FASD is a Whole Body Diagnosis, Part 1: Bowel and Allergy Problems And Sleep Apnea

Rod Densmore, M.D.,
Father of an adult who has FAS

SESSION A6 8th International Research Conference on Adolescents and Adults with Fetal Alcohol Spectrum Disorder

Review, Respond and Relate*: Integrating Research, Policy and Practice around the World April 19, 2018*

Health Survey n=541

(Himmelreich M, Lutke CJ, Travis E. 2017 Plenary Panel: The Lay of The Land: Final Results of a Health Survey of 500+ Adults with Diagnosed FASD. 7th International Conference on FASD. UBC. Vancouver. March 4, 2017)

Condition	Gen. Pop. rate	Rate in FASD	Increase of ?
Irritable Bowel Syndrome (IBS)	11%	**20%**	2x
GERD (Reflux)	20%	**42%**	2x
Crohn's disease	0.8%	2.4%	**3x**
Ulcerative colitis	0.3%	2.2%	**7x**
Celiac	0.7%	2.2%	3x
Sleep Apnea	2.4%	**15.2%**	**6x**
Epipen Carried	2.2%	9.6%	4x

Motivation two : Longitudinal care of folks like these who have FASD

- Summer, aged 24, very low iron (ferritin 6!!); has heavy periods and celiac disease impairs iron absorption; very “slowed down”… motivation and task completion is impaired and cannot remember to take pills…iron sucrose infusions have helped++
- Jerry, 55 yr. old fit fellow, has reflux— this leads to sinusitis, chronic cough and asthma…

Reference: Internal Medicine Comprehensive Review and Update, Harvard Medical School, Boston, June 2017

- 7:15-8:00 Acute Renal Failure: What's New?
- 8:00- 8:45 Venous Thromboembolic disease: A Practical Approach
- 845: 9:15 The Human Microbiome and Gut Health: New Frontiers
- 9:15- 9:45 New Frontiers in Vitamin D
- 9:45-10:15 Kidney Stones: What You Need to Know
- 10:30-11:15 Update in Management of Chronic Kidney Disease including End Stage Renal Disease
- 11:15-12:00 Renal Cases (interactive session)
- 12:00-1:00 Dysnatremias
- LUNCH
- **TURN OVER NOTE PAGES…WRITE PATIENTS NAMES ON THE TALKS…MY "TO DO" LIST (85)**

Microbiome

- “We depend on a vast army of microbes to stay alive: a **microbiome** that protects us against germs, breaks down food to release energy, and produces vitamins”

  (Oxford Dictionary)
- In us…there are 30 trillion human cells and 38 trillion microbes; we have about 20,000 genes and we have about 10,000 species of microbes (mostly in our gastrointestinal tract)

Microbiome

- The microorganisms in a particular environment, e.g. a part of the body…. AND…*Not just the gut*
- Skin, vagina, mouth, nasal passage all have pattern of normal microbes…usual ratios out of balance = symptoms e.g. not enough lactobacilli to maintain normal vaginal acidity…bothersome overgrowth of bacteria we call BV
- *Not just bacteria*…viruses, bacteriophages, protozoa and fungi too

Gut Microbiome

- Breaks down polysaccharides in food
- Synthesizes vitamins
- Prevents dangerous bacteria (like shigella and salmonella) from overgrowing
- Helps to program maturation of the immune system

