Transplantation Immunology

Molecular and human Genetics
Jiwaji University
Gwalior

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- Transplantation
- Grafts
- Donors
- Recipients or hosts
- Orthotopic transplantation
- Heterotopic transplantation

Nobel Prize in Physiology or Medicine 1912

- Alexis Carrel (France)
- Work on vascular suture and the transplantation of blood vessels and organs

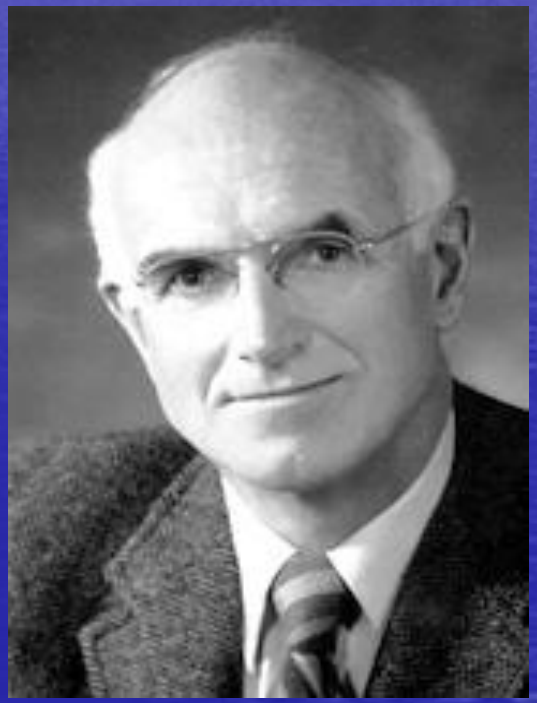
Nobel Prize in Physiology or Medicine 1960

- Peter Brian Medawar (1/2)
- Discovery of acquired immunological tolerance
  - The graft reaction is an immunity phenomenon
  - 1950s, induced immunological tolerance to skin allografts in mice by neonatal injection of allogeneic cells

Great events in history of transplantation

Nobel Prize in Physiology or Medicine 1990

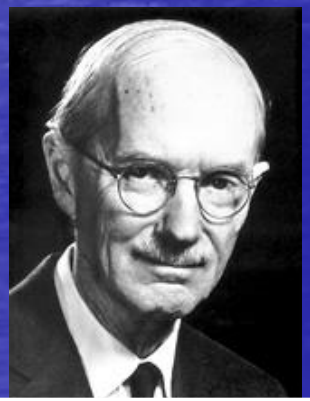
- Joseph E. Murray (1/2)
- Discoveries concerning organ transplantation in the treatment of human disease
  - In 1954, the first successful human kidney transplant was performed between twins in Boston.
  - Transplants were possible in unrelated people if drugs were taken to suppress the body's immune reaction

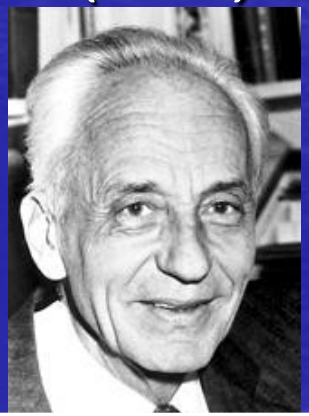


Great events in history of transplantation

Nobel Prize in Physiology or Medicine 1980

- George D. Snell (1/3), Jean Dausset (1/3)
- Discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions
  - H-genes (histocompatibility genes), H-2 gene
  - Human transplantation antigens (HLA) ----MHC





Great events in history of transplantation

Nobel Prize in Physiology or Medicine 1988

- Gertrude B. Elion (1/3) , George H. Hitchings (1/3)
- Discoveries of important principles for drug treatment
  - Immunosuppressant drug (The first cytotoxic drugs) ----- azathioprine

Great events in history of transplantation

Today, kidney, pancreas, heart, lung, liver, bone marrow, and cornea transplantations are performed among non-identical individuals with ever increasing frequency and success

Introduction

- Transplantation immunology - sequence of events that occurs after an allograft or xenograft is removed from donor and then transplanted into a recipient.

- A major limitation to the success of transplantation is the immune response of the recipient to the donor tissue.

Classification of grafts

- **Autologous grafts (Autografts)**
  - Grafts transplanted from one part of the body to another in the same individual
- **Syngeneic grafts (Isografts)**
  - Grafts transplanted between two genetically identical individuals of the same species
- **Allogeneic grafts (Allografts)**
  - Grafts transplanted between two genetically different individuals of the same species
- **Xenogeneic grafts (Xenografts)**
  - Grafts transplanted between individuals of different species

Immunology of Transplant Rejection

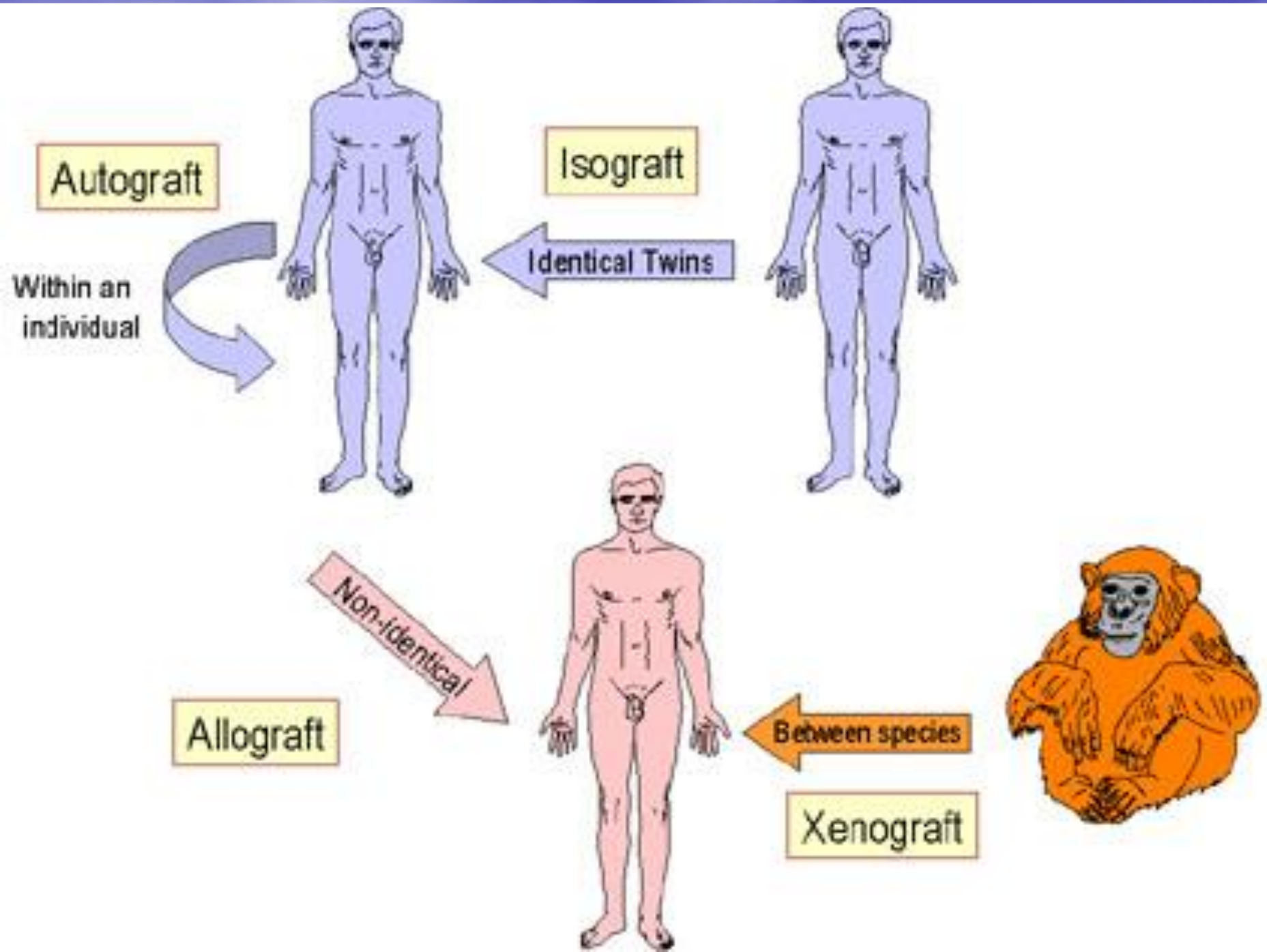
Components of the Immune system involved in graft Rejection :

1) Antigen presenting cells –
   - Dendritic cells
   - Macrophages
   - Activated B Cells
2) B cells and antibodies –
   - Preformed antibodies
   - Natural antibodies
   - Preformed antibodies from prior sensatization
   - Induced antibodies
3) T cells
4) Other cells –
   - Natural killer cells
   - T cells that express NK cell – associated Markers
   - Monocytes/Macrophages

The Immunology of Allogeneic Transplantation

- Recognition of transplanted cells that are self or foreign is determined by polymorphic genes (MHC) that are inherited from both parents and are expressed co-dominantly.

