Slide 1

Cutting edge research in IBD:

What does it tell us
and
where are we heading?

Joshua Korzenik, MD
MGH Crohn's and Colitis Center
Harvard Medical School

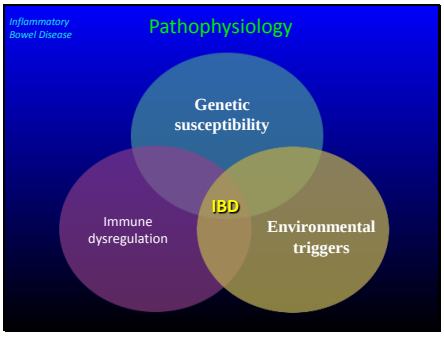
Slide 2

Pathophysiology and aetiology of IBD

- "I can only regret that the aetiology of the condition remains in obscurity but I trust that ere long further consideration will clear up the difficulty."

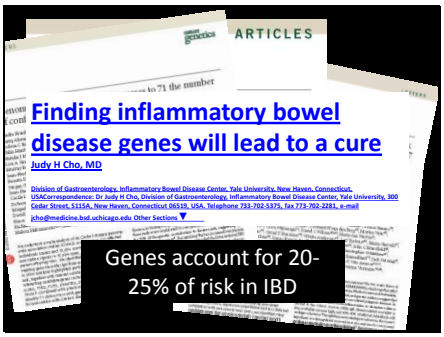
-- T. K. Dalziel, 1913
British Medical Journal

Slide 3



Slide 4

Slide 5



Slide 6

Healthy/Control Population[1]

- NOD2 L1007fs (rs2066847-insC)
  - CD - 13% or 104,000
  - Healthy -6% or **18.5 million in the US**
- IL23R (rs2201841-CC)
  - CD - 14% or 112,000
  - Healthy - 5 % or **15.4 million in US**
- Autophagy (ATG16L1300A- GG)
  - CD – 34% or 270,000
  - Healthy - 25% **or 77 million in the US**

Csongei et al. World J Gastro 2010;16:176-183

Slide 7

Diseases of Modern Times

Ulcerative colitis
Early description:
Wilks 1875

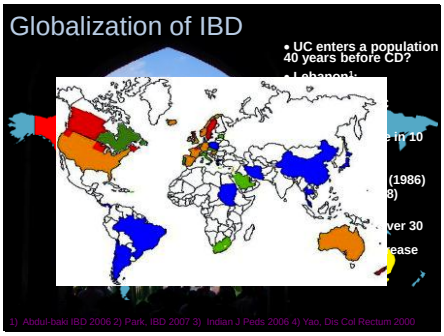
The Journal of the American Medical Association

Burrill B Crohn, M.D.

Crohn's disease
First described:
Dr T.K. Dalziel 1913

Slide 8

Globalization of IBD



1) Abdul-baki IBD 2006 2) Park, IBD 2007 3) Indian J Peds 2006 4) Yao, Dis Col Rectum 2000

Slide 9

Environmental Influences

Known
- Smoking
- NSAIDs
- Appendectomy
- Breastfeeding
- Microbiome (?)
- Diet (?)

Probable
- Antibiotic use
- Vitamin D
- Childhood infections

Speculative
- Hygiene
- Eczema
- Exercise
- Oral contraceptives
- Stress
- Furry pets
- Periodontitis
- Raw pork
- Unpasteurized milk
- Medications
- Air pollution

Slide 10

Smoking

Effects

- Reduces risk of UC
  - Milder course (?)
  - Reduces risk of pouchitis
  - Reduces risk of PSC
- Increases risk of Crohn's
  - Worsens disease course
  - More rapid post-op recurrence
  - ? Associated with ileal [1]

Possible Mechanisms

- 4,000 chemicals
- Nicotine
  - Reduces pro-inflammatory cytokine: Il-1β, TNF, Il-8[2]
  - Suppression of macrophage activity[3]
  - Reduction of superoxide production