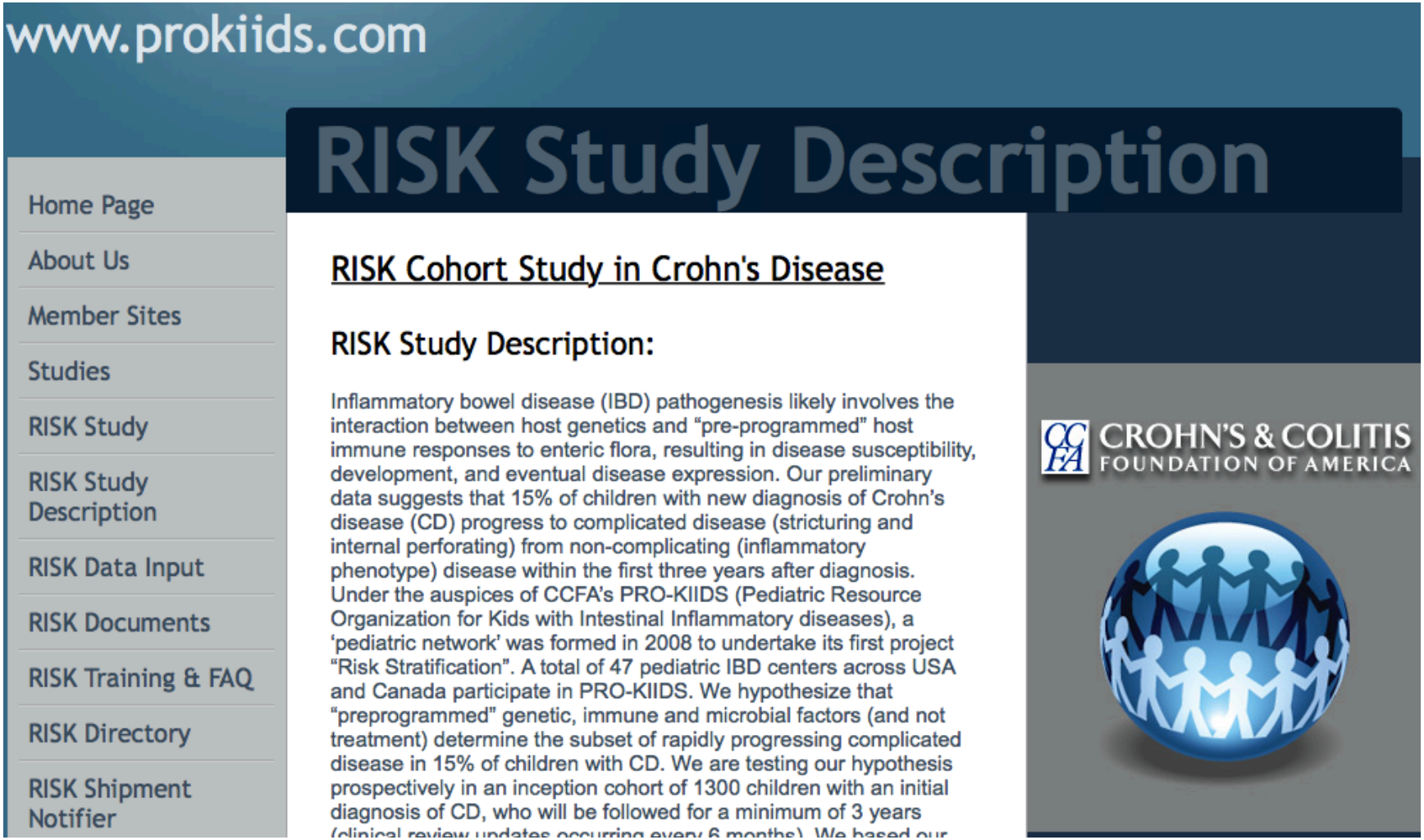
Microbiome miscellaneous

- PPI's (rabeprazole, pariet, etc.) do influence the microbiome
- **Smoking hurts the microbiome**
- Triglycerides and LDL cholesterol is influenced by the microbiome
- Altered microbiome can increase risk of coronary artery disease, obesity and metabolic syndrome
- Gluten free might be needed but it decreases a helpful bacteria (veillonellaceae)
- **Buttermilk is great from microbiome…increases good bacteria**
- **More diversity of bacteria is good/less diversity is bad**

Infant Microbiome

- Vaginal delivery = early exposure to bacteroides which is good…positive effect for 6-18 months!
- C section means later exposure to bacteroides and this is associated with increase asthma and autoimmune problems
- Change food= change microbome!
- But also, as matures…bacteria change over time…ruminococcaceae increases short chain fatty acids that are good for T cells maturation
- Antibiotic in first few months…sure, **if really needed,** but it does change ruminococcaceae so don’t use if antibiotics can be avoided

Altered microbiome in Kid's Crohn's



Challenge: 1000 kids…do the 30-40 with FASD have a characteristic pattern of microbiome changes? (they have increased inflammation)

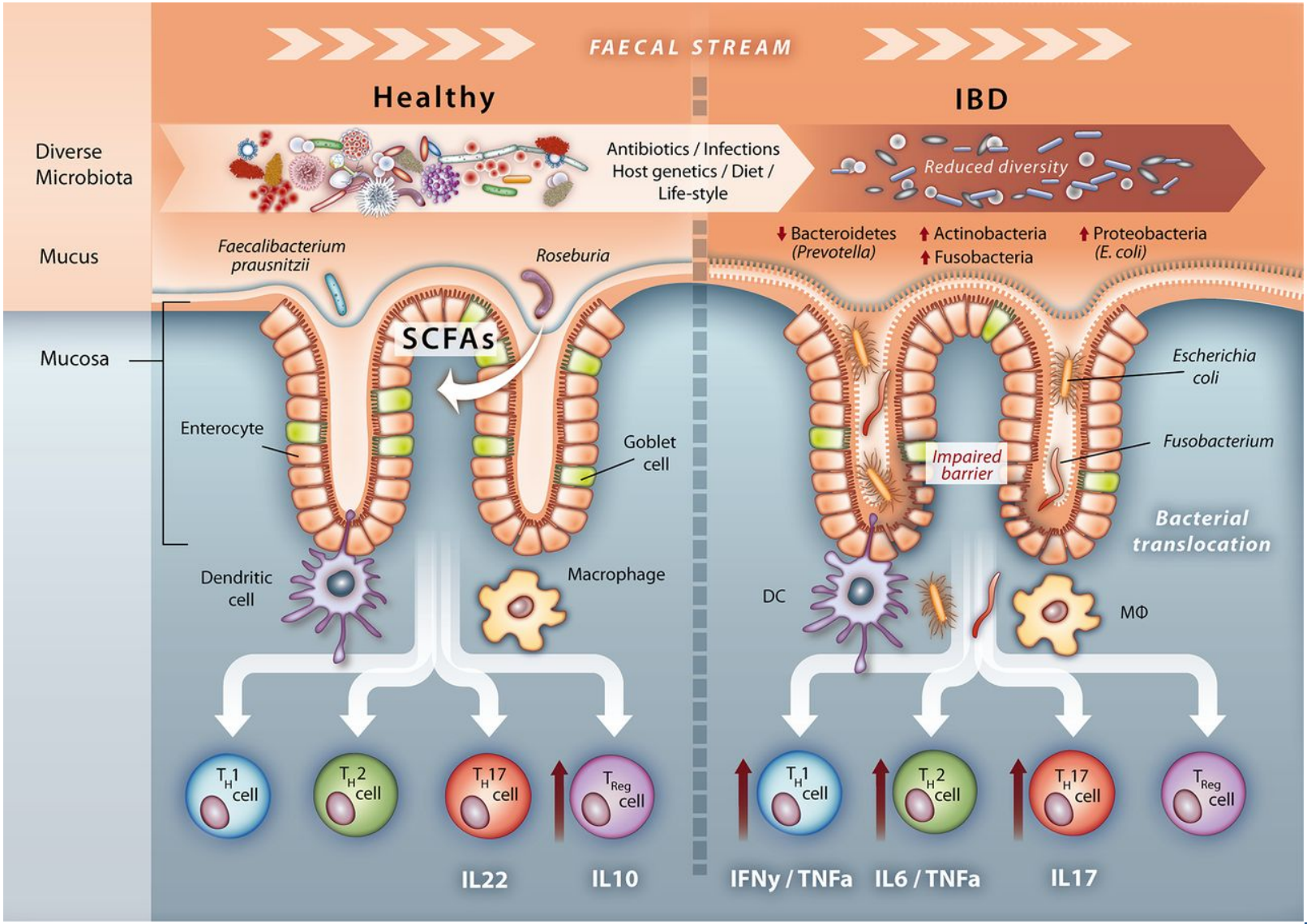
Microbiome and Type 1 Diabetes
(autoimmune attack of pancreatic islet cells so those cells cannot make insulin any more)