- Alloantigens elicit both cell-mediated and humoral immune responses.


Autograft
Within an individual
Isograft
Identical Twins
Non-identical
Allograft
Between species
Xenograft

Graft Rejection

- **Grafts rejection is a kind of specific immune response due to:**
  - **Specificity**
  - **Immune memory**
- **Grafts rejection can be divided into:**
  - **First set rejection**
  - **Second set rejection**

Immunologic Basis of Allograft Rejection

I. Transplantation antigens

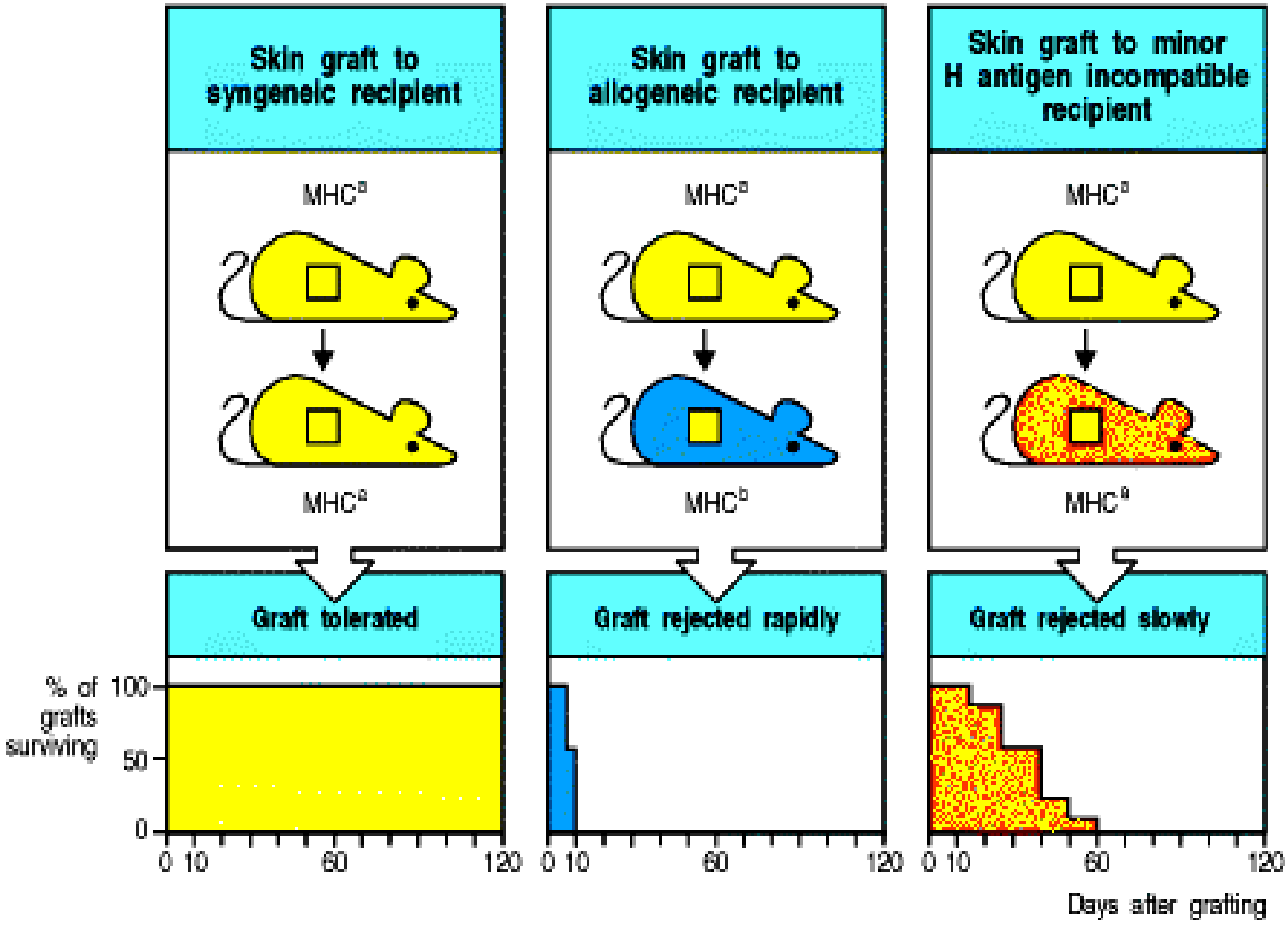
- Major histocompatibility antigens (MHC molecules)
- Minor histocompatibility antigens
- Other alloantigens

1. Major histocompatibility antigens

- Difference of HLA types is the main cause of human grafts rejection

2. Minor histocompatibility antigens

- Also cause grafts rejection, but slow and weak
- Mouse H-Y antigens encoded by Y chromosome
- HA-1～HA-5 linked with non-Y chromosome


Skin graft to syngeneic recipient
Skin graft to allogeneic recipient
Skin graft to minor H antigen incompatible recipient
MHC^a
MHC^a
MHC^b
MHC^a
Graft tolerated
Graft rejected rapidly
Graft rejected slowly
% of grafts surviving
100
50
0
0 10 60 120
0 10 60 120
0 10 60 120
Days after grafting

3. Other alloantigens

- Human ABO blood group antigens
- Some tissue specific antigens
  - Skin＞kidney＞heart＞pancreas ＞liver
  - VEC antigen
  - SK antigen

II. Mechanism of allograft rejection

- Cell-mediated Immunity
- Humoral Immunity
- Role of NK cells

1. Cell-mediated Immunity

- Recipient's T cell-mediated cellular immune response against alloantigens on grafts

Molecular Mechanisms of Allogeneic Recognition

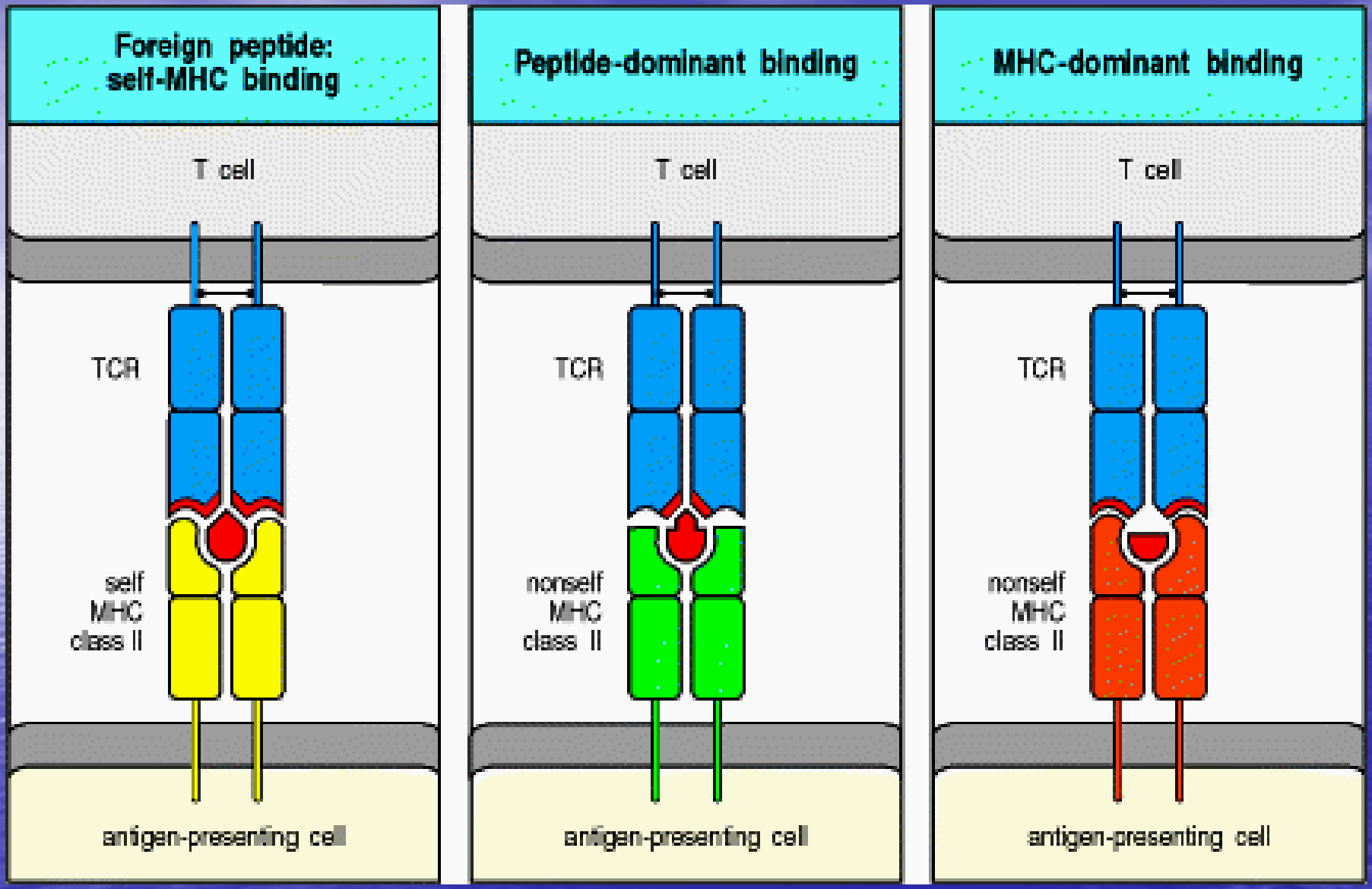
- Many T cells can recognize allogenetic MHC molecules

