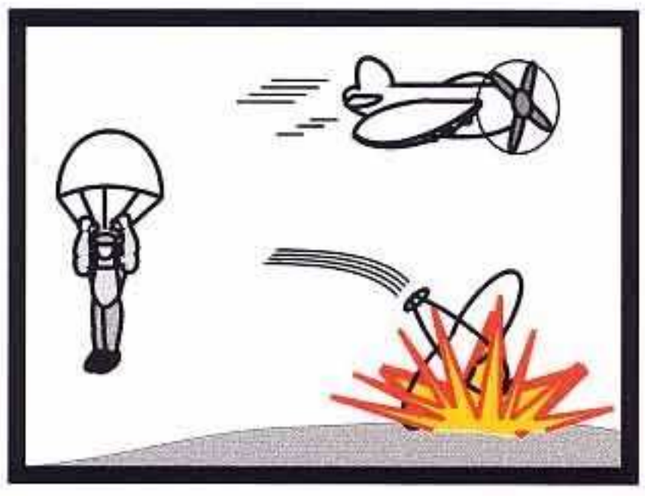
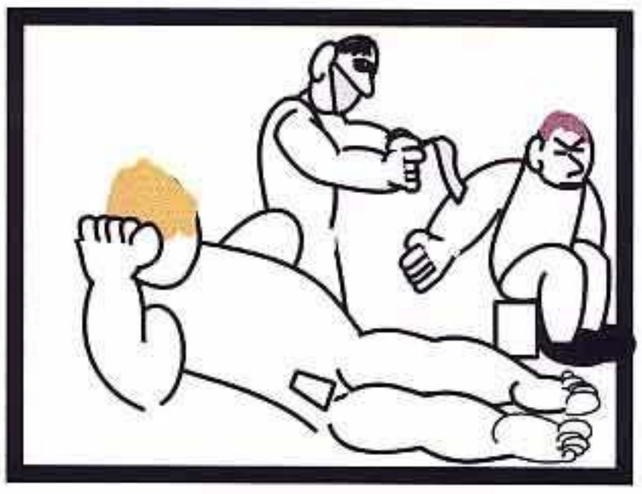
# CHAPTER ELEVEN

# TRANSPLANTS

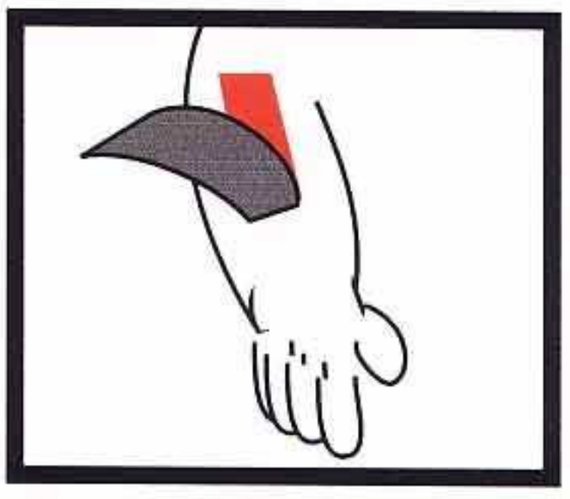
# TRANSPLANTATION CAME OF AGE DURING WORLD WAR TWO



Many of the badly burned pilots required skin grafts.



At first, skin was taken from any donor.



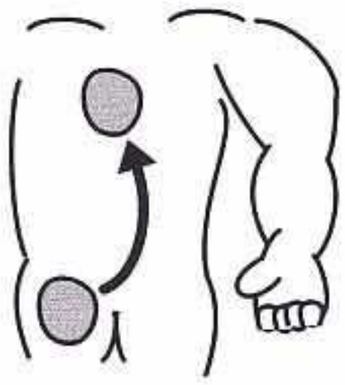
But it invariably peeled away after a few days.

**Easy reading**

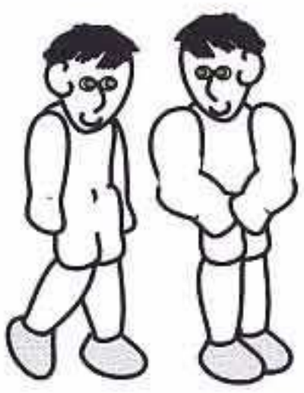
Technical information

Today, organ transplants are much more successful through the advent of many anti-rejection drugs and modern tests.

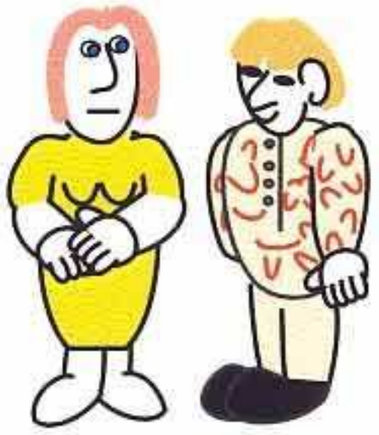
## TRANSPLANT TERMINOLOGY



Autograft: When tissue (ie skin), is moved from one part of the body to another site.



Syngraft: An organ donated from an identical twin.



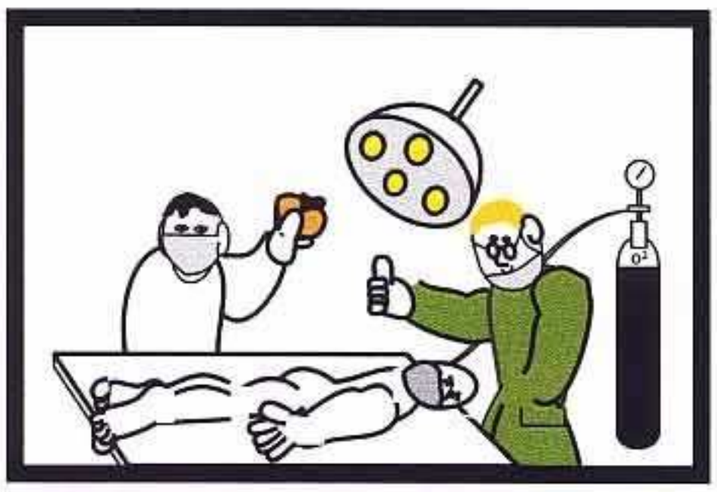
Allograft: An organ which came from a genetically different person.


Xenograft: This is an organ taken from another species (ie a pig).

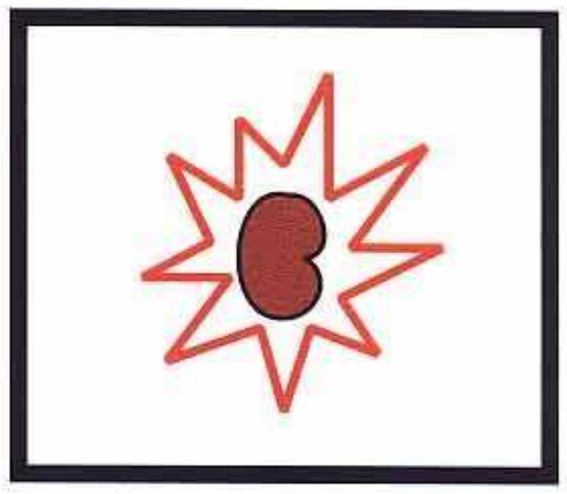
A donor is the person who gives an organ and a recipient is the person who receives it.

# ACUTE ORGAN REJECTION

**This is what would almost invariably occur, if modern drugs and tests were not available.**



**This patient is just about to receive a kidney transplant.**



**10 to 14 days later, it starts to fail and dies.**

T cells entering the graft, destroy it.

## SO WHY WOULD T CELLS ATTACK A HEALTHY GRAFT?

**T cells entering a graft, would find that their 'hands' fitted the 'attack' and 'defence' proteins. However no foreign material is attached to them (see pages 85 and 115).**

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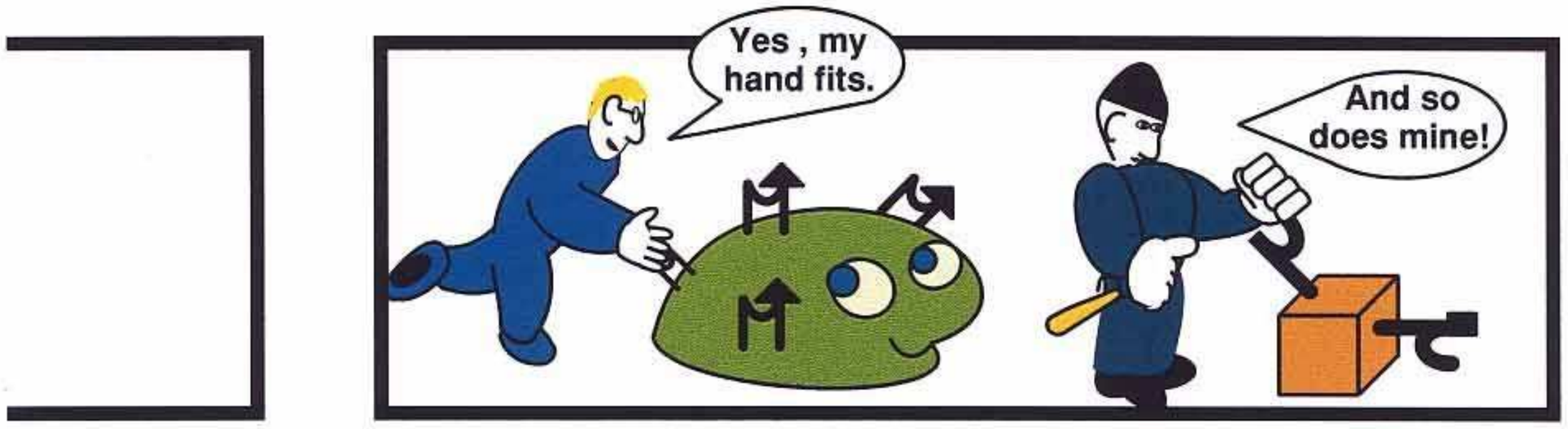
There are actually small shape variations at the top of the 'attack' and 'defence' proteins, inherited from our parents. How we acquire these is shown on page 240.

# INSIDE THE GRAFT



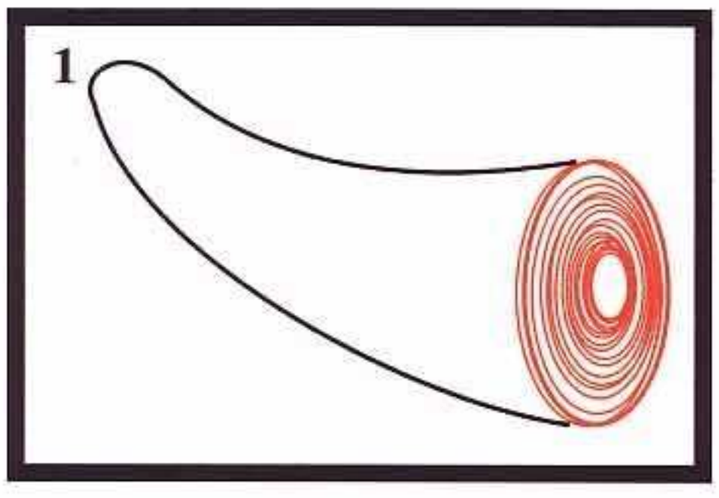

**Both T helper and T cytotoxic cells mistakenly 'believe' that they are confronted with an infection which must be eliminated.**


Inside the transplant are these shaped 'attack' and 'defence' proteins.

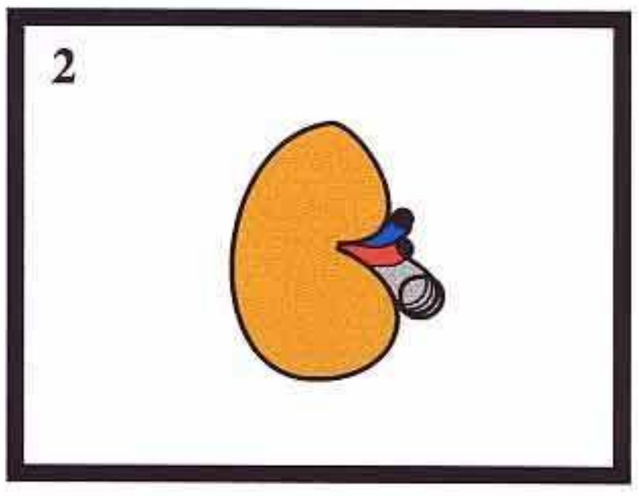
But the recipient has these shaped 'attack and 'defence' proteins.

