FASD is a Whole Body Diagnosis, Part 2: Rheumatoid Arthritis, Asthma, Immune Compromise, Dementia and Prevention of Diabetes and Cardiovascular Disease

(Sleep Apnea moved to part one)

Rod Densmore, M.D.,

Father of an adult who has FAS

SESSION B6 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*

Motivation one: Myles', CJ's, Emily's Health Survey (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 ?
Asthma	8.3%	**36%**	4x
Dementia (early)	0.0086%	0.9%	**104x**
Heart Rhythm (SVT)	0.2%	5.7%	**27x**
High Blood Pressure (Ages 18-44)	8%	16%	2x
Rheumatoid arthritis	0.6% (*too low)	6.6%	**11x**
Sleep Apnea	2.4%	**15.2%**	6x
Restless Legs syndrome	10%	**18.5%**	2x
Chest Infections	**23.6%**	**41.9%**	**2x**
Sinus Infections	12.5%	34.4%	3x
Adult Chronic Ear Infections	0.25%	**36.7%**	147x

Motivation two: Longitudinal care of patients with FASD

- Everett: 36, lost custody of kids, Diabetic…diet compliance issues, Heart attack at 38, cholesterol high, walk alongside/encourage/never give up…step kids thriving…entrance scholarships U of A engineering
- Chloe: 27, 340 lbs., medication compliance issues, refusal of weight loss surgery, Diabetic x 3 yrs., blood sugar 26!...hospitalized, fixed dental caries… “I got a B”….circadian sleep issues…motivation and concentration…quit ecstasy 6 yrs. ago…way to go!

References 1

- My notes from: Internal Medicine Comprehensive Review and Update, Harvard Medical School, Boston, June 2017
- UpToDate Medical Reference, January, 2018
- Hopkins Arthritis:https://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-pathophysiology-2/
- More references are listed at the end

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

Rheumatoid Arthritis (RA): What is wrong?

- Chronic , progressive joint inflammation
- Exact cause unknown, but **many** factors influence disease progression (just wait!)
- *If untreated* can cause pain and **joint destruction**
- **D**isease **M**odifying **Ar**thritis **D**rugs (DMARDS)
- Most common inflammatory arthritis (lifetime risk males 1 in 59, females 1 in 28)

Rheumatoid Arthritis (RA)

- The mother (and father) of chronic autoimmune inflammation-mediated diseases!

Autoimmune Disease (5%)

- Every T and B (white blood) cell needs to attack pathogens but—even if “armed and dangerous”– it must also be able to tolerate exposure to the self (not attack self)
- “Disease” happens when tolerance–inducing mechanisms fail to eliminate self-reactive “armed and dangerous” T and B cells.

Autoimmune disease requires (all 3):

- 1) your cell membranes must have a type of **M**ajor **Histocompatibility C**omplex (MHC) that can present a self-antigen
- 2) you need to have T (and B) cells that have receptors that recognize that self-antigen
- 3) there must be environmental factors *(like an infection*) that cause a **breakdown in the tolerance mechanisms** that are supposed to eliminate self-reactive lymphocytes

*“Like an infection” theory of molecular mimicry

Sompayrac L. 2016. How the Immune system works 5th Ed. Chichester, U.K. Wiley Blackwell

- Suppose a genetically susceptible person is *attacked by a microbe that *activates T cells *whose receptors just happen to cross react with a *self-antigen
- Simultaneously an *inflammatory reaction takes place in tissues containing the self-antigen
- This inflammation *activates antigen presenting cells to *re-stimulate those self-reactive T cells
- And the inflammation in these tissues also causes *changes to (the MHC part) of cell membranes making those cells even better targets for destruction by killer T cells

RA: how does it develop?

- (Suppose a genetically susceptible person is *attacked by a microbe that *activates T cells *whose receptors just happen to cross react with a *self-antigen)
- Microbe: mycobacterium tuberculosis
- Self –antigen: a protein found in cartilage
- A type of IgM antibody that binds IgG antibodies is common in the joints in RA
- Self-reactive “helper” T cells attract ++++macrophages into the joints
- IgM-IgG complexes activate joint macrophages…these release mediators esp. tumor necrosis factor (TNF) which cause joint inflammation++++

*RA: How does it develop?
1) ***Predisposing*** Factors

- Females: **Estrogen** inhibits T suppressor cells and increases T helper cells function; estrogen receptors are on synovial cells and memory T cells; Males with RA often have lower levels of testosterone and the androgenic hormone DHEA
- **Genetics: 1) Human Leukocyte Antigen (HLA)** with specific binding areas (to antibodies) called **DR-beta *0401, etc.**; 2) parts of the gene (SNP's) that code for TNF promoters, and 3) SNPs that relate to T-cell activation

RA: How does it develop?
2) ***Environmental*** developmental factors #1

- Cigarette **smoking** (esp. with "DR.."HLA type)…**length of time** smoking links to increased risk of disease and more severe disease
- ?bacterial infection "triggers" (TLR's) **Toll-like receptors (esp. TLR-3 and 4) which are found in inflamed synovium**; TLR's stimulate antigen presenting cells…which increase immune response and leads to inflammatory mediator release
- **Gum disease** (esp. with "DR.."HLA type) bacteria makes "citrullinated peptides"…breaks tolerance to similar peptides…**(Anti-CCP)** anticitrullinated peptide antibodies: damage our joints and are a diagnostic test

RA: How does it develop?

2) ***Environmental*** developmental factors #2

- Gut microbiome…early days but increased Prevotella copri and reduced bacteroides were seen in new-onset untreated RA
- Viral infection trigger? E.g. Epstein Barr (Mono)
- “Super antigens” (staph endotoxin) *and*
- “Heat Shock Proteins” (heat, infection, injury) can **activate 10% of our T cells! (1000X HLA cell surface antigens)**

RA: How does it develop?

2) *Environmental* developmental factors #3

- Autoantibodies: Rheumatoid Factor (RF) in 60% and **anti CCP** in 80% newly diagnosed…and 18-30% ***1.5 yrs. prior*** to diagnosis
- Occupational exposure: silica, “World Trade Center Dust,” electrical work, wood work, asbestos
- Obesity significantly increases RA risk
- Possibly PTSD and Atopic Dermatitis are also associated with increased RA risk

RA ***differential diagnosis***: get ye to a rheumatologist!

