

PEDIATRIC - IBD

SHIMON REIF, MD

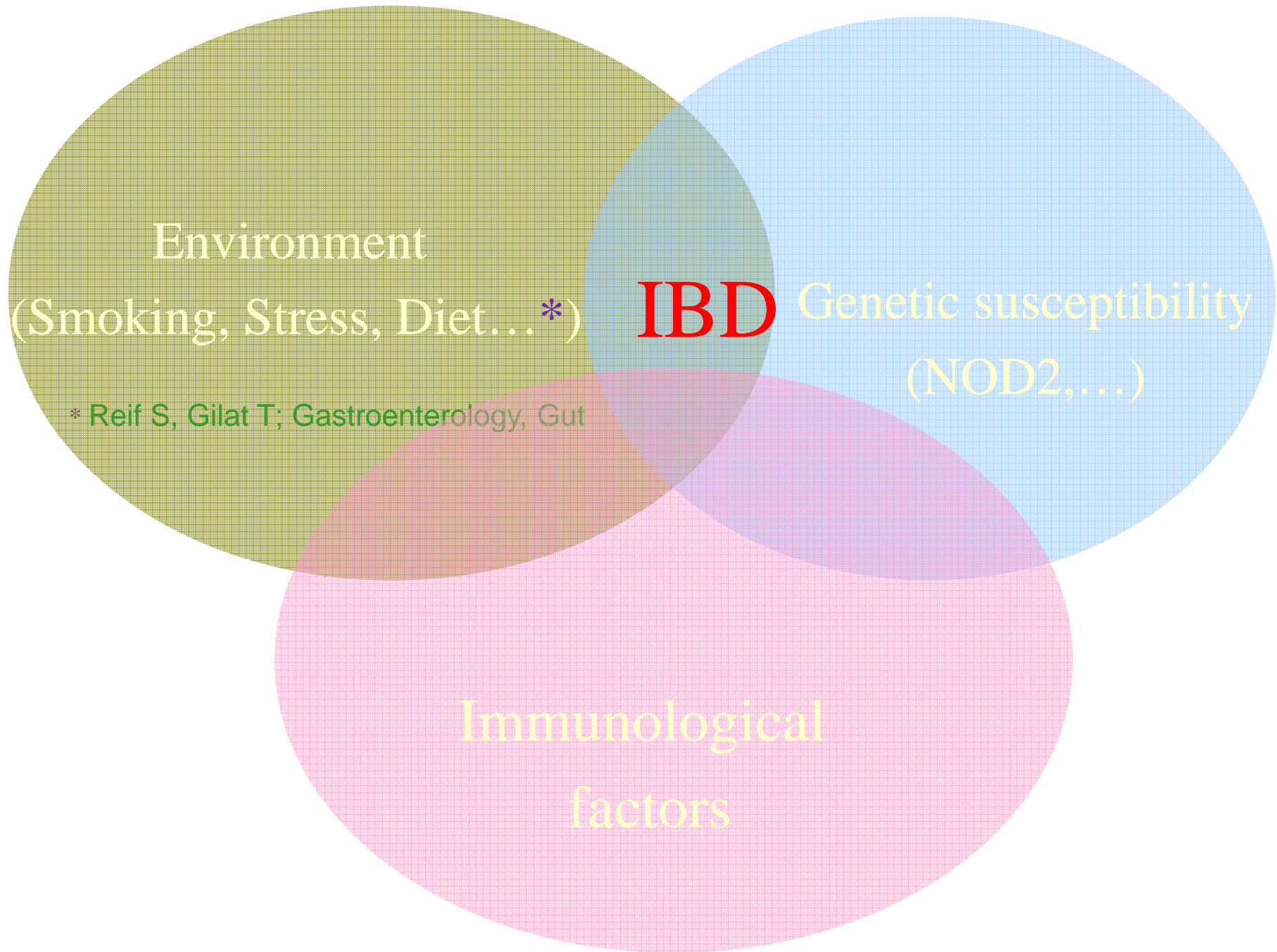
DEPARTMENT OF PEDIATRICS

HADASSAH MEDICAL CENTER

DISCLOSURE

- IBD IN 30 MINUTES – NO WAY!!!
- Highlights in Pediatric IBD – yes, we can do
- IBD in the "קהילה" – Impossible

IBD is the same disease in the community or in the hospital



Environment

(Smoking, Stress, Diet...*)

* Reif S, Gilat T; Gastroenterology, Gut

IBD

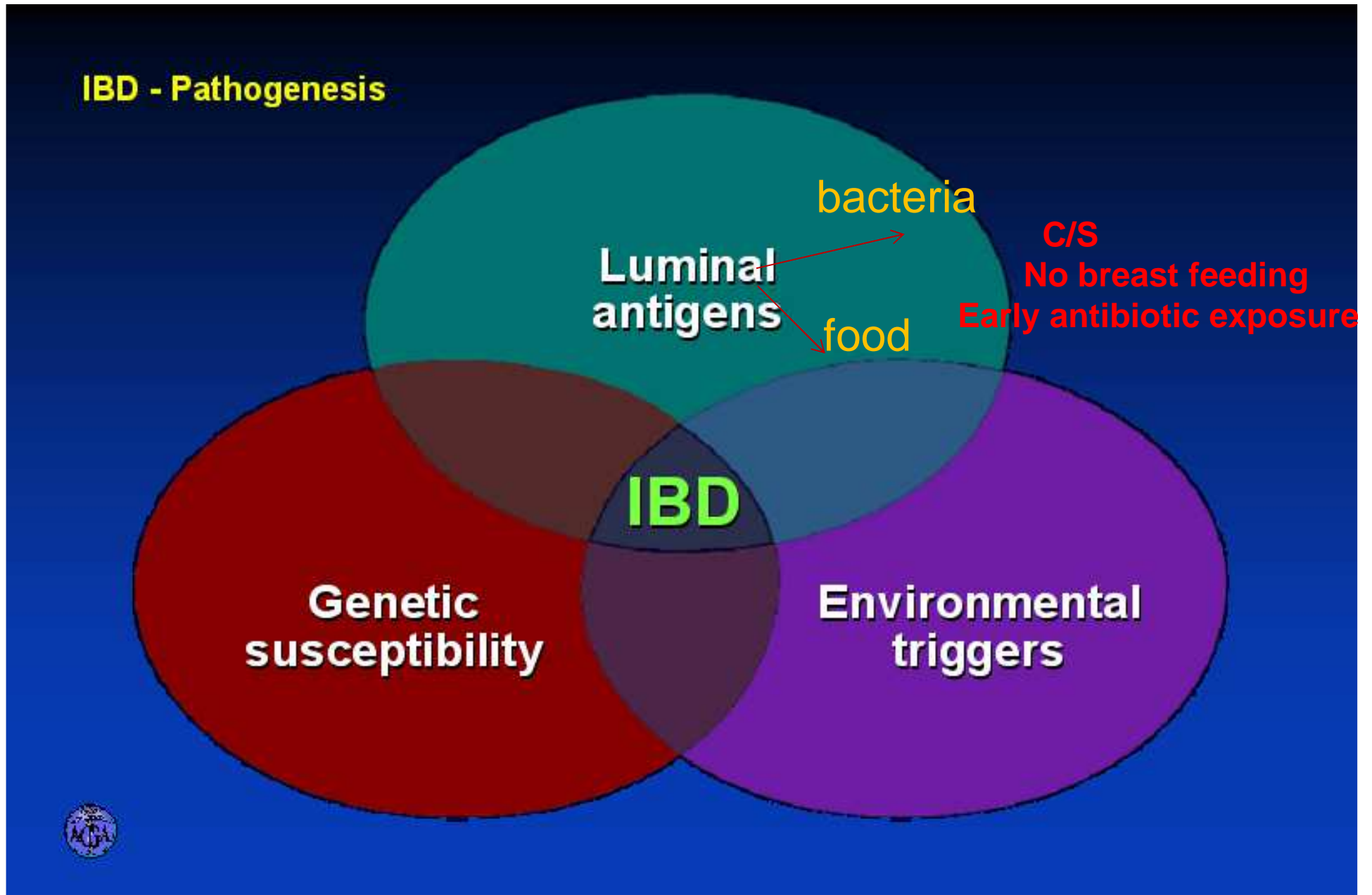
Genetic susceptibility

(NOD2,...)

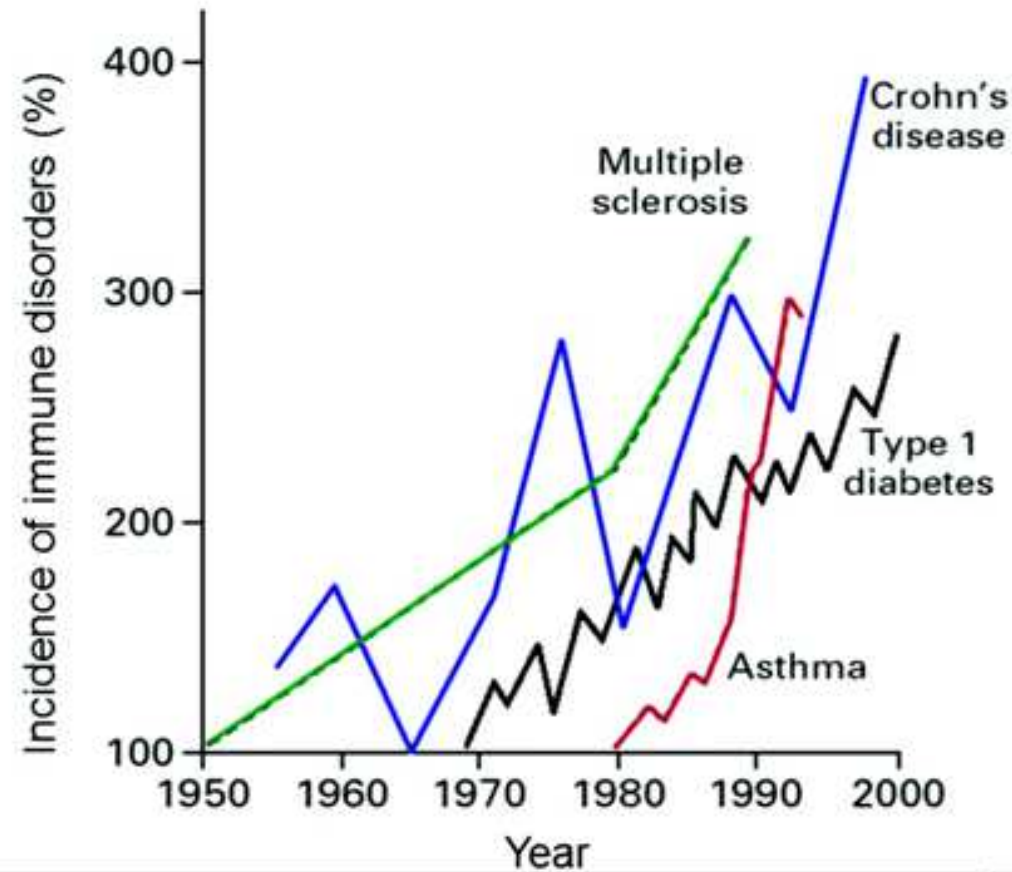
Immunological

factors

Gene-Environment Interaction



The Increasing Incidence of Immunoregulatory Disorders



IBD: A Disease of the Rich?