## CHRONIC ORGAN REJECTION

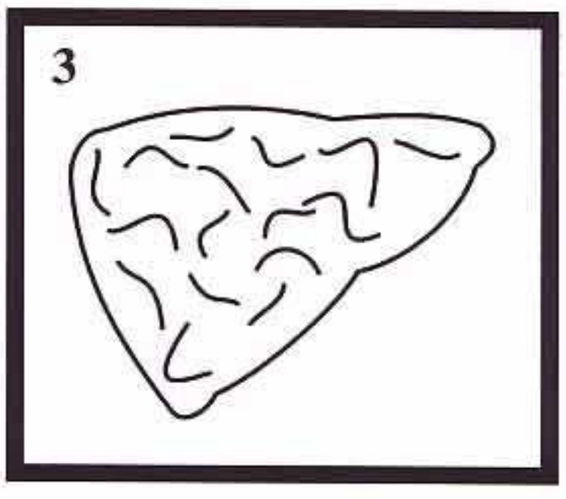
**Years after receiving a transplant, it can gradually fail.**
**This is usually due to one or more causes:-**



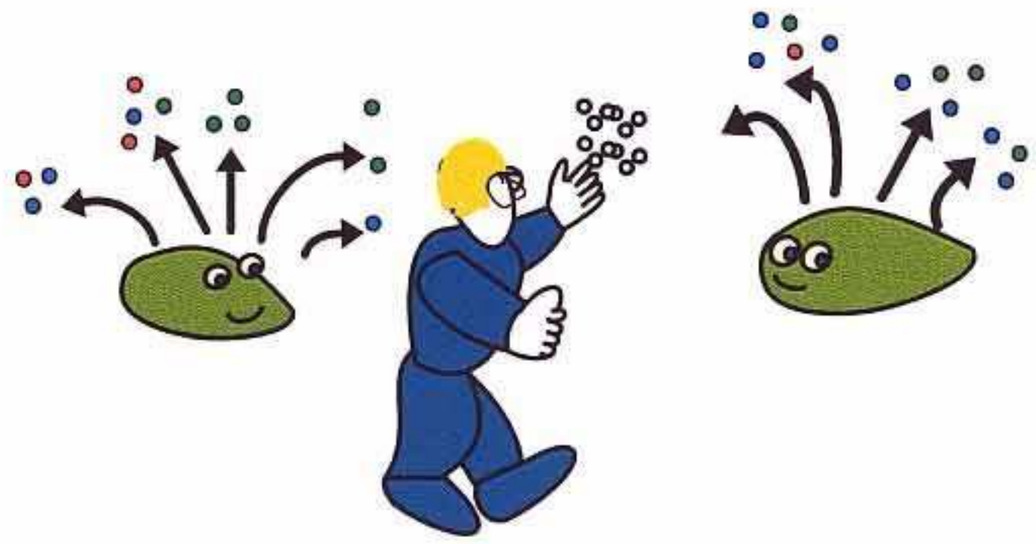

**Inflammatory damage to the arterioles and / or occlusion of the graft's blood vessels.**




**Thickening of the glomerular basement membrane inside a kidney transplant.**

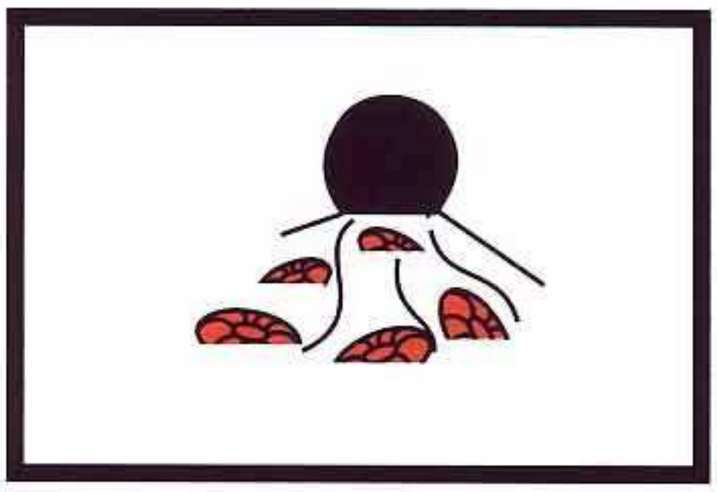



**Generalised fibrosis inside the transplant.**

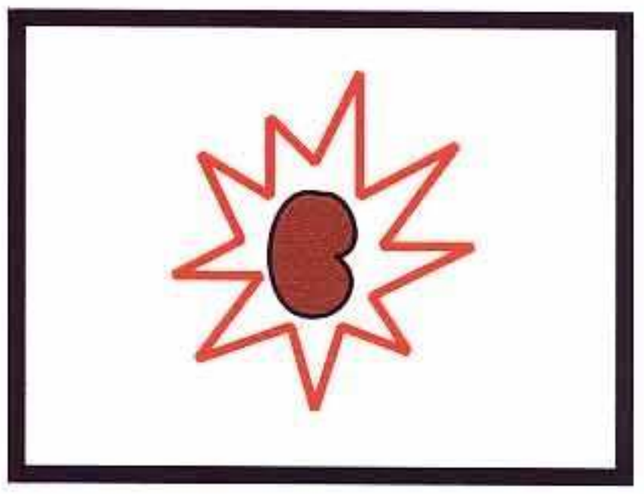


The above could result from T helper cells stimulating the resident macrophages into releasing growth factors, over a prolonged period of time.

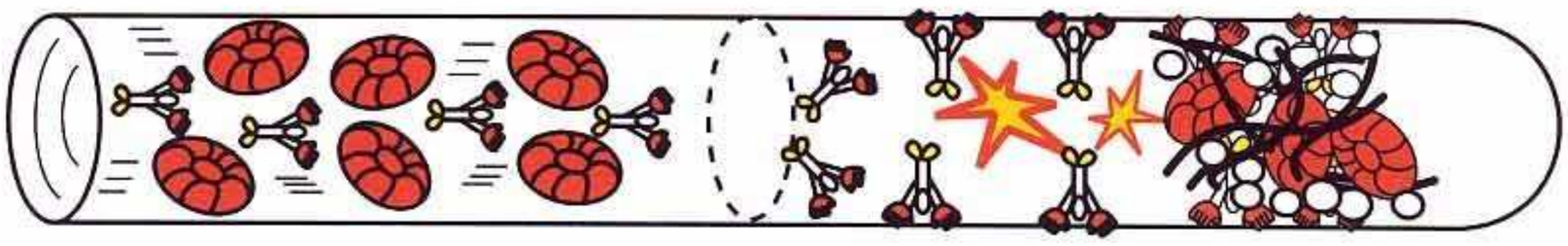
# HYPERACUTE ORGAN REJECTION



**As the operation finishes, blood starts flowing into the transplant.**



**Minutes later, the graft has been rejected and is dead.**



Anti-graft antibodies enter the transplant
and 'grab' the sides of its blood vessels.

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Complement is activated.

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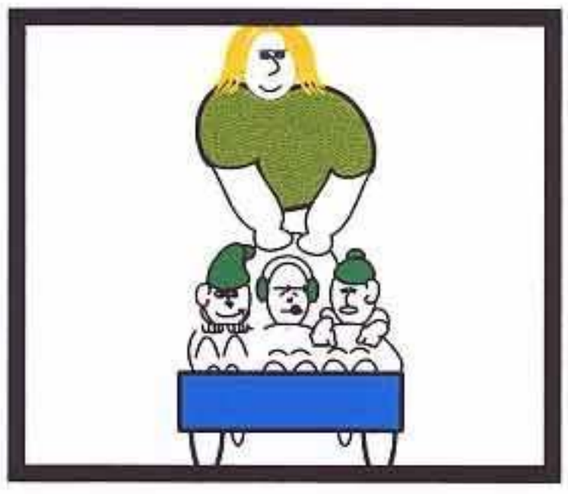
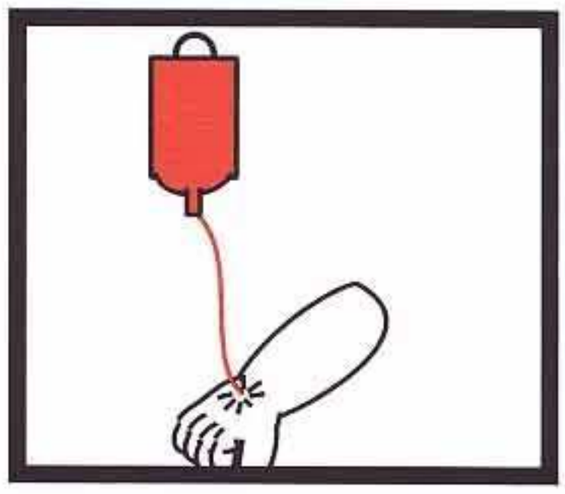
This causes blood clots to form inside
the graft and occlude its arteries.

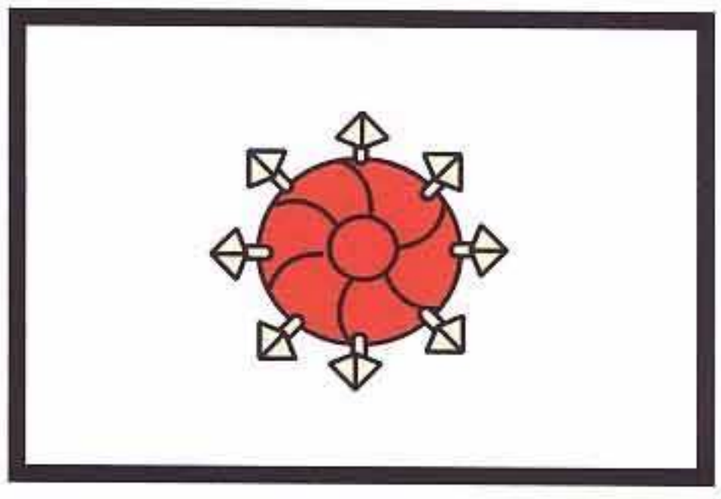
# WHO MAY HAVE ANTI-GRAFT ANTIBODIES IN THEIR BLOOD?



**Mothers who have given birth to a large number of children.**



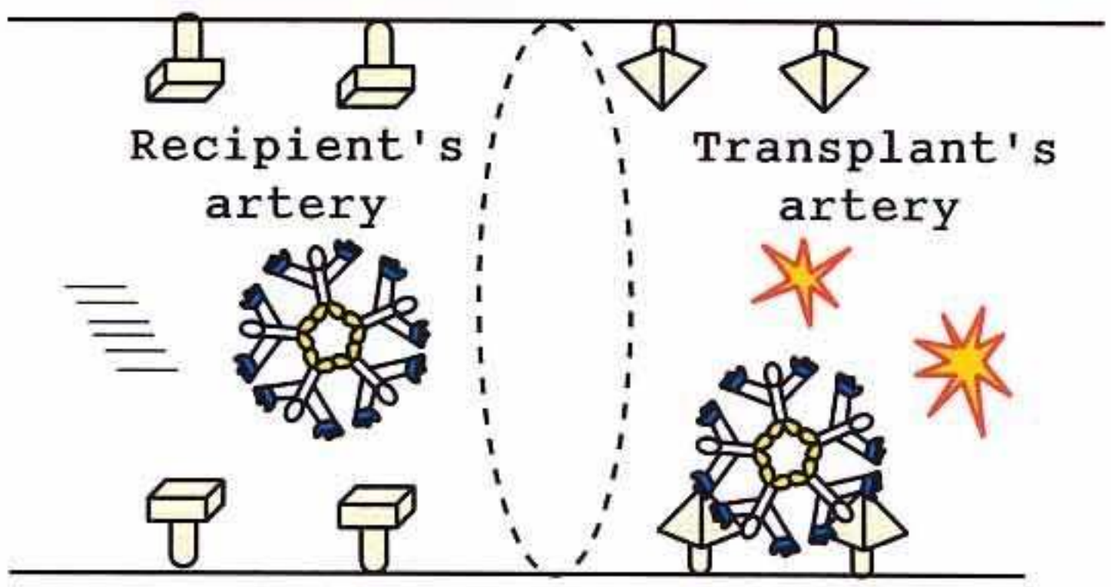
**People who have been given a large number of blood transfusions.**



**Receiving a transplant from a donor with an incompatible blood group** **(see page 226).**

If you reject a transplant from someone (ie skin), then you will not be able to receive a second transplant, like a kidney from the same person. Antibodies with 'hands' fitting their tissue, will now be present.