- Finland: 6X Diabetes type 1 vs. Europe
- XS Bacteroides and low Actinobacter
- Microbiome changes a year before Type 1 Diabetes is diagnosed
- Plan: replace the missing microbes

Microbiome future

- Severe Clostrium difficile : fecal transplant is better than antibiotics
- Inflammatory Bowel Disease: Standard of care med (Infliximab) has only a 50% response rate…if add 7 types of bacteria to normalize microbiome get a better response
- Maybe adjusting microbiome in rheumatoid arthritis could be beneficial

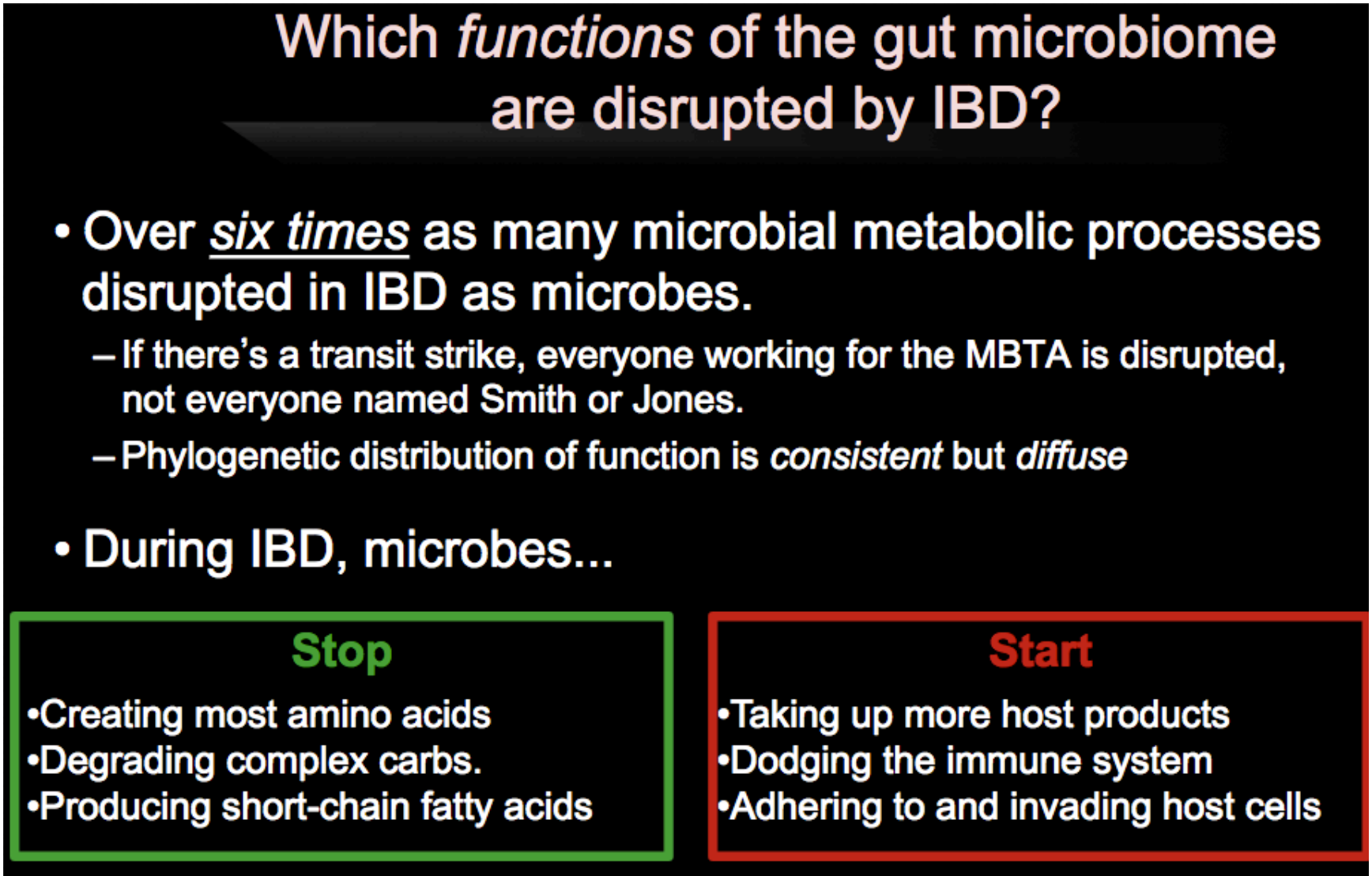
Microbial signatures of a healthy gut and Inflammatory Bowel Disease (IBD). Under healthy homeostasis the microbiota is diverse.



