IMMUNOLOGY
OF
TRANSPLANTATION

Transplantation

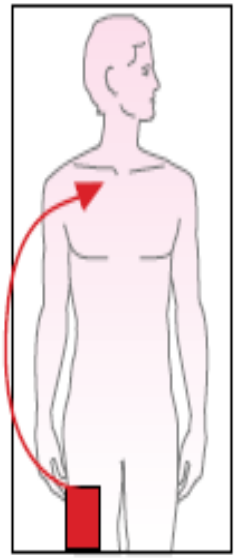
- When an organ or tissue becomes irreparably damaged (disease or injury)

or

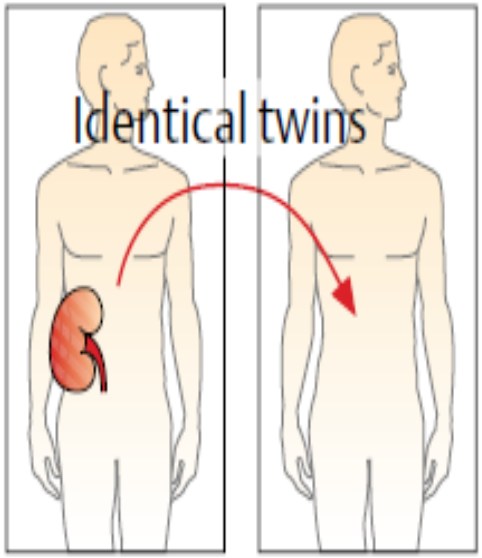
- when its congenitally defective or absent

TRANSPLANTATION or GRAFTING

Graft or Transplant: Transfer of living cells, tissues and organs from one part of the body to another or from one individual to another.



