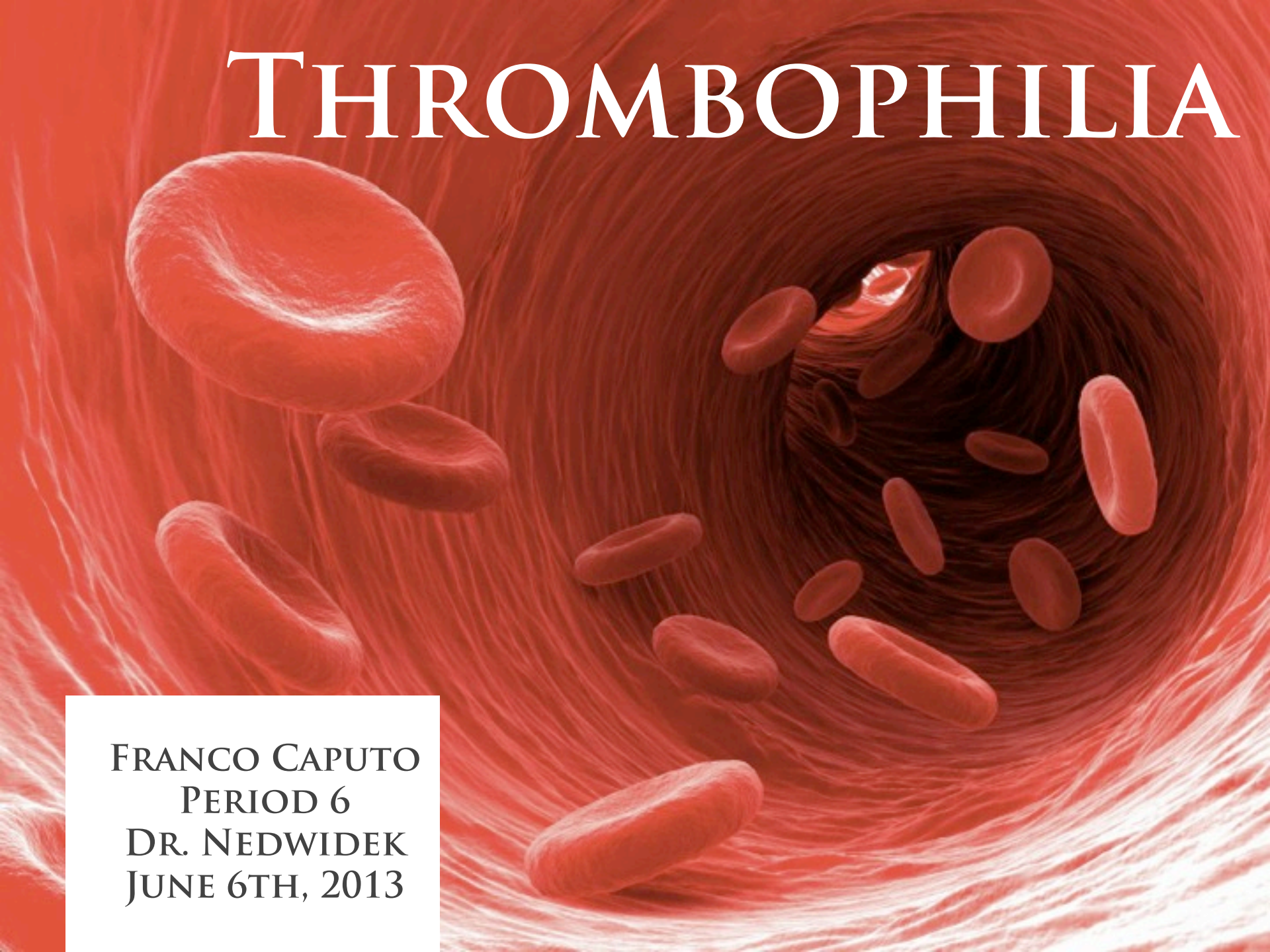
Thrombophilia



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Period 6
Dr. Nedwidek
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Physiology

