

Inflammatory Bowel Disease: Diagnosis, Treatment and Referral



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Inflammatory Bowel Disease - Overview

- Introduction/Epidemiology
- Pathogenesis
- Clinical Manifestations
- Conventional Therapies
- Cancer Risk

Inflammatory Bowel Disease - Introduction

Definition

Chronic idiopathic autoimmune inflammatory disorders involving some or all layers of the gut wall

Ulcerative Colitis (UC)

Mucosal / submucosal only

Crohn's Disease (CD)

All layers of wall at risk

Inflammatory Bowel Disease - Epidemiology

In North America:

- Incidence: 5-29 per 100,000 people per year
- Prevalence: ~ 1.3 million persons
- New cases: estimated 20,000-100,000 per year*
- Gender distribution:
 - ◆ Crohn's disease: Slight female predominance
 - ◆ Ulcerative Colitis: Slight male predominance
- Age incidence -- Bimodal distribution
 - ◆ Peak onset: 15 to 25 years of age
 - ◆ Second peak incidence: 50 to 65 years of age

*Loftus, *Gastroenterology*, 2004;126:1504

Inflammatory Bowel Disease – Epidemiology Arab Countries (prevalence estimates 2004)

- Gaza strip 2,649 1,324,991
- Iraq 50,749 25,374,691
- **Jordan** 11,222 5,611,202
- Saudi Arabia 51,591 25,795,938
- Syria 36,033 18,016,874
- West Bank 4,622 2,311,204

Risk Factors for Inflammatory Bowel Disease

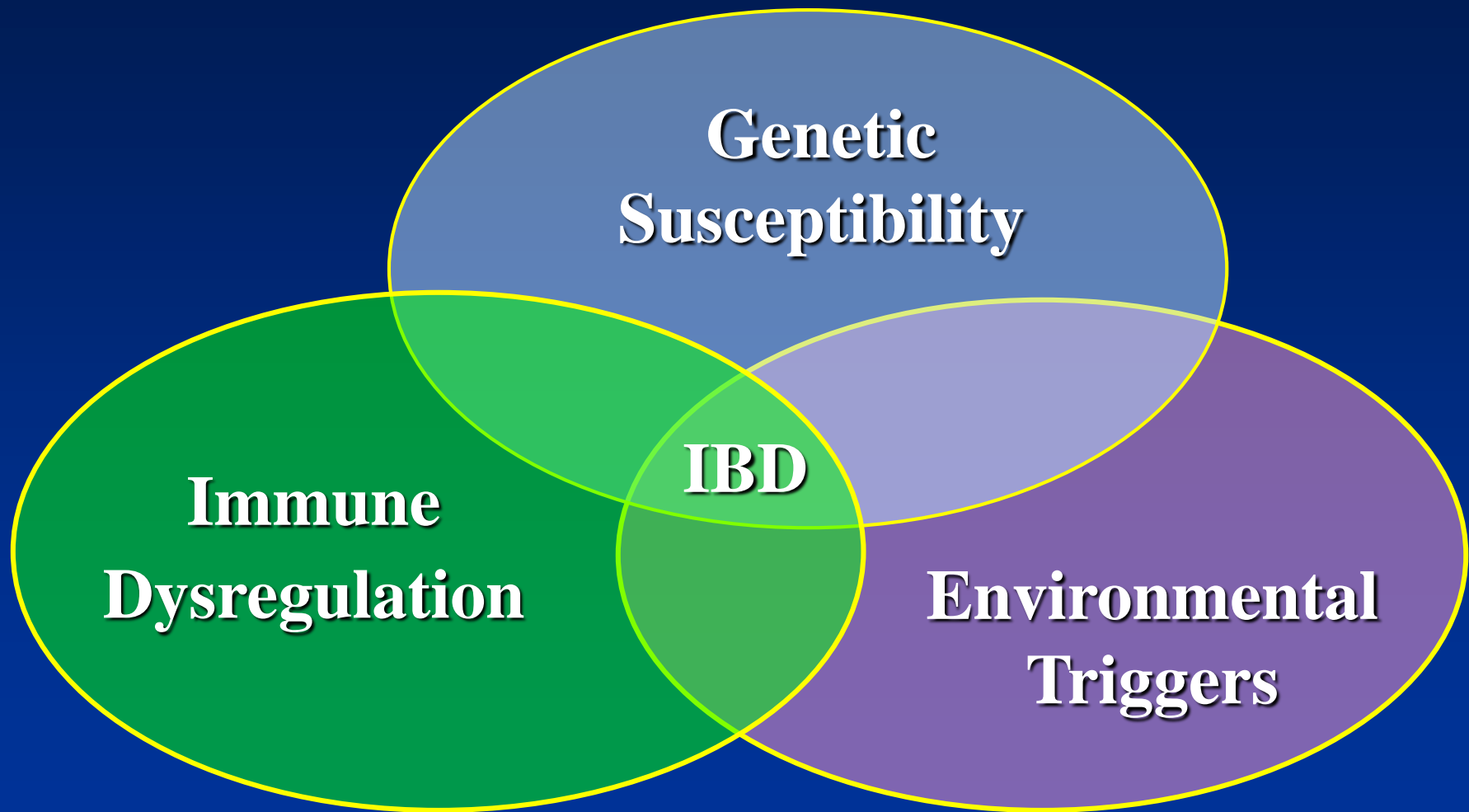
Known

- Family history of IBD
- Cigarette smoking
 - ◆ Risk for CD
 - ◆ Protective for UC
- Appendectomy
 - ◆ Risk for CD
 - ◆ Protective for UC

Possible

- Oral contraceptives
- Diet: sugar, fat
- Breastfeeding (protective)
- Childhood infections
- Measles infection
- Mycobacterium paratuberculosis infection

Inflammatory Bowel Disease (IBD)



IBD: Genetics



- 10-25% of patients have a 1st degree relative with IBD
- Lifetime risk for siblings and offspring of IBD patients: ~10%
- Monozygotic twins – often share disease pattern and age of onset
 - ♦ Concordance – CD (58%) > UC (6%)
- Genome search – loci on chromosomes 3, 5, 6, 12, 14, 16, 19
- Mutation of **CARD 15** on chromosome 16 implicated in CD not UC

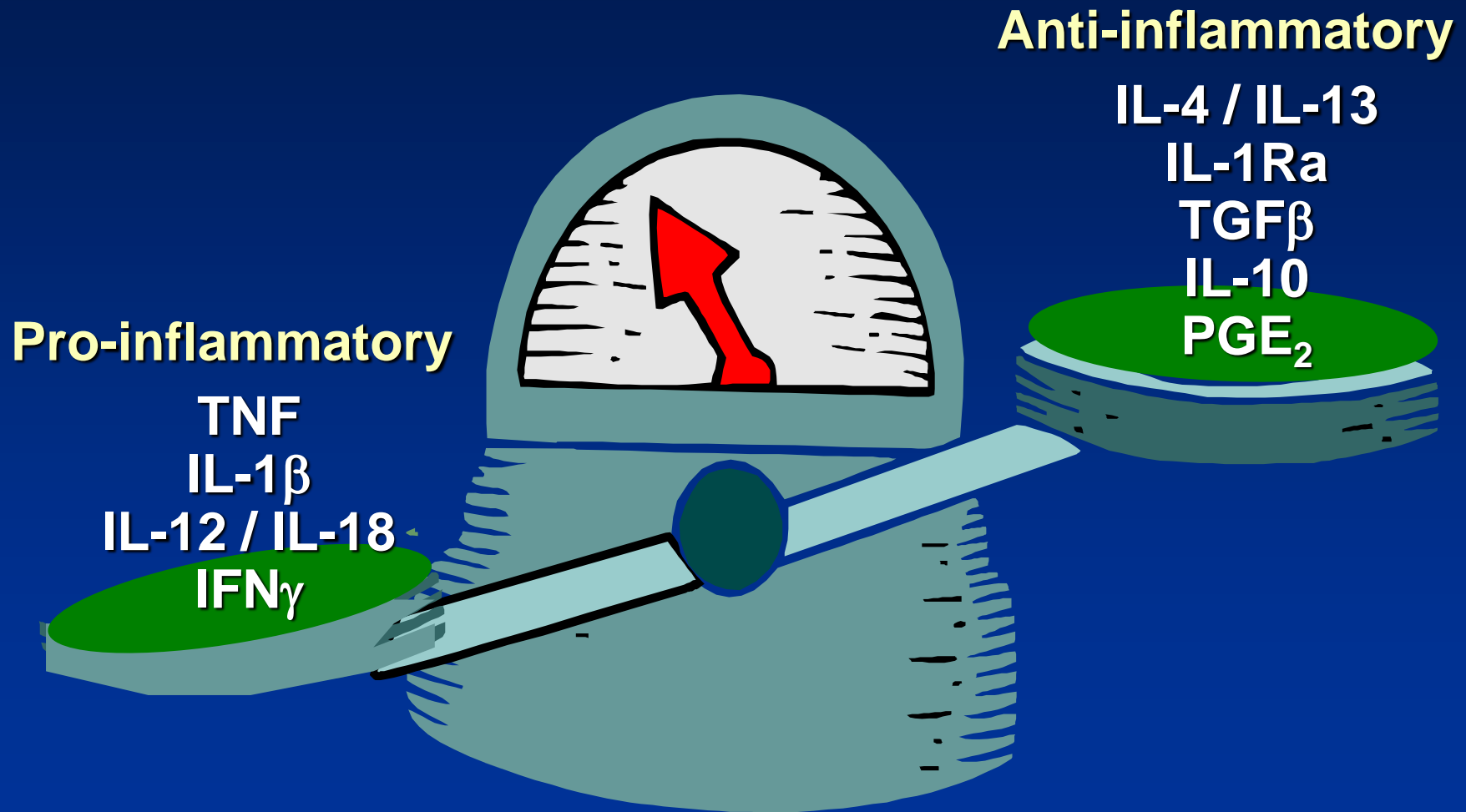
Ahmad et al. Gastroenterology 2004;126:1533

