

# Transplantation

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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

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

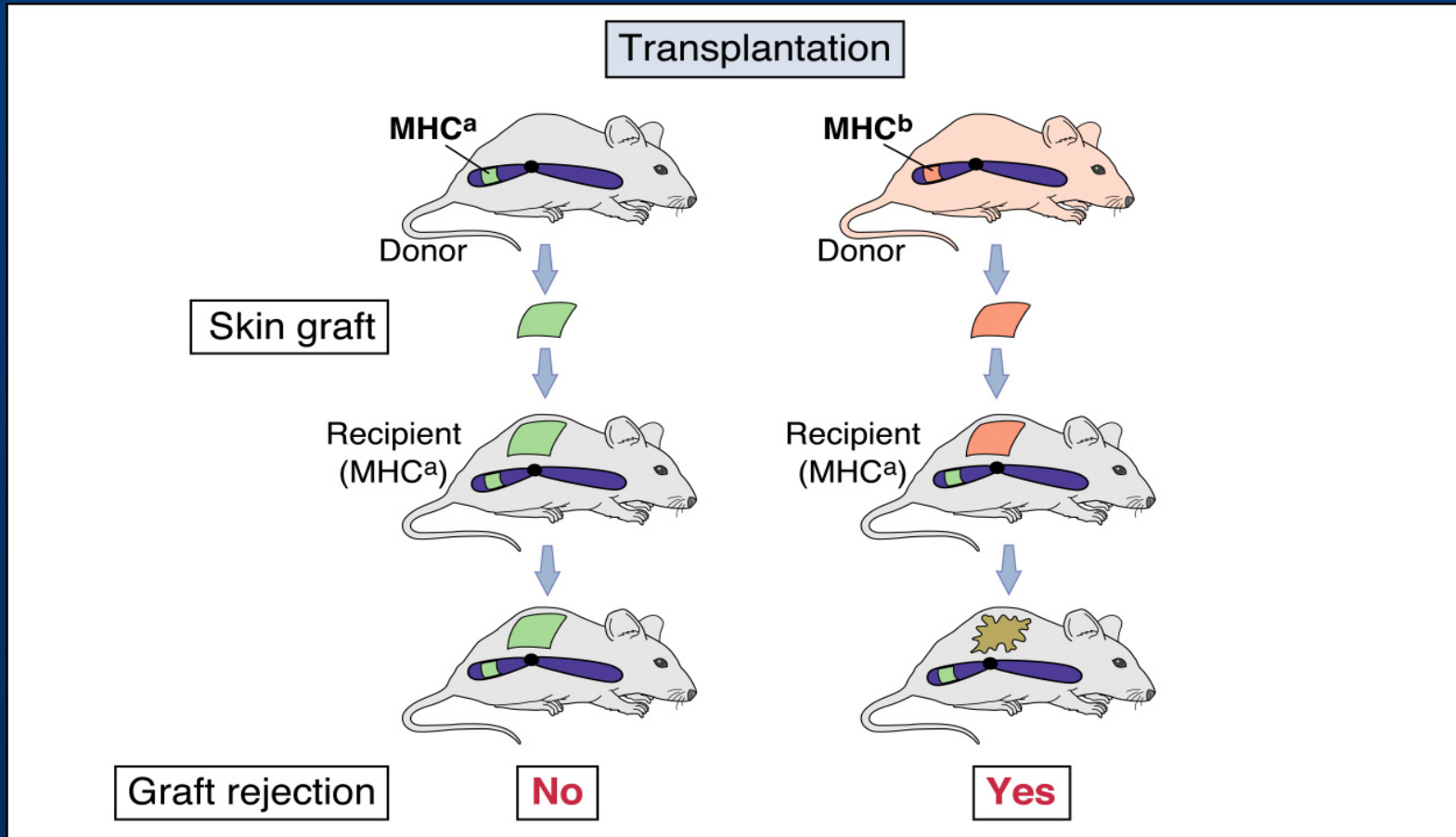
# Minor HLA genes and Transplantation

- 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)

