The Coagulation Cascade

Intrinsic Pathway: the contact activation pathway
Triggered by the exposure of negative charge on collagen;
High molecular weight kininogen, prekallikrein and factor XII
all form a complex on the collagen, and this causes the
following amplification cascade. This plays a minor role.

Extrinsic Pathway: the tissue factor pathway
This is the PRIMARY, MOST IMPORTANT PATHWAY.
Triggered by the exposure of tissue factor in the damaged blood vessel
wall to the circulating factor VII.

From "William Hematology" by Lichtman et al, especially chapter 115 by Monroe III
The COAGS: What the hell are we measuring

**PT: Prothrombin Time**

- A test of the EXTRINSIC PATHWAY as well as the FINAL COMMON PATHWAY
- Basically, you add tissue factor to a sample of plasma, and measure the time it takes for the sample to clot.
- The tissue factor activates the extrinsic pathway, which in turn activates the final common pathway; so the PT actually measures BOTH pathways.

The rate of the extrinsic pathway is mainly influenced by the amount of Factor VII you have.
Factor VII has a short half-life and depends on Vitamin K.

Testing the PT is a way of looking at the function of the Vitamin K-dependent enzymes; namely II, VII and X Factor IX is also vitamin-K dependent, but is not tested.

**INR: international normalized ratio**
Comparison of a given PT to an average PT. An INR of 2 means blood is clotting twice as slowly as normal.

**aPTT: Activated Partial Thromboplastin Time**

- A test of the INTRINSIC PATHWAY, as well as the FINAL COMMON PATHWAY.
- Basically, you add some “partial thromboplastin” to the blood sample, together with calcium.

Thromboplastin was a weird surrogate for tissue factor; or rather, it is a tissue factor-like protein, already bound to some phospholipid, and derived from cow placenta. Partial thromboplastin is just the phospholipid part. There isn’t any tissue factor there. Thus, there is no extrinsic factor activation in the test.

In order to kick off the INTRINSIC PATHWAY, some sort of negatively charged substance must be added.
(in the living tissue, this is collagen exposed by cutting the vessel).

In the laboratory, instead of collagen we use kaolin (a clay mineral) or silica.
The phospholipid and calcium are required for the tenase and prothrombinase complexes of the final common pathway. The calcium also participates in the intrinsic pathway.

**aPTT WILL NOT PICK UP FACTOR VII DEFICIENCY.**

Even if you have 50% less of any given factor, your PT and aPTT should remain roughly normal.

**Mixing studies**

- Mixing studies distinguish between factor deficiencies and factor inhibitors.
- Lets say your sample of plasma is giving a high PT or aPTT
- grab your suspicious plasma sample, and mix it with normal blood, 50:50.
- Obviously, if some sort of “factor inhibitor” is present, the normal blood will also be affected, and the resulting mixture will give abnormal aPTT and PT results.
- If there is a factor deficiency, the mixed sample will result in a normal PT or aPTT.

From “William Hematology” by Lichtman et al, especially chapter 115 by Monroe III
Half-lives of the Coagulation Cascade Factors

- **Factor XII**: Half life 60 hrs
- **Factor XI**: Half life 52 hrs
- **Factor IX**: Half life 18-24 hrs
- **Factor VIII**: Half life 8-12 hrs
- **Factor VII**: Half life 3-6 hours
- **Factor X**: Half life 30-40 hrs
- **Factor II (Prothrombin)**: Half life 60-70 hrs
- **Factor I (Fibrinogen)**: Half life 72-120 hrs
- **Protein C**: Half-life 6 hrs

In absence of vitamin K, the first factors to be depleted are factor VII and protein C. The extrinsic pathway is turned off; the measured PT will be high, but blood can still clot via the intrinsic pathway.

**If there is no protein C, the normal inhibition mechanism of the intrinsic pathway is turned off.**

This means there is an increased tendency to clot via the intrinsic pathway.

Thus, the first day of warfarin therapy is a day of thrombotic diathesis.
Friends of the coagulation cascade

FFP: fresh frozen plasma

- The liquid portion of the blood, separated and frozen within 8 hours of collection
- 250ml bags
- It contains pretty much all the factors:
  - **Factor VII of the EXTRINSIC pathway** (so, it decreases your PT)
  - **Factors XI and IX of the INTRINSIC pathway** (so, it decreases your aPTT)
  - **Factors X and II (Prothrombin) of the COMMON pathway** (so, it decreases both PT and aPTT)
- Thus, it replaces all of the factors which go missing in warfarin therapy or Vitamin-K deficient liver disease
- Unfortunately, there isn’t much factor VIII. Its solubility is too low at low temperatures, and FFP (once thawed) doesn’t contain enough of it.

Cryoprecipitate

- The cold insoluble fraction of FFP
- Separated by slowly thawing FFP to about 6 degrees, and then centrifuging away all the plasma.
- 20-50ml bags
- It contains:
  - **Factors VIII of the INTRINSIC pathway** (so, it decreases your aPTT)
  - **Fibrinogen**
  - **Von Willebrands factor** is also supplied, since it is bound to Factor VIII in circulation

Prothrombinex

- **Purified Factors II, IX and X. ..And a little VII.**
- thus, it all but replaces the Warfarin-induced factor deprivation.
- Some factor VII will still have to come from somewhere.
- The bleeding warfarinized patient will need some of this, as well as some FFP (probably 1 unit) to replace the Factor VII, as well as Vitamin K to ensure there will be more endogenously synthesized factors to follow.

Biostate™

- **Purified Factor VIII**, for hemophiliacs.
- Fairly straightforward activity and indication.

From “William Hematology” by Lichtman et al, especially chapter 115 by Monroe I
Vitamin K

- Required for the synthesis of Factor II, VII, IX and X.
- Normalizes INR within 24 hrs after administration

**Functional factors**

Reduced Vitamin K

Oxidized vitamin K

Vitamin K epoxide Reductas

NAD

NADH

Gamma-glutamyl-carboxylas

Factor precursors

Desmopressin: DDAVP, 1-desamino-8-D-arginine vasopressin

- This is the synthetic form of vasopressin
- It acts on storage sites in vascular endothelium, rapidly releasing stored vWF and Factor VIII.
- The storage bodies are called Weibel-Palade bodies
- Normally, von Willebrand Factor and factor VIII are bound together and circulate around as a soluble complex

Thus, Desmopressin shortens APTT. But....

It also does a bunch of other useful things:
- Increases the density of platelet surface glycoprotein receptors
- Thus, increases platelet aggregation
- Also, increase activity of tissue plasminogen activator antigen.

Desmopressin is the only drug useful for treatment of platelet dysfunction induced by clopidogrel, aspirin, NSAIDs in general, and uraemia.

Tranexamic acid and Eta-Aminocaproic Acid

- Synthetic derivative of the amino acid LYSINE.
- It is a PLASMIN INHIBITOR.

Plasmin interacts with fibrin by binding to LYSINE residues on fibrin.
Tranexamic and eta-aminocaproic acid are competitive inhibitors of this binding.
Of the two, Tranexamic acid is 10 times more potent.
According to the CRASH-2 trial, it reduces all cause mortality in trauma patients.

From "William Hematology" by Lichtman et al, especially chapter 115 by Monroe III