Hugot, et al. Nature. 1996;379:821

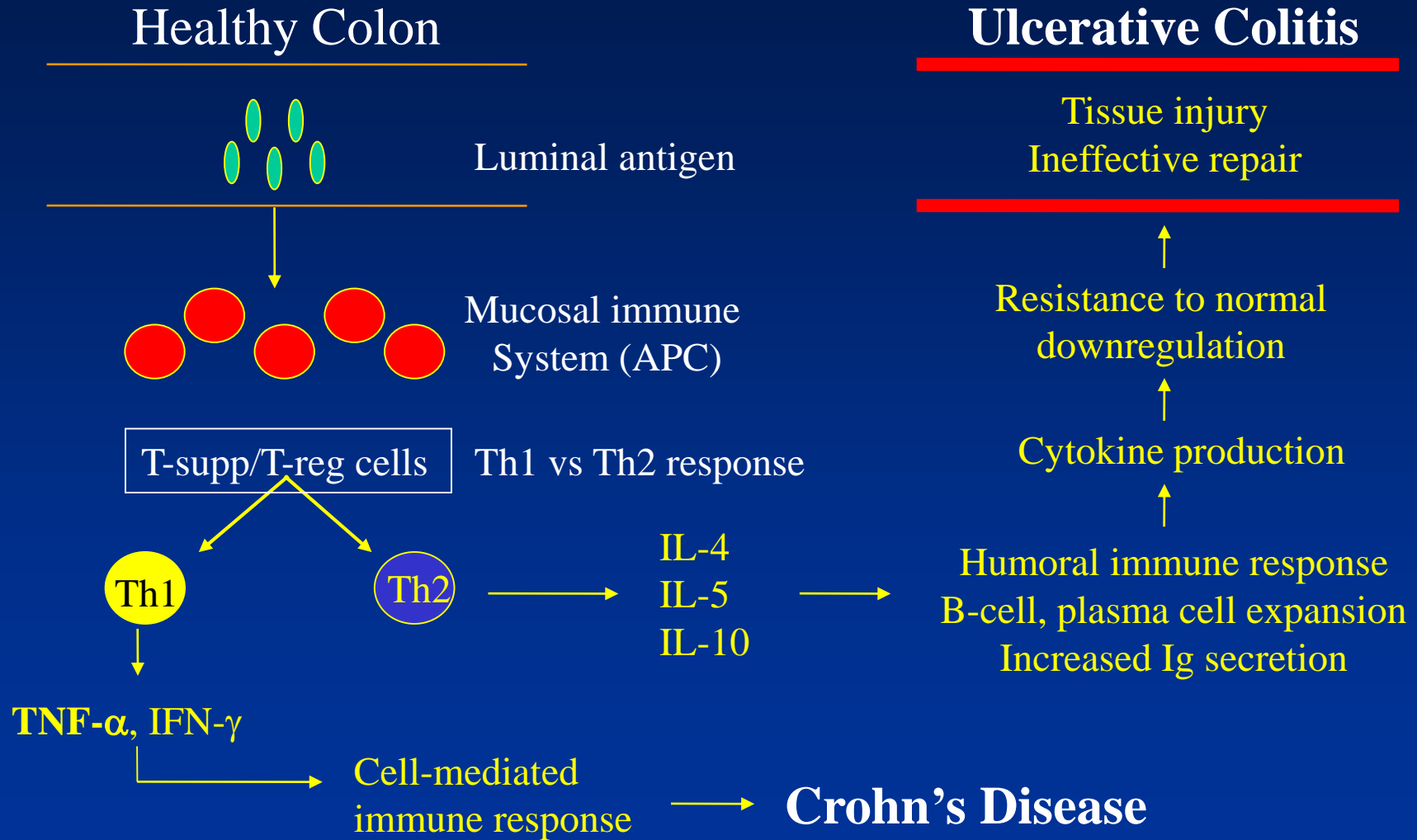
IBD: Environmental Triggers

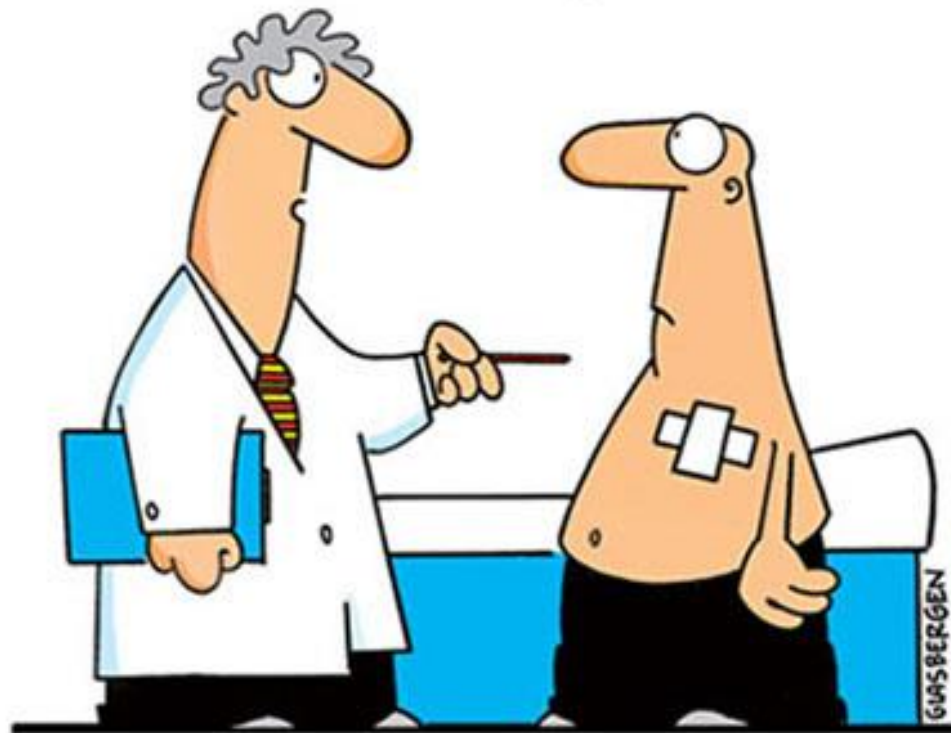
- Smoking: protective in UC, detrimental in CD
- NSAIDs
- Stress
- Infections