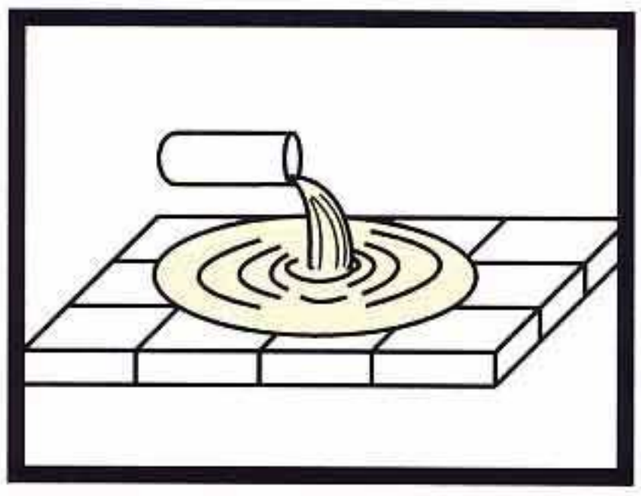
## INCOMPATIBLE ABO BLOOD GROUPS



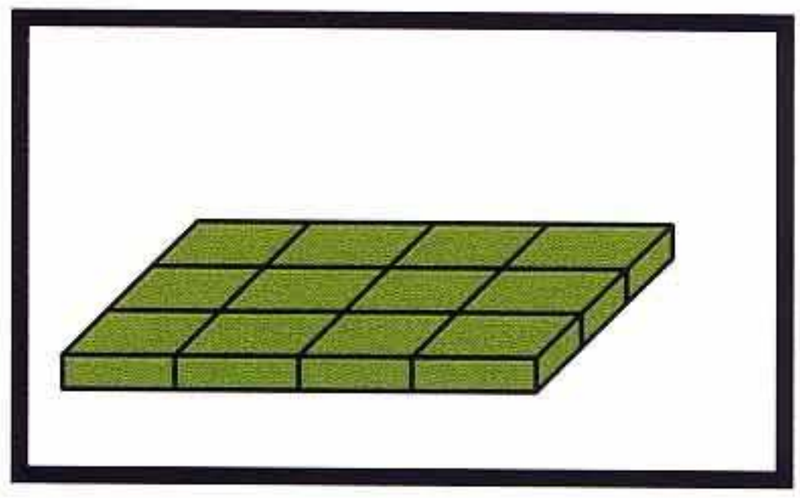

ABO blood group markers (see page 167) also line our blood vessels. Hence a transplant taken from a donor with an incompatible blood group, is doomed from the start.

# HOW TO DETECT IF SOMEONE HAS ANTI - GRAFT ANTIBODIES IN THEIR BLOOD

**Blood is taken from someone who needs a kidney transplant.**



**Their serum is now applied to a small piece of tissue from the proposed organ.**



**A dye is then applied to the tissue.**

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**If the tissue now turns green, no anti-graft antibodies are present.**

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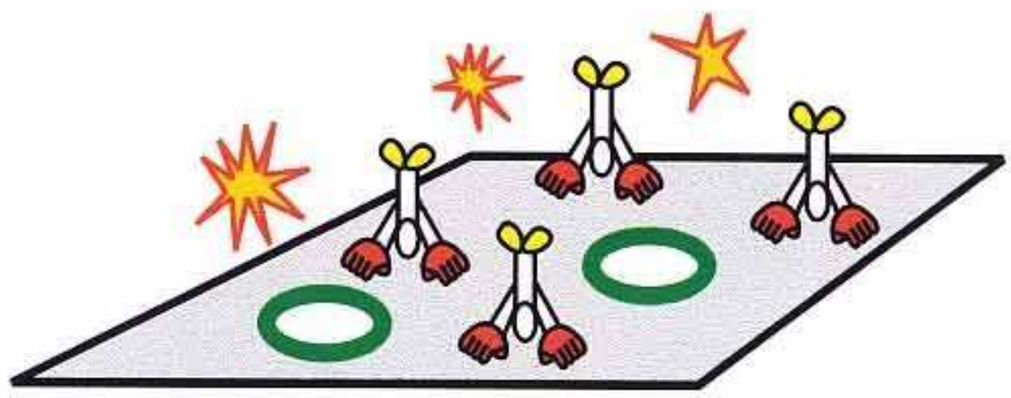
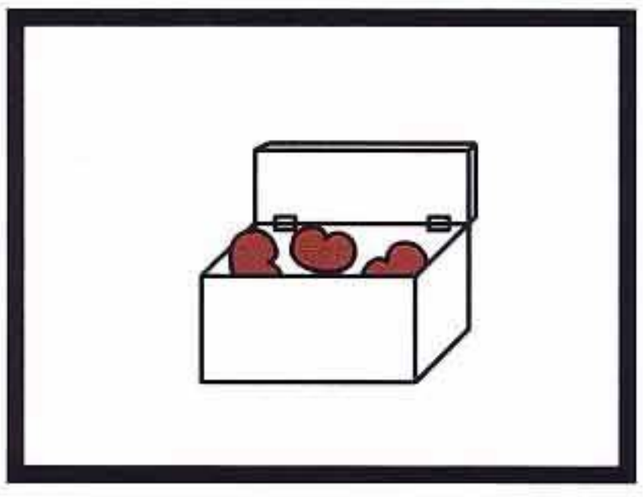
**But if the tissue had turned red, it would have shown that anti-graft antibodies were present.**

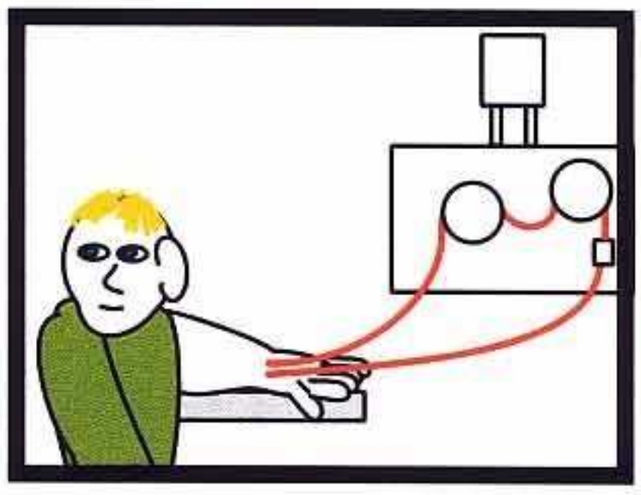


If anti-graft antibodies are present, they will attach onto the tissue sample and activate complement. Holes are punched through its surface (see page 37). The dye can now enter and react with the nuclear material inside and turn the tissue red.

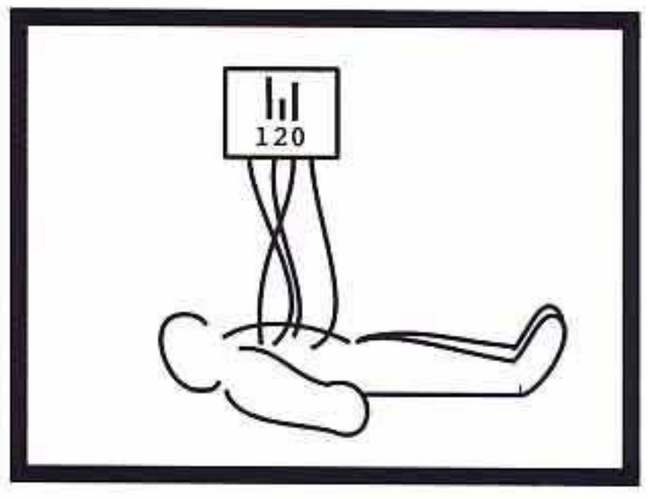
# WHY ARE KIDNEYS THE MOST SUCCESSFUL ORGAN TO TRANSPLANT?



**Kidneys, unlike other organs, can be stored until a suitable recipient is found.**

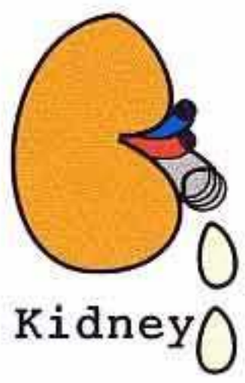


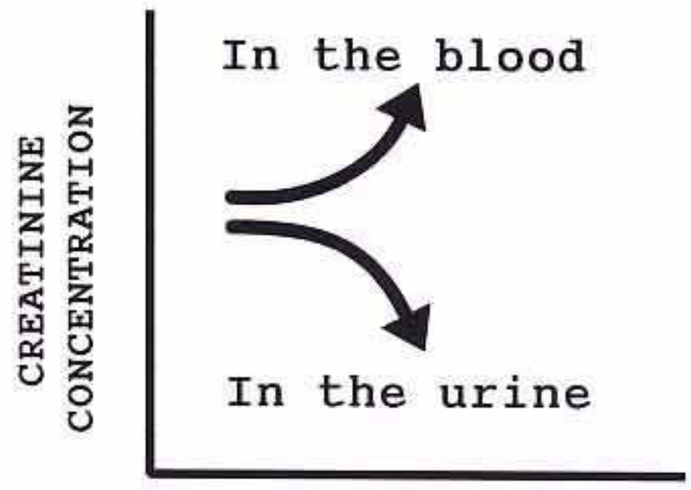
**If both kidneys should fail, dialysis can be started until a suitable kidney is found.**




**But when other organs fail, a patient becomes very ill and needs a transplant quickly.**

## CREATININE CLEARANCE


Creatinine, a waste product from muscle cells, is excreted in the urine by our kidneys.

So if a transplanted kidney starts to fail, less creatinine is filtered out of the blood.

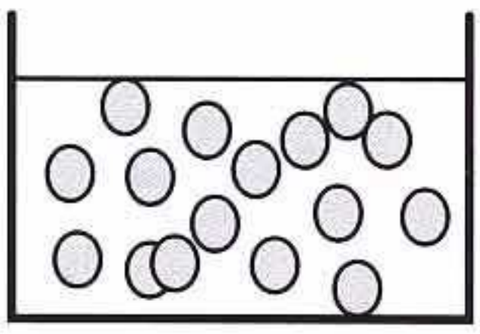
## A MIXED LEUCOCYTE REACTION

**T cells from the recipient and the proposed transplant are mixed together and left for a few days.**

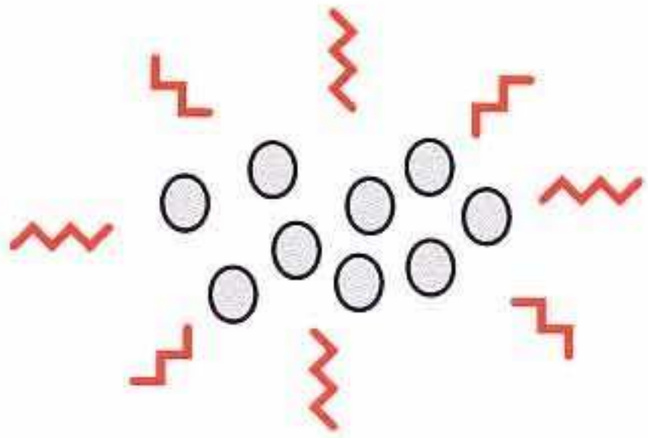

**If both sets of cells coexist peacefully, then the transplant should be accepted.**


**But if a conflict starts, then it is likely that this transplant will be rejected.**

HOW TO DETECT IF THE T CELLS ARE ATTACKING EACH OTHER



The T cells are placed in a medium containing radioactive thymidine.

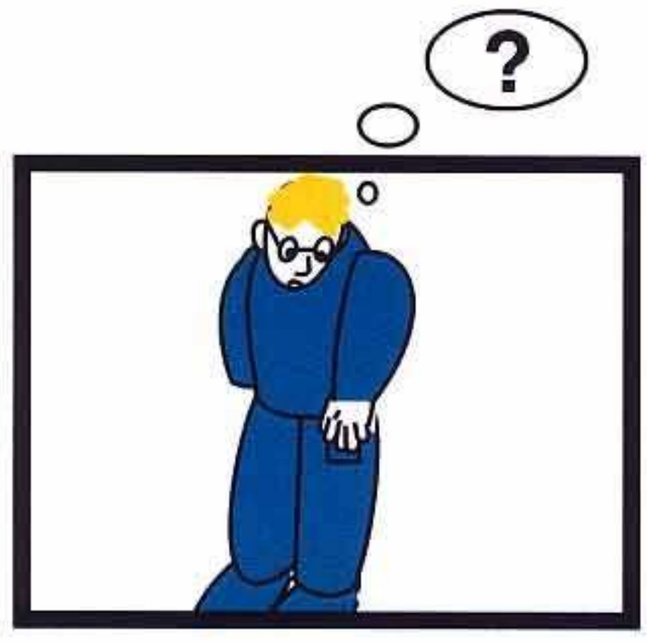


A few days later they are measured for radioactivity.