Felix Sommer et al. Gut doi:10.1136/gutjnl-2016-313678

GUT

From: *The Human Microbiome and Gut Health*, June 5, 2017 Dr Ramnik Xavier



From: *The Human Microbiome and Gut Health*

June 5, 2017 Dr Ramnik Xavier

- During inflammatory bowel disease, microbes:

STOP	START
Creating most amino acids	Taking up more host products
Degrading complex carbs	Dodging the immune system
Producing short-chain fatty acids	Adhering to and invading host cells

- MANY functions of the gut microbome are disrupted in IBD
- If there is a transit strike, EVERYONE is disrupted not just the people called Smith or Jones

What patients want to know

- **What is wrong,** what went awry, what is not working?
- **How did that happen?**
- Given these realities, **what will become of me?**
- Given all of the above, **what should we do about it?**

"the ultimate in destigmatizing is to explain it"

Dr. Clara Brichant-Petit Jean, APA meeting, 2016

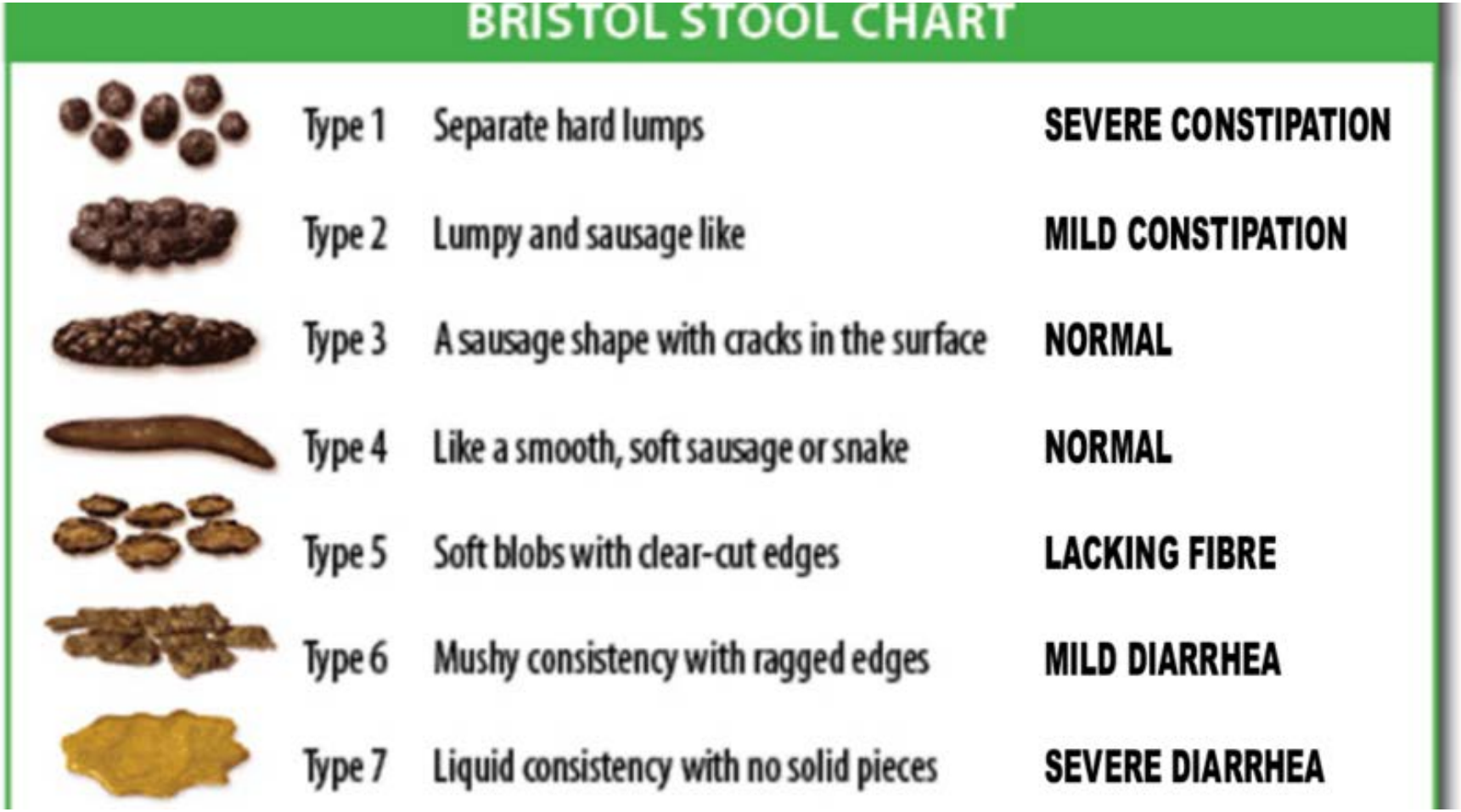
Our template for these sessions

- **What is wrong?.....WHAT**
- **How did that happen?.....HOW**
- **What will become of me?.....USUAL COURSE**
- **What should we do about it?...PLAN**

Irritable bowel syndrome (IB**S**) What?

- Recurrent Abdominal Pain at least one day a week x 3 months; onset at least 6 months ago
- 2/3: 1) Pain with defecation 2) change of stool frequency or 3) change of stool form (next slide)
- No structural or metabolic abnormalities
- Higher prevalence of physical, emotional, and/or sexual abuse (association not cause)
- 3/1 female/male

Irritable bowel syndrome (IBS): Stool form?



IBS What? Rule out red flags

- Bleeding
- Fever
- Persistent diarrhea
- Severe constipation
- Weight loss
- Night pain and abnormal bowel function
- Family: cancer, inflammatory bowel disease, celiac
- Onset over age 50

Irritable bowel syndrome: How?

- Psychosocial factors/Stress….altered vagus nerve activity and changes in sympathetic tone sacral levels S2,3,4 …leads to both
- Altered motility
- Altered sensation

Irritable bowel syndrome: Usual course?

- **Changes**
- From constipation predominant to diarrhea predominant to mixed to alternating; 75% change subtypes in 1 yr.!

Irritable bowel syndrome: Plan?

- Investigate red flags; refer if weight loss, rectal blood, constipation that is not helped with fiber
- Screens: Thyroid, anemia, electrolytes, liver, ESR, occult blood and consider sigmoidoscopy if younger but do colonoscopy if over 50

Irritable bowel syndrome: Plan?