Inflammatory Bowel Disease - Pathogenesis



IBD – Pathogenesis/Immune Dysregulation

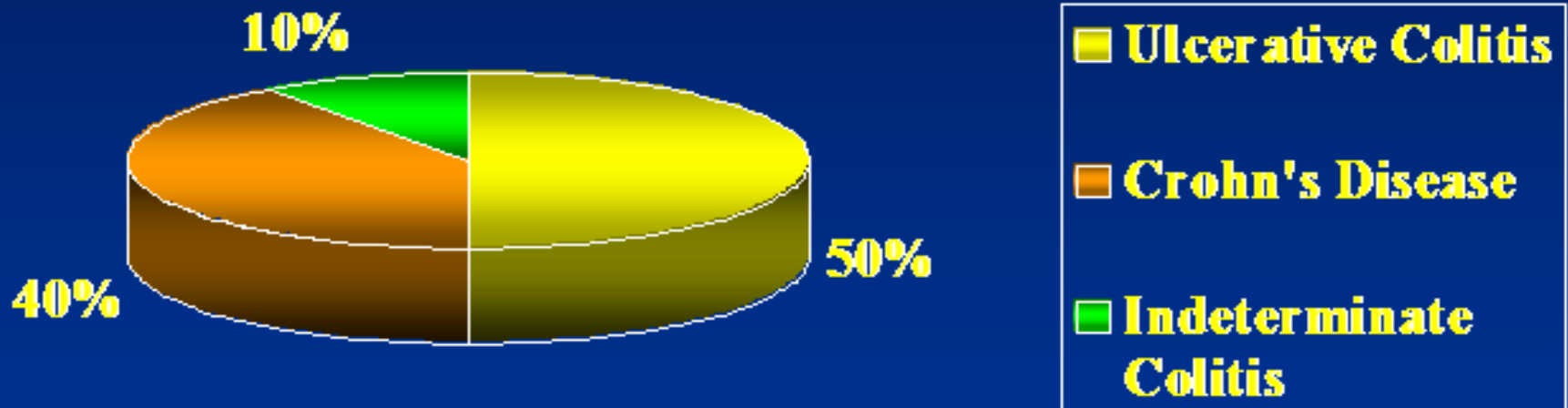




“It’s a pacemaker for your heart.
Plus, you can download apps for your liver,
kidneys, lungs, and pancreas!”

Ulcerative Colitis vs Crohn's Disease

Presentation



Inflammatory Bowel Disease - Clinical Presentation



Ulcerative Colitis vs Crohn's Disease

Symptoms

Ulcerative Colitis

- ◆ Rectal bleeding
- ◆ Fecal urgency / tenesmus
- ◆ Diarrhea (bloody)
- ◆ Lower abdominal cramping

Crohn's Disease

- ◆ Diarrhea (non-bloody)
- ◆ Weight loss
- ◆ Fever
- ◆ Perianal drainage/pus
- ◆ Right lower quadrant pain

Inflammatory Bowel Disease - Clinical Presentation

- Signs

- ◆ Those with mild or moderate disease usually look well
- ◆ Severe attacks:
 - fever
 - tachycardia
 - abdominal tenderness
 - distension
 - decreased bowel sounds
- ◆ Clubbing suggests chronic disease

- Lab evaluation

- ◆ Acute phase reactants:
 - ESR, CRP elevation
- ◆ Leukocytosis
- ◆ Anemia
- ◆ Reduced serum albumin
- ◆ Hypokalemia
- ◆ Abnormal LFT's
- ◆ Stool:
 - leukocytes, RBC's

Inflammatory Bowel Disease: Serum Antibodies (p-ANCA and ASCA)

Perinuclear antineutrophil cytoplasmic antibody (p-ANCA)

- 60-80% ulcerative colitis

Duerr et al, Gastro 1991; 100

Winter et al, J Pediatr 1994; 125

- Seen in sclerosing cholangitis, pouchitis, persists after colectomy
- Not related to disease activity
- Less common in CD (5%)

Anti-Saccharomyces cerevisiae antibody (ASCA)

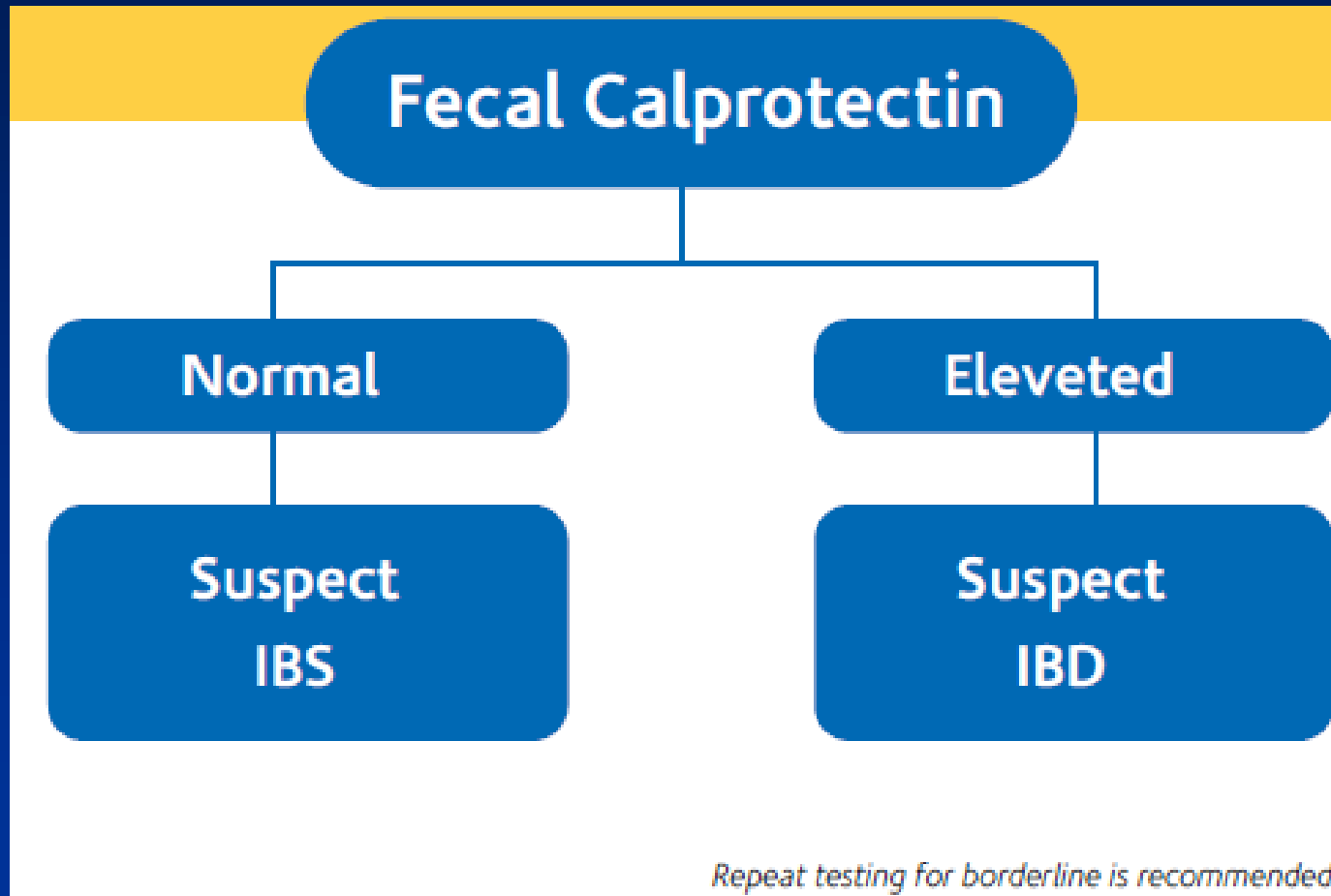
- 60% Crohn's disease
- May be associated with more aggressive phenotype (fibrostenosis)

