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| 5B-5 |
| **Basic Science Question:** |
| What is the mechanism of action of Warfarin? |
| **Report:** |
| The body undergoes hemostasis to prevent blood loss. There are three simultaneous steps:1. Vascular spasm – the blood vessel constricts when you get a cut
2. Platelet plug formation – platelets get “sticky” in response to injury and go to the site to form a plug at a site. The key here is that this plug is transient.
3. Coagulation cascade – stabilizes the platelet plug by wrapping it in the insoluble protein fibrin. This step makes the plug into an actual blood clot.

Proteins are produced by the liver in their inactive form – these are called zymogens or proenzymes. They must be cleaved to become active. The body systemically activates the factors in a positive feedback loop where each activated factor activates the next factor in sequence. So, the proteins circulate as the inactivated form until they are needed, which prevents them from reacting when not wanted. The coagulation cascade has two pathways: intrinsic and extrinsic. These two pathways involve many factors and eventually converge to a “common pathway”* The intrinsic pathway of coagulation is triggered by internal damage to the wall of the vessel. When there is damage to the lumen of the vessel and collagen is exposed to blood, it activates platelets. This activates factor XII and a cascade begins.
* The extrinsic pathway of coagulation is triggered by trauma. Factor VII and factor III form an enzyme complex to cleave factor X, which activates the common pathway. Factor XIII is activated at the top.

Warfarin is a type of blood thinner and anticoagulant, which means it inhibits blood clots by inhibiting blood clot factors. Many clotting factors are secreted by the liver and the platelets. Of the 12 clotting factors in the coagulation cascade, II, VII, IX, and X area activated and bind to Ca2+. In order to be activated, the reduced form of Vitamin K must carboxylate them. During the carboxylation, Vitamin K goes from its reduced form to its oxidized form. In order to keep activating those factors (to continue the cascade), Vitamin K must return to its reduced form. Vitamin K epoxide reductase is the enzyme that reduces Vitamin K.Warfarin competitively inhibits Vitamin K epoxide reductase, so vitamin K remains oxidized. As reduced Vitamin K depletes, we have a build up of oxidized Vitamin K, which can no longer carboxylate the factors. Since the factors cannot be carboxylated, they remain as zymogens and are fail to activate the next factor in the pathway! Thus, the coagulation cascade is halted and the blood clot does not form.  |
| **References:** |
| Implementation of a Computerized Decision Support System for Warfarin Dosing in Hemodialysis Patients: A Study of Effectiveness and Safety - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/The-coagulation-cascade-and-sites-of-Warfarin-inhibition-Adapted-from-Ferguson-et-al\_fig1\_295955649Patel S, Singh R, Preuss CV, et al. Warfarin. [Updated 2020 Mar 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470313/?report=classic |