Laboratory investigation in the Bleeding Patient

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Introduction

- Bleeding is common
- May consume significant resources
  - Crossmatched blood
- Lab results may be missinterpreted
- There is often an assumption that the cause is the abnormal blood tests
  - May be the other way round
- Investigation is mostly not in the lab!

Typical Case in EAU

- 52 year old male
- Presents to EAU with haematemesis
  - Fresh red blood
  - ‘toilet pan full’

What would we like to know from the lab tests?

- How much has he bled?
  - What volume has he lost
- Is he still bleeding?
- Where is he bleeding from?
- Does he have adequate clotting to stop the bleeding?
  - Is there a bleeding tendency
- Does he need blood component support?

How much blood has he lost?

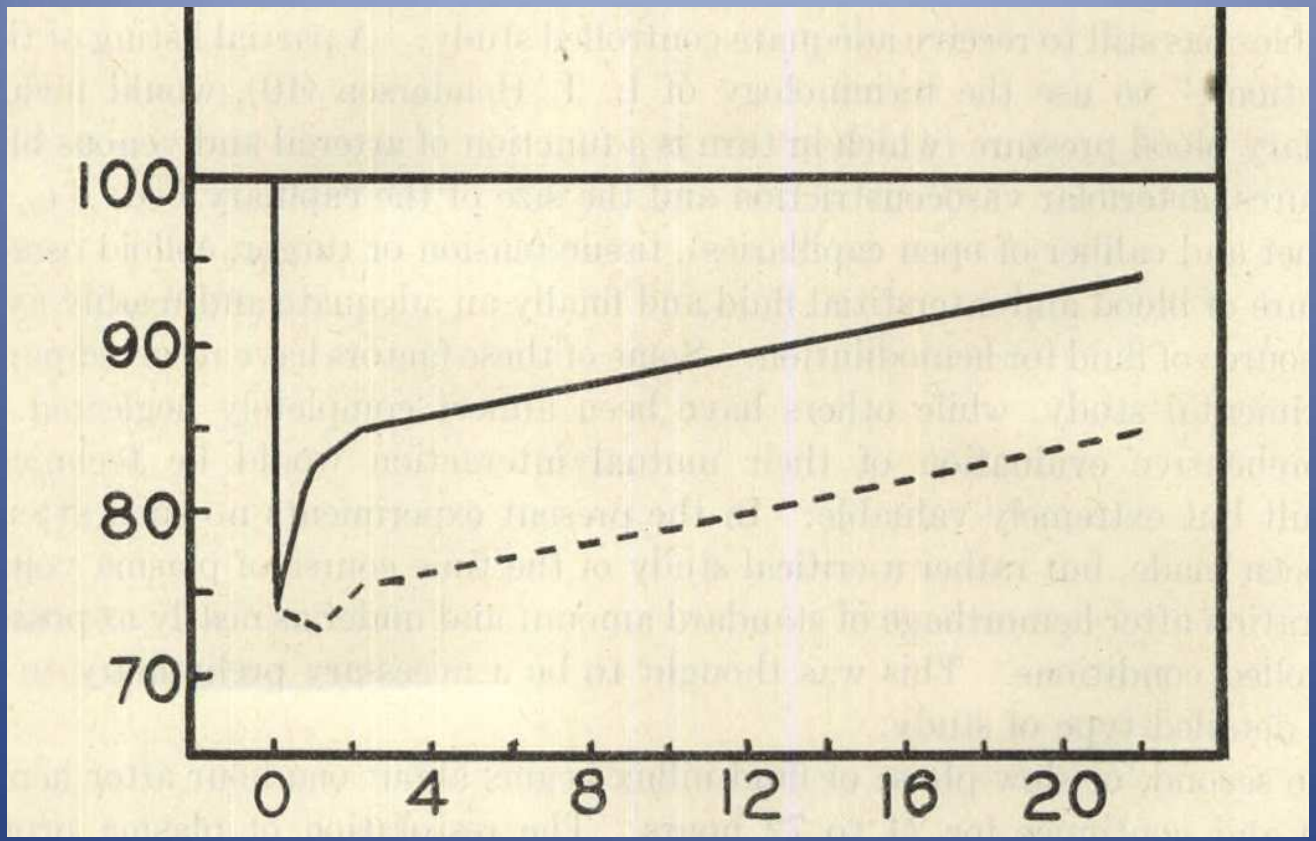
- FBC
  - HB 130
  - Wbc 12
  - Plts 430
- But how do we interpret this?

