MEDICINE
KING SAUD UNIVERSITY

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Renal Block

Lecture Two

Transplantation

IMMUNOLOGY
436's TEAMWORK

Objectives:

- To understand the **diversity** among human leukocyte antigens (**HLA**) or **major** histocompatibility complex (**MHC**)
- To know the **role of HLA** antigens in transplant **rejection**
- To be familiar with **types of immune responses** mediating transplant rejections and importance of tissue matching
- To understand the **principles of management after** transplantation

- **Important.**
- **Extra notes.**
- **Doctors' notes**

Major Histocompatibility Complex and Transplantation

HLA &. MHC

Both are group of antigens or proteins that are found in the surface of cells and in the genetic makeup or DNA. Their functions are also very similar. They identify and prevent a foreign protein or cell in entering or its spreading in an organism's body. in coordination with the immune system which attacks these foreign bodies.

The main difference between the two groups is that MHC is often found in vertebrates while HLA is found only in humans. To simplify, HLA is the human body's version of MHC.

- Major histocompatibility complex (MHC) proteins were discovered for the first time with the advent of **tissue transplantation**.
- The success of tissue and organ transplantation depends upon the donor's and recipient's "**human leukocyte antigens**" (HLA) encoded by HLA genes.
- These proteins are **allo-antigens**. (alloantigen is any antigen present in only some individuals, that stimulates the production of antibodies in those who lack it)

MHC Class I Proteins:

MHC Class I are glycoproteins found on surface of virtually all the **nucleated cells**.

- **Cytotoxic T cell** kills virus infected cells in association with **class I MHC** proteins.

MHC Class II Proteins:

MHC Class II glycoproteins are normally found on the surface of **antigen presenting cells** (macrophages, B cells, dendritic cells and Langerhans cells).

- **Helper T cell** recognize antigen in association with **class II MHC** proteins.

MHC Genes:

- Genes for HLA proteins are clustered in the MHC complex located on the short arm of chromosome **6**.
- Three genes HLA-**A**, HLA-**B** and HLA-**C** code for **Class I MHC** proteins.
- HLA-**D** loci encode for **Class II MHC** proteins ie, D**P**, D**Q** and D**R**.

MHC Genes

Each individual has two "**haplotypes**" i.e, two sets of these genes one paternal and one maternal.

MHC class	I			II			III	
Region	A	B	C	DP	DQ	DR	C4, C2, BF	
Gene products	HLA-A	HLA-B	HLA-C	DP	DQ	DR	C' proteins	TNF-α TNF-β
Polymorphisms	47	88	29	More than 300 HLA-D				

*MHC Class II Has more effective results than Class I due to its high number of polymorphisms

Minor HLA genes and Transplantation:

Minor HLA genes **(unknown)**:

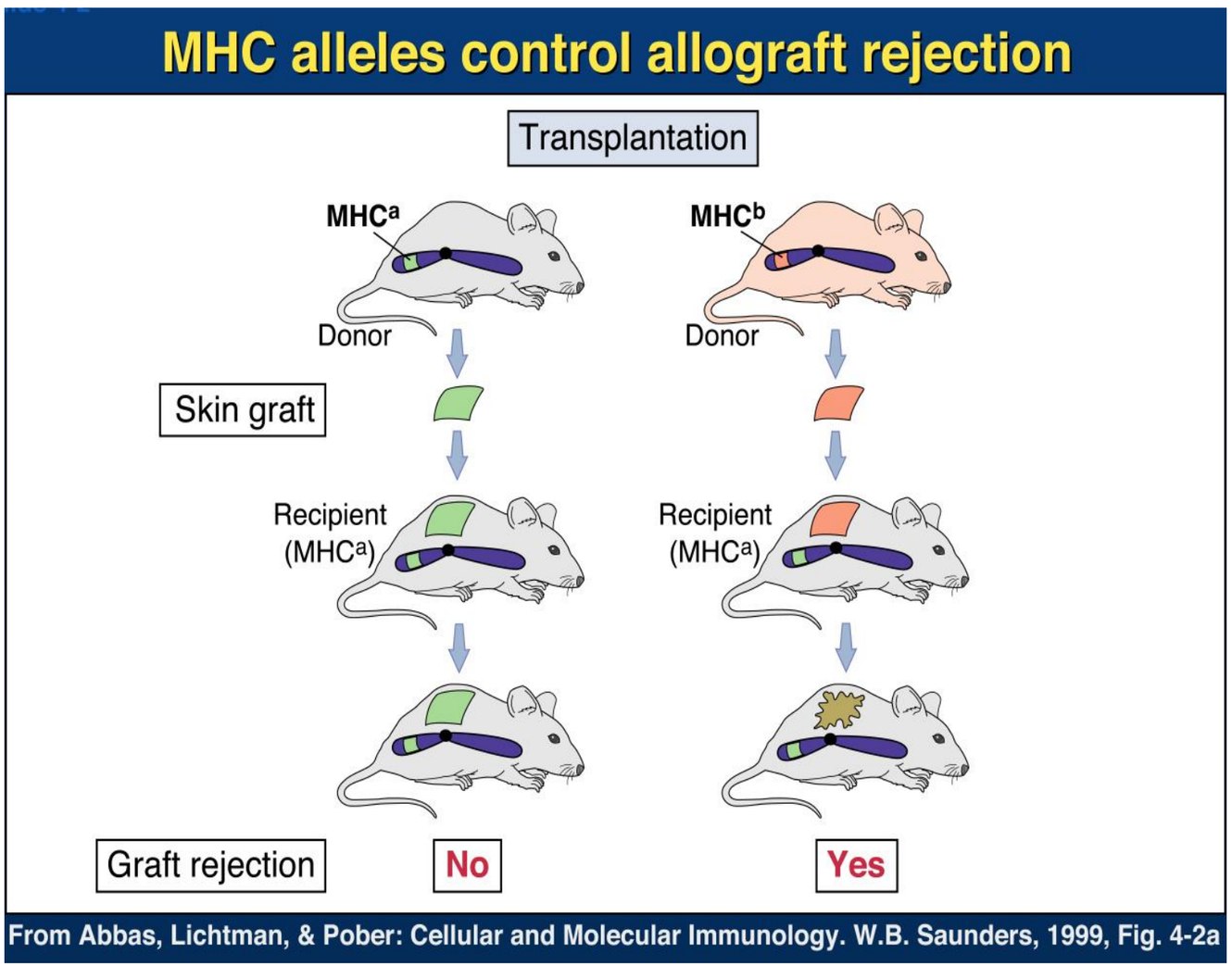
- They mount a **weak immune response**.
- Play role in **chronic rejection** of a graft.
- There are **no laboratory tests** to detect minor antigens.