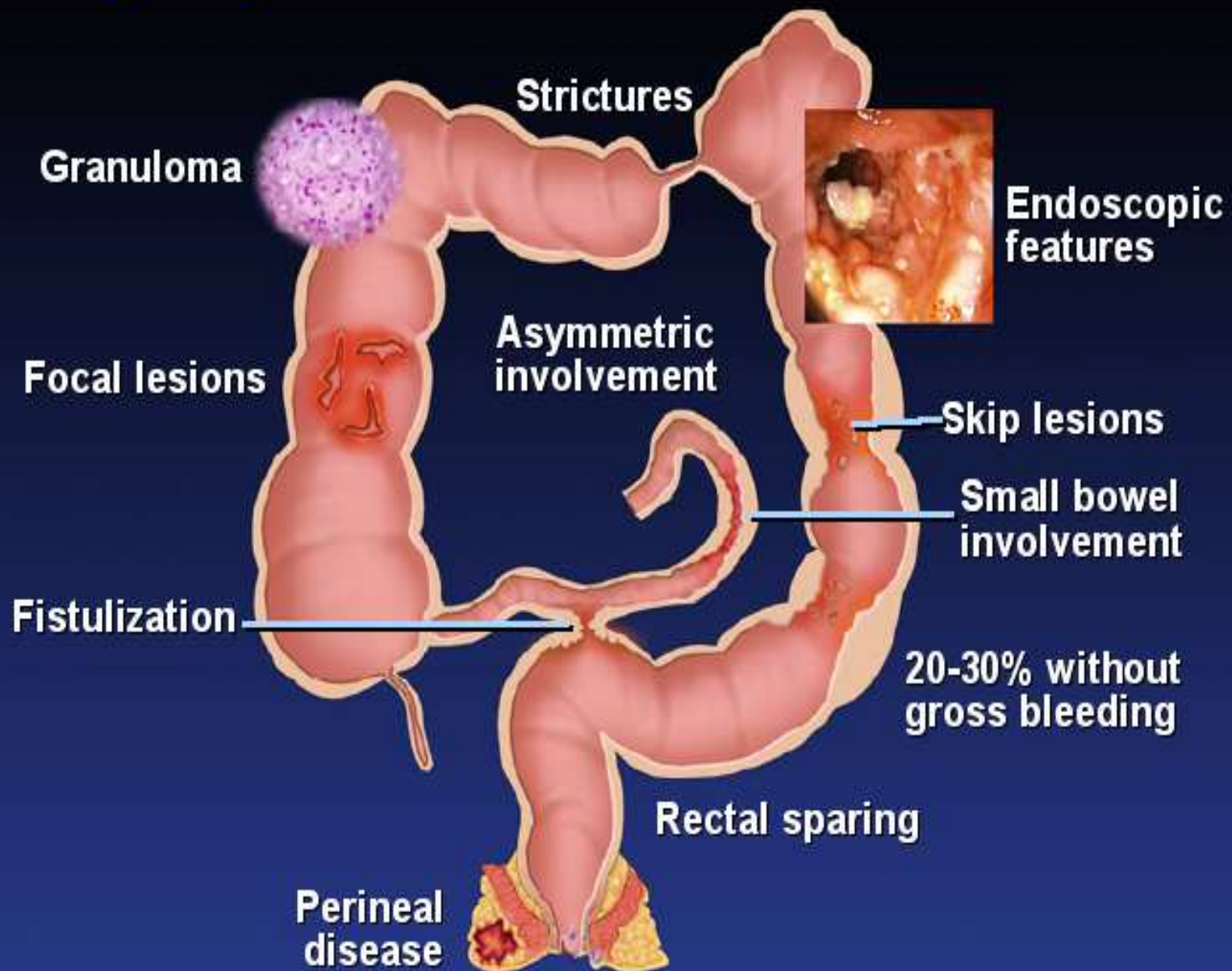


Pathogenesis

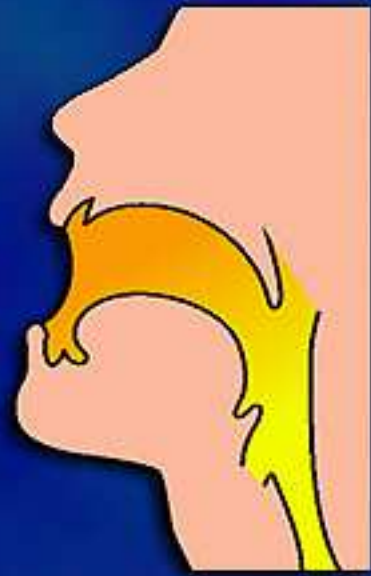
imbalance between innate and immunologic system

- The normal gut's immune system is normally in a state of “physiologic” inflammation reacting to the antigenic load presented to it by microbes and food
- In IBD there is impairment of this natural immunologic response (innate)
- Instead there is unchecked over response of the immunologic response
- Tissue damage, increased permeability

CD - Distinguishing Features



Crohn's Disease: Anatomic Distribution



UPPER GI – L4

Small bowel
alone
(33%) – L2

Ileocolic
(45%) – L3

Colon alone
(20%) – L1

Frequency of involvement

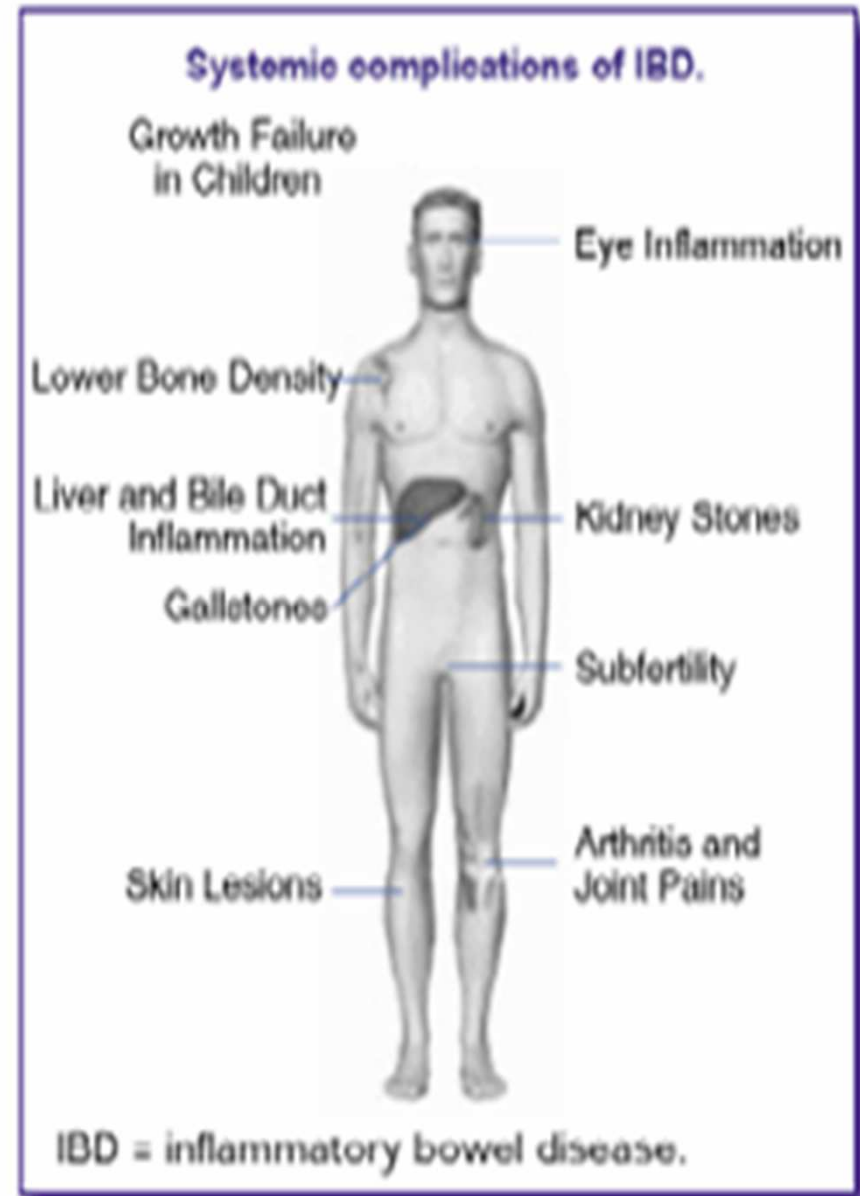


Most

Least

Extraintestinal Manifestations of IBD

- Skin
 - Erythema nodosum
 - Pyoderma gangrenosum
- Joints
 - Peripheral arthritis
 - Sacroileitis
 - Ankylosing spondylitis
- Eye
 - Uveitis
 - Episcleritis
 - Iritis
- Hepatobiliary complications
 - Gallstones
 - PSC
- Renal complications
 - Nephrolithiasis
 - Recurrent UTIs



Inflammatory Arthritis



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Aphthous Stomatitis



Erythema Nodosum



Courtesy of J-F Colombel, MD.

Pyoderma Gangrenosum

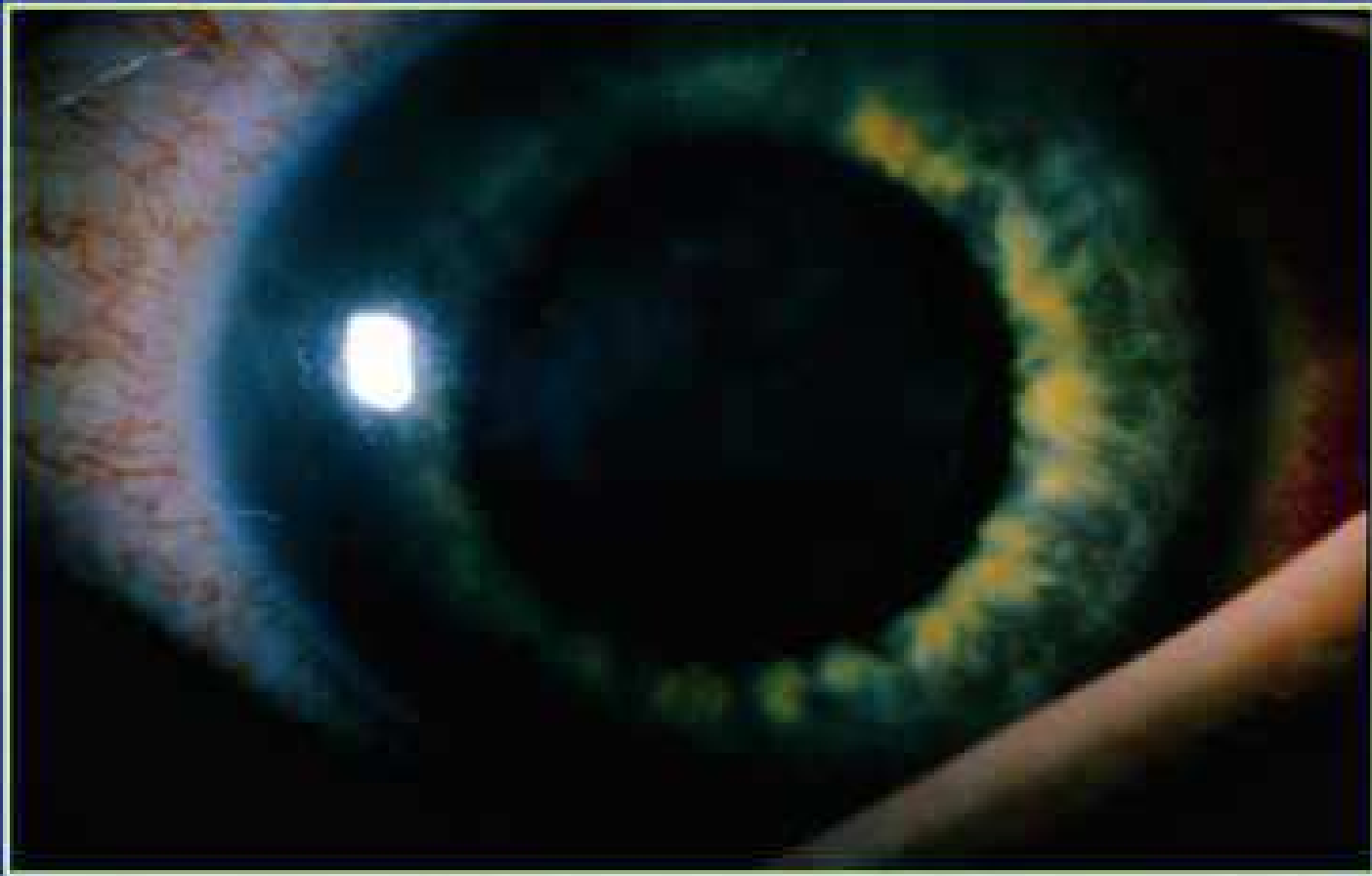


Sacroiliitis in IBD



Courtesy of J-F Colombel, MD

Uveitis

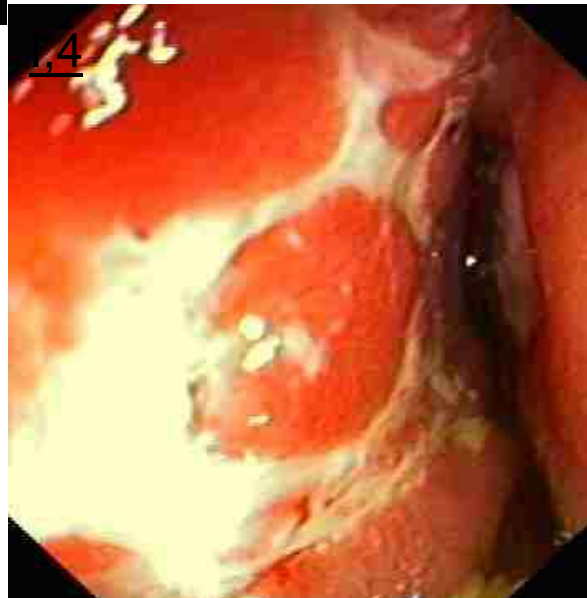
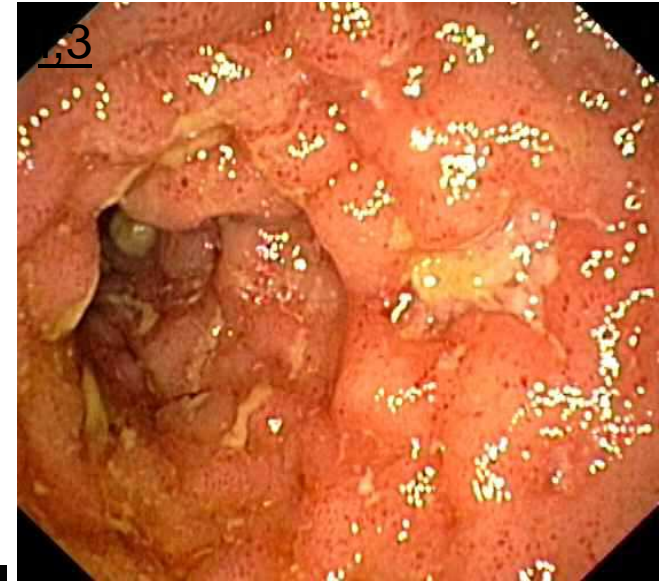