Physiological factors

- Blood loss initially causes loss of circulating volume
- Volume is replaced initially by protein poor fluid influx
- And then by albumin containing extracellular fluid

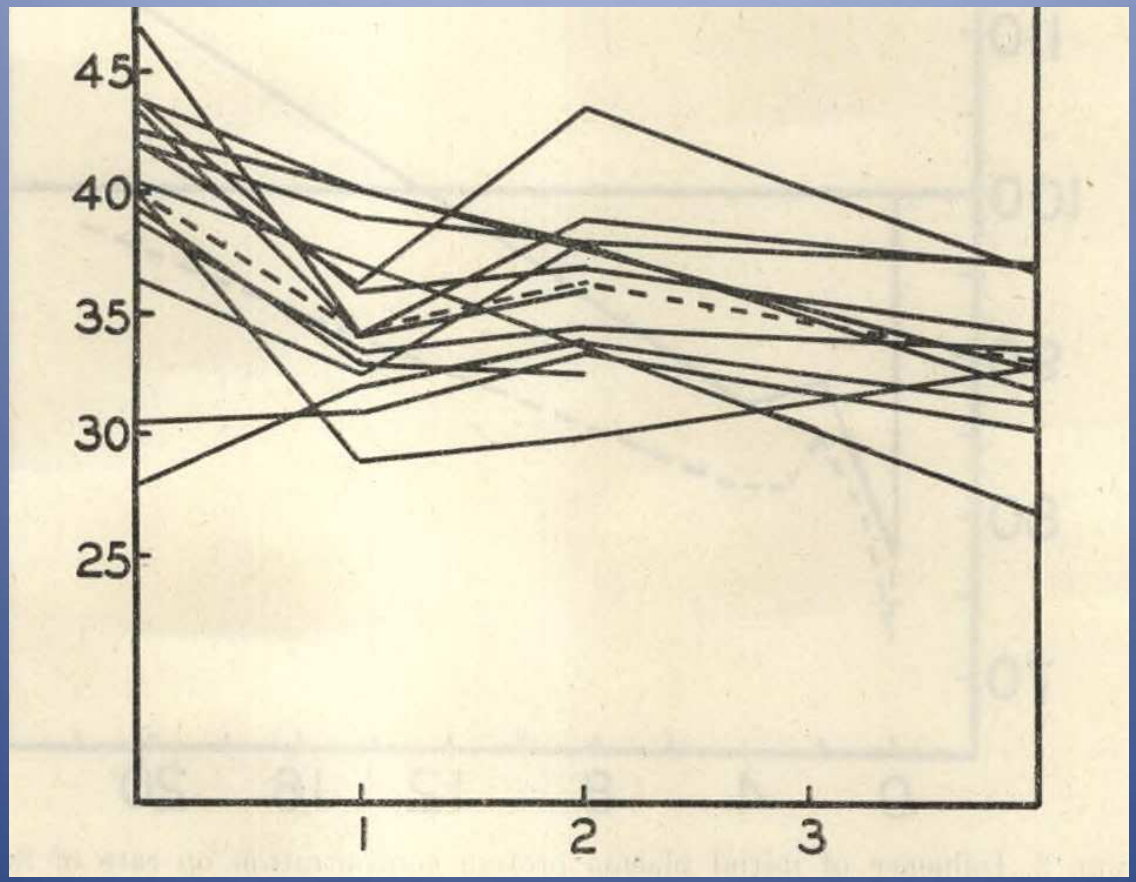
- Restoration of blood volume after single bleed may take 20-60hrs (or more)

Blood volume and plasma protein changes following haemorrhage (in dogs)



– T Miller 1944

Change in HCT following bleed (in dogs)



- T Miller 1944

Other factors?

- When did the bleed start?
  - How long after the bleed is he presenting
- What was the Hb before the bleed?
- Have fluids been given?
  - How much?
  - When?
  - Often underestimated?

How much blood loss?

- Don’t know!
- Clinical picture will be more informative.