1) Russel IBD 1998; 4:182. 2) Van Dijk a Eur J Pharmacol 1995; 278: 1017. 3) Madrestsma J Immunol 2001;167:6518

Slide 11

1930-1960's

Stress: Psychosomatic Hypothesis (UC)

- "Well-marked time relationship between ..emotional disturbance and symptoms."
  -- Murray, Am J Med Sci,1930
- UC patients "couldn't cope, giving up." "Diarrhea is substituted for real accomplishment." "..childish, dependent personality"
- "Degree of difference so gross as to make a control group unnecessary."
  -- Wittkower, BMJ, 1938

Slide 12

Stress?

- Was loss of a child associated with a flare of UC or Crohn's or the development of IBD?
  - Denmark: registry of all parents who has lost a child below the age of 17.
  - Parents already with IBD: flare (hospitalization)?
  - Parents without IBD: subsequent development of IBD?
  - Followed for up to 17 years after death of child.
- No association with flare or development of IBD

Li et al, Psychological Streess and IBD, Am J Gastro, 2004

Slide 13

Medications: NSAIDs

Effects

- Increased flares[1]
- Increased hospitalizations[2]
- Selective COX-2 inhibitors safer[3]
  - 10% flare at 6 weeks
- Celecoxib for 2 weeks safe[4]
  - RCT demonstrated no increase in flares

Mechanism

- Indomethecin reduces neutrophil microbicidal function[5]
- Phenylbutazone reduces superoxide production[6]
- Reduction in chemotaxis and cell migration

1) Kaufman Ann Intern Med 1987;107:513 2) Evans *Gut* 1997;**40**, 619-22.3) Mahadevan Gastro 200297:91. 4) Sandborn Clin Gastr Hep 2006. 5) Horan Immunopharmacology 1983;6:97.6) Peman J Antimicrob Chemo 1994;34:965.

Slide 14

Environment and Microbiome

- Acquisition of Flora:
  - Mode of delivery
    - C-section associated with early onset CD[1]
    - Not a consistent finding[2]
  - Breast feeding[3]:
    - Crohn's disease (n=17): OR 0.67 (0.52-0.86)
      - Best studies (n=4): OR 0.45 (0.26- 0.79)
    - UC (n=17): OR 0.77 (0.69-0.96)
      - Best studies (n=4):0.56 (0.38-0.81)
- Alteration of Flora
  - Gastrointestinal infections (discordant twins)[4]
    - UC OR 5.5; CD OR 8
  - Antibiotic use 2-5 years prior to diagnosis[5]
    - CD OR: 1.32 (1.05-1.65)

1) Ponsby, IBD 2009;15:858. 2) Sontag,IBD 2007;13:1385. 3) Klement, Am J Clin Nutr,2005 4) Halvarson IBD 2006 5)Card,GUT, 2004

Slide 15

Hygiene hypothesis

- Indoor plumbing
- Uncrowded living conditions
  - CD: OR 0.3 (0.1-0.8)
- Having own towel
  - Increased risk CD
- Owning a pet
  - CD +/- : OR 2.0 (0.9-4.5) OR: 0.66 (0.46-0.96) (not UC)
- Day care and childhood infections:
  - Increased risk of CD

1) Amre, AJG, 2007 2) Bernstein, AJG,2007 3) Halvarson IBD 2006

Slide 16

Vitamin D

Risk and Benefit in IBD

- Lower levels associated with new onset Crohn's disease[1]
- Therapeutic benefit?
  - Vitamin D3- maintenance of remission (13% vs 28% - p= 0.06)
  - BXL-62 (low calcemic effect) VDR agonist may act as therapeutic agent[3]

Mechanisms

- Reduced interferon-γ in CD associated with low vit D[4]
- NOD2
- Augment bactericidal function

1) Leslie Am J Gastr 2008;103:1451. 2) Jorgensen. Aliment Pharmacol 2010;36:377. 3) Laverny Immunolog Letters 2010 15;131:49. 4) Treble Alimet Pharmacol 2004 19;1063.