Sclerosing Cholangitis in IBD

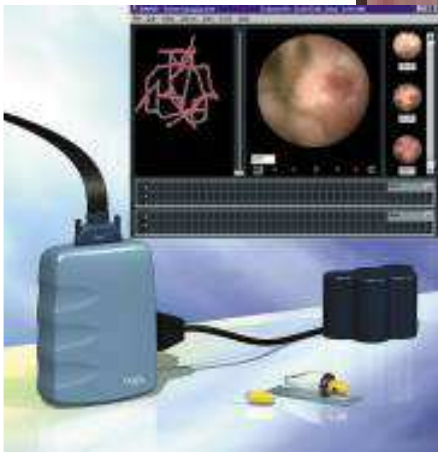
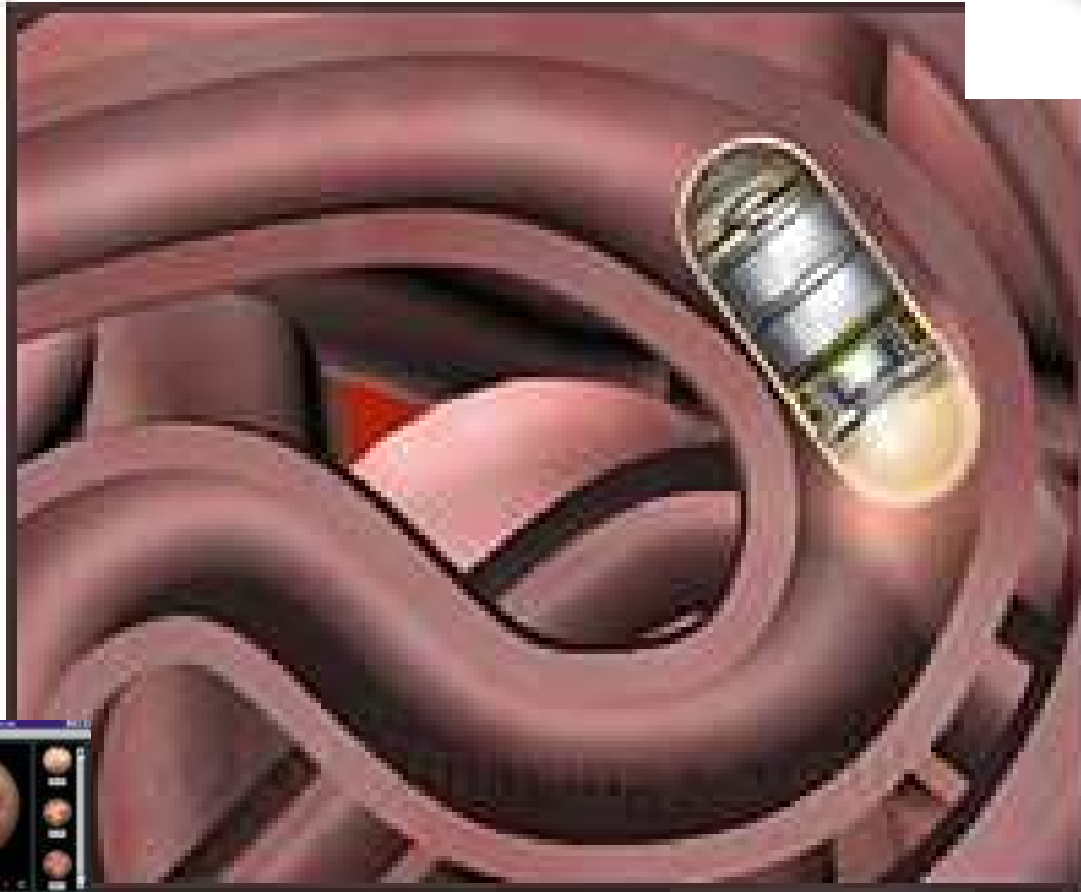


Courtesy of J-F Colombel, MD.

endoscopic appearance



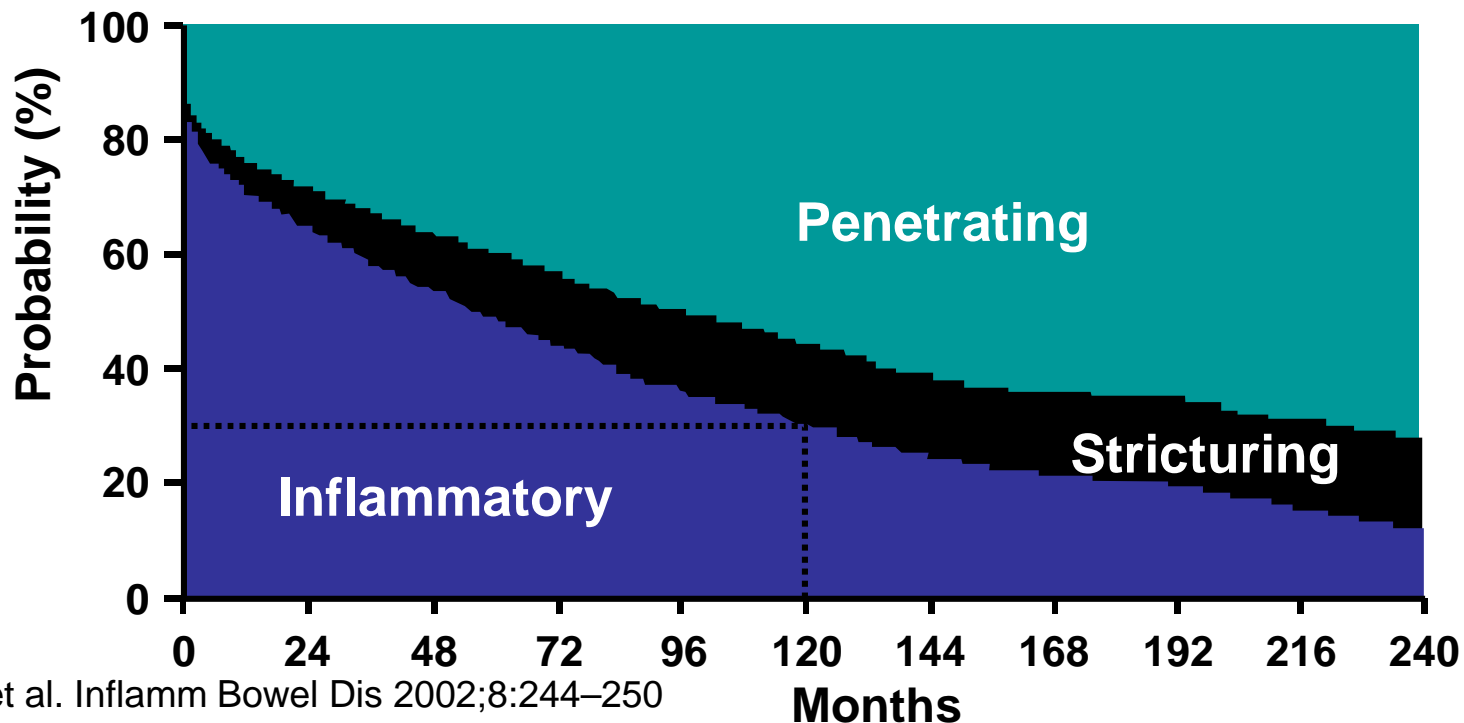
The Capsule (WCE)





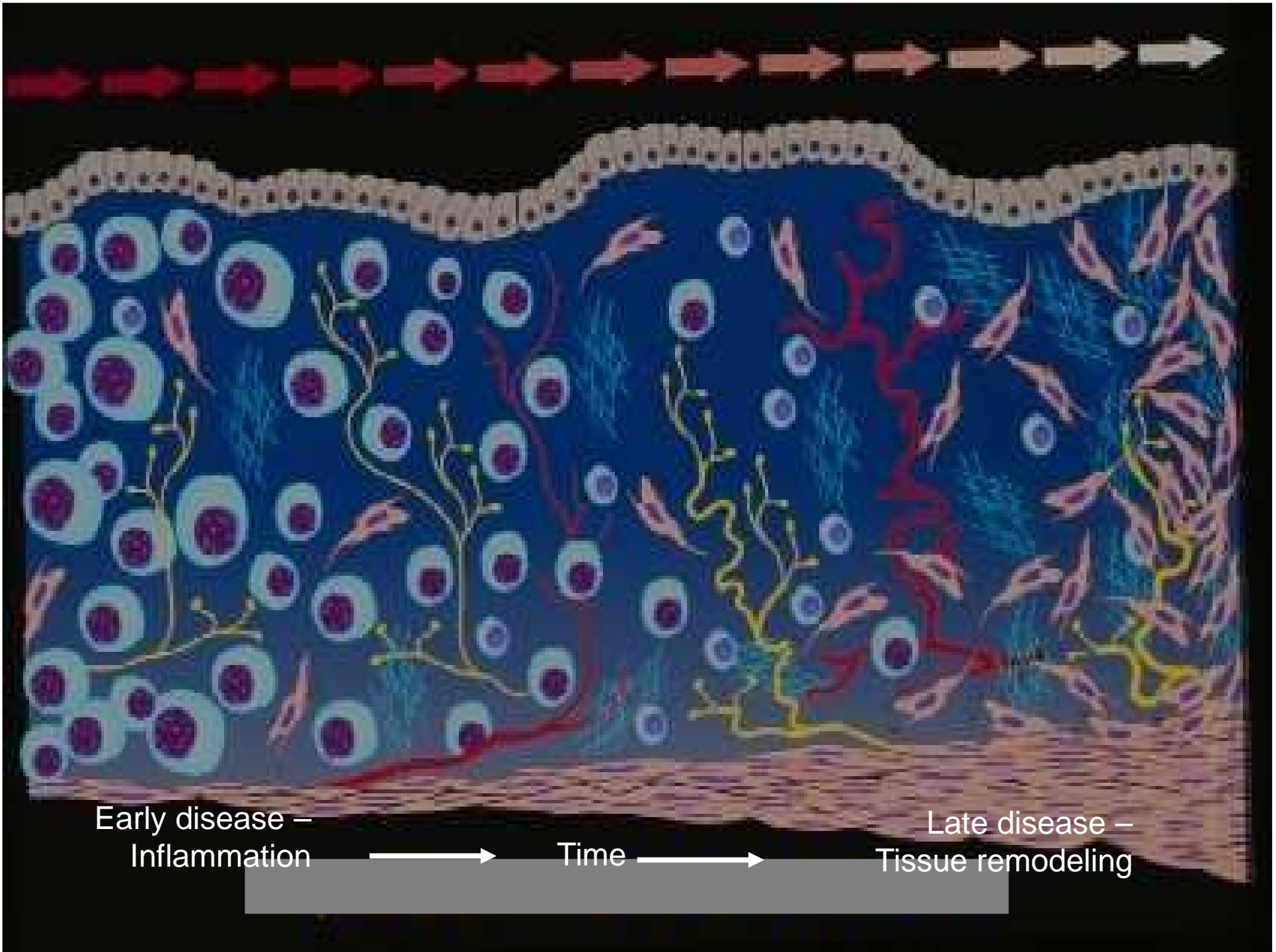
Natural history of Crohn's disease: 90% of patients develop stricturing or penetrating complications

- Retrospective study of 2,002 CD patients with regular follow-up in a single University
- More than 70% develop complications within 10 years