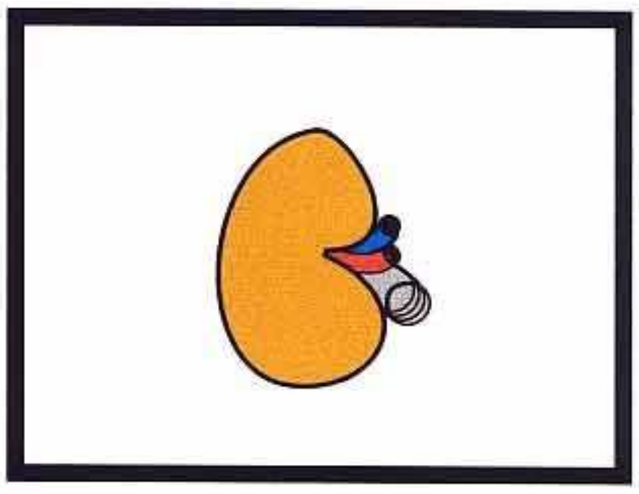
In a conflict, the T cells will start to replicate (see page 115). But to do this they must absorp thymidine.

## CYCLOSPORIN

**This anti-rejection drug, has significantly lengthened the time a transplant survives.**




**Cyclosporin stops T helper cells releasing factors which would damage a transplant.**



**Unfortunately, this drug can be toxic to the kidneys.**

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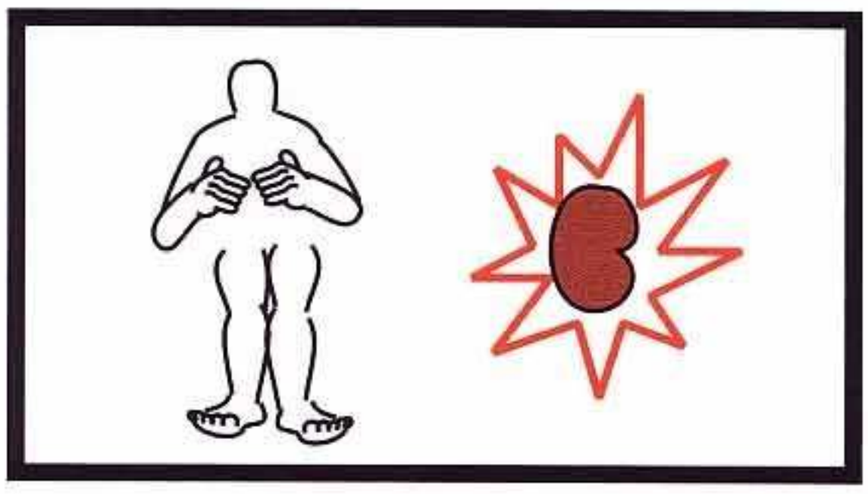
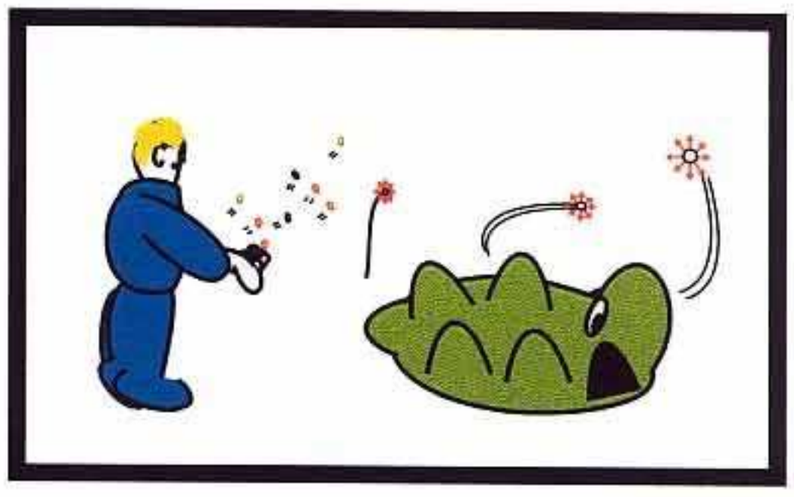
Cyclosporin stops gene transcription inside the T helper cells. This prevents them from releasing factors like interleukin-2 and gamma interferon, which would signal the graft's destruction.

# AZATHIOPRINE

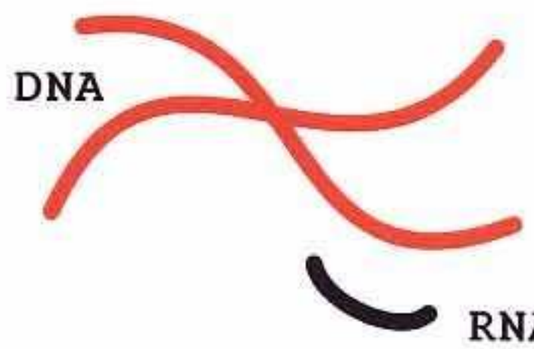


**Azathioprine is used in the treatment of certain autoimmune diseases and to help prevent transplant rejection.**



**It appears to limit the production and discharge of cytokines from macrophages and T helper cells.**

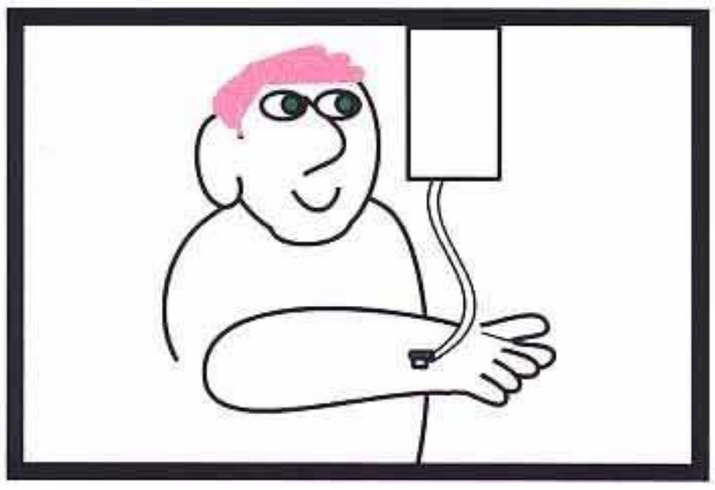
**After receiving a transplant, the patient must take immunosuppressive drugs for the rest of their life. Unfortunately this greatly increases the risks of acquiring certain cancers and life-threatening infections. Perhaps a new approach is needed for the 21st century!**




Azathioprine, being an antimetabolite, affects RNA synthesis (see page 130).

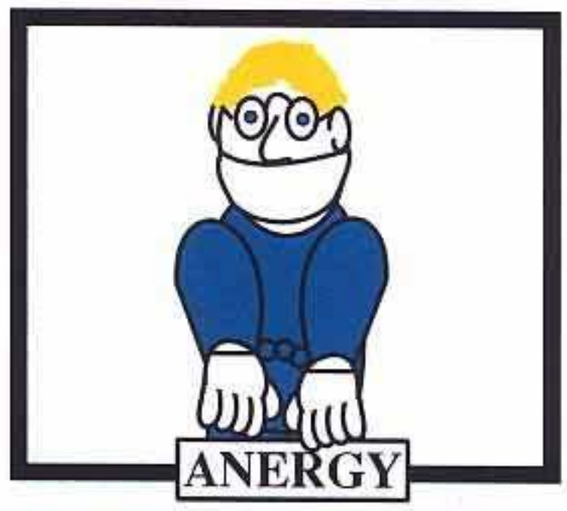
## SIMULECT

**This recently developed anti-rejection drug, uses monoclonal antibodies (see page 258).**

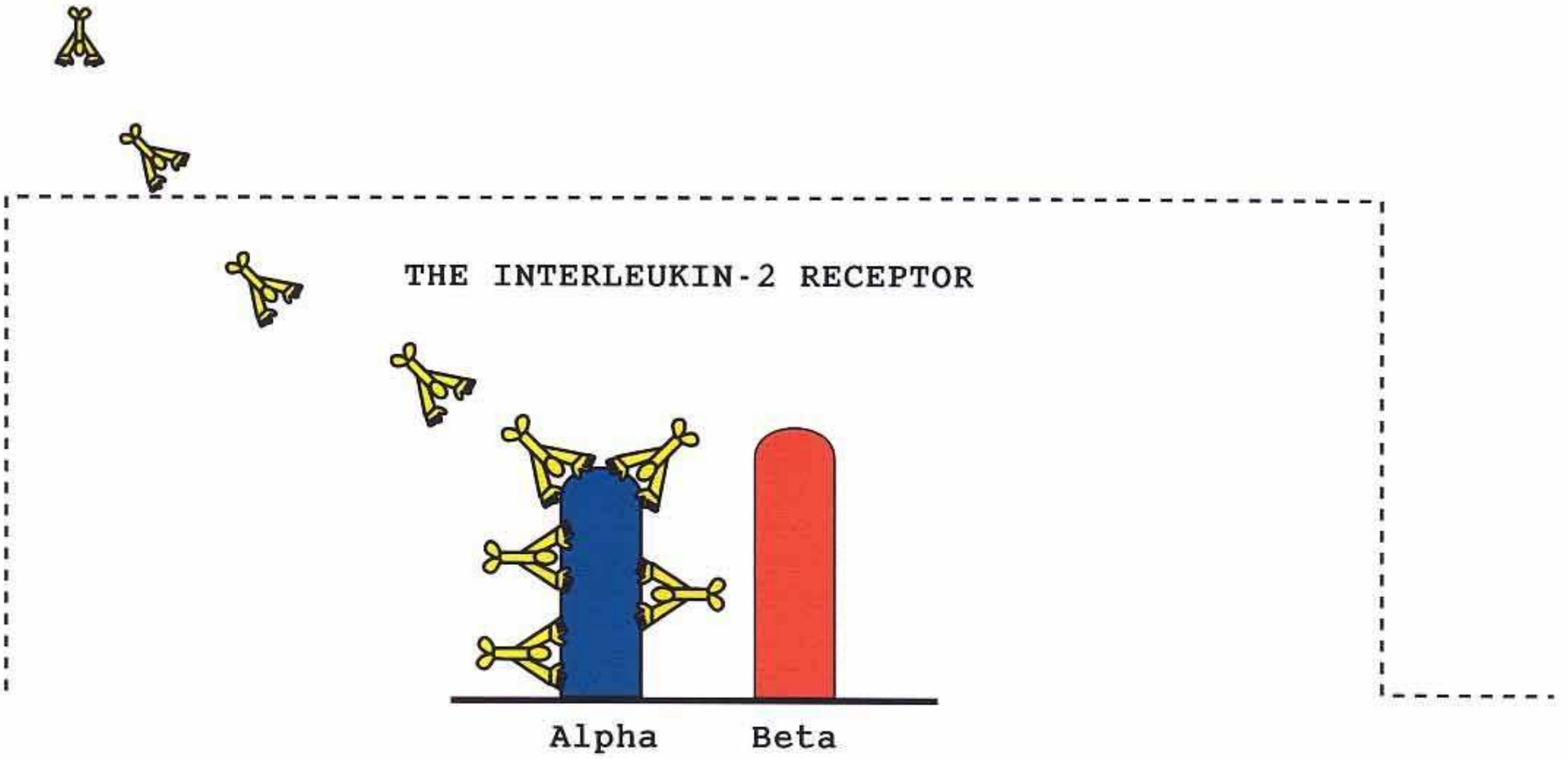


**Simulect is given just prior to transplant surgery. It contains antibodies which will attach on-to all the patient's T helper cells.**

