

Transplantation

Immunology Unit
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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

Major Histocompatibility Complex and Transplantation

- 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**

MHC Class I and II 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 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

Major Histocompatibility Complex and Transplantation

- 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, DP, DQ and DR

Major Histocompatibility Complex and Transplantation

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				

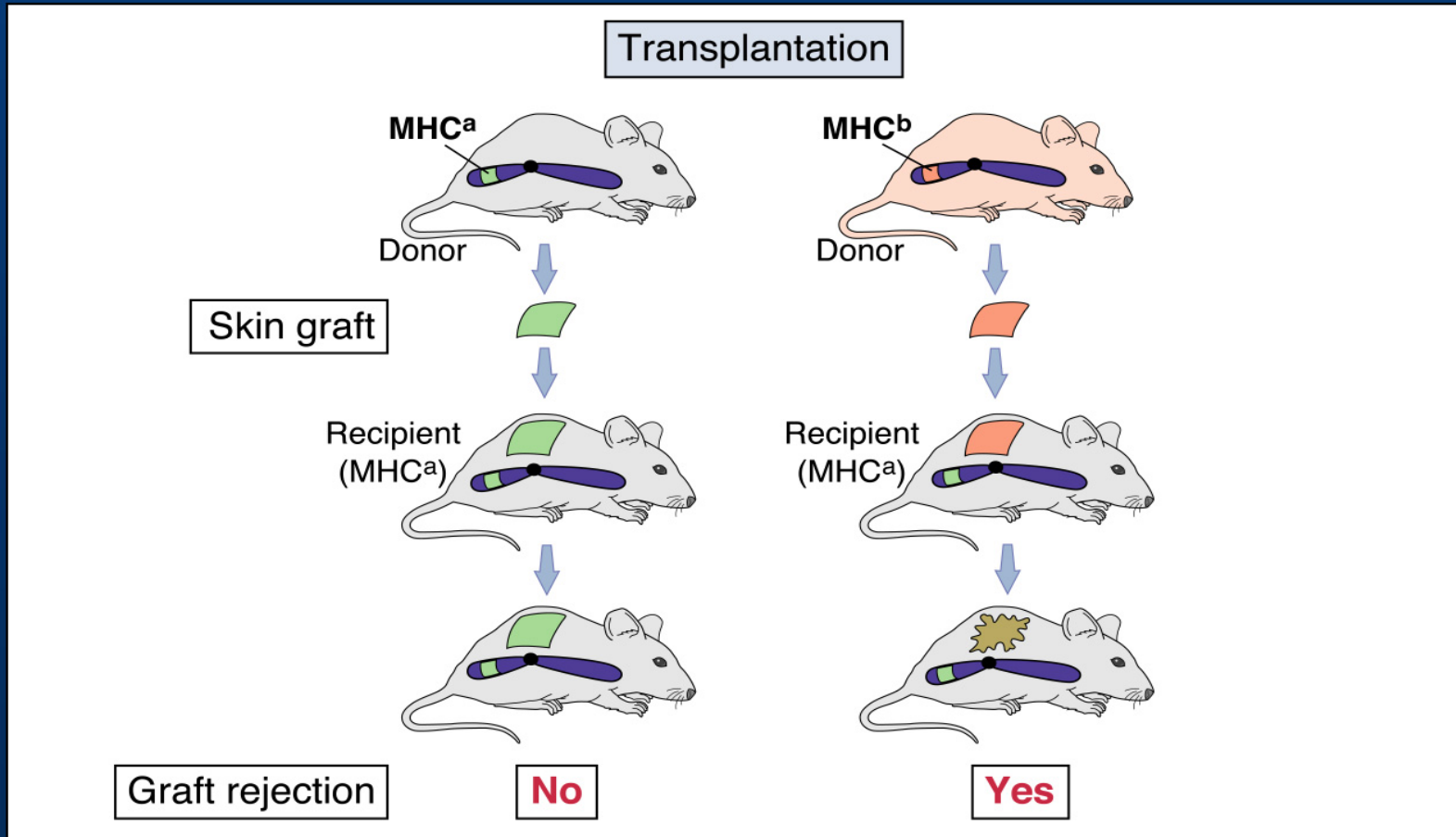
Minor HLA genes and Transplantation

- 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

Transplantation antigens

Slide 4-2

MHC alleles control allograft rejection



From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 4-2a

Transplantation

- Types of transplants:
 - Autografts, Autologous grafts
 - Donor and recipient are same individual
 - Common in skin grafting; bone marrow
 - Syngeneic grafts or (isograft)
 - Donor and recipient are genetically identical
 - Animal models; identical twins