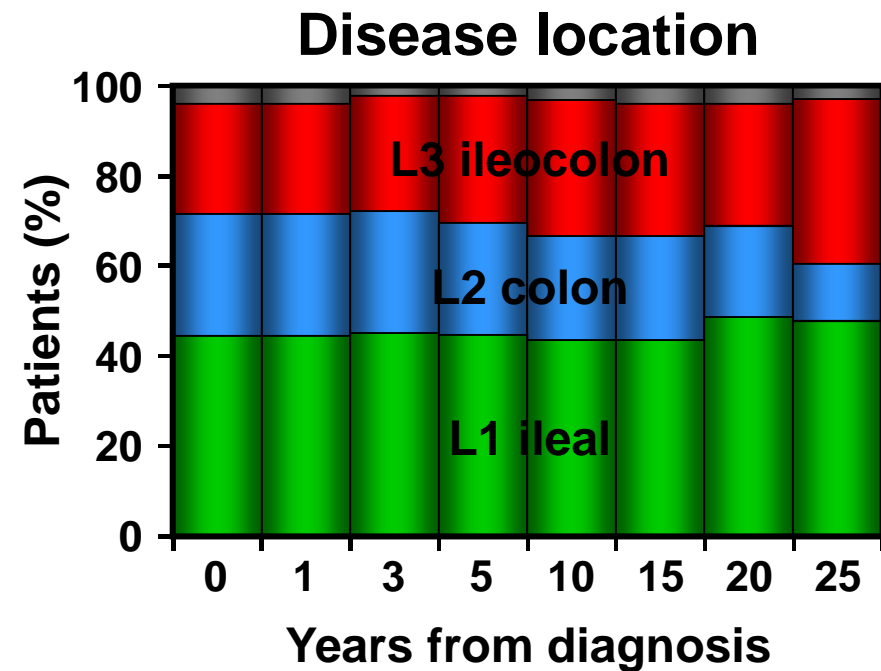
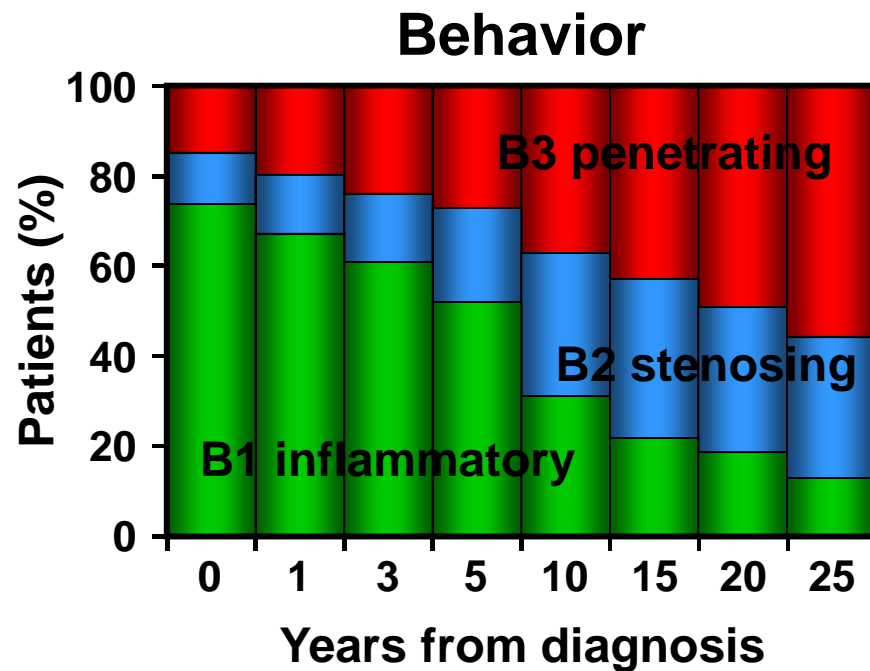
Cosnes J, et al. Inflamm Bowel Dis 2002;8:244-250

Wolters F, et al EC-IBD. Scand J Gastroenterol 2006



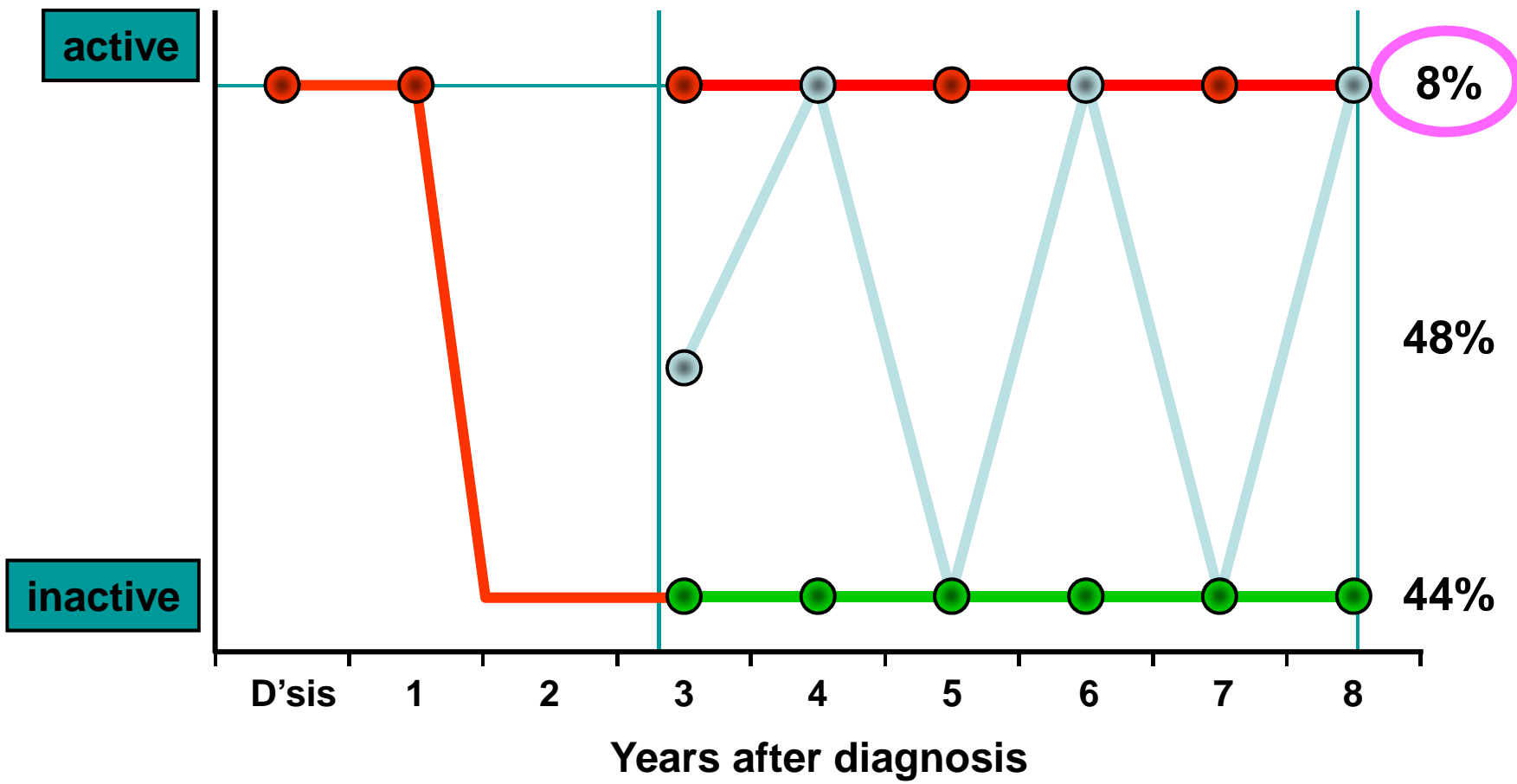
Changes in Crohn's disease behavior and location

- Retrospective study of 297 CD patients with regular follow-up in a single University Hospital



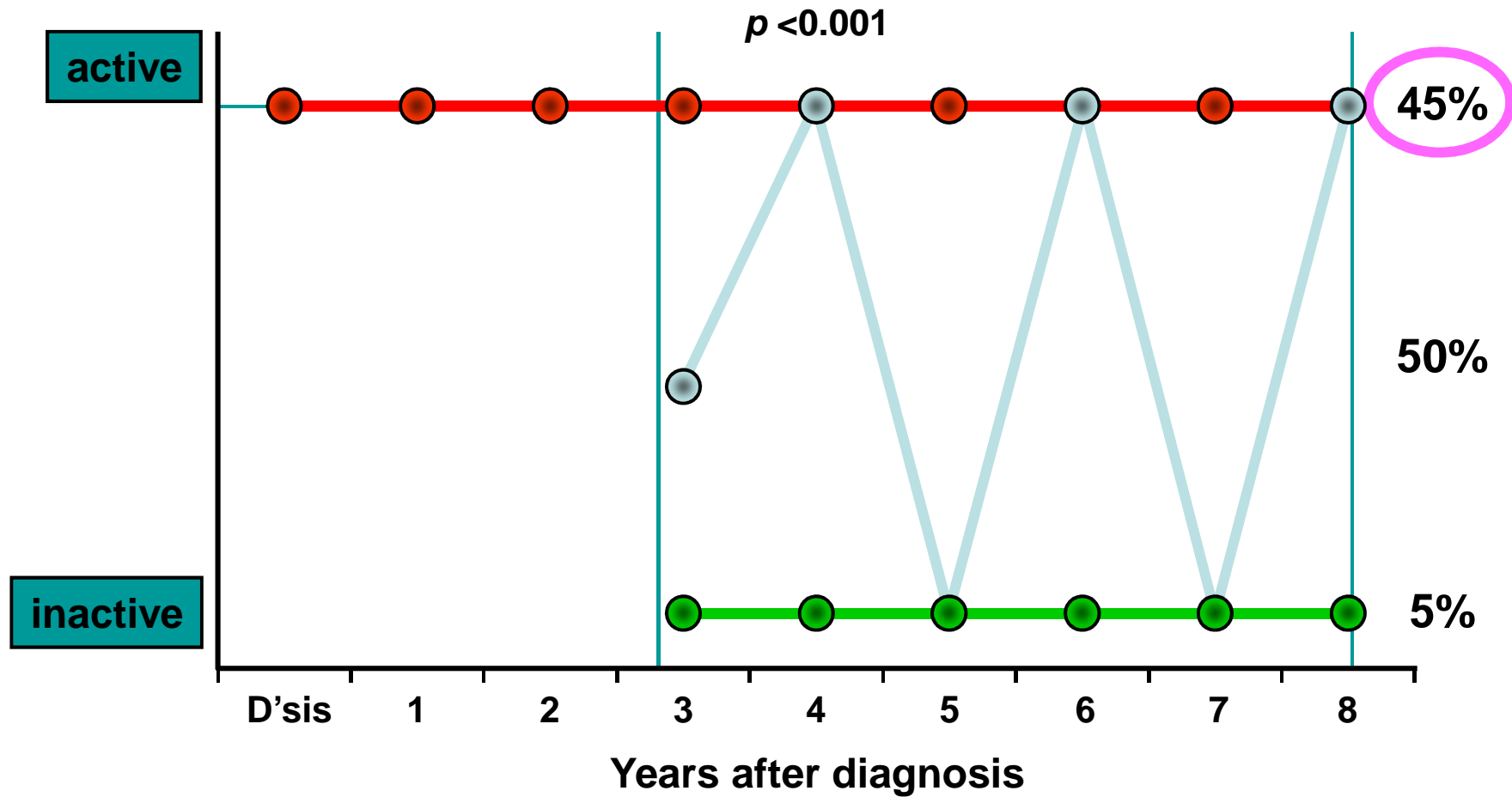
■ = L4 upper GI

Indolent course Crohn's disease



Munkholm P, et al. Scand J Gastroenterol 1995;30:699-706

Aggressive course Crohn's disease



Goals of Therapy for IBD

- Inducing remission
- Maintaining remission
- Restoring and maintaining nutrition
- Maintaining patient's quality of life
- Prevention of complications
- Surgical intervention (selection of optimal time for surgery)

Signs:

Fever
Mass
Growth

Symptoms:

Pain
Stool
frequency
Well-being

Function:

Appetite
Sleep
Job Performance
Social
relationships

Levels of Improvement

- Clinical response
 - Patient feels better, but is not well – just less sick
- Clinical remission
 - Patient feels well
- Laboratory remission
 - Hematocrit, CRP, ESR, albumin normal
 - Fecal markers – **calprotectin**
- Remission on imaging
- **Endoscopic remission - “mucosal healing”**

Therapy for Crohn's disease

First line therapy

5-ASA
budesonide
antibiotics
(metronidazole,
Cipro, rifaximin,

Immunomodulators/ Second line therapy

corticosteroids
budesonide
azathioprine/6-MP
methotrexate

Biologic Therapy

infliximab
adalimumab
certolizumab pegol
natalizumab

Biologics - in development

mesenchymal stem cells
abatacept
thalidomide
anti IL-12 (ABT-874)
Trichuris suis
probiotic therapy
visilizumab (anti-CD3)
Adacolumn (leukocytapheresis)
golimumab
fontalizumab

Nutritional therapy

elemental diet
TPN

Investigational Immunomodulators

mycophenolate mofetil
leflunamide
FK 506
thioguanine
stem cell transplant

Current Therapy for IBD is Sequential and Based on Disease Activity

Mild	Moderate	Severe
Aminosalicylates	Oral/Parenteral Glucocorticoids	Parental Glucocorticoids Anti-TNFα Cyclosporine-A
Antibiotics nutrition	nutrition	Bowel Rest
Oral Glucocorticoids	Thiopurines Methotrexate	Surgery
Thiopurines Methotrexate	Anti-TNFα	
Anti-TNFα		

