2001b(7): Explain the main difference between the intrinsic and extrinsic pathways of coagulation

General: Coagulation is a bio-amplification system by activating a cascade of circulating precursor enzymes

- Ultimate aim → convert soluble fibrinogen to stable fibrin → combined with platelets forms a firm and stable haemostatic plug.

There are 2 historical pathways:

- Intrinsic & Extrinsic → Both activate the common pathway

**Intrinsic pathway:** a sample of blood in a tube would spontaneously clot → clotting is intrinsic

  - Activated by: (-) charged surfaces *in vivo* (collagen, subendothelial connective tissue) & *in vitro* (glass)
  - Factors: XII, XI (↓ in haemophilia B), IX (↓ in haemophilia A)
  - Activation time: 1 - 6 min (slow)

**Extrinsic pathway:** requires something other than what is in blood for activation

  - Activated by: Factor VII activation by tissue factor (TF) on subendothelium
  - Factors Involved: VII
  - Time to Activation: 15s (fast)

**Common Pathway**

  - Activated by: Intrinsic (via VIIa in the presence of Ca²⁺) & Extrinsic pathways (via IXa in the presence of Factor VIII and Ca²⁺)
  - Factors Involved: X, II, V

**Drugs**

  - Warfarin: Decreases production of factors II, VII, IX, X. Main effect: Decreased activity of extrinsic and common pathways
  - Heparin: Facilitates activity of antithrombin III (ATIII) in inhibiting activity of Xa and IIa of common pathway (LMWH only inhibits Xa activity)

**Investigations**

  - APTT: Measures activity of intrinsic pathway via contact activation (glass) in the presence of PF3, Ca²⁺ (↑ w heparin)
  - PTT/INR: Measures activity of thromboplastin in the presence of PF3, Ca²⁺ (↑ w warfarin)

**Sepsis/inflammation** results in ↑ factor VIII production → enhanced intrinsic pathway activation

  - Killakrein, XII and XI are thought now to have a more important role in inflammation than coagulation

Recent evidence suggests an alternate pathway for activation of intrinsic pathway:

  - Factor VIIa → activates Factor IX
    - May have a larger role than extrinsic pathway activation of common pathway (VIIa activation of X

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