**Following surgery, some of the T helper cells now entering the transplant, start to attack it.**

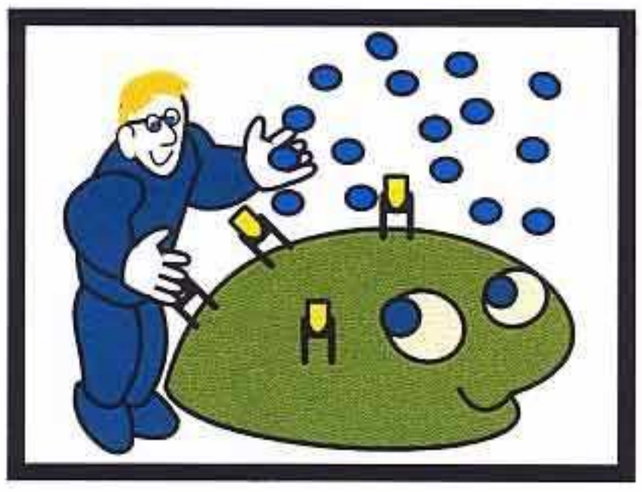



**The attached antibodies now take effect. They appear to 'switch off' these T helper cells.**

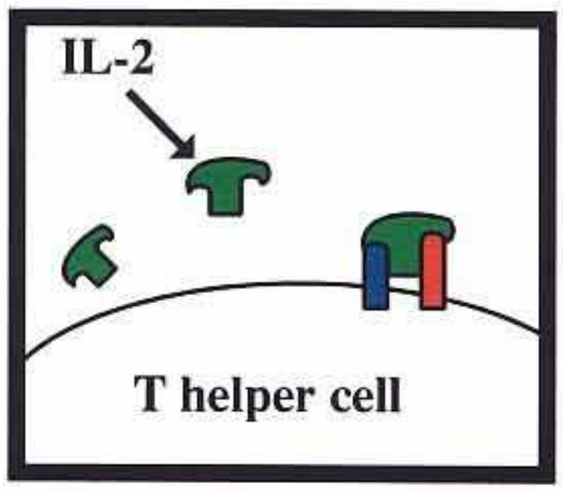



The 'hands' of these antibodies, only fit the alpha chain of the T helper cell's interleukin-2 receptor.

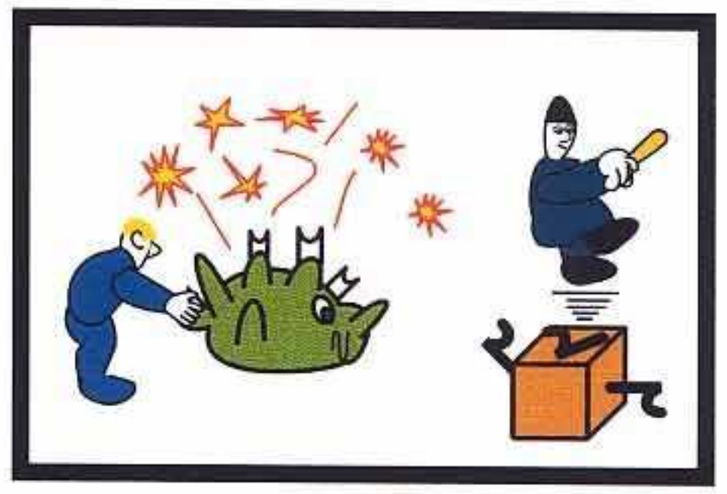
# WHY IS THE INTERLEUKIN - 2 RECEPTOR SO IMPORTANT?



This T helper's 'hand' fits and it receives the second signal, interleukin-1 (IL-1).




The T helper will now release interleukin - 2 which must bind onto its interleukin-2 receptor.



Only now can it release the cytokines which will activate any T cells and macrophagses which are close by.

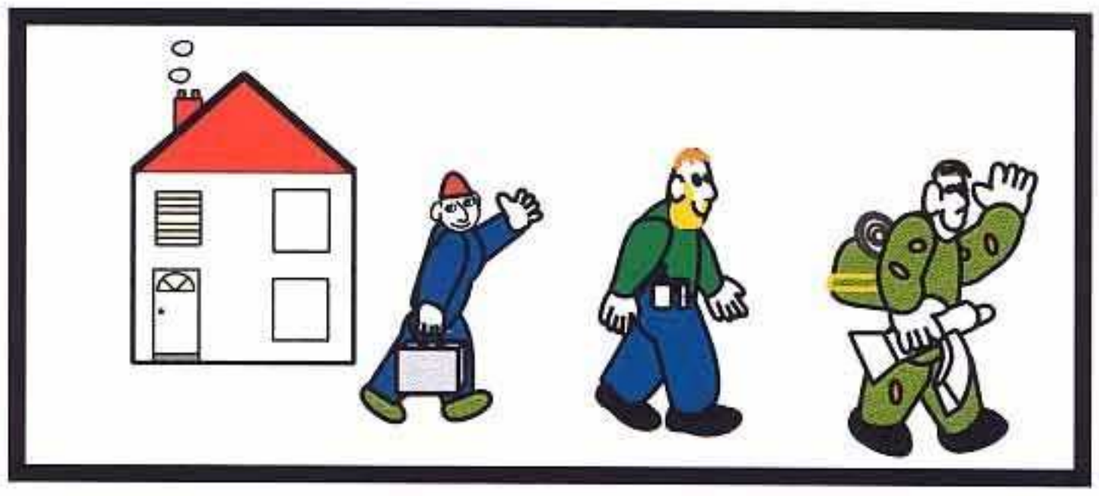
But when antibodies attach onto the alpha receptor, they block the interleukin-2 (IL-2).

**ANERGY**

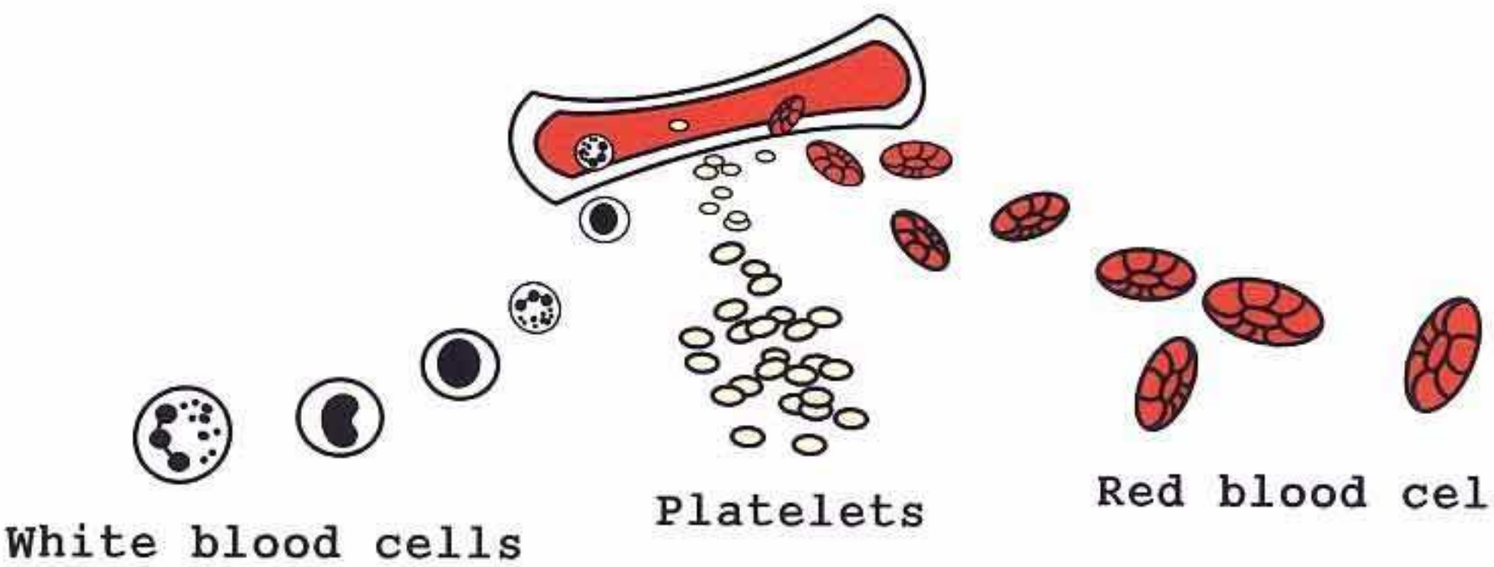
The drug only remains active for about 4 weeks. However, early results indicate that little or no immunosuppression is needed following transplant surgery.

If it is possible to 'switch off' active T helper cells, it might now be possible to cure many autoimmune disorders.

# THE BONE MARROW

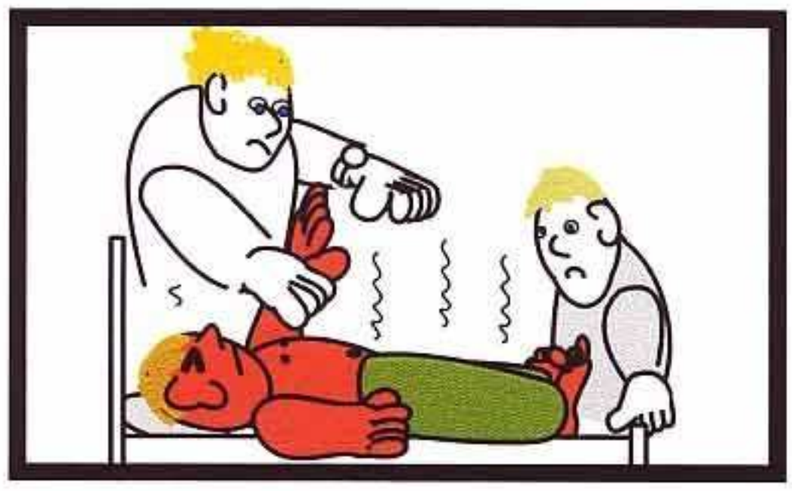


**The bone marrow is where blood cells are born and develop, before entering the circulation.**




Some of the main factors to appear from the bone marrow, are immune cells like neutrophils, platelets (which enable blood to clot) and red blood cells.

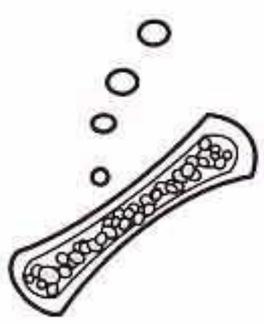
## DOCTOR GRAY WAS WORRIED ABOUT JASPER



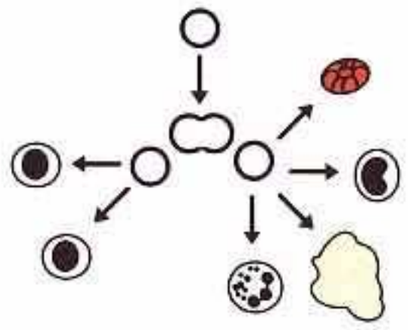
Young Jasper had a variety of symptoms which included a high temperature and bruising.

Sadly, blood and bone marrow samples confirmed that he has leukaemia.

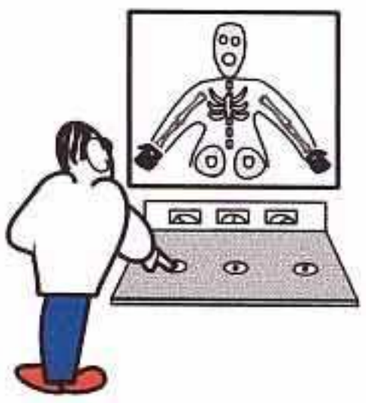
### WHAT CAN ADVERSELY AFFECT BONE MARROW FUNCTION?



Useless leukaemic cells filling up the bone marrow.

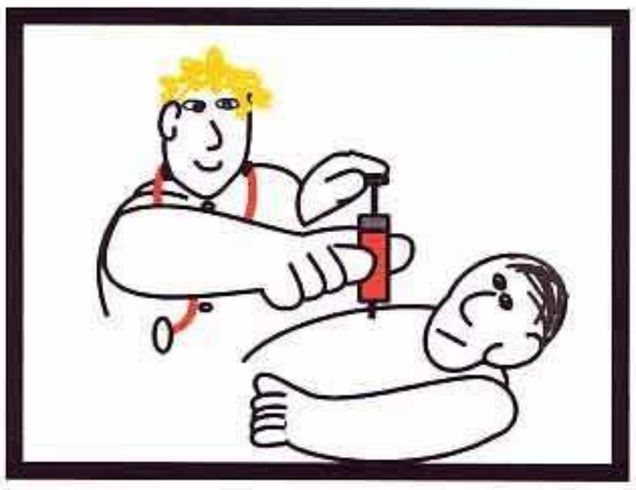


Inherited gene defects affecting cells in the marrow (see page 294).