Slide 17

Vitamin D and Nurses Health Study

- NHS- 121,700 nurses age 30-55
- 1,877,1110 person-years over 16 years
- 106 cases of CD; 106 cases of UC
- validated 25(OH)D prediction score

Highest Quartiles of vitamin D:

- Risk CD of 0.58 (95%CI 0.33-1.00)
  - p(trend)=0.04
- Risk UC of 0.45 (95%CI 0.24-0.85)
  - p(trend)=0.01.

Anantakrishnan, Gastroenterology, 2012

Slide 18

Dietary Risk Factors

- Breastfeeding
- Increased refined sugar[1]
  - Not secondary to disease or zinc deficiency
- Decreased complex carbohydrates[2]
- N-6 fatty acids (arachidonic acid) UC RR 4.12- CI 1.56-11.04
- Fast food: increased risk in UC and CD[1]
  - OR 3.4 (1.3-9.3)
- Coffee: protective in UC and CD
- Unpasteurized milk[3]
  - OR 0.49 (0.33-0.95)
- Processed meat (RR 5), Meat (3.2), sulfur (2.7) and alcohol (2.7) associated with flares of UC[4]

1) Persson,Epidem, 1992 2)Sakamoto IBD, 2006 3)Bernstein, AJG, 2007 4) Jowett GUT, 2004 5) da Silva, Gastro 2010

Slide 19

Is the dietary influence through the microbiome?

Slide 20

Reduced diversity in fecal microbiota in CD

Stool: 6 CD, 6 healthy controls

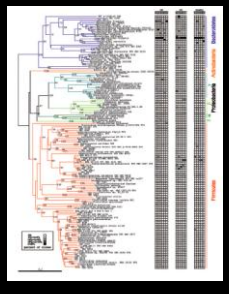
CD: in remission and ileal disease

2 DNA libraries; 25,000 clones each

1520 16s; 1190 identified

125 non-redundant OTUs (95 not in culture collections, 66 novel)

Firmicutes: 43 in HC; 13 in CD



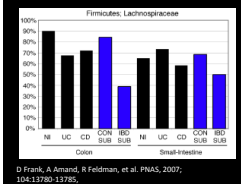
Manichanh et al. Gut 2006; 55:205-11

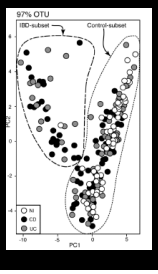
Slide 21

Microbial community imbalances in IBD

190 resected specimen from UC, CD, controls

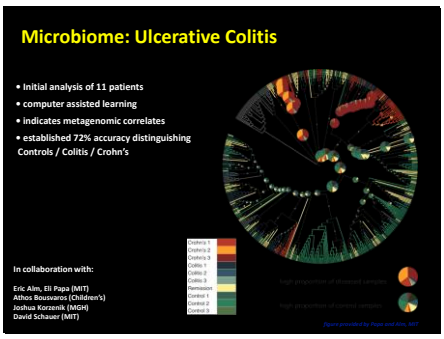
IBD- depleted *Bacteroidetes* and *Lachnospiraceae* while *Acinetobacter* and *Proteobacteria* is more abundant in IBD





D Frank, A Amand, R Feldman, et al. PNAS, 2007; 104:13780-13785.