Vasilauskas et al, Gut 2000

- Predictive of more relapsing disease course in pediatric CD

Desir et al, Clin Gastro and Hep 2004

Calprotectin



Ulcerative Colitis vs Crohn's Disease

Endoscopic Appearance

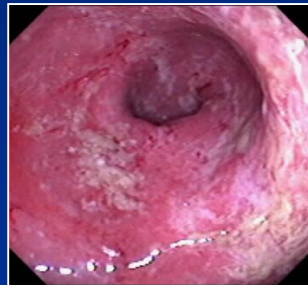


Normal colon

Ulcerative Colitis

Crohn's Disease

Friability
Exudate
Spontaneous bleeding



Diffuse ulceration



Cobblestoning

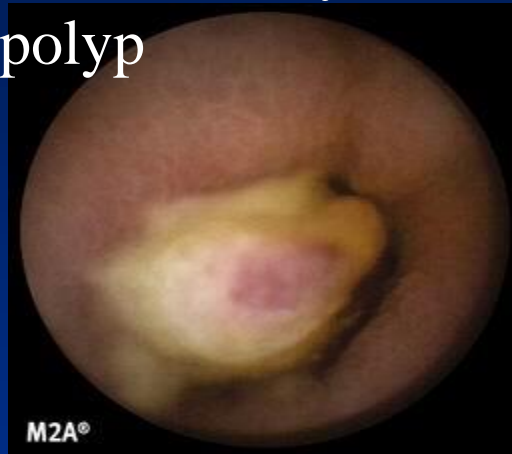


Focal ulceration



Small Bowel Capsule Endoscopy

Inflammatory
polyp



Ileitis



Crohn's disease



Linear Erosions



Ulcerative Colitis vs Crohn's Disease

Disease Distribution

Ulcerative Colitis

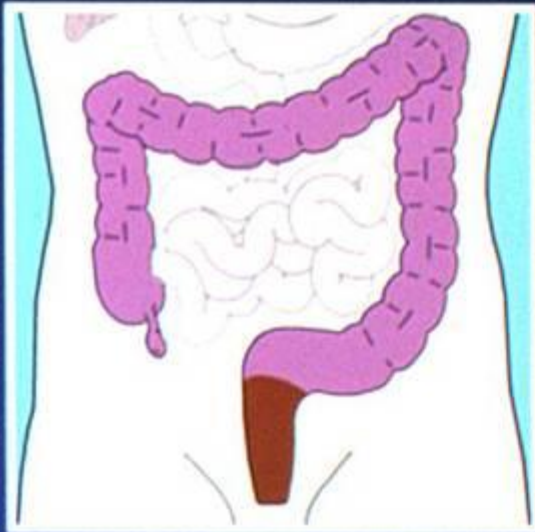
- ◆ Rectum → Cecum
- ◆ Confluent / Contiguous
- ◆ Ileal involvement uncommon
- ◆ No perianal disease

Crohn's Disease

- ◆ Anywhere from “mouth to anus”
- ◆ Segmental / Skip Lesions
- ◆ Rectum usually spared
- ◆ Ileal involvement common
- ◆ Perianal disease common

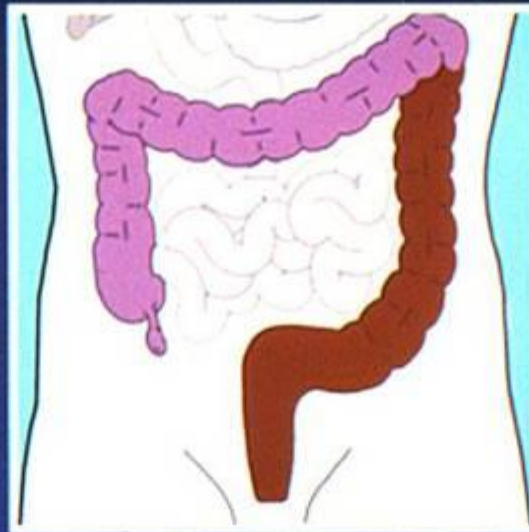
Ulcerative Colitis – Disease distribution