? The recipient' T cells recognize the allogenetic MHC molecules

- Direct Recognition
- Indirect Recognition

Direct Recognition

- Recognition of an intact allogenetic MHC molecule displayed by donor APC in the graft
- Cross recognition
  - An allogenetic MHC molecule with a bound peptide can mimic the determinant formed by a self MHC molecule plus foreign peptide
  - A cross-reaction of a normal TCR, which was selected to recognize a self MHC molecules plus foreign peptide, with an allogenetic MHC molecule plus peptide



- **Cross recognition**

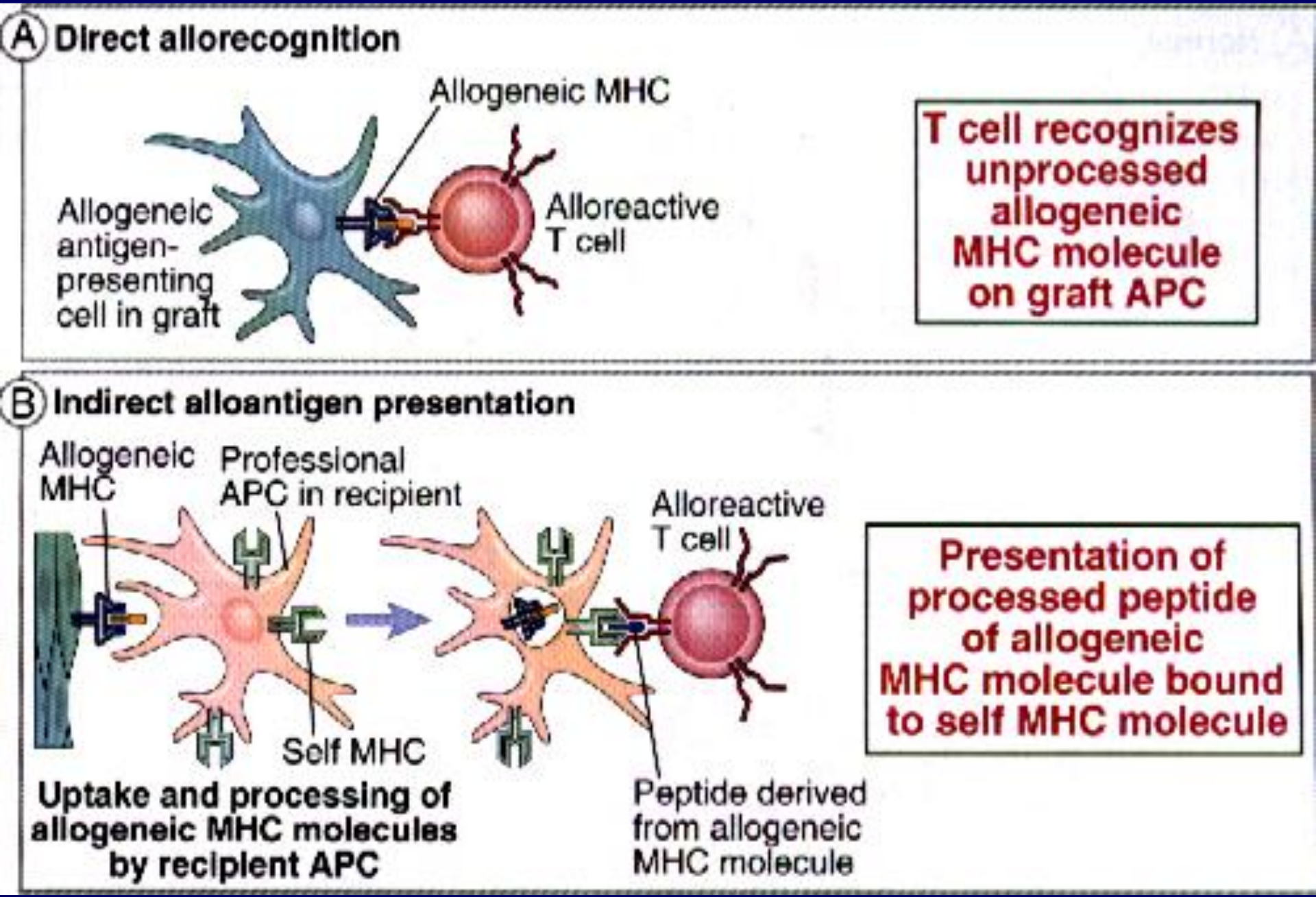
- **Passenger leukocytes Concept**
  - Donor APCs that exist in grafts, such as DC, MΦ
  - Early phase of acute rejection
  - Fast and strong

？ Many T cells can recognize allogenetic MHC molecules

- Allogenetic MHC molecules (different residues)
- Allogenetic MHC molecules–different peptides
- All allogenetic MHC molecules on donor APC can be epitopes recognized by TCR of host

Indirect recognition

- Uptake and presentation of allogeneic donor MHC molecules by recipient APC in “normal way”
- Recognition by T cells like conventional foreign antigens


A Direct allorecognition
Allogeneic MHC
Allogeneic antigen-presenting cell in graft
Alloreactive T cell
T cell recognizes unprocessed allogeneic MHC molecule on graft APC
B Indirect alloantigen presentation
Allogeneic MHC
Professional APC in recipient
Alloreactive T cell
Self MHC
Uptake and processing of allogeneic MHC molecules by recipient APC
Peptide derived from allogeneic MHC molecule
Presentation of processed peptide of allogeneic MHC molecule bound to self MHC molecule

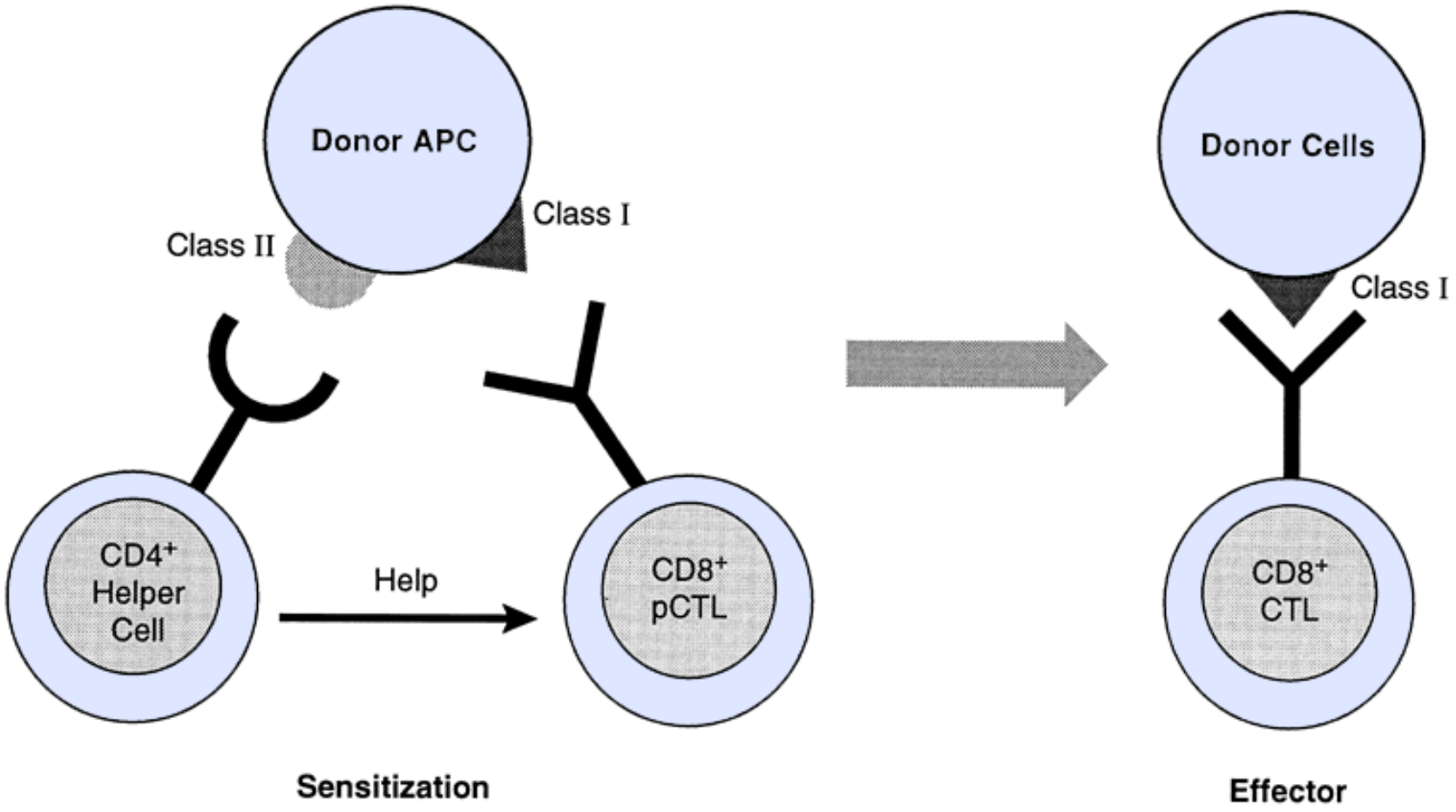
- Slow and weak
- Late phase of acute rejection and chronic rejection
- Coordinated function with direct recognition in early phase of acute rejection