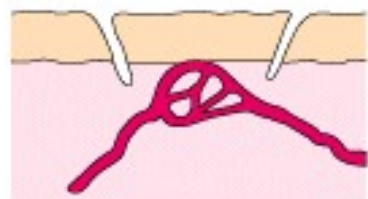
- Major Barrier to transplantation is the immune response
  - T cells play primary role
  - B cells can/do play a role
  - Classic adaptive/acquired immune response
    - Memory
    - Specificity

# 1<sup>st</sup> set versus 2<sup>nd</sup> set reactions

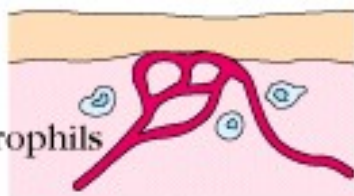
(a) Autograft acceptance



Days 3-7: Revascularization



Days 7-10: Healing

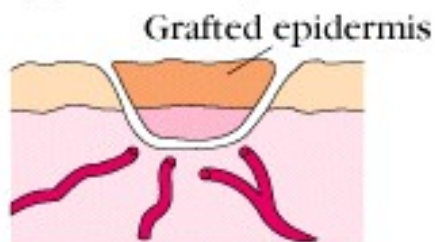


Neutrophils

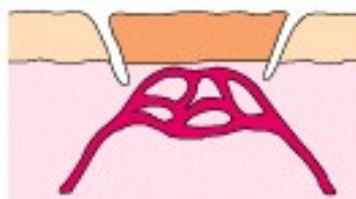
Days 12-14: Resolution



(b) First-set rejection



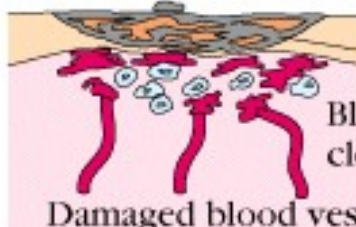