Transplantation

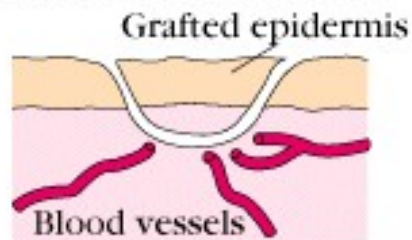
- Types of transplants:
 - **Allogeneic grafts**
 - Donor and recipient are same species, but genetically unrelated
 - Common heart, lung, kidney, liver graft
 - **Xenogeneic grafts**
 - Donor and recipient are different species
 - **Artificial grafts**

Transplantation (Rejection)

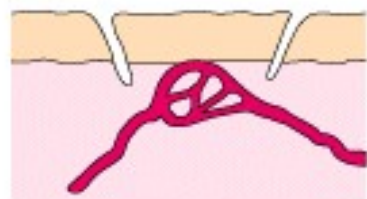
- Major Barrier to transplantation is the immune response
 - T cells play primary role
 - B cells can/do play a role
 - Classic adaptive/acquired immune response
 - Memory
 - Specificity

1st set versus 2nd set reactions

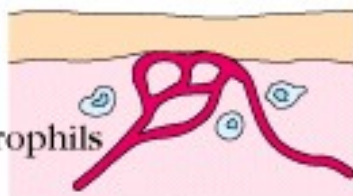
(a) Autograft acceptance



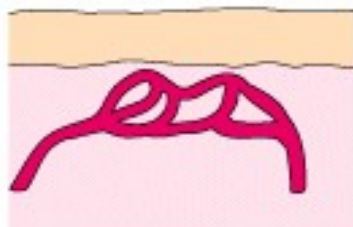
Days 3-7: Revascularization



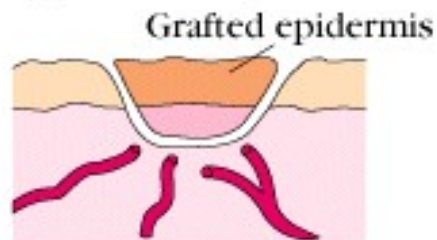
Days 7-10: Healing