Difference between Direct Recognition and Indirect Recognition

	Direct Recognition	Indirect Recognition
Allogeneic MHC molecule	Intact allogeneic MHC molecule	Peptide of allogeneic MHC molecule
APCs	Recipient APCs are not necessary	Recipient APCs
Activated T cells	$CD4^+$T cells and/or $CD8^+$T cells	$CD4^+$T cells and/or $CD8^+$T cells
Roles in rejection	Acute rejection	Chronic rejection
Degree of rejection	Vigorous	Weak

Role of $CD4^+$T cells and $CD8^+$T cells

- Activated $CD4^+$T by direct and indirect recognition
  - Cytokine(s) secretion
  - MΦ activation and recruitment
- Activated $CD8^+$T by direct recognition
  - Kill the graft cells directly
- Activated $CD8^+$T by indirect recognition
  - Can not kill the graft cells directly


Donor APC
Class II
Class I
CD4+
Helper
Cell
Help
CD8+
pCTL
Sensitization
Donor Cells
Class I
CD8+
CTL
Effector

2. Humoral immunity

- Important role in hyperacute rejection (Preformed antibodies)
  - Complements activation
  - ADCC
  - Opsonization
- Enhancing antibodies /Blocking antibodies

3 .Role of NK cells

- Host KIRs can't recognize allogeneic MHC on graft (NK help??)
- Cytokines secreted by activated Th cells can promote NK activation (NK cells actively involved)

Classification and Effector Mechanisms of Allograft Rejection

Classification of Allograft Rejection

- Host versus graft reaction (HVGR)
  - Conventional organ transplantation
- Graft versus host reaction (GVHR)
  - Bone marrow transplantation
  - Immune cells transplantation

I. Host versus graft reaction (HVGR)

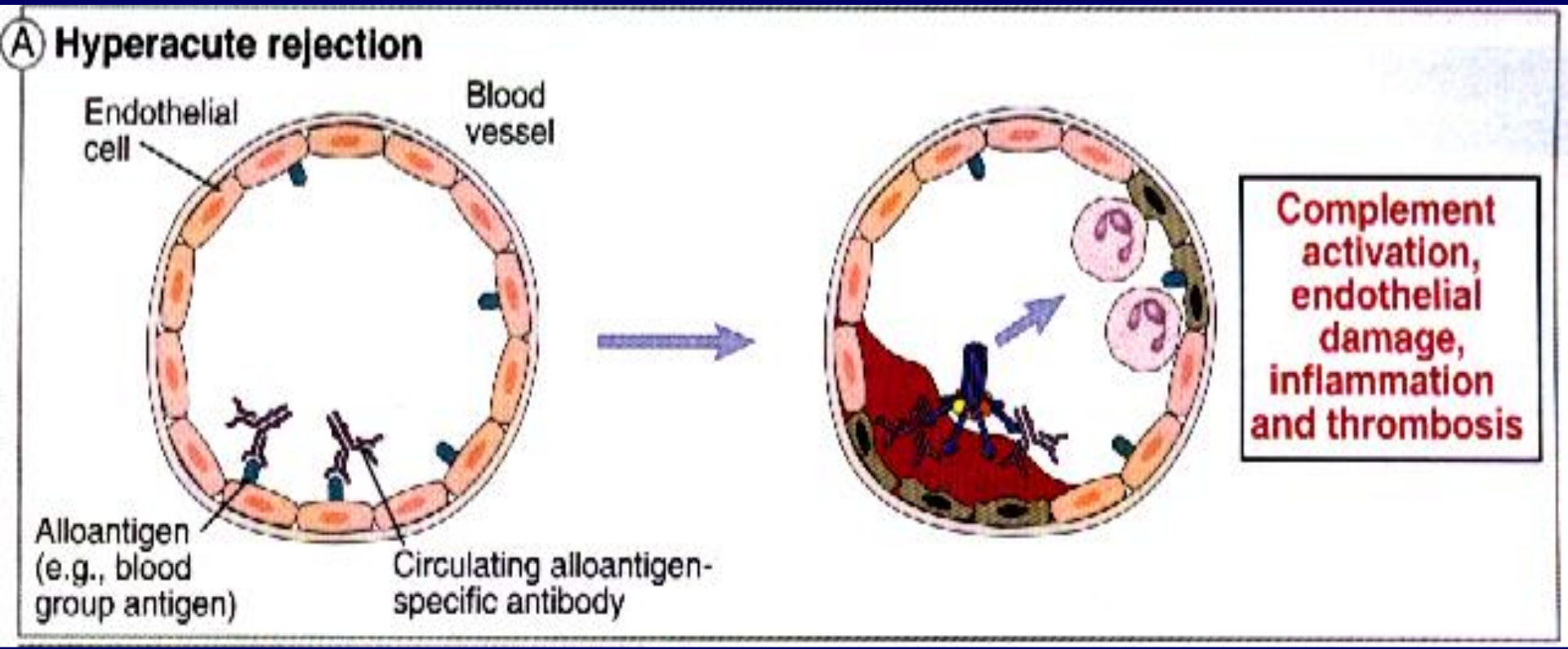
- Hyperacute rejection
- Acute rejection
- Chronic rejection

1. Hyperacute rejection

- Occurrence time
  - Occurs within minutes to hours after host blood vessels are anastomosed to graft vessels
- Pathology
  - Thrombotic occlusion of the graft vasculature
  - Ischemia, denaturation, necrosis

- Mechanisms
  - Preformed antibodies
    - Antibody against ABO blood type antigen
    - Antibody against VEC antigen
    - Antibody against HLA antigen

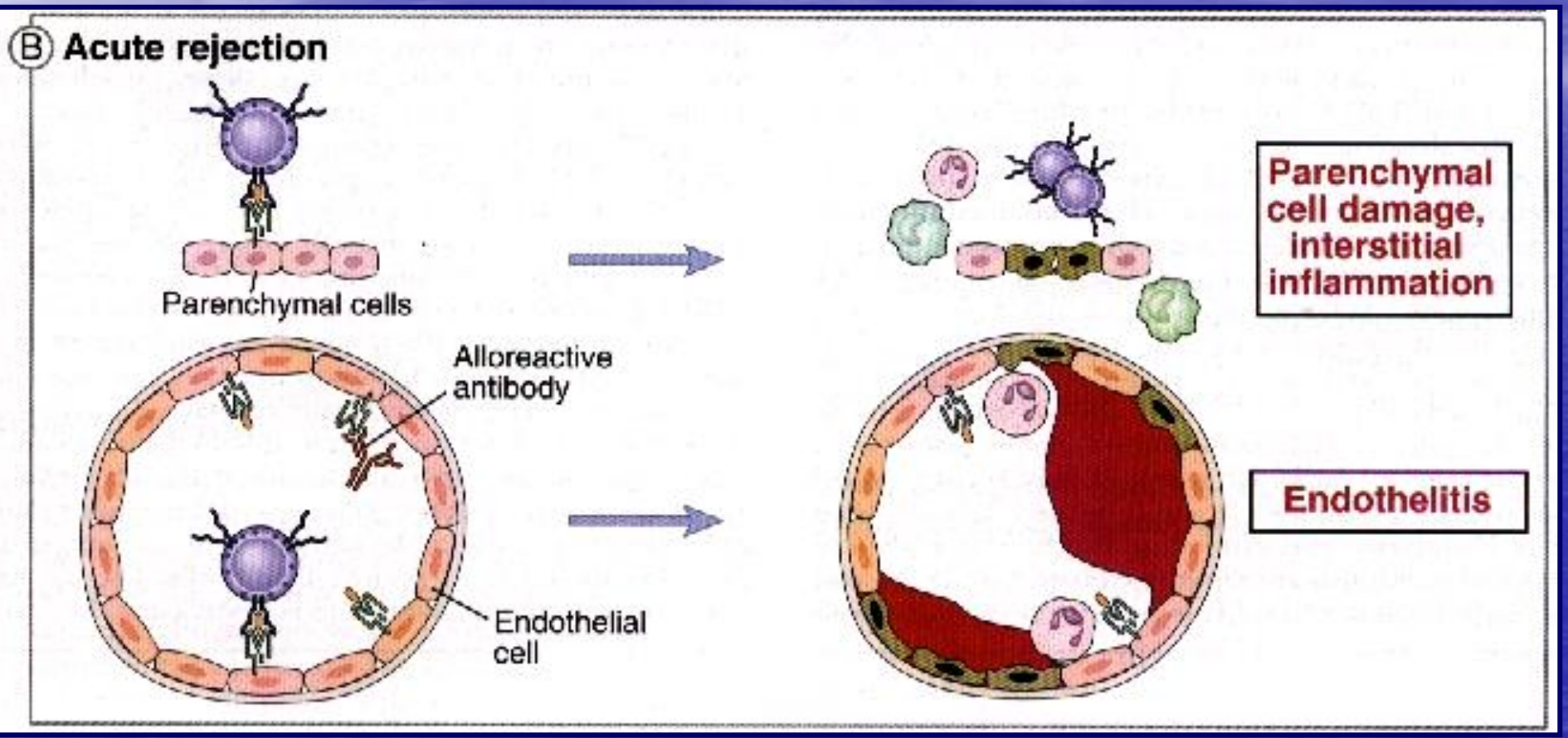
- Complement activation
  - Endothelial cell damage
- Platelets activation
  - Thrombosis, vascular occlusion, ischemic damage