- Two main types: Factor V Leiden thrombophilia and prothrombin thrombophilia (hyperprothrombinemia).
- Causes deep vein thromboses (DVTs), or pulmonary emboli (PEs).
- DVTs are abnormal blood clots that form in the veins, around the valves, due to an overabundance of clotting factors. They normally form in the deep veins of the legs, but rarely, they can form in the brain, eyes, liver, and kidneys.
- Cause pain, red coloration of the skin of the leg, increased warmth of the leg, and severe swelling. These clots can become very large, and can block blood flow completely: if the clot is large enough, it can cause death. When there is a DVT, there is a large risk of an embolism: when a piece of the DVT breaks off and gets attached somewhere else in the body, especially the lungs. These PEs cause severe pain when deep breathing, coughing up blood, as well as chest pain and shortness in breath.
- Women with thrombophilia are 2/3 times more likely to have a miscarriage during their second and third trimesters of pregnancy. During pregnancy and the first 6 weeks after giving birth, there is an increased chance of getting a DVT.
- Generally only a 10% chance that the disease will manifest, with an increasing risk with age.
- 3-8% of caucasians in the US and Europe have at least one copy of this gene defect, which causes a 3-8 in 1,000 chance of the disease manifesting.
- 1 in every 5000 people are homozygous for the gene defect, which causes a two in 25 chance of the disease manifesting.
- 50% to 70% of the clots formed in an individual with thrombophilia are caused by something, and are not spontaneous.
- Several factors can provoke a DVT. Major surgery, such as orthopedic surgery; cancer treatment; immobilization due to surgery, travel; plaster casts for broken legs; hospitalization; smoking; obesity; and birth control pills and hormone replacement therapyincrease the chance of a clot forming.
- People with type A, B, and AB are at a higher risk for developing a DVT.