  Major difference between major HLA genes and minor HLA genes that the major can cause acute rejection while the minor cause chronic rejection.

Transplantation Antigens:

The first transplantation didn't show any rejection because the Graft was from the same individual.

As for the second transplantation there was a rejection because the donor is not the recipient, obviously the immune system will act once a foreign Graft shows up.



Types of Transplantation

1- Autografts, Autologous grafts:

- Donor and recipient are **same individual**.
- Common in skin grafting; bone marrow.

2- Syngeneic grafts or (isograft):

- Donor and recipient are **genetically identical**.
- Animal models; identical **twins**.

3- Allogeneic grafts:

- Donor and recipient are **same species**, but **genetically unrelated**.
- Common heart, lung, kidney, liver graft.

4- Xenogeneic grafts:

- Donor and recipient are **different species**. (من حيوان إلى إنسان)

5- Artificial grafts

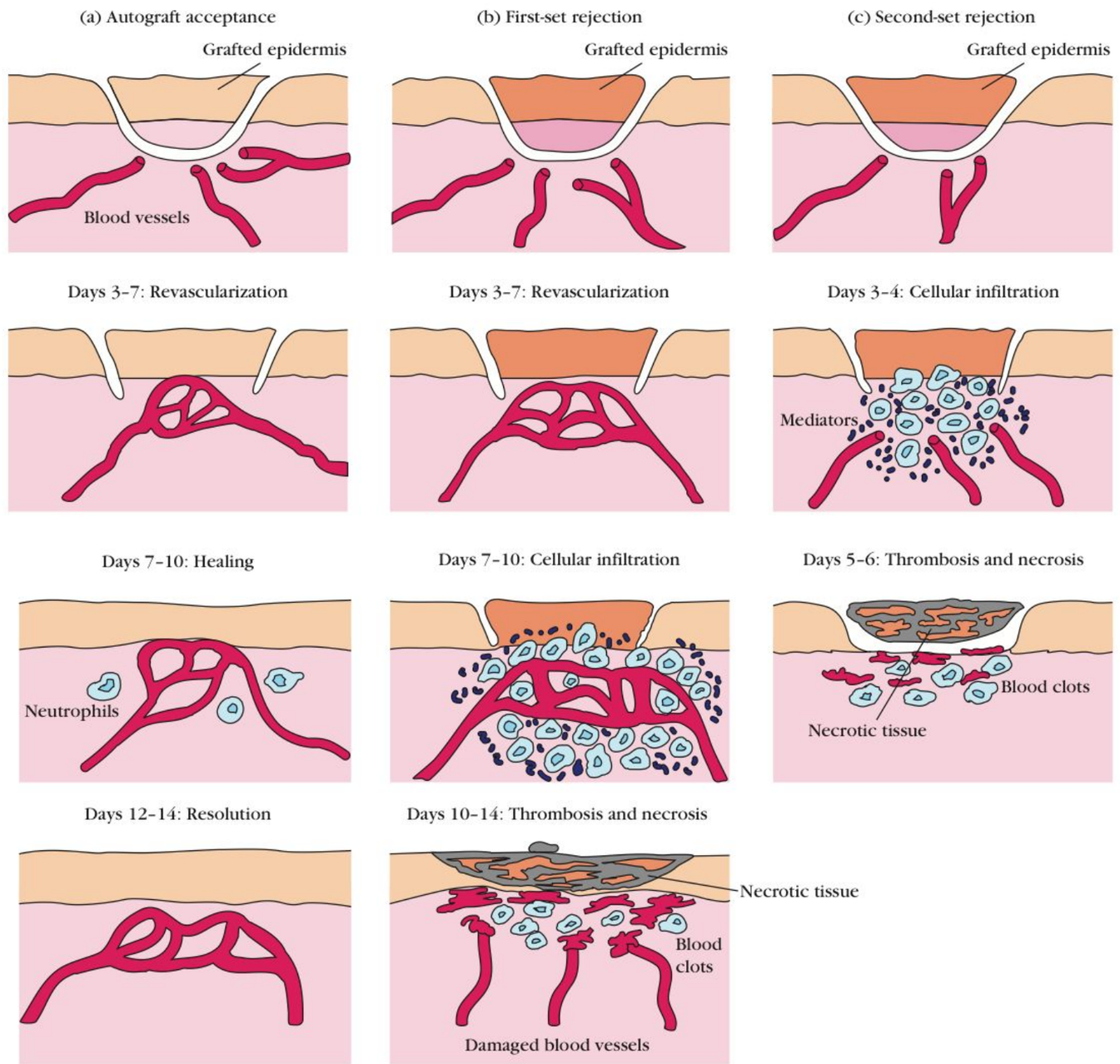
Rejection:

<u>Major Barrier to transplantation is the immune response</u>.