- What if significant anaemia?
  - Same factors need to be considered (esp fluids)
  - Must consider whether this may be a chronic

Look for signs of chronic anaemia

- Low MCV and MCH?
  - Suggestion of Fe deficiency?
  - Or anaemia of chronic disease
- High MCV
  - Suggestion of B12/Folate deficiency?
  - Or hypothyroidism?
  - Or haemolysis?
  - Or liver disease?
  - Or alcohol excess?

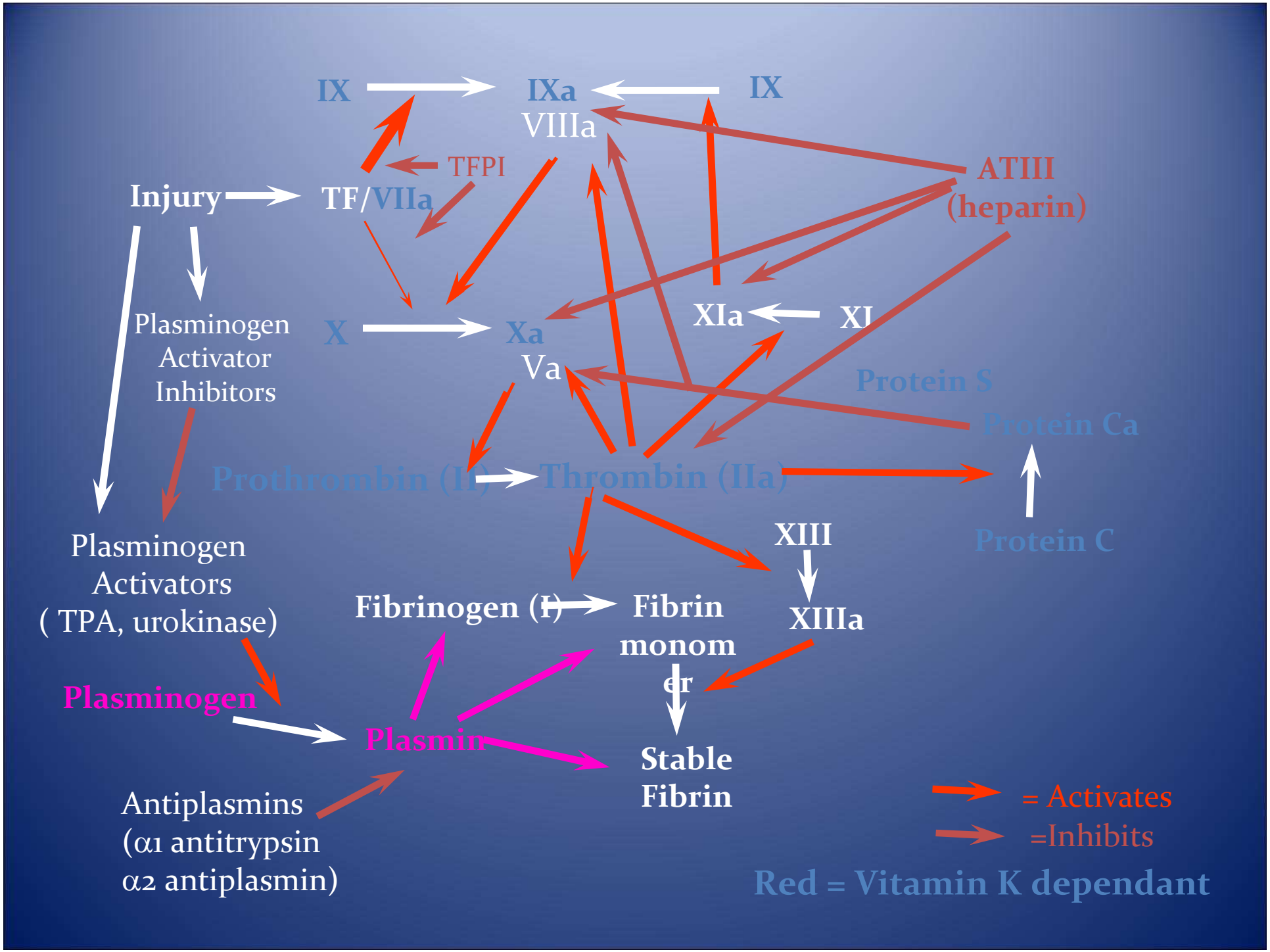
Is he still bleeding?