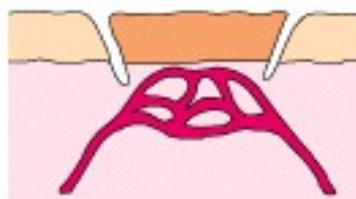
Days 12-14: Resolution



(b) First-set rejection



Days 3-7: Revascularization



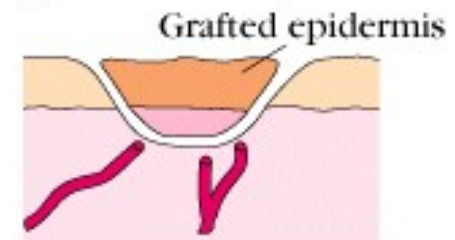
Days 7-10: Cellular infiltration



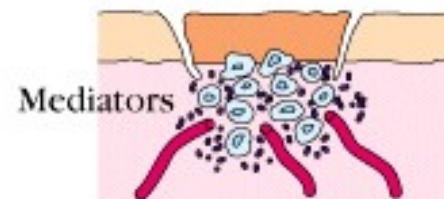
Days 10-14: Thrombosis and necrosis



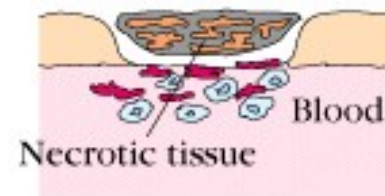
(c) Second-set rejection



Days 3-4: Cellular infiltration



Days 5-6: Thrombosis and necrosis

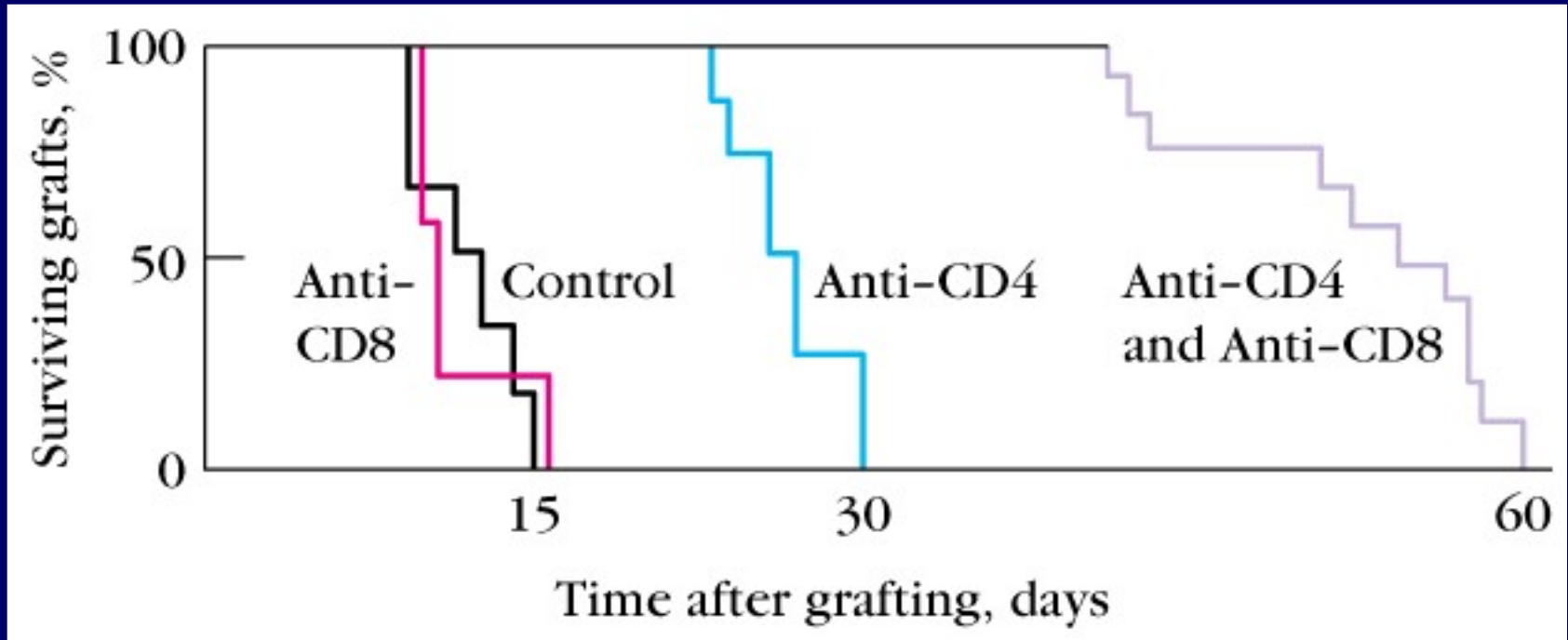


Necrotic tissue

Blood clots

Damaged blood vessels

Role of CD4⁺ versus CD8 T⁺ cells



Injecting recipient mice with monoclonal antibodies to deplete one or both types of T cells

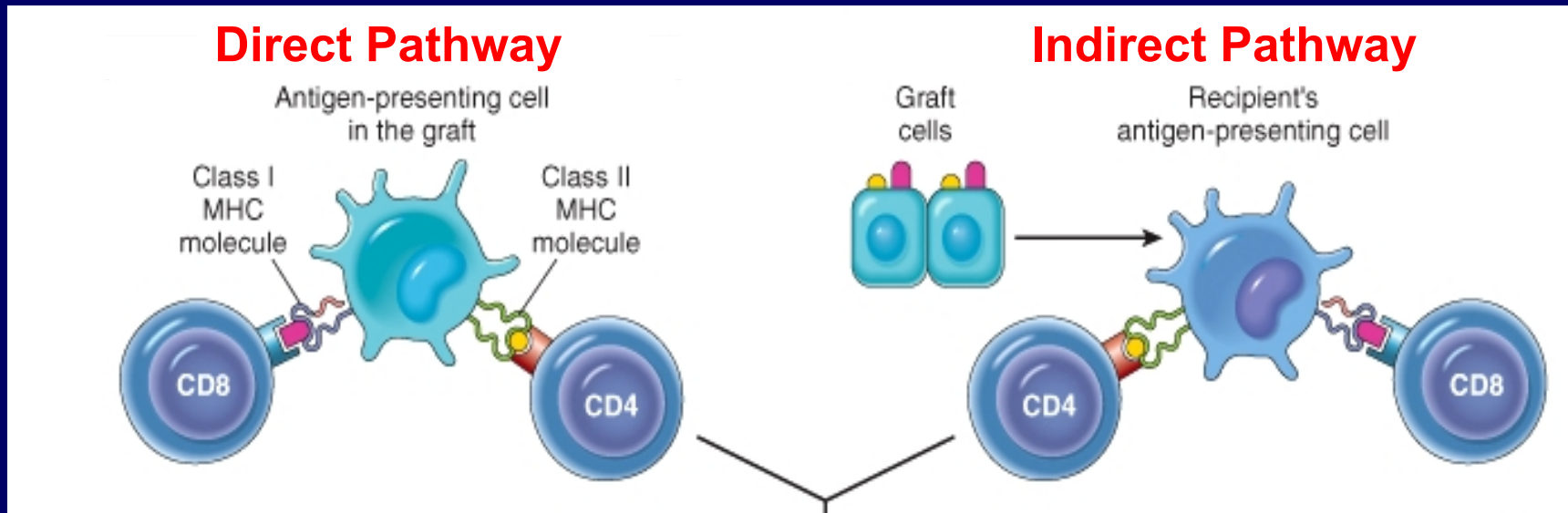
Transplantation

- 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**)
 - B cell deficient mice reject allografts