Slide 22



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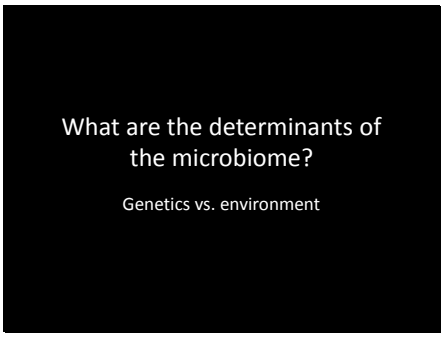

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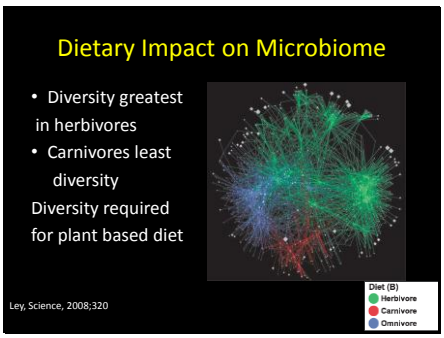


Slide 25

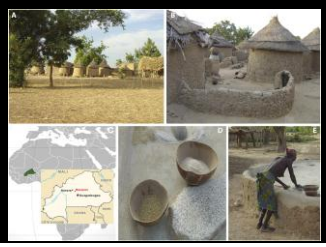
Environmental studies

Paleonutrition: A Brief History of the Colon

- High fiber content 100-150 gms/day
- Colonic salvage
- SCFA
  - Lowland gorilla obtains as much as 57% of calories from colonic fermentation[1]
- Colon as a nutritional organ
- Influence on flora

1) Popovich, J Nutrition, 1997;127:2005

Slide 26



De Filippo C et al. PNAS 2010;107:14691-14696

©2010 by National Academy of Sciences

PNAS

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Intestinal Flora

- Radical change of gut flora in over past century
  - Diet: Increase in refined sugar; Decrease in complex carbohydrates
  - Refrigerators: Decreased bacterial ingestion
  - Antibiotics: risk for development of Crohn's disease
- Alteration in flora in industrialized world
  Less *Bifidobacteria*, more *Bacteroides* in English flora vs. rural African flora [1]
  Microbiome of children from Burkina Faso

- Revision of hygiene hypothesis?
  - Gut flora:
    Past: accessory innate immune organ
    Current: factor in innate immune impairment

1. Tomkins, J Hygiene, 1981;;2) De Filippo Proc Nat Acad Sci USA, 2010;102:14691.

Slide 28

2012

Risk Factors

- Appendectomy
- Smoking and IBD
- Breast feeding[1]:
- Hygiene hypothesis[2,3]:
- Gastrointestinal infections (discordant twins)[4]:
- Antibiotic use 2-5 years prior to diagnosis[5]
- NSAID use
- Diet

1) Klement, Am J Clin Nutr,2005 2) Amre, AJG, 2007 3) Bernstein, AJG,2007
4) Halvarson IBD 2006 5)Card,GUT, 2004

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Slide 30

Early Therapy

- Cod liver oil enemas
- Dakin's solution
- IV typhoid vaccine
- Diplococcus vaccine
- Anti-dysentery serum
- Abdominal irradiation
- Slop diets/soured milk
- Porcine stool extract

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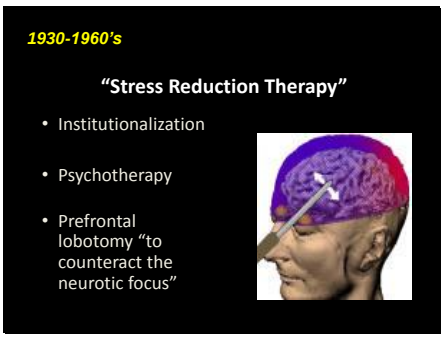

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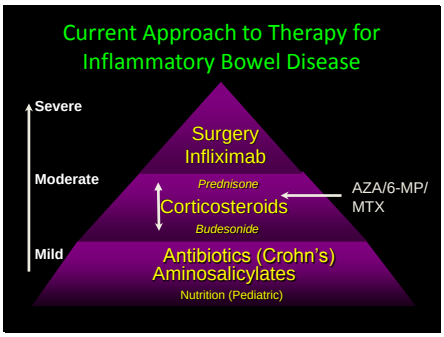
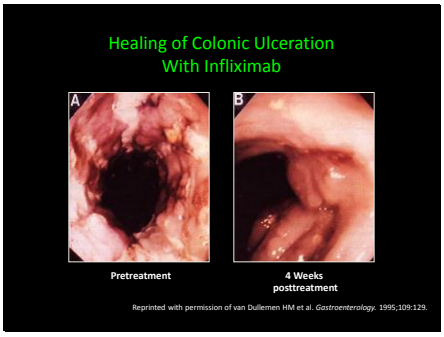