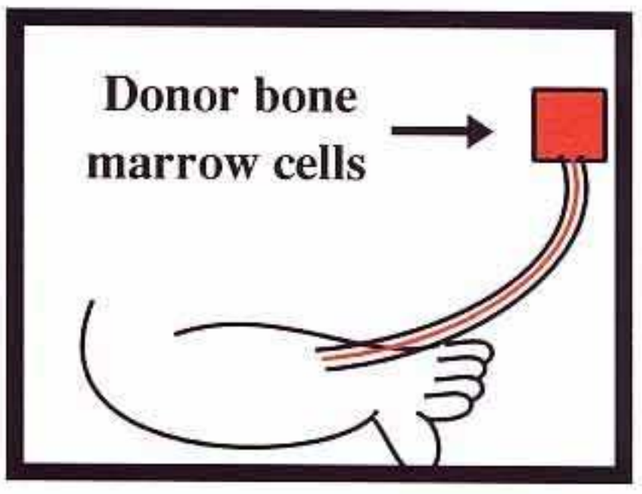


Large doses of radiotherapy and cytotoxic drugs.

Jasper undergoes his chemotherapy.



In the meantime, a donor was found and some of his bone marrow removed.

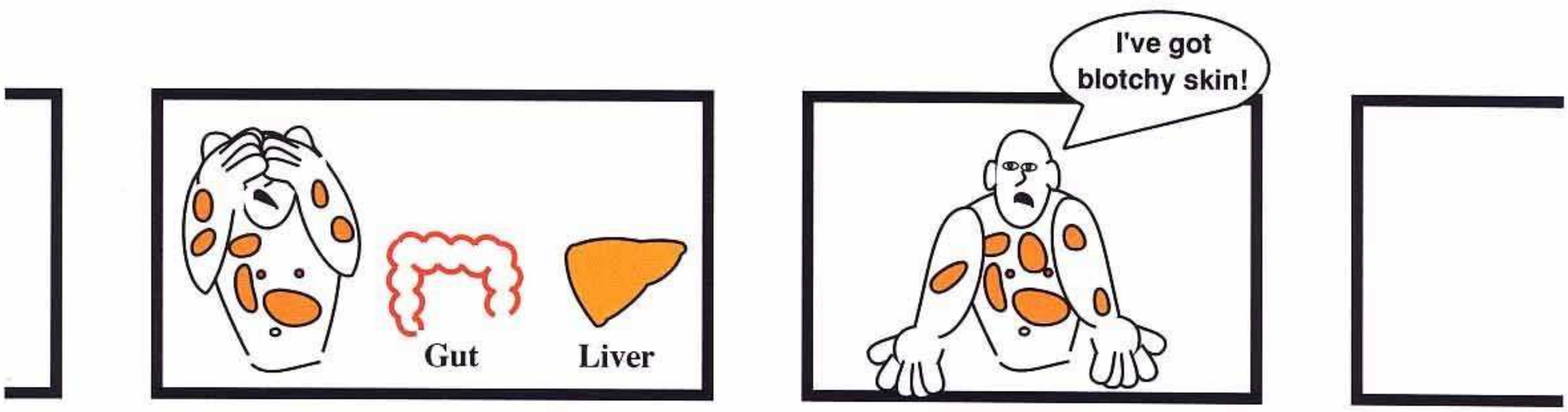



On entering one of Jasper's veins, the cells will find their own way to his bone marrow.

---

To prepare Jasper's body for a bone marrow transplant, his bone marrow is emptied of all resident cells. Then, when he is given the bone marrow cells, these will have space to move into and hopefully start to repopulate his bone marrow.

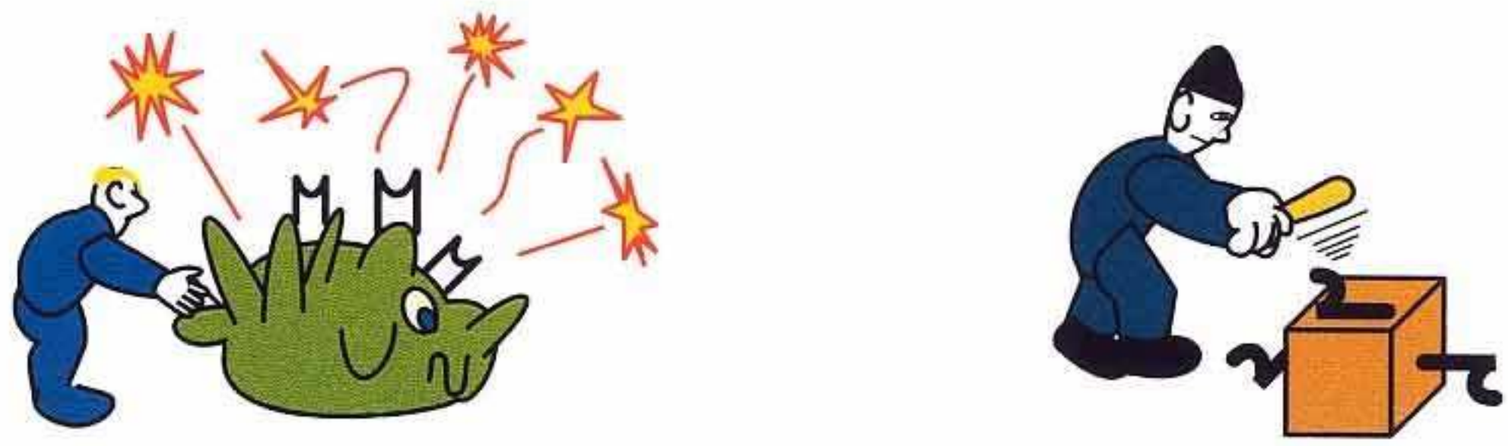
# GRAFT - VERSUS - HOST DISEASE




**Jasper starts to experience serious side effects to his skin, gut and liver.**

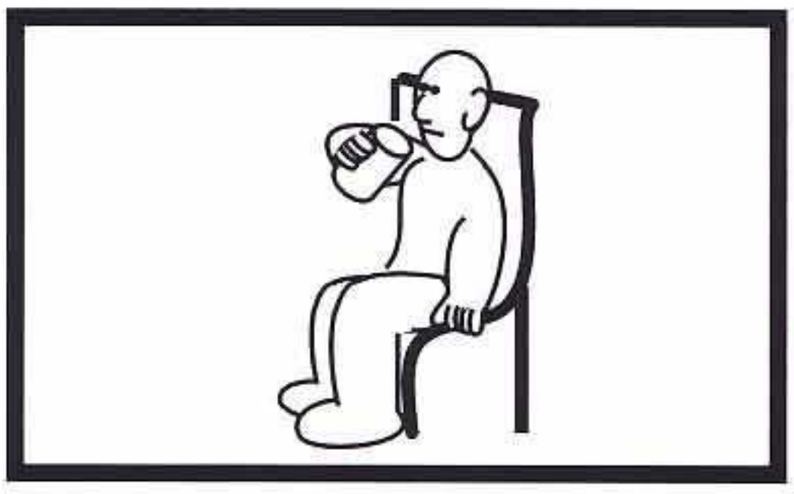
**The infused cells have started to attack Jasper and could kill him.**

**This can occur when incompatible bone marrow cells are given to a host with few, if any, of their own immune cells.**

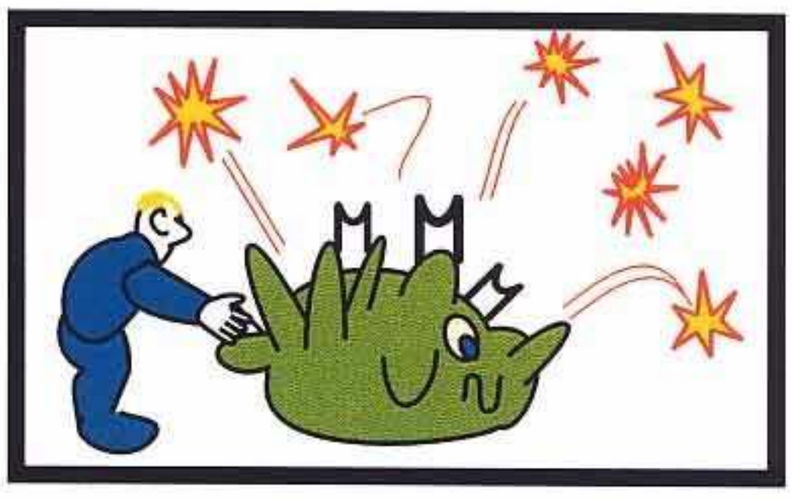


Mature T cells entering Jasper, perceive that they are encountering infected material, because their 'hands' fit his 'attack' and 'defence' proteins.

## DANGER



**Jasper must now undergo further chemotherapy, to quickly kill off the infused cells, before they kill him!**



**Ironically, part of the damage is due to the infused T cells, stimulating his resident macrophages.**

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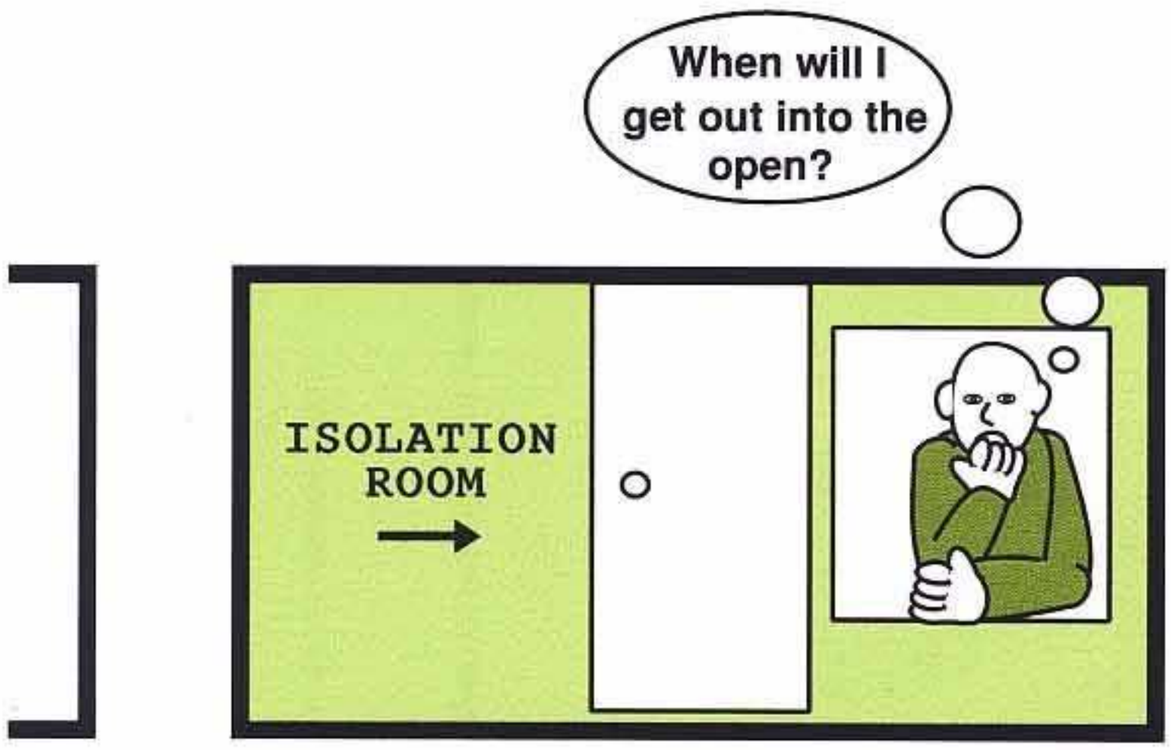
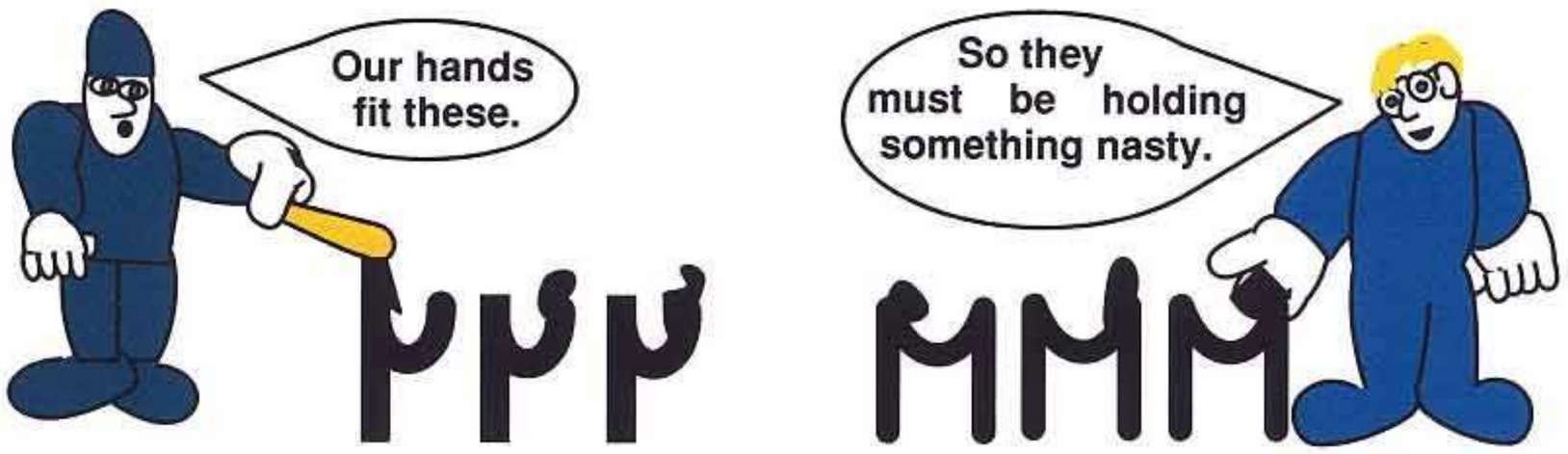
If the mature T cells are removed from the extracted bone marrow before it is given to the patient, then the risks of a graft-versus-host reaction occurring are minimised.




