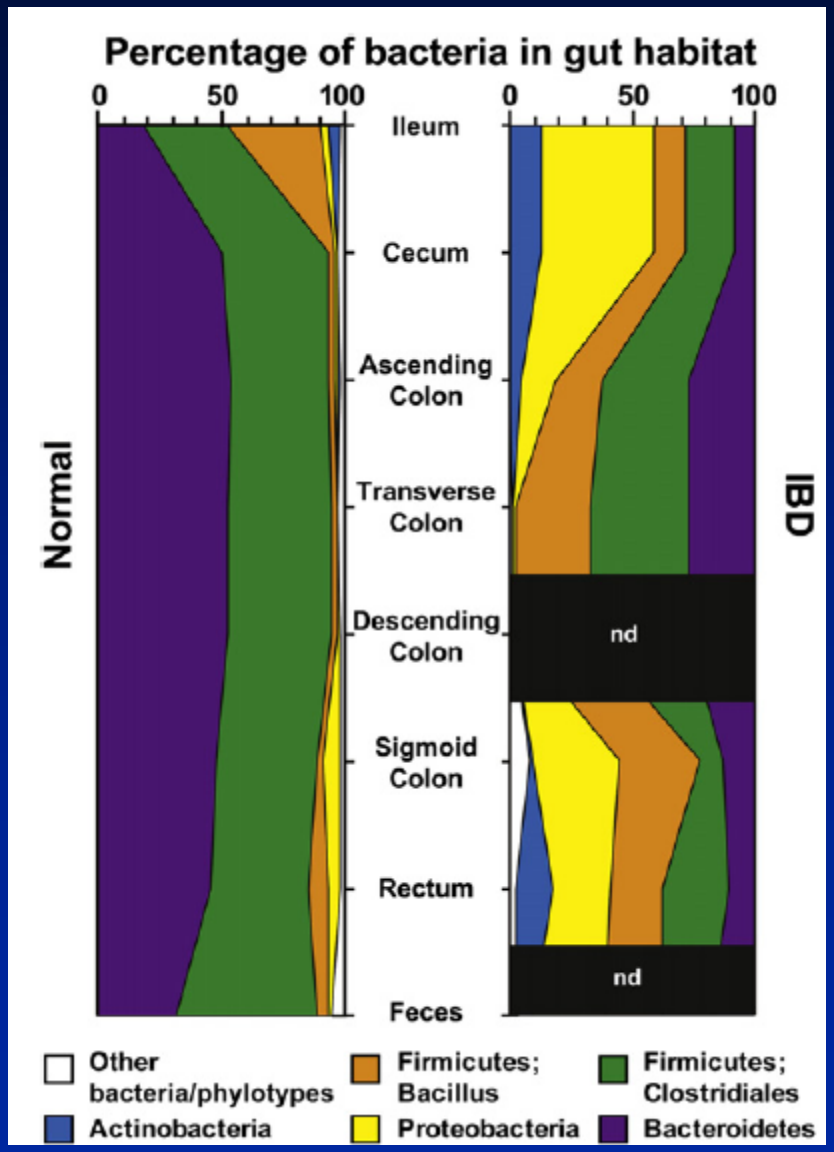
‘Heritability’ of the intestinal microbiome



- Microbiota ‘inherited’ from mothers
- Modified by genetic and environmental factors

Turnbaugh et al, Nature 2009

Altered bacterial phyla identified in the human gut microbiota of IBD



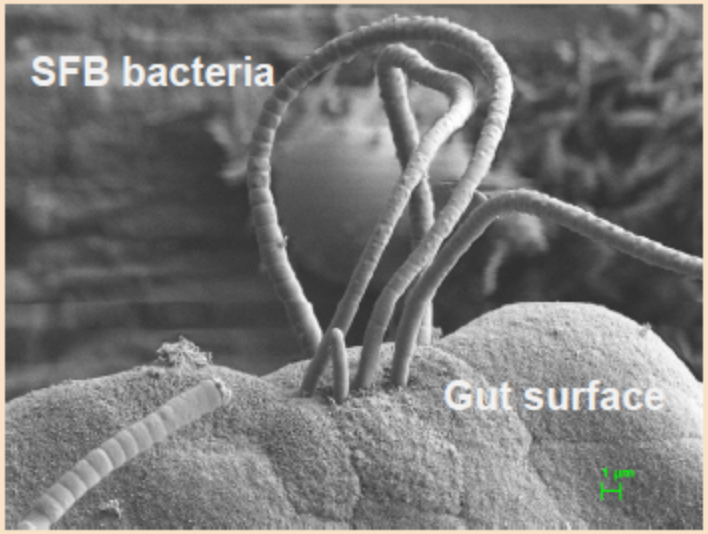
- Decreased abundance and diversity of Bacteroidetes in IBD
- Altered composition of Firmicutes and Maintenance of Proteobacteria in IBD
- Some Proteobacteria (E. coli) are adherent to the epithelium via binding to CEACAM6

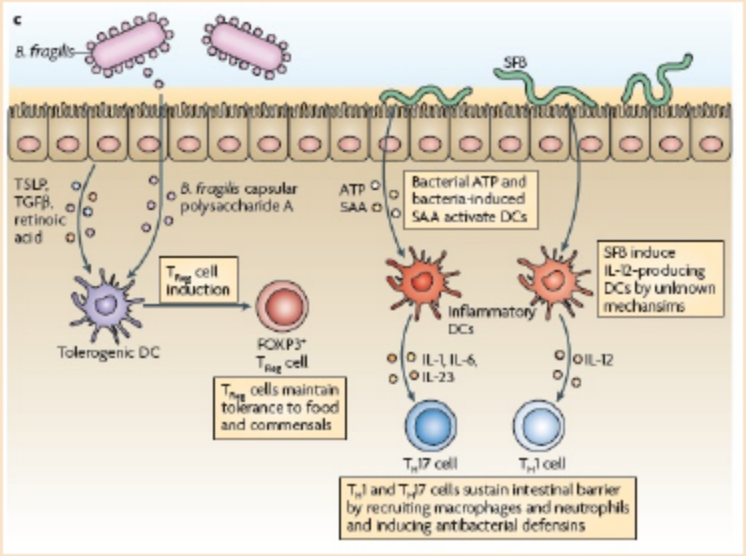
Frank DN et al, PNAS 2007
Peterson DA et al, Cell Host & Microbe 2008
Barnich N et al, J Clin Invest 2007

Injurious and Protective bacteria at the Intestinal Surface Associated With Crohn's Disease

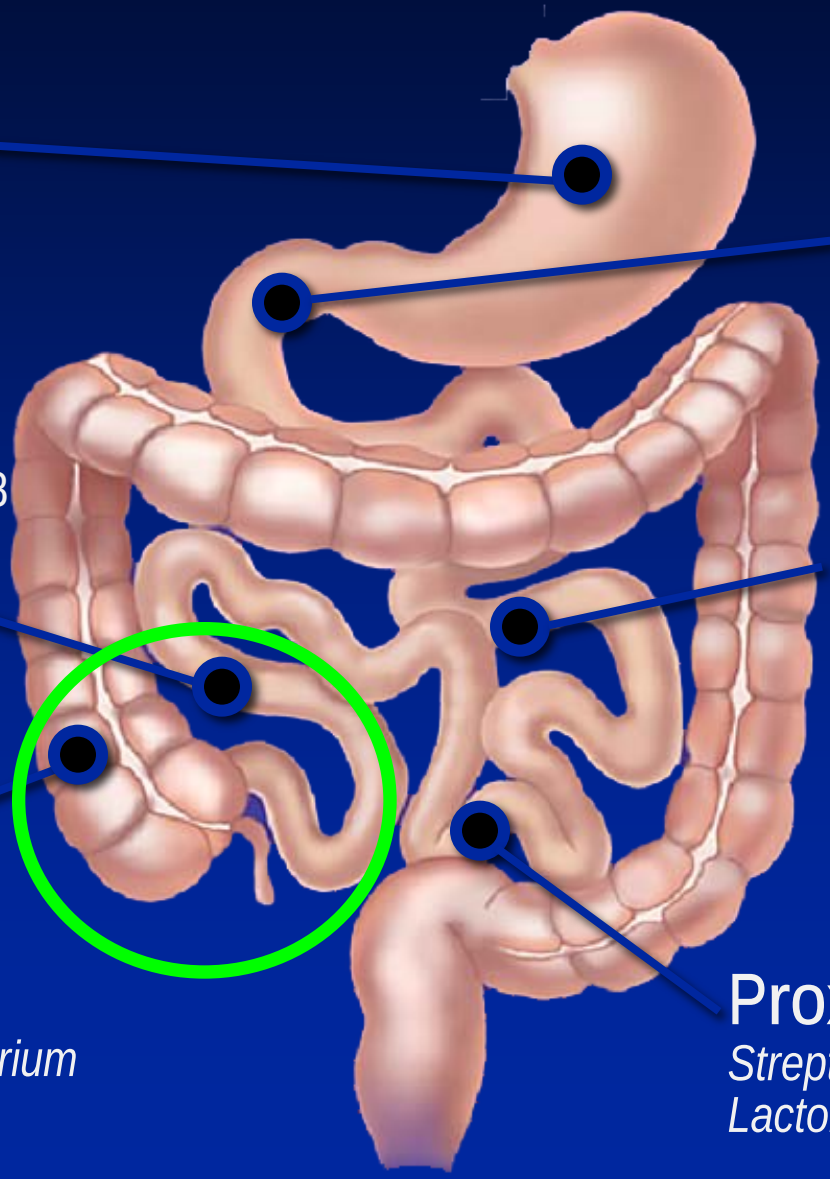
Bad bacteria candidates
Elevated in patients and in flares
Products damage intestine
- Adherent/invasive *E. coli*
- Segmented filamentous bacteria
- Lachnospiraceae (CBir)

Good bacteria candidates
Reduced in patients and in flares
Products protect intestine
- *Faecalibacterium prausnitzii*
- *Lactobacillus ssp.*
- *Bacteroides fragilis*





Dominant Gastrointestinal Bacteria in Normal Humans



Stomach $0\text{-}10^2$
Lactobacillus
Candida
Streptococcus
Helicobacter pylori
Peptostreptococcus

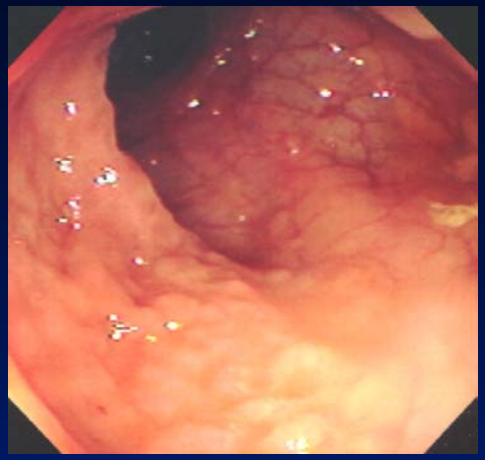
Duodenum 10^2
Streptococcus
Lactobacillus

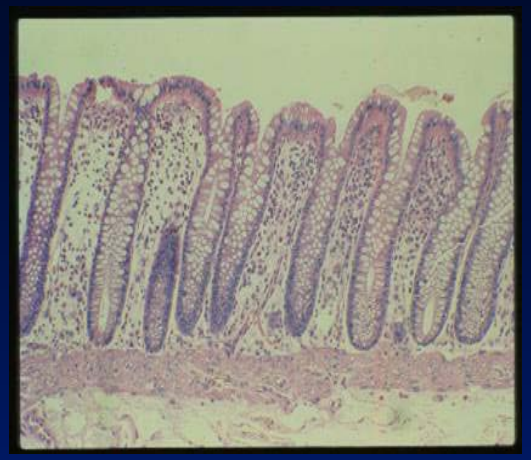
Distal Ileum $10^7\text{-}10^8$
Clostridium
Bacteroides sp
Coliforms

Jejunum 10^2
Streptococcus
Lactobacillus

Colon 10^{11}
Bacteroides
Bifidobacterium
Clostridium coccoides
Clostridium lepium/fusobacterium

Proximal Ileum 10^3
Streptococcus
Lactobacillus





Normal GI mucosa

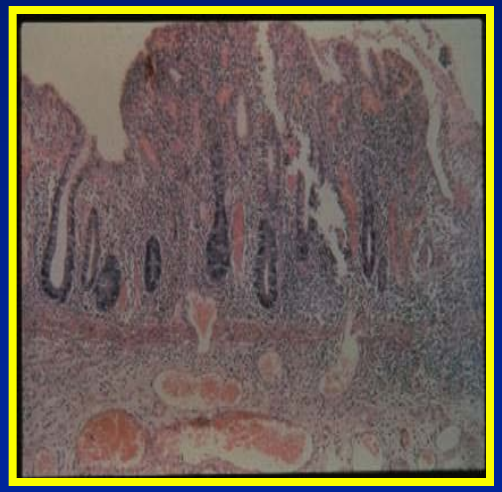
Surface area with external environment

Largest immune organ in body

Physiologic inflammation

Oral tolerance

"You are only 10% human"