Slide 33



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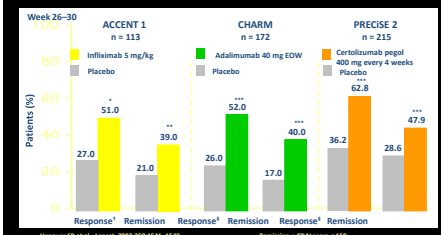
Overview of Results of Long-Term Anti-TNF Trials

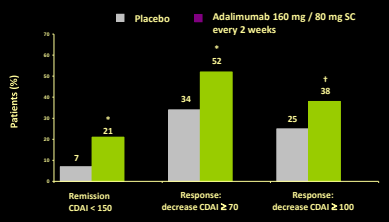


Hanauer SB et al. *Lancet*. 2002;359:1541–1549.
Colombel J et al. *Gastroenterology*. 2006;131:950.
Schreiber S et al. *Gut*. 2005;54(Suppl VII):A82.

Remission = CDAI score < 150
† Decrease in CDAI score of ≥ 70 points and ≥ 25%
‡ Decrease in CDAI score of ≥ 100 points
*P < .0002; **P < .003; ***P < .001

Slide 35

Loss of response or intolerant to infliximab, Treatment with adlimumab vs placebo



Sandborn WJ. Am J Gastroenterol. 2006;101:S1147.

* P < 0.001 vs placebo
† P < 0.01 vs placebo
Full analysis population

Slide 36

Lessons from Anti-TNF Trials

- Complete and durable remission/fistula closure is possible for a subset of patients
- Anti-TNF agents have a "steroid-sparing"
- Initial non-responders do not respond to continued treatment
- Loss of response may respond to dose escalation
- Those who lose response may respond to a second (or third) agent

Slide 37

Anti-TNF agents: Adverse effects

- Infusion reactions (infliximab)
  - Acute 3.8%
  - Delayed 2.8%
- Immunogenicity
- Infection (8.2% overall, 4% serious)
  - Risk of TB: black-box warning
- Autoimmune phenomena
  - ANA (57%)
  - anti-ds/ssDNA, anti-histone Ab
  - Lupus-like syndrome (0.6%)
- Demyelinating disease (0.2%)
- Psoriasis
- Worsening of / increased mortality in CHF
- Hepatic failure
- Cancer/ Lymphoma
- Death (1-2%?)

Colombel JF, et al. Gastroenterology 2004;126:19.
Vermeire S, et al. *Gastroenterology.* 2003;125:32.

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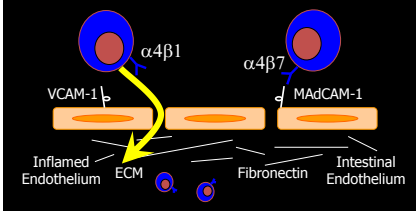
CELL ADHESION MOLECULES

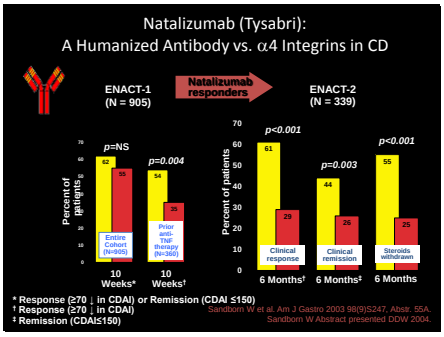
Slide 39

α4 integrins are key intestinal adhesion molecules



Podolsky et al. *JCI* 1993;92:372-80
Hesterberg PE et al. *Gastroenterology* 1996;111:1373-80