Sadly, a bone marrow transplant minus mature T cells, may now take much longer to repopulate a person's bone marrow.

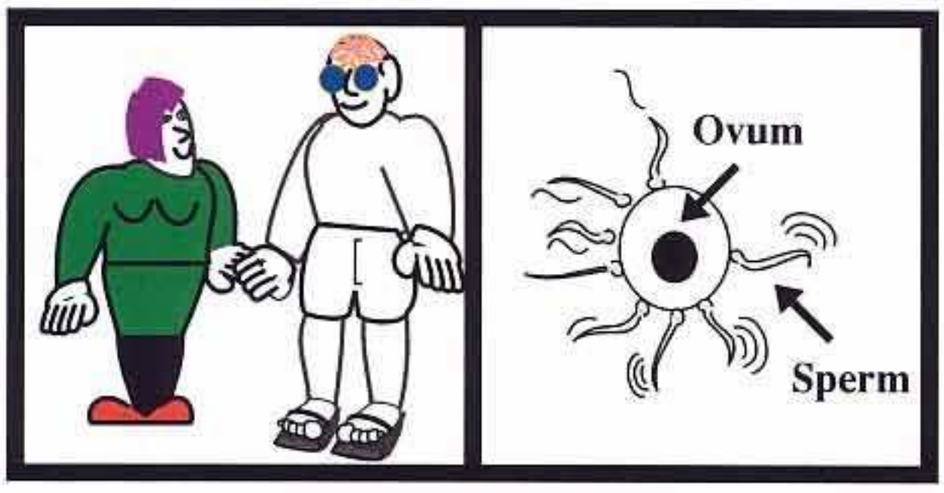
And while poor Jasper has only a few immune cells to protect him, he is at risk from life-threatening infections.

**People with a severely depleted immune system may be referred to as 'immuno - compromised'.**

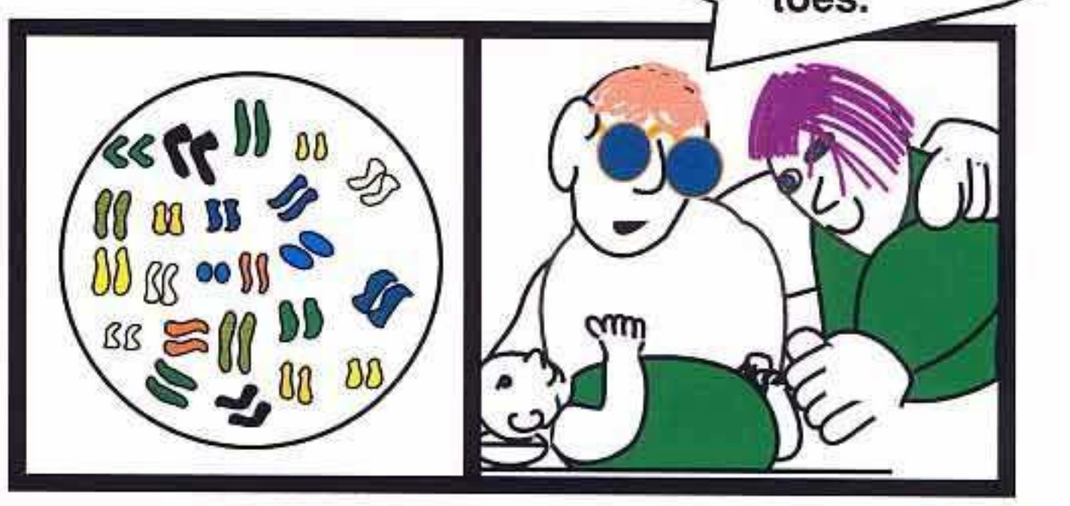



The problem, is that T cells in the extracted bone marrow, came from someone with different shaped 'attack' and 'defence' proteins. How we acquire these shapes, is now shown on the following pages.

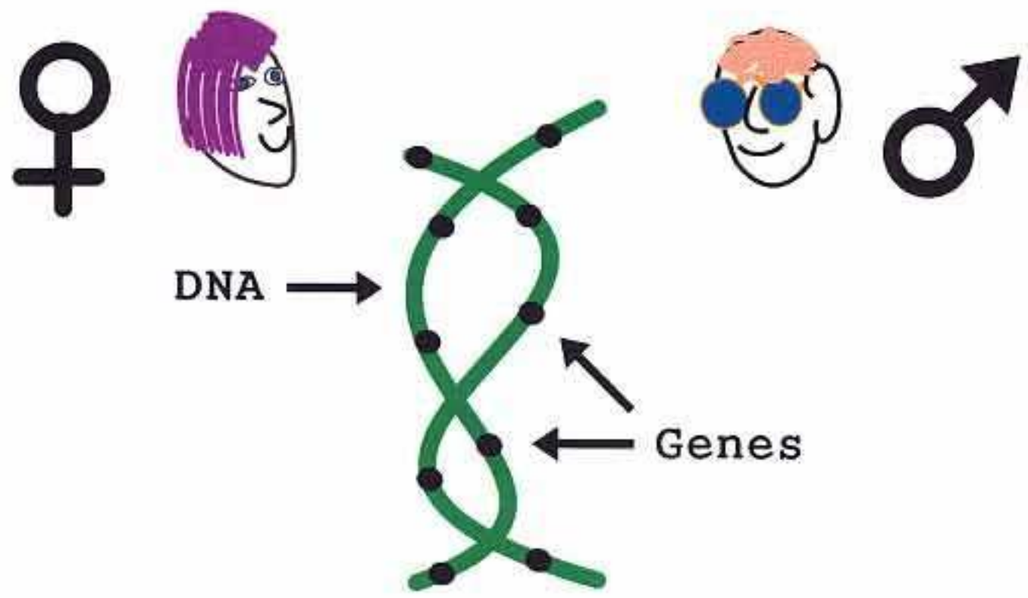
# KERRY AND STEVE DECIDE TO MAKE A BABY




A sperm carrying 23 chromosomes, fertilises the mother's ovum, which also contains 23 chromosomes.

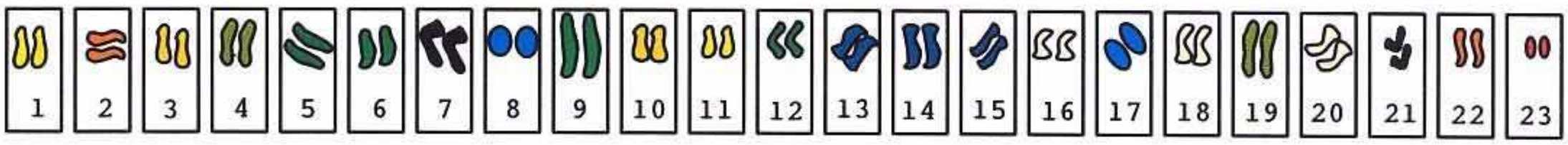



As the fertilised ovum now contains 23 pairs of chromosomes, the resulting baby will have characteristics (traits), from both parents.

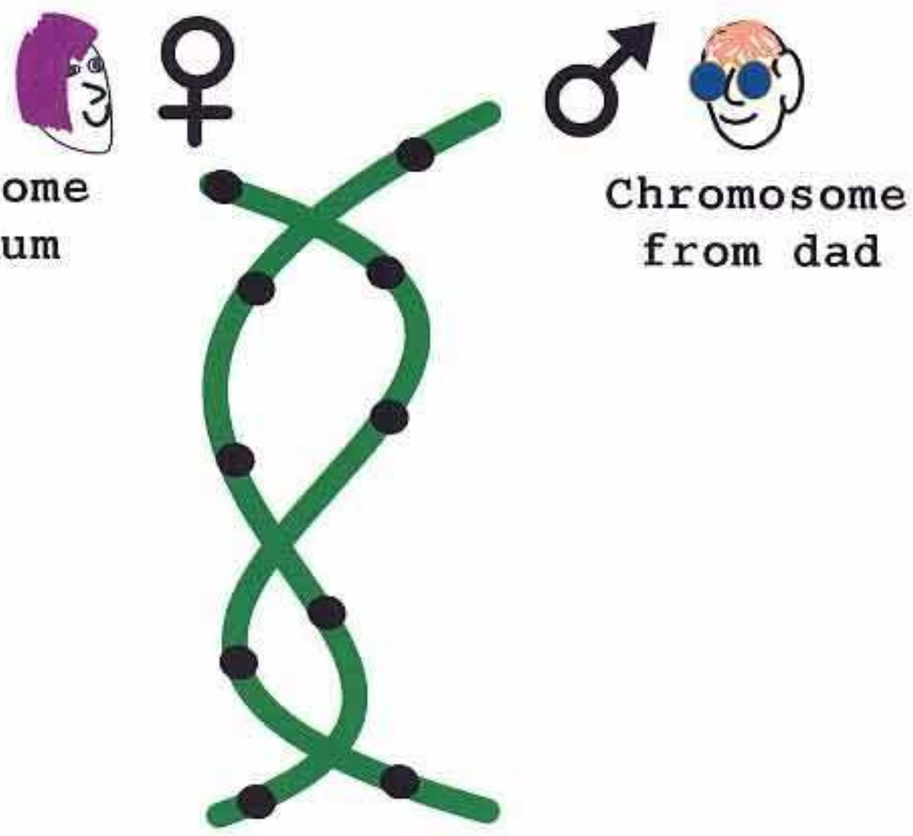


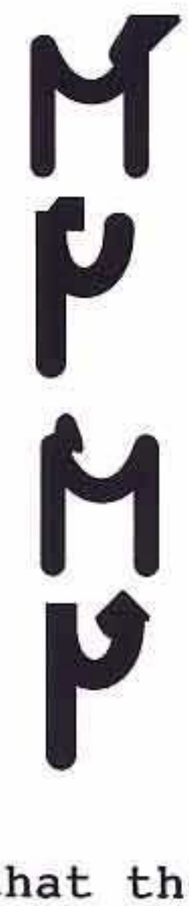

Each pair of chromosomes, has a strand of DNA from the mother and another strand of DNA from the father.

## A CHILD GETS ITS GENES FROM BOTH PARENTS




In every nucleated cell in your body, are 23 pairs of chromosomes. Half of each pair comes from mum and the other half comes from dad.