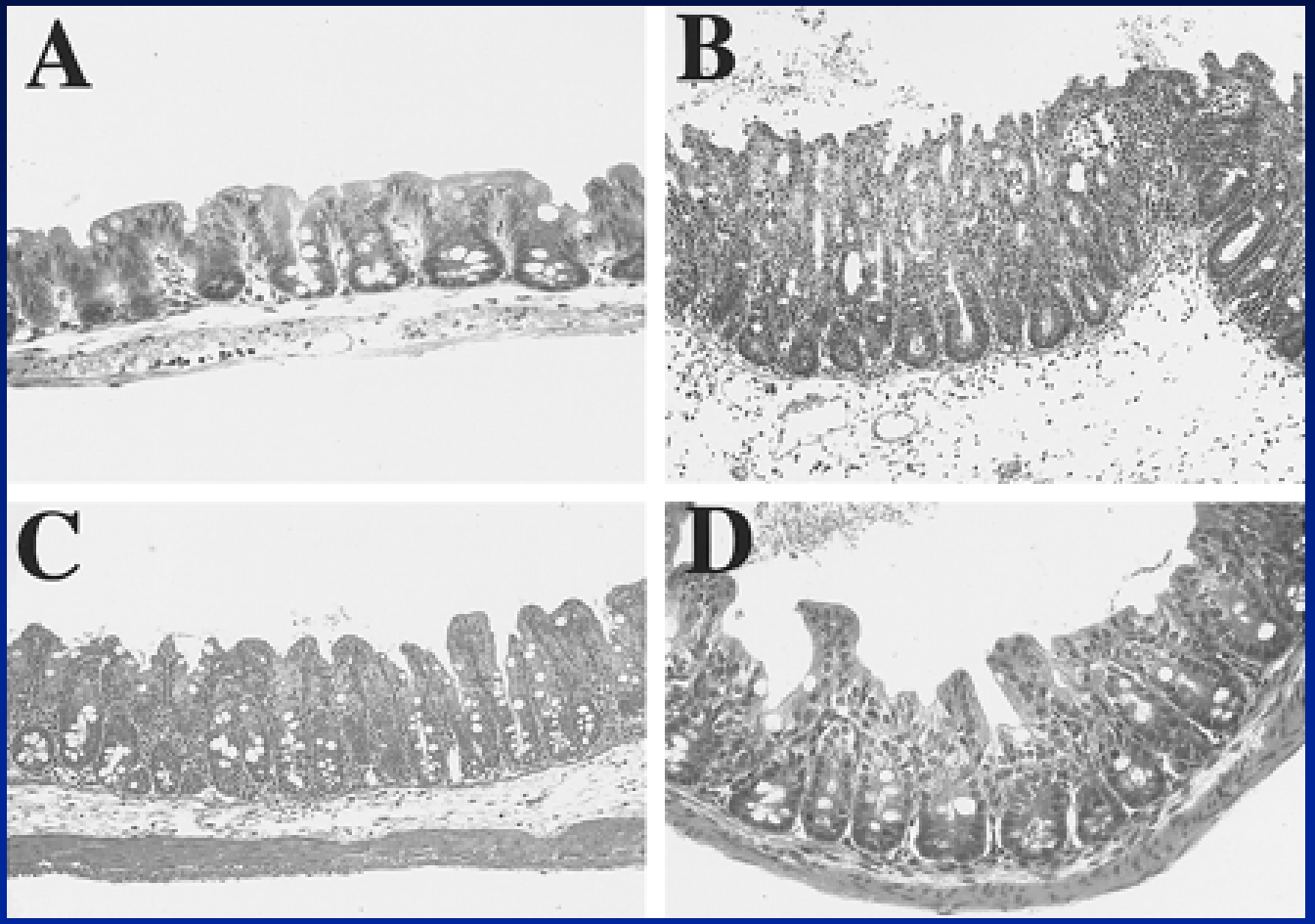
Crohn's disease

Destructive chronic inflammation

No "autoimmune target" identified in body

Impaired tolerance to enteric flora?

Normal enteric flora and gut inflammation



Ogawa H et al. Am J Physiol Gastrointest Liver Physiol **279: G492-G499, 2000**

Immune reactivity to dietary and enteric flora antigens in Crohn's disease & control patients

Patient number	Upper 99% CI limit Background	Mean proliferative response to each antigen									
		Milk	Cabbage	Cereal	Citrus	Peanuts	*E. coli*	Bacteriodes	Klebsiella	Bake yeast	Brew yeast
C1	362		559				894	7639	8937		
C2	114						347		139		
C3	343	645	788			2649	491		2250		
C4	141	559	357			320	206				226
C5	57	1107	885	1179	317		386	212	324	384	242
C6	405										
C7	440		688			597					486
C8	128										
C9	1455						1473				
C10	58	503	912	309		677	250	192		120	330
C11	2010										
C12	105	440	20600	12690	26650	3846	7481				
C13	143		225	271		6181	299				
C14	2249		25410					4699	4677		
C15	82	1848	629	317	263	684	1081		441		
C16	112		469	346	206	432	170				158
C17	146			1880		339	752				
C18	146	456		1308	147	631		300	8482		
C19	268					294		6582	6260		
C20	376					674					454
C21	959	1249		1200	1753		1861	1590			2329
C22	111	446	401	348	468	1156	240	374	278	120	249
C23	199										
C24	48										
C25	241										
C26	328										
C27	340	638	655	575		1143	561	1396		486	768
C28	110										
C29	260	1240	1080	457		1440	458			360	444
C30	31	124	37	52	118		46	55			
C31	390	1869	1659	1840	806	2143	838	1497	2134	1529	1901

Subject number	Upper 99% CI limit Background	Mean proliferative response to each antigen									
		Milk	Cabbage	Cereal	Citrus	Peanut	*E. coli*	Bacteroides	Klebsiella	Bake yeast	Brew yeast
H1	1261										
H2	1383										
H3	708										
H4	1289										
H5	611	8917	800	1173		625					778
H6	669										
H7	238										
H8	1405										
H9	61									68	
H10	53										
H11	55										
H12	148		207	179			420		794		
H13	504										
H14	393										
H15	190										
H16	506										671
H17	1944										
H18	772										
H19	278										
H20	176										
H21	238										
H22	403										793

Crohn's disease

controls

van den Bogaerde J *et al*. Aliment Pharmacol Ther. 2001; 15:1647-53.

II. Medical Treatment Goals in IBD

Drug therapy for IBD 2013

First line therapy

5-ASA
Balsalazide

Antibiotics
(metronidazole,
Ciprofloxacin,
rifaximin,
Amoxicillin,
Ceftin, Minocycline,
Tetracycline)
budesonide
Budesonide enema

Nutritional therapy

Elemental diet
Polymeric diet
TPN
Omega 3 fatty acids
Curcumin

Immunomodulators/ Second line therapy

Steroids
Azathioprine/6-MP
Methotrexate

Investigational Immunomodulators

Mycophenolate mofetil
Leflunomide
FK 506
Thioguanine
Thalidomide
Cyclophosphamide

Biologic Therapy

infliximab
adalimumab
certolizumab pegol
natalizumab

In development

vedolizumab
golimumab
Ustekinumab
tofacitinib
Stem cell transplant
GM-CSF
Trichuris suis
FMT

Natural History of Crohn’s disease

- Heterogeneity of Crohn’s disease.
- Mild, Moderate and Severe CD phenotypes.

1998 - Tale of 2 boys

Patient -1

- 12 year old boy with weight loss and diarrhea
- Diagnosis – Crohn's disease of ileum and colon
- Treated with steroids + immune modifiers

Patient -2

- 13 year old boy with weight loss and diarrhea
- Diagnosis – Crohn's disease of ileum and colon
- Treated with steroids + immune modifiers

With permission, S Kugathasan MD

2003 - Tale of 2 boys

Patient -1

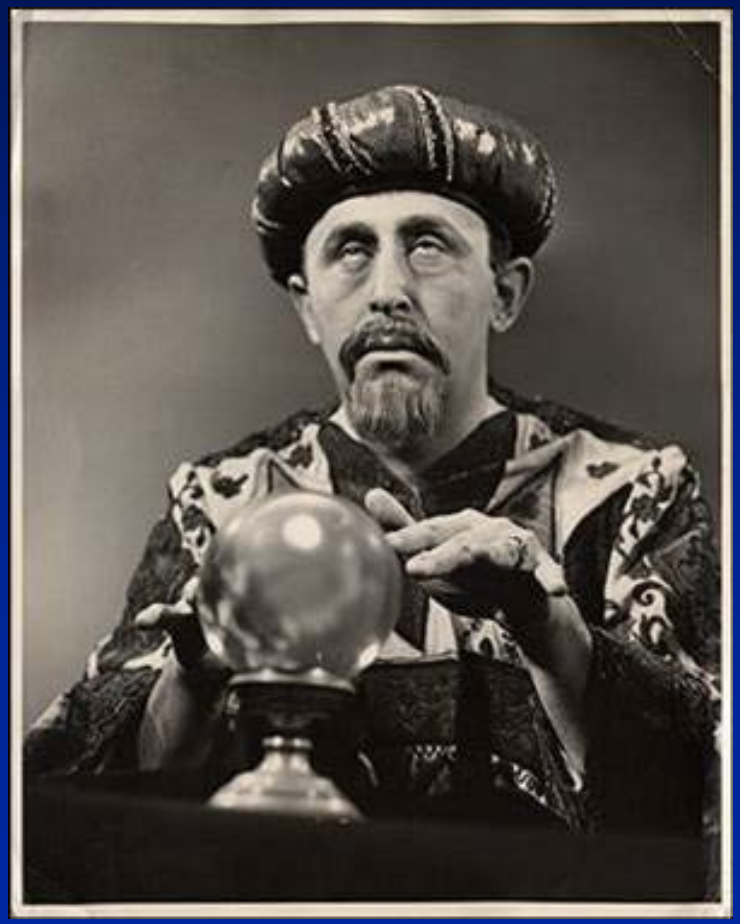
- He had been in clinical remission for first 2 years
- Relapse required a short course of steroids
- Normal growth and timely puberty
- He has been in remission since then
- Repeat colonoscopy – all lesions were healed.

Patient -2

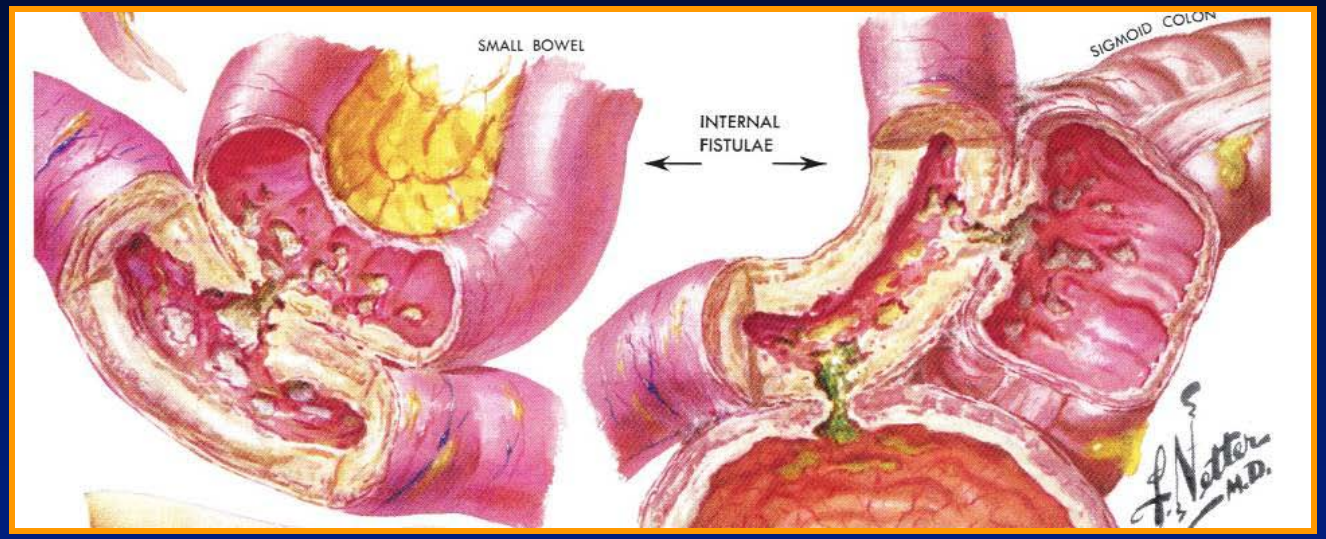
- Became steroid dependent; no response to most meds. Allergic to biologic therapy retreatment following episodic dosing.
- 1st surgery in 6 months
- Recurrence of Crohn's
- Delayed puberty
- Stunted growth
- More steroids, tube feeding
- Bowel perforation needed 2nd surgery
- Further hospitalization and TPN
- 3rd surgery for 'ostomy'
- Doing OK, hoping to get his bowel reconnected in future

With permission, S Kugathasan MD

What we need for IBD diagnosis, prognostication and clinical management



Crohn's Disease: 1960's historical perspective



Treatment: Prednisone and sulfasalazine.

Goals of Surgery:

- **Relieve obstruction (and penetrating complications)**
- **Discontinue medical therapy (chronic steroids)**

No post-op maintenance therapy.

Wide excision, wide anastomosis to maintain lumenal patency.