- Viral Polyarthritis: e.g. **Hep B or C**, Rubella, Flu
- Crystalline arthritis esp. pseudogout
- Lyme disease but this is usually a monoarthritis
- Systemic rheumatic diseases e.g. Lupus, Schleroderma, Polymyalgia, Sarcoidosis, Sjogren's
- Fibromyalgia
- Osteoarthritis

Zhang, X., et al. 2011. **Prenatal alcohol exposure (PAE) alters the course and severity of adjuvant-induced arthritis in female rats.** Brain Behav. Immun. (2011), doi:10.1016/j.bbi.2011.11.005

- **Background:** children with FASD have **impaired immunity**—e.g. increased incidence of bacterial infections, lower eosinophil, neutrophil and gammaglobulin levels **and reduced mitogen-stimulated increases in leukocytes.** Rodent models of FASD are similar; also, their immune deficits are **exacerbated by chronic intermittent stress**.
- **Observation:** Increased TNF-alpha, IL-6 and IL-1Beta levels in prenatally alcohol–exposed (PAE) rodents versus controls
- **Result:** PAE females had a more prolonged course of disease and greater severity of inflammation compared to controls. Also, PAE females showed immune changes before any clinical signs of disease were apparent
- **Conclusion:** prenatal alcohol exposure has both direct and indirect effects on inflammatory processes, altering both immune and HPA (STRESS AXIS) function, and likely, the normal interactions between these systems.

RA: *environmental* developmental factors… “Take Homes”

- Cigarette smoking…MAJOR risk factor
- Obesity…significant risk factor
- Gum disease…regular dental hygiene
- Gut Microbiome: Buttermilk
- Avoid asbestos, silica, maybe wood, electrical
- Treat significant ongoing stress/PTSD
- Avoid significant infections (~~super antigens~~)…vaccinations

RA Treatments #1: Vaccines (generalities…**see doctor/ infectious disease specialist before using vaccines)**

- **No *"live"*** vaccines: (smallpox, measles/mumps/rubella, chickenpox, influenza nasal spray, rotavirus, zoster/shingles ("old vaccine"), yellow fever, polio, BCG for TB)
- Yes: Pneumococcal, Intramuscular Influenza, Hepatitis B, Human papilloma, zoster ("new vaccine [that needs 2 doses]) **ONLY if not** using certain biologic drugs (such as infliximab, abatcept and others…**SEE DOCTOR)**

RA Treatments #2:

- Early disease: methotrexate ***unless*** 1) wants to/ or is likely to get pregnant (men too) and/or 2) cannot have ONE or less alcoholic beverages per week (liver toxicity)
- Sulfasalazine is alternative (same action as Methotrexate: decreased cell proliferation and decreases T cells)
- Moderate disease: methotrexate (40%)…need more?...do TB test then add tumor necrosis factor inhibitor (TNFi) e.g. entanercept…need more: newer biologic such as abatacept (blocks T cell activation), rituximab (anti- B cell) or tocliizumab (antibody that binds to interleukin 6 receptor)

RA Monitoring… Watch for:

- Malignancies: *Increased* Lymphoma, Hodgkin's, Lung **esp. with smoking**; *less* Breast, Colon
- Infections: especially with newer therapies
- Heart Disease: especially young women!
- Treatment (with anti-inflammatory agents: methotrexate, TNFi, etc.) reduces Diabetes risk
- Osteoporosis: 30-40% increased hip and other fracture related to osteoporotic bones

RA: “ but these DMARDS have side effects”

- Prognosis without treatment… **after 10 years**: some muscle wasting and loss of range of motion; shortened life expectancy 3-7 years (same as Hodgkin’s, Diabetes, Stroke)
- Prognosis without treatment… **after 20 years**: more than 80% severely disabled (pre-methotrexate) and 33% mortality

Asthma: What is wrong?

- ***Variable*** obstruction of airways**;** airways are hyper-responsive to irritants…airways contract
- **Symptoms:** intermittent wheezing (beware: lack does not exclude), cough…esp. at night, shortness of breath, chest tightness
- **Triggered by**: exercise, infection, dander, smoke, dust, mold, pollen, weather change, emotion, menstrual cycles.

Asthma: How does it happen?

- Genetic predisposition to develop specific IgE antibodies versus common environmental allergens (Atopy) is strongest risk factor
- There are several types of asthma and each has its own mechanisms:

*Asthma types

- Allergic asthma: family history of eczema, seasonal allergies, eosinophils+++, inhaled corticosteroids work well
- Non-allergic asthma: polys++, steroids less helpful
- Late onset asthma: esp. women, steroids less helpful
- Asthma with fixed airflow limitation: due to remodeling
- Asthma with obesity: stomach bypass can improve asthma control

Asthma: How does it happen?

- Early…(minutes) **Immediate hypersensitivity reaction**: Mast cells detect and then release histamine, prostaglandins and leukotrienes which contract airway smooth muscles.
- Later…(several hours later) **late phase** response is due to influx of **innate** immune cells (monocytes, dendritic cells and neutrophils) and **adaptive** immune cells (helper and memory T lymphocytes, eosinophils and basophils)…mediators released cause airway muscle constriction and airway wall inflammation

Narrowed airway by half…

- **Reduces FLOW** of air by?
- 30%
- 50%
- 80+%

Flow is related to radius to the 4^{th} power…
So, 1/2 the radius gives $1/16^{th}$ the flow!!!

