Molecules, organelles, cells, tissues, organs, and body as a whole in disease

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Virchow’s concept*

\textit{Omnis cellula e celula =}
All living cells arise from pre-existing cells

This revised previous notions of spontaneous creation of cells from non-living matter

Corollary: all disease is result of cellular damage, even when initial target of injury is stromal framework

* Virchow appears to have plagiarized this concept from Schwann and Remak. The epigram was coined by Raspail. Virchow popularized it
The patient of pathologists is the cell

- Epidemiologist
- Physician/nurse practitioner/veterinarian
- Physiologist/anatomist
- Histologist/physiologist/endocrinologist
- Pathologist
- Molecular biologist
- Chemist/molecular biologist
- Molecular geneticist

The cellular basis of disease

- Please see Dr. Montgomery’s lecture from Friday
  - Some diseases target particular organelles:
    - Genetic disease: nuclear (DNA) and mitochondrial (DNA)
    - Cancer: nuclear DNA
    - Storage diseases: lysosomes
    - Membrane receptors: multiple, including autoimmune disease
    - Others
  - Many infectious diseases are cell-type specific:
    - ‘Neuronotropic’ infections: rabies
    - ‘Epitheliotropic’ infections: many herpesviruses

Determining consequences of cellular injury -1

- Critical nature of affect tissue/organ
  - How vital the organ
  - Spare capacity
  - Capacity for repair:
    - Labile
    - Stable ("quiescent")
    - Permanent
- Extent – diffuse vs. focal vs. multifocal
- Intensity – severe vs. moderate vs. mild
- Duration – acute vs. subacute vs. chronic
Death due to damage of vital organ

Major organ damage:
- Brain
- Heart

Massive blood loss:
- Internal
- External

Post-traumatic injury, bovine brain

Determining consequences of cellular injury - 2

- Location in body
- Host factors:
  - Nutrition
  - Age
  - Stress
  - Species
  - Sex
  - Genetic susceptibility
  - Blood supply
  - Secondary complications (esp. infection)
- Integrity following injury:
  - Effects on parenchyma, vessels, connective tissue framework

Gas gangrene (blackleg) in an ox
1/19/2011

Blackleg

Clostridial myositis pathogenesis
- step by step development of disease

Clostridium chauvoei enters body (ingestion)
- Latent bacterial spores in muscle (carried by macrophages?)
- Low oxygen tension in tissue (e.g., injection or trauma)
  - C. chauvoei proliferate
  - Cellulitis + edema + hemorrhage
  - Gas gangrene
  - Death in 12 – 36 hours

Clostridial organisms in muscle

- C. chauvoei
- Enzymes produced:
  - Alpha toxin = hemolysin
  - Beta toxin = DNase
  - Gamma toxin = hyaluronidase
  - Delta toxin = hemolysin
  - Neuraminidase = neuraminic acid
- Targets cellular components and extracellular components
- Death due to combination of tissue damage and shock
**Homeostasis**

- Normal cell (homeostasis)
- Stress, increased demand
- Injurious stimulus
- Adaptation
- Cellular injury
  - Cell death
- Inability to adapt

**Lesions**

- Injury
- Structural change ("lesion")
- Molecular change
  - Cell
  - Tissue
  - Organ
- Inborn error
- Functional change
- Symptoms/Signs
- Effect on other tissues, organs and systems

**Morphological changes generally linked to functional changes (= disease) but:**

- Functional disturbance **without** lesions:
  - Metabolic disturbances:
    - Milk fever
    - Hypomagnesemia
    - Fatal arrhythmias
  - Some intoxications:
    - Lead
    - 1080
    - Strychnine
    - Botulism
    - Tetanus
    - Tetrodotoxin

- Lesions **without** functional abnormality:
  - Benign tumors
  - Low grade bleeding
  - Age-related degenerations
  - Some, not all
  - Incidental lesions
When a tissue, organ or system begins to fail, it results in predictable, medically relevant complications in other organs, tissues and/or systems.

Pathology is "physiology under stress" ↓ "pathophysiology"

Understanding syndromes of complications is basis for detection in live patient, based on good clinical examination, supplemented by laboratory tests or biopsy.

When a major organ fails, the body fails

- Removing wastes
- Electrolyte balance
- Blood pressure
- Stimulating RBC

Doberman Pinscher juvenile nephropathy

- One of multiple familial nephropathies
  - Genetics undefined
  - Similarities to some human nephropathies
- Renal disease:
  - Targets renal glomeruli
  - Concurrent disease of tubules and interstitium
- "End-stage renal disease"
Consequences of renal failure - 1

- Fluid/electrolytes
  - Dehydration
  - Edema
  - Hyperkalemia
  - Metabolic acidosis
  - Ca / Phosphate
  - Secondary hyperparathyroidism
  - Renal osteodystrophy

- Blood pressure
  - Hypertension
  - Congestive heart failure
  - Cardiomyopathy
  - Pulmonary edema
  - Uremic pericarditis