Probability of Surgery for Crohn's Disease

Years After Diagnosis	Patients (%)			
	1 Surgery	2 Surgeries	≥ 3 Surgeries	No Surgery
5	37	7	5	51
10	39	11	12	39
15	34	14	22	30

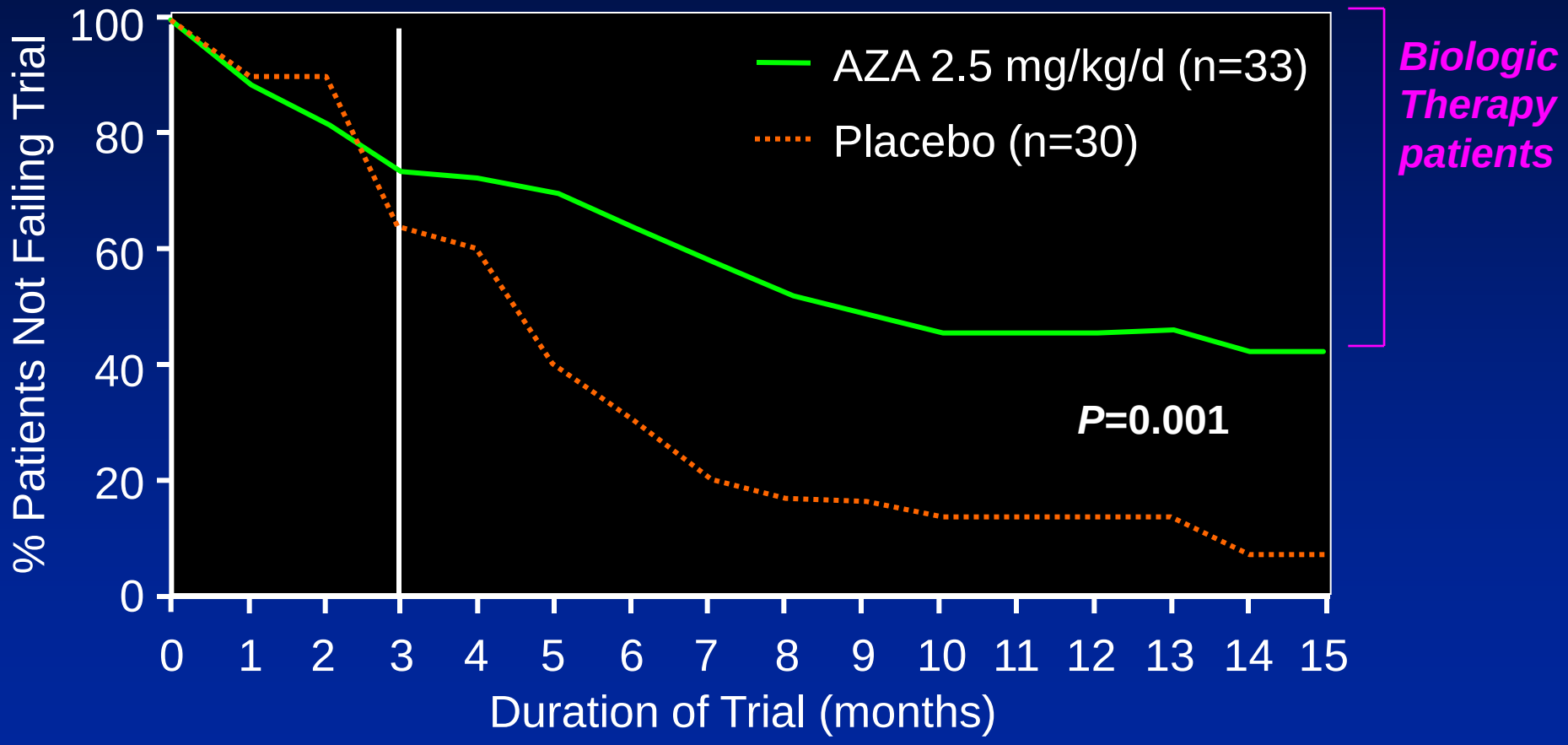
moderate

severe

mild

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

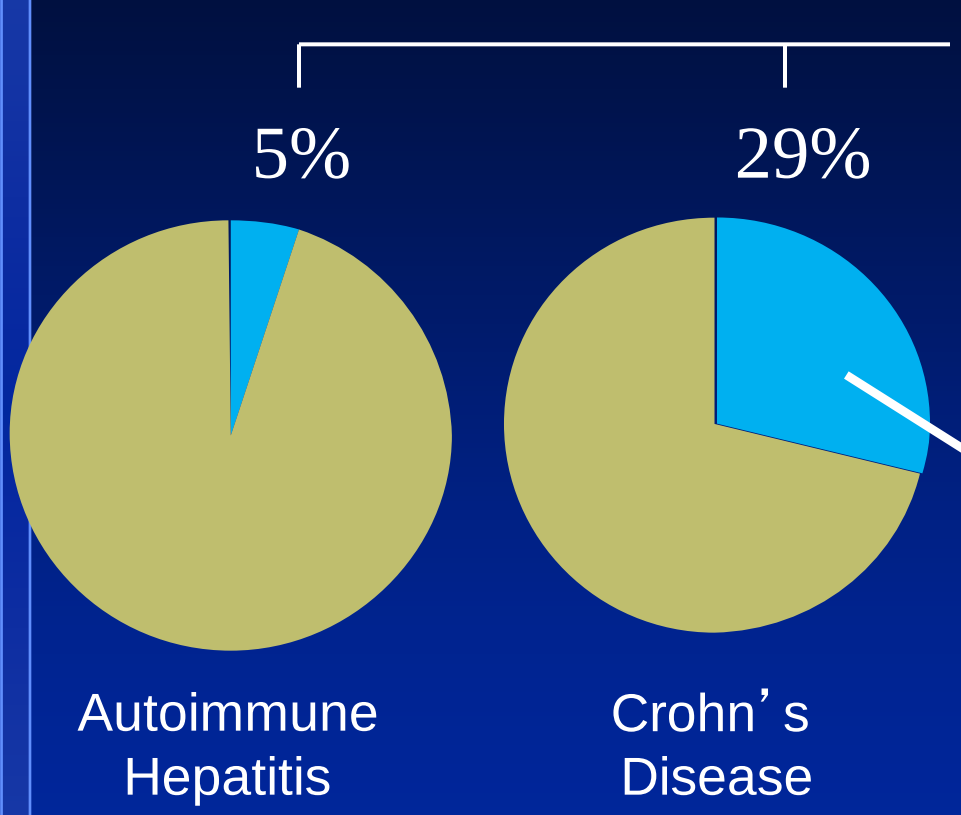
Efficacy of Azathioprine as Maintenance Therapy in Patients with Active Crohn's Disease



* Remission induced by prednisolone tapered over 12 wk

Candy S, et al. *Gut.* 1995;37:674.

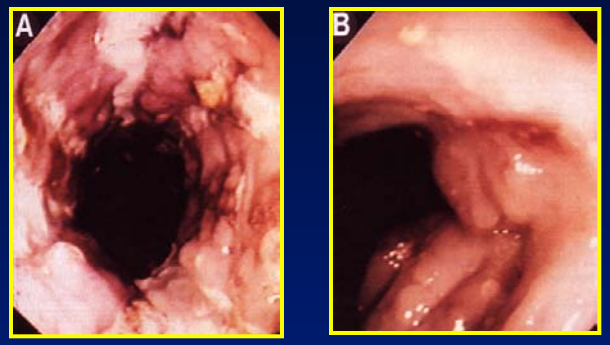
Azathioprine Intolerance in CD: Rates of Early Adverse Reactions



10%: Severe adverse reactions to azathioprine/6MP, including fevers, headache, pancreatitis, respiratory failure, blistering skin lesions within 4 weeks of initiation

JS Bajaj et al. *Am J Gastroenterol*. 2005;100: 1121-1125.

Biologic era in IBD management: Healing of refractory ulceration/fistula with Infliximab



Pretreatment

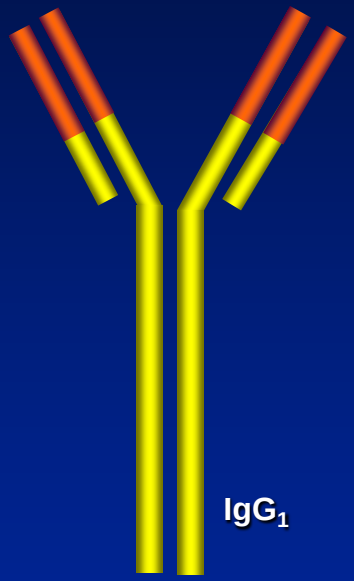
4 Weeks posttreatment

van Dullemen HM et al. *Gastroenterology.* 1995;109:129.

Present DH, et al. *N Engl J Med.* 1999;340:1398–1405.

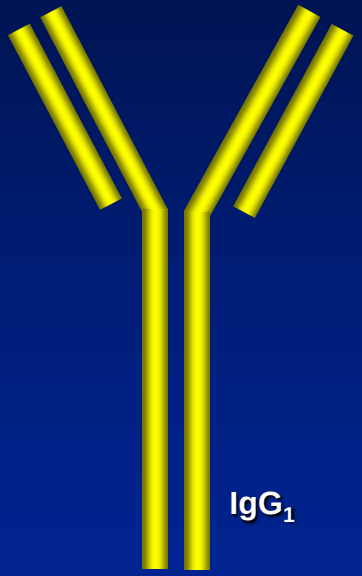
Construct of Anti-TNF-α Biologic Agents

Infliximab



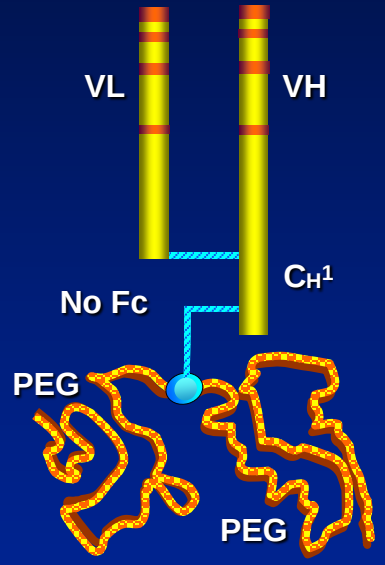
Chimeric monoclonal antibody (75% human IgG_1 isotype)

Adalimumab



Human recombinant antibody (100% human IgG_1 isotype)

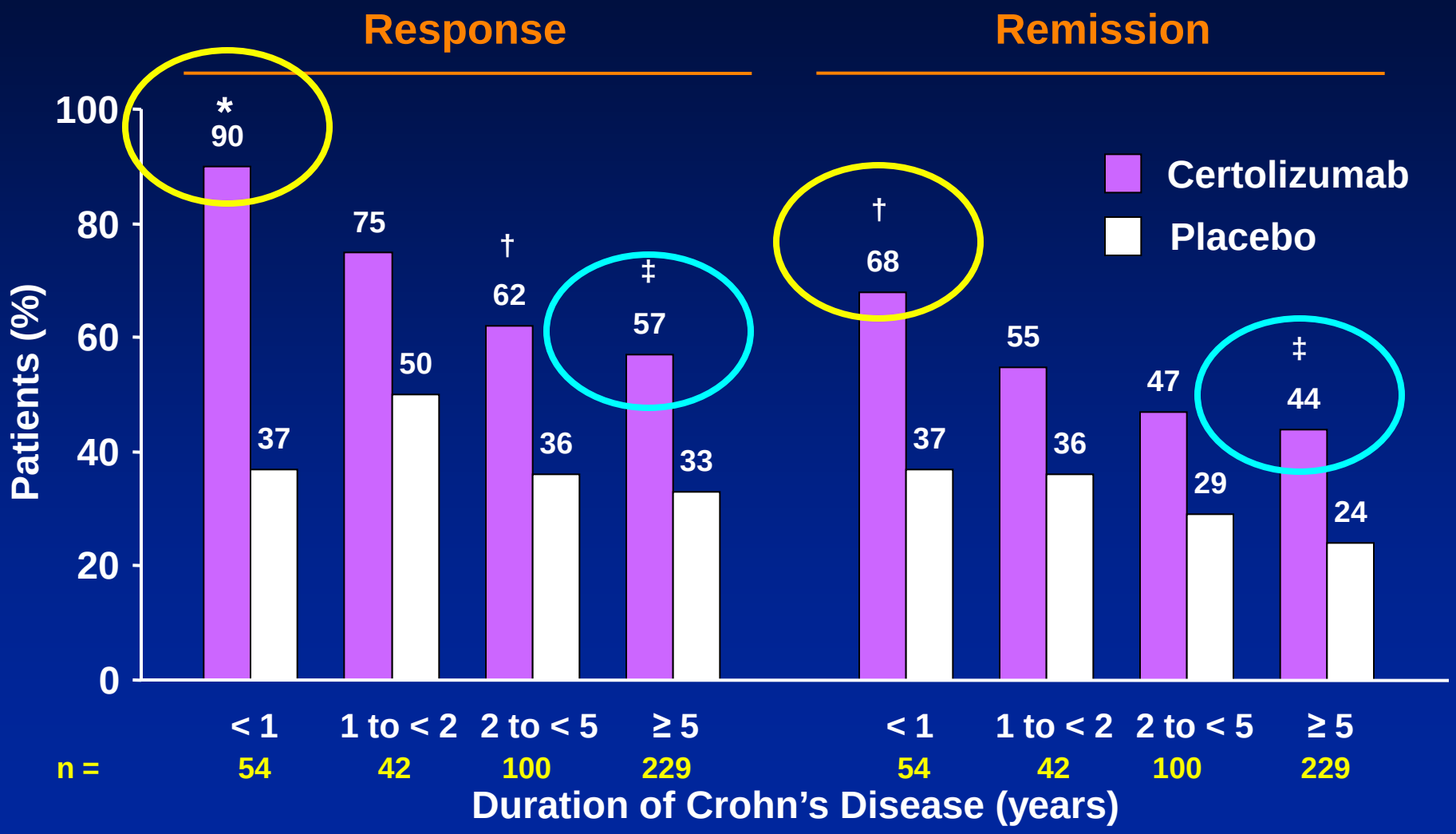
Certolizumab Pegol



Humanized Fab' fragment (95% human IgG_1 isotype)

Mouse
Human
PEG, polyethylene glycol.