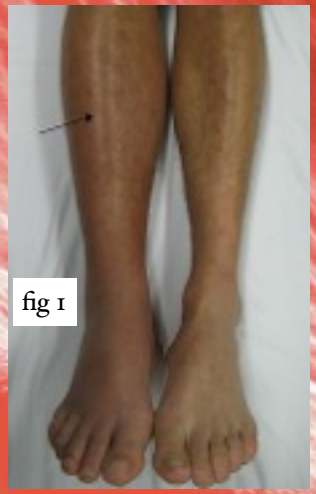


fig 1

fig 2

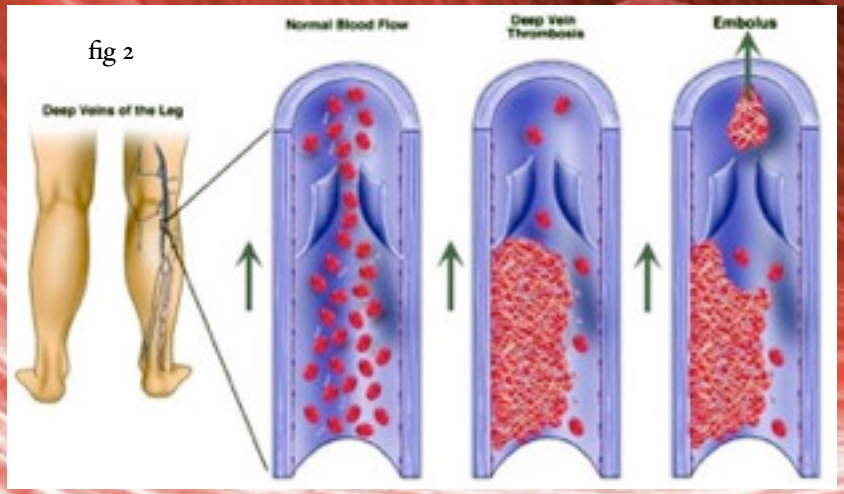


fig 3

Molecular Cause

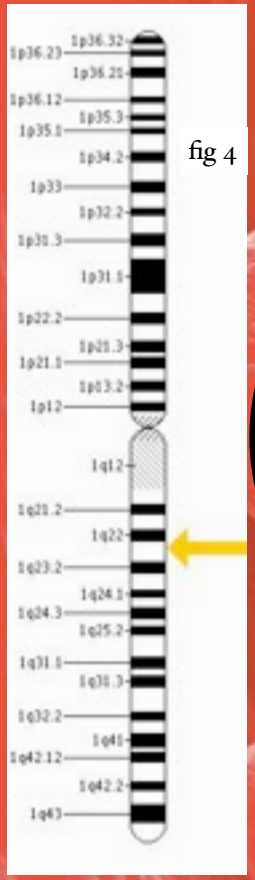


fig 4

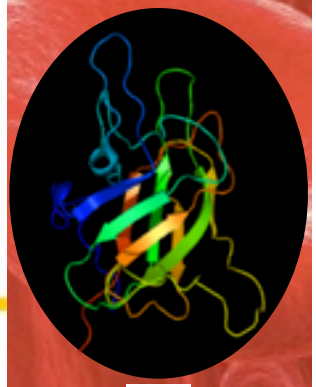


fig 5

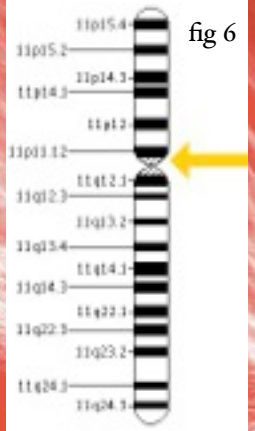


fig 6

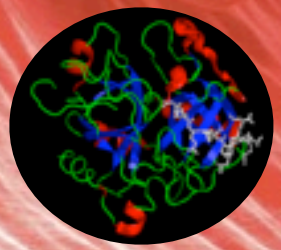
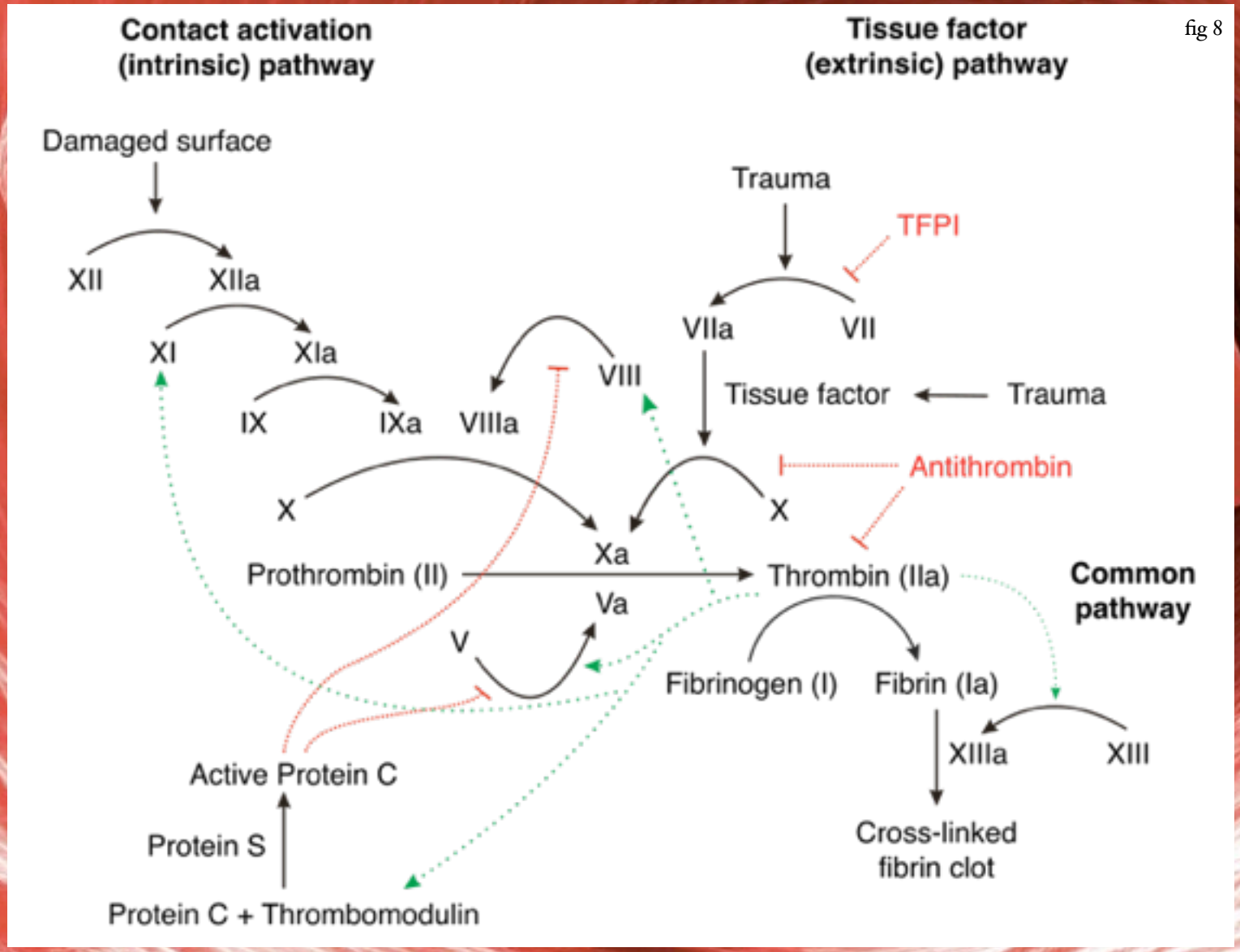