- Positive Diagnosis: not celiac and not cancer
- Less fructose and gluten
- Stress management: moderate anxiety/depression: https://cmha.bc.ca/programs-services/bounce-back/
- If reducing caffeine, alcohol, spicy foods, onions, garlic, sorbitol, and xylitol ineffective then *Low FODMAP Diet*: (fermentable oligosaccharides, disaccharides, monosacchardes and polyols) https://www.healthline.com/nutrition/low-fodmap-diet
- Low FODMAP is not too restrictive...see next slide

- **Protein:** Beef, chicken, eggs, fish, lamb, pork, prawns and tofu
- **Whole grains:** Brown rice, buckwheat, maize, millet, oats and quinoa
- **Fruit:** Bananas, blueberries, kiwi, limes, mandarins, oranges, papaya, pineapple, rhubarb and strawberries
- **Vegetables:** Bean sprouts, bell peppers, carrots, choy sum, eggplant, kale, tomatoes, spinach and zucchini
- **Nuts:** Almonds (no more than 10 per sitting), macadamia nuts, peanuts, pecans, pine nuts and walnuts
- **Seeds:** Linseeds, pumpkin, sesame and sunflower
- **Dairy:** Cheddar cheese, lactose-free milk and Parmesan cheese
- **Oils:** Coconut oil and olive oil
- **Beverages:** Black tea, coffee, green tea, peppermint tea, water and white tea
- **Condiments:** Basil, chili, ginger, mustard, pepper, salt, white rice vinegar and wasabi powder

Gastro**e**sophageal **R**eflux **D**isease (GERD) What is it? How does it cause problems?

- **Acidy** stomach contents come **backwards** up the food tube (esophagus)
- Symptoms: 1) heartburn, acidy taste, chest pain that settles with antacids (6-10 Tums, etc.), 2) swallowing can become **obstructed**: stricture or narrowing of esophagus**; Chronic reflux=irritation**… Barrett's, Adenocarcinoma 3) **Laryngopharyngeal Reflux**: Cough, Throat clearing, Laryngitis, Asthma, Dental enamel problems

GERD Usual course?

- Population-wise seems to be increasing over time; prevalence is rising 50% in last 11 years!

GERD How

- GERD: Gastroesophageal Reflux: lax **lower** espohageal sphincter

- Laryngopharyngeal Reflux: lax **upper** espohageal sphincter

GERD Treatment

- Which **lifestyle modifications** work?

A) **Weight loss**

B) **Head of bed up 6-8 inches** (by blocks under head of bed /feet to wall), hospital style bed, or wedge pillow)

C) **Avoid irritants:** caffeine, alcohol, chocolate, mint, spicy foods; use lower acid foods

"Mattress Genie"

GERD Treatment

- Meds: (to reduce acid) Proton Pump Inhibitors - **(PPI's)** (rabeprazole 20 mg daily is the least expensive one here in B.C.) Recent concerns re long term use…unconvincing and unresolved (Laterza L, et al. 2018. Risk factors for gastric cancer: is it time to disregard PPIs? Gut. doi: 10.1136/gutjnl-2017-315621)

- **Gaviscon:** neutralizes the acid pocket above the food x 3 hours…Bicarbonate plus "Alginate" (antacid and "seaweed") dose: 10-20 ml. after meals and at bed time

Inflammatory Bowel Disease (IBD): Crohn's (CD) and Ulcerative Colitis (UC)…What/How

- **Progressive cascade of inflammation** involving (up to) the full thickness of the bowel wall:
  a) Crohn's: anywhere from mouth to anus
  b) Ulcerative colitis: large bowel
- Outside the gut: anemia from blood loss, arthritis, skin and eye inflammation

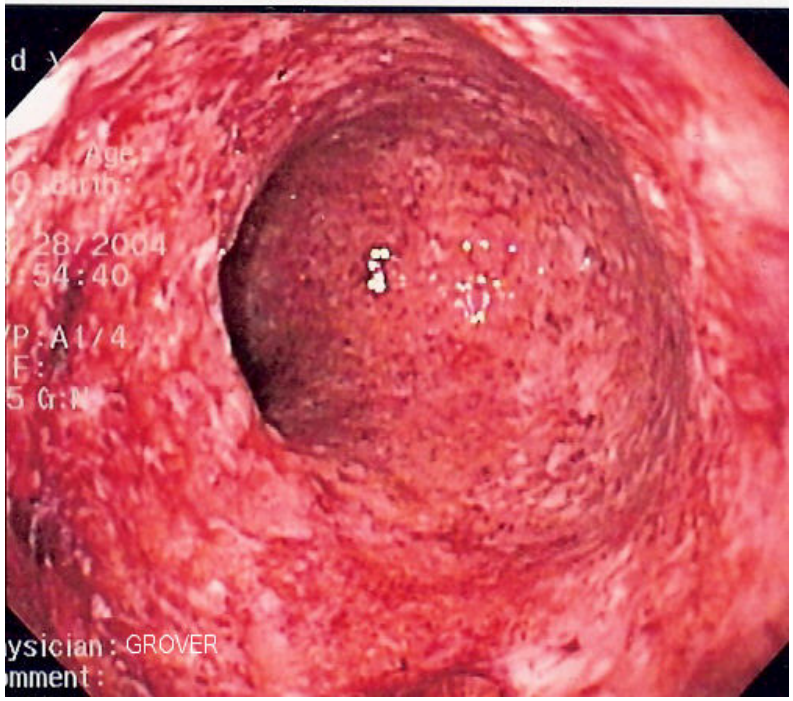


Image: Wikipedia

In IDB does the body attack itself?