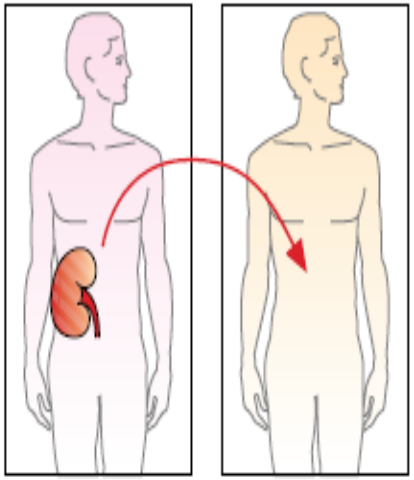
Autologous



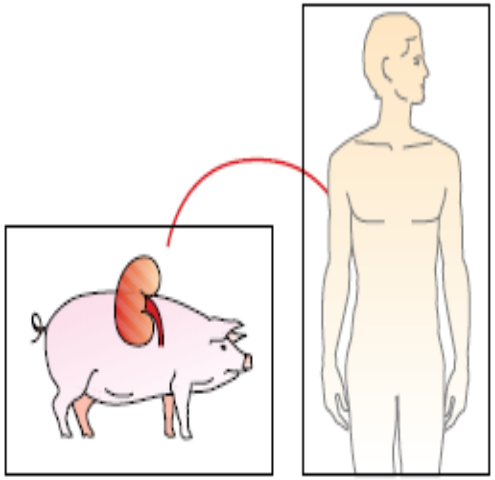
Syngeneic

Based on genetic(and antigenic) relationship between DONOR & RECIPIENT

A. Transplantation types

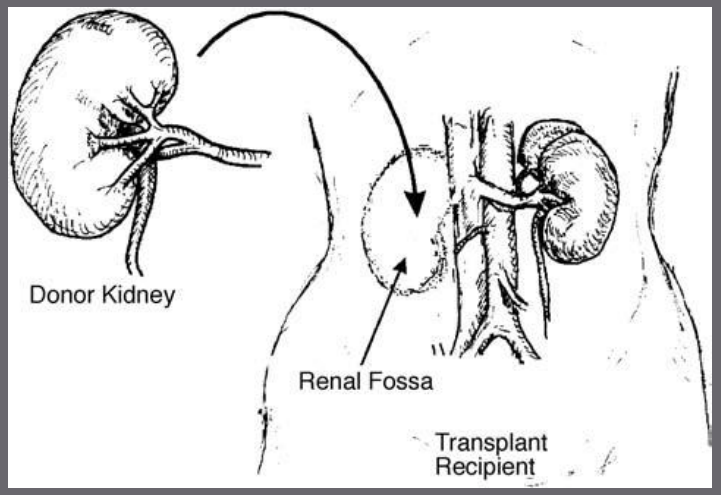


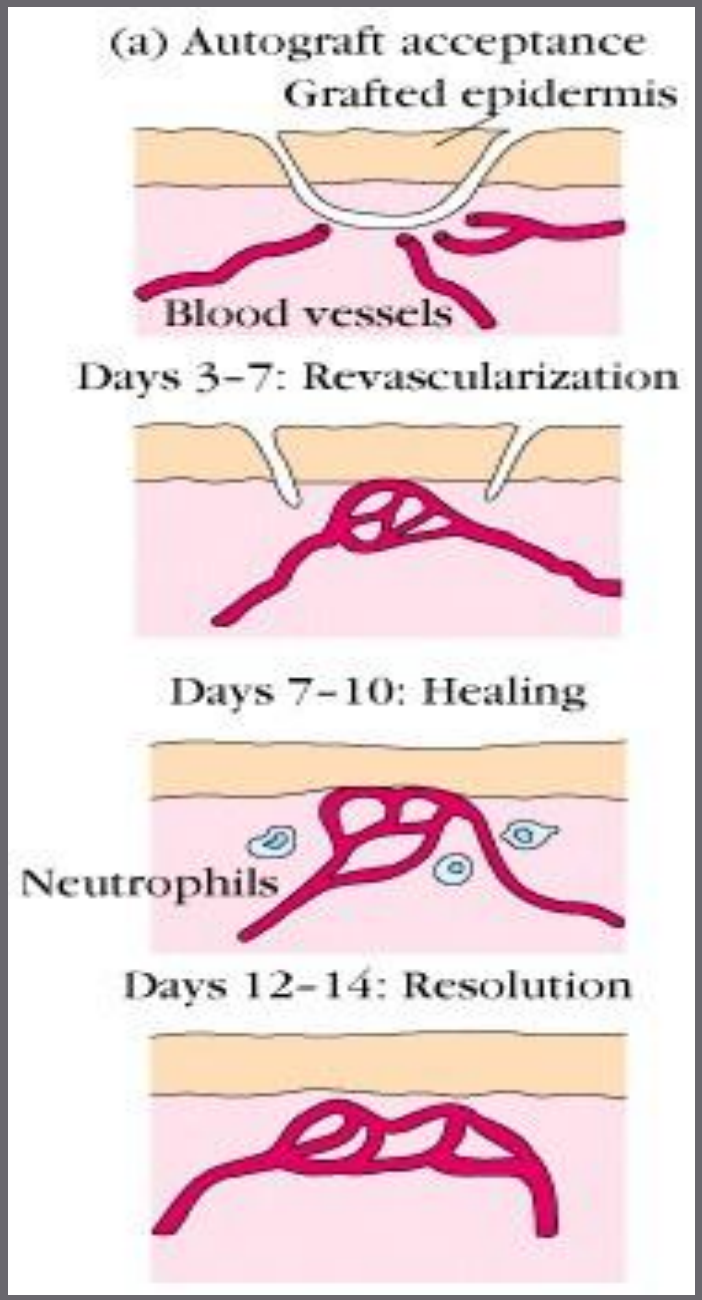
Allogeneic



Xenogeneic

- **Based on**:
  - Organ or tissue transplanted
  - Anatomical site of origin of transplant & site of its placement:
    - Orthotopic: normal sites
    - Heterotopic: abnormal sites
  - Fresh or stored:
    - Vital grafts
    - Structural (static) grafts: bone/artery



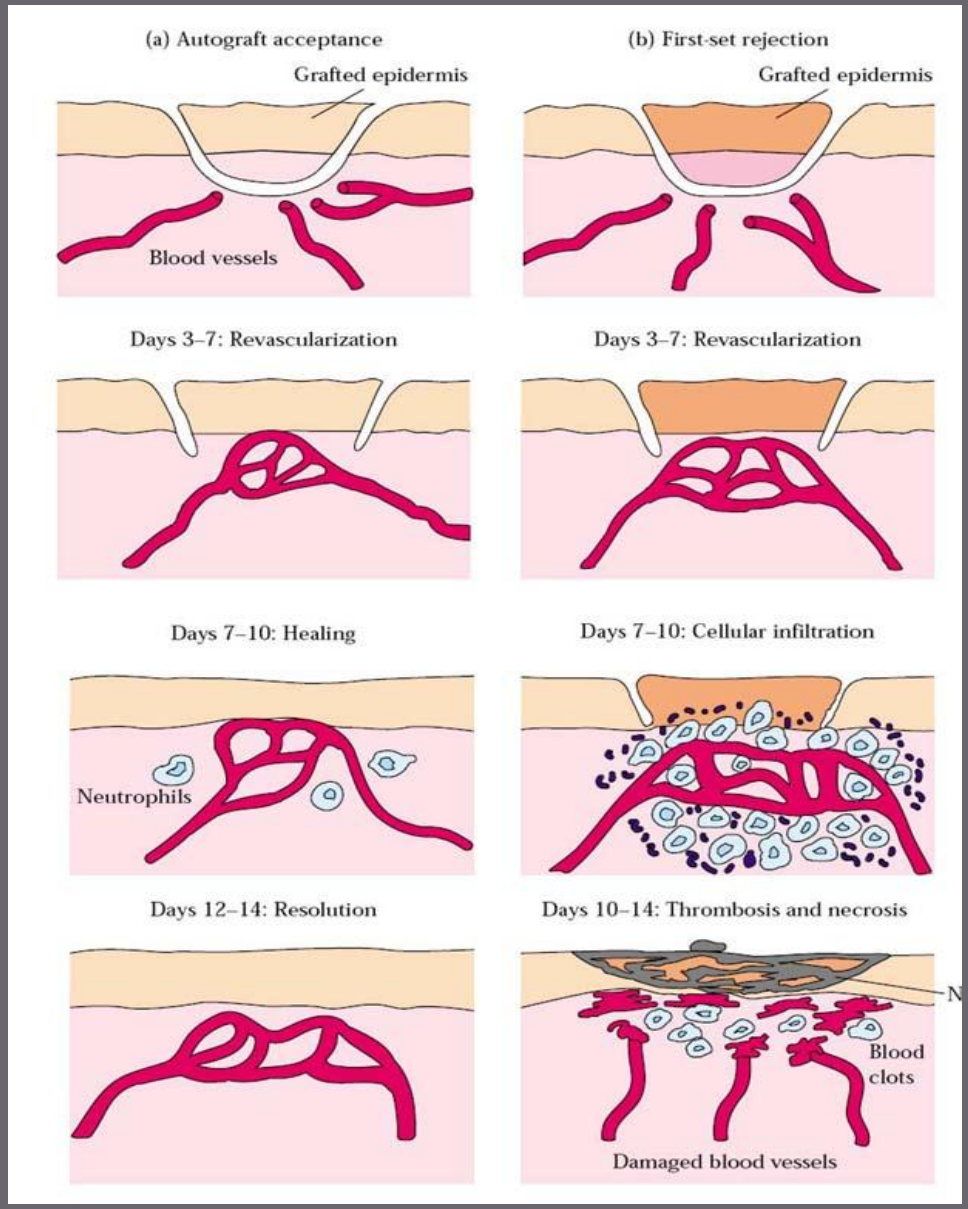


Autografting

- Transfer of self tissue from one body site to another in the same individual
- Genetic homology of the tissue-immune system does not respond
- Use:
  - skin grafts
  - hair