fig 7

- Autosomal dominant
- Factor V Leiden is caused by a mutation on the q leg of chromosome 1 (fig 4), in location 1q23 (bps 169,481,191 to 169,555,768). It is a missense point mutation that codes for an amino acid in position 1691 of the F5 gene. It changes the amino acid arginine to glutamine at position 506 (R506Q) of the protein. This results in a mutated coagulation factor V protein.
- Prothrombin thrombophilia is caused by a mutation on the p leg of the 11th chromosome (fig 6), in location 11p11 (bps 46,740,742 to 46,761,055). It is a point mutation in the coagulation factor II (F2) gene. It changes the nucleotide guanine with adenine at position 20210 (G20210A). It is a missense mutation, which affects the 3' untranslated region of the mRNA, which causes the gene to be overactive, and an abundance of prothrombin (coagulation factor II) is made.
- Normally, in humans, activated coagulation factor V, Va, interacts with activated coagulation factor X, Xa. Together, they convert prothrombin(coagulation factor II) into thrombin, which converts fibrinogen to fibrin, which forms the clot.
- Activated protein C (APC) deactivates activated coagulation factor V by cleaving it in certain places, in order to stop the clot. Position 506 is one of the sites where APC normally cleaves coagulation factor V. In Factor V Leiden thrombophilia, position 506 is mutated, and APC is unable to deactivate the F5 protein, and the rate at which it's deactivated slows down. With extra activated coagulation factor V, excess fibrin is in turn made, which will cause unnecessary clotting.
- In prothrombin thrombophilia, the mutation causes the gene to be overactive, and too much prothrombin (coagulation factor II) is made. With extra prothrombin in the blood, it is turned into thrombin, which makes fibrin, and causes excess clotting.