2. Acute rejection

- Occurrence time
  - Occurs within days to 2 weeks after transplantation, 80-90% of cases occur within 1 month
- Pathology
  - Acute humoral rejection
    - Acute vasculitis manifested mainly by endothelial cell damage
  - Acute cellular rejection
    - Parenchymal cell necrosis along with infiltration of lymphocytes and MΦ

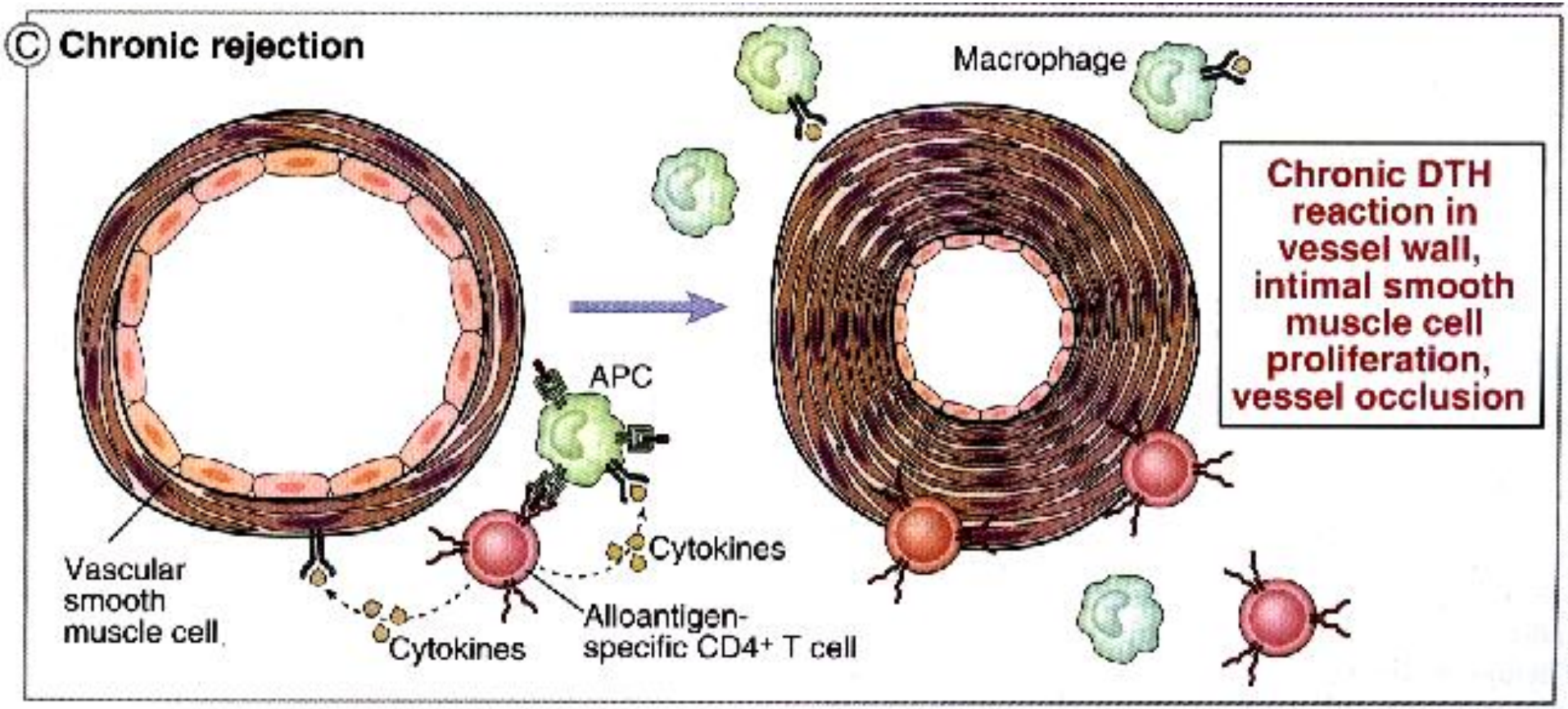
- Mechanisms
  - Vasculitis
    - IgG antibodies against alloantigens on endothelial cell
    - CDC
  - Parenchymal cell damage
    - Delayed hypersensitivity mediated by CD4+Th1
    - Killing of graft cells by CD8+Tc

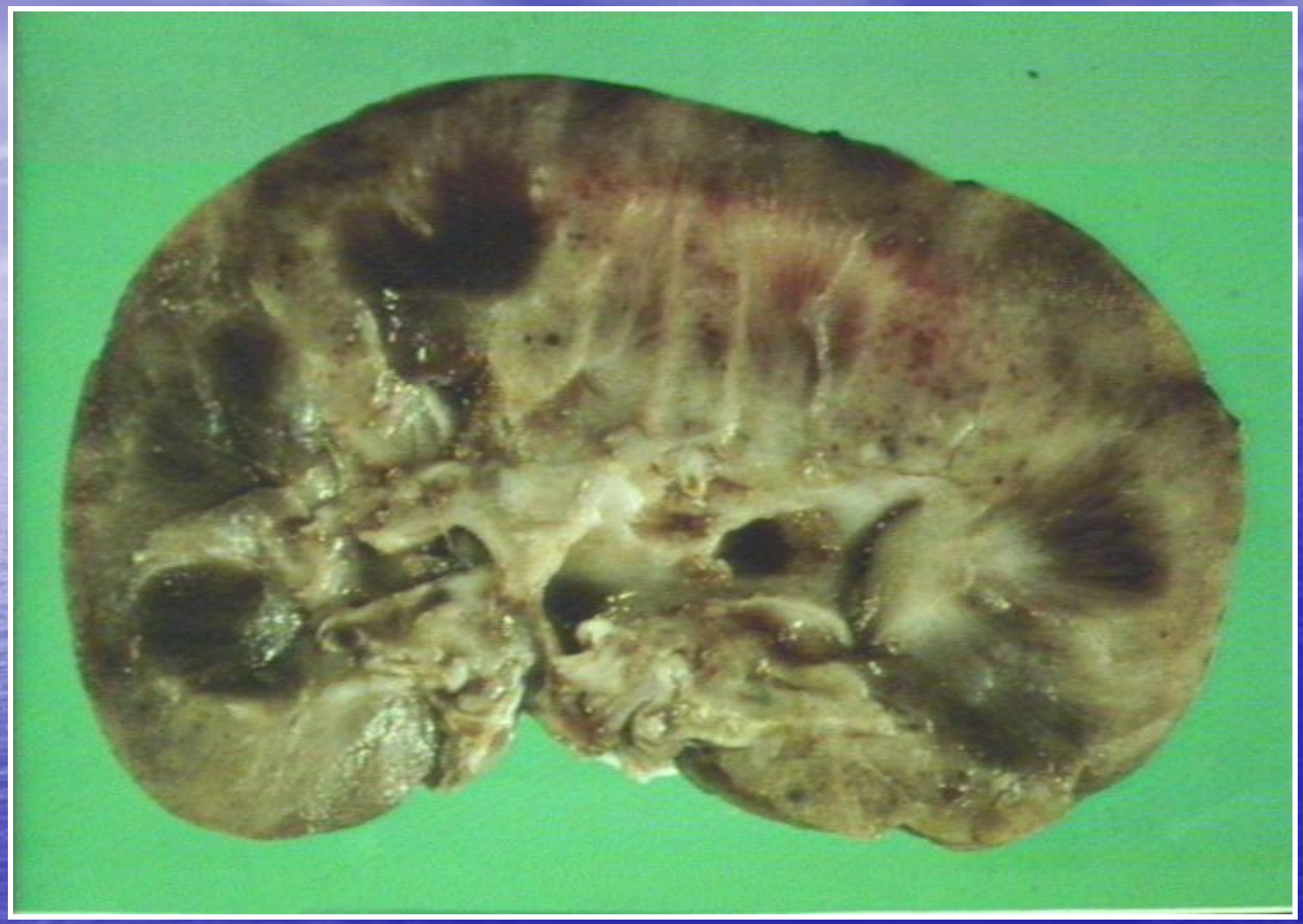

B Acute rejection
Parenchymal cells
Alloreactive antibody
Endothelial cell
Parenchymal cell damage, interstitial inflammation
Endothelitis