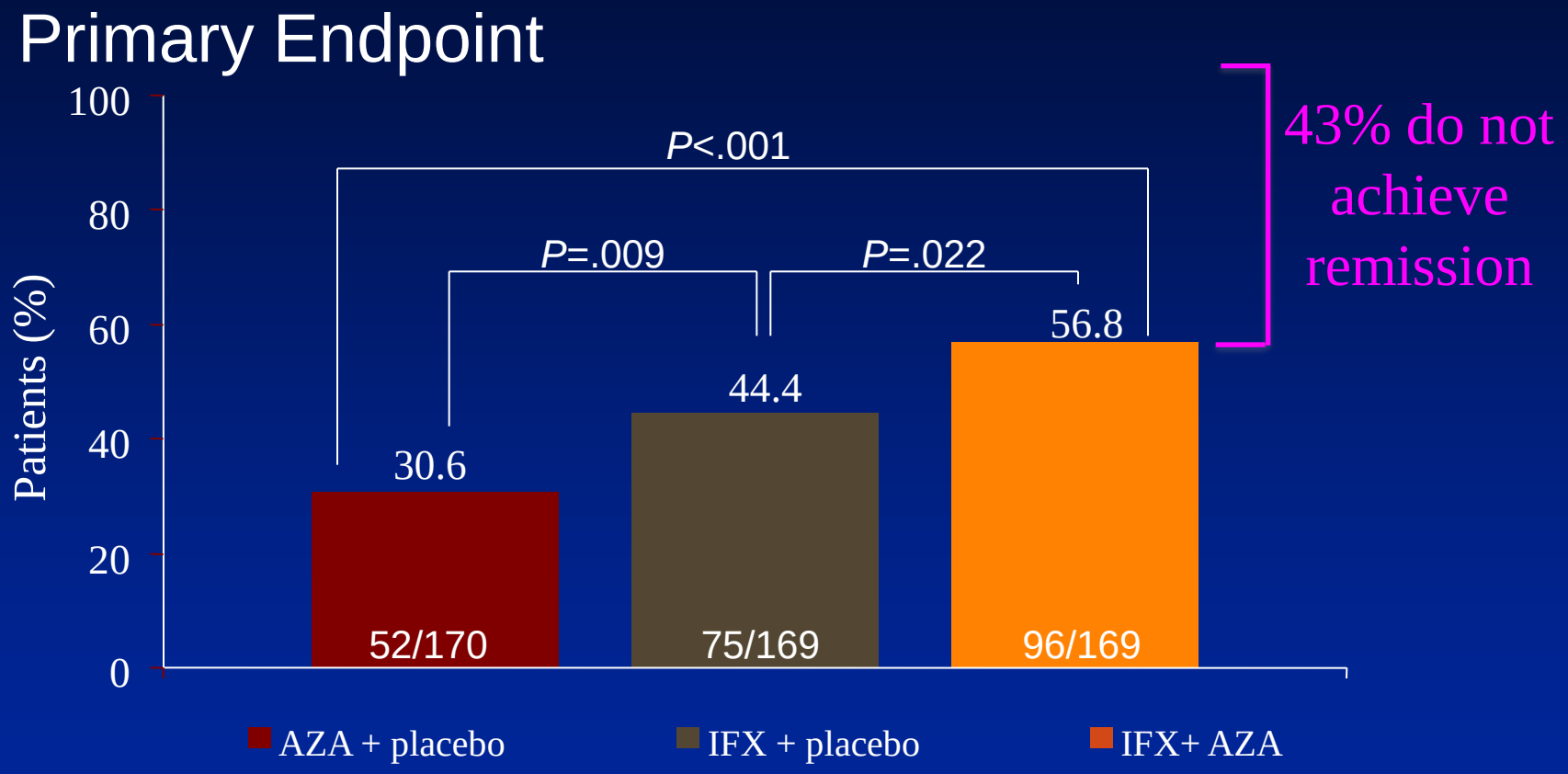
PRECiSE 2: Week 26 Clinical Response or Remission by Duration of Crohn's Disease



*$P < 0.01$; †$P < 0.05$; ‡$P < 0.001$ vs placebo.

Sandborn WJ, et al. *Am J Gastroenterol*. 2006;101(Suppl 2):S394. Abstract 1109.

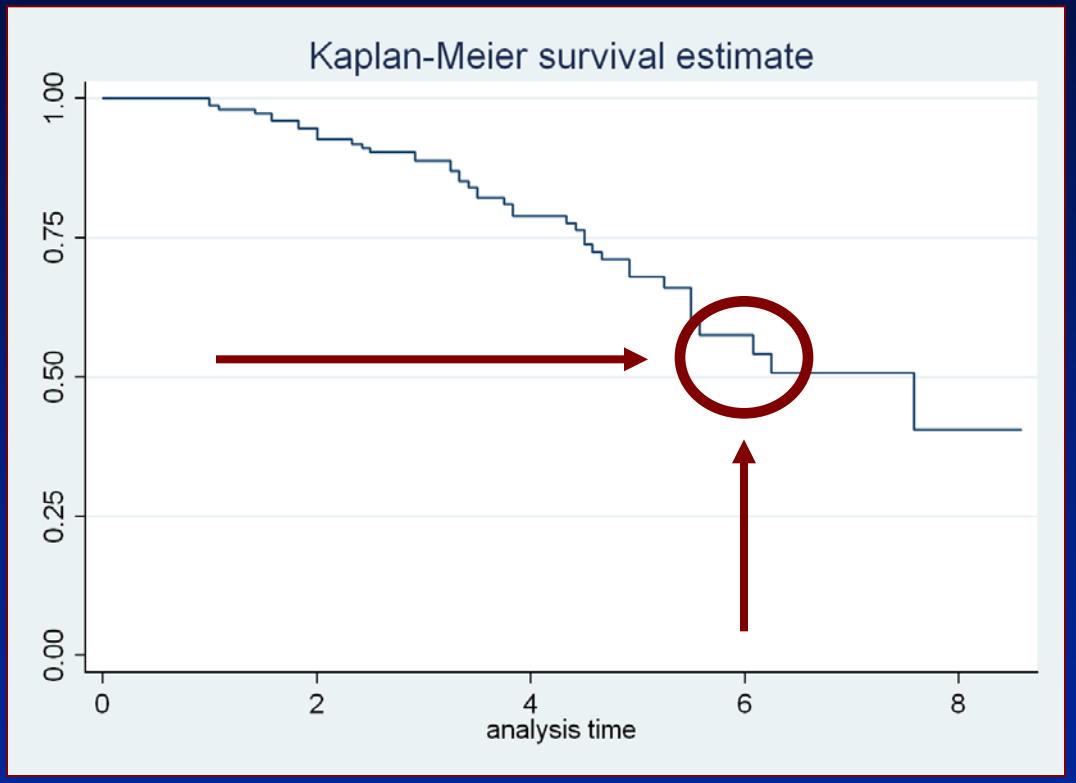
Corticosteroid-Free Clinical Remission at Week 26 in the SONIC Study



Colombel JF et al. *N Engl J Med.* 2010;362:1383-1395.

Durability of Infliximab for CD

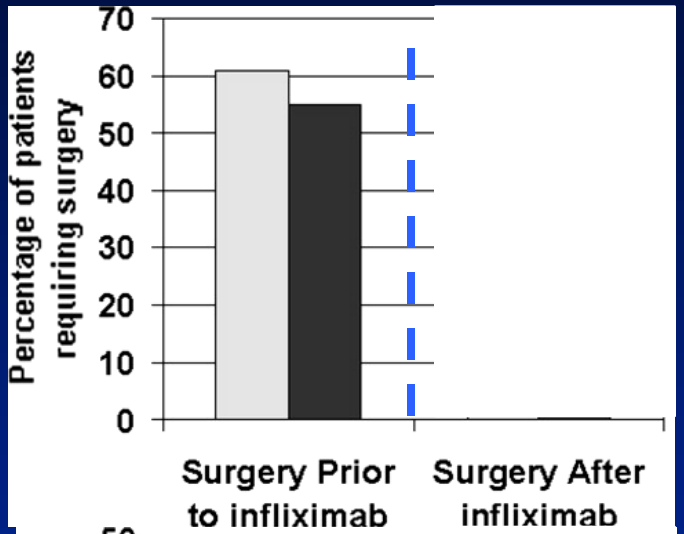
- 50% of CD patients have discontinued infliximab by 6 years of maintenance therapy (n=153)
- 82% of these patients were on combination immunosuppression

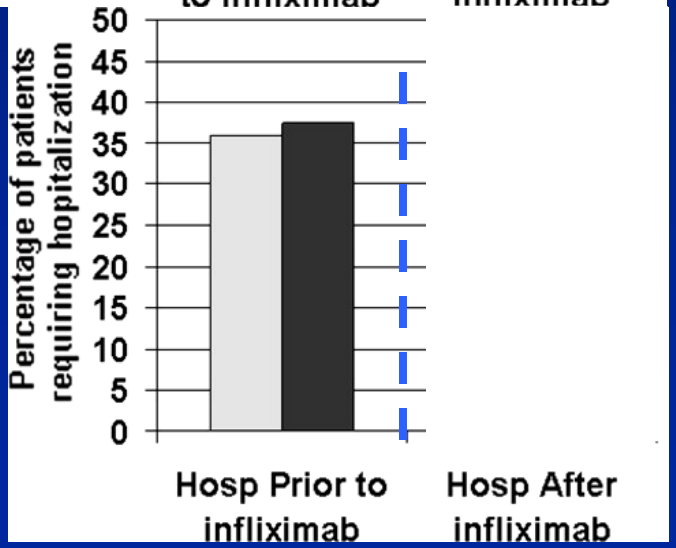


Gonzaga J et al. *Inflamm Bowel Dis.* 2009;15:1837-1843.

Effect of Prior Episodic Dosing on Long-term Performance of Infliximab Maintenance: Hospitalizations and Surgeries at 3 years

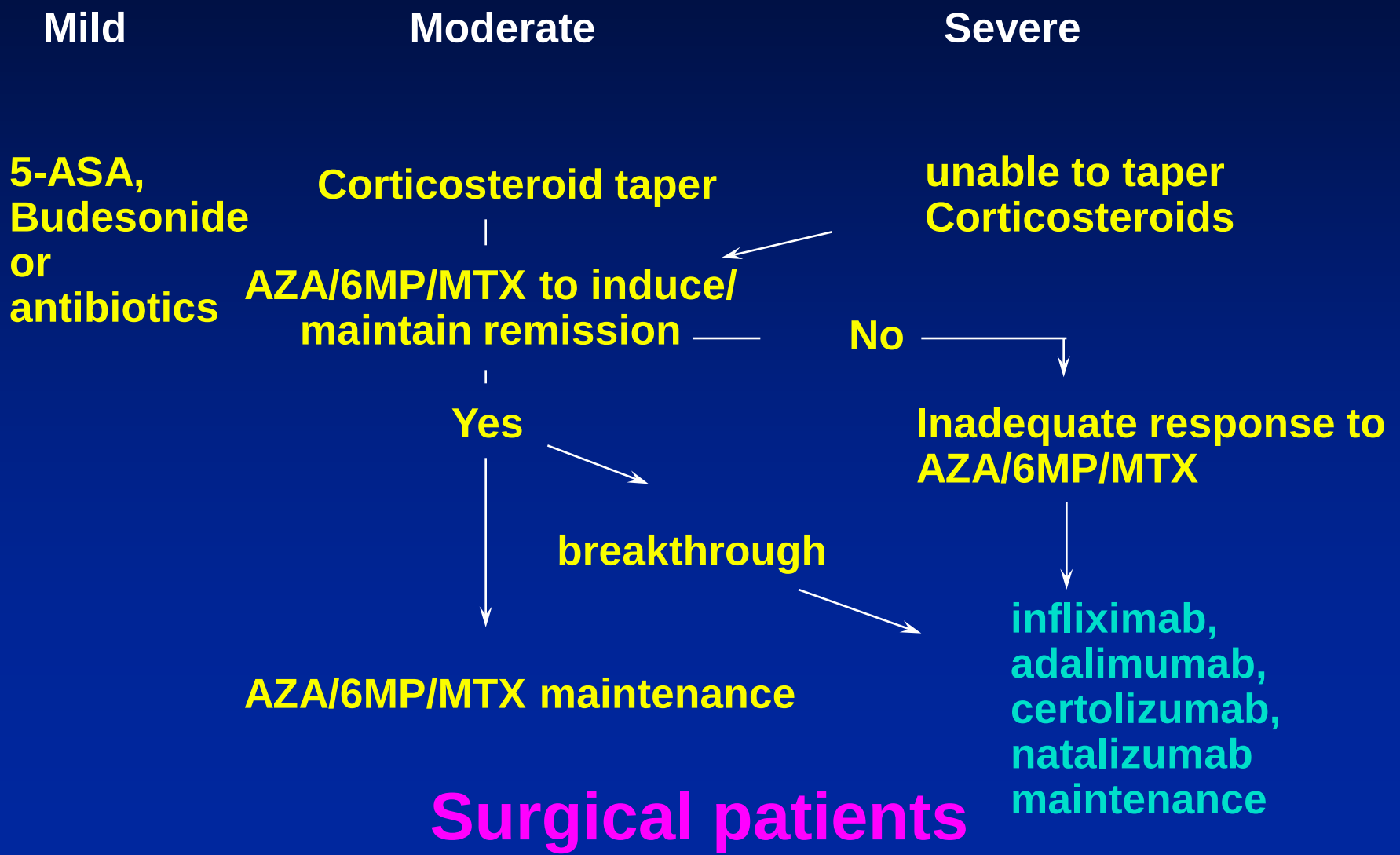
- 40 patients with prior irregular dosing
- 61 patients with scheduled maintenance
- Total excess cost in the PI exposure cohort of $11,464 during the third year of infliximab maintenance therapy per patient