Days 3-7: Revascularization



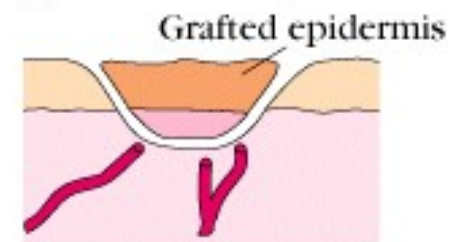
Days 7-10: Cellular infiltration



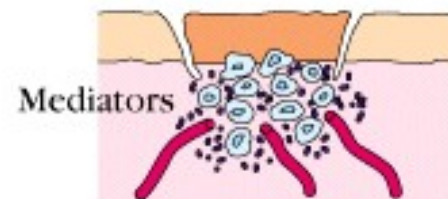
Days 10-14: Thrombosis and necrosis



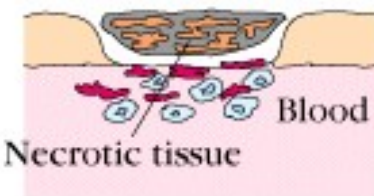
(c) Second-set rejection



Days 3-4: Cellular infiltration



Days 5-6: Thrombosis and necrosis



Necrotic tissue

Blood clots

Necrotic tissue

Blood clots

Damaged blood vessels

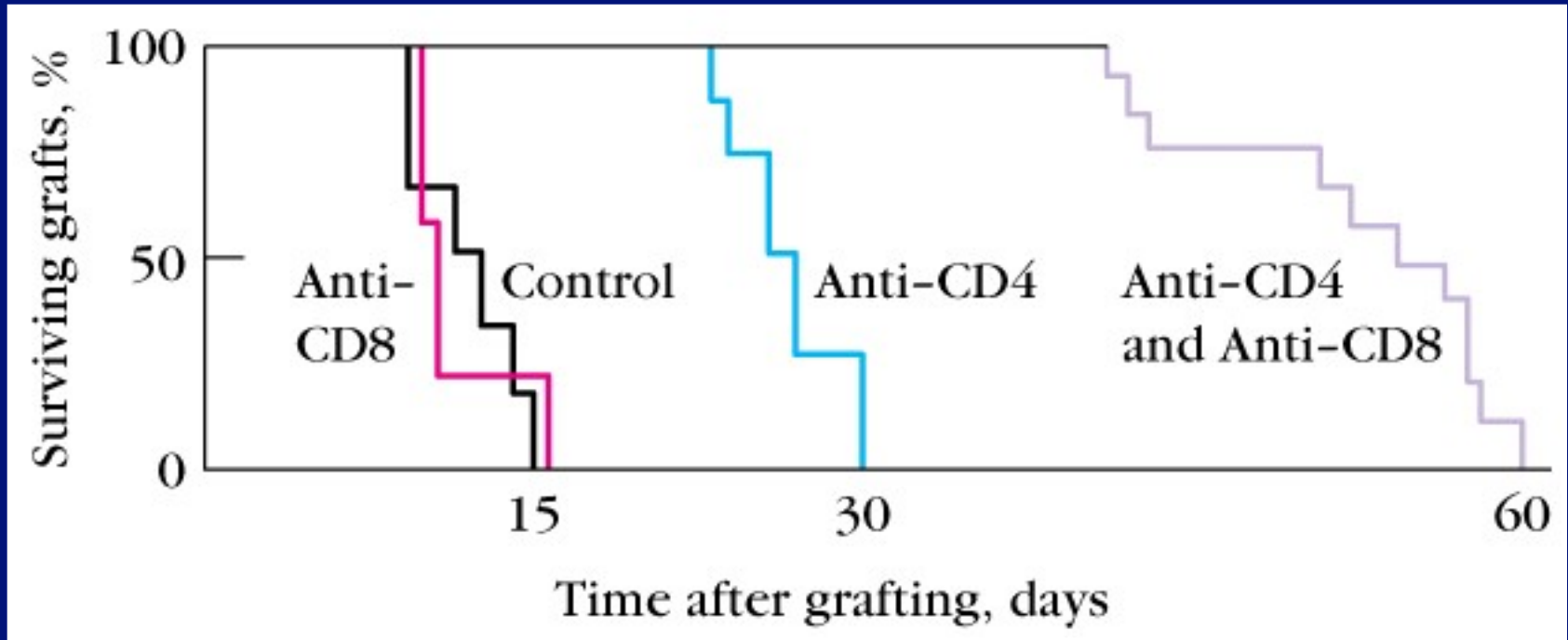
# Transplantation

- 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



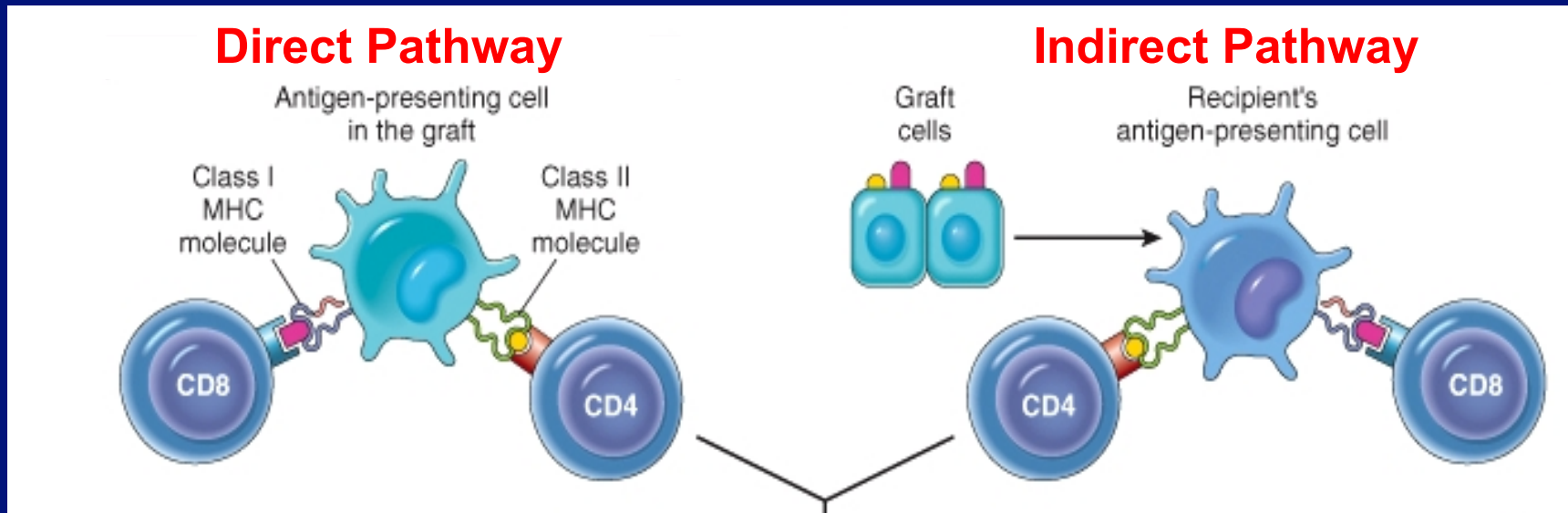
Nude mouse has a transplant of rabbit skin