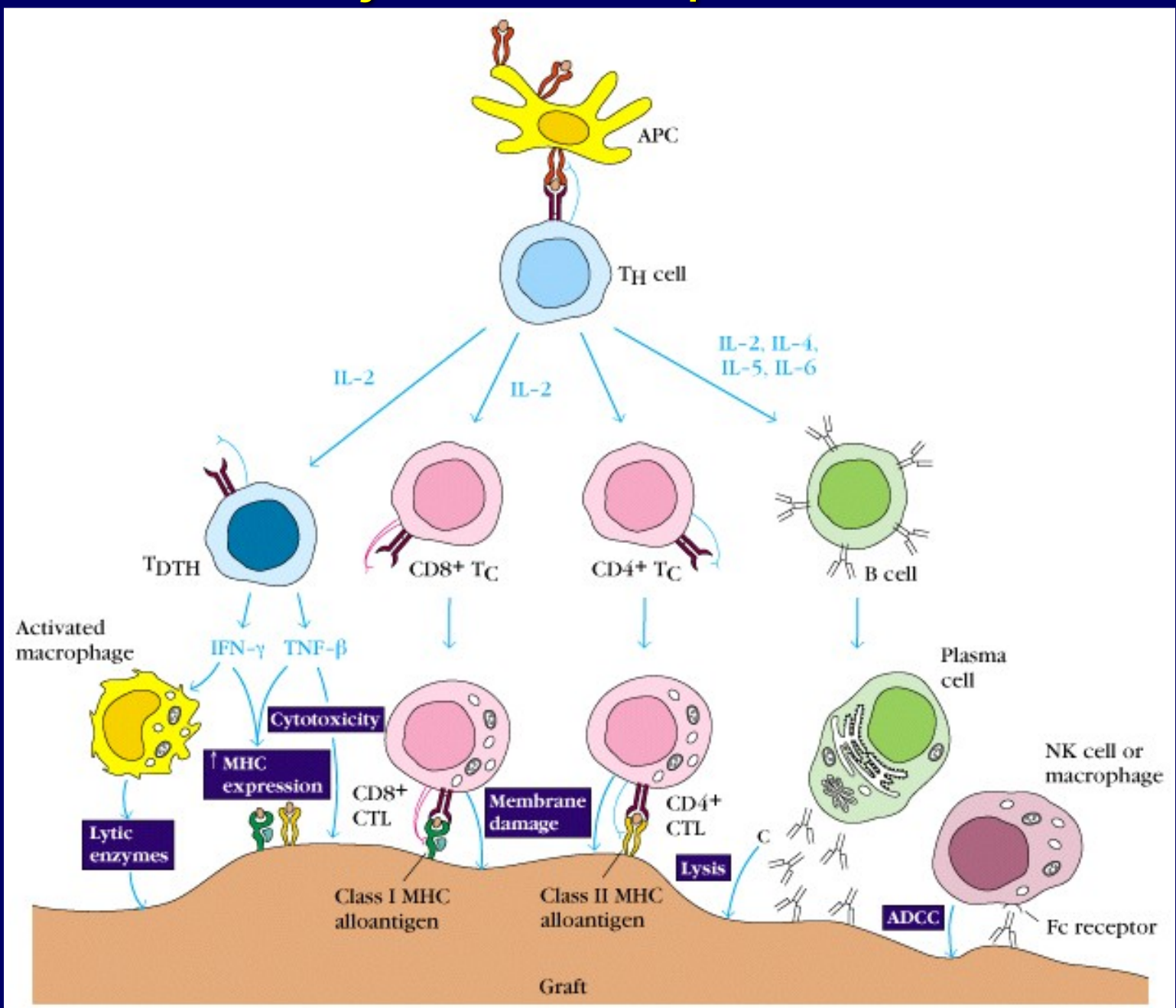


Nude mouse has a transplant of rabbit skin

Mechanisms involved in Graft Rejection

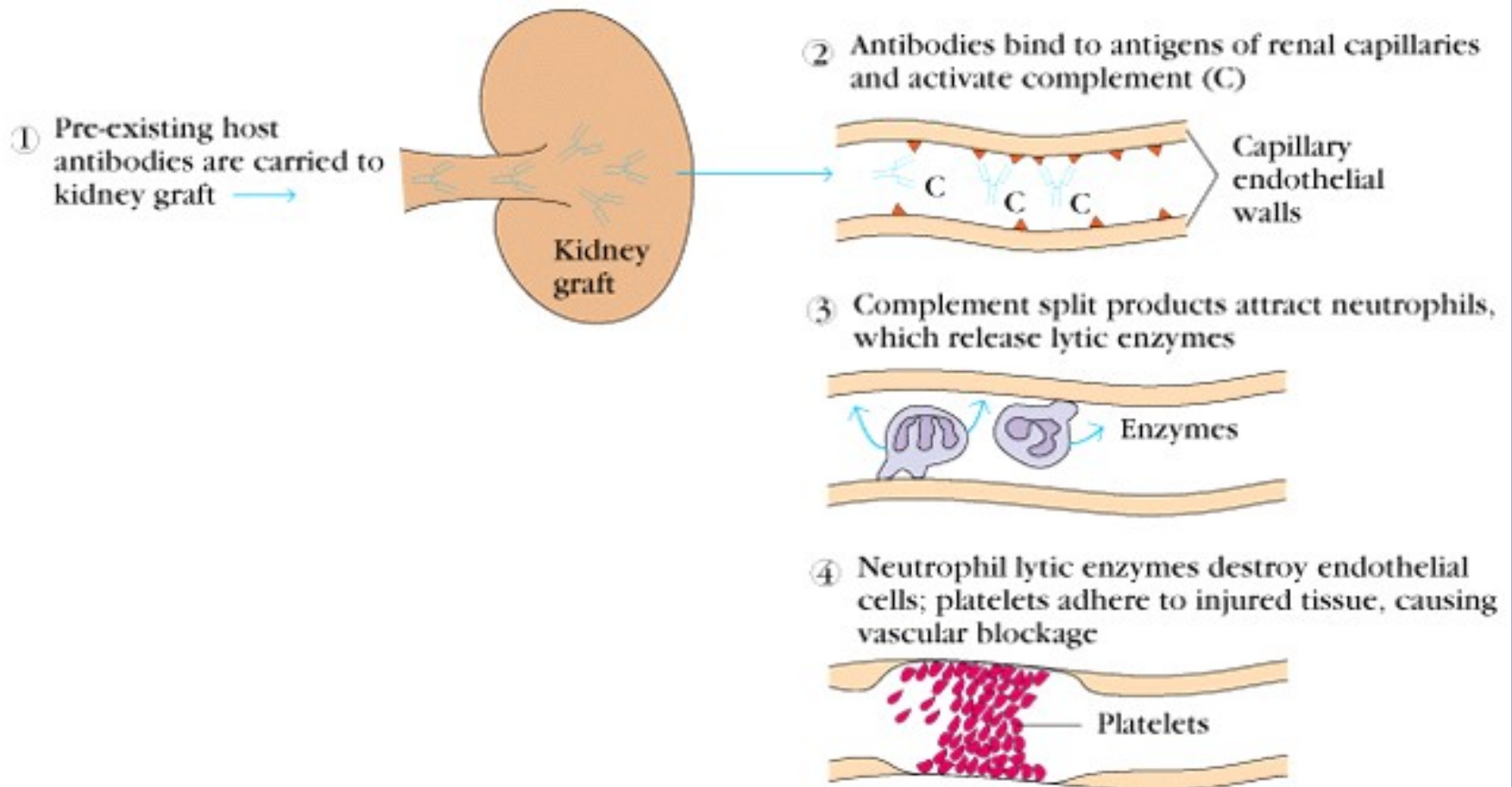


Rejection Response



Clinical manifestations of graft rejection

- I. Hyperacute rejection: very quick
- II. Acute rejection: about 10 days (cell mediated)
- III. Chronic rejection: months-years (both)



Chronic Rejection

- This occurs months to years after engraftment
- Main pathologic finding in chronic rejection is atherosclerosis of the vascular endothelium
- Main cause of chronic rejection is not known
 - Minor histo-compatibility antigen miss match

