Lesions and disease in the context of evolution

Nothing in biology makes sense except in the light of evolution
- Theodosius Dobzhansky (1900–1975)

Disease categories (types of insult)

1. Idiopathic
2. Trauma/physical
3. Age-related
4. Nutritional
5. Intoxication
6. Infectious
7. Genetic/developmental
8. Immune-mediated
9. Neoplastic
What I used to think in vet school
Animal
+ = Lesion = Disease
Insult

What I now think
Animal
+ = Lesion = Disease
Insult Species Age Sex Nutrition Immunological status “Stress” Chance/fate/dumb luck Tissues affected Treatment Genetics of agent (when infectious), esp. virulence factors Genetics of host

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Idiopathic = we don’t yet know real basis

“Spontaneous” fatal gastric rupture in a horse – WNVL 0909122

Trauma/physical

Gun shot trauma, brain

Trauma is necessarily random

CWD
- Chronic neurodegeneration of cervid species
- Predation by mountain lions:
  - Infected deer more likely to be killed by mountain lion than by hunters (females OR = 8.5, male deer OR = 3.2)
- Vehicle collisions:
  - Infected deer more likely to die in collisions (estimated relative risks=1.6-15.9)
Age-related

Atrophy of cerebral cortex, horse

Nutritional

Toxic

Blister beetle cystitis
Evolutionary adaptation has "no eyes to the future"

Natural selection operates on "What works best today" principal

1. Efficient conversion of food to body fat
   - Short term benefit: survival (subsistence-level environments)
   - Long term disadvantage: obesity, type II diabetes, hypertension, dyslipidemia (industrial societies not at war)

2. Minimal pigment in limbus/eyelids of Hereford cattle
   - Short term benefit: attractive to breeders/buyers
   - Long term disadvantage: squamous cell carcinoma at high altitudes (UV irradiation)

3. Lightly pigmented human skin:
   - Short term benefit: enhanced UV-dependant vitamin D synthesis
   - Long term disadvantage: skin cancer in sunnier climates

Infection - 1

- Animals (including people) co-evolved with infectious agents for millennia
- The job of infectious agents is to replicate
  - No guaranteed tendency to become more OR less pathogenic over time
- Immune system anticipates frequent infections early in life
- Infection runs gamut:
  - Subclinical infection → fatal disease
  - Infection does NOT = disease – e.g., WNV in people
    - 80% of infected people: no clinical signs
    - 20% of people: some clinical signs
    - ~0.6% of WNV-infected people: severe clinical disease
    - Death rate (seropositive, symptomatic individuals): 3.9%

Infection - 2

Consequences of exposure to infection determined by:

1. Virulence of infecting agent:
   - Direct or indirect:
     - Direct destruction of infected cells
     - Release of exotoxins
     - Endotoxin
     - Immunological suppression
     - Adhesion factors
     - Antigenic variation
     - Proteases
     - Others
   - Ability to evade host protective mechanisms
     - Survival inside cells
     - Granuloma formation
     - Cyst formation
     - Reduce MHC expression
Consequences of exposure to infection determined by:

1. Genetic makeup of infectious agent
2. Genetic makeup of infected host
3. Others:
   - Immune status (natural or medically-induced)
   - Route of entry
   - Amount of agent
   - Medical intervention
   - Age
   - Nutritional status
   - Physiological status (malnutrition; pregnancy; "stress")
Immune-mediated disease

- Autoimmune diseases: due to inappropriate activation of T-, B- or both against bodily antigens
  - Autoantibodies make up substantial part of normal plasma Abs
  - Suppressor mechanisms hold these in check
  - Women x3 more likely to develop autoimmune disease than men
  - High incidence of asthma and type I diabetes in people in wealthy countries (antiseptic environment/low parasite burdens)
- Other immune-mediated diseases:
  1. Hypersensitivity states
  2. Immune deficiency states
  3. Some drug reactions
  4. Material antibodies to progeny's antigens (esp. RBCs and platelets)
  5. Transplantation rejection and reactions to blood transfusions
  6. Many infections in which the major driver of disease is excessive, minimal or dysregulated immune response to pathogen