- Hematologic
  - Anemia
  - Bleeding tendency

Maxillae/mandibles - dog
Thyroids/parathyroids - dog
Consequences of renal failure - 2

- **Gastrointestinal**
  - Nausea
  - Vomiting
  - Bleeding
  - Eosinophilitis
  - Gastritis
  - Colitis
- **Dermatological**
  - Sallow color (people)
  - Pruritis
  - Dermatitis
- **Neuromuscular**
  - Myopathy
  - Peripheral neuropathy
  - Encephalopathy

Serosal aspect, ribcage of two dogs

Gastrointestinal
- Nausea
- Vomiting
- Bleeding
- Esophagitis
- Gastritis
- Colitis

Dermatological
- Sallow color (people)
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Neuromuscular
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Stomach (surface) – dog
Close up of gastric mucosa - dog
Acute gastritis - human  Fibrinous pericarditis - human

Tongue - dog  Colonic mucosa - dog

Events in renal failure - 1

- ↑ nitrogenous wastes
- ↑ intracellular Na⁺ and water
- ↓ intracellular K⁺
- ↑ substances normally cleared by kidney (hormones)
- ↓ hormones and other mediators produced by the kidney
- ↓ basal body temperature
- ↓ lipoprotein lipase activity
Manifestations of renal disease

- Azotemia = ↑ blood urea nitrogen + creatinine
  - Function of glomerular damage
  - Uremia = azotemia + biochemical/clinical signs
- Hypoproteinemia:
  - Function of daily protein loss
  - Hypoalbuminemia → edema
  - Hyperlipidemia
- Oliguria:
  - More common in acute/peracute renal failure

Events in renal failure - 2

- Sodium and water retention
- Hyperkalemia
- Metabolic acidosis
- Changes in mineral metabolism → disorders of bone
- Cardiovascular and pulmonary disorders
- Hematologic abnormalities
- Neuromuscular abnormalities
- Gastrointestinal abnormalities
- Endocrine abnormalities
- Dermatologic abnormalities

Renal failure consequences: Na⁺ and water

- Sodium/water retention:
  - CHF, hypertension, ascites, edema
- Sensitivity to extra-renal sodium and water loss
  - Vomiting, diarrhea, fever, sweating
  - Symptoms: dry mouth, dizziness, tachycardia.
- Clinical control
  - Avoid excess salt and water intake
  - Diuretics
  - Dialysis
Renal failure consequences: potassium

- Hyperkalemia (GFR below 5 mL/min)
  - GFRs >5 mL/min: compensatory aldosterone-mediated K transport in DCT
  - Exacerbation of hyperkalemia:
    - Exogenous: K-rich diet
    - Endogenous: infection and trauma

Renal failure consequences: acidosis

Decreased acid excretion and ability to maintain physiologic buffering:
- GFR > 20 mL/min: moderate acidosis

Renal failure consequences:

- Fluid and salt overload
  - CHF and pulmonary edema
  - Hypertension
- Hyper-reninemia: hypertension
- Pericarditis
- Accelerated atherosclerosis: linked to factors above and metabolic abnormalities (Ca alterations, hyperlipidemia)
Renal failure consequences: RBC

- Anemia due to lack of erythropoietin
- Bone marrow suppression:
  - Uremic poisons: leukocyte suppression → infection
  - Bone marrow fibrosis
- Increased bruising, blood loss (surgery) and hemorrhage

Renal failure consequences: neuromuscular

- Peripheral neuropathies
- CNS abnormalities:
  - Renal encephalopathy
    - Mild or moderate: sleep disorders, impaired concentration and memory, irritability
    - Severe: myoclonus, stupor, seizure, coma

Renal failure consequences: GIT

- Uremic gastroenteritis: mucosal alterations
- Gastric ulceration: secondary to hyperparathyroidism?
- Uremic fetor: bad breath due to ammonia
- Non-specific abnormalities:
  - Anorexia, nausea, vomiting, diverticulosis, hiccoughs
Renal failure consequences: reproductive

- Insulin: prolonged half-life due to reduced clearance (metabolism)
- Female: low estrogen levels
- Male: impotence, oligospermia and germinal cell dysplasia:
  - Low testosterone levels

Renal failure consequences: skin

- Pallor due to anemia
- Skin color changes: accumulation of pigments
- Ecchymoses and hematomas: clotting abnormalities
- Pruritis and excoriations: Ca deposits from secondary hyperparathyroidism

Renal failure consequences: bone disease

- Decreased Ca++ from the gut
- Over-production of PTH
- Altered vitamin D metabolism
- Chronic metabolic acidosis
Recap: from cell to body

- **Cellular injury** is focus of pathologist
  - Other approaches just as valid: genome; molecular; proteome; organ or system; patient; population
  - Basis for:
    - Reliance on systematic examination of carcass
    - Histological and ultrastructural examination
- **Example of cellular injury causing organ injury and systemic illness:**
  - End stage renal disease leading to "uremia"
  - These are protean effects – chronic renal failure can present in various ways