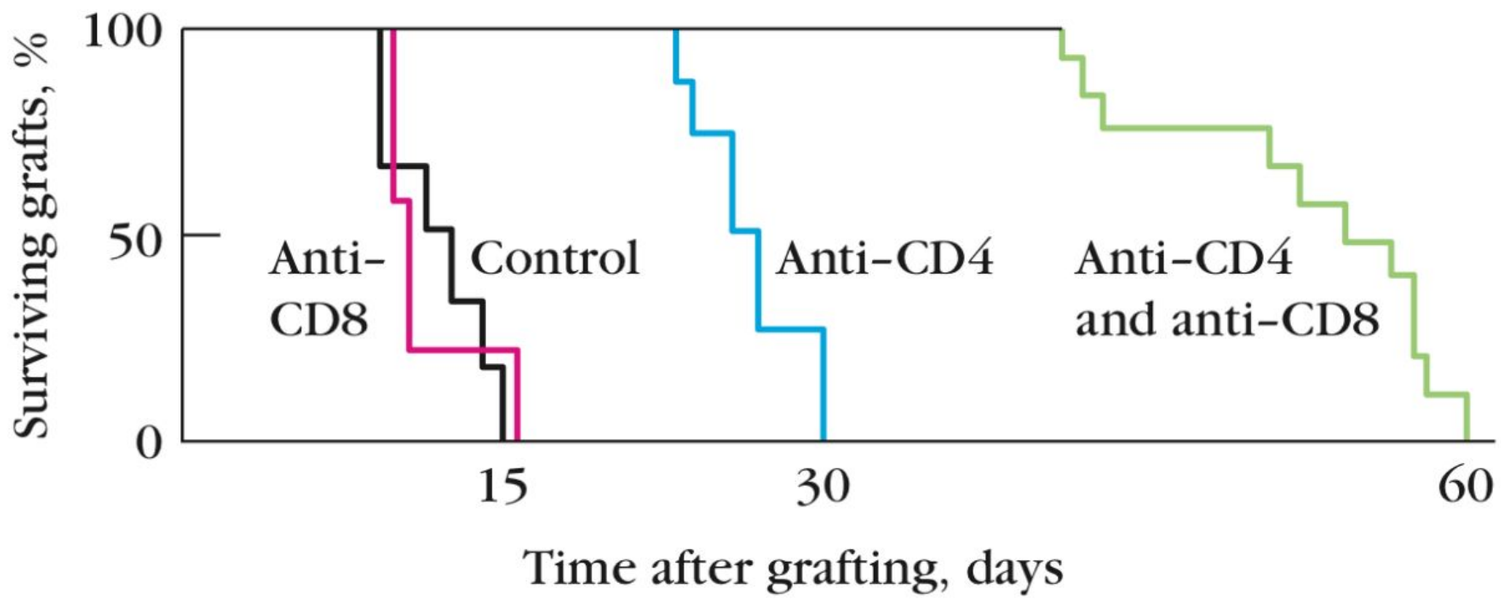
- T cells play primary role.
- B cells can/do play a role.
- Classic adaptive/acquired immune response:
  - Memory
  - Specificity

1st set vs 2nd set reactions:

The 2nd set reaction occurs faster due to the memory from the first exposure.



Role of CD4+ vs CD8 T+ cells:



Injecting recipient mice with monoclonal antibodies to deplete one or both types of T cells will in adding more days for the surviving Graft

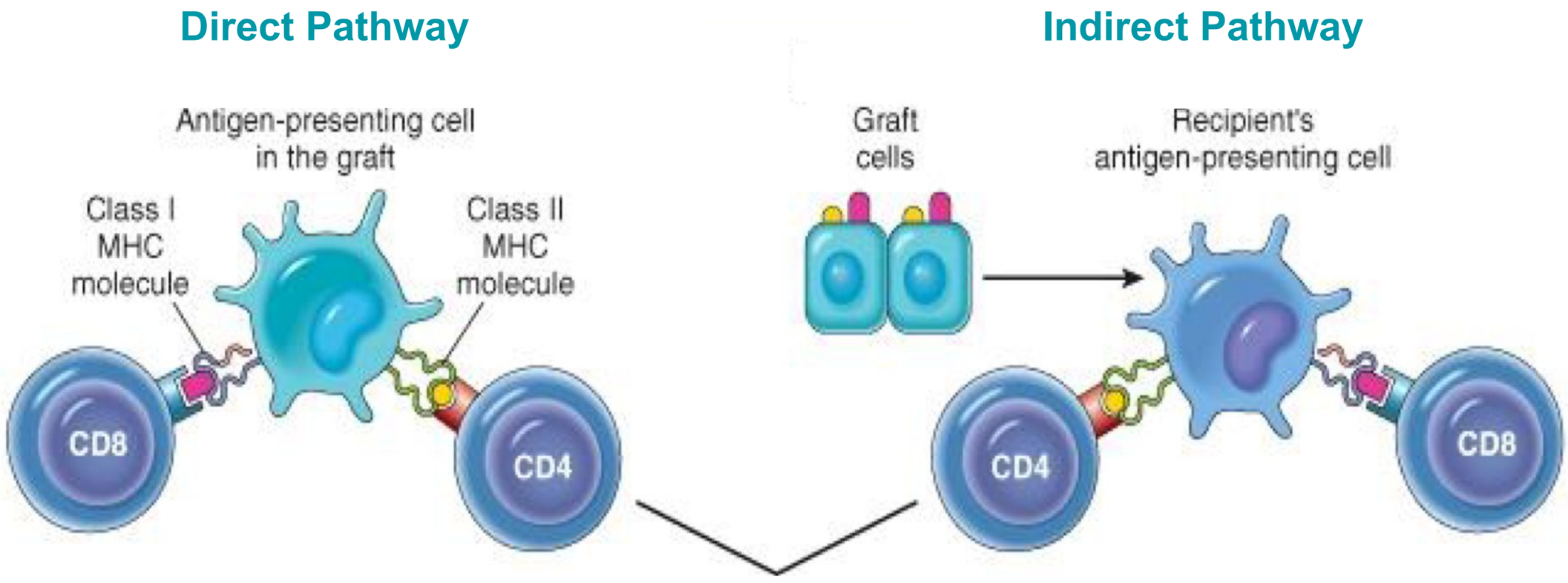
It shows that CD8 is not involved.