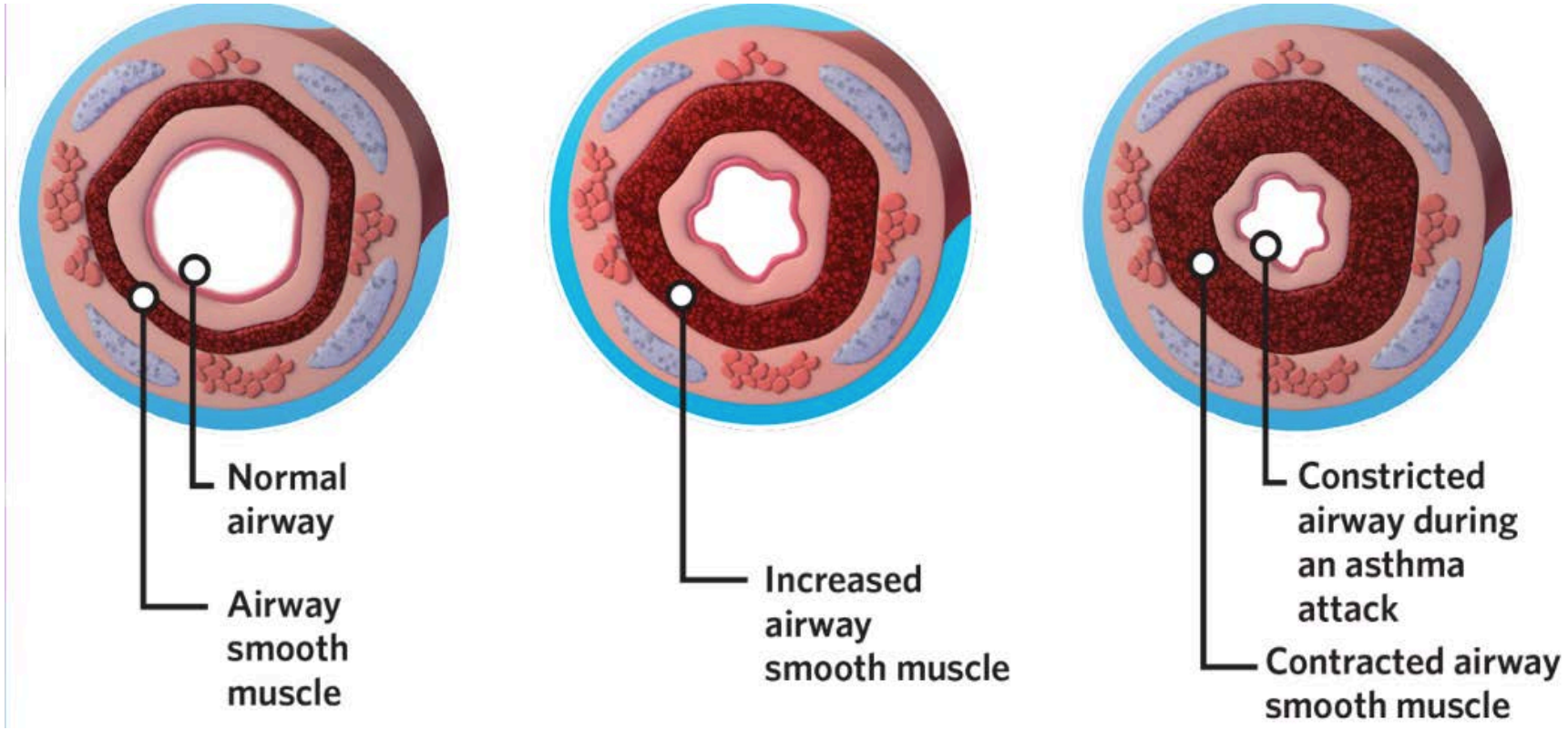


Image: http://www.bostonscientific.com/content/dam/bostonscientific/BT/general/bt_asthma_airways-hd.png

Asthma: **How does it happen?**

Pathogenesis of asthma. Liu M. 2018. UpToDate Medical Reference

- Physical barriers: skin, membranes e.g. airway epithelial cells have Toll-like (TLR 4) receptors- they recognize lipopolysaccharide [gm. neg. bacteria *and dust and dander*] then release allergy cytokines e.g**. IL-5, 13**, 25, 33, TSLP, which in turn activate:
- Innate lymphoid cells Type 2 to make **IL-4, 5, 13**, which:
- Activates **eosinophils** to release TGF which causes airway smooth muscle to contract
- Dendritic Cells and Macrophages present antigens to T helper lymphocytes which make **IL-3** that activates basophils to release IL-4 and IL-13 which cause smooth muscle contraction and IL-5 which further activates eosinophils.

Asthma: **How does it happen?**
Activated Mast cells:

- **Early:** pre-formed mediators released (minutes) e.g. histamine, TNF: edema, airway constriction
- **Later:** Induced production of cytokines and chemokines (hours): increase inflammation and recruit more inflammation cells to the airway

Newer $$$$ treatments

cytokine	mechanism	drug
IL-5	Regulates eosinophil production in the bone marrow and survival	Antibody vs. IL-5: e.g. reslizumab
IL-13	Deposits eosinophils in the airway, mucous gland overgrowth, fibrosis (scarring) of the airway OUCH!	Antibody vs. IL-13 lebrikizumab
IL-4	Makes uncommitted T cells into T helper cells (which activate basophils and cause airway muscle contraction), switches B lymphocytes from making IgG and IgM to IgE, and releases VCAM that attracts more eosinophils, basophils and T cells	Antibody vs. IL-4 that reduces both IL-4 and IL-13 is dupilumab

Asthma: **what will become of me?**

- **Risk is subclinical progression**
- Monitor lung function test every 2 years **minimum**
- **Self-perception is spectacularly impaired!**

Asthma: what will become of me?

One or more of these **risk factors** increases risk of flare **even if symptoms are well controlled**

- Uncontrolled symptoms
- Frequent use short acting beta agonist (Salbutamol)
- Poor compliance/technique (use “aero chamber!”)
- FEV1 less than 60% predicted
- Smoking/allergic exposures
- Obesity/Sinusitis/Food allergy
- High eosinophil count in sputum or blood
- Pregnancy
- Psychological/ socioeconomic issues
- History of Intubation/ ICU
- Over one severe flare in last 12 months

Asthma meds

QUICK RELIEF	EXAMPLE	LONG TERM CONTROL	EXAMPLE
"Rescue" Short acting B2-agonists (SABA)	Salbutamol	Oral steroids (OCS) and inhaled steroids (ICS)	Prednisone Fluticasone (Flovent) Budesonide (Pulmicort)
Anticholin-ergic	Atrovent	Long-acting beta-agonists (LABA)…MORE NEXT SLIDE	Fomoterol (Oxeze)
		Long acting muscarinic agent (LAMA) (blocks muscarinic receptor)	Tiopropium (Spiriva or Respimat)
		Combination ICS and LAMA	Budesonide/fomoterol (Symbicort)
		Leukotriene Modifiers (LTRA)	Monteleukast (Singulair)-if exercise induced and allergic
		Methylxanthines	Theophylline

Newest: antibodies such as Omalizumab (binds free IgE) , Mepolizumab or Reslizumab (antibody to IL-5…suppresses eosinophils)

Sorry I ***hate*** acronyms too: LABA

- (LABA) long acting beta agonist such as ~~salmeterol in advair~~ (kind of slow) or fomotorol (quite fast) in symbicort
- LABAs are really helpful: they act on B2 receptors to relax smooth airways muscles for 12 hours
- Reduce release of inflammatory mediators from mast cells
- Use LABA **WITH ICS** and **only** for moderate to severe asthma that remains uncontrolled
- ~~Salmeterol~~ if African American or African Canadian

Asthma: “but I don’t want steroids”

- Improves Quality Of Life, prevents hospitalizations and death
- Reduces need for short acting beta agonist
- Improves symptoms and lung function tests
- Most effective long term control medication
- Minimal absorption but can suppress HPA
- Ciclesonide (Alvesco) is pro-drug that is converted to steroid in the lung…**very** small amount of free drug outside the lung

“Triad”…remember Leukotriene Modifiers (LTRA)

- 1) Nasal Polyps
- 2) ASA or NSAID (like ibuprofen of naproxen) sensitivity(triggers asthma)
- 3) Asthma
- **Use Monteleukast (Singulair)**