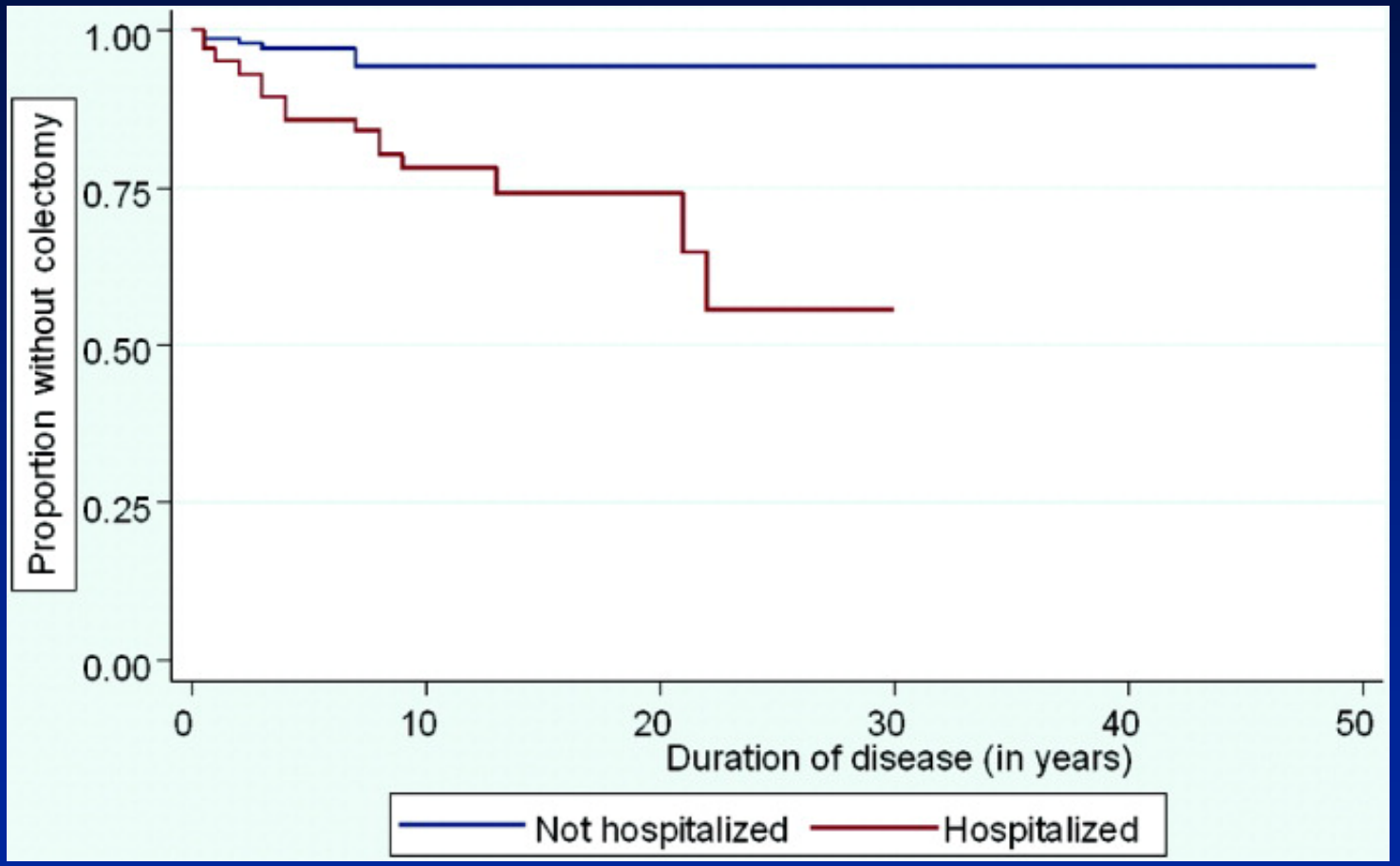
Stein DJ et al. *Inflamm Bowel Dis*. 2010;16:1173-1179.

Crohn's disease - medical management algorithm:
No partial obstruction or abscess detected



Can we predict which UC patients are at risk of colectomy?

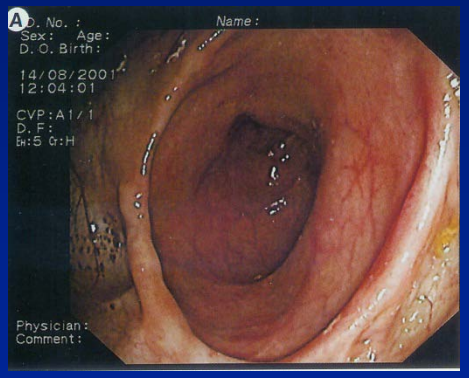
Risk of colectomy and history of medical hospitalization for UC (n=246; 103 hospitalized)

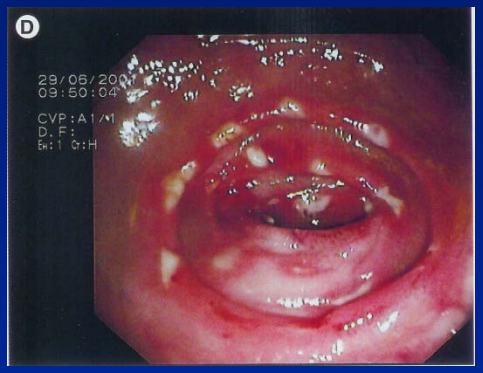


Ananthakrishnan AN, McGinley EM, Binion DG. Inflamm Bowel Dis 2009; 15: 176-81.

How do we assess IBD patient status in the clinic?

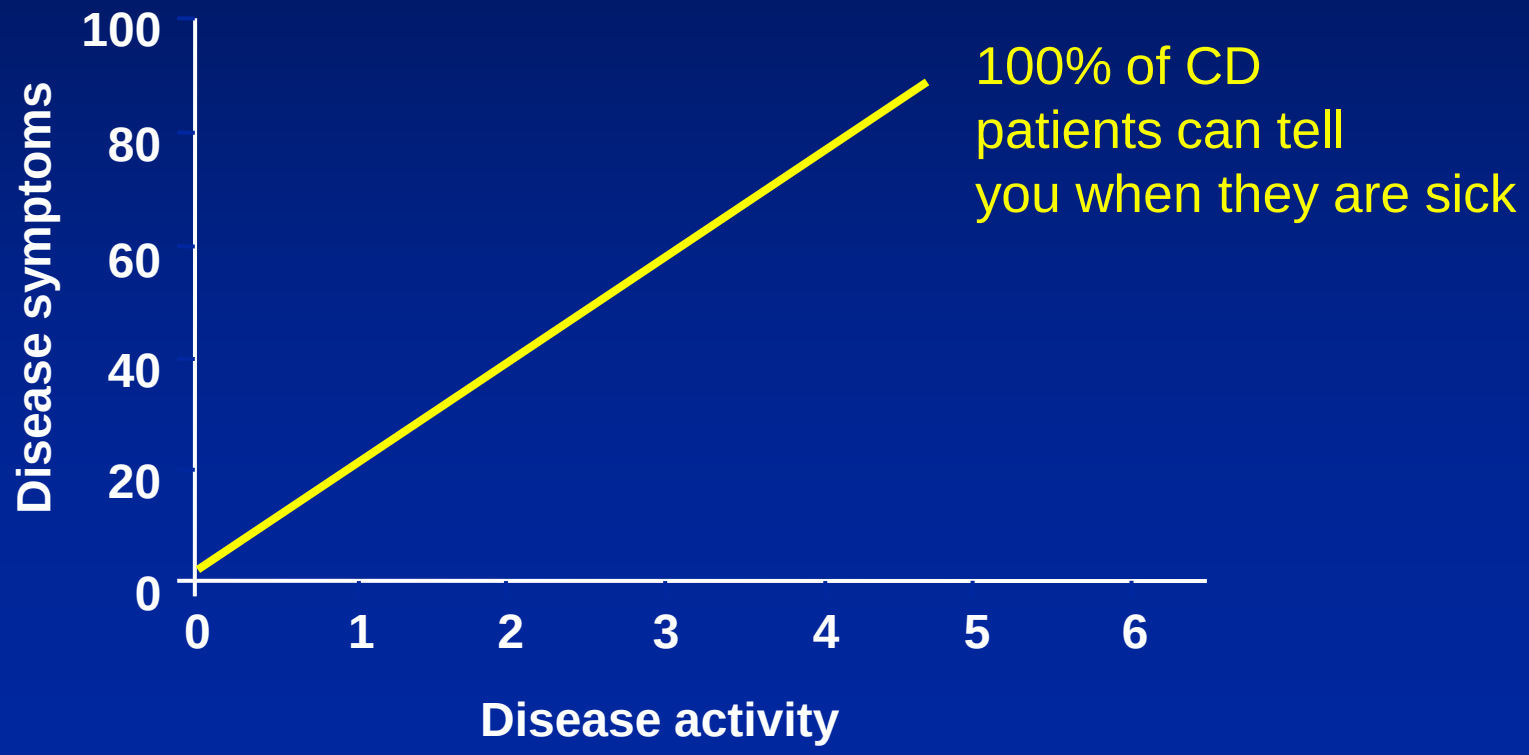
- Question: “How have you been doing?”
- Patient answer: “Pretty good.”





Symptom based therapy in Crohn's disease

- **Assumption – patients are symptomatic when their disease is active, and patients with no symptoms are "fine." This is the basis for all Phase II-III trial recruitment and clinical care in Crohn's disease.**

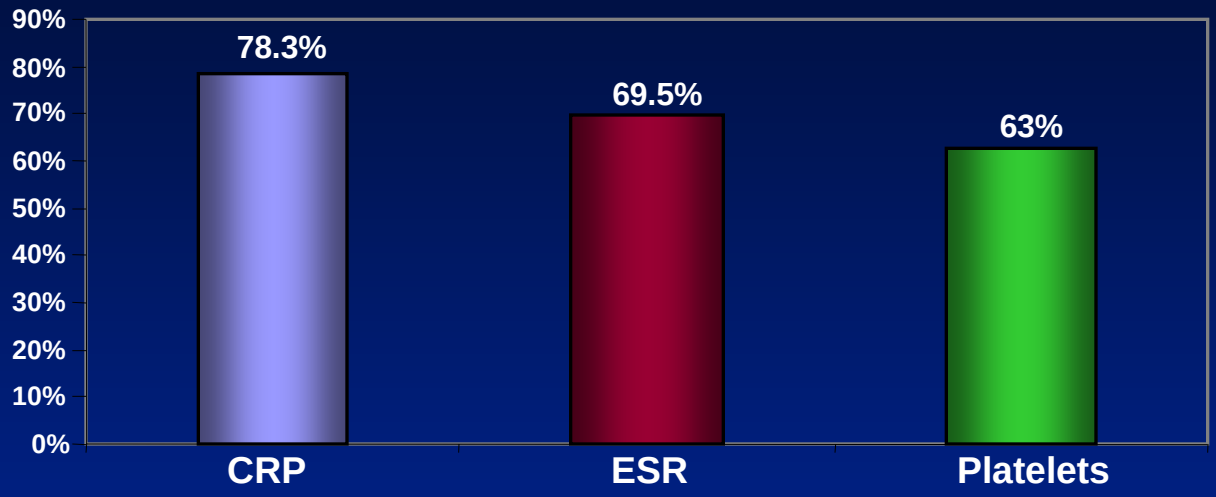


IBD management – Inflammatory markers

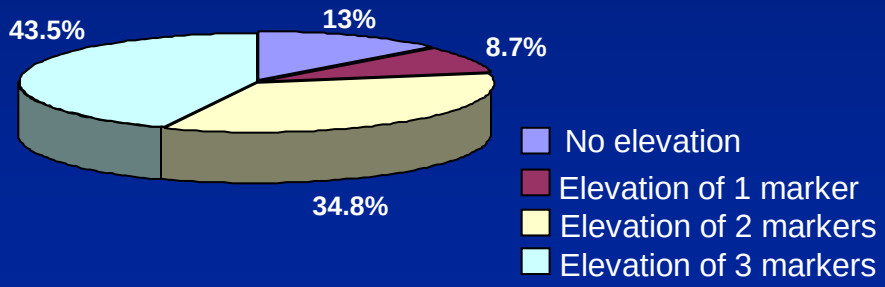
- C-reactive protein
  - Produced in liver
  - Binds pneumococcal C protein
  - Half-life of 19 hours
  - Genetically determined
- Erythrocyte Sedimentation Rate (ESR)
  - Non-specific
- Platelet count
  - Response to IL-6 acute phase

Solem CA et al. Inflamm Bowel Dis 2005: 11; 707-12.
Florin TH et al. Scand J Gastroenterol 2006: 41; 306-11.
Sachar DB et al. J Clin Gastroenterol 1986: 8; 647-650.

Inflammatory markers in hospitalized UC patients



Rate of marker positivity in hospitalized patients



Surgical outcome: 16/46 encounters (34.7%) required colectomy for refractory disease.

Issa M, *et al*. *Am J Gastroenterol* 101: S469, 2006.

Harvey-Bradshaw Index of Crohn's disease activity

Simplified clinical index of Harvey and Bradshaw

General wellbeing (0 = very well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible)
Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe)
Number of liquid stools daily
Abdominal mass (0 = none, 1 = dubious, 2 = definite, 3 = definite and tender)
Complications: arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, aphthous ulcers, anal fissure, new fistula, abscess (score 1 per item)

Harvey RF and Bradshaw JM. *Lancet*. 1980; 1(8167)514.

Health-related Quality of Life: SIBDQ

- Important in chronic diseases which can build up a cumulative impact over time.