T cells:

T cells play **primary role in 1st and 2nd set rejection** reactions:

- Nude mice accept allografts (no T cells due to genetic modification resulting in **absent thymus**). (This experiment proves the role of T cells in rejection, because no thymus means no maturation of T cells)
- B cell deficient mice reject allografts. (this proves that antibodies don't play a major role in rejection)
- (Here we're talking about acute rejection only because antibodies can cause hyperacute rejection, as mentioned in the next page)

Mechanisms involved in Graft Rejection:



Direct pathway:
Antigen presenting cell in the Graft acts with T cells of the recipient

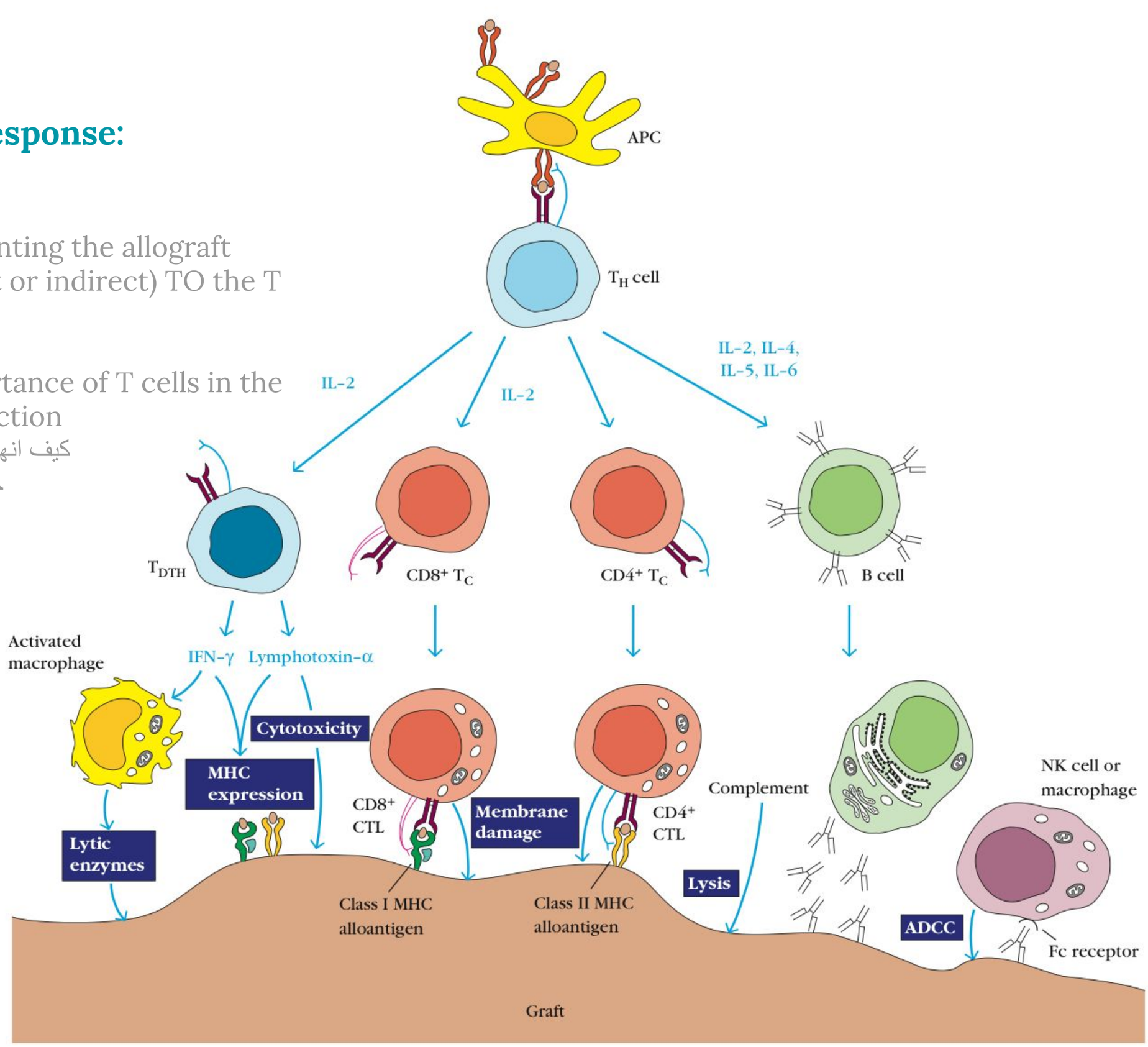
Indirect pathway:
Antigen presenting cell of the recipient presents the antigen of the Graft to T cells