Asthma: treatment

- Canadian asthma guidelines (2012): http://www.rxbriefcase.com/info/email/CTS2012_guideline_update.pdf
- Remember: avoid: beta blockers (even in eye drops!!), sulfites, dust mites, mice, cockroaches, dander, smoke
- Flu shot (annual) and pneumonia shot--Pneumovax 23 (ask physician how often…probably every 10 years)

*Intermittent Asthma: lowest risk

- **As needed short acting beta agonist for:**
- Symptoms or SABA use less than twice a month
- No night time symptoms (awakening/ cough/ shortness of breath)
- No risk factors or flares for over 12 months

Asthma: mild

- Low dose inhaled steroid plus “as needed” short acting beta 2 agonist is reasonable if:
- Asthma symptoms are infrequent but has **one or more risk factor**
- Asthma symptoms are **2x per month to 2x per week**
- **Night** time symptoms (awakenings) more than once a month

Moderate Persistent Asthma

- Any of: Daily symptoms of asthma, daily need for SABA rescue meds, nocturnal awakenings more than once a week, some limitation of normal activity…needs:
- Low dose ICS with long acting beta agonist (LABA) (Symbicort or ~~Advair~~) plus SABA rescue as needed, **or**
- Low dose ICS plus LTRA or (theophylline…NOT COMMON)

Severe Persistent (Poorly Controlled) Asthma

- Symptoms throughout the day
- Nocturnal awakenings nightly
- Recue SABA several times a day
- Extreme limitations of activity…needs:
- Medium dose ICS/ LABA or
- High dose ICS plus LTRA or Theophylline
- **Add tiopropium (Spiriva)** which is a long acting (once a day) antimuscarinic

*Asthma and Depression?

Dr Ghanshyam Pandey. Deconstructing the Neurobiology of Depression: Central and Peripheral **Immune Markers in Depression and Suicide.** American Psychiatric Assoc Meeting. Atlanta 2016

- Youth hospitalized for severe asthma had a significantly elevated risk of suicidal behaviour
- ? Link between marked immunological abnormalities of asthma and suicidal thinking
- Other studies: Increased TNF alpha, IL-6, IL-1 *and* the mRNA that helps produce 1) these inflammatory cytokines *and* 2) their receptors
- “Target: anti-TNF (too toxic but works in treatment resist. depression) … Toll-like receptors are a better target…TLR’s are up regulated in depression and then they make excess cytokines. TLR-3 is on neurons, other TLR’s are on microglia and glial cells. Inc.TLR-3 and 4 in depression and suicide.

Types of Immune Compromise

- Immune **Under**-reaction to **external** threats like bacteria and **internal** threats such as cancer cells leads to **infections and cancer**
- Immune **Over**-reaction to **external** allergens leads to **allergies** and to **internal** allergens leads to **auto-immune diseases**
- 3 Key Factors in balance for optimal immunity: 1) tolerance (of self), 2) recognition of potential infection or cancer, and 3) efficient clearing of pathogens

Infections in FASD

- Chest and sinus infections are 2-3 x more common and chronic ear infection in adults is reported to be over 100x more in FASD common (Himmelreich M, et al. 2017)
- Chronic or recurrent otitis media in FASD: 77.3% (Popova S, et al. 2016)
- ***Siblings*** of children with FAS had an increased risk of death due to infectious disease (Burd L. 2004)
- Bodnar, Hill, Weinberg (2016): Kids with FASD have more minor (ear and respiratory) and major (e.g. sepsis) infections; adult animals with PAE have enhanced disease severity of influenza caused by an impaired immune response to that virus

Serious infections in FAS

(Johnson S, 1981…ancient but wow!)

- 5/13 pneumonia, 2/13 meningitis, 1 sepsis
- **GET pneumonia and meningitis and H Flu shots**
- **ANY DOC, ANY LAB can easily check these***

Same versus age-matched controls	Impaired /different versus age- matched (also IUGR) controls
Absolute neutrophil* and lymphocyte* counts	**Marked eosinophilia***
Total hemolytic complement	More likely to have abnormal **gammaglobulins ***
Tests of delayed cutaneous sensitivity	Decreased E rosette-forming Lymphocytes
Nitroblue, tetrazolium dye reduction assays	Lower EAC rosette-forming lymphocytes
	Diminished mitogen-induced stimulation responses to mitogens (phytohemagglutinin, concanavalin A, pokeweed mitogen)

Sepsis= a good process gone amuck

Sompayrac L. 2016. How the Immune system works 5th Ed. Chichester, U.K. Wiley Blackwell

- Our powerful immune system is designed to “pounce” on **localized** invaders
- But what if the invasion is “everywhere?”
- E.g. E. coli **in the bloodstream**: this bacterium sheds LPS (lipopolysaccharide)***** from its membrane
- ***** activator ++++of macrophages and natural killer cells of our innate immune system
- Normally, positive feedback loop: activated macrophages and Natural Killer cells “Amp each other up” and destroy **localized** pathogens…but…
- If process is whole body…massive TNF release causes vasodilation, leaking, edema and septic shock

George is “just not right”

- Listless, irritable, low oxygen, no fever, want to get him to doc but he says he is fine and I’m just nagging
- Immune system in 40 yr. old with pneumonia: hot and cold, sweaty, fever++, a monkey could dx pneumonia
- George is 70 (or HIV+ve, or Hep C+ve or on steroids {prednisone 5 mg a day] for asthma, or ???FASD????) **and presentation is subtle**…10 days on iv antibiotics and 2 d in ICU…low enough BP from sepsis he is being worked up for cardiac ischemia
- Take home point: **pounce!** If chills//hot and cold: 1) you should have pounced yesterday, 2) maybe you are too late 3) don’t listen to the patient “ I hear I was a bad boy”
- And like George’s wife **have deep index of suspicion…**1)decreased self awareness and 2) blunted immune response even to serious infections means unimpressive symptoms….the edge of the cliff is damn close!!!

Flu:
Mice with PAE have: (McGill et al. 2009)

- impaired adaptive immune responses:
- Decreased virus-specific lung CD8 T cells,
- reduced production of influenza-specific antibody following influenza infection
- **So why don't we be careful to avoid friends with flu and be sure to get a flu shot, and get our families flu shots also**

Cancer in FASD (early days…but some ideas so far)

- Neuroblastoma, ?Rhadomyosarcoma (Burd L, 2014),
- Prostate (Sarkar DK , 2015),
- Testicle (higher % undescended testicles in FASD),
- Breast (Animal data: Polanco et al. 2010; my observations: 2 patients with bilateral mastectomies in their 30's.)
- Cervical* (just observational)
- *But: screening is sensible and easily available, plus unless you check (with mammograms and PAPs) these are almost impossible to recognize early

Cancer 1 (kids under 10)