Shapes from the father

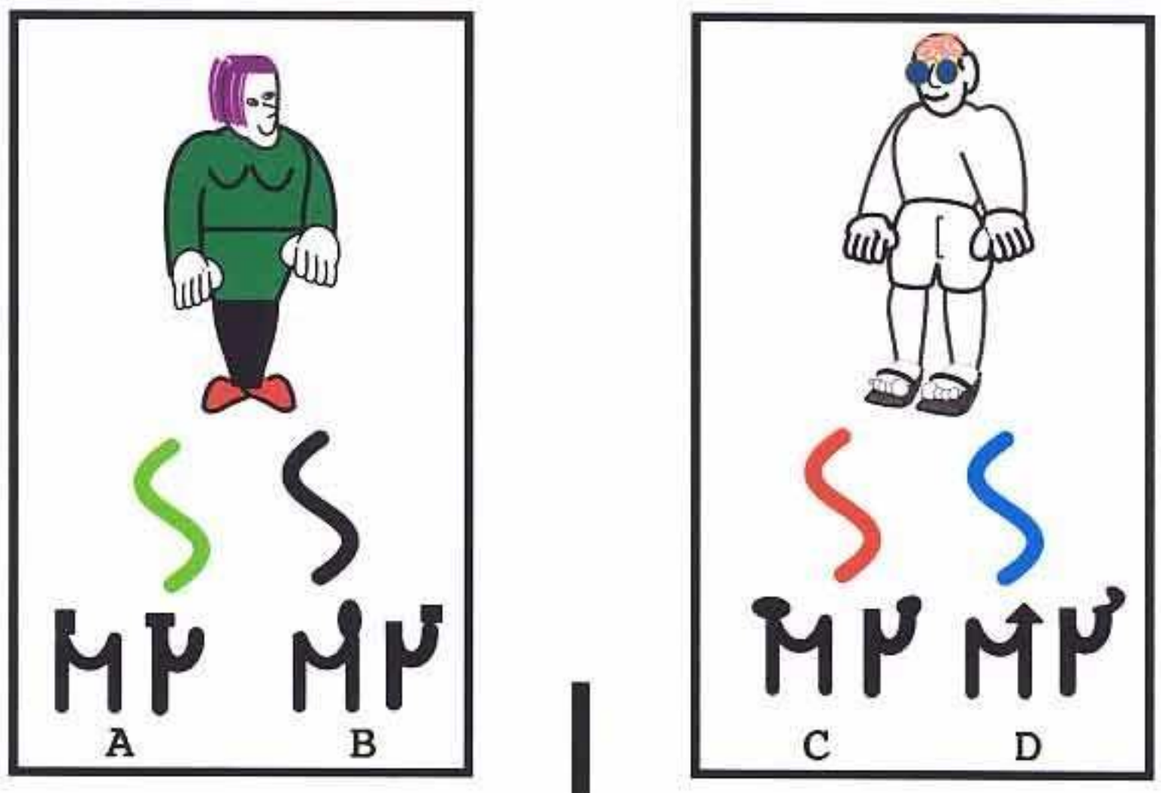
Shapes from the mother

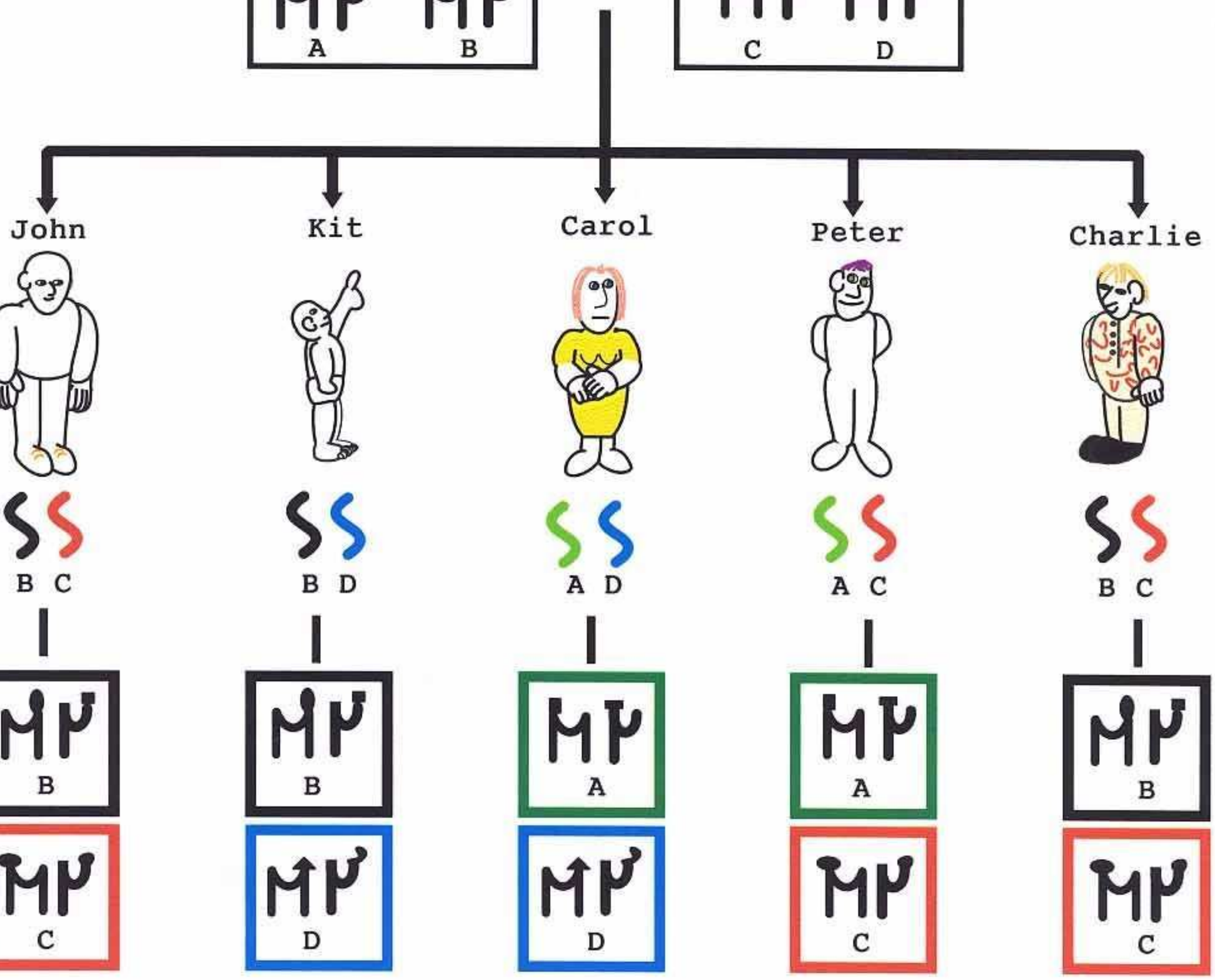
Along chromosome number 6, are the genes that code for the 'attack' and 'defence' proteins.

But note that there are 2 sets of 'attack' and 'defence' proteins. One set from dad and the other from mum.

A child will get one strand of chromosome No.6 from one parent and the other strand of chromosome No.6 from its other parent.

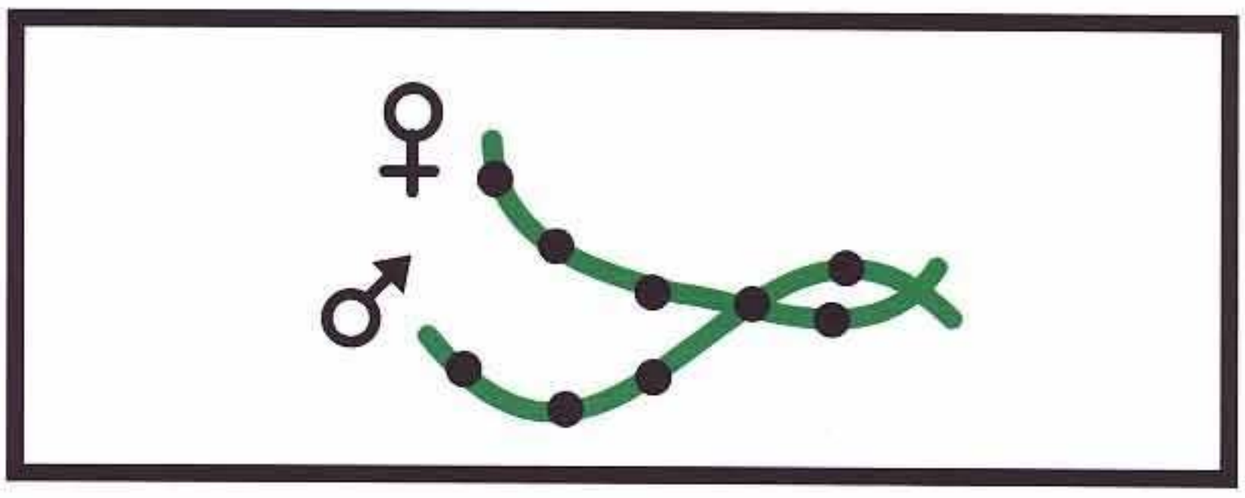
Genes along chromosome No.6 code for both the 'attack' and 'defence' proteins.



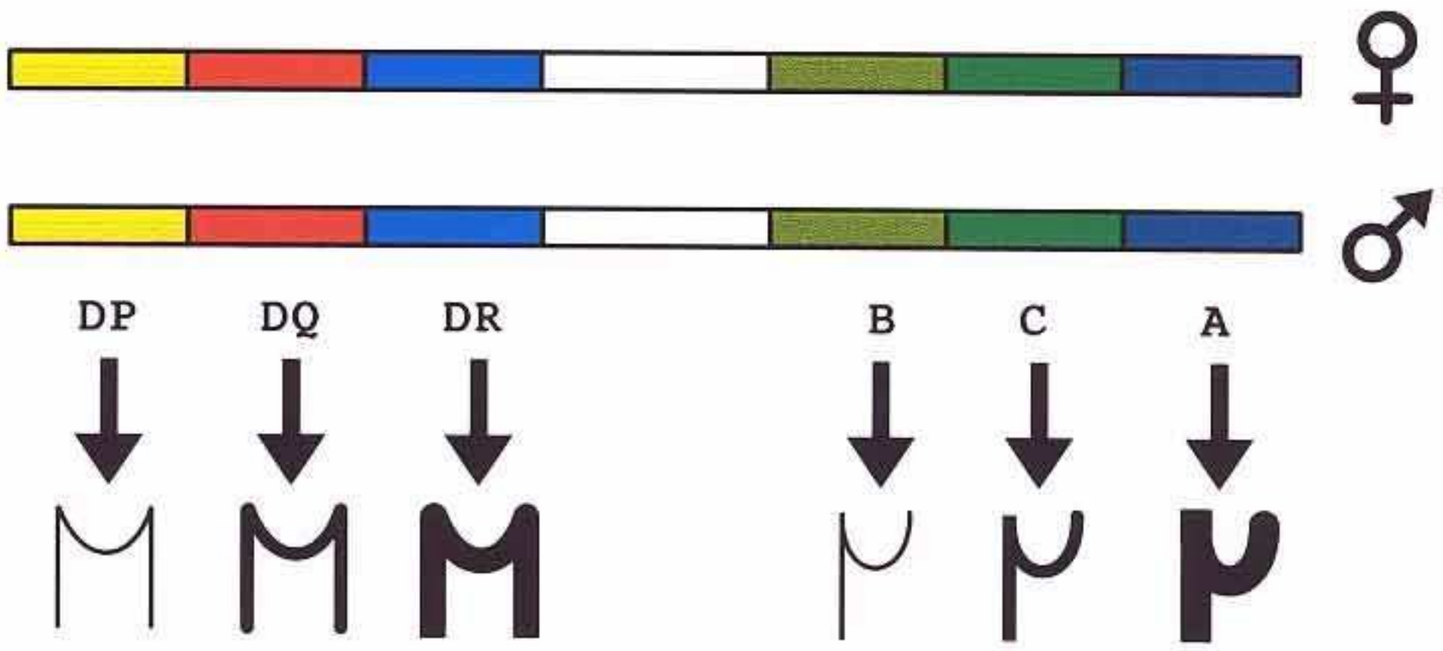

If Kerry and Steve have 5 children, it is possible that only 2 of their offspring will inherit the same gene combination and therefore the same shaped 'attack' and 'defence' proteins.

# A CLOSER LOOK AT CHROMOSOME NUMBER 6



**The string of genes along chromosome number 6 coding for the 'attack' and 'defence' proteins, are called the "major histocompatibility complex" (MHC)**
**(see pages 77 and 110).**

Here the genes making up the MHC have been enlarged.




Everyone has 3 types of 'attack' proteins: DP, DQ and DR...
..... and 3 types of 'defence' proteins: A, B, and C....
.....inherited from each parent.

## TISSUE TYPES

There are many different shaped 'attack' and 'defence' proteins and each of us inherits a certain set of shapes from our parents. It is this set of shapes, which constitutes someone's tissue type.