Rejection Response:

1- APC presenting the allograft (either direct or indirect) TO the T helper cell

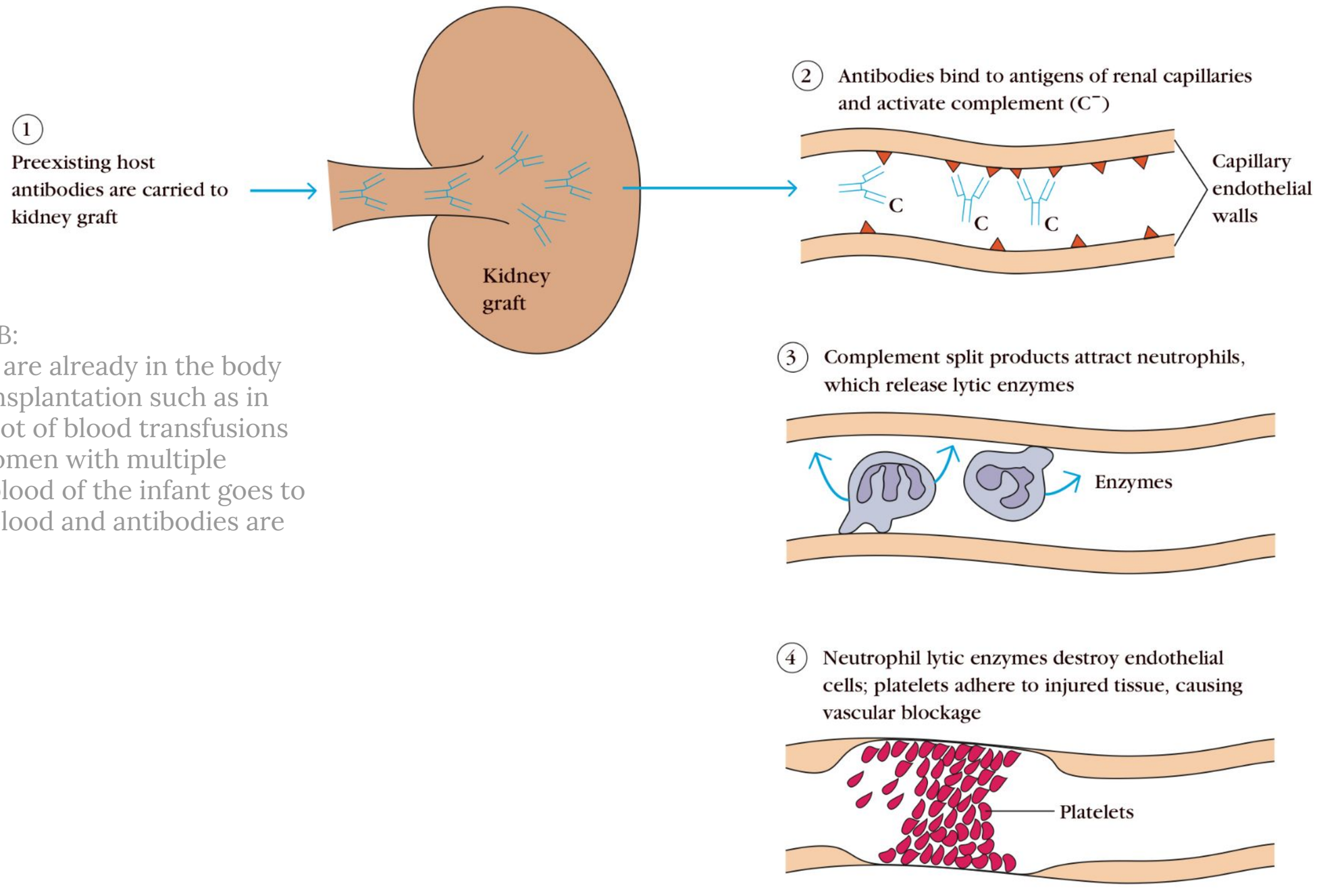
2- The importance of T cells in the rejection reaction

كيف انها تشكل نسبه كبيره جدا من التلف عكس B cell (435)



Clinical manifestations of graft rejection:

- Hyperacute rejection: very quick. (could be due to a previous transplantation)
- Acute rejection: about 10 days (cell mediated).
- Chronic rejection: months-years (both).



Pre-existing AB:
the antibodies are already in the body before the transplantation such as in people with a lot of blood transfusions and even in women with multiple pregnancies (blood of the infant goes to the maternal blood and antibodies are produced)

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Chronic Rejection:

- This occurs months to years after engraftment.
- Main pathologic finding in chronic rejection is atherosclerosis of the vascular endothelium.
  ((435) why there is atherosclerosis? recipient T cells react and secrete cytokines which leads to proliferation of vascular smooth muscle > atherosclerosis)
- Main cause of chronic rejection is not known

- Minor histocompatibility antigen mismatch .