- Incorporates patients' view point; understand impact of disease on individual patients' lives.
- Influenced by
  - Demographic characteristics
  - Disease and treatment
  - Coping skills and social support
  - Co-morbid illness
- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)
  - 10 item questionnaire, items derived by stepwise regression.
  - 4 domains – bowel, systemic, social, emotional
  - All items score on a 7-point scale (1=bad, 7=optimal)

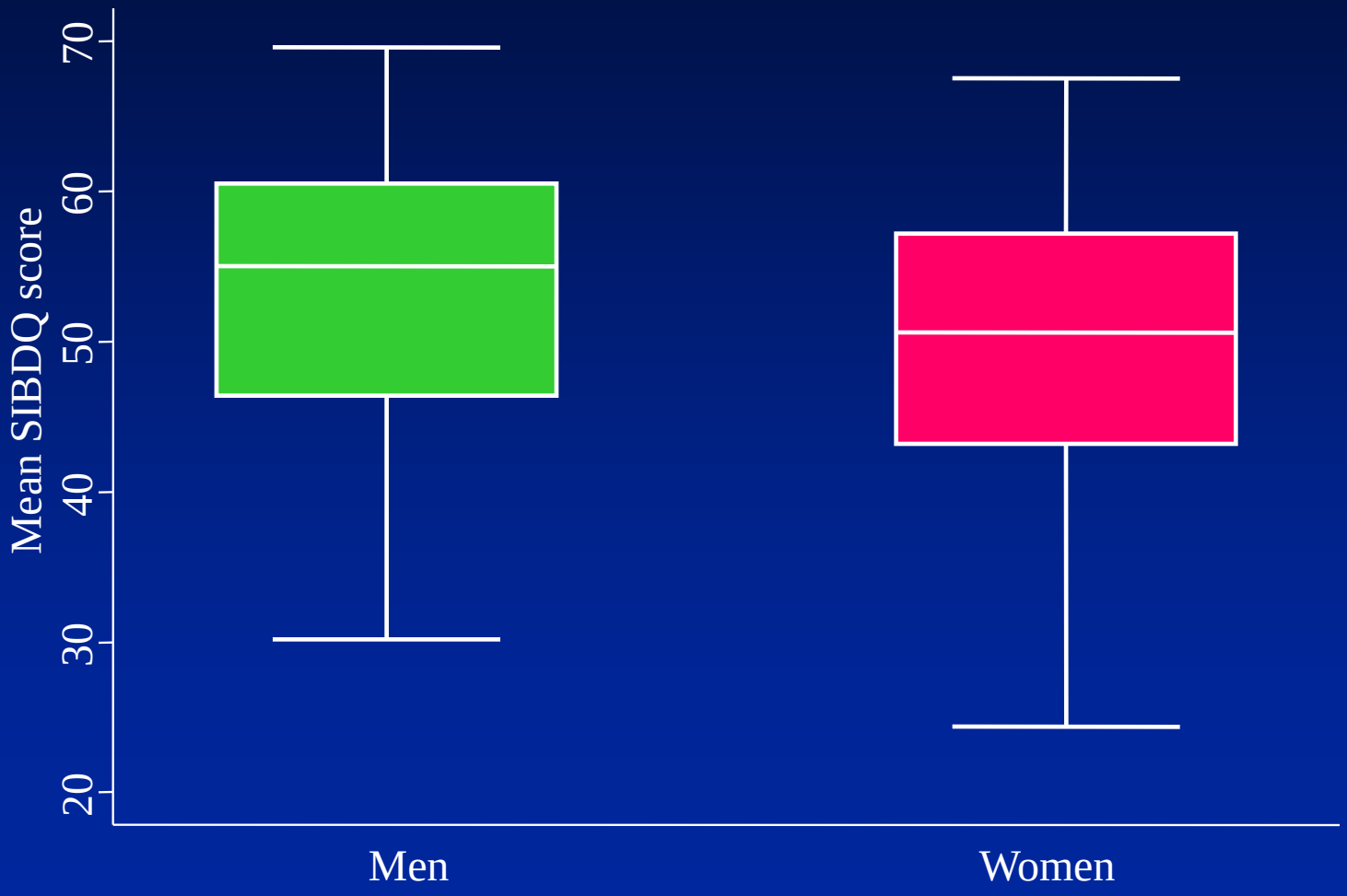
Irvine EJ, et al. Am J Gastroenterol. 1996 ;91:1571-8.
Jowett SL, et al. Am J Gastroenterol. 2001;96:2921-8.

The SIBDQ

1. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks?
2. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problems?
3. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done over the past 2 weeks?
4. **How often during the last 2 weeks have you been troubled by pain in the abdomen?**
5. How often during the last 2 weeks have you felt depressed or discouraged?
6. Overall, in the last 2 weeks, how much of a problem have you had passing large amounts of gas?
7. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be?
8. How often during the last 2 weeks have you felt relaxed and free of tension?
9. How much of the time during the last 2 weeks have you been troubled by a feelings of having to go to the toilet even though your bowels were empty?
10. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problems?

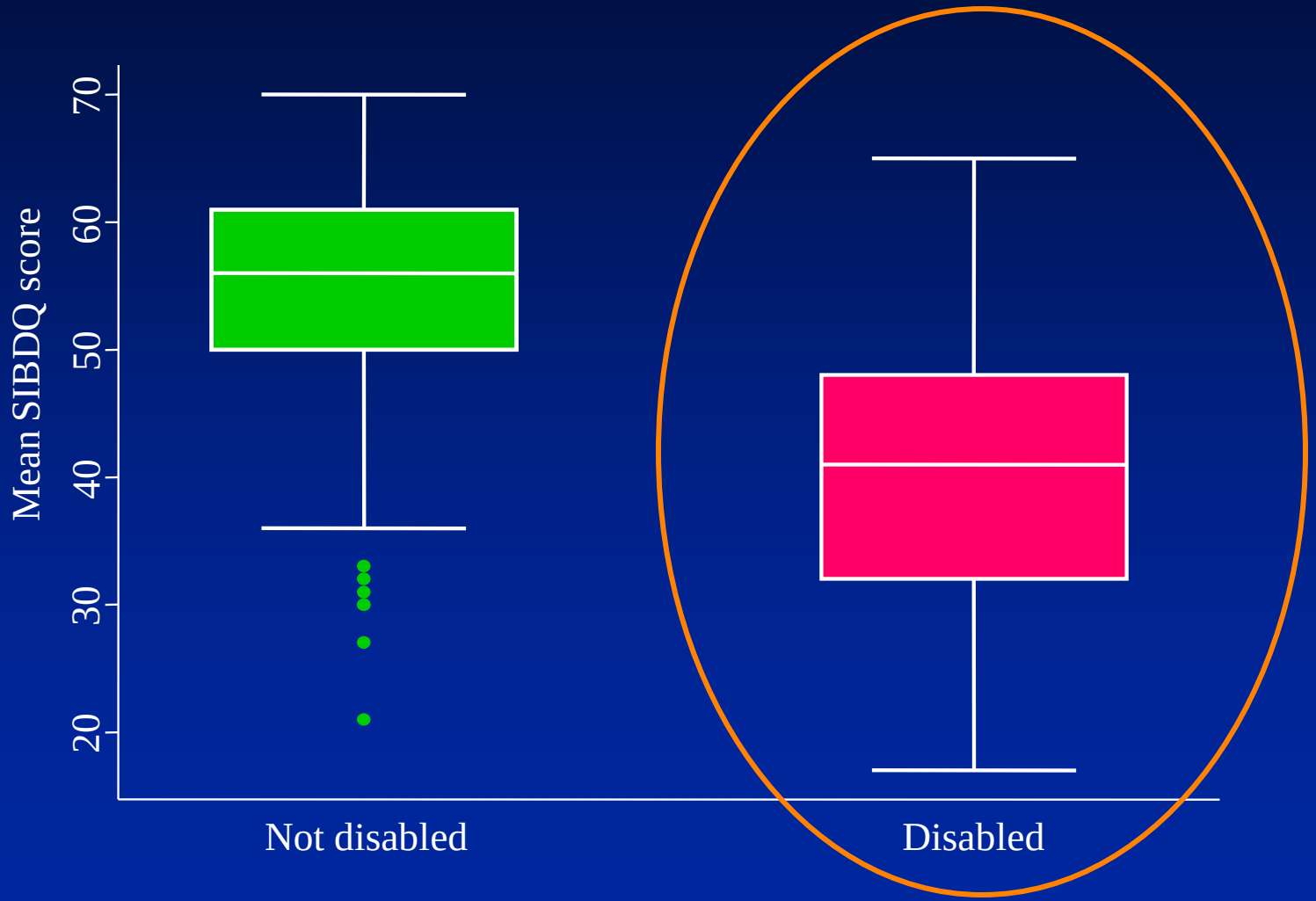
Irvine EJ, et al. Am J Gastroenterol. 1996 ;91:1571-8.
Jowett SL, et al. Am J Gastroenterol. 2001;96:2921-8.

Health-related Quality of Life: SIBDQ in >5000 clinic visits



Beaulieu DB et al. Gastroenterology 134(4), Suppl 1: A-199, 2008.

Work disability in Crohn's disease

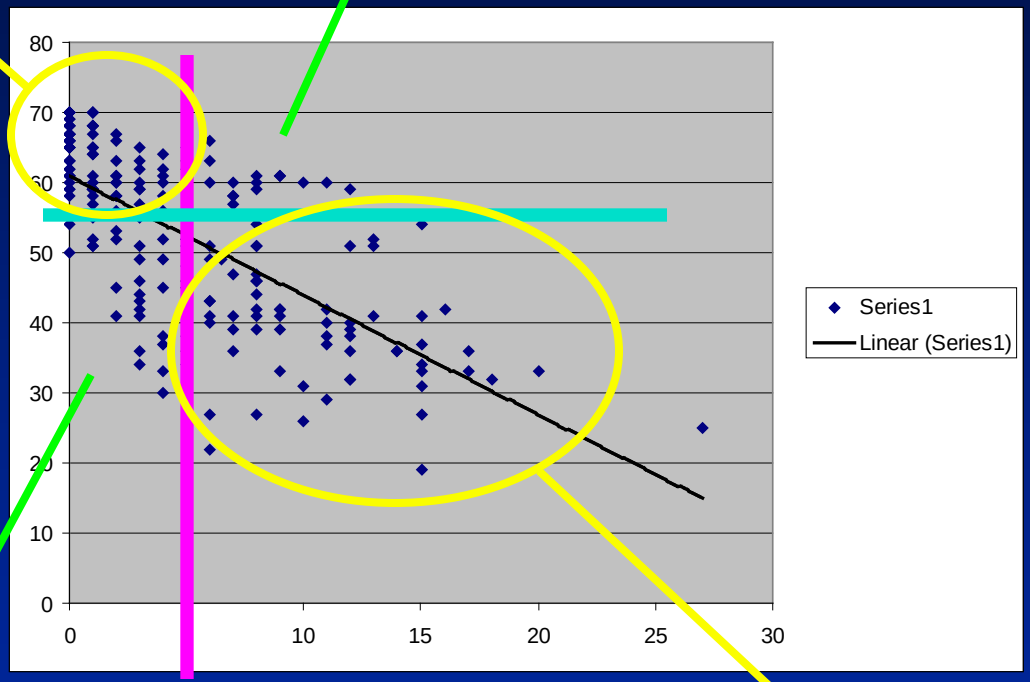


Ananthakrishnan AN *et al*. Am J Gastroenterol. 2008 Jan;103(1):154-61.

SIBDQ and Harvey Bradshaw in routine Crohn's disease clinical care UPMC IBD Center

Feels well, doing well

?



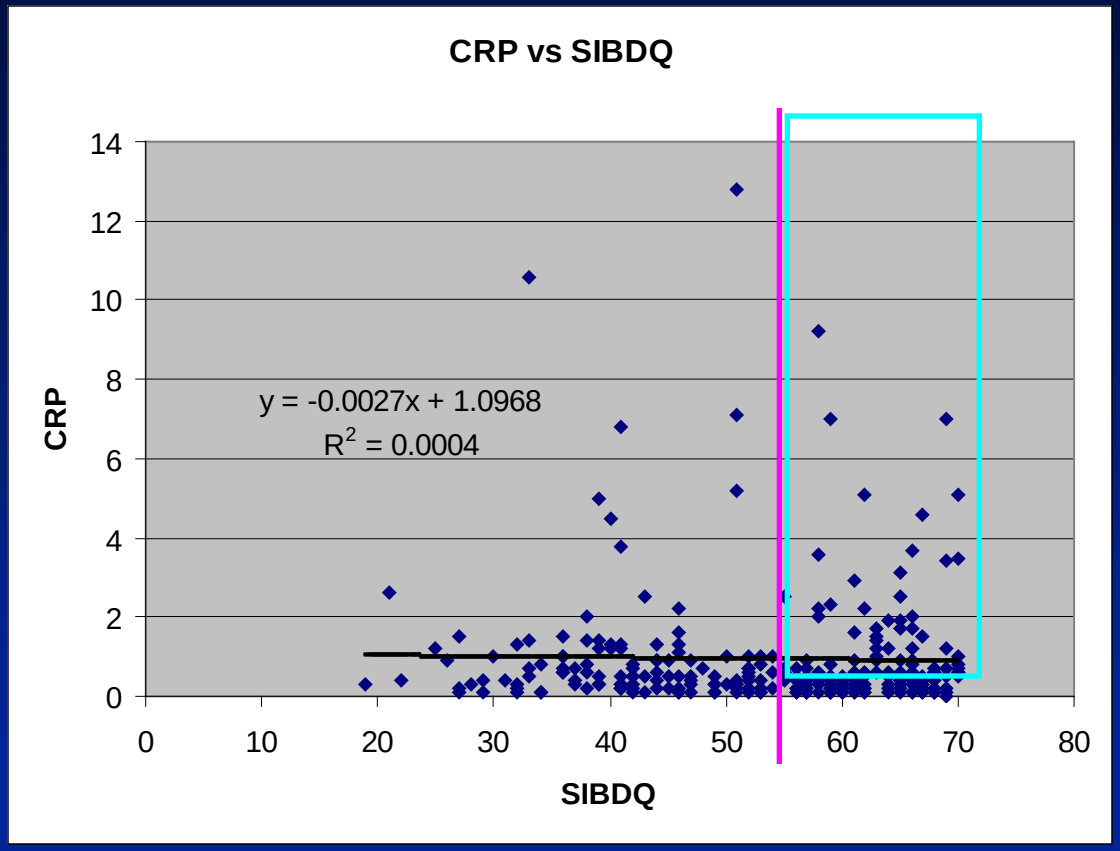
?