# Role of CD4<sup>+</sup> versus CD8 T<sup>+</sup> cells

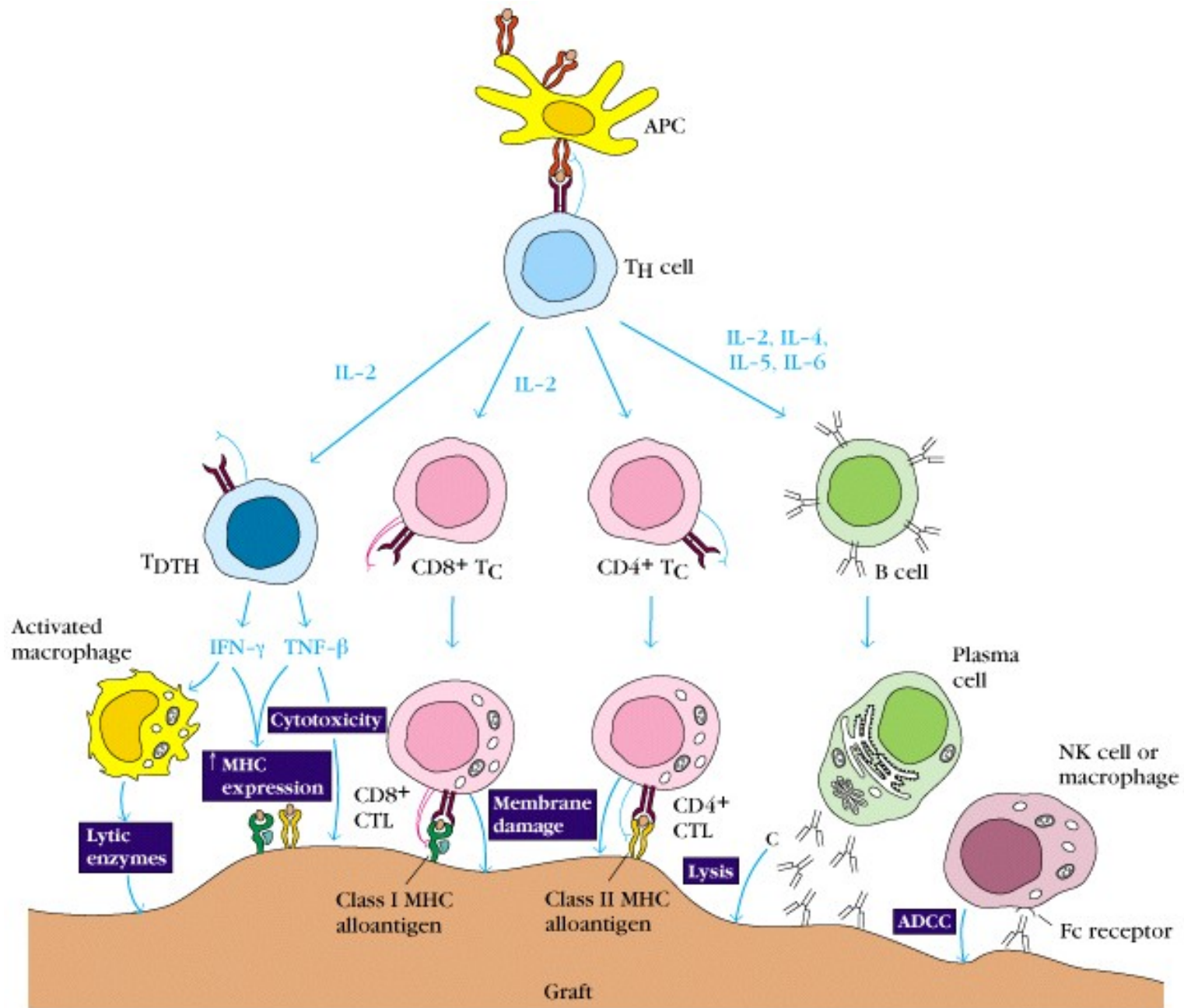


Injecting recipient mice with monoclonal antibodies to deplete one or both types of T cells