Graft vs Host (GVH) Reaction (graft attacking the recipient):

- Occurs in about two thirds of bone marrow transplants.
- Occurs because grafted immunocompetent T cells proliferate in the irradiated immunocompromised host and reject cells with foreign proteins resulting in severe organ dysfunction.
- **Donor's** Tc cells play a major role in destroying the recipient's cells.
- Symptoms are: maculopapular rash, jaundice, hepatosplenomegaly and diarrhea.
- GVH reactions usually end in infections and death.

HLA Typing in the Laboratory:

Prior to transplantation laboratory test commonly called as ***HLA typing or tissue typing*** to determine the closest MHC match between the donor and recipient is performed.

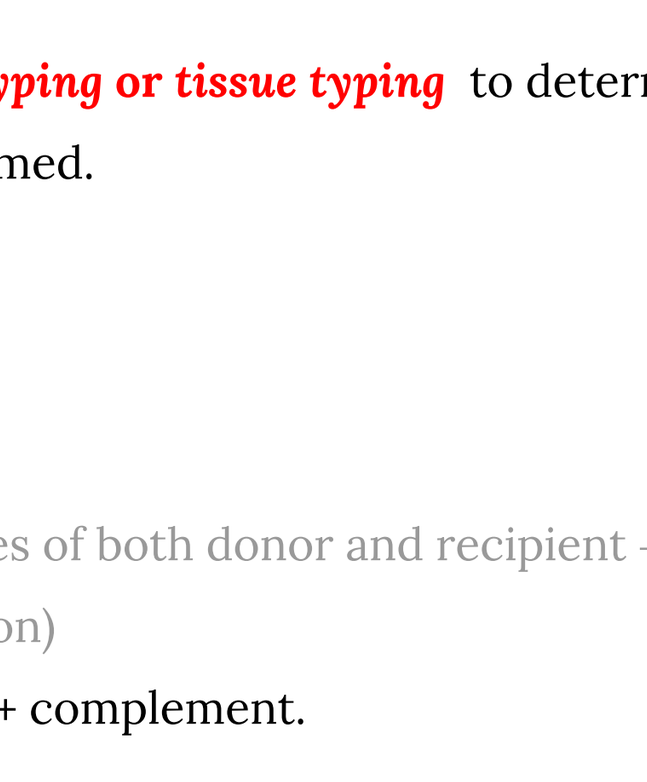
Methods:

- DNA sequencing by Polymerase Chain Reaction (PCR)
- Serologic Assays
- Mixed Lymphocyte Reaction (MLR) (mixing the lymphocytes of both donor and recipient → 3-4 days → if there is multiplication of cells →no transplantation)
- Crossmatching – (Donor) lymphocytes +(Recipient) serum + complement.

Tissue Matching

Effect of HLA class I & II matching on survival of kidney grafts

Mismatched HLA class II shows a huge decrease in the graft survival and it can be much more with class I mismatching, but mismatching in class I alone doesn't make that big decrease



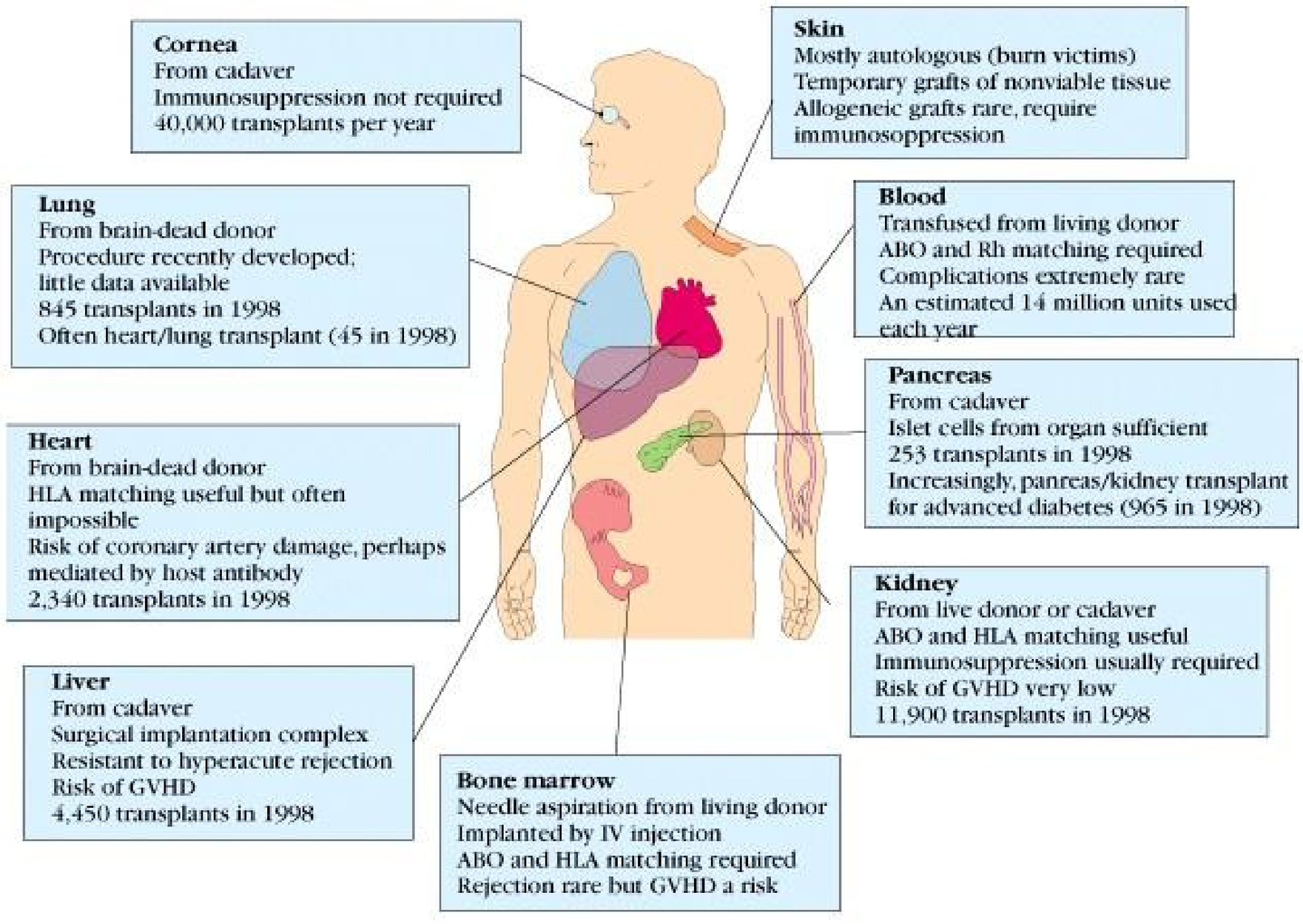
Curve no.	HLA mismatches (no.) Class I	Class II
1	0	0
2	1 or 2	0
3	3 or 4	0
4	0	1 or 2
5	1 or 2	1 or 2
6	3 or 4	1 or 2