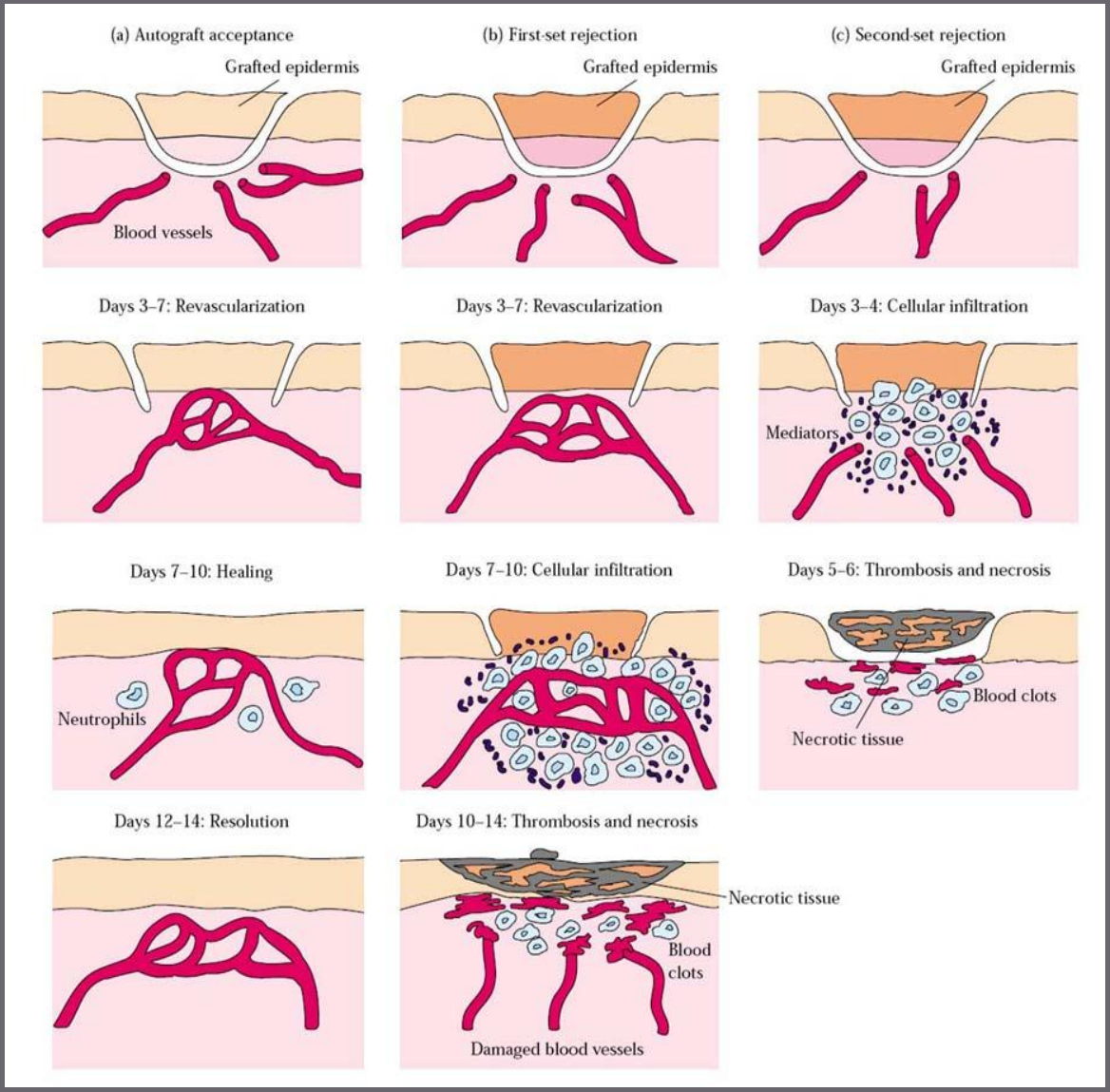
The Allograft reaction

- **First Set Response**
  - Skin graft from a genetically unrelated animal of same species
  - Initial acceptance
  - Thrombosed and necrosed
  - Mainly by T lymphocytes



Second Set Response

- If an animal has rejected a graft by the first set response, another graft from the same donor is applied – rejected in an accelerated manner
- Mainly by antibodies