Neoplasia

- Tumor: purposeless overgrowth of cells
- Cancer: a malignant neoplasm
- Lifetime risk of clinical cancer (human): 1:3
- Occurs in all multicellular species:
  - “Reversion to unicellular selfishness”
- Cancer an inherent trade-off due to:
  1. Need for stem cells (repair function)
  2. Intrinsic mutability of genes (basis for evolution)
  3. DNA repair mechanisms (incomplete fidelity is the best it can do)
  4. Presence of critical genes, esp. for cell growth, cell suppression, apoptosis
  5. Inflammation (reactive oxygen; cytokines/chemokines)
- Most cancers occur later in life:
  - Biologically irrelevant, since reproduction occurred
  - Age less important than duration of mutagenic exposure

Genetic/developmental disease

- No variation = no evolution
  - Genes are intrinsically mutable
  - DNA damage due to:
    - Mistakes each DNA replication cycle, with faulty repair
    - Endogenous/exogenous damage due to chemicals, radiation or viral injury
  - Embryogenesis/early fetal development an inherently complex choreography:
    - The wonder is that the body ever gets it right, not that it occasionally goes wrong!
- Most genetic variation (single nucleotide polymorphisms; SNP) are neutral
  - Some: deleterious
  - Some: beneficial
Cystic fibrosis

- 10,000,000 carriers (USA)
- 30,000 affected individuals (USA)
- 1,400 mutations of CF gene
- Median survival: 37 years (USA)
- Disease results in:
  1. Thick mucus in lung/pancreas
  2. Recurrent infections
  3. Slow growth rate
- Defective chloride channel (CFTR - cystic fibrosis transmembrane conductance regulator)

Hypothesis: heterozygotes (carriers) benefit from being less likely to develop severe diarrhea due to bacterial toxins

Disease and MHC

- MHC = major histocompatibility complex
  - Class I = on surface of all cells
  - Class II = in surfaces of immunological cells
- Functions:
  - Self antigens
  - Identification of non-self (infectious agents; neoplastic cells)
  - Immunological/inflammatory responses
- If a species was genetically identical, pathogens could mimic self antigens and escape detection
- Specific HLA alleles predict risk for some diseases
  - Ankylosing spondylitis: B27 = RR: 90 – 100%
  - Insulin-dependant diabetes: DR3/DR4 = RR: 30%
  - Rheumatoid arthritis: DR4 = RR: 4%
  - Chronic active hepatitis: DR3 = RR: 13%

Genetic disease

- Founder effect:
  - Accidental: inbred populations
  - Deliberate: selective breeding for desired traits
- Response to infections:
  - Resistance to TB: Tay-Sach's disease
  - Resistance to malaria: sickle cell disease
  - Resistance to plague: resistance to HIV
Diseases to which one breed is predisposed

Beagle
Pulmonic stenosis; coronary arteritis; juvenile polyarteritis syndrome; congenital hypotrichosis; black hair follicular dysplasia; Ehlers-Danlos syndrome; lymphocytic thyroiditis; thyroid neoplasia; severe combined immunodeficiency; IgA deficiency; pyruvate kinase deficiency; Factor VII deficiency; primary hyperlipidemia; epiphyseal dysplasia; intervertebral disc disease; GM1 gangliosidosis; epilepsy; corneal dystrophy; glaucoma; lens luxation; cataract; retinal dysplasia; generalized PRA; microphthalmia; hypochondroplasia; renal amyloidosis

How disease may evolve in an individual - 1

INSULT

Stage 1: local response

Homeostasis restored

How disease may evolve in an individual - 2

INSULT

Stage 2: Systemic spillover

Homeostasis restored
Stage 3: Systemic inflammatory response ("sepsis" or "septic shock") - SIRS
Overwhelming or persistent release of pro-inflammatory mediators

Stage 4: Multiple organ dysfunction syndrome ("multiple organ failure") - MODS
Overwhelming or persistent release of anti-inflammatory mediators

Stage 5: Immunological dissonance
Massive amounts of both types of mediator released, but balance lost
CA brush rabbit + myxoma virus = benign skin tumor

Brazilian jungle rabbit + myxoma virus = benign skin tumor

European rabbit + myxoma virus = myxomatosis

Basis for disease: SIRS + immunological suppression

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Homeostasis in health and disease

Too much

Inflammatory response
Clotting reaction
Blood pressure
Nutrition
Immunological response
Tissue repair

Too little