Tissue Matching:

- **Bone marrow**: tissue matching is required

- **Kidney**: tissue matching is not required BUT useful

***- cornea**: tissue matching is not required because it's not vascularized, Risk of rejection is ABSENT*



General Immunosuppression Therapy:

1- Mitotic inhibitor: azathioprine (pre & post).

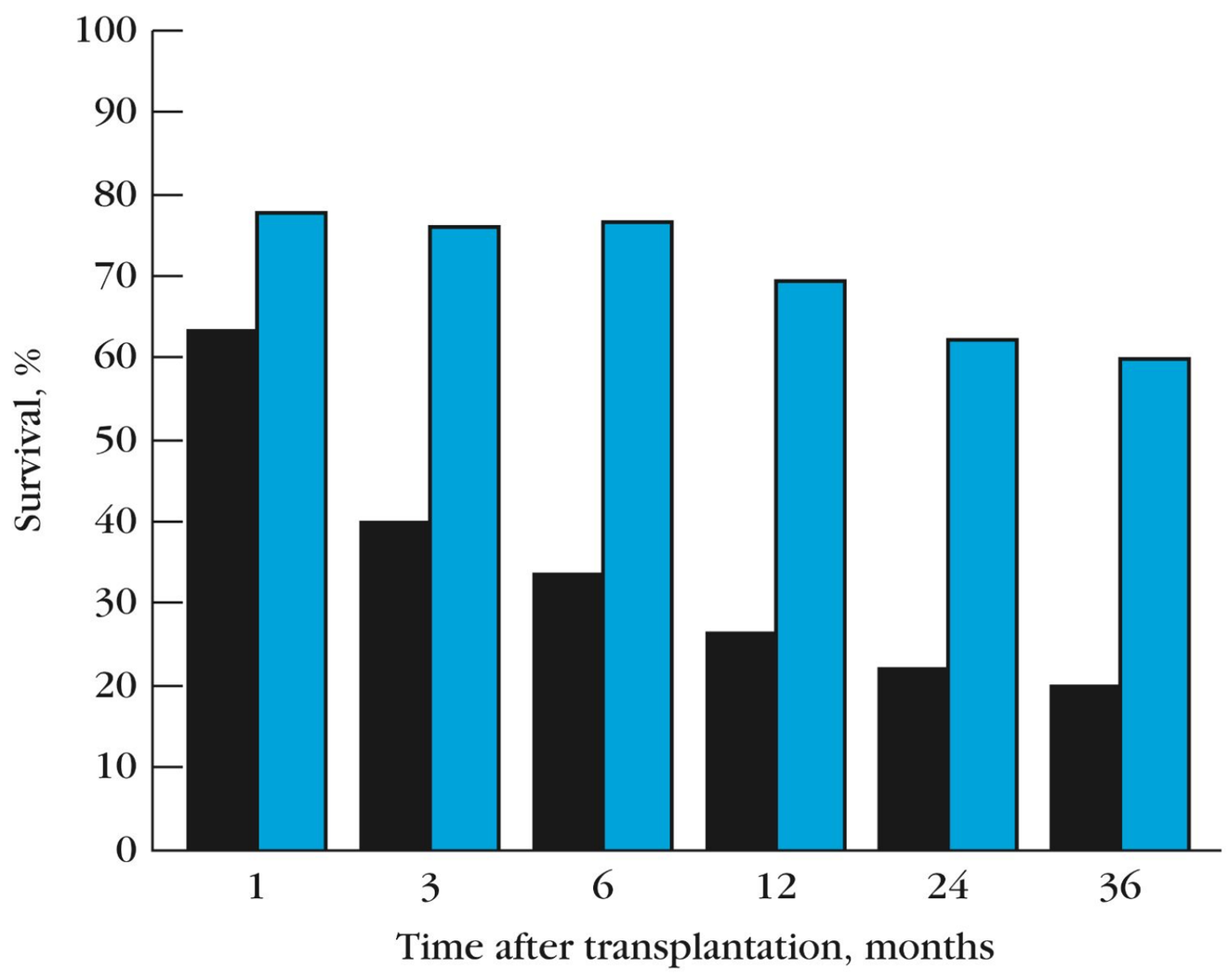
2- Corticosteroids.