HB score

Feels poorly, doing poorly

Higher SIBDQ, better QOL. Higher HB, worse disease activity

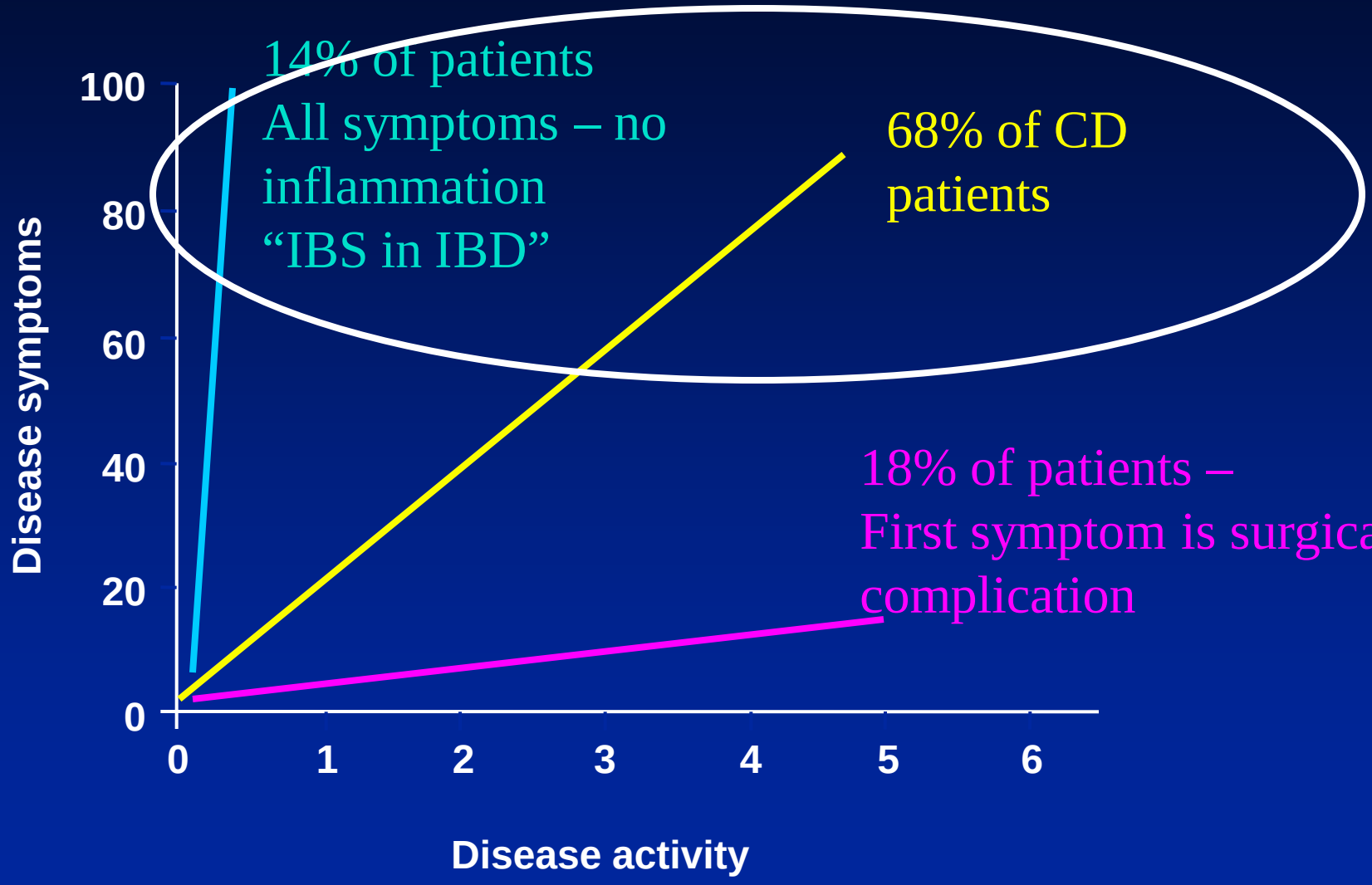
Crohn's disease: Disconnect between CRP and SIBDQ



Patients who feel well
CRP > 0.5 mg/dL

Patients who feel well
SIBDQ > 55

The correlation of disease symptoms and activity in Crohn's disease



UPMC IBD Center algorithm for Medical and Surgical management of IBD

- Rapid progression to immunomodulators
- Limitation of steroid use
- Maintenance of remission therapy – guided by symptoms, labs and endoscopy
- Identification of infections/adverse drug reactions/functional symptoms
- Infliximab, adalimumab, certolizumab for AZA/6MP/MTX breakthrough/failure
- Identification and surgical treatment of obstruction/abscess
- Post-operative maintenance of remission therapy

III. Nutritional Management of IBD

Malnutrition in IBD

Red flags

- Weight loss:
  - results from anorexia, malabsorption and intestinal losses rather than hypermetabolism
  - at time of dx: 85% of pediatric CD and 65% of pediatric UC lose wt
  - 20-75% of adults experience it with exacerbation

- Anemia:
  - occurs in 54-80%.
  - Vitamin B12 and folic acid deficiency, bone marrow suppression secondary to drug therapy and anemia of chronic disease.

Causes of Malnutrition

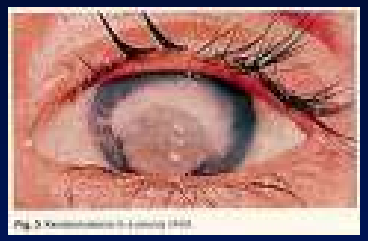
- Decreased nutrient intake
  - Iatrogenic dietary restrictions
  - Intake –associated pain and Sitophobia.
  - Altered taste: Zinc/copper/nickel deficiency,Metronidazole.
  - Anorexia
- Iatrogenic
  - Surgical complications: resections and bypass
  - Medications (Corticosteroids/ca, Sulfasalazine/folate, Cholestyramine/fat + fat soluble vit and ca deficiency)
- Increased requirements
  - Hyper catabolic state (fever, sepsis)
  - Growth in children

Hypoalbuminemia	25-80
Anemia	60-80
Iron deficiency	39-81
Vitamin B12 deficiency	20-60
Folic acid deficiency	36-54
Calcium deficiency	13
Magnesium deficiency	14-33
Potassium deficiency	6-20
Vitamin A deficiency	11
Vitamin C deficiency	*
Vitamin D deficiency	75
Vitamin K deficiency	*
Zinc deficiency	40-50
Copper deficiency	*

Frequency % of Nutritional deficiencies in IBD patients

Perkal et al. Gastro Clin N Am. 1989 18(3):567

Nutrition deficiencies



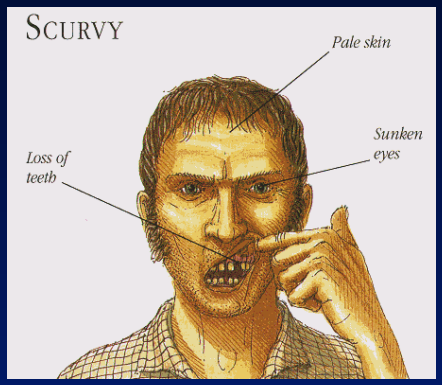
- **Vitamins**
  - **Vit A:**
    - **night blindness**
    - **supplements 5.000-10.000 IU/day**
    - **watch for toxicity: liver, skin changes and risk for bone fractures**

  - **Vit B12**
    - **due to TI involvement or resection**
    - **manifests as anemia, glossitis, neurologic changes: paresthesias, confusion, poor memory**
    - **IM injection and nasal spray supplements available at 100-1000 mcg/month**

  - **Folic Acid:**
    - **in 40% of CD pts and 60% in UC pts**
    - **low intake. drugs**
    - **protective effect against dysplasia and colorectal cancer in UC.**

Nutrition deficiencies

- **Vitamin C**
  - causes bleeding, impaired wound healing
  - oral supplement 500-1000mg/day



- **Vitamin D**
  - occur in 75% of CD and 35% in UC
  - causes osteoporosis, bone pain.
  - oral supplement 400-800 unit/day

    new data supports higher replacement – 4000 IU orally per day

- **Vitamin K**
  - result from fat malabsorption, antibiotics
  - oral supplement 5mg/day

General nutrition consideration in IBD

- No single uniformly effective dietary protocol for pts with IBD
- Dietary restrictions are questionable
- Controlled studies did not support low residue neither high fiber low refined sugar diet in maintaining remission in CD pts
- Exclusion of specific foods on the basis of individual clinical intolerance improves the clinical course of IBD *especially cereals, dairy products and yeast.

Riordan AM et al. Treatment of active Crohn's disease by exclusion diet: East Anglian multicentre controlled trial. Lancet 1993;342:1131.

General nutrition consideration in IBD

- Every patient with IBD should consider daily multivitamin (children's chewable is well tolerated).
- IBD patients with history of CD resection or colectomy with J pouch reconstruction should have vitamin B12 monitored / replaced with subcutaneous injections.
- IBD pts should receive low dose folic acid and Vit B12 to protect against the thromboembolic complications of raised homocyteinaemia.
- All IBD patients should have vitamin D monitored and replaced with oral supplementation (especially if on frequent steroids)
- Avoid oral Magnesium, potassium or iron supplements – may cause diarrhea, mucosal injury

IV. Summary – How to achieve optimal medical and nutritional management of IBD

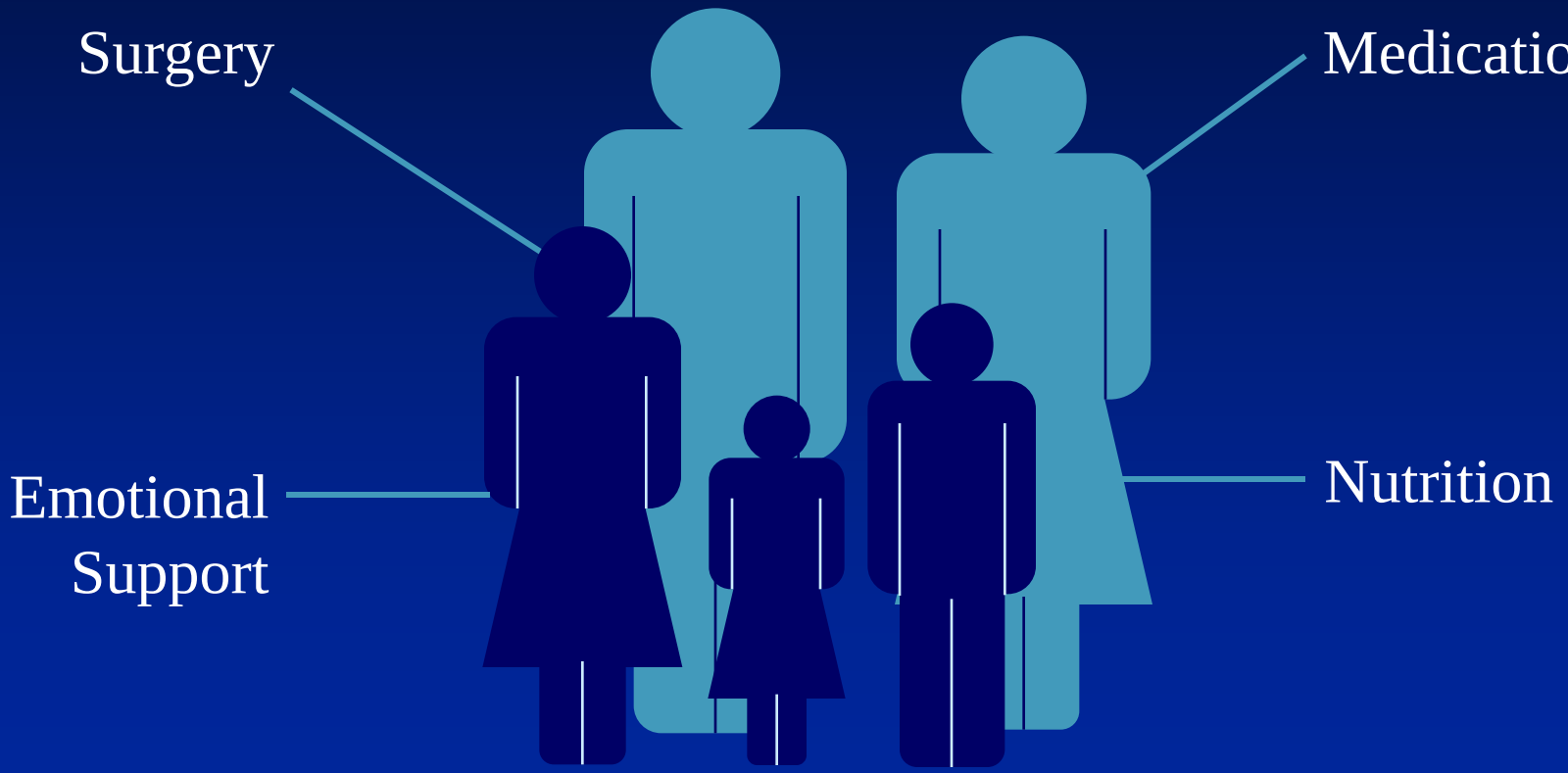
Take charge!

