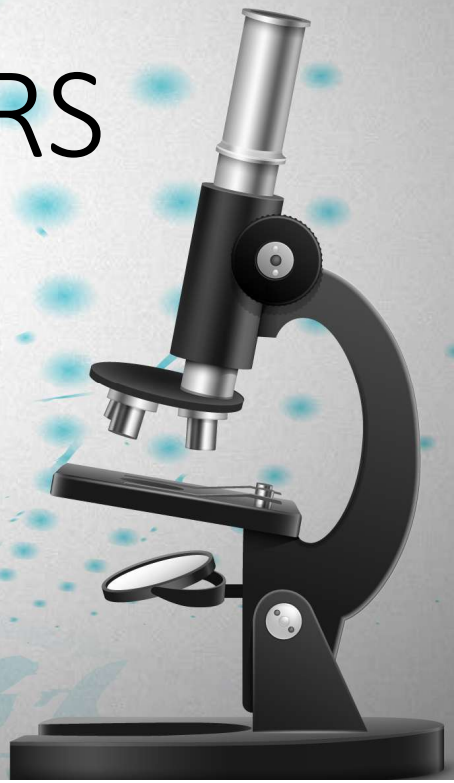
INFLAMMATORY MARKERS

Ronald Dalmacio

Chemical Pathology



OVERVIEW

- Inflammatory markers
  - CRP
  - Ferritin
  - Procalcitonin
  - ESR

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INTRODUCTION

- **INFLAMMATION:**
  - Normal response of the body to infection/injury causing a set of local cellular and vascular responses. Release of chemicals triggers an immune response to fight off infection or heal damage

- Acute vs chronic
  - Chronic response:
    - Unresolved injury or infection
    - Persistent lifestyle impact: Smoking, Alcohol, poor diet etc

- The good and the bad
  - Assists in tissue repair and combats infections
  - Ongoing, low-grade persistent inflammation contributes to Type 2 diabetes mellitus, cardiovascular disease, Alzheimers disease, autoimmune diseaseetc.

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INFLAMMATORY PATHWAY

- Acute response
  - **Vascular changes**
    - Vasodilation >> Increased blood flow >> Increased blood vessel wall permeability >> Exudate infiltrates affected tissue
    - Deposit of clotting factors and antibodies locally
    - Reduced blood vessel flow and increased vessel permeability >> White blood cells emigrate to extravascular tissue
  - **Cellular changes**
    - Local accumulation of white blood cells
      - Phagocytes (Neutrophils)
      - Monocytes >> macrophages
    - Directed to affected site by chemotactic factors
  - **Chemical mediation**
    - Chemical releases from plasma, white blood cells, platelets, mast cells, endothelial cell lining, and injured tissues
      - Includes: Histamine, lysosomal compounds, Complement proteins, cytokines, prostaglandins
  - Proinflammatory >> anti-inflammatory