# Mechanisms involved in Graft Rejection



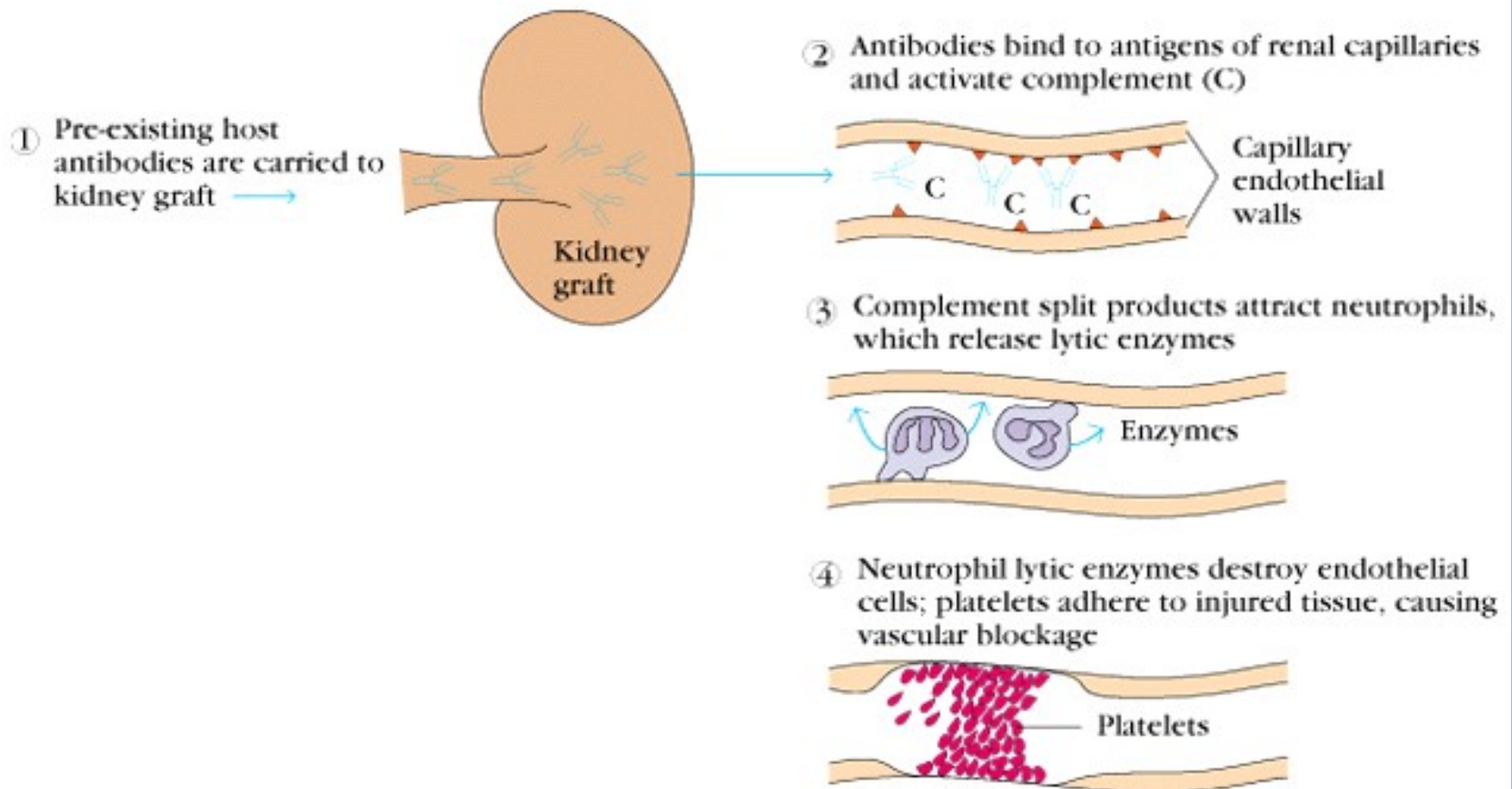
# Rejection Response





# 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

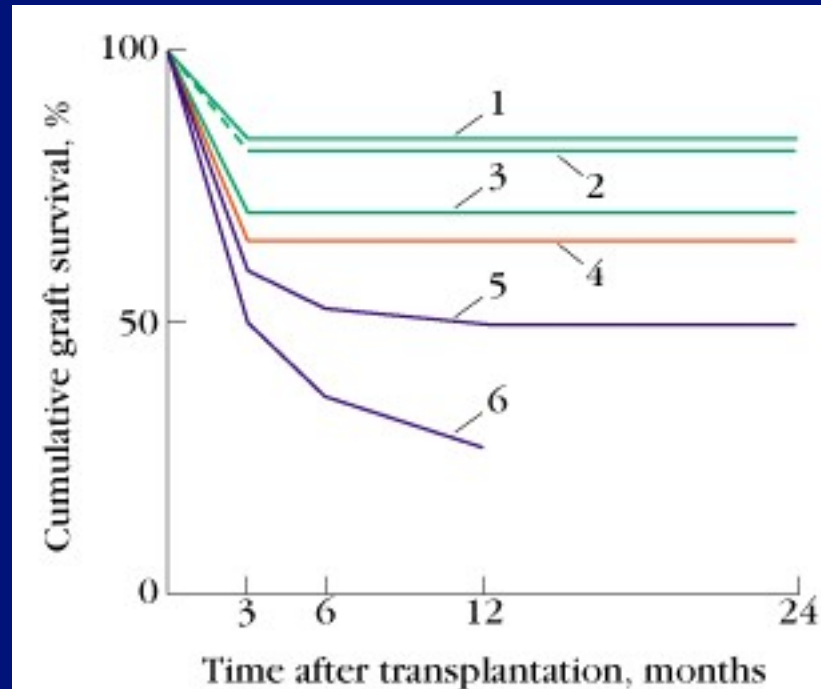
- Occurs in about two thirds of bone marrow transplants
- Occurs because grafted immunocompetent T cells proliferate in the irradiated immunocompromised host and reject cells with foreign proteins resulting in severe organ dysfunction
- Donor's Tc cells play a major role in destroying the recipient's 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

## Cornea

From cadaver  
Immunosuppression not required  
40,000 transplants per year

## Skin

Mostly autologous (burn victims)  
Temporary grafts of nonviable tissue  
Allogeneic grafts rare, require immunosuppression

## Lung

From brain-dead donor  
Procedure recently developed;  
little data available  
845 transplants in 1998  
Often heart/lung transplant (45 in 1998)

## Blood

Transfused from living donor  
ABO and Rh matching required  
Complications extremely rare  
An estimated 14 million units used each year

## Heart

From brain-dead donor  
HLA matching useful but often impossible  
Risk of coronary artery damage, perhaps mediated by host antibody  
2,340 transplants in 1998

## Pancreas

From cadaver  
Islet cells from organ sufficient  
253 transplants in 1998  
Increasingly, pancreas/kidney transplant for advanced diabetes (965 in 1998)