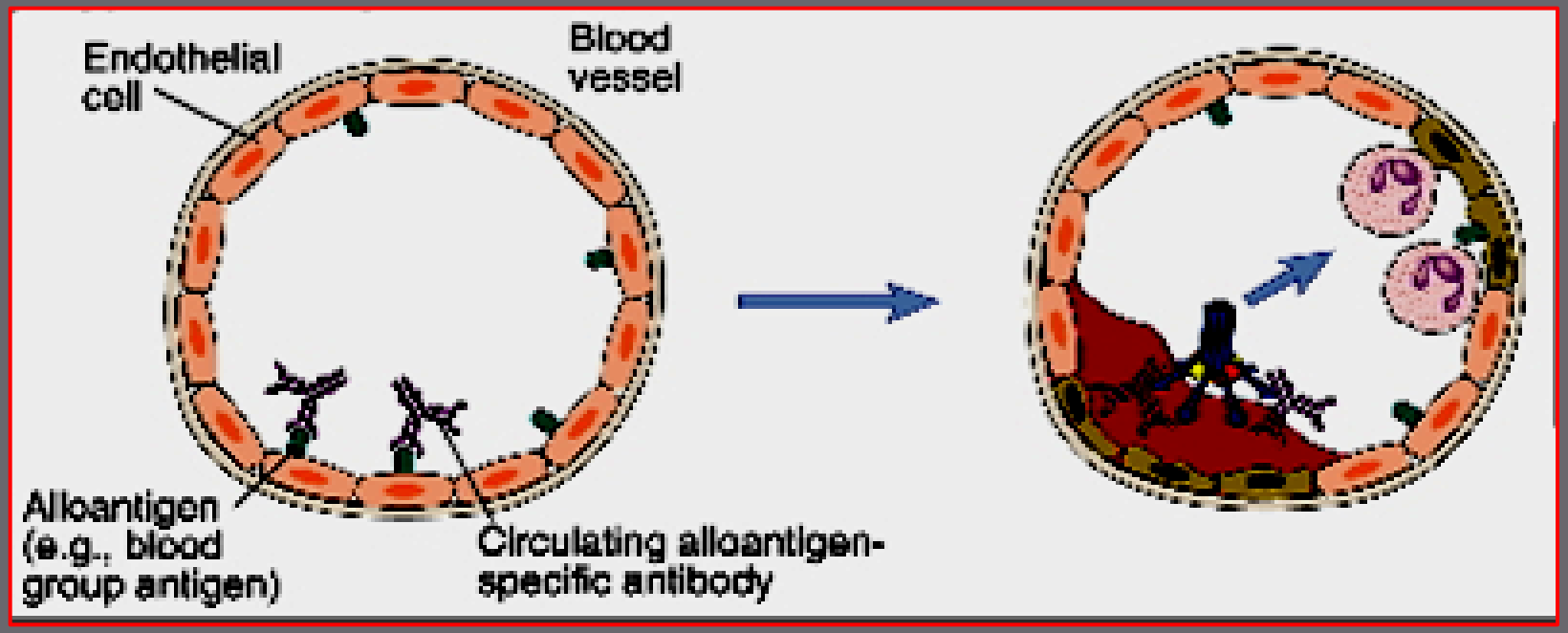
Effector Mechanisms of Allograft Rejection

- Hyperacute Rejection
- Acute Rejection
- Chronic Rejection

Hyperacute Rejection

- **WHITE GRAFT RESPONSE**
- Pre-existing specific antibodies in high titres in the host circulation bind to donor endothelial antigens
- Activates Complement Cascade
- Characterized by thrombotic occlusion of graft
  - Graft remains pale
  - Rejected within minutes or hours, even without an attempt at vascularization