- Serial FBC's?
  - Same factors need to be taken into account
- Reticulocyte count?
  - Rises after 3-5 days.
  - Peaks at 10 days following bleed.

Is his clotting adequate?

- Needs to be able to clot to plug the hole!
- Is there an underlying clotting problem?
- Has he used them all up?

- What is it that we need to measure?


IX
IXa
VIIIa
IX
TFPI
ATIII
(heparin)
Injury
TF/VIIa
Plasminogen
Activator
Inhibitors
X
Xa
Va
XIa
XI
Protein S
Protein Ca
Prothrombin (II)
Thrombin (IIa)
Protein C
XIII
Plasminogen
Activators
(TPA, urokinase)
Fibrinogen (I)
Fibrin
monom
er
XIIIa
Plasminogen
Plasmin
Stable
Fibrin
Antiplasmins
(α1 antitrypsin
α2 antiplasmin)
= Activates
=Inhibits
Red = Vitamin K dependant

Clotting tests?

- INR (or Prothrombin time)
  - Mostly dependent on ‘liver factors’
    - Factors II, VII, IX, X
  - Prolonged in
    - liver failure
    - Warfarin therapy
    - Factor VII deficiency
    - DIC/Consumption

- APTT
  - Sensitive to deficiencies in the ‘intrinsic pathway’
    - Factors XII, XI, X, VII, IX……..II
  - Prolonged in:
    - Unfractionated heparin therapy
    - Haemophilia – FVIII, FIX deficiency
    - FXII, FXI deficiency
    - Antiphospholipid syndrome
    - Contact factor deficiencies…….
    - DIC/Consumption

- Fibrinogen?
  - Cant make a clot without Fibrinogen (Factor 1)!
  - Low in:
    - Congenital deficiency
    - DIC/Consumption
- But are you being given an actual fibrinogen level?

Derived versus measured Fibrinogen

- The fibrinogen level can be ‘derived’ from the rate of formation of the clot in the PT/INR test
  - Produced automatically by anaylsers
  - Rapid and cheap
- Can also be measured directly using functional assay – Clauss fibrinogen
  - More accurate
  - Especially when levels are low

Fibrinogen in the bleeding patient?

- Laboratory practice will vary
  - Clauss for all?
  - Screen with derived?
- Clauss should be used if level may be low
  - Ie. May need to replace
- Which result are you getting?

What about other anticoagulants?

- LMWH
  - Act mostly on FXa
  - Have no or little effect on routine clotting results
  - Can assay anti-Xa activity – not in emergency
- NOACS/DOACS
  - May not affect routine clotting at therapeutic levels
  - May get varying results with different reagents

- Dabigatran (direct thrombin inhibitor)
  - May affect the INR/APTT
  - Normal results may suggest a low level
  - Normal TT excludes residual effect
- Rivaroxaban (direct Xa inhibitor)
  - May affect the INR/APTT (not TT)
  - May have ‘prophylactic’ levels with normal results
- BUT – Only in labs where the sensitivity of their reagents has been confirmed

Interpreting Patient results (1)

- INR 10
- APTT 1.5
- Fibrinogen 4.5

- Disproportionate rise in INR
- Almost certainly on warfarin

Interpreting patient results (2)

- INR 1.0
- APTT 2.1
- Fib 3.8

- Isolated prolongation of APTT
- Is he on unfractionated heparin?
- Is he a haemophiliac?
- Does he have acquired haemophilia?
- Does he have anti-phospholipid syndrome?
- Does he have a clinically irrelevant factor deficiency

Interpreting patient results (3)

- INR 2.0
- APTT 1.8
- Fibrinogen 1.2

- Suggests consumption/DIC

Does Renal failure contribute?

- End stage renal disease
  - May have platelet dysfunction
  - Due to ‘uraemic toxins’
- Dialysis patients
  - Often use heparin
- New onset renal dysfunction
  - Are they on LMWH or a DOAC?
    - These are renal excreted
    - May be ‘supratherapeutic ‘

Conclusions/Take home messages

- Need to understand what question is being asked of the lab tests
- Hb may be a poor indicator of blood loss
- Clotting is a complex process
  - Lab tests are imperfect
- Effects of DOACS are hard to measure, and reagent dependent