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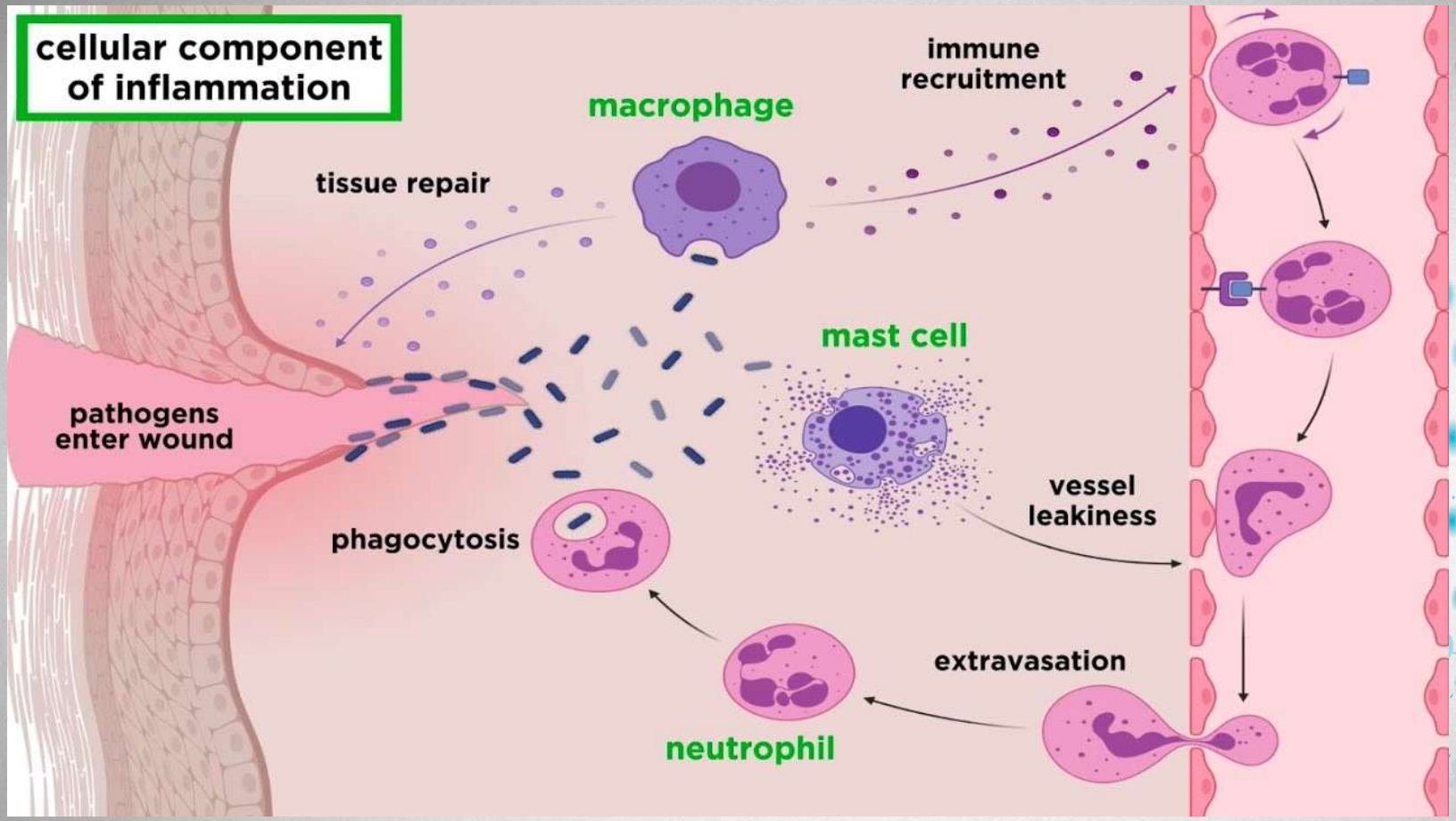
cellular component of inflammation
immune recruitment
macrophage
tissue repair
mast cell
pathogens enter wound
vessel leakiness
phagocytosis
extravasation
neutrophil

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ACUTE PHASE RESPONSE

- **ACUTE PHASE RESPONSE**
  - Broadly refer to a large group of behavioural, physiological, biochemical and nutritional changes occurring during periods of inflammation
  - Acute phase reactant (APR) changes reflect alterations in synthesis by the liver
- Positive acute phase reactants
  - Erythrocyte sedimentation rate (ESR)
  - C-reactive protein (CRP)
  - Procalcitonin (PCT)
  - Ferritin
  - Including: Caeruloplasmin, fibrinogen, A1AT, haptoglobin, IL-1 receptor antagonists, hepcidin, ferritin
- Negative acute phase reactants
  - Albumin
  - Transferrin
  - Transthyretin

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NOTABLE
ACUTE PHASE REACTANTS