Hyperacute Rejection



1. Preformed Ab, 2. complement activation,
3. neutrophil margination, 4. inflammation,
5. Thrombosis formation

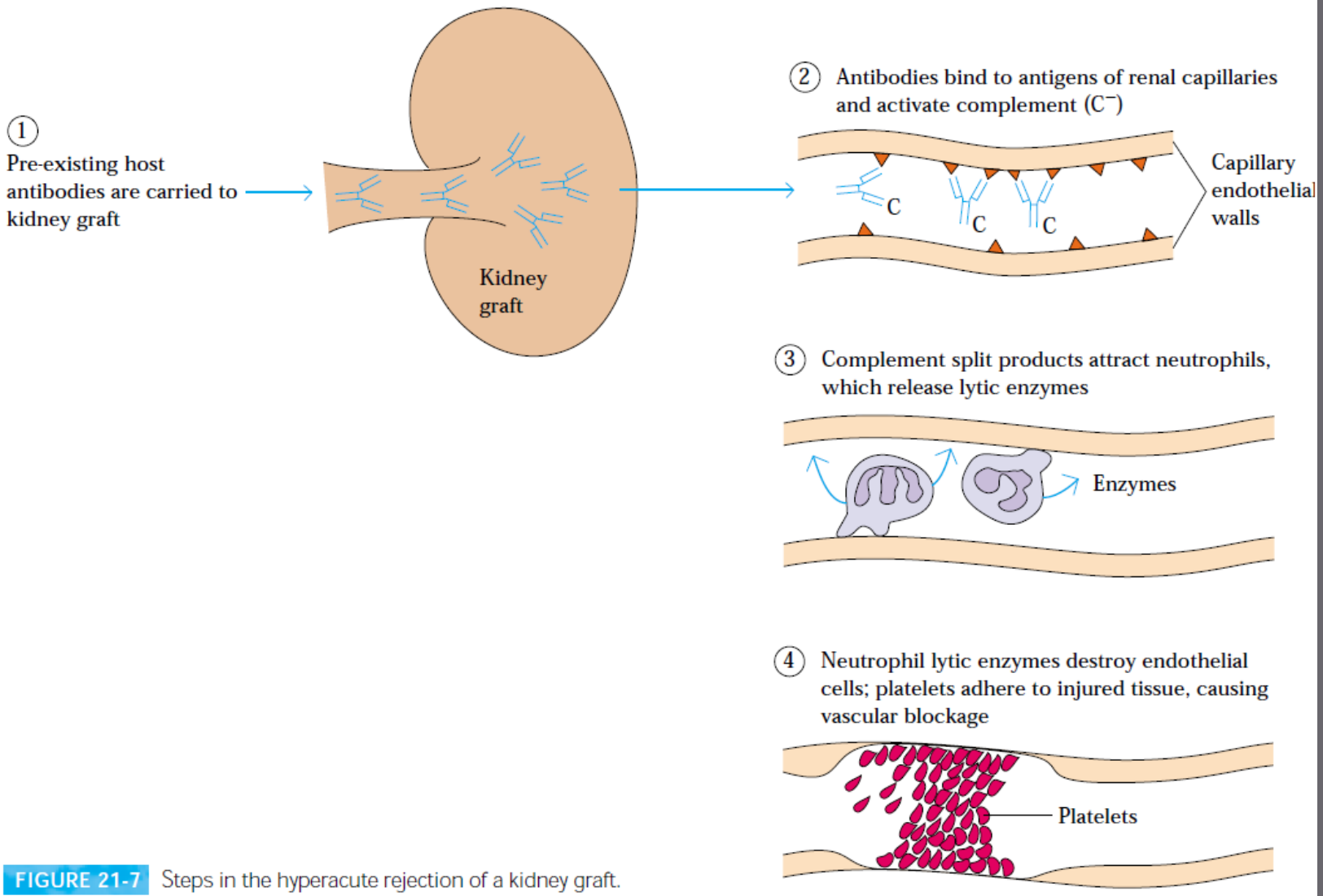


FIGURE 21-7 Steps in the hyperacute rejection of a kidney graft.

Immunological Enhancement

- Humoral antibodies can act in opposition to CMI by inhibiting graft rejection
  - Described by Kaliss in tumor transplants
- Enhancing effect can be passively transferred to normal animals by injection of serum from immunised animals-effect is due to humoral antibodies

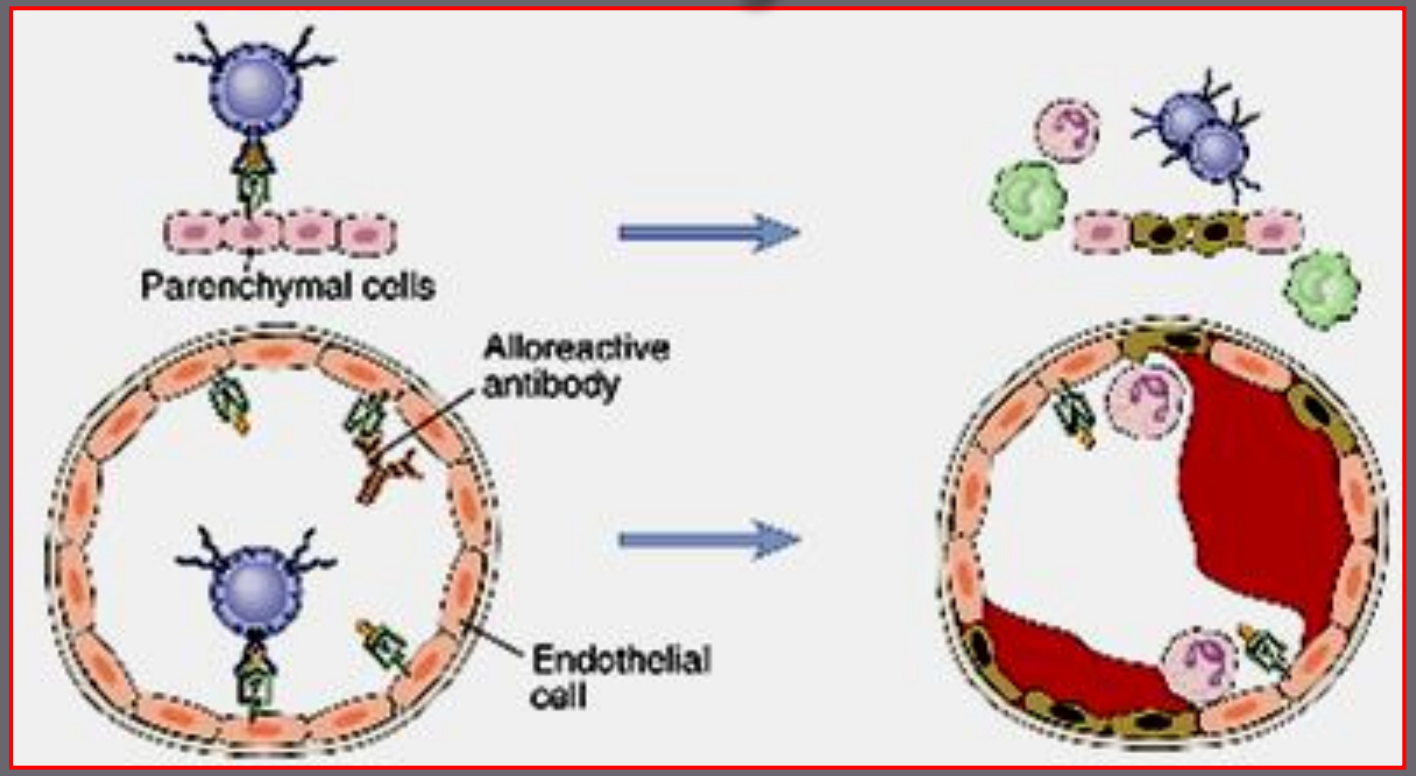
Antibodies can cause enhancing effect in various ways.