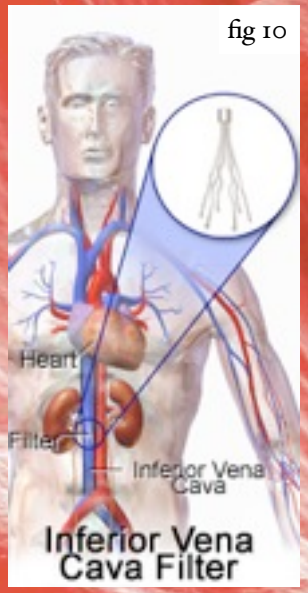
Clotting Cascade



Treatments, Risks & Limits

fig 9

fig 10



- DVTs can be prevented by movement, to avoid giving a chance for the clots to form. Exercise can keep blood flowing, and prevent the clot from forming. It is important to eat healthy, drink fluids, stay in good shape, and to avoid smoking, hormone therapies, pregnancy, and birth control pills.
- If the individual has already had a DVT there are methods used to prevent it from happening again.
- Pressure stockings can be used to promote good circulation. They are tight around the ankle, and gradually become looser as they go up the leg. This creates pressure, and keeps the blood from clotting.
- It is most important to regularly visit the doctor for checkups.
- There is no straightforward treatment. There's a 90% chance that an affected individual does not get any symptoms at all, therefore treatment is rarely necessary.
- There are a few palliative treatments that can be used if the disease manifests.
- Anticoagulants, or blood thinners, such as warfarin or heparin, can be used to treat an already-formed clot.
- Anti-platelets are sometimes used to make the platelets in the blood less able to form a clot. Thrombolytics, or clot busters, are used to break the clot apart - they are generally used to treat strokes, heart attacks, or PEs. They are only used in emergencies, because they cause sudden bleeding.
- If the patient can't take blood thinners, thrombin inhibitors are used, which interfere with the clotting of blood.
- In extreme circumstances, vena cava filters are used. They are inserted into the vena cava, and catch emboli before they can reach the lungs.
- There are no cures or treatments currently studied.

Proposal/Limits

*In both forms of thrombophila, the mutated protein is made in the liver, and then circulated in the blood, inactive, until the body receives an injury, when it is activated by a series of events and protein interactions. If the liver was able to make a normal protein, then the disease would be virtually cured.

*The proposed treatment is a liver transplant from an individual without the mutated DNA sequence. The liver would need to be homozygous for the correct gene, and not have the mutated one. For Factor V Leiden thrombophilia, instead of making coagulation factor V that couldn't be deactivated, it would make the wild type, normally functioning F5 protein, and clotting would become normal. For Prothrombin thrombophilia, instead of having an overactive gene for the production of prothrombin, the liver would have a normally functioning gene, and there production of prothrombin would slow down, and clotting would become normal.

*A liver transplant could be given by a living or deceased individual. Because of the liver's ability to re-grow, a living person can donate a piece of their liver to be used in a liver transplant (usually a family member).

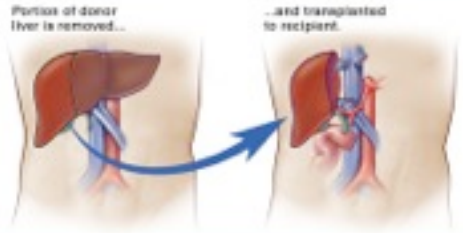
*In order for a person to be compatible to donate their liver, they must be around the same size as the affected individual, and they must have the same blood type. They must also have similar major histocompatibility complex (MHC) proteins. MHCs are proteins found on the surface of all cells to help the immune system identify foreign objects. If the new liver does not have similar MHC proteins as the recipient, the liver will be rejected.

*Half of the donor's liver is transplanted into the recipient's body, and they both grow back into normally-sized livers. The patient only has to stay in the hospital for 1 week to 12 days. The surgery involves attaching the new liver to the recipient's blood vessels and bile ducts, and may take up to four to eight hours.

*There are many risks to a liver transplant. There are many risks of the anesthesia. The patient can have reactions to the medicine or breathing problems. The recipient requires large amounts of blood transfusions because of the amount of blood lost during the surgery. There is also a chance of heart attack or stroke whilst the surgery is being performed.

*Infection is a big problem, because the recipient has to take medication to suppress the immune system so it won't reject the liver. With a suppressed immune system, infections are much easier to get, and can be very dangerous.

*The final risk of the surgery is a DVT. If the patient does not move their legs after the surgery, there is a chance of a DVT forming. However, soon after the surgery, the chance will go away, because the disease will be cured.



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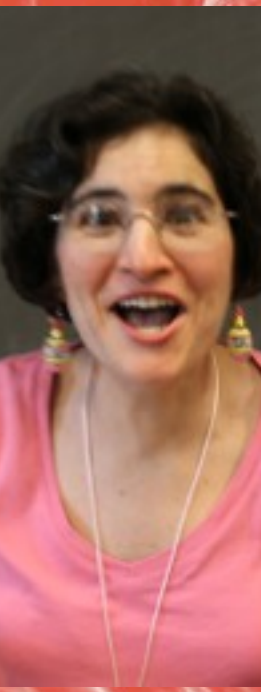
Picture Sources



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