3- Cyclosporin.

4- Total lymphoid irradiation.

Immunosuppressive Therapy:

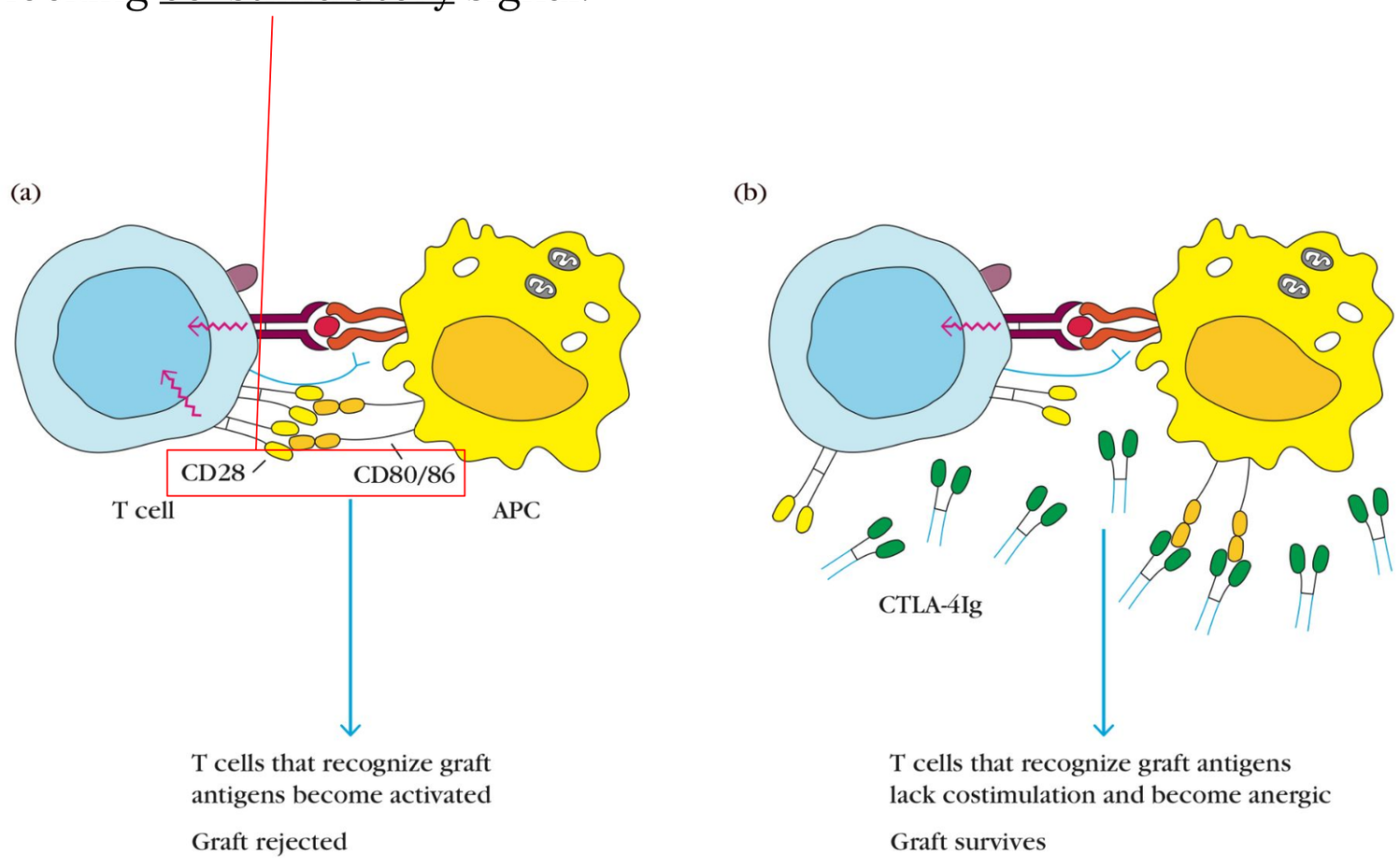
Survival of Graft increases with immunosuppressives throughout the month



Specific Immuno-Suppression Therapy:

a) Monoclonal antibodies against T cell components or cytokines.

b) Agents blocking <u>co-stimulatory</u> signal.



Immunosuppressive Therapy:

<u>Downsides:</u>

- Must be maintained for life.
- Toxicity.
- Susceptibility to infections.
- Susceptibility to tumors.

Take home message

- HLA or MHC molecule miss-match can stimulate humoral and cell mediated immunity which is the main cause of rejection of transplants.
- Cell mediated immune responses play a major role in transplant rejection.
- Tissue matching particularly for HLA-D antigens is important for successful transplantation.
- immunosuppressive therapy is usually required after transplantation.

MCQs

1- Most important cell in rejection reactions:

a) T cytotoxic b) T helper c) B cell d) plasma cell

2- Atherosclerosis of the vascular endothelium associated with which type of rejection:

a) Hyperacute rejection b) Acute rejection c) Chronic rejection

3- Genes for HLA proteins are clustered in the MHC complex located on:

a) short arm of chromosome 16

b) short arm of chromosome 6

c) long arm of chromosome 6

d) long arm of chromosome 16

1-B
2-C
3-B
4-D

4- which of the following genes encode for Class II MHC:

a) HLA-A b) HLA-B c) HLA-C d) HLA-D

Useful videos:

Organ Transplants

MHC 1 , MHC 2 Review and HLA types To 8:30

Graft Rejection, Direct vs indirect Pathways

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