- Neuroblastoma*: Neuroblasts will mature into neurons of the sympathetic nervous system or adrenal medulla cells or might ***fail to mature and keep growing and dividing**
- Many of us have little clusters left by age 3 months but these eventually die off (immune surveillance?)
- Tumor abdomen, chest, pelvis, neck and/or excessive release of “adrenaline” (sweaty, fast heart beat, diarrhea)
- Plan: Pediatrician/ pediatric neurologist NOW

Cancer 2

- Rhabomyosarcoma* is a malignant soft tissue tumor that can be found in sinuses, on the face, trunk, legs or arms
- Rhabdomyoblasts are cells that mature into skeletal muscle…but if they ***fail to mature and keep growing and dividing**
- Early biopsy of any weird soft tissue masses

Cancer 3 (Men)

- **Testicle:** (higher likelihood of undescended testicles in FASD) if not descended by 4 months it is likely to not resolve: Pediatric Urologist…surgery reduces risk of testicular cancer
- **Prostate:** 1) bribe, 2) rectal exam, 3) PSA…Rod's suggestion: this is not simple: discuss Dr Sarkar's 2015 article with a urologist and plan prevention/early surveillance at least 10 yrs. before family members had a diagnosis or symptoms of prostate cancer
- HPV vaccine (versus high risk HPV16,18)
- "Anal PAP" test if high risk e.g. MSM

Cancer 4 (Women)

- **American Cancer Society:** (See References) Alcohol increases: Breast, Mouth/Throat/Esophagus, Liver, Colon/Rectal Cancers
- **Breast:** alcohol- 1 drink* per day: small increase; 2-3 drinks per day: 20% increase, maintain a healthy weight and regularly exercise (*12 ounces beer, 5 ounces wine, 1.5 ounces distilled spirits)
- Mammograms by age 45 ***if average risk***
- Emerging: MRI (*and* mammograms) if high risk or if "extremely dense" breasts on mammogram
- **Cervix:** HPV vaccine, regular PAP tests, Chlamydia, Smoking, Diet low in fruits and vegetables

Dementia: **What is wrong**

- Alzheimer's: (34%) amyloid deposits and plaques **between** neurons plus tau protein deposits inside neurons
- Vascular dementia (18%)
- Frontotemporal dementia (12%)
- Alcohol-related dementia (10%)
- Lewy body dementia (9%)
- Others (19%)

Dementia: How did it happen?

Dr Alby Elias. **Risk of Alzheimer's Disease in PTSD: Amyloid and Tau PET studies.**
2016 American Psychiatric Association Conference, Atlanta

- Vets with PTSD *also* have impaired declarative memory, fragmented memory with blackouts, impaired vision/taste/**smell, slower processing speed, impaired executive function (trail making, digit span tests), impaired verbal learning**
- PTSD comorbidities: Substance abuse, Anxiety, Depression, Traumatic Brain Injuries also cause cognitive impairment
- 5 years before dementia starts: hippocampal atrophy…a trigger?
- PET scans for amyloid: see it starting 15 yrs. before Alzheimer's is diagnosed. (some early Tau evidence too)
- So far… monoclonal antibodies can clear amyloid at an early stage: Aducanumab (https://clinicaltrials.gov/ct2/show/NCT01677572)

Dementia: **what will become of me?**

Livingston G, et al. Dementia prevention, intervention and care. Lancet 2017; 390:2673

"Intensive risk factor modification"…35% of dementia cases are attributable to a combination of:

- Low education attainment
- High blood pressure in midlife
- Obesity in midlife
- Hearing loss
- Late-life depression
- Diabetes
- Physical inactivity
- Smoking
- Social isolation

Dementia:, **what should we do about it?**

"I run this dairy farm…I want to help dad but I cannot be running back and forth all the time…cows won't get milked!"

- Rule out: Anemia, Thyroid, Diabetes, smoking, EKG (a. fib), BP 130/85, Depression screen, sleep apnea
- Vit D, Vit E, pepper/spicy food, max. 1 drink with dinner, daylight by 10AM, some chores/routines, crib nights with his non-smoking buddies
- **NO gravol**, benadryl, oxybutinin, amitriptyline
- Change rabeprazole to ranitidine and bed tilt
- Donepezil (aricept) helps restore acetylcholine memantidine (ebixa) helps block excess glutamate
- [Atorvastatin highish dose (80 mg), 3000mg of EPA+DHA omega 3]

E.g. Edward with Rosacea

- 49, FASD, shaken baby, in and out of prison till 44
- Rosacea and /or acne and/or retinal inflammation: **minocycline…** (CJM Kane)
- Exercise: a paper route
- Music/fun in a group
- Trazodone (or mirtazepine) for good slow wave (restorative) sleep
- [2700 mg EPA plus **DHA** (3x 900mg)]
- **“I wrote a letter to my landlord!”**
- **“I like my little life”**

So how do we decrease inflammation?

Kendall-Tacket K. 2010 Psychoneuroimmunology of Chronic Disease: Exploring the Links Between Inflammation, Stress, and Illness. Washington, DC: American Psychological Assoc. Press.

- Omega 3's
- Adequate (high quality) sleep
- Exercise
- ASA
- Statins
- Minocycline
- Alendronate and other bisphosphonate (osteoporosis) medications

Prevention of Diabetes: What is wrong

- Diabetes is not enough insulin to pump glucose from the blood into the body's cells
- Type 1 "juvenile" auto-immune attack that kills pancreatic beta cells-beta cells (that make insulin)
- Type 2 "adult onset" anti-insulin factors from fat cells make it hard for insulin to work…then, eventually, beta cells gradually fail and metformin's effectiveness gradually reduces

Diabetes: what will become of me?

http://guidelines.diabetes.ca/fullguidelines

- Prevent “macro-vascular” **heart attacks/angina, stroke, amputations** (sugar control, [ASA], ACE inhibitor or ARB, statin, some new meds)… and
- Prevent “micro-vascular” problems in **retina and kidney** (HbA1c-about 7) “for every 10% decrease in HbA1c there is a 43% reduction in risk!!”…also low amount of albumin in urine (ACR)
- Caveat: Optimal: Blood pressure, Smoking, Cholesterol, Stress reduction/treatment of depression all have **HUGE** risk reduction when patient is diabetic

Diabetes: what should we do about it?

- **Type 1: basal plus short acting insulin or short acting in an insulin pump**
- **Type 2: early lifestyle and metformin aggressive intervention…add basal insulin and/or sulfonylurea if HbA1C above 7…and if you still cannot get to 7…see:**
  And You Thought LAMA's Were Bad!
- **BASAL INSULINS:**

Type	Generic names	Company names
Intermediate (1-2x daily)	NPH	Humulin N, Novolin N
Long acting (1x daily)	Glargine	Lantus
Long acting (1xdaily usually)	Detimir	Levemir

And You Thought "LAMA's" Were Bad!