Inductive Therapies

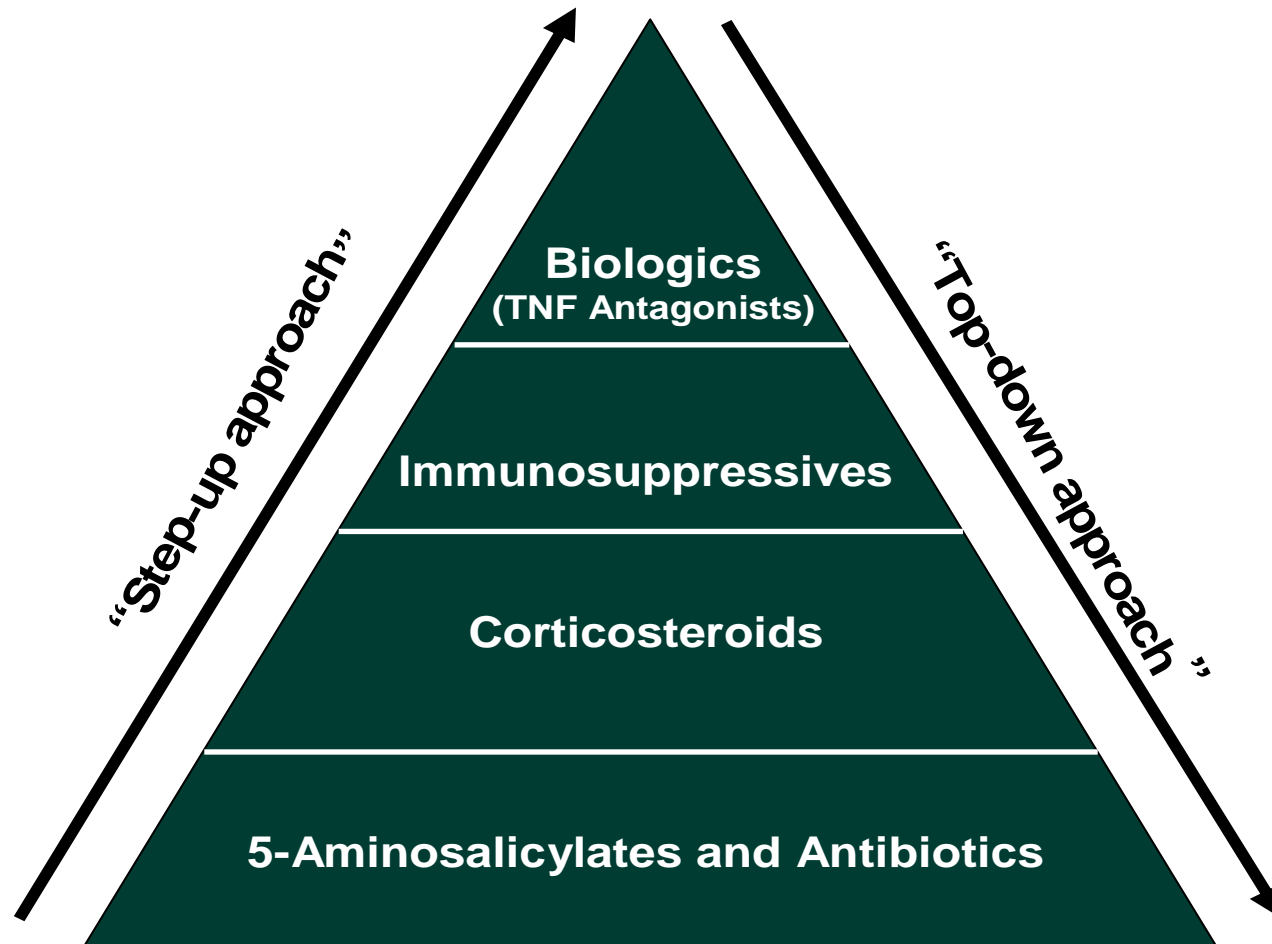
- UC
 - Aminosalicylates
 - Corticosteroids
 - Cyclosporin
 - Anti-TNF
- CD
 - Aminosalicylates
 - Corticosteroids
 - Antibiotics
 - Anti-TNF

Maintenance Therapies

- Immunosuppressors
 - Thiopurines
 - Methotrexate
- Aminosalicylates/Salazopyrin – mainly for UC
- Anti-TNF

NOT corticosteroids

Step-up vs Top-down Approach



5-Aminosalicylates

Mesalamine (Rafasal, Pentasa, Asacol) – oral / topical

Salazopyrine (Sulfasalazine)- oral
(sensitivity to Sulfa, G6PD-def)

Effective in mild Crohn's colitis

Not proven effective in Crohn's disease of small bowel

Effective in ulcerative colitis

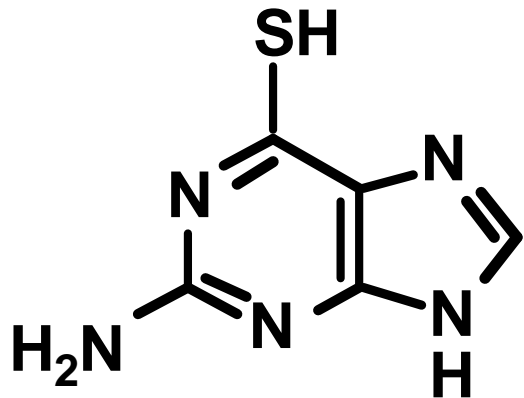
Long-term prevention of CRC

SE: Anorexia/ Dyspepsia/ Nausea

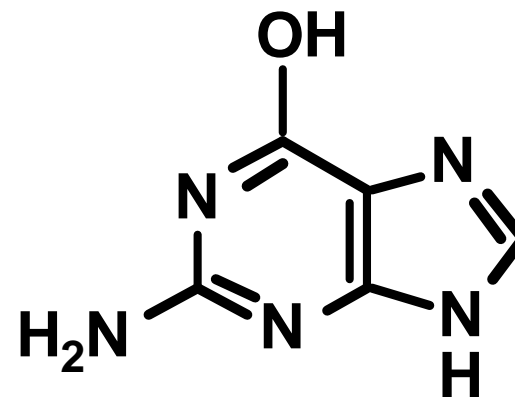
Hemolysis / Agranulocytosis

Nephropathy / Pneumonitis: Rare (<0.3%)

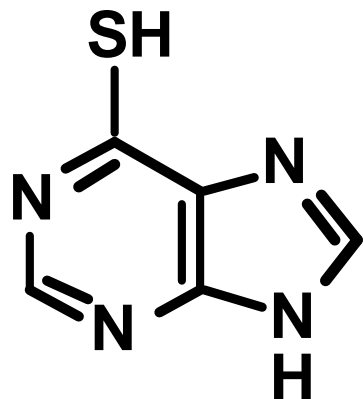
Thiopurines and Natural Purines



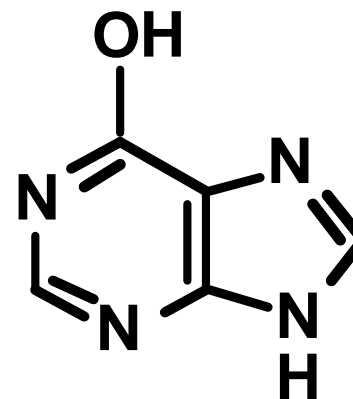
6-Mercaptopurine



Hypoxanthine



6-Thioguanine



Guanine

Thiopurines

Type A- toxic metabolites

- General malaise and nausea (11%)
- Infectious complications (7.4%)- CMV, opportunistic
- Hepatitis (0.3–1.3%)
- **Myelosuppression** (1.4–5%)

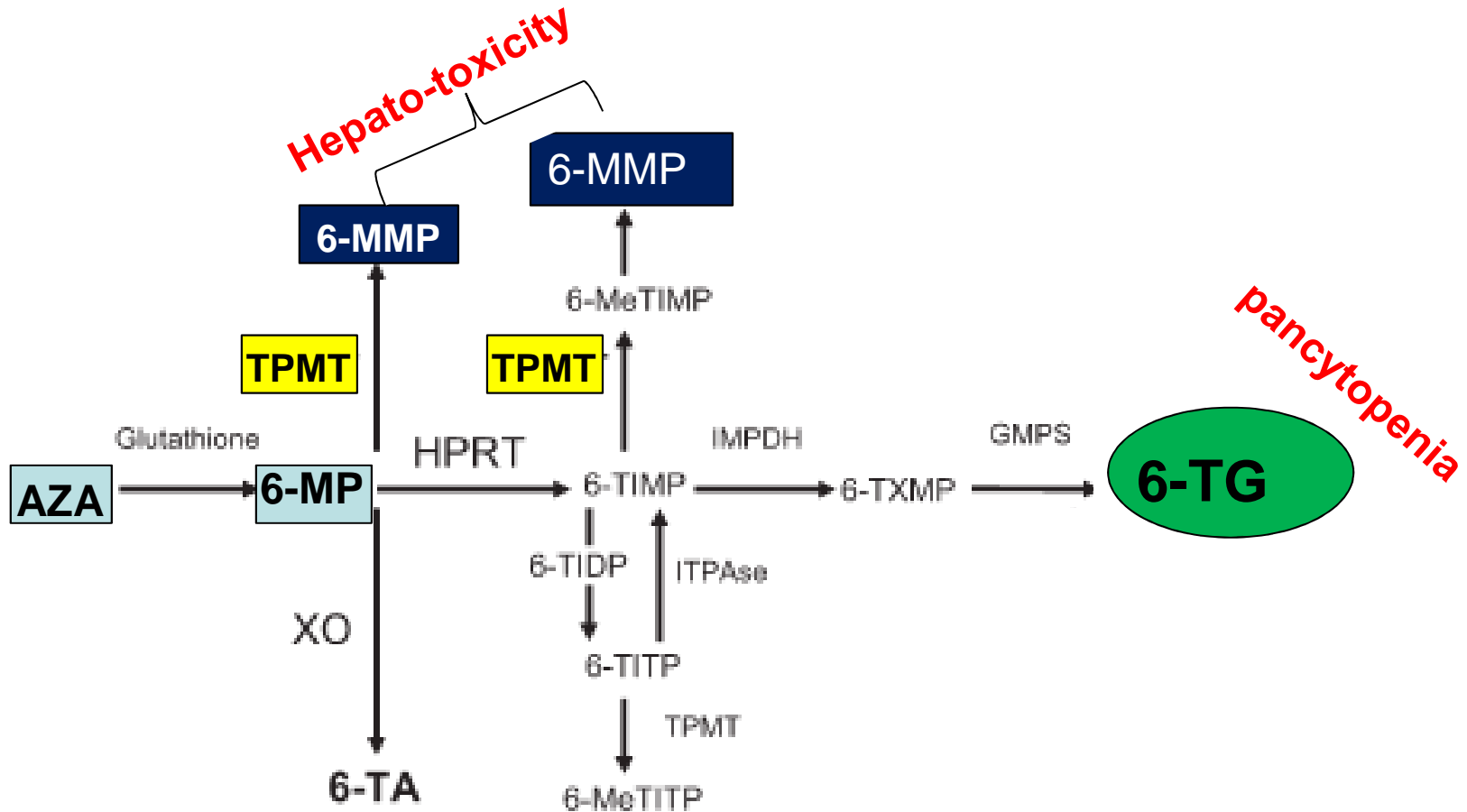
Type B- Immune-mediated (2%)

often occur within 2–4 weeks after start of treatment

Fever, Rash and Arthralgia

Pancreatitis (1.4–3.3%) - idiosyncratic reaction

Thiopurine metabolism



11% of population – Intermediate TPMT levels (homozygous)
 Higher 6-TG levels- require lower doses, high response rate

Methotrexate

In Crohn's disease – induction therapy
Maintenance of remission

In UC – not proven to be effective

Adverse events:

Teratogenic (and toxic to sperm)