- **Afferent inhibition**: Combine with antigens released from graft so that they are unable to initiate an immune response
- **Central inhibition**: Antibodies may combine with lymphoid cells of appropriate specificity, by a negative feedback influence, render them incapable of responding to the antigens of the graft.
- **Efferent inhibition:** By coating the surface of cells in the graft so that sensitised lymphocytes are kept out of contact with them

Acute Rejection

- Vascular and parenchymal injury mediated by T cells and antibodies that usually begin after the first week of transplantation if there is no immunosuppressant therapy
- Incidence is high (30%) for the first 90 days

Acute Rejection

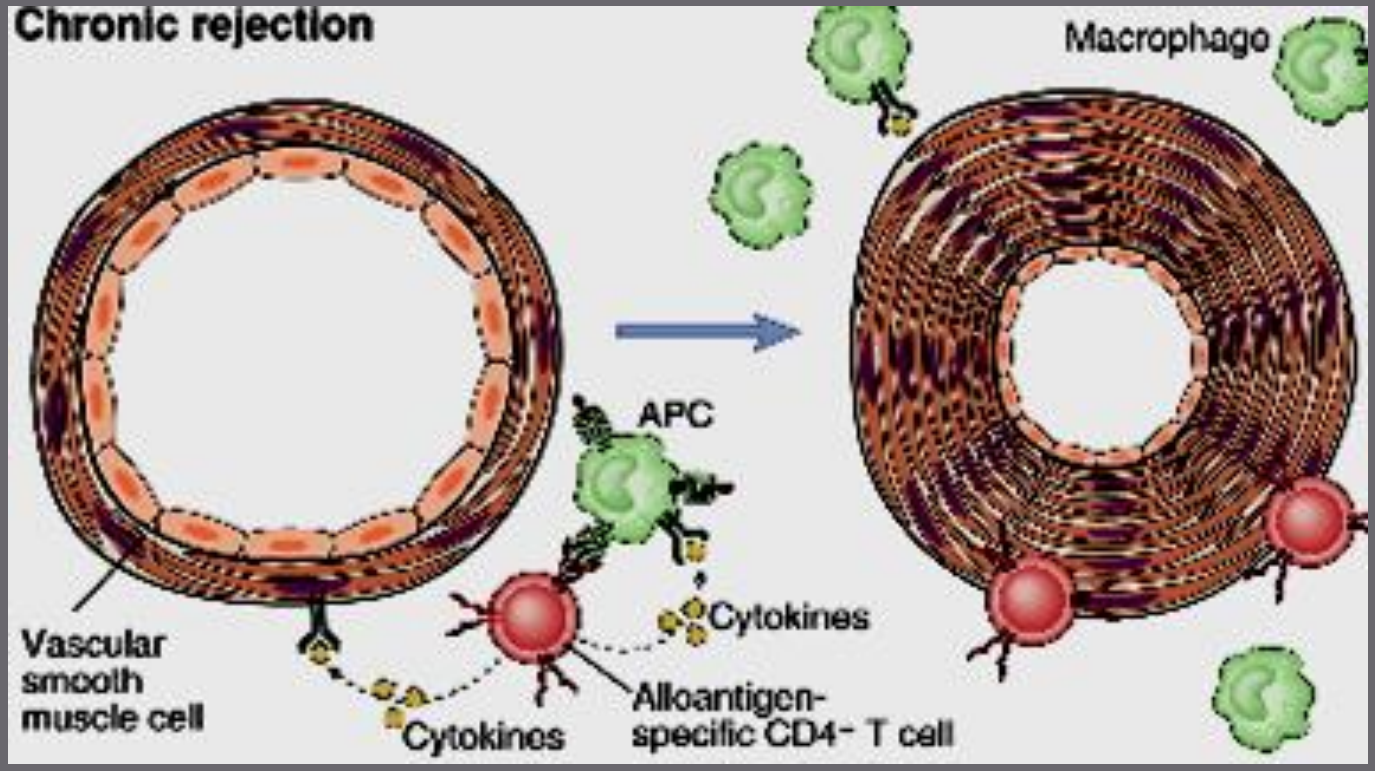


T-cell, macrophage and Ab mediated, myocyte and endothelial damage, Inflammation

Chronic Rejection

- Occurs in most solid organ transplants
  - Heart, Kidney, Lung, Liver
- Characterized by:
  - fibrosis
  - vascular abnormalities
  - loss of graft function over a prolonged period