- Not really…not without “external trigger”
- Body’s immune system needs to be **triggered first by external factors** such as microbial infection…then body’s response to that microbial infection is (mis) directed towards attacking bowel wall
- **ASCA is antibacterial antibody** and is elevated in Crohn’s (35-50% CD: IgA vs. under 1% UC; 50-80% CD: IgG vs. 20% UC)
- **pANCA is an antibody to white blood cells** (70% of UC have pANCA vs. 20%of CD [these CD folks have disease mostly limited to large bowel])

How severe? Tells you how to treat

- UC or Colonic CD: colonoscopy
- Small bowel: CT or MRI
- Younger people: 20-30 CT's is too much radiation so MRI is better (but takes longer and costs more)

Usual Course of IBD…depends

- How severe, how extensive?
- Genetics
- Smoking Cessation**
- Stress Reduction*
- Vitamin D*
- Adequate Sleep*
- 50% few/mild relapses
- About 30% CD stricture/abscess; UC hemorrhage, colonic perforation

CD…(can be transmural) penetrates the whole thickness of bowel wall

- Usually lesions stay where they presented
- 50% just have slight chance to progress---don’t over treat! (With too much steroid)
- But 30%: quite aggressive…can penetrate through bowel wall: fistula/abscesses and narrows bowel forming **strictures**
- **KEY: treat with aggressive immune modulators before irreversible damage to bowel wall**

UC…disease of mucosa or “inner lining” layer of bowel wall

- Usually progresses “up” from where first diagnosed…after 20 yrs. pan-colitis (whole colon involved) 50%
- Diagnosis can change rarely to Crohn’s (inflammation goes deeper into bowel wall) in 5-10%

More severe: new possibilities:

- **First achieve remission**: steroids
- **Then MAINTAIN steroid-free remission**:
- 1) **Immunomodulator** like Azathioprine (inhibits DNA and RNA synthesis so fast replicating cells such as T and B white blood cells are reduced)
- 2) **Anti-TNF** like Infiximab (an antibody that binds TNF-alpha [which is a key part of the autoimmune reaction])
- 3) **Anti-Integrin** like Vedolizumab (binds to integrin which is like lymphocyte glue….result: less inflammation in the gut) thanks to Dr Andrew Lazarovits @ U. of Western Ontario
  or Anti-Interleukin 12/23 like Ustekinumab (IL12 and IL23 are proteins that regulate the immune system and immune-mediated inflammatory disorders

Celiac: What?

- Chronic, small intestine, immune-mediated

Attack of gut lining cells

That is precipitated by dietary gluten

In genetically predisposed individuals

Small Intestine: especially **duodenum**

Celiac: How?

- **Gluten** is a protein in wheat, rye or barley…and sort of in oats (often contaminated and some have cross-reactivity)
- **Gliadins** are wheat peptides (mini-proteins)
- **Secalins** are Rye peptides
- **Hordeins** are Barley peptides

Avenins are Oat peptides and they are similar to gliadins, secalins and hordeins

Celiac: How

- Pizza---stomach---gliadin
- Duodenum: gliadin is bound to secretory IgA in the mucosal membrane…Marshall is called
- Marshall: “I’m gonna get my buddies (immune cells) to destroy you!”……NOPE!
- Instead…**IgA-gliadin** is bound to **Transferrin receptor (overgenerous welcoming committee)** that takes the IgA-gliadin through the gut liner cells (enterocyte) and into the lamina propria (sacred deep space)… “You ain’t welcome here!”

Celiac: How?

- IgA-gliadin (smuggled by tranferrin factor) into lamina propria (sacred deep space where it ain't got no right to be)
- Gliadin has an amide group busted off and **de-amidated gliadin** is eaten by macrophages and then burped up on a *specific serving platter*…Celiac has too many HLA DQ2 or HLA DQ8 serving platters!

Celiac: How?

- T helper cell (CD4+ T cells) “let me take those **de-amidated gliadin** varmits off the serving platters …but T helpers
- 1) release cytokines like interferon gamma and tumor necrosis factor that hurt the small intestine liner cells…and
- 2) stimulate B cells to pump out more IgA anti-gliadin antibodies, **anti-transglutamidase antibodies (anti tTG) and anti mesial antibodies (EMA’s)**…**(diagnosis [if severe])** ….and
- 3) NASTY! Attract T Killer CD 8+ cells: attack and destroy inflamed cells (that line the gut!)

Celiac-usual course

- On average: symptoms (bloating/diarrhea/slow to grow) 4-10 years before diagnosed; for each case 50 are undiagnosed
- BUT>>>Most new diagnoses present with non gut symptoms: Calcium (and Vit. D not absorbed enough): osteopenia (thin bones) / pathologic fractures/ and Secondary hyperparathyroidism, bleeding disorders and anemia, neuropathy (pins and needles and numbness) or ataxia (anti-tTG attacks cerebellum), edema, skin rash (anti-tTG deposits in dermis) , infertility, periods stop (amenorrhea)

Celiac diagnosis

- REQUIRES 1) biopsy from distal (lower) duodenum and 2) antibodies: anti-tTG or EMA (or IgA to gliadin)

Celiac: how to treat?

- Strict adherence to gluten-free diet (wheat, barley, rye and initially oats)
- BUT 3X cost of regular diet and gluten free not fortified so thiamine, folate, B2, niacin are low
- Treat nutritional deficiencies: iron, calcium, folate, vitamin D, vitamin B12, zinc, copper
- Check bone strength (bone mineral density)

Celiac “take homes”…underdiagnosed!

