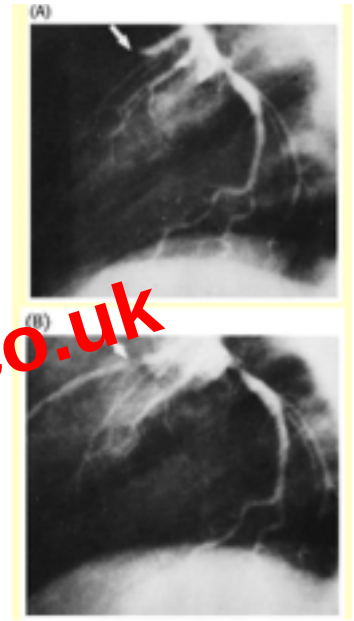
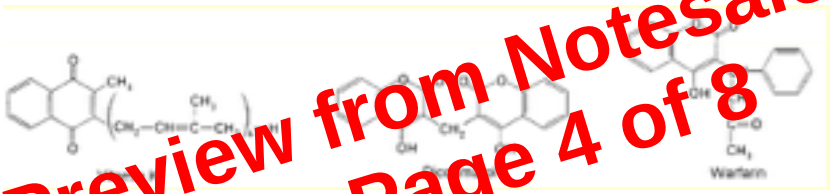
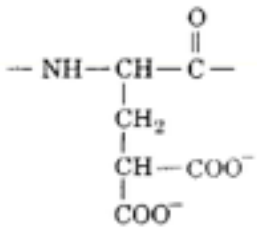
Prothrombin's pro-peptide consists of three domains; an N terminal, a 40-residue Gla domain. Followed by two **kringle** domains of about 115 residues. Gla and kringle domains occur in several of the proteins involved in clot formation and lysis. A finally the actual thrombin domain.
The Kringle domains get there name from there shape and are curled by by disulphide bonds. The Gla domain gets its name from the large number of amino acids residues gamma carboxyl glutamate. There significance need a look back to the actual synthesis of the molecule. Prothrombin as well as many other molecules are sythesied in the liver, and the synthesis requires the presence of vitamin K. If you don't have vitamin K in your diet then prothormbin can only be produced into a form that cant be swell activate by stuart factor (factor 10). The activation of it falls to about 1-2% of the normal rate. This is difficult to understand because the analysis of these proteins shows that they are the same in terms of primary sequence. So why is one activated normally and the other by 1-2% of normal. Studying the structure of the normal prothrombin using NMR showed the presence of these glutamate residues. The reason they weren't shown before is because they where extracted for analysis by acid hydrolysis to cut it up into individual amino acids which destroys the carboxyl glutamate residues. Because the acid hydrolysis turns the carboxyl glutamate back to just glutamate.

The abnormal prothrombin is thus made in the absence of vitamin K but also if its in the presence of these vitamin K antagonists Such as dicumarol or warferin. Dicumerol is a substance found in sweet clover thats gone off. Sweet clover is fed to cattle and it was found that f this clover spoiled the cattle developed a bleeding disorder. Warfarin is used as a vitamin K antagonist, it was also used as a rat poison as the rats at sit and it thinned there blood causing internal bleeding. It is given to humans for blood thinning agents. This is because the blood doesn't circulate as efficiently they create blood clots. Preventing the actions of vitamin K with warferin then creates a prothrombin with a reduced ability to activate and thus is less likely to form clots. It prevents the pooling blood to clot called thrombosis which can have adverse affects of blocking circulation. It may be given to elderly people because of poor circulation or after surgeries to prevent the advanced blood clotting from the intensional damage by surgery.





So why are these Carboxy glutamate residue important form the formation of blood clots? what do thy actually do? The normal prothrombin with its gamma-carboxyglutamate residues was found to be able to bind calcium ions (important). However the abnormal prothrombin cant bind calcium ions. The binding of calcium ions provides a means of anchoring the prothrombin to a phospholipid membrane. The calcium can then link to negatively charged phospholids membranes because they have positive charges but these negatively charged membranes are only present on the inside of your cellular membranes not the outside. This means that the prothrombin will only bind to damaged cells that have exposed internal structures. Anchored in the site itself cuts off to form thrombin. So only an open wound will activate the production of thrombin. Now we question the significance of the binding to theses membranes as stuart factor doesn't act on the carboxyl-glutimate part of prothrombin to activate it. It intact works further down the molecule sort of central to release thrombin. However by itself factor ten (stewart) isn't very good activating the prothrombin. but the binding to the phospholipids with calcium ions present it stimulates the conversion by a fold x20,000.



There is another factor involved in the activation of thrombin, we need calcium ions and phospholipids but the production of thrombin is autocatalytic. That is for its own activation it acts on the Factor 5 molecule (proaccelerin). Its autocatalytic because thaw faster the activation of factor 5 the faster the activation of prothrombin. However the activated proacclerin is subject to degradation by thrombin. Over a longer time scale thrombin acts to destroy the factor 5 molecule. This shows a way of stopping the clot propagating away from the sight of injury by shutting the clotting system down.