Chronic Rejection



Macrophage – T cell mediated

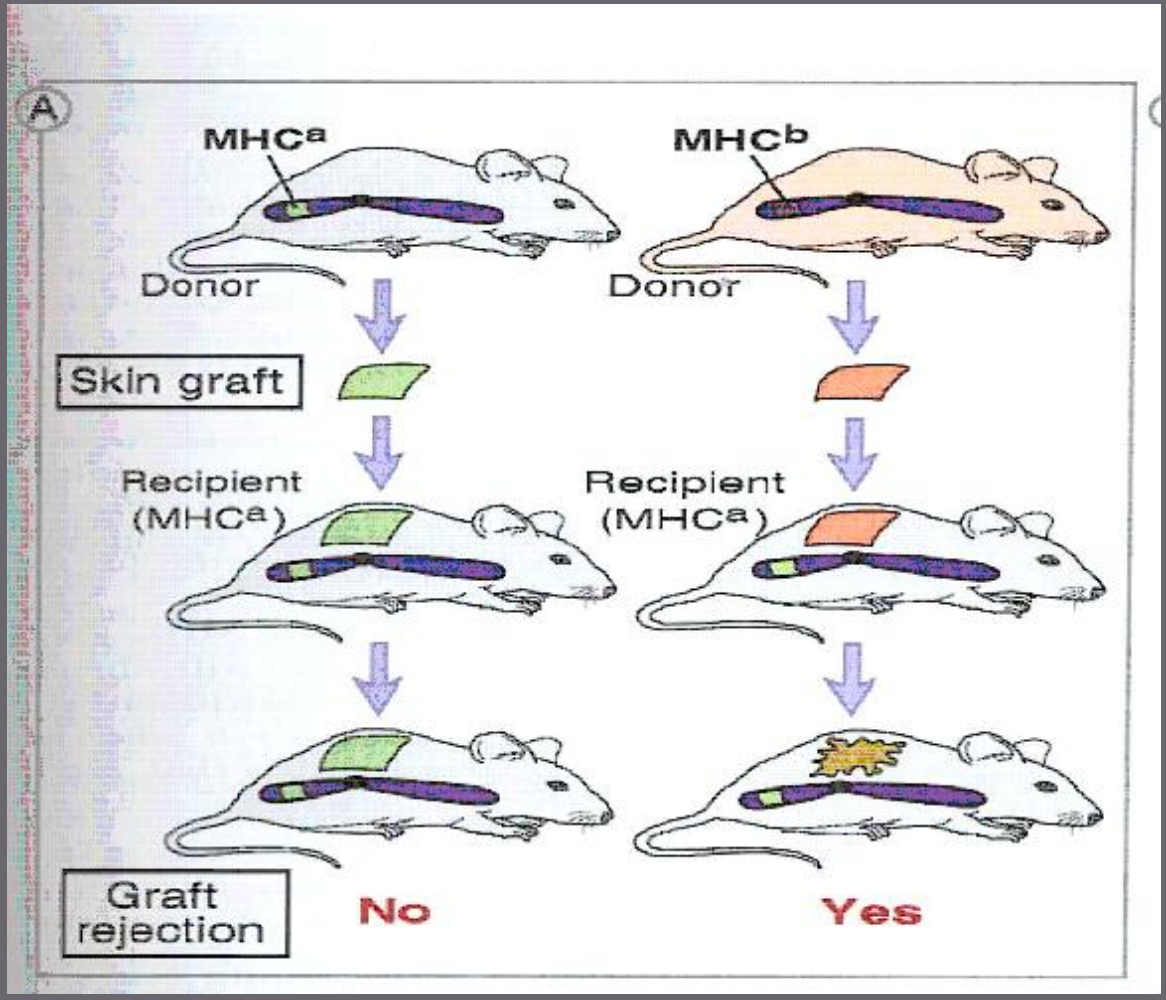
Concentric medial hyperplasia

Chronic DTH reaction

Histocompatibility antigens

- Antigens that participate in graft rejection are called transplantation or histocompatibility antigens:
  - ABO blood group
  - HLA system