Add-on drugs (to basal insulin and metformin) ***in Type 2 DM***

Drug type	Generic e.g.	Comments
Biguanide	metformin	Reduces liver glucose output; not OK if poor kidney /liver function; diarrhea in some can be intolerable
Sulphonylurea	Gliclazide and glimepiride	But: weight gain, NOT if Asian because high % **hypo**glycemia (esp. glyburide)
Glucagon-like peptide (GLP)-1 agonists	$$ Liraglutide +6	Stimulates insulin secretion, weight loss (reverse insulin-caused wt. gain) 1x daily injection; **reduces cardiovascular mortality,** no if pancreatitis history
DPP 4 Inhibitors	$$ Sitagliptin +3	By mouth, but only reduces A1c by 0.6% but easy to use, e.g. elderly and cannot tolerate metformin
Sodium glucose co-trans-porter 2 inhibitors (SGLT-2)	Empagliflozin +2	Inhibit glucose reuptake in kidney, some weight loss**, reduces cardiovascular mortality** esp. men
~~Thiazolidnediones (TZD's)~~	~~1 pioglidazone 2 rosiglitasone~~	BUT: 1) bladder cancer, 2) cardiovascular harm

Insulin pumps (**type 1 DM** treatment)

Dr. Steven Russell www.bionicpancreas.org New technology: 5 yrs. from now: radical changes in how Type 1 is managed… **"you will not recognize it"**

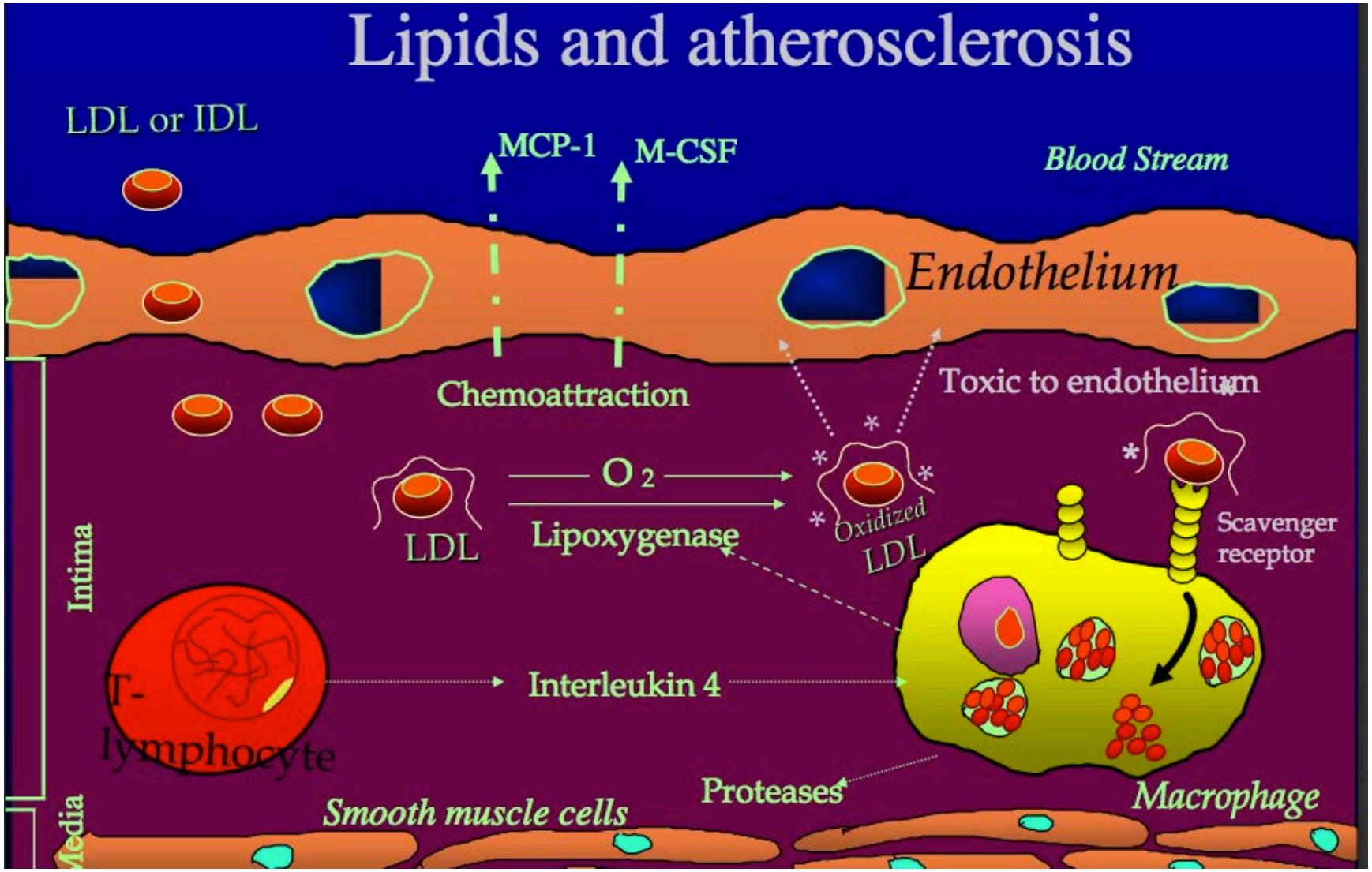
- Too low (below 3.3mmol/l) tremor, confusion, sweating, seizures, death
- Too high (above 8.6 mmol/l) heart disease (2-5X), amputations, blindness, kidney failure
- Continuous glucose monitoring* (CGM): e.g. Dexcom G6 (2018) "talks" to your smart phone CGM is safer esp. if hypoglycemia unawareness (Type 1 and Insulin dependent type 2) * avoid acetaminophen
- Bionic pancreas= CGM plus algorithms and pumps for insulin and glucagon (rescue for hypoglycemia); "iLET" is one device undergoing clinical trials

Prevention of Cardiovascular Disease

- **1) Coronary artery (arteriosclerosis)…**you guessed it!...**a chronic inflammatory process!** (of the deeper layers of arteries)
- **2) Sudden Coronary Artery Dissection (SCAD)** is a newly recognized issue often stress-related and often in younger women…**weakness in artery wall** can lead to dissection
- **2) Long QT syndrome…risk factor for severe heart rhythm problems**

Coronary Artery Disease (atherosclerosis)…How?

Slide: Dr Mason Freeman Controversies in Lipid Management, Internal Medicine Comprehensive Review and Update, Harvard U. June 2017 Boston



Coronary Artery Disease (CAD)

what will become of me

- Risk calculators estimate usefulness of various treatments; e.g. http://tools.cardiosource.org/ASCVD-Risk-Estimator
- Practically: if family is high risk , or diabetic, or high blood pressure…LDL less than 2mmol/L
- Dr Mason Freeman: “LDL is never optimal”
- Cecil, 75, you can keep these doc!
- Usually: statin medication

Coronary Artery Disease treatments

Do they actually reduce MI, angina, bypass/stents, strokes, death??