30%



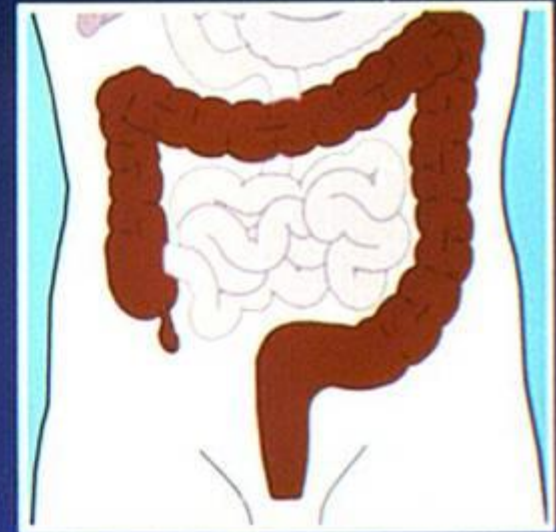
Proctitis

40%



Left-sided Colitis

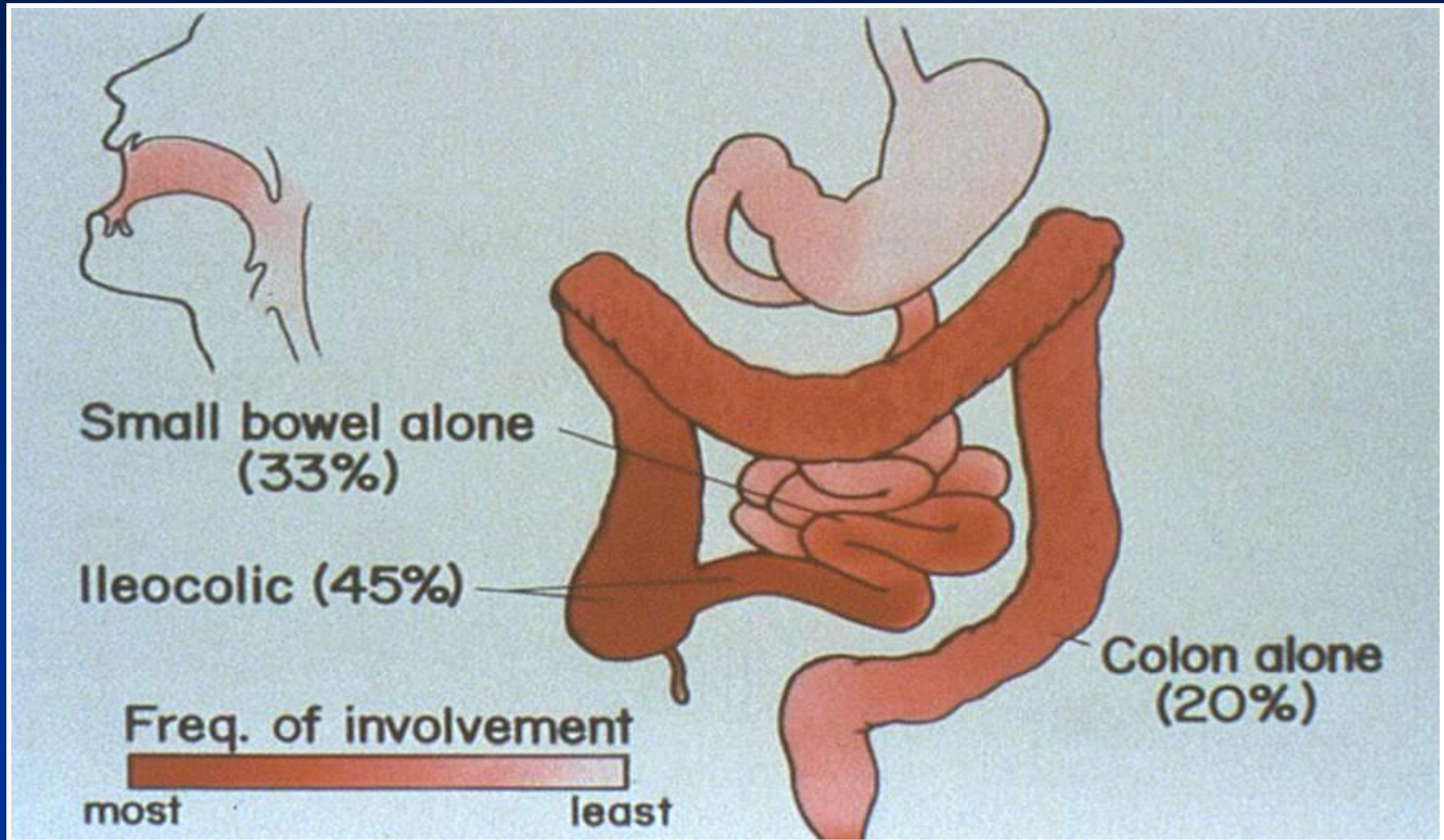
30%



Total Colitis

Mild \longrightarrow Severe

Crohn's Disease – Disease distribution

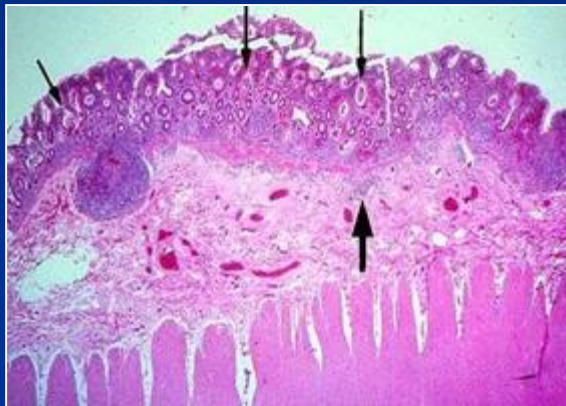


Ulcerative Colitis vs Crohn's Disease

Histology/Depth of Disease

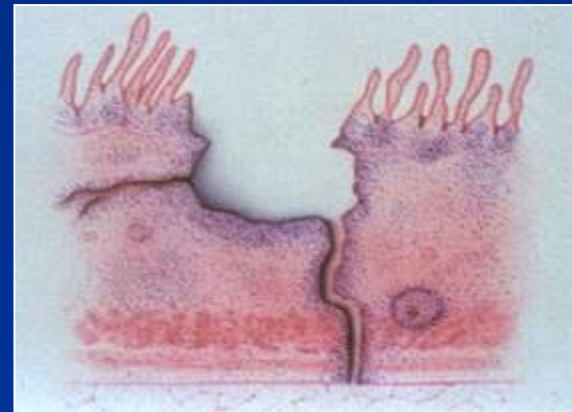
Ulcerative Colitis

- ◆ Mucosal and submucosal only
- ◆ No granulomas seen



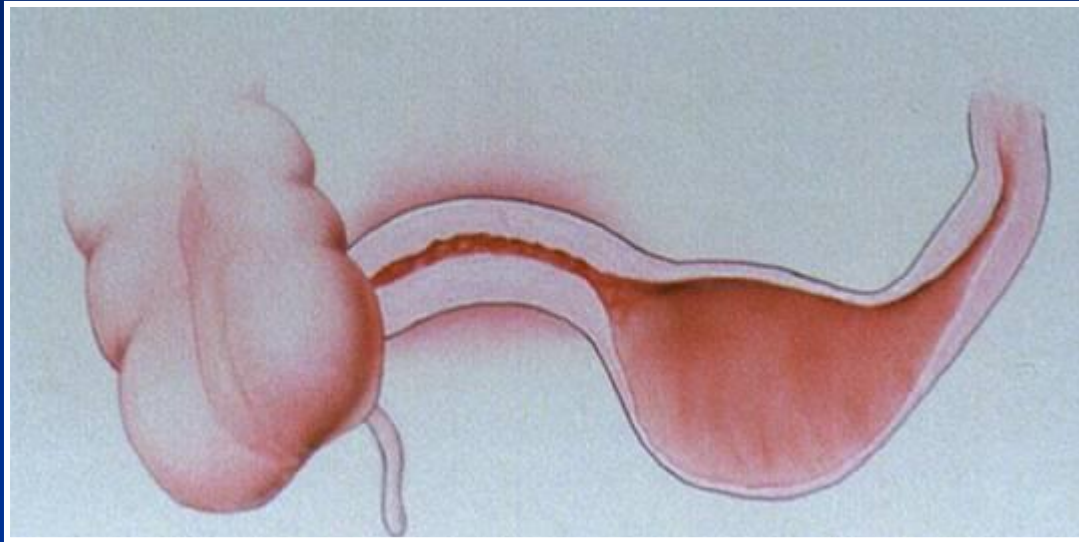
Crohn's Disease

- ◆ * Transmural disease *
- ◆ Granulomas occasionally seen



Complications of Crohn's Disease

Crohn's Strictures

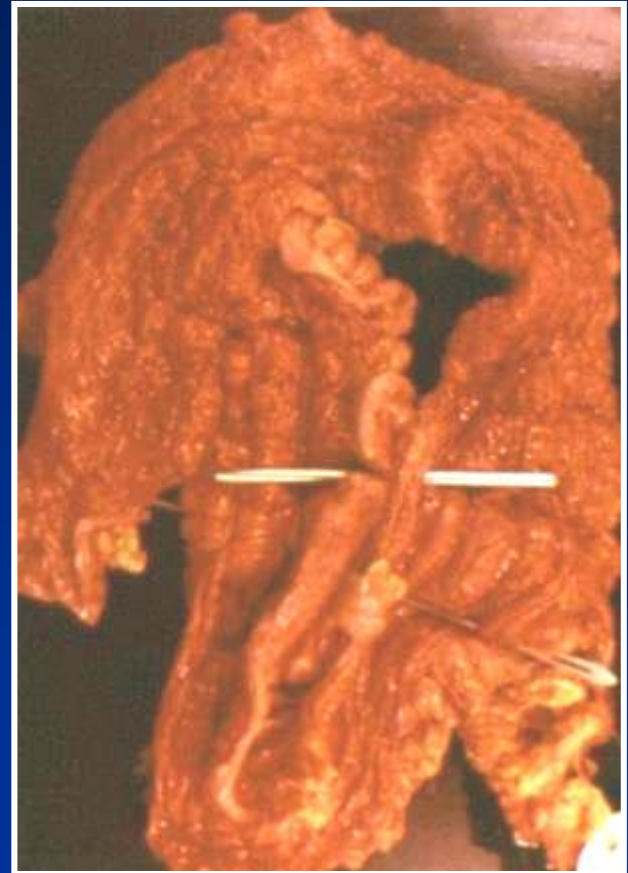


Complications of Crohn's Disease

Crohn's Fistulae

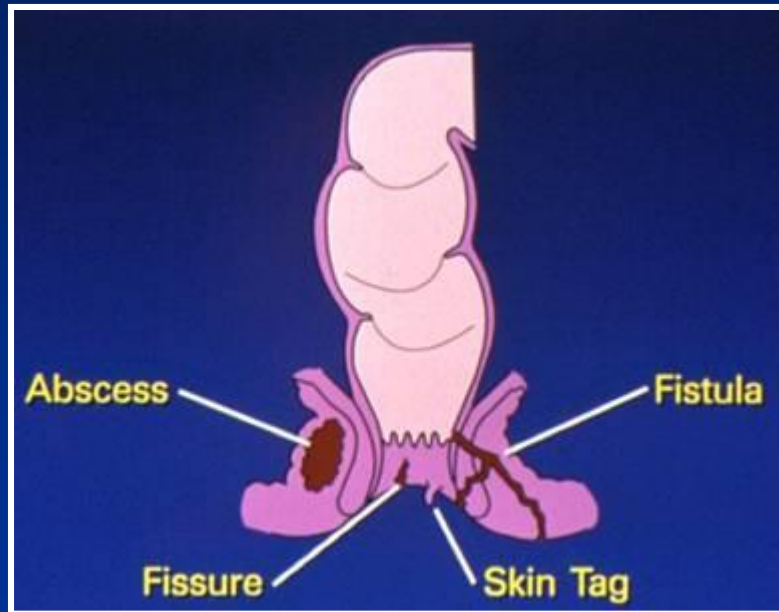


Entero-enteral fistula



Complications of Crohn's Disease

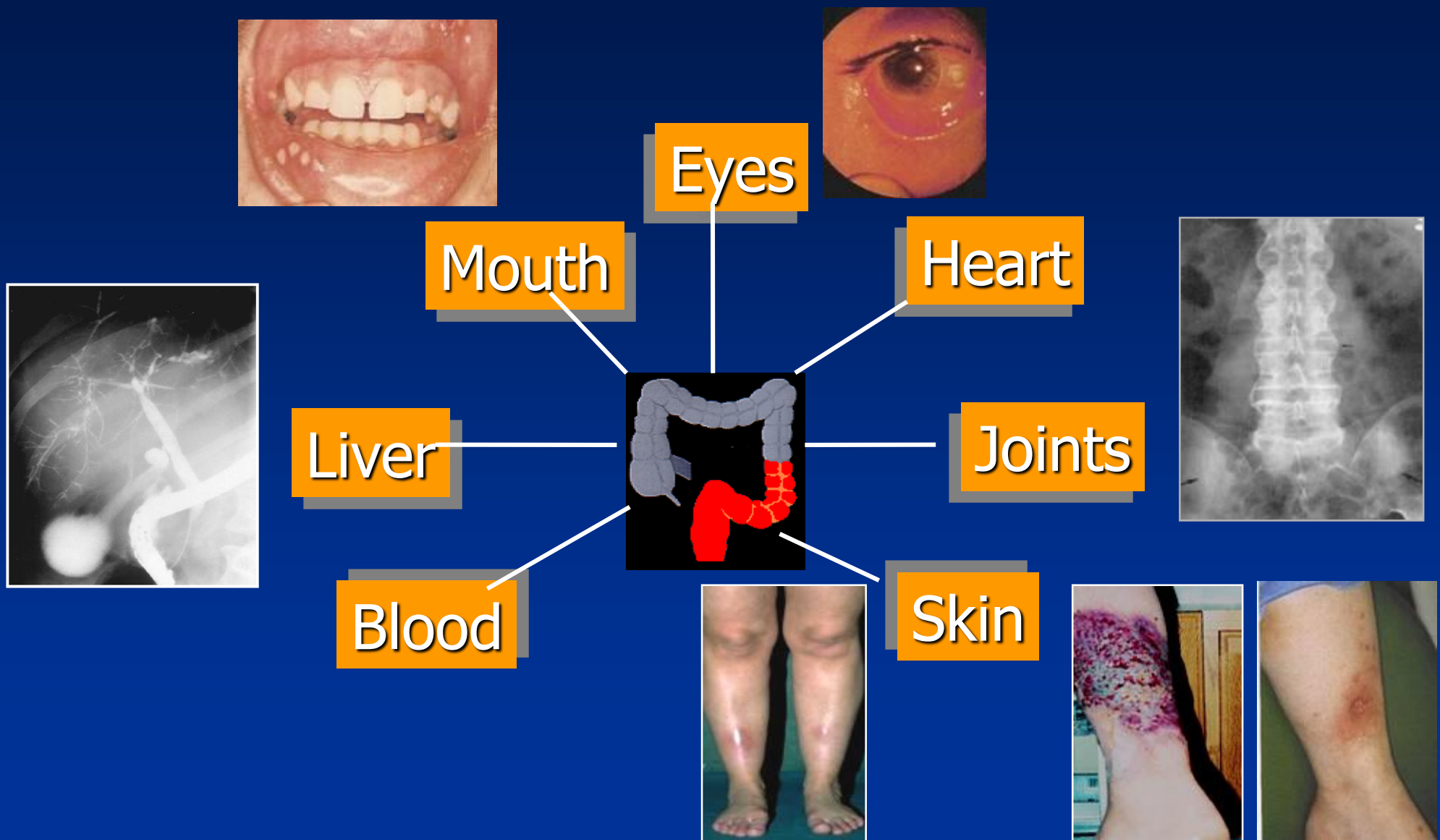
Crohn's Fistulae



Perianal fistula



Extraintestinal Inflammatory Bowel Disease





**“Your x-ray showed a broken rib,
but we fixed it with Photoshop.”**

Inflammatory Bowel Disease: Treatment Goals

- Diagnosis and prompt therapeutic response