- Consider diagnosis with diarrhea/bloating family history BUT
- Osteoporosis, arthritis, infertility, fatigue, constipation, thyroid, skin and neurologic disease
- TTG IgA is best initial test
- Diagnosis: TTG or EMA, *and* positive biopsy…if eating full gluten diet (x 2 weeks+) …increases chance of detection

Allergy: What

- An *immediate* (within minutes) IgE-mediated *reaction to molecules called antigens that are from outside your own body*
- Can be mild (atopy-stuffy nose, skin easily inflamed by irritants, minor occasional hives)
- But can be severe: life threatening anaphylaxis (where epipen needed)
- *Allergen* = an antigen that causes an allergic reaction

Allergy: What

- React to allergens from…
- What *we touch* (latex, certain chemicals in soaps or lotions)
- What *we eat* (certain foods or medications)
- What *we breath in* (pollens, dust, mold, animal dander)
- What is *injected* (bee sting)
- Excellent resource: https://www.osmosis.org/learn/Type_I_hypersensitivity

Food allergies

- More common allergens: peanut (only 20% ever outgrow this), shellfish, tree nut, milk , egg, wheat
- If have fatal food anaphylaxis…70-100% also have asthma (asthma is a big risk factor)

Allergy: How (do we get all that IgE?)

- Often **have genetic** predisposition (for T helper cells) to over-react to allergens
- **Part one *"Sensitization"* initial exposure to allergen**: dendritic cell or macrophage grab the allergen and migrate to lymph nodes where they 1) Make a surface co-stimulating molecule on their surface and 2) Present allergen on a platter to "naïve" T helper cells
- once naïve T Helper has bound to antigen and co-stim. molecule it has been "primed"…then it releases IL-4
- Which tells B cells to quit making IgM and instead**, make IgE specific to the allergen**
- These specific IgE antibodies also like to bind to Mast Cell Fc episilon receptors and gear up this mast cell (and other basophils) for combat (release of tons of toxic chemicals) sensitized mast cells (to the allergen)

Allergy

- **Then part two**: (can be dangerous) Subsequent exposure to same allergen…**BUT** now have: 1) sensitized mast cells and basophils (histamine and toxin factories) and primed T helper cells
- Allergen binds to IgE on sensitized mast cell…releases pro-inflammatory mediators: 1) histamine (H1 receptors in bronchi…contract, and dilates blood vessels [edema and hives]), 2) proteases, and 3) chemicals that activate eosinophils…result: swelling, inflammation++, brochospasm

Allergy= overproduction of IgE by Atopics

- Allergens (Inside: dust mite, cockroaches, rodents, pets, certain foods or Outside: mold spores or plant pollens) cause minor responses in non-allergic people, who make IgG, but atopic people respond by making 1000-10000X the amount of IgE
- E.g. **first** exposed to pollen…make large amounts of IgE specific to that allergen; IgE attaches to Mast Cells…**subsequent** exposure=Mast Cell (and basophil) degranulation…immediate symptoms
- Then cytokines from helper T cells (IL-5) "tell" bone marrow to make +++eosinphils, which migrate to the area and cause more inflammation.
- Atopics produce IgE (not IgG) because their helper T cells are type 2 (Th2) and secrete IL-4 and IL-5* in response to allergen; then…
- Allergen-specific B cells produce IgE not IgG**
- *production of IL-4 and IL-5 is blocked by steroids
- ** allergy shots increase the ratio of IgG/IgE

Allergy: anaphylaxis treatment

- Give into the muscle (I.M. Intramuscular) NOT subcutaneous
- **Lie down**…mid outer thigh
- Dose: 0.01 mg per kg up to 0.5 mg of 1mg per 1ml. Adrenaline
- **12-36% need a 2nd dose so use Epipen Dual Pack**
- O2, I.V., H1 Antihistamine within 30 min, glucocorticoids x 24-48 hours
- No Beta blockers!! Even eye drops!

Allergy: desensitization treatment

"tells" allergen-specific B cells to make IgG not IgE

- (New: sublingual under the tongue for ragweed and dust mite…**not reliable**)
- Does increase tolerance to allergens
- Common: dust, ragweed, grasses, cat dander, pollens
- **Not** if using beta blockers or ACE inhibitors or pregnant or immune deficient
- If maintain 2-3 years 60% less meds and symptoms
- Dr. Des Horan: "best Allergists have ++questions not that many tests"

Sleep Apnea: what is wrong

- Esp. when *very* relaxed (REM + slow wave sleep) muscles relax enough that airway is no longer "splinted open" by muscle tone…**"obstructive"**
- Low oxygen (and /or high carbon dioxide) caused by inadequate air exchange is not detected by (brainstem chemoceptor) receptors well enough for them to "tell" the adjacent "wake up" (reticular activating) center to rouse the person…**"central"**

Sleep apnea: causes, symptoms, how bad?

- **Obstructive:** small jaw, big tonsils, reduced muscle tone in pharynx
- **Central:** reduced serotinergic nerve receptors in brainstem
- Symptoms: snoring, daytime sleepiness, morning headache, witnessed apnea, Choking or gasping during sleep
- Apnea Hypopnea Index= number of respiratory obstructive events that happen for each hour of sleep (**AHI** Important #!!!)