Folate antagonist:

add folate Rx to prevent nausea, stomatitis

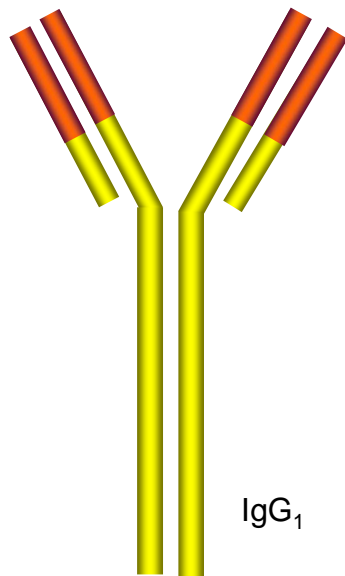
Diarrhea, hair loss, mild leukopenia

Hepatic Fibrosis

Severe Intestinal pneumonitis

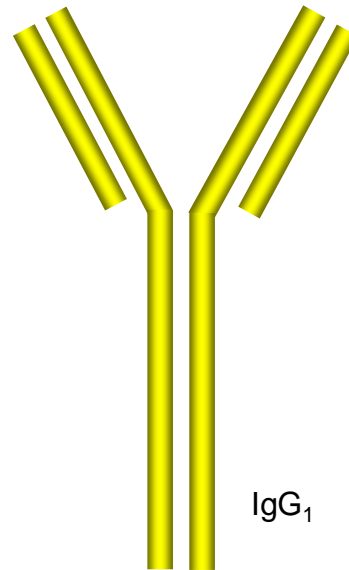
Construct of Anti-TNF- α Biologic Agents

Infliximab



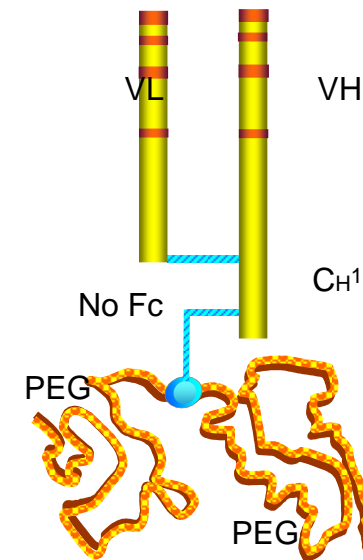
Chimeric monoclonal antibody (75% human IgG₁ isotype)

Adalimumab



Human recombinant antibody (100% human IgG₁ isotype)

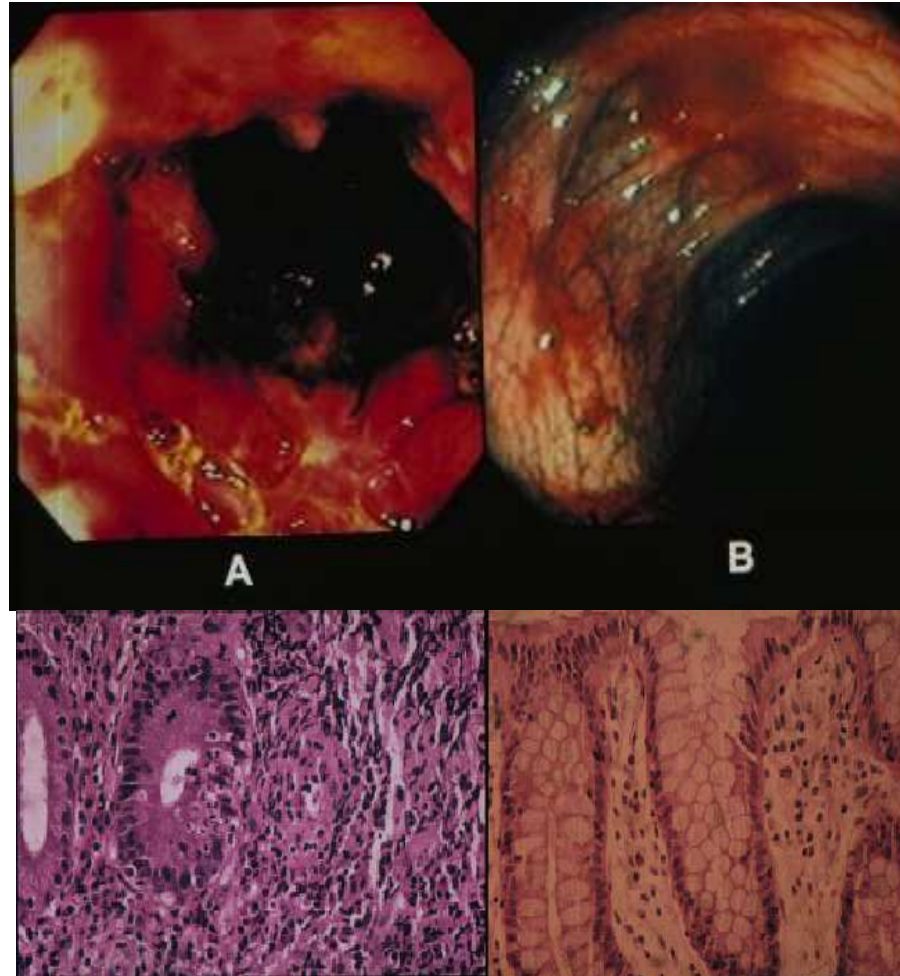
Certolizumab Pegol



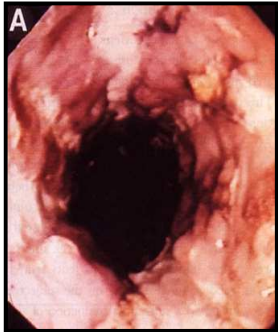
Humanized Fab' fragment (95% human IgG₁ isotype)

 Mouse
 Human
PEG, polyethylene glycol

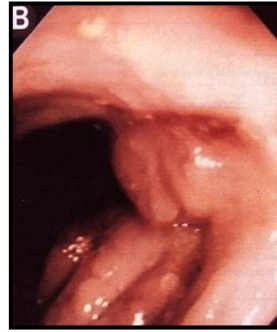
Mucosal and histologic healing after infliximab in Early CD



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



Pretreatment



4 Weeks
posttreatment

pretreatment



2 weeks



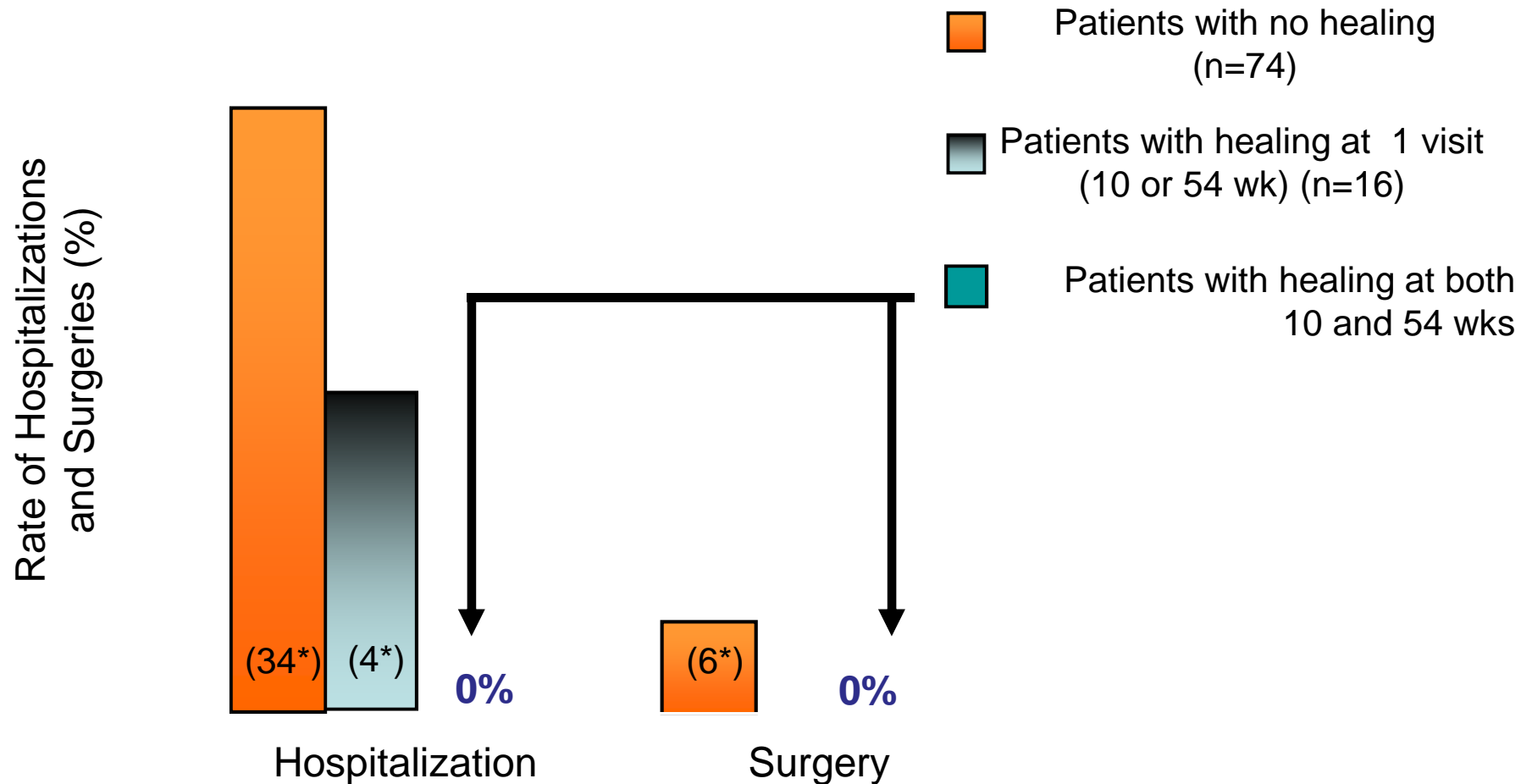
10 weeks



18 weeks



Endoscopic Healing and Reduced Hospitalizations and Surgeries: Infliximab maintenance for Crohn's disease



Infections associated with infliximab

Tuberculosis

?

Other infections

- Bacterial [Pneumococcal] infection
- Opportunistic infections:
 - *Pneumocystis jiroveci (carinii)*
 - Histoplasmosis, Cryptococcosis, Coccidioidomycosis
 - Listeriosis
- Reactivation of viral infections
 - HBV, HCV
 - EBV, CMV
 - HSV

Summary of Infliximab Safety Data (cont.)

Malignancies

- In clinical trials of all TNF inhibitors, more cases of lymphoma were observed compared with controls and the expected rate in the general population¹
 - Patients with RA² and CD^{3,4} may be at higher risk for developing lymphoma
- Occurrence of other malignancies is consistent with expected rate^{5,6}

Hepato-splenic Lymphoma

Pediatric case reports ~10

All combined therapy Infliximab and AZA

¹SPC Remicade, July 2007 ²Keystone E. J Rheumatol. 2005;32(suppl 74):8-12; ³ Bernstein CN et al. Cancer. 2001;91:854–62.;

⁴Greenstein AJ et al. Cancer. 1985;56:2914–21; ⁵Data on file, Centocor; ⁶Askling et al. Ann Rheum Dis 2005;64:1421–1426

⁷<http://www.emea.europa.eu/humandocs/Humans/EPAR/remicade/remicade.htm> - Scientific discussion

Vaccinations for IBD patients

When first seen

	Item	Comment
General	As for general population	
	Check immune status as appropriate (table 2)	
At diagnosis of IBD†	Varicella vaccine (if no history of chickenpox <i>and</i> negative VZV serology)	
	Hepatitis B (if HBV serology is negative)	
	Pneumococcal polysaccharide vaccine	
	Influenza (trivalent inactivated)	
	Human papilloma virus (in young women, if not already given as part of national vaccination strategy)	
Annually	Influenza (trivalent, inactivated)	
Booster	Pneumococcal polysaccharide vaccine (3–5 years)	
Discretionary	Travel vaccines: take advice from appropriate specialist; live vaccines (eg, yellow fever, oral poliomyelitis) should be avoided if on immunomodulators*	
	Chest x ray, tuberculin skin test, or interferon γ release assay prior to anti-TNF therapy‡	

בדיקות מומלצות באבחנה/לפני התחלת טיפול:

- 1) בדיקה לדלקת כבד נגיפית מסוג B : HB-Surface-Ag, HB-Surface-Ab, HB-Core Ab .
- 2) בדיקה לדלקת כבד נגיפית מסוג A : HAV IgG .
- 3) בדיקה לדלקת כבד נגיפית מסוג C : HCV Ab .
- 4) בדיקה לוורוס השלבקת VZV-IgG .
- 5) HIV-בדיון עם המטופל.
- 6) סרולוגיות ל-EBV* ול-CMV* : (* לבדיקות אילו אין עדיין משמעות טיפולית).
- 7) ספירת דם, תפקודי כבד.
- 8) צילום חזה.
- 9) תבחין עורי לשחפת (PPD).