- Reduce LDL with Statins: (atorvastatin, rosuvastatin, [most potent], pravastatin [least likely to cause muscle pain], simvastin [can add ezetimibe]
- Stop if really achy and miserable, if liver function 3X+ normal, if CPK is more than 2-3X
- Vit D helps tolerance to statins… “they” say replace if it is low…but in Canada we are all low, eh?
- Stains: Help reduce risk even if low baseline cholesterol
- Triglycerides: optimize statins and diabetes treatments (old pre-statin data: fibrates reduced adverse cardiac events; Now…a Cardiologist *might* add gemfibrozil if very high triglycerides and diabetic but TRICKY**)
- Therapy to increase HDL? Not shown to help reduce adverse events
- **TRICKY not for do it yourselfers!!!!

Coronary Artery Disease treatments

- ASA 81 mg **not enteric coated** is more bioavailable ("Children's Chewable") No real role for ASA in *primary* prevention…with diabetics and for *secondary* prevention (of a second or third stroke or heart attack) talk with a cardiologist. This area is changing yearly with respect to optimal recommendations.
- If cannot tolerate stains and need them…and you are *very* good at arguing: new possibilities;
- Ezetimibe…one study adding this to simvastatin resulted in very potent lipid lowering; $5 per pill in USA; reduces cholesterol absorption form intestine
- Alirocumab is an antibody to PCSK-9; a group of African Americans have extremely low activity of PCSK-9 and have crazy low LDL and MI rates

Alirocumab or Evolocumab

- PCSKP-9 is a protein that binds to the LDL receptor; marks that receptor for removal…so that receptor cannot remove as much LDL from the blood
- These drugs are monoclonal IgG antibodies that block PCSK9 (so LDL receptors are increased …so…they remove more LDL from the blood)
- Retail cost USA $14,000/yr.

Fish oils and CAD (for your interest)

Dr Mason Freeman

Controversies in Lipid Management, Internal Medicine Comprehensive Review and Update, Harvard U. June 2017 Boston

- 2000-4000 mg of omega 3 (EPA plus DHA) per day can lower triglycerides
- Most convincing evidence that fish oils lower risk if the patient recently had a heart attack (MI)
- Less evidence of risk reduction in a patient with normal triglyceride levels and no MI
- Concentrated fish oil: Lovaza
- Epanova: processed EPA and DHA to make more bioavailable…trials: “EVOLVE”
- Vascepa is a new 1000mg EPA tablet

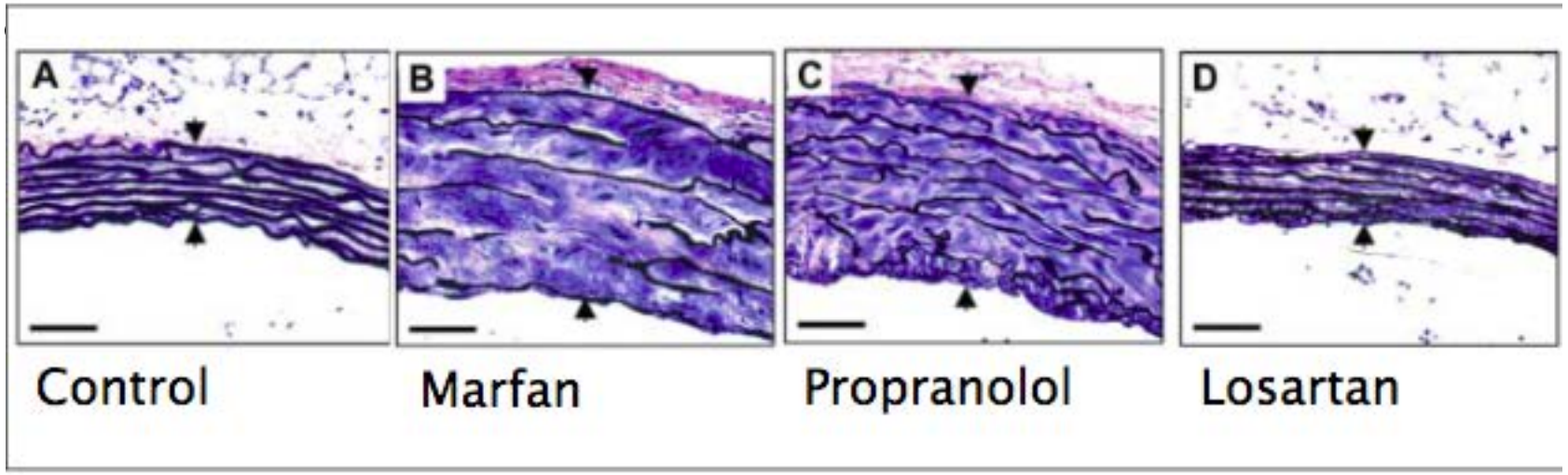
Sudden Coronary Artery Dissection (SCAD)

- New to me, mostly young women under a lot of social stress…can develop occluded arteries and have MI
- **Their coronary arteries do not have much, if any, plaque…**
- **Most do *not* have diabetes, high blood pressure, abnormal cholesterol, family history of CAD or diabetes**
- **Risk factors for SCAD: postpartum (relaxed connective tissue…pelvis relaxes to allow more room for delivery, fibromuscular dysplasia, extreme emotional stress (40%) or exercise (24%), connective tissue disease like Lupus, Marfan Syndrome, Turner's Syndrome, hormones (both progesterone and estrogen)**
- **Perfect storm: postpartum, cocaine, smoker, energy drinks, over-the-top emotional stress, PTSD, just started back on BCP, and has to move furniture**
- **Oh God…don't use cocaine! (or "energy" drinks)**
- **Fibromuscular dysplasia like Marfan's syndrome**