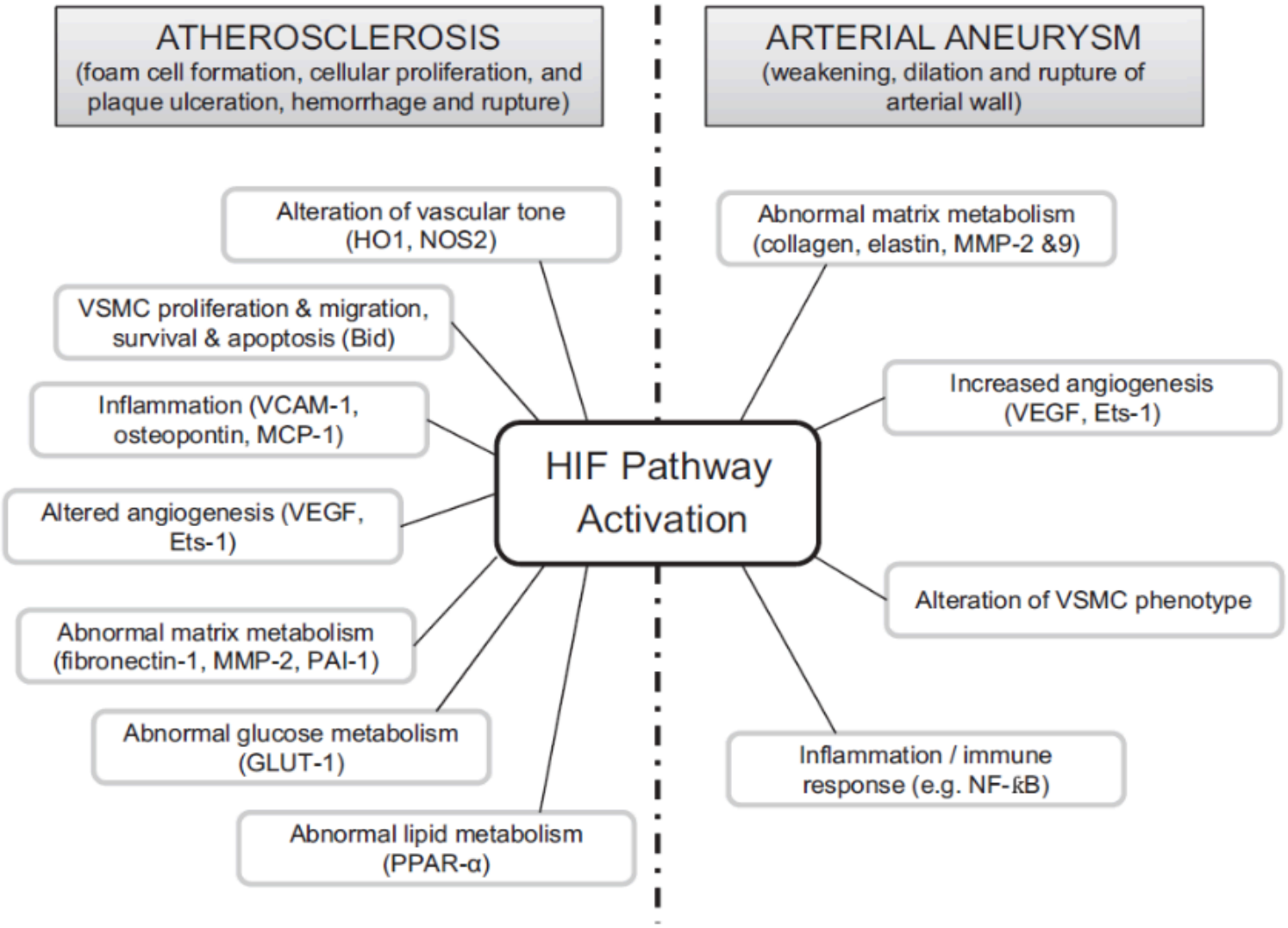
Sleep apnea: assessment

- **Q: Home sleep study or polysomnogram (hosp)?**
- **A: home only if it can give you information about your sleep…?Restless Legs???***
- **Mild: AHI 5-15 events per hour**
- **Moderate: AHI 15-30 events per hour**
- **Severe: AHI 30-120 events per hour (30 is sure not 100!!)**
- **How long do you spend with oxygen saturation less than 88%?...over 5 minutes is a risk factor for coronary artery disease.**

Sleep Apnea: why does low oxygen cause problems?

- Increases Hypoxia-inducible factor 1 alpha (HIF-1 alpha)…leads to increased chance of:
- Stroke, heart attack, death from stroke
- Atrial fibrillation and ventricular tachycardia
- Higher blood pressure, higher sympathetic tone, venous thromboembolism (DVT and PE)
- Short term memory impairment, mood disorders, work: more accidents and lower performance
- Accelerated cancer growth/malignancy

*Dr James Mojica *Obstructive Sleep Apnea* 2017 Int Med Comp Rev



Lim CS et al. *J Vasc Surg* 2013; 58: 219 - 230

Sleep Apnea treatment

- Obese (or not) *and methadone*: TEST THEM
- Fitness to drive can be a useful “convincer”
- ~~Tennis ball in middle of back~~
- Oral appliance to bring jaw forward: can destroy teeth but might help thin patient with **mild positional OSA**; treatment failure 40%
- (**C**ontinuous) **P**ositive **A**irway **P**ressure CPAP masks are best treatment for moderate to severe OSA: reduce death and cardiac events
- Variety: total face, just nasal or mouth and nose masks
- Goal: AHI less than 5

Sleep apnea: **what should we do about it?...two of my patients**

- **Ryan with Autism: *very*** gradual introduction to CPAP mask…20 lbs. lighter, Fewer "PRNs"
- **My friend the lady surgeon: "I was so cranky I took everything out of her (my 11 yr. olds) room when she talked back to me *again.*"** **…**CPAP, 35 lb. weight loss, better mood, more endurance at work
- Why I get excited: **(way) less cardiac rhythm problems**

Sleep apnea…honesty from a doc

https://www2.gov.bc.ca/gov/content/transportation/driving-and-cycling/driver-medical/driver-medical-fitness/driver-medical-fitness-information-for-medical-professionals/quick-access-to-chapters-and-medical-conditions/18-sleep-disorders#18.6.1

- Very hard to get someone to use mask if they are bound and determined not to
- Fitness to drive: Confirmation whether condition is treated or untreated
  - **If untreated**: an assessment from a sleep specialist or respirologist confirming that AHI is < 20
  - **If treated**: confirmation that treatment is successful
- History of sleep at the wheel within the past five years
- Opinion of treating physician whether the driver understands the nature of the condition and the potential impact on driving: (will they report if they get sleepy at the wheel and will they pull over?)