3. Chronic rejection

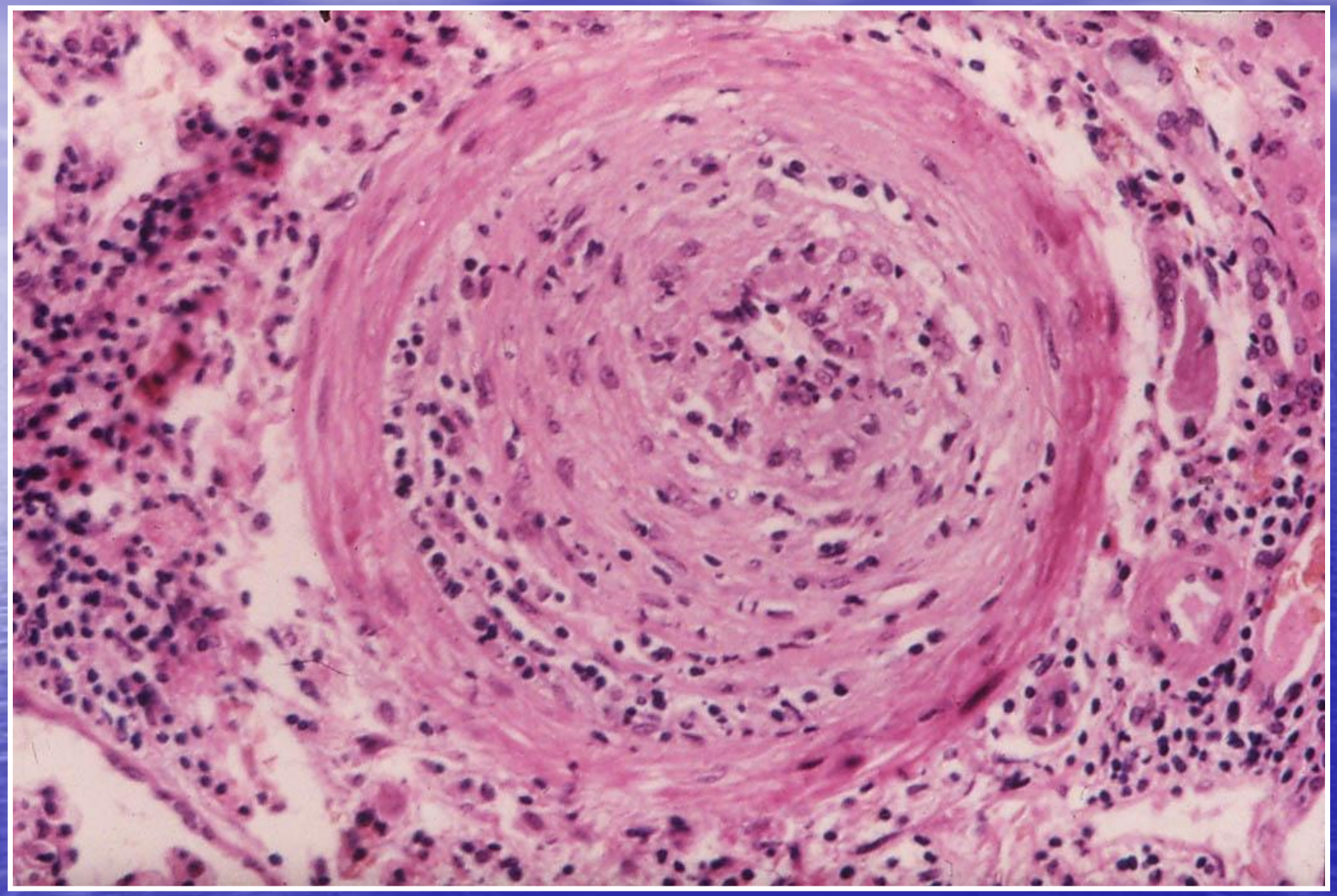
- Occurrence time
  - Develops months or years after acute rejection reactions have subsided
- Pathology
  - Fibrosis and vascular abnormalities with loss of graft function

- **Mechanisms**
  - Not clear
  - Extension and results of cell necrosis in acute rejection
  - Chronic inflammation mediated by CD4+T cell/MΦ
  - Organ degeneration induced by non immune factors


C Chronic rejection
Macrophage
Chronic DTH reaction in vessel wall, intimal smooth muscle cell proliferation, vessel occlusion
APC
Cytokines
Vascular smooth muscle cell
Cytokines
Alloantigen-specific CD4+ T cell



