(1)

In the human body, each cell contains 23 pairs of chromosomes, one of each pair inherited through the egg from the mother, and the other inherited through the sperm of the father. Of these chromosomes, those that determine sex are X and Y. Females have XX and males have XY. In addition to the information on sex, 'the X chromosomes carry determinants for a number of other features of the body including the levels of factor VIII and factor IX.'1 If the genetic information determining the factor VIII and IX level is defective, haemophilia results. When this happens, the protein factors needed for normal blood clotting are effected. In males, the single X chromosome that is effected cannot compensate for the lack, and hence will show the defect. In females, however, only one of the two chromosomes will be abnormal. (unless she is unlucky enough to inherit haemophilia from both sides of the family, which is rare.)2 The other chromosome is likely to be normal and she can therefore compensate for this defect.

There are two types of haemophilia, haemophilia A and B. Haemophilia A is a hereditary disorder in which bleeding is due to deficiency of the coagulation factor VIII (VIII:C)3. In most of the cases, this coagulant protein is reduced but in a rare amount of cases, this protein is present by immunoassay but defective.4 Haemophilia A is the most common severe bleeding disorder and approximately 1 in 10,000 males is effected. The most common types of bleeding are into the joints and muscles. Haemophilia is severe if the factor VIII:C levels are less that 1 %, they are moderate if the levels are 1-5% and they are mild if they levels become 5+%.5
(2)
Those with mild haemophilia bleed only in response to major trauma or surgery. As for the patients with severe haemophilia, they can bleed in response to relatively mild trauma and will bleed spontaneously.

In haemophiliacs, the levels of the factor VIII:C are reduced. If the plasma from a haemophiliac person mixes with that of a normal person, the Partial thromboplastin time (PTT) should become normal. Failure of the PTT to become normal is automatically diagnostic of the presence of a factor VIII inhibitor. The standard treatment of the haemophiliacs is primarily the infusion of factor VIII concentrates, now heat-treated to reduce the chances of transmission of AIDS.6 In the case of minor bleeding, the factor VIII:C levels should only be raised to 25% with one infusion. For moderate bleeding, 'it is adequate to raise the level initially to 50% and maintain the level at greater that 25% with repeated infusion for 2-3 days. When major surgery is to be performed, one raises the factor VIII:C level to 100% and then maintains the factor level at greater than 50% continuously for 10-14 days.'7 Haemophilia B, the other type of haemophilia, is a result of the deficiency of the coagulation factor IX - also known as Christmas disease.

This sex-linked disease is caused by the reduced amount of the factor IX. Unlike haemophilia A, the percentage of it's occupance due to an abnormally functioning molecule is larger.

The factor IX deficiency is 1/7 as common as factor VIII deficiency and it is managed with factor VIII concentrates. Unlike factor VIII concentrates which have a half-life of 12 hours, the half-life of factor IX concentrates is 18 hours. In addition, factor IX concentrates contain a number of other proteins, including activated coagulating factors that contribute to a risk of thrombosis. Therefore, more care is needed in haemophilia B to decide on how much concentration should be used.

The prognosis of the haemophiliac patients has been transformed by the availability of factor VIII and factor IX replacement. The limiting factors that result include disability from recurrent joint bleeding and viral infections such as hepatitis B from recurrent transfusion.8

Since most haemophiliacs are male and only their mother can pass to them the deficient gene, a very important issue for the families of haemophiliacs now is identifying which females are carriers. One way to determine this is to estimate the amount of factor VIII and IX present in the woman. However, while a low level confirms the carrier status, a normal level does not exclude it. In addition, the factor VIII and IX blood levels are known to fluctuate in people and will increase with stress and pregnancy. As a result, only a prediction of the carrier status can be given with this method.

Another method to determine the carrier status in a woman is to look directly at the DNA from a small blood sample of several members of the family including the haemophiliacs. In Canada, modern operations include Chorionic Villous Sampling (CVS) and it helps analyze the DNA for markers of haemophilia at 9-11 weeks of pregnancy. (Fig. 1)9 A small probe is inserted through the neck of the mother womb or through the abdomen under local anaesthetics. A tiny sample from the placenta is removed and sent for DNA analysis.

Since this process can be done at 9-11 weeks after pregnancy, the pregnancy is in it's relatively early stages and a decision by the mother (and father) to terminate the pregnancy will not be as physically or emotionally demanding on the mother than if she had it performed in the late stages of the pregnancy.

Going back to the haemophiliacs, many have become seropositive for HIV infections transmitted through factor VIII and IX concentrates and many have developed AIDS. In Canada, the two drugs currently undergoing clinical

testing for treatment of HIV disease are AZT and DDI. For the use of AZT, the major complication is suppression of normal bone marrow activity. This results in low red and white blood cell counts.The former can lead to severe fatigue and the latter to susceptibility to infections.10 DDI is provided as a powder, which must be reconstructed with water immediately prior to use. The most common adverse effect so far is the weakness in the hands and legs. However, it appears that DDI is free of the bone marrow.11 AZT and DDI both represent the first generation of anti-retroviral drug and it is the hope of many people that they
will be followed by less toxic and more effective drugs.

As it can be seen, haemophilia is one of those sex-linked diseases that must involve the inheritance of both recessive and deficient chromosomes. It is mostly found in males and since every male has a Y chromosome, it is a general rule that the male will not pass it to his male offsprings. Haemophiliacs can have either inherited the disease or they could have had a mutation. In either case, these people must try to live a normal life and must avoid any activities that can result in trauma.