## Liver

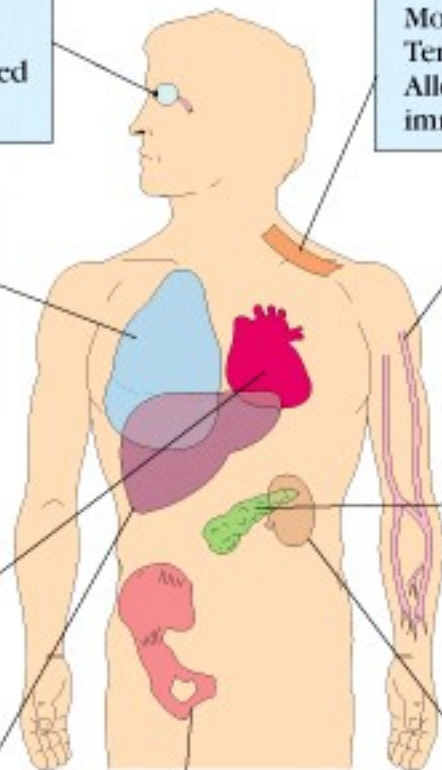
From cadaver  
Surgical implantation complex  
Resistant to hyperacute rejection  
Risk of GVHD  
4,450 transplants in 1998

## Kidney

From live donor or cadaver  
ABO and HLA matching useful  
Immunosuppression usually required  
Risk of GVHD very low  
11,900 transplants in 1998

## Bone marrow

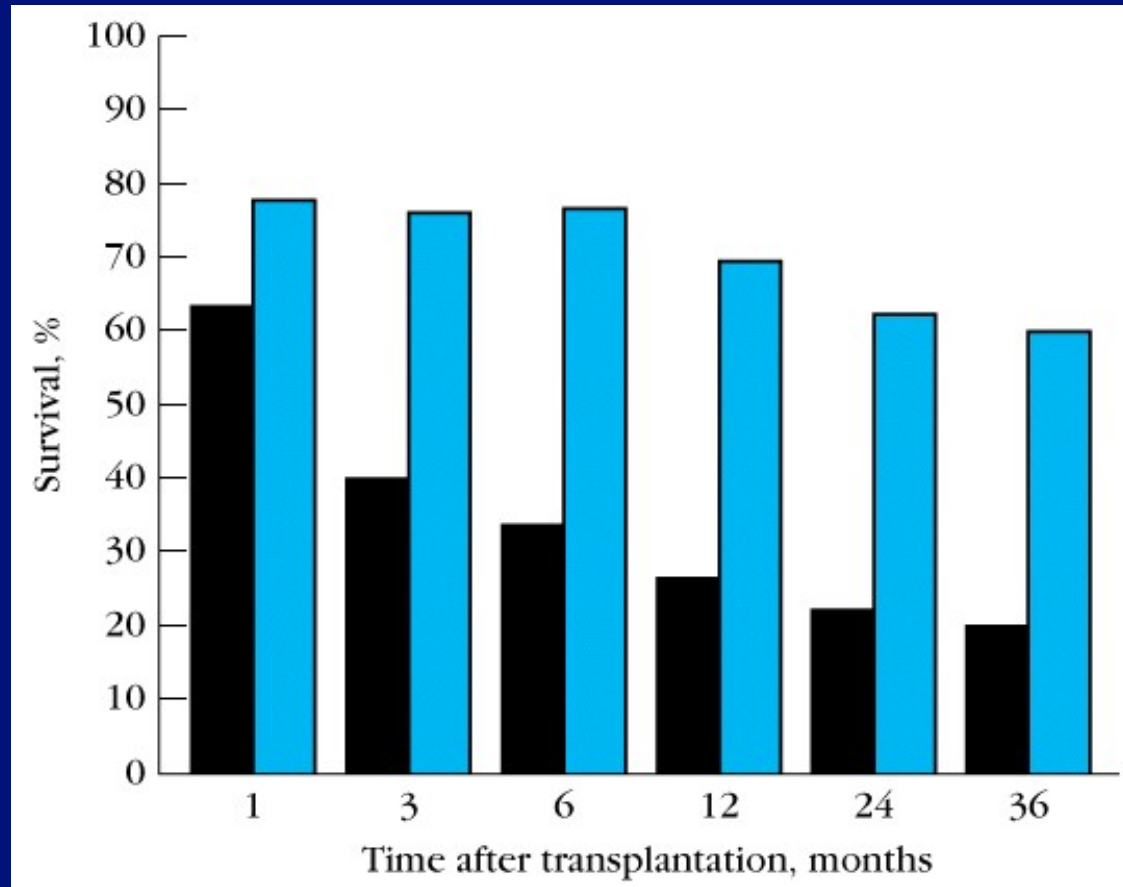
Needle aspiration from living donor  
Implanted by IV injection  
ABO and HLA matching required  
Rejection rare but GVHD a risk