Kidney Transplantation----Graft Rejection

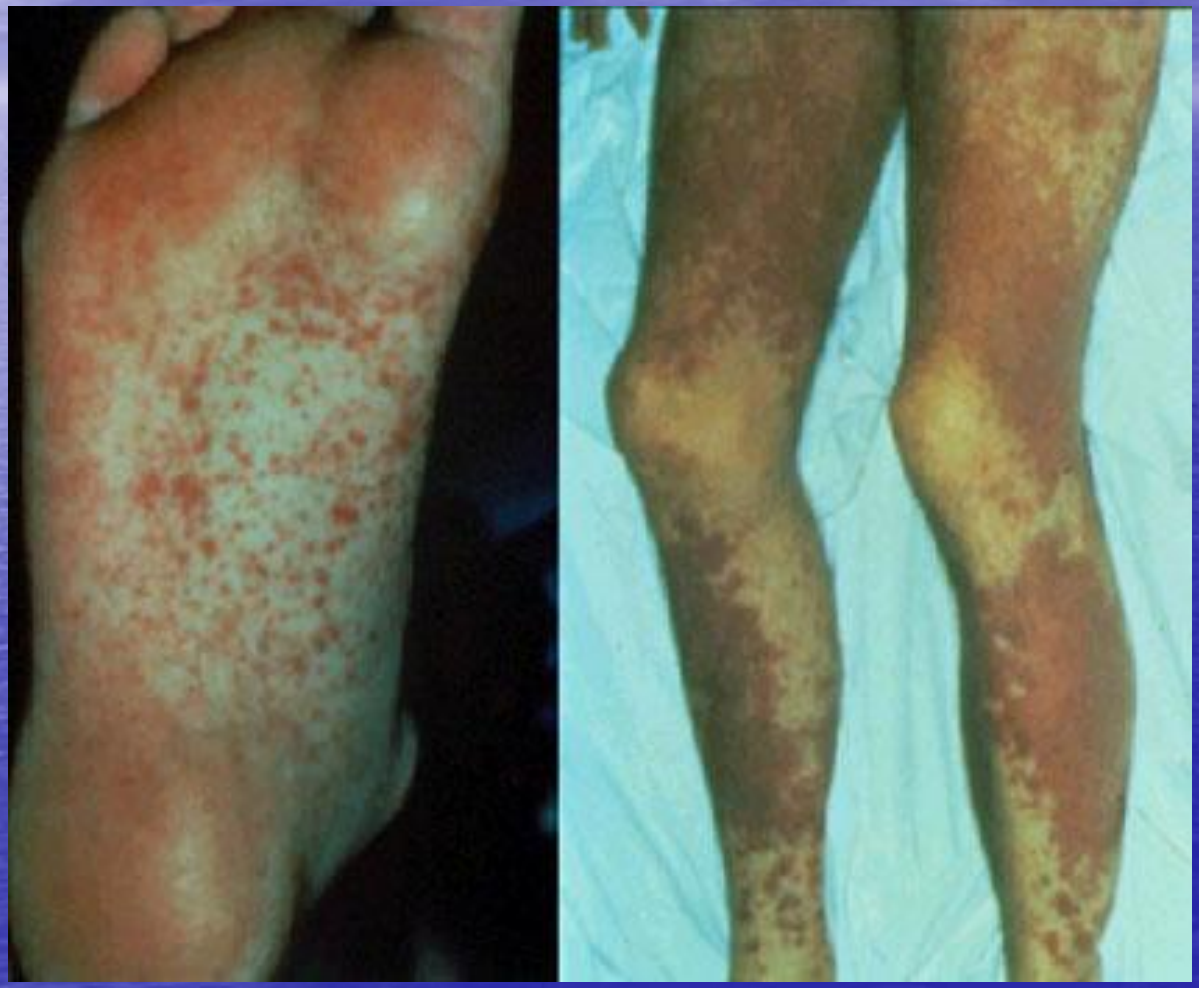


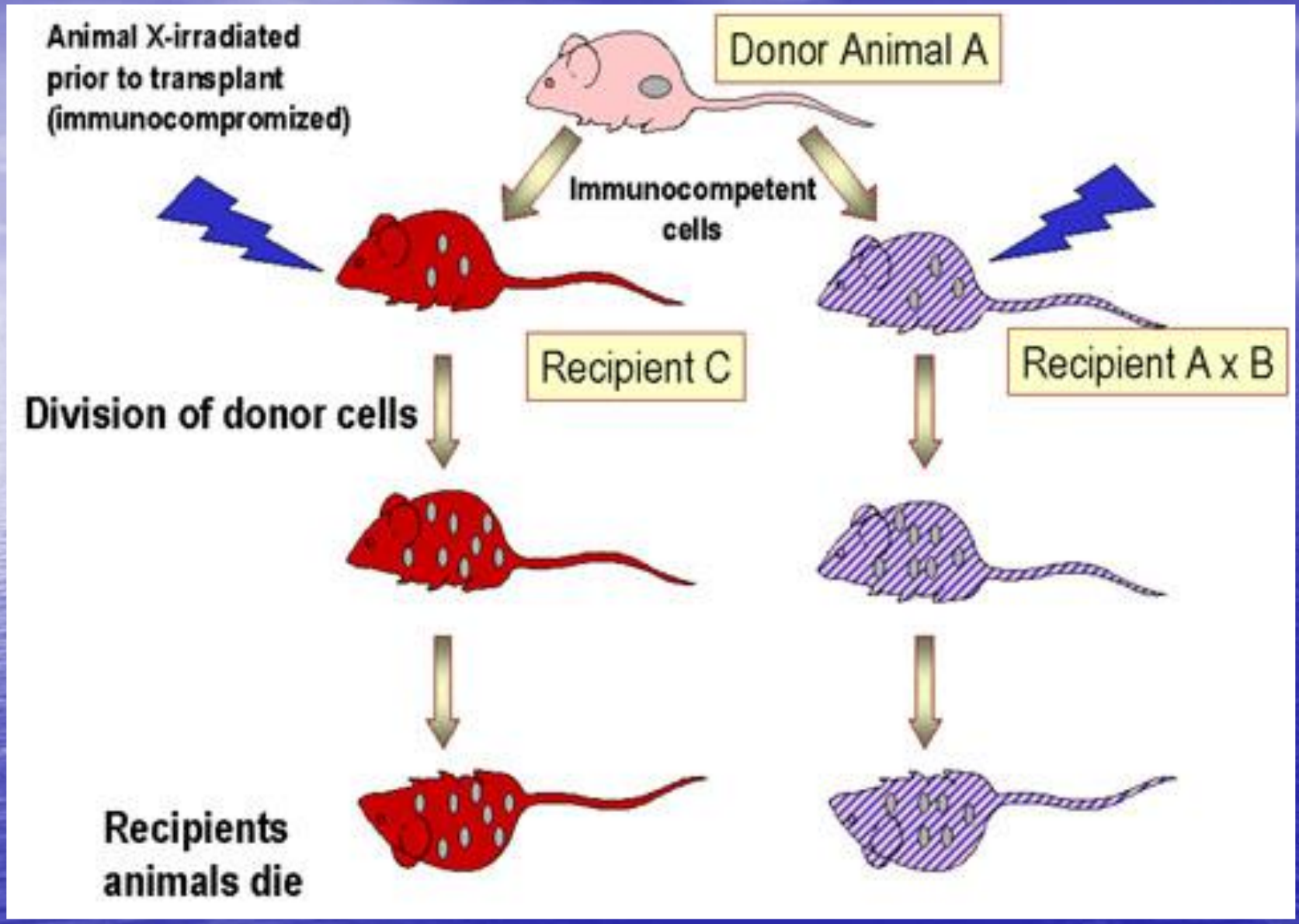
Chronic rejection in a kidney allograft with arteriosclerosis

II.Graft versus host reaction (GVHR)

- Graft versus host reaction (GVHR)
  - Allogenetic bone marrow transplantation
  - Rejection to host alloantigens
  - Mediated by immune competent cells in bone marrow
- Graft versus host disease (GVHD)
  - A disease caused by GVHR, which can damage the host

- Graft versus host disease





- **Graft versus host disease**

Conditions

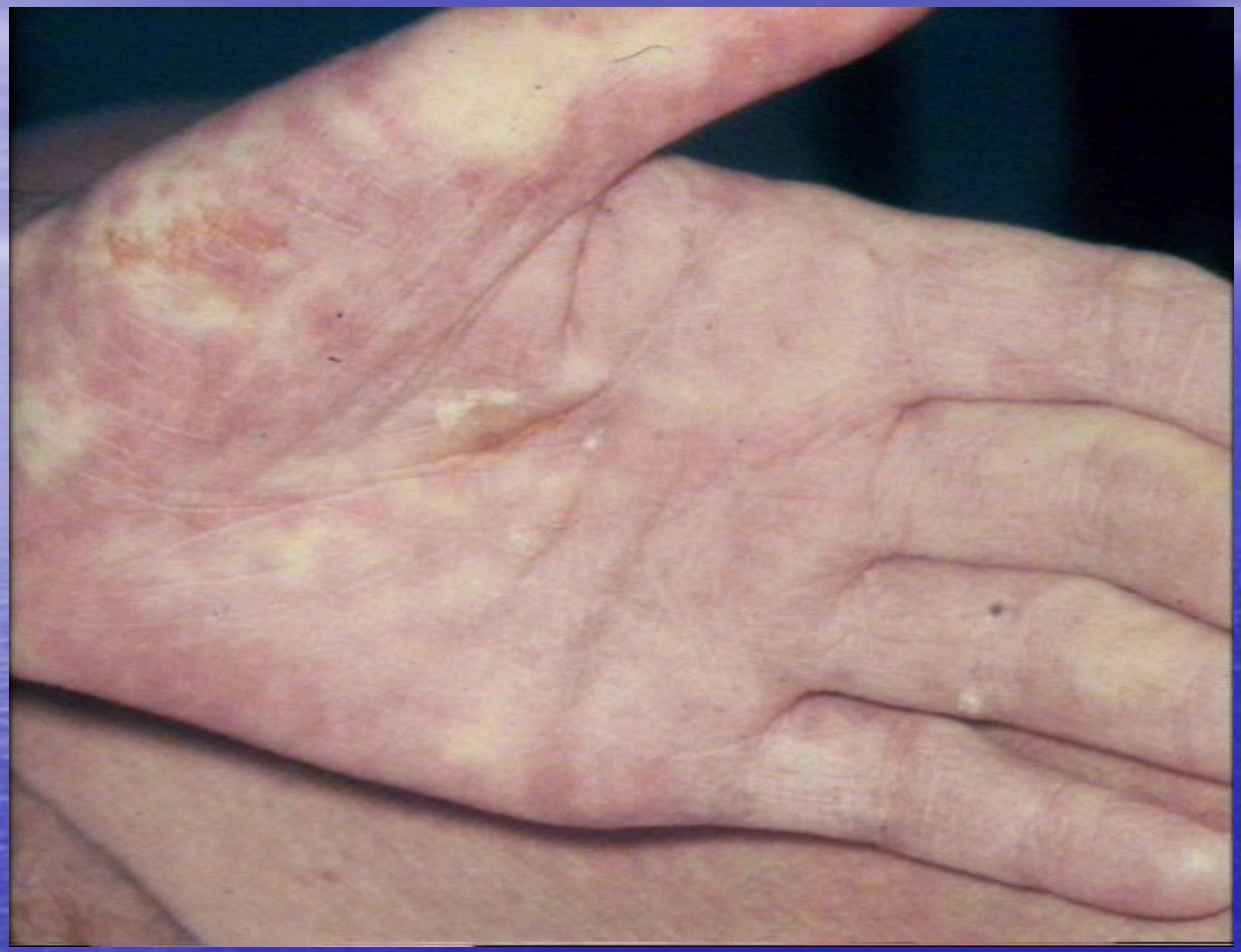
- Enough immune competent cells in grafts
- Immunocompromised host
- Histocompatability differences between host and graft

- Bone marrow transplantation
- Thymus transplantation
- Spleen transplantation
- Blood transfusion of neonate

In most cases the reaction is directed against minor histocompatibility antigens of the host

1. Acute GVHD

- Endothelial cell death in the skin, liver, and gastrointestinal tract
- Rash, jaundice, diarrhea, gastrointestinal hemorrhage
- Mediated by mature T cells in the grafts



- Acute graft-versus-host reaction with vivid palmar erythema

2. Chronic GVHD

- Fibrosis and atrophy of one or more of the organs
- Eventually complete dysfunction of the affected organ