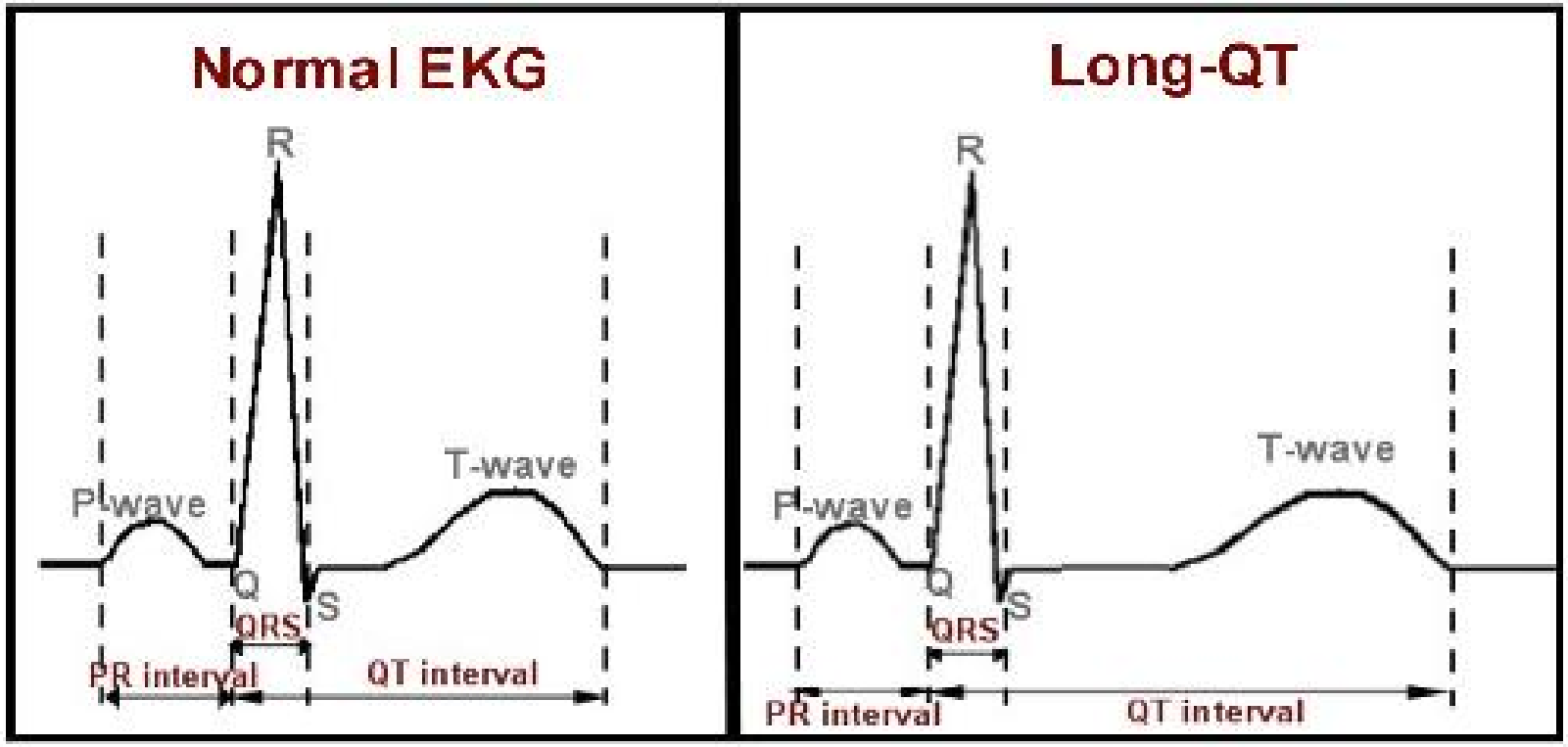
Marfan Syndrome

Eric Isselbacher, Thoracic Aortic Aneurisms, Int. Med. Comp. Rev. and Update, 2017

- Weak artery walls can lead to aneurism (unsafe "ballooning" of artery wall; can even rupture)
- Excessive TGF-Beta signaling weakens the wall…Losartan, an angiotensin II receptor blocker inhibits activity of TGF-beta…restores normal



Long QT syndrome



Q: So What?

A: Specific heart rhythm problems; if too long…“torsade de pointes” which can be fatal

Prevention of rhythm problems if QT is long

https://www.crediblemeds.org university-based non-profit

- Inherited Long QT…see cardiologist and avoid anything that could make it worse.
- Best: talk to your doctor or nurse practitioner *and* pharmacist…a general principle if QT is long…beware, **especially a combination** of the following… (This is **not a complete list** of conditions or drugs that can contribute to long QT problems):
- **Low potassium or low magnesium**
- **Some pain meds: hydrocodone, methadone, methotrimeprazine**
- **Cocaine**
- **Some common antibiotics: erythromycin, azithromycin, ciprofloxacin, clarithromycin, levofloxacin, moxifloxacin**
- **Some common psychiatric meds: amitripyline and other tricyclics, escitalopram, citalopam,**
- **Some common antifungals e.g. ketoconazole**
- **Gut meds: domperidone, cisapride, ondansetron**
- **Others: quinidine, propofol, sevoflurane, sotolol, thioridazine, haloperidol, terfenadine, amiodarone**

References 2

- American Cancer Association: Alcohol Use and Cancer https://www.cancer.org/cancer/cancer-causes/diet-physical-activity/alcohol-use-and-cancer.html
- Bodnar TS, et al. 2016. Evidence for an immune signature of prenatal alcohol exposure in female rats. Brain Behav Immun. 2016 Nov; 58: 130–141. doi: 10.1016/j.bbi.2016.05.022
- Burd L, et al. 2004. Increased sibling mortality in children with fetal alcohol syndrome. Addict Biol. Jun; 9(2): 179-86
- Burd, L., Peterson, L. and Kobrinsky, N. (2014), Fetal alcohol spectrum disorders and childhood cancer: A concise review of case reports and future research considerations. Pediatr. Blood Cancer, 61: 768–770. doi: 10.1002/pbc.24886
- Johnson S, et al. 1981. Immune deficiency in fetal alcohol syndrome. Pediatr Res. Jun;15(6): 908-11
- 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

References 3

- McGill J, Meyerholz DK, Edsen-Moore M, et al. Fetal exposure to ethanol has long-term effects on the severity of influenza virus infections. *Journal of immunology (Baltimore, Md : 1950)*. 2009;182(12):7803-7808
- Polanco TA, Crismale-Gann C, Reuhl KR, Sarkar DK, Cohick WS. 2010.Fetal alcohol exposure increases mammary tumor susceptibility and alters tumor phenotype in rats. Alcohol Clin Exp Res. Nov; 34(11):1879-87.
- Popova S, et al. 2016. Comorbidity of Fetal Alcohol Spectrum Disorder: a systemic review and metanalysis. Lancet Vol 387 No.10022 p978-87
- Sarkar D.K. 2015. Fetal Alcohol Exposure Increases Susceptibility to Carcinogenesis and Promotes Tumor Progression in Prostate Gland. In: Vasiliou V., Zakhari S., Seitz H., Hoek J. (eds) Biological Basis of Alcohol-Induced Cancer. Advances in Experimental Medicine and Biology, vol 815. Springer, Cham
- Terasaki LS, et al. 2016. Effects of Moderate Prenatal Alcohol Exposure during Early Gestation in Rats on Inflammation across the Maternal-Fetal-Immune Interface and Later-Life Immune Function in the Offspring. J Neuroimmune Pharmacol. 2016 Dec; 11(4): 680–692. doi: 10.1007/s11481-016-9691-8