Slide 40



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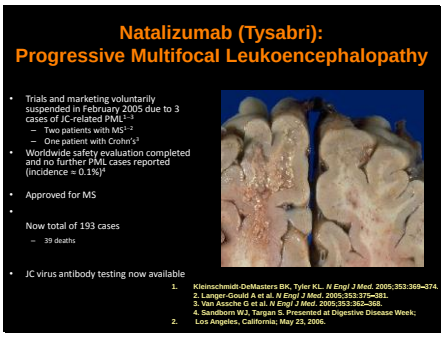

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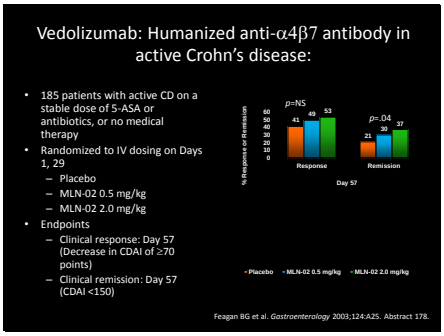

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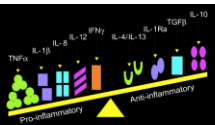
Biologics Under Investigation in IBD



- Cytokine strategies
  - Il-1ra (anakinra)
  - Antibodies to Il-4, Il-6, Il-8, Il-12, Il-15, Il-16, Il-17, Il-18, Il-23
  - Il-10, Il-11
- Anti-cell adhesion molecules
  - Antibodies to ICAM-1, VCAM-1, VLA-4, α-4 , α4β7
  - Antisense compound to ICAM-1
  - Anti NF-κB, anti-OX40, anti-ZAP
- Other approaches
  - rhuGrowth hormone, KGF- (failed in UC trial), rosiglitizone, PAF inhibitor, reflexponide (topical steroid), tacrolimus, EGF, RDP
- Anti-TNF Strategies
  - Chimeric antibodies
  - "Humanized" antibodies
  - "Fully human" antibodies
  - Antibody fragments
  - Antisense compound
  - TNF-BP1
  - Thalidomide

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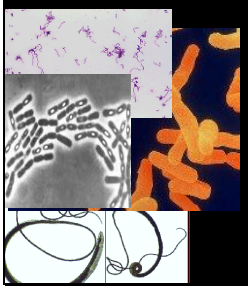
Biotech vs Low Tech



Antibiotics

Probiotics

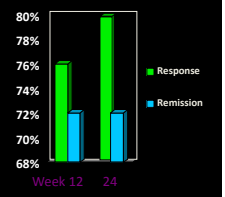
Prebiotics

Parasites

Slide 45

Helminth Ova in Active Crohn's Disease

- 24 week open study
- 29 pts CDAI 220-450
- 2500 *T. suis* ova q 3 wks
- Response
  - >100 point ↓ CDAI
- Remission
  - CDAI<150



Weinstock et al, Gut, 2005

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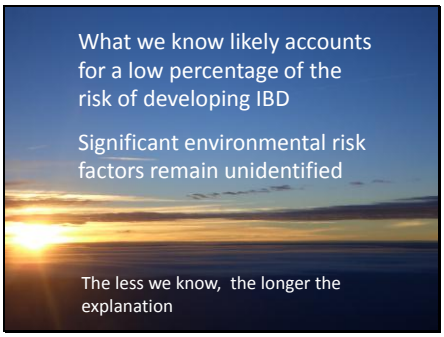
Probiotics

UC and "Human Probiotics"

- Rationale:

  Fecal enemas used in recurrent *C. difficile*
- Six patients with longstanding UC
- Received daily infusions for 1 week
- 6/6 "cured"

Borody et al, J Clin Gastroenterol. 2003 37:42-7.

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