Both acute and chronic GVHD are commonly treated with intense immunosuppresion

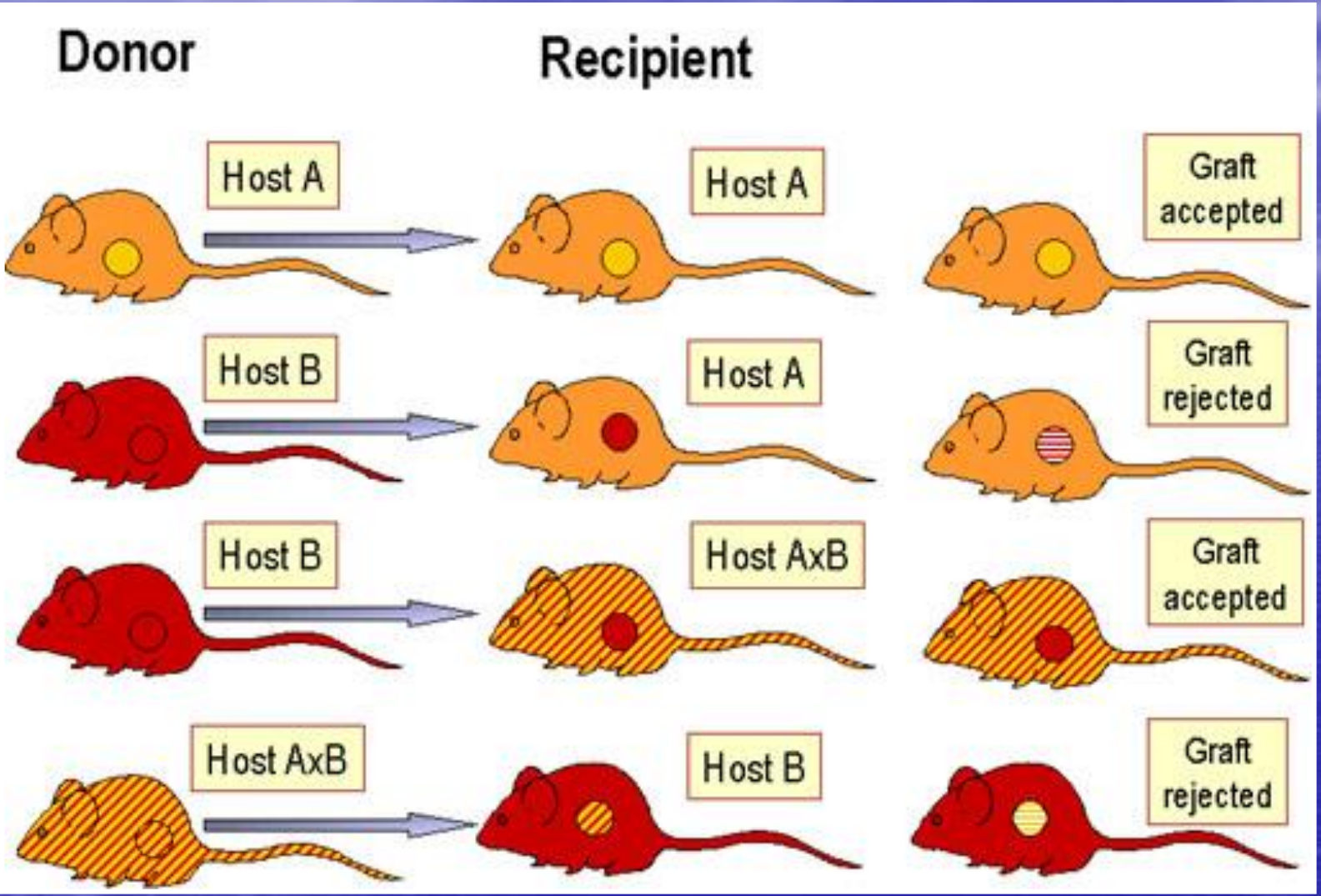
- Uncertain
- Fatal

Prevention and Therapy of Allograft Rejection

- Tissue Typing
- Immunosuppressive Therapy
- Induction of Immune Tolerance

I. Tissue Typing

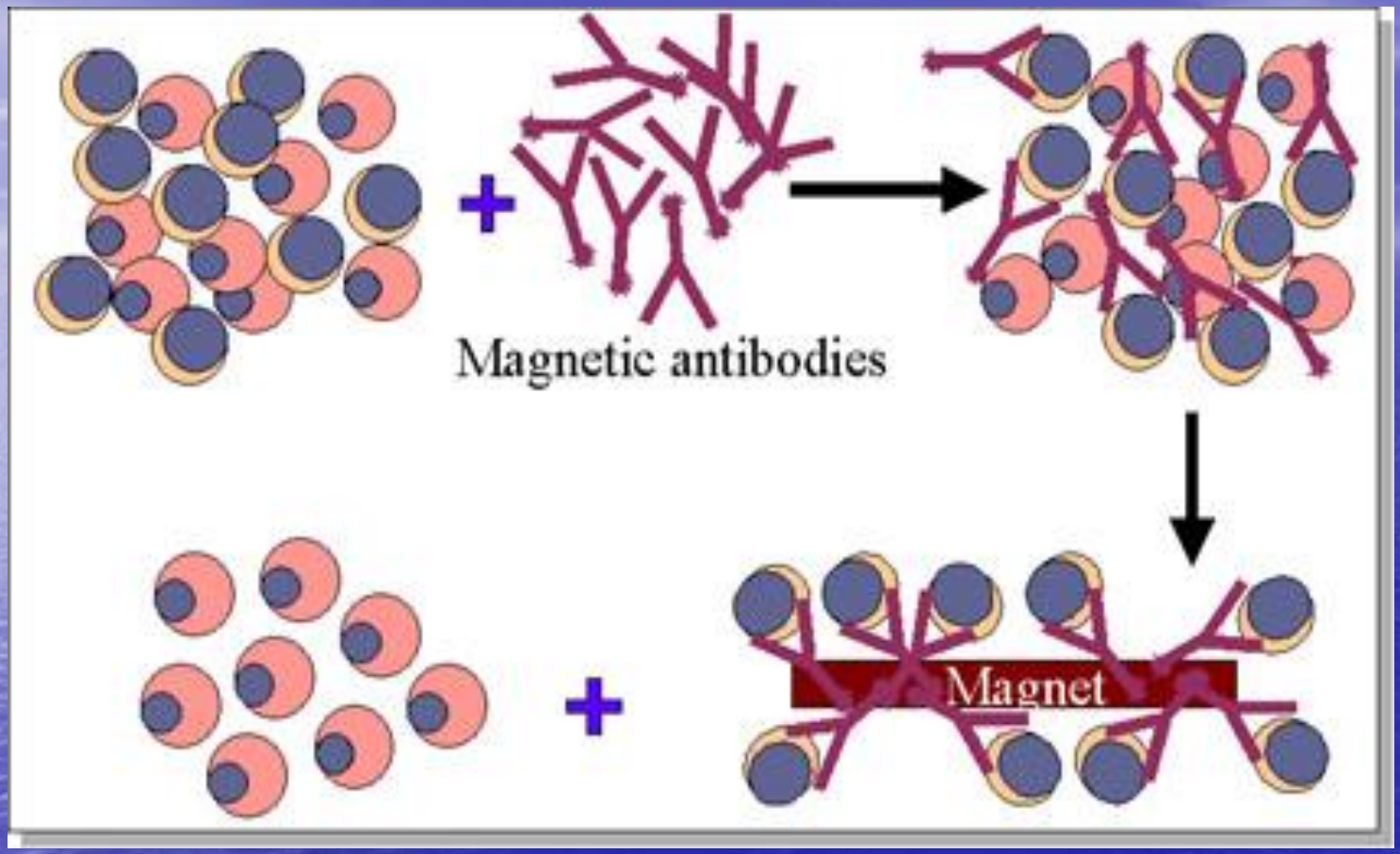
- ABO and Rh blood typing
- Crossmatching (Preformed antibodies)
- HLA typing
  - HLA-A and HLA-B
  - HLA-DR



- **Laws of transplantation**

II. Immunosuppressive Therapy

- Cyclosporine(CsA), FK506
  - Inhibit NFAT transcription factor
- Azathioprine, Cyclophosphamide
  - Block the proliferation of lymphocytes
- Ab against T cell surface molecules
  - Anti-CD3 mAb----Deplete T cells
- Anti-inflammatory agents
  - Corticosteroids----Block the synthesis and secretion of cytokines



- Removal of T cells from marrow graft

III. Induction of Immune Tolerance

- Inhibition of T cell activation
  - Soluble MHC molecules
  - CTLA4-Ig
  - Anti-IL2R mAb
- Th2 cytokines
  - Anti-TNF-α，Anti-IL-2，Anti-IFN-γ mAb
- Microchimerism
  - The presence of a small number of cells of donor, genetically distinct from those of the host individual