Be an active participant in your care

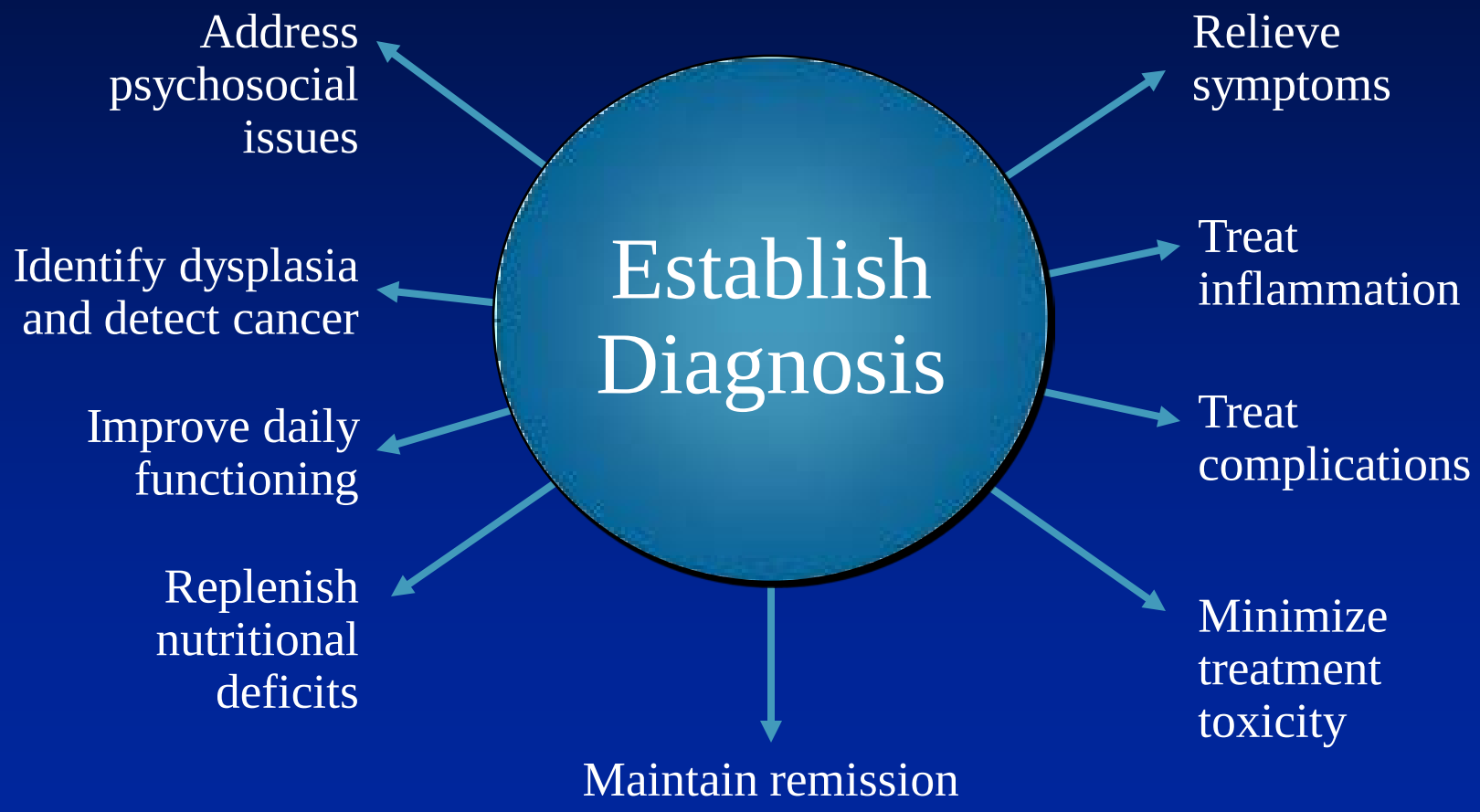
Understand the goals of treatment

Ask questions – including what to do if it isn’t working

Treatment of Inflammatory Bowel Disease



IBD: Management Goals



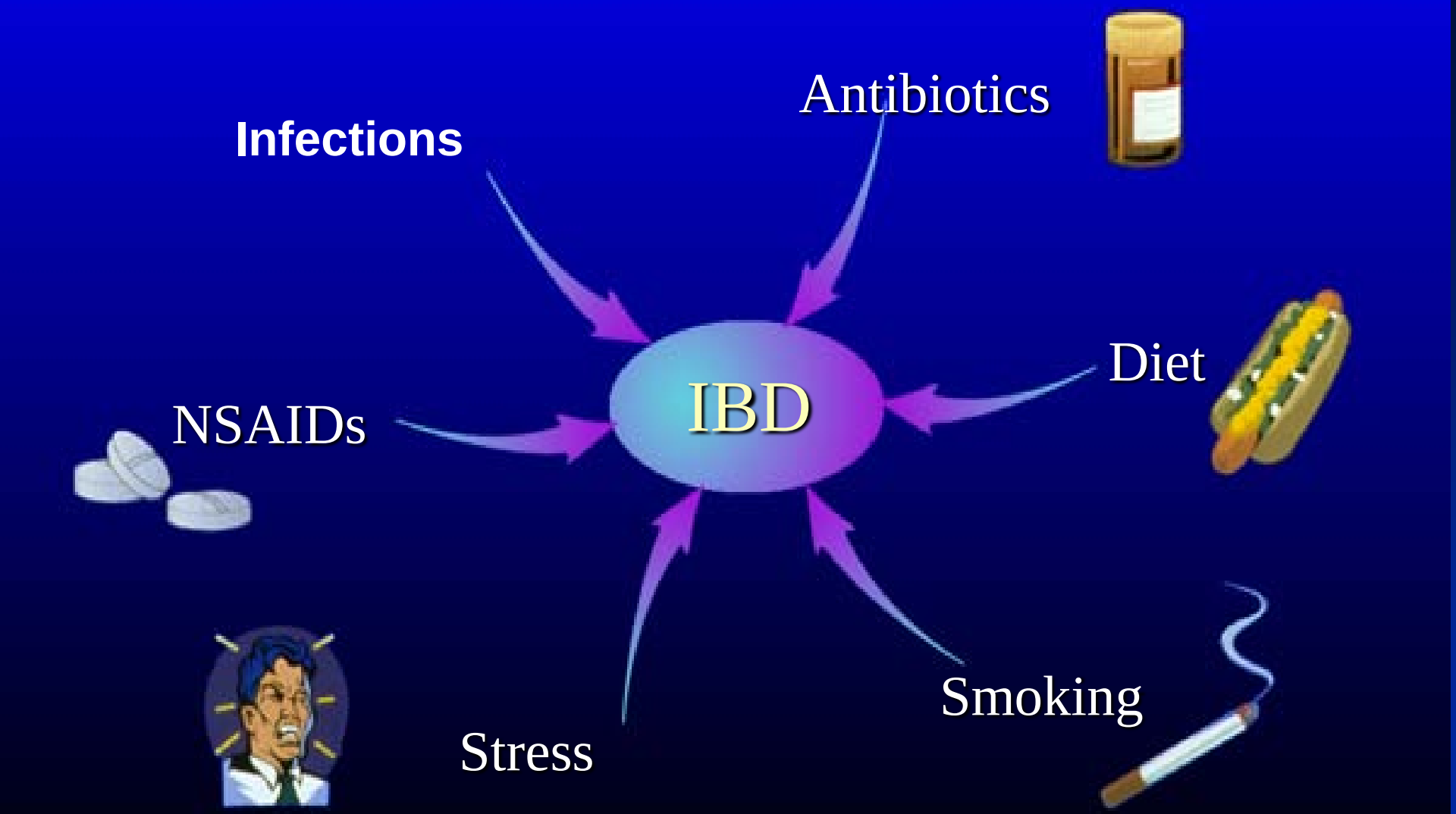
Goals of treatment – I
Inducing remission

- 1. If you are sick, you have to get better
  - Medications
  - Surgery
  - Identifying complicating factors – infections, drug side effects, symptoms unrelated to inflammation

Goals of treatment – II
Maintaining remission

- 2. Once you are better, emphasis should be on keeping you well
  - Medications
  - Smoking (avoid)
  - Avoid drug side effects - NSAIDs

Environmental Triggers



IBD and *Clostridium difficile*

Anaerobic bacillus associated with pseudomembranous colitis

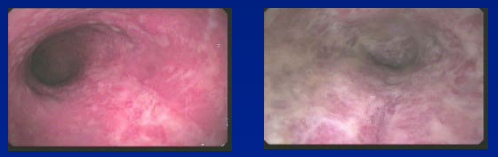
Increasing incidence and severity in North America. Doubling of cases in past 10 years. Cost $1.1 billion annually

Increased *C difficile* susceptibility and severity in IBD patients

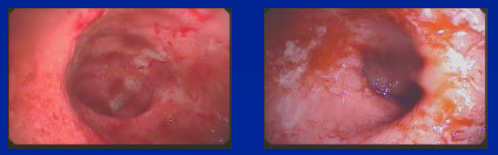
Associated with disturbance in flora – antibiotics, NPO, diverted bowel segments

Food is "prebiotic" for normal enteric flora when treating *C difficile*

Endoscopic appearance of *C difficile*

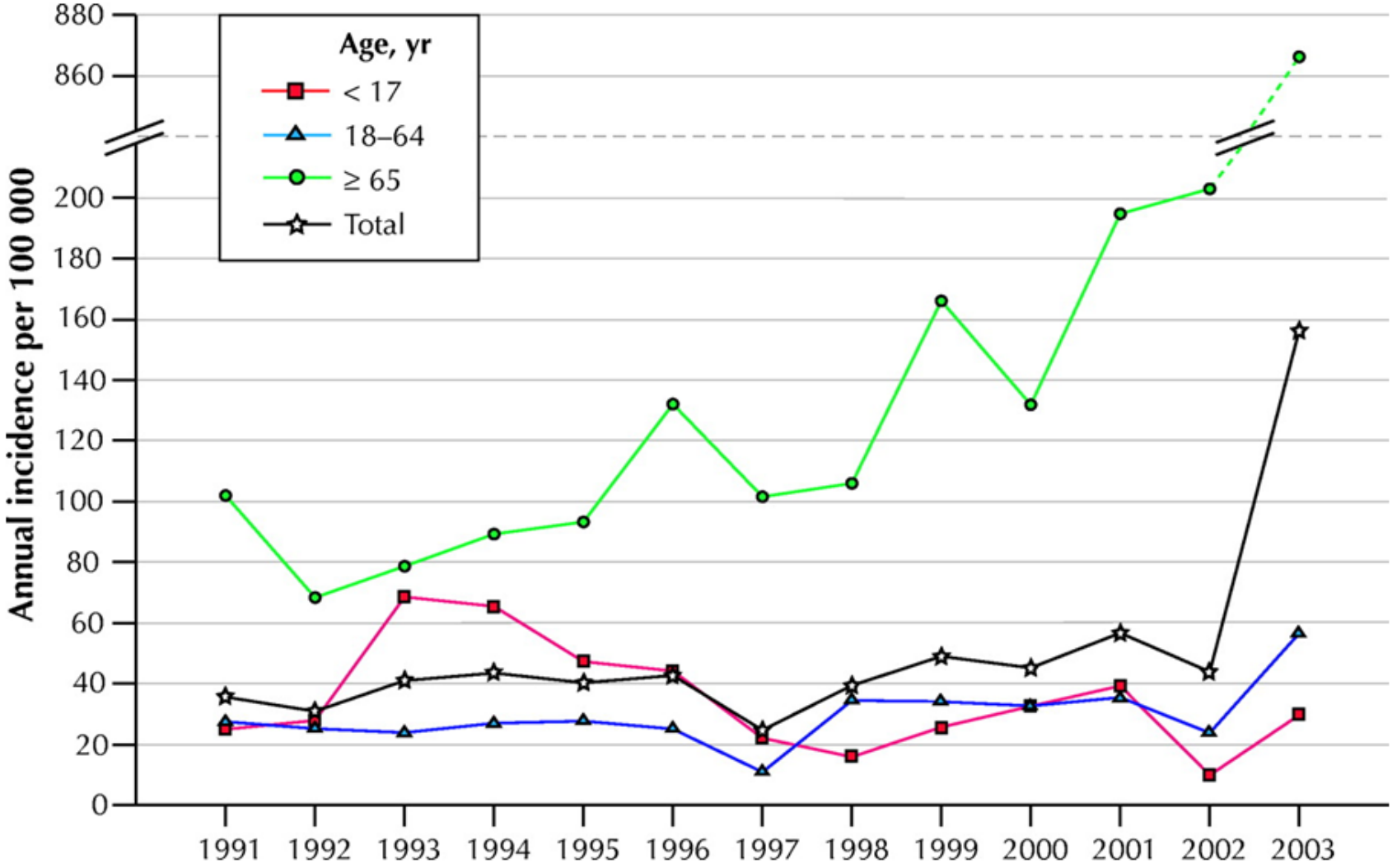


Ulcerative Colitis and *C difficile*



Issa M et al. Clin *Gastroenterol Hepatol.* 2007;5: 345-51.
Ananthakrishnan A et al. Gut 2008; 57: 205-10.
Lundeen S et al. J Gastrointest Surg 2007; 11: 138-42.

Fig. 1: Annual incidence (per 100 000 population) of Clostridium difficile-associated diarrhea (CDAD) in Sherbrooke, Que., 1991–2003.



Pépin J et al. CMAJ 2004;171:466-472

Goals of treatment – III
IBD issues over the lifetime

- 3. What to watch out for in the longterm
  - Drug side effects
  - Bone health
  - Pregnancy issues
  - Cancer prevention

What you can do to help

- Ask questions from your health care providers
- Keep a copy of your medical records at your home
  - Americans frequently move
  - Encounter different health care providers/systems
- Get information
  - Reliable sources
  - Crohn's and Colitis Foundation of Ameica (www.ccfa.org)
  - National Institutes of Health (www.nih.gov)
- Use common sense
  - Take good care of yourself – healthy diet, good quality sleep and exercise

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