- Induction of complete remission
 - ◆ Low side-effect profile to enhance compliance
- Maintenance of clinical remission
 - ◆ Medical vs. surgical remission
 - ◆ Steroid sparing
- Education and improvement of quality of life

Inflammatory Bowel Disease - Treatment

Factors influencing choice of therapy:

- **Diagnosis**
 - ◆ Ulcerative colitis or Crohn's disease?
- **Extent of disease**
 - ◆ UC: proctitis vs. distal / left-sided colitis vs. pancolitis
 - ◆ CD: colon only vs. ileocolonic vs. proximal GI disease
- **Severity**
 - ◆ mild vs. severe disease
- **Refractoriness**

Inflammatory Bowel Disease - Treatment

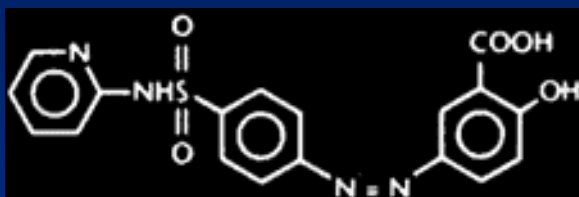
Conventional therapies:

- Aminosalicylates
- Corticosteroids/Budesonide
- Immunomodulators
- Antibiotics
- Anti-metabolites
- Biologic Modifiers

Inflammatory Bowel Disease - Treatment

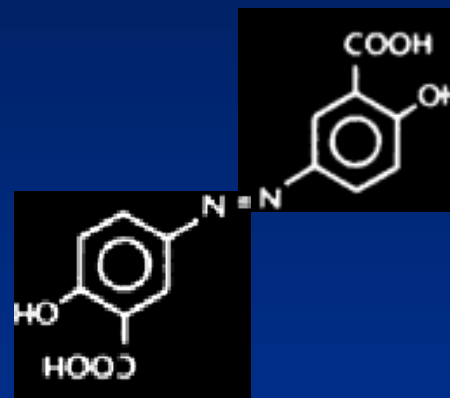
Aminosalicylates

Sulfasalazine (Azulfidine)



Sulfapyridine ↑ 5-ASA
Azo bond

Olsalazine (Dipentum)



Mesalamine

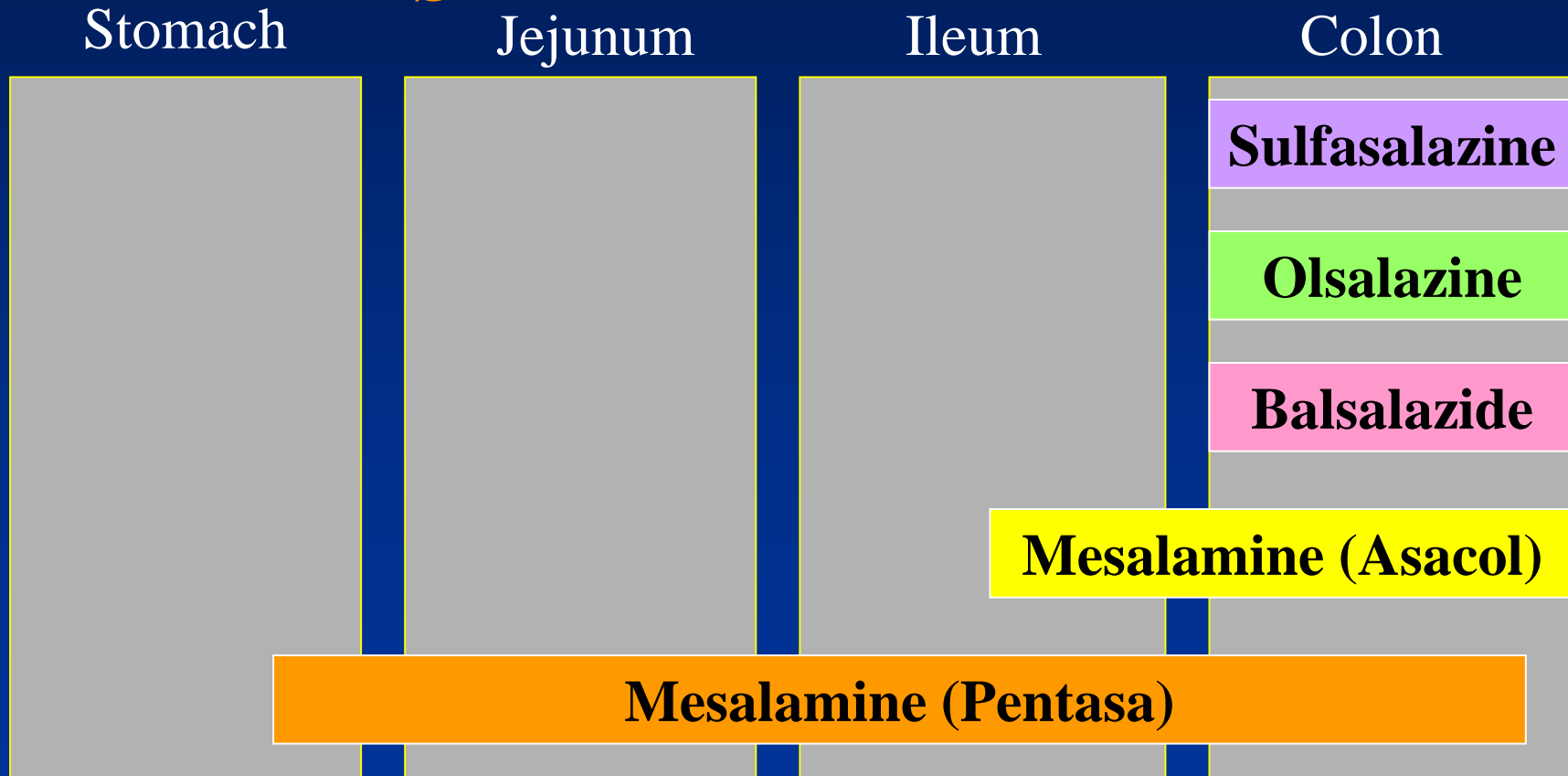
5-ASA -- ethylcellulose granules (**Pentasa**)
5-ASA -- Eudragit-S coating (**Asacol**)