Graft-versus-Host (GVH) Reaction

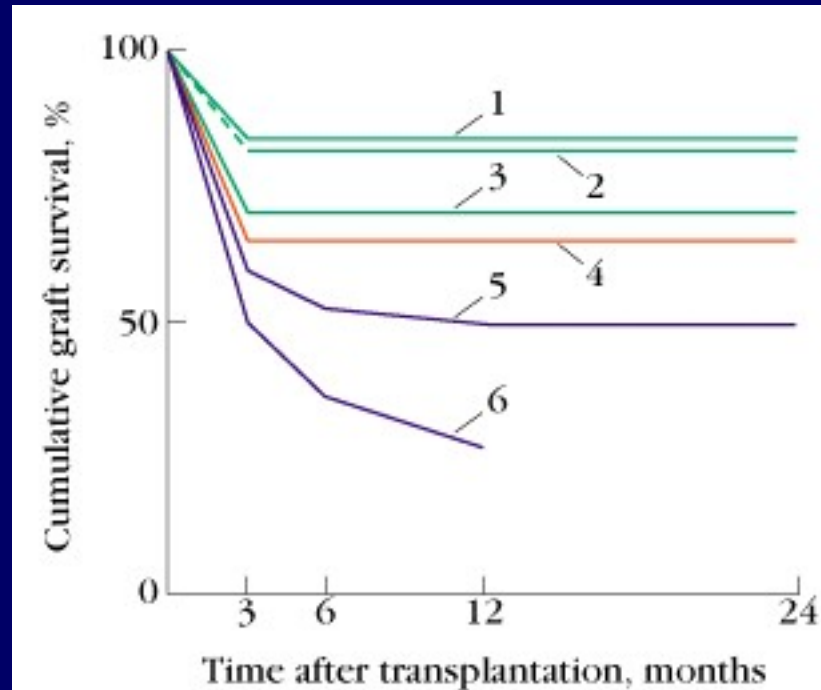
- Occurs in about two thirds of bone marrow transplants
- Occurs because grafted immunocompetent T cells proliferate in the irradiated immunocompromised host and reject cells with foreign proteins resulting in severe organ dysfunction
- Donor's Tc cells play a major role in destroying the recipient's 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)
 - Crossmatching – (Donor) lymphocytes +(Recipient) serum + complement.