C-REACTIVE PROTEIN
FERRITIN
PROCALCITONIN
ERYTHROCYTE SEDIMENTATION RATE

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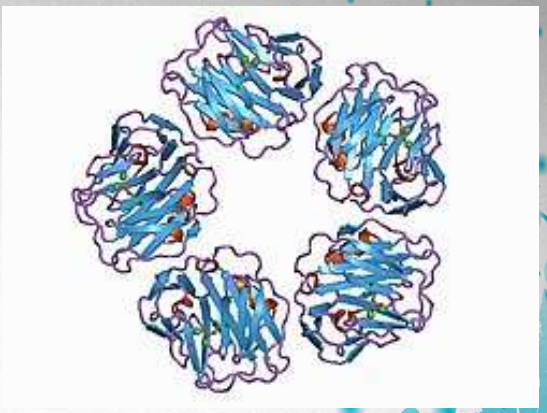
C-REACTIVE PROTEIN (CRP)



- Discovered in 1930 in patients with pneumococcal pneumonia
- Structure: Cyclic pentamer with central pore (Pentraxins)
  - Forms: Pentameric (Anti) vs monomeric (Pro)
- Kinetics:
  - Rise 6-8 hours
  - Peak 24-48 hours
  - T1/2 ~19hours
- Function:
  - Anti-inflammatory
  - Pro-inflammatory
    - Activation of complement system
    - Activates inflammatory cytokines, tissue factor and
  - Promote recognition/elimination of pathogens
    - Bind phosphocholine
  - Assists in clearance of necrotic/apoptotic cells
    - Activates complement system
  - Pathologically: CRP binding to autoantibodies >> Idiopathic thrombocytopenic purpura (ITP)

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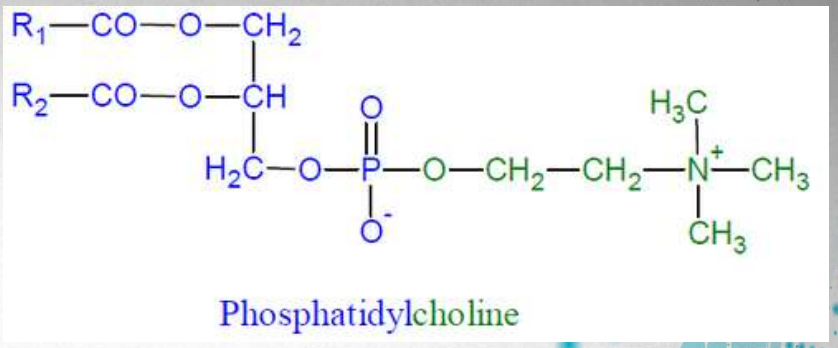

Phosphatidylcholine

- Aspects of synthesis:
  - Induced by IL-6 >> upregulates CRP gene transcription
  - Responds rapidly to inflammatory process (Increase and decrease)
    - Chronic increase indicates ongoing process
- Synthesis is non-specific
  - Acute and chronic processes
  - Causes:
    - Cellular/tissue injury with exposure of phosphocholine
      - Precursor to phosphotidylcholine (Phospholipid)
    - Infections
    - Trauma (incl. surgery)
    - Autoimmune disease
  - Specific causes:
    - hsCRP:
      - Cardiac screening/risk
      - Also increased in:
        - Atherosclerosis, metabolic syndrome, obesity and insulin resistance

- CRP vs hsCRP
  - Analytical differentiation denoting higher assay sensitivity
  - Assess for low-grade inflammation (Chronic)
- Reference ranges
  - CRP 0.5 – 5 mg/L
  - hsCRP <1 mg/L
- hsCRP
  - Cannot be used in place of CRP (Normal CRP does not rule-out raised hsCRP)
  - Testing performed in patients who appear well

HIGH SENSITIVE CRP	2.2	H	< 1.00 mg/L

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INTERPRETATION:
   <1 mg/L   -  LOW RISK
1 - 3 mg/L   -  MODERATE RISK
   >3 mg/L   -  HIGH RISK
 >5.0 mg/L   -  Consider active infection/inflammation