Balsalazide (Colazal)

5-ASA -- 4-amino benzoyl
beta alanine

Inflammatory Bowel Disease - Treatment

Regional Delivery of ASA



Inflammatory Bowel Disease - Treatment

Aminosalicylates

Efficacy

- Induction / maintenance of remission in up to 75%

Dose

- Clinical effects follow dose-response (2-4.8 gm/day)
- All have similar efficacy at equimolar concentrations

Indications

- Induction or maintenance of remission in *mild to moderate* UC or CD

Formulations

- Oral
- Rectal
 - ♦ Suppository
 - ♦ Foam
 - ♦ Enema

Inflammatory Bowel Disease - Treatment

Corticosteroids

Efficacy

- 70-90% response rate expected

Dose

- Prednisone 40-60 mg/day tapered by 5 mg over 8-12 wks

IV dosing

- Hydrocortisone: 300 mg/day
- Solumedrol: 40-60 mg/day

Indications

- Induction of remission in *moderate to severe* UC or CD
- **** No role for maintenance**

Prognosis

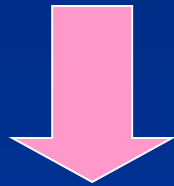
- Steroid requirement predicts 30-40% risk for surgery at 1 year

Faubion, et al *Gastroenterol*, Aug 2001

Inflammatory Bowel Disease - Treatment

Budesonide

- Nonhalogenated glucocorticosteroid
- Steroid-like mechanism of action
- pH-dependent coating releases in ileum and right colon with extensive **first-pass hepatic metabolism**



Minimal steroid side effects

Efficacy

- 60% response rate expected

Dose

- Budesonide 9 mg QD x 8 wks

Indication

- Induction of remission in mild to moderate right-sided CD
- **** Potential role for maintenance**

Budesonide: Safety

- Minimal acne, hirsutism, moon face and minimal suppression of HPA axis
- Daily dosing has less ↓ in plasma cortisol vs. bid dosing¹
- Rare nausea, distention, fatigue, perianal irritation
- At 2-years, no impact on development of osteoporosis²
- Slight decrease in bone marrow density at 2 years³
 - Budesonide 8.5 mg daily vs. prednisone 10 mg daily vs. non steroid therapy

¹Rutgeers et al. NEJM 1994;331:842

²Stockbrugger et al. Gastro 2003;124:A26

³Cino et al., Am J Gastro 2002

Inflammatory Bowel Disease - Treatment

Immunomodulators (Azathioprine/6-MP)

- Purine analogs
 - ◆ inhibit purine ribonucleotide synthesis
- Potential side effects:
 - ◆ Myelosuppression
 - ◆ Hepatitis
 - ◆ Pancreatitis
- Onset:
 - ◆ 8-12 weeks
 - ◆ too slow to use for induction

Efficacy

- 50-80%

Dose

- AZA: 1.5-2.5 mg/kg/day
- 6-MP: 1-1.5 mg/kg/day

Indications

- Steroid-dependent chronic UC or CD
- Maintenance of remission after steroids, cyclosporin or infliximab
- Post-operative prophylaxis

Azathioprine and 6-Mercaptopurine: Safety

- Enzyme thiopurine methyl-transferase (TPMT)
 - ◆ TPMT enzyme activity predicts efficacy and toxicity
- 6TG and 6MMP metabolite levels
 - ◆ 6TG level (230-400): efficacy
 - ◆ High 6-MMP level (>5700): hepatotoxicity
 - ◆ Hepatitis seen in up to 13%
- Pancreatitis: most common allergic reaction 3-15%
- ? Neoplasm risk; use in pregnancy controversial

Inflammatory Bowel Disease - Treatment

Cyclosporin A

Indications

- Severe, steroid-refractory active ulcerative colitis (salvage to avoid colectomy)
- Refractory Crohn's-related fistula
- Inhibits T-cell mediated responses

Methotrexate

Indications

- Induction / maintenance of remission for steroid-dependent CD; efficacy ~ 30%
- Patients that fail or intolerate 6-MP /AZA or infliximab
- Inhibits purine synthesis
- Induction 25 mg IM/SC weekly, maintenance 15mg weekly

Inflammatory Bowel Disease - Treatment

Tacrolimus

- FK506, Prograf
- Calcineurin inhibitor of choice for transplantation

Indications

- Severe, steroid-refractory active ulcerative colitis
- Refractory Crohn's-related fistula

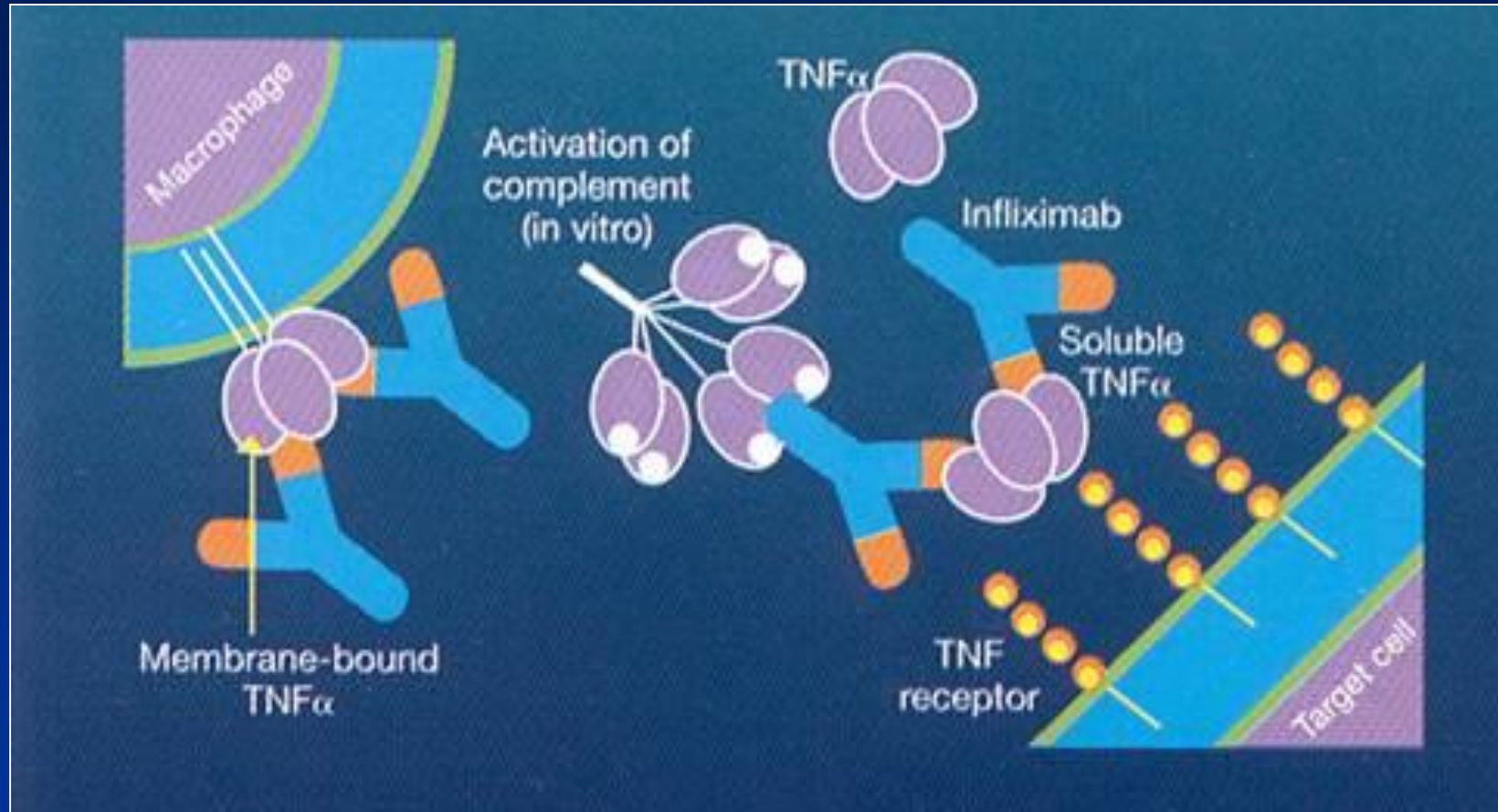
- 38 patients refractory UC
- IV in 18, oral in 20 (.1-.2 mg/kg)
- 18/38 responded, 13/38 remission
 - ♦ **Fellerman. IBD 2002;8:317**
- 48 patients with fistulizing CD
- Oral .2 mg/kg
- 43% TAC with improvement vs. 8% placebo
 - ♦ **Sandborn et al. Gastro 2003;125:380**