חיסונים מומלצים:

- 1) שפעת עונתית + H1N1 - מידי שנה.
 - 2) Pneumovax - מידי 5 שנים לקראת/לפני התחלת אימונומודולטורים/ביולוגיים.
 - 3) לחולה לא מחוסן : חיסון לצהבת נגיפית מסוג B.
 - 4) לחולה לא מחוסן : חיסון לצהבת נגיפית מסוג A.
 - 5) לחולה לא מחוסן : חיסון ל-VZV* (*מומלץ להימנע מחיסון זה בחולה שכבר מטופל בטיפול אימונומודולטורי/ביולוגי).
 - 6) למטופלת בגיל 9-26 : חיסון ל-HPV, ניתן לשקול חיסון גם למטופלת מעבר לגיל 26.
- יש להימנע מחיסון חי/מוחלש במי שכבר מטופל בתכשירים אימונומודולטורים/ביולוגיים.**

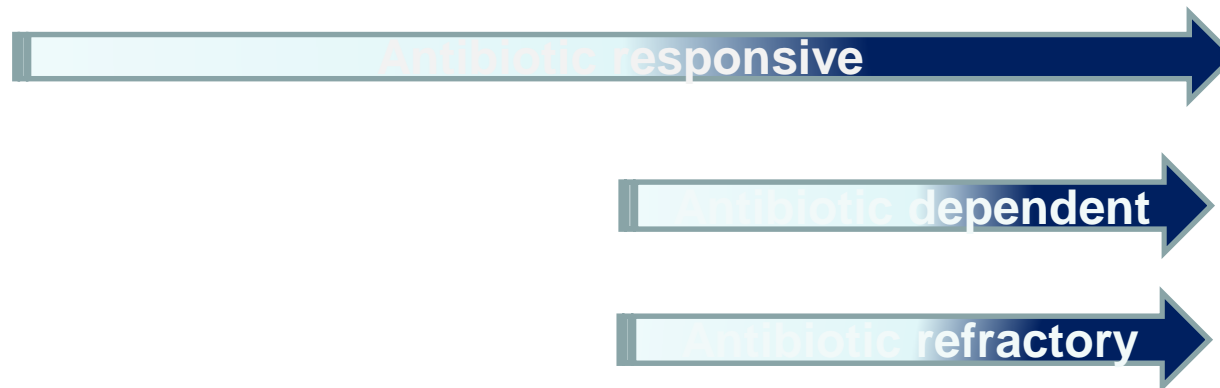
Surgery for IBD

General Concepts

- Majority will need surgery: 78% over twenty years
- Surgery generally indicated for *complications* of disease
- Surgery must be directed at area of bowel responsible for complication

Pouchitis: disease phenotype

Acute	Recurrent acute	Chronic	Crohn's like 3-13%
<ul style="list-style-type: none">• Increase in bowel movements• Urgency• Cramps• Rectal bleeding• Fever	<ul style="list-style-type: none">• <4 episodes/year	<ul style="list-style-type: none">• > 4 weeks of symptoms/treatment	<ul style="list-style-type: none">• Fistulizing• Fibrostenotic• Inflammatory



IBD Management Summary

- There is no “one size fits all” to IBD therapy
 - Therapy and decision making are tailored to the individual
- Algorithms are based upon available evidence
 - Evidence is in constant flux
- Success of algorithms depends upon optimization of each step of therapy and considerable judgment about each outcome
 - Skillful application of medical therapy makes all the difference in outcomes

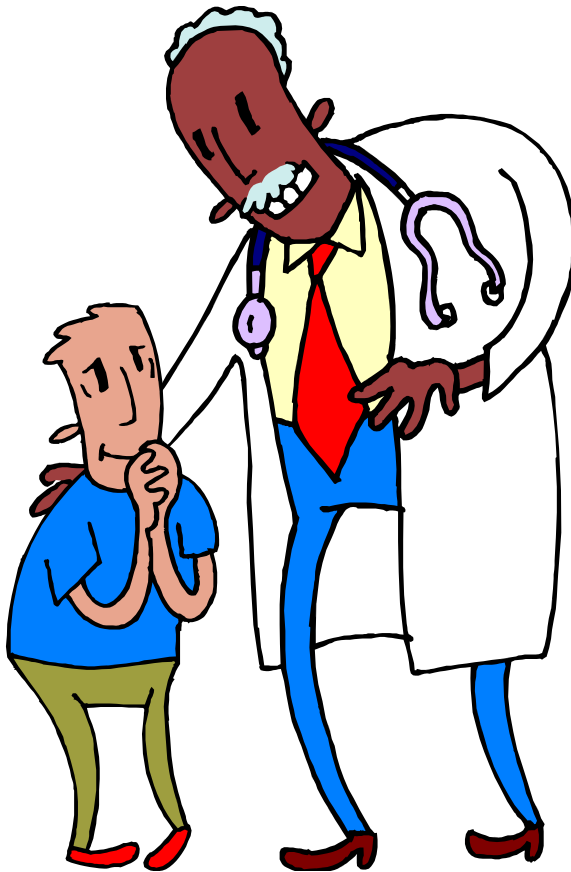
Pitfalls for Pediatric IBD

- 25% of all IBD are children
 - CD > UC 4:1
- Growth failure is unique to pediatric IBD
 - **30-50% of CD ped. Pts**
 - 10% of UC ped. Pts
- Malnutrition/micronutrient deficiencies more likely due to increased metabolic needs for growth

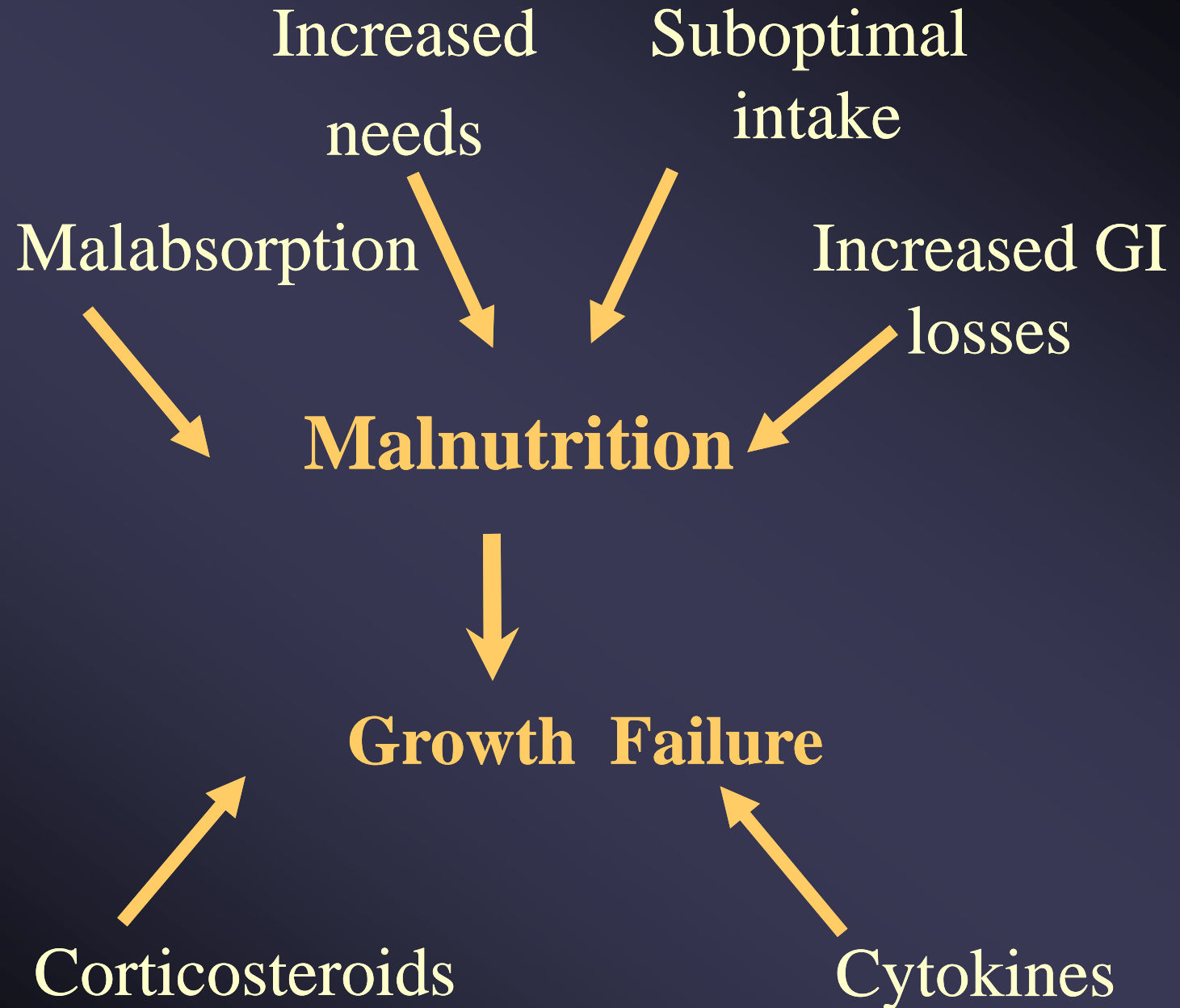
Nutrition

- Growth/Nutrition is a problem before we meet the pt.
 - Possible direct effects of inflam. mediators
 - Anorexic effects of inflam. mediators
- Patients don't feel well
 - Post-prandial pain --> dec. intake
 - anorexia (intake 55-80% of RDA of cal. Needs)

Steroids – The Bad Guy



- alter linear growth
- proteolytic/ osteolytic
- inhibit bone growth



Nutritional Treatment

- Reduce antigenic load
- Increase caloric consumption
- Correct micronutrient deficiency
- Primary therapy
- Adjuvant therapy
- Preventive
- Complications

Nutritional Treatment

- TPN – complications
- Elemental diet – Its value not proved
- Polymeric diet – Same benefit as elemental
- Special diet: Glutamine, Butyrate, TGF β
- N-3 fatty acid
- Probiotics
- Prebiotics

Enteral Nutrition

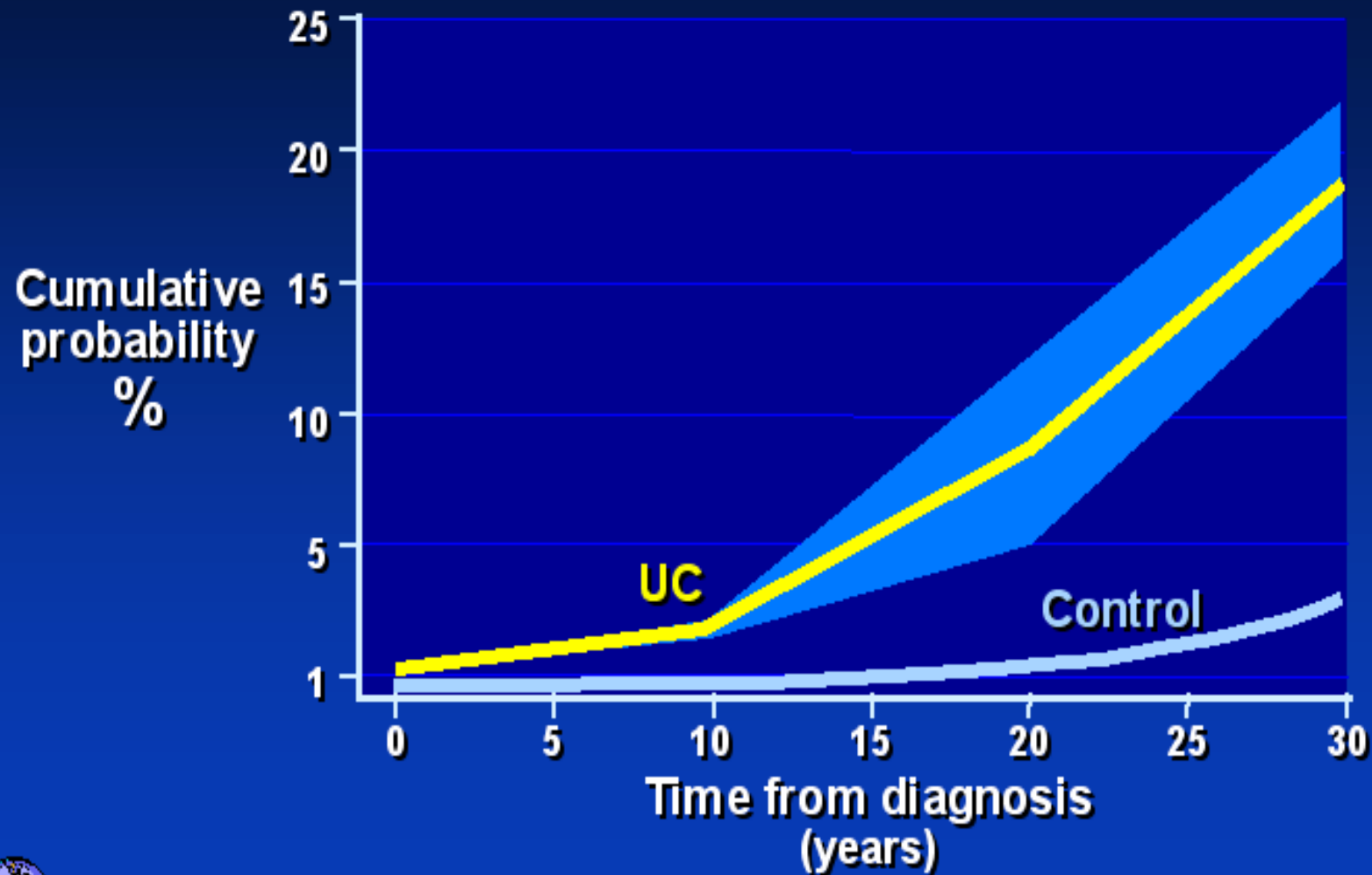
- Possible Mechanisms:
- Decrease antigen load to the GI tract
- Alter intestinal microbial flora
- Dec. intestinal synthesis of inflammatory mediators via reduction of dietary fat
- Provision of micronutrients to diseased bowel
 - Mostly small bowel
 - Motivated patient/family