Us-CRP is an independent risk factor for cardiovascular
disease. Combining Us-CRP with a lipid screening
significantly improves risk prediction and identifies in
whom aggressive primary prevention efforts e.g. weight loss,
exercise, cessation of smoking and diet are indicated.
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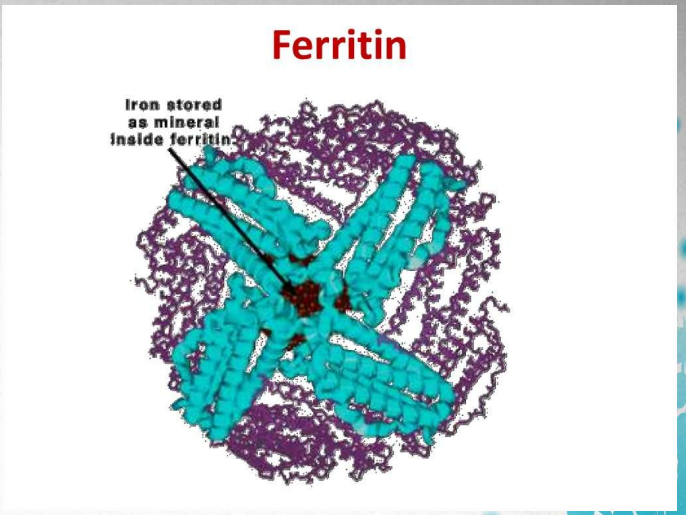
FERRITIN



- Discovered in 1937
- Globular protein shell
  - Iron storage in core (2/3 of all iron stores)
- Positive acute phase reactant
- Kinetics
- Diagnostic utility
  - Iron deficiency
  - Iron overload, e.g. Haemachromatosis
  - Chronic disease
- Immunomodulatory effect of ferritin
  - Possible pro-inflammatory cytokine effect
  - Lymphocyte modulation
    - Immunosuppresive effect (Impairs T-cell proliferation, B-cell maturation and immunoglobulin production)

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- Diagnostic pitfalls
  - Hyperferritinaemia is not synonymous with iron overload
  - Low/normal ferritin does not exclude inflammatory response
  - Ranges differ by gender. Upper limit (WHO):
    - Male 300 ug/L
    - Female 200ug/L
  - Genetic variants may cause an increase
    - Haemachromatosis

30 - 200 ug/L: Normal for healthy individuals.
<30 ug/L: Highly suggestive of iron deficiency (ID).
30 - 70 ug/L: Suggestive of ID in the presence of inflammation.
Ferritin >70 ug/L and transferrin saturation < 20%: Anaemia of chronic disease (ACD)/ID-ACD combination - recommend reticulocyte haemoglobin content and/or serum soluble transferrin receptor testing to differentiate.

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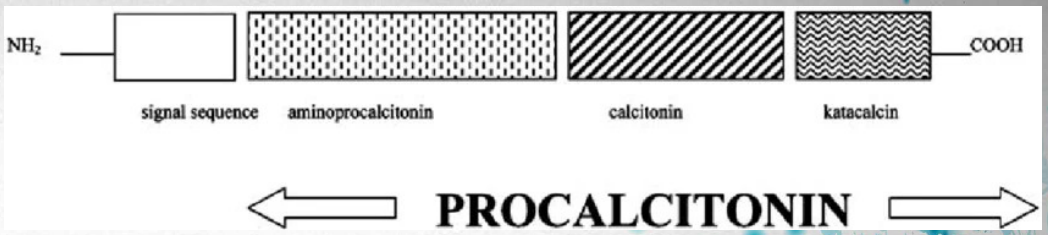
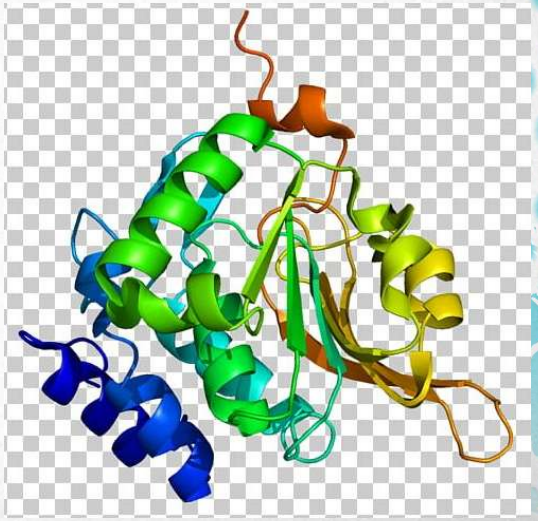
PROCALCITONIN (PCT)