Inflammatory Bowel Disease - Treatment

Antibiotics

- Metronidazole
 - ◆ 1 gm or 10 mg/kg qd
 - Ciprofloxacin
 - ◆ 1 gm qd
- Has been used as monotherapy for mild active UC or Crohn's
 - Primarily used as adjuncts to therapy for induction of remission in mild, moderate, or severe disease; perianal CD
 - Maintenance limited by side effects (metronidazole) and cost (ciprofloxacin)
 - no studies conducted to evaluate use in maintenance

Infliximab (Remicade)



Inflammatory Bowel Disease - Treatment

Infliximab (Remicade)

Indications

- Induction of remission for moderate-severe Crohn's disease
- 1st line therapy for fistulizing CD
- Should be avoided in fibrostenotic disease / bowel obstruction

Response

- ~ 60-80%

Dosing

- 5 mg/kg IV infused over 2 hr at 0, 2 and 6 weeks induction
- 5 mg/kg IV every 8 weeks for maintenance

Infliximab: Safety

- Serious adverse events
 - ◆ Tuberculosis – disease reactivation¹
 - ◆ Opportunistic infection – aspergillosis, listeriosis, Pneumocystis; overall rate 0.43 cases per 1000 pts
 - ◆ Lymphoma - ↑ risk primarily in RA pts
- Immunogenicity
 - ◆ Antibody development – allergic reactions
 - ◆ Neutralizing antibodies – lower efficacy²
 - ◆ Use of antimetabolites (AZA, 6MP, MTX); IV hydrocortisone

¹Stuck et al. Rev Infect Dis 1989;11:954

²Baert et al. NEJM 2003;138:807

Adalimumab (Humira)

- Recombinant human IgG1 monoclonal antibody specific for human TNF. Binds specifically to TNF-alpha and blocks interaction with p55 and p75 cell-surface TNF receptors
- Induction dose: 160 mg SC once (administer by either dividing dose into 4 injections on day 1 or over 2 days), then follow with 80 mg SC once at week 2
- Maintenance: 40 mg SC q2wk beginning at week 4

Certolizumab Pegol (Cimzia)

- pegylated humanized antibody Fab' fragment of tumor necrosis factor alpha (TNF-alpha) monoclonal antibody
- Certolizumab pegol binds to and selectively neutralizes human TNF-alpha activity

Vedolizumab (Entyvio®)

An integrin receptor antagonist indicated for the treatment of adult patients with moderately to severely active ulcerative colitis and Crohn's Disease who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator, or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Inflammatory Bowel Disease

Unconventional therapy

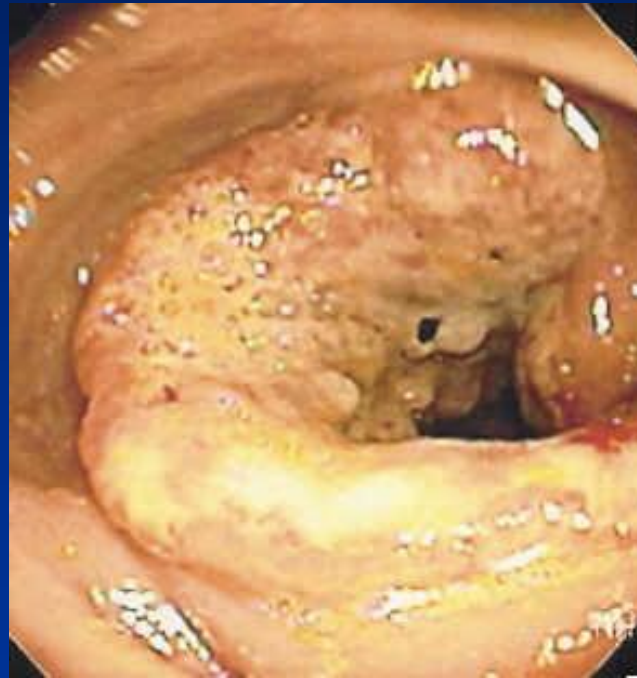
- Probiotics: *Escherichia coli* strain Nissle 1917
 - ◆ Modify host bacteria to down regulate immune response
 - ◆ Equivalent relapse rates vs. mesalamine in UC
 - » **Rembacken et al. Lancet 1999;354:635**
- Omega-3 fatty acids in Crohn's disease
 - ◆ Lowers concentration of eicosanoids (modulators of immune response)
 - ◆ RCT 4.5 g qd ω -3 fatty acid vs. placebo
 - ◆ 59% vs. 26% placebo in remission at 1 yr
 - » **Belluzi et al, NEJM 1996:334:1557**

Inflammatory Bowel Disease

Safety in Pregnancy/Lactation

Drug	Preg/Lactation	Comments
5-ASA	B / S	Very safe
Prednisone	C / S	No human studies
Budesonide	C / S	No human studies
Metronidazole, Ciprofloxacin	B / NS C / NS	Short-term use safe ? Long-term safety
AZA, 6-MP	D / S?	Controversial
Methotrexate	X / NS	Teratogenic
Infliximab	B / S?	Safe during pregnancy

Inflammatory Bowel Disease: Colon Cancer



Risk Factors for Colon Cancer in Ulcerative Colitis and Crohn's colitis

Risk Factor	Importance
Extent of disease	++++
Duration of disease	++++
Primary Sclerosing Cholangitis	+++
Young age at onset	+
Positive family history	+
Severity of Inflammation	?

**Choi PM, et al. *Gastroenterol Clin North Am* 1995;24:671-87.
Eaden J. *Am J Gastroenterol* 2000;95:2710-2719.**

Prevention of Colon Cancer in UC/CD

- Colonoscopy surveillance
 - ◆ Starting 8-10 years after diagnosis of UC, 15 years after diagnosis of Crohn's colitis, every 2 years
 - ◆ Multiple biopsies, minimum 32
- Surgery (ileo-anal anastomosis)
 - ◆ DALM, high grade dysplasia, ? low grade dysplasia
- Chemoprevention
 - ◆ 5-ASA 1.2 gm once daily (**Eaden, APT, 1999**)
 - ◆ Folic acid 1 mg daily (**Lashner, Gastro, 1997**)
 - ◆ Ursodiol 300 mg bid (PSC) (**Tung, Ann Int Med, 2001**)



“Wait a minute!
If this is his
spleen, then
what’s that?”

*Things You Don't Want
to Hear the Surgeon Say*



Thank You