Elemental Formulas

- Common practice for remission is elemental or semi-elemental formula
- **However!!!!**
- Bad taste
- May need for NGT/G-tube
- Formula composition for protein and/or fat source have not proven to make a difference in studies
- **Thus no proven beneficial effect over non elemental formula**

UC - Complications

Risk of Colorectal Cancer



IBD - Colorectal Cancer

Increased risk

- Long duration
- Anatomical extent
- PSC
- Family history of CRC

Possible protection

- 5-ASA
- Folate
- Tight medical control



PROTECTION

- Surveillance colonoscopy

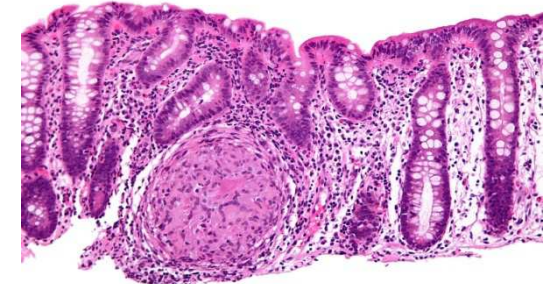
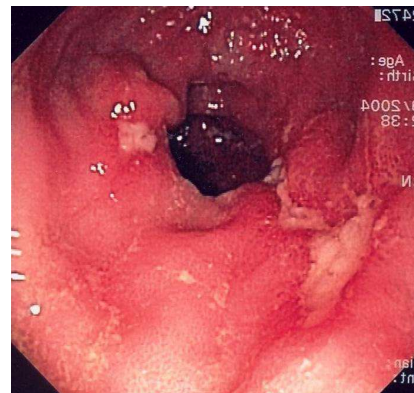
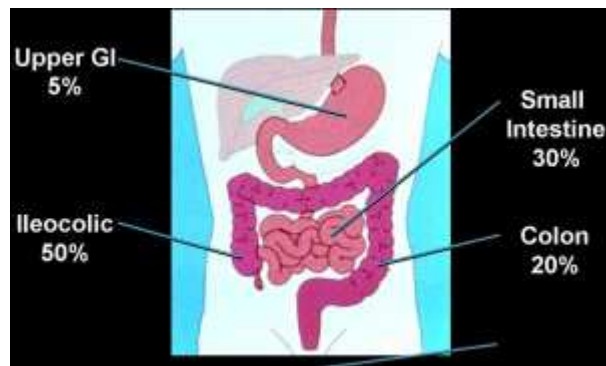
Multiple biopsies

- Procto-colectomy (for UC)

The definition of Crohn's Disease Is the Same in Children and Adults

- Same locations of bowel affected
- Appears to be the same disorder
- Same gastrointestinal symptoms
- Same endoscopic appearance
- Same biopsy appearance

however!!!!



Pediatric Vs Adult IBD

- Pediatric phenotype may be more severe, and aggressive (penetrating)
- Relatively stable in adults in contrast to children where disease extension is common
- Lower incidence of positive serologic tests (ASCA, p-ANCA)
- Response to current therapies appears similar
- Growth remains a unique pediatric problem
- Dosing and safety cannot be extrapolated from adult studies and require independent study

Pediatric Vs Adult IBD

- Age can affect clinical expression
- distribution varies by age <10 years, higher colonic only, for CD
>10 years, more similar to adults
- **Upper GI involvement is common in children**

In young children it may be difficult to distinguish CD from UC because of the primary colonic phenotype for young children with CD.

Initial diagnosis may change in up to 10-15%

Doctor, will my IBD have an effect on my child?"

Aims: To investigate short- and long-term morbidity and/or developmental defects in offspring of mothers who have IBD during pregnancy

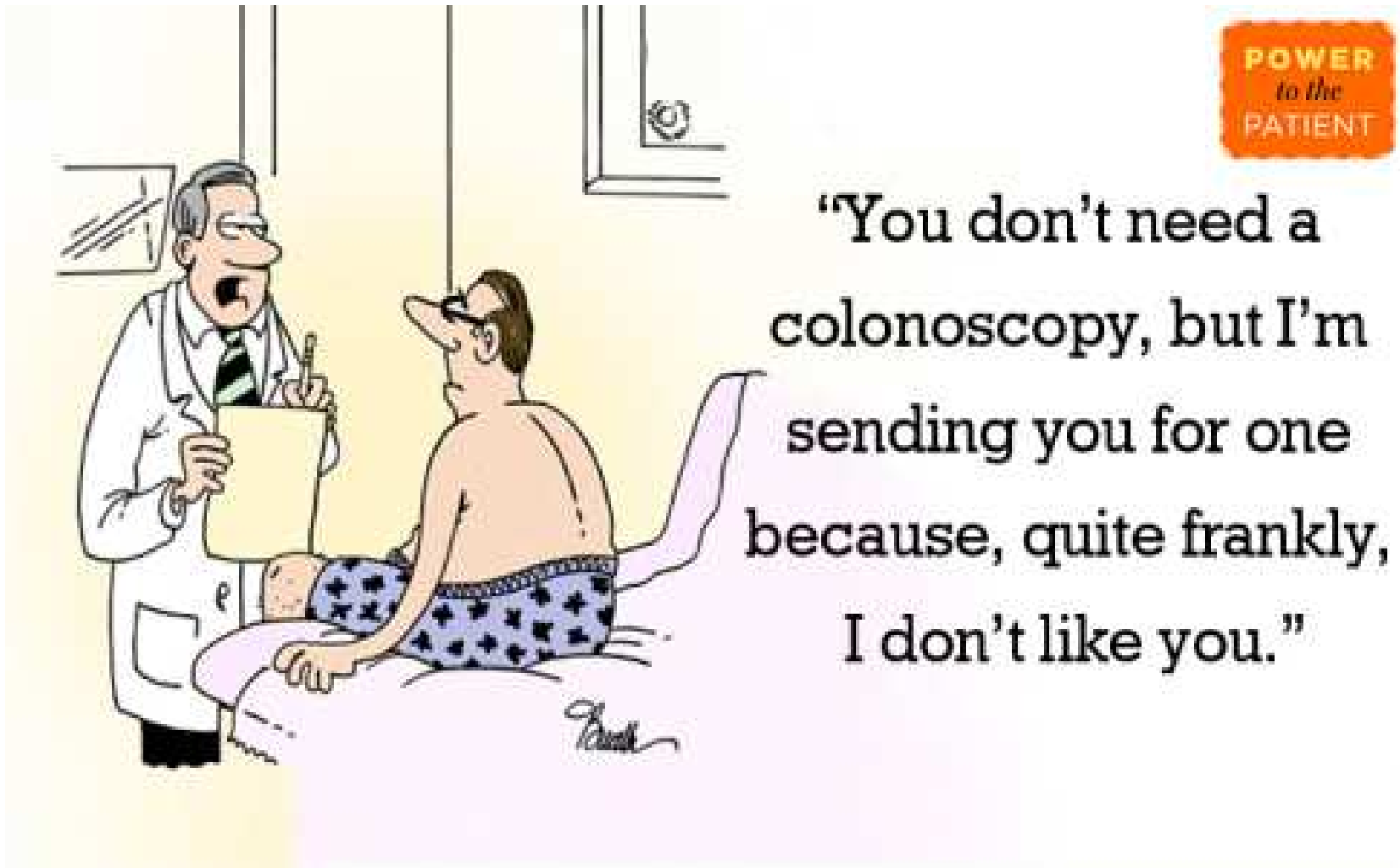
MAIN FINDINGS – short term

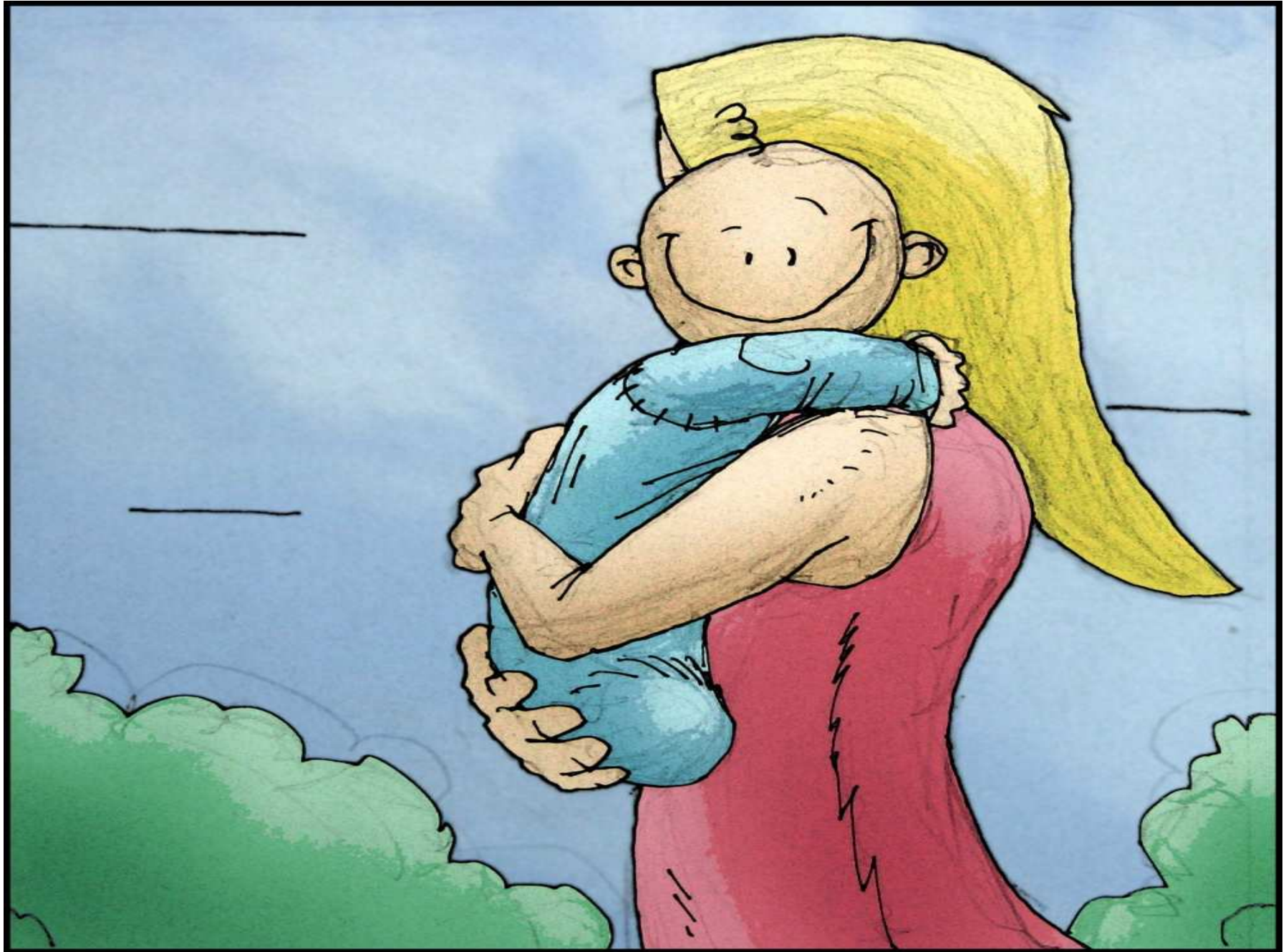
- Newborns to IBD mothers-significantly lower birth weights vs. controls: 3.13 ± 0.6 vs. $3.27 \text{ kg} \pm 0.45$, $p=0.005$
- Mothers with IBD had more spontaneous abortions
- No difference in preterm birth
- Slight increase in congenital anomalies

IBD in pregnancy has a long-term effect on

	IBD (%)	Control (%)	P
>3 Intercurrent infections, 1 st , 2 nd , 3 rd year	23, 20, 17	42, 46, 53	0.001
Wheezing bronchitis	9	18	<0.05
Atopic dermatitis	5.5	11.1	0.028
IBD	2.8	0	0.045
ADHD	5	0.8	0.03
	More methylphenidate (ritalin) use in CD (5.4%) vs. UC (0%) offspring (p=0.02)		When adjusted for smoking 0.05
Gross motor abnormalities	4.4	0.7	0.04

Meaningful Response: The clinician's perspective





THANK YOU