- Procalcitonin is a precursor peptide to calcitonin (Regulation of calcium levels)
  - Produced in
    - C-cells of the thyroid
    - Extra thyroidal tissue during infection/inflammation
- Clinical reponses
  - Synthesis increased due to bacterial endotoxin release and inflammatory cytokines
- Kinetics
  - Rise 2 – 4 hrs after infection (Sepsis)
  - Peak 24 – 48 hrs
  - T1/2 24hrs



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- Clinical utility
  - Identifies presence of bacterial infection with systemic spread
    - Discrimination between bacterial vs non-bacterial inflammatory causes
  - Antibiotic stewardship
    - Guides reasonable use of antibiotics (Duration/commencement)
    - Earlier detection than blood culture
  - ICU patients: Determines 28 day risk of mortality
- PCT vs CRP
  - PCT rises faster than CRP
  - Specific for bacterial infections

ERYTHROCYTE SEDIMENTATION RATE (ESR)

- Indirect acute phase reactant
  - Not a Specific analyte, but a haematological response
- Method:
  - Westergren method
  - Measures the distance (mm) that RBC settle in anticoagulated whole blood, in an upright tube, over an hour
- Pathophysiology
  - In response to inflammation, plasma protein elevation cause rouleaux formation leading to RBC aggregation. This response causes rapid settling of the RBC
    - Influenced by Acute phase reactants in blood, incl.:
      - Fibrinogen
      - Immunoglobulins, monoclonal proteins
      - Non-inflammatory causes: RBC size, number, shape

- Increased ESR
  - Common causes:
    - Infectious/inflammatory disease: Systemic or localised
    - Malignancies
      - Incl. Monoclonal proteins
    - Tissue injury or ischaemia
    - Trauma
  - Non-inflammatory causes
    - Increased age
    - Female gender and pregnancy
    - Anaemia
    - Kidney disease (Esp. ESRD)
    - Obesity (incl. Metabolic syndrome)
    - Smoking
- Decreased ESR
  - Erythrocyte factors: Changes in shape or number
  - Raised bile salts
  - Heart failure
  - Hypofibrinogenaemia
  - Suppressed inflammatory response:
    - Medications: Glucocorticoid, high0dose salicylate, IL-6 inhibitors

ESR – Multiple Myeloma

- CRAB criteria
  - Hyper**C**alcaemia
  - **R**enal disease
  - **A**naemia
  - **B**one pain
- Other:
  - Neurological disease
    - Extradural spinal cord compression
    - Radiculopathy
    - Peripheral neuropathy
    - Encephalopathy (Hyperammonaemia)
    - Other CNS involvement
  - Infections
  - Hyperviscosity
- Diagnostics
  - SPE, UPE, immunofixation
  - Free light chain analysis (incl. Bence Jones protein)
  - Bone marrow analysis

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CONCLUSION

- Inflammatory markers are non specific
- Acute phase reactants should not be solely used for diagnosis
- Correlate with clinical picture
- Adjunct to other clinical/laboratory findings

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THANK YOU

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