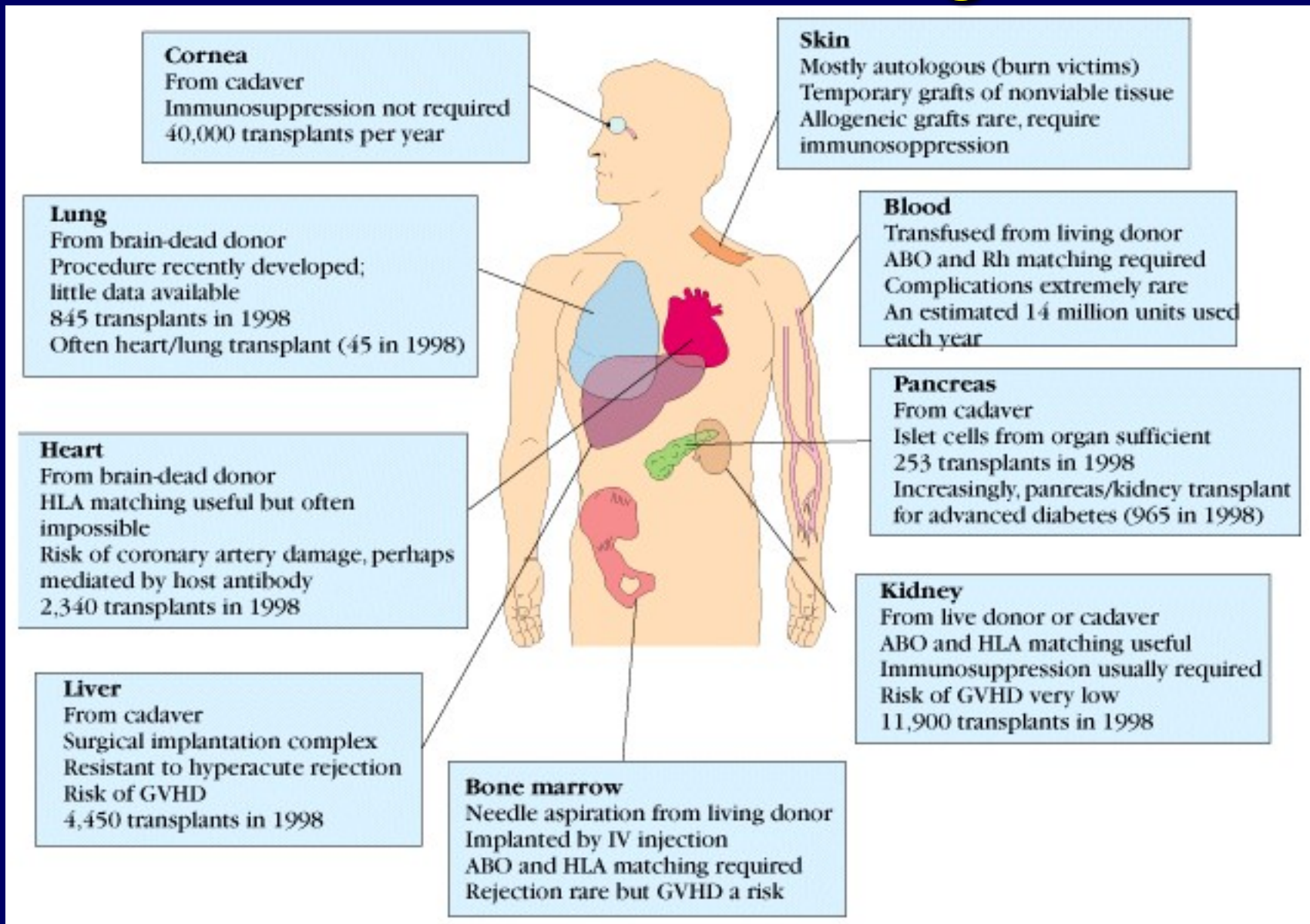
Tissue Matching

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



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

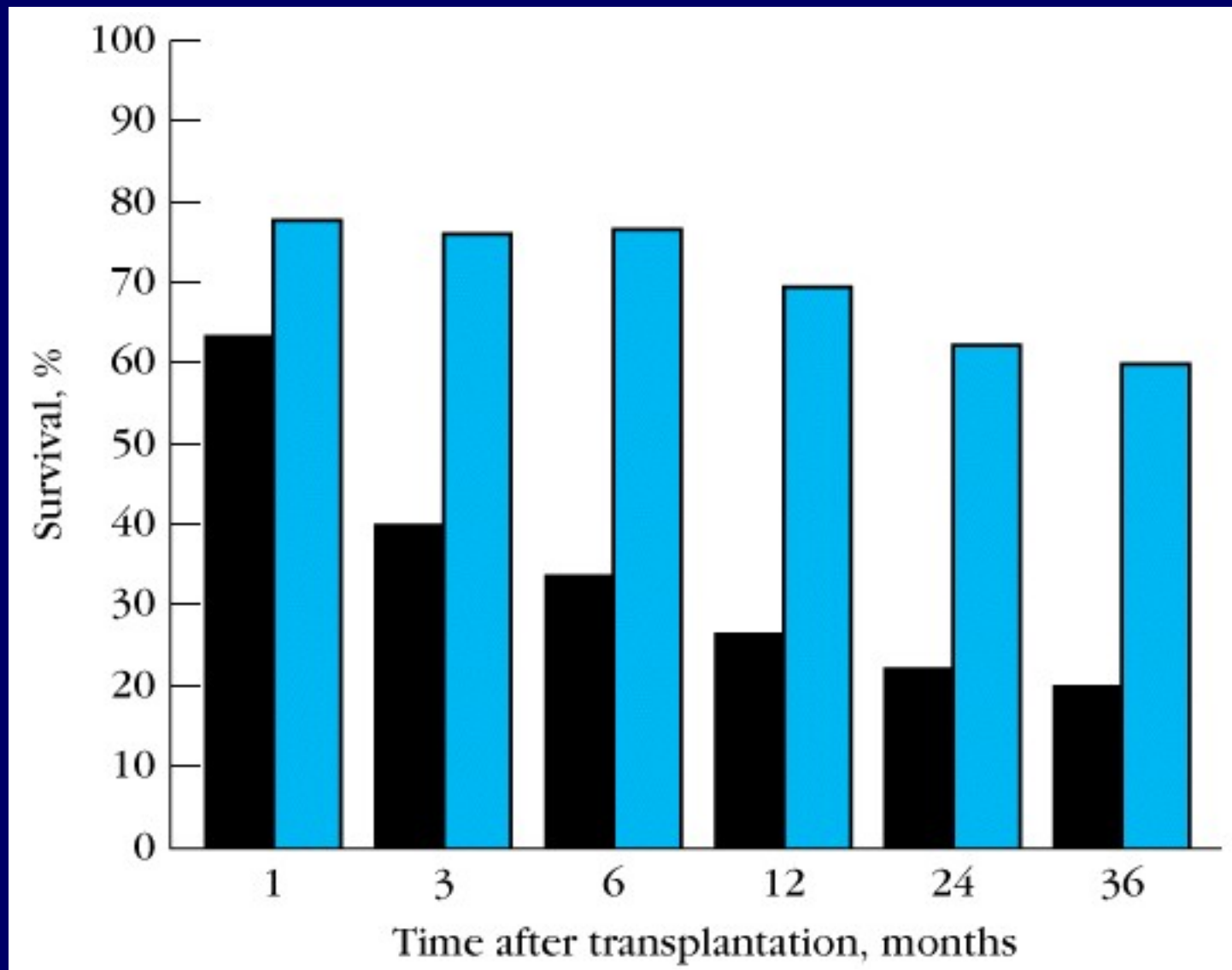
Tissue Matching



General Immunosuppression Therapy

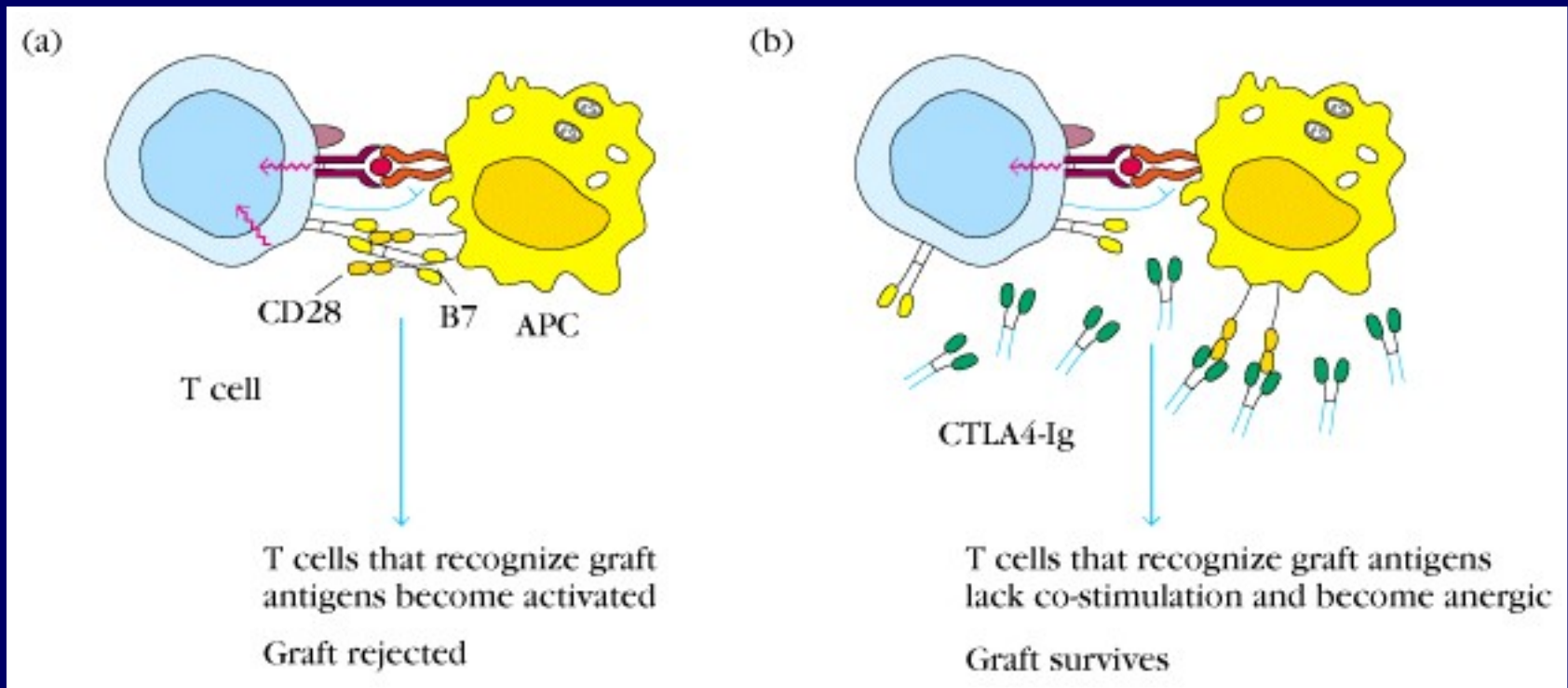
- 1) Mitotic inhibitor: azathioprine (pre & post)
- 2) Corticosteroids
- 3) Cyclosporin
- 4) Total lymphoid irradiation

Immunosuppressive Therapy



Specific Immuno-suppression therapy

- a) Monoclonal antibodies against T cell components or cytokines
- b) Agents blocking co-stimulatory signal



Immuno-suppressive Therapy

- Downsides
 - 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
- Immuno-suppressive therapy is usually required after transplantation

Thank you