# General Immunosuppression Therapy

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

# Immunosuppressive Therapy

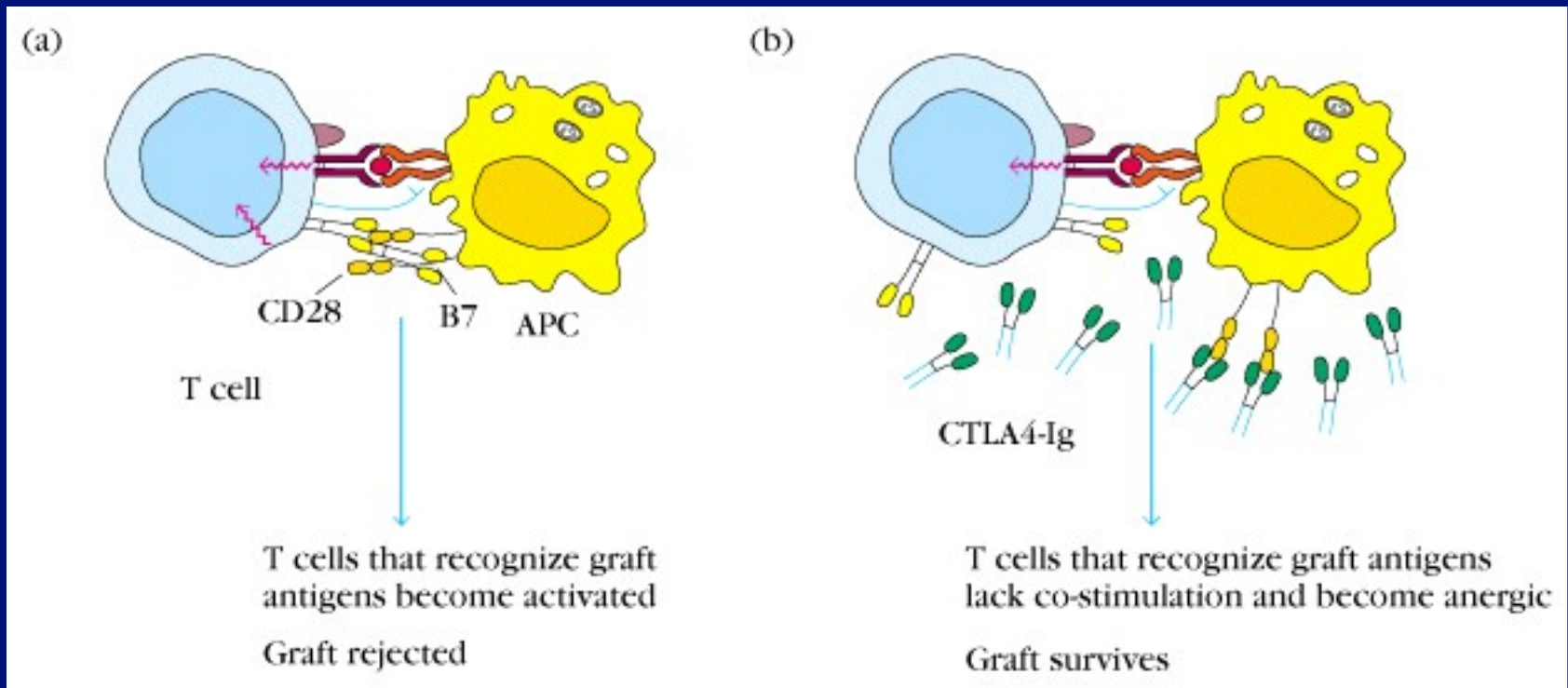


Comparison of the survival rates of liver transplants following azathioprine versus cyclosporin A treatment. Transplant survival rates are shown over a 3-year period for 84 liver transplant patients immunosuppressed using a combination of azathioprine plus corticosteroids (black) compared with another 55 patients treated with cyclosporin A plus corticosteroids (blue). [Sabesin SM, Williams JW. 1987. Current status of liver transplantation. Hospital Practice 22:75]



# 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**