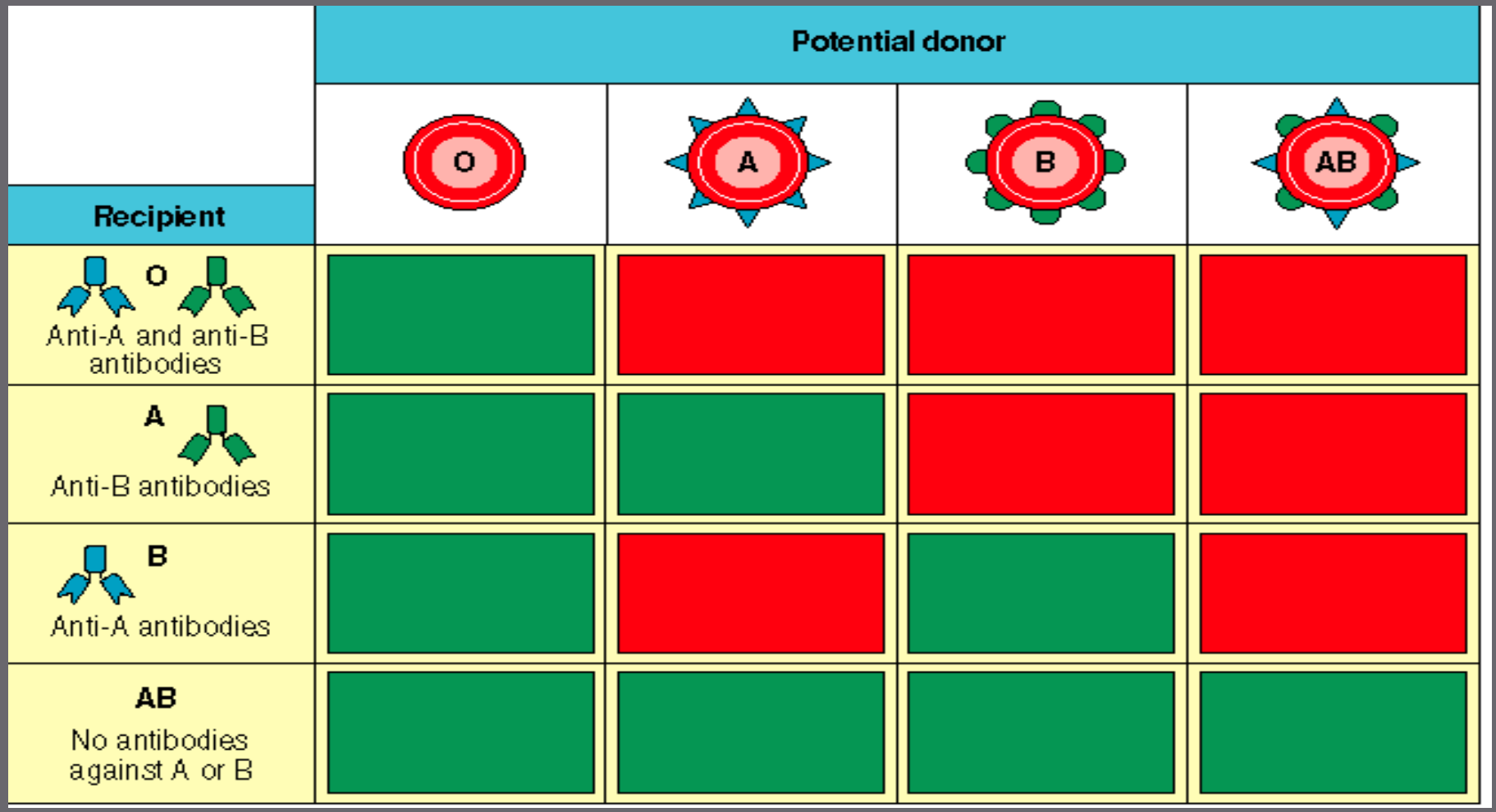
MHC Restricted Allograft Rejection



Histocompatibility testing

- Blood Grouping :
  - ABO blood grouping
- HLA compatibility:
  - Tested by HLA typing and tissue matching
  - HLA typing identifies the HLA antigens expressed on the surface of leucocytes

Most Common Transplantation -Blood Transfusion-



Methods of HLA typing

- Microcytotoxicity test
- Molecular methods:
  - RFLP with southern blotting
  - PCR using sequence specific primers
- Tissue matching

MICROCYTOTOXICITY

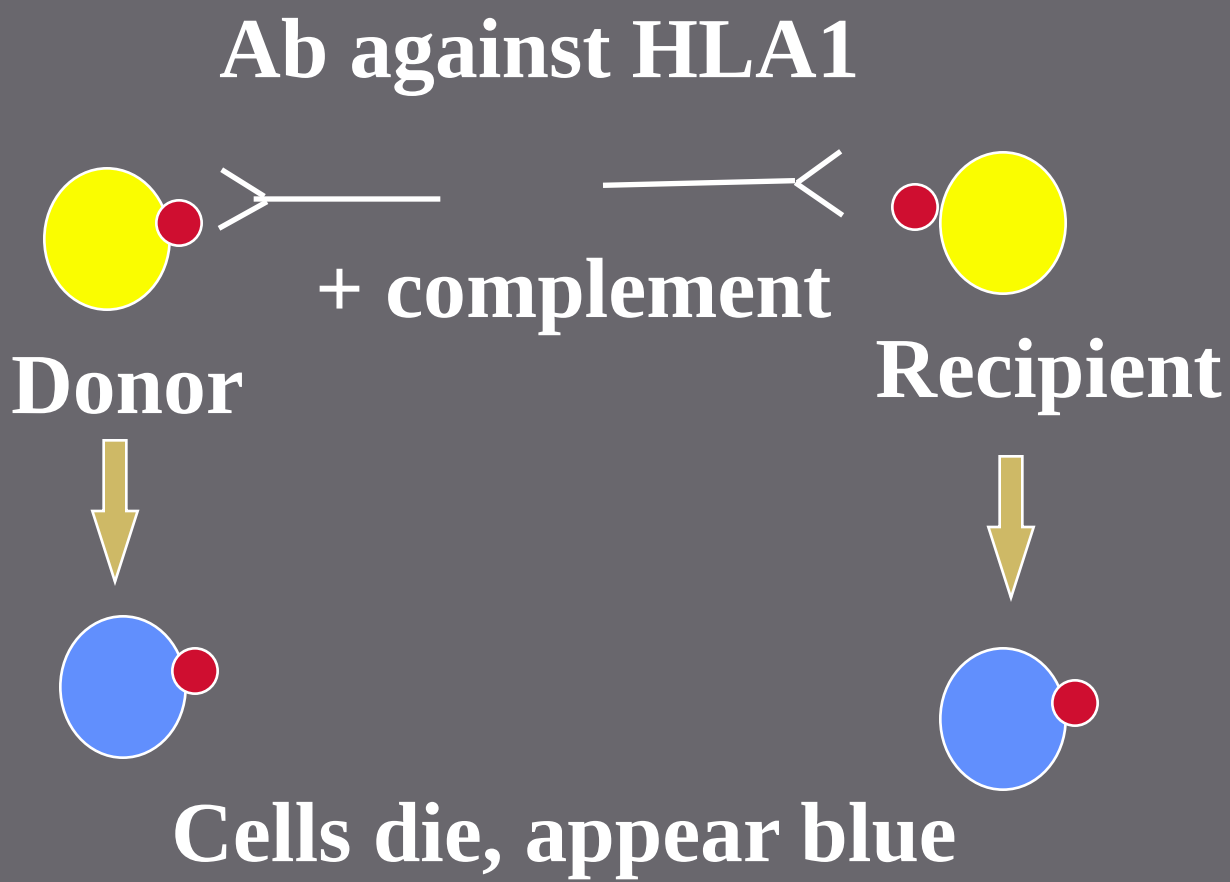
- Tests for complement mediated lysis of peripheral blood lymphocytes with a standard set of typing sera. Micro-cytotoxicity assay, utilizes serum with known anti-HLA antibodies that recognize particular HLA loci (HLA-A, HLA-B, HLA-C, HLA-DQ, HLA-DR /not DP) in order to match genetically similar individuals in hopes of performing a tissue transplantation.

Principle of Microcytotoxicity test

- Viable lymphocytes are incubated with HLA specific antibodies
- Complement is added, incubate
- Cells carrying antigens corresponding to the HLA antiserum are killed by complement mediated membrane damage
- Detected by addition of eosin or trypan blue which stains only dead cells
- Antisera for HLA typing obtained from:
  - Multigravidae-placental fluid
  - Multiple blood transfusion recipients
- Now replaced by monoclonal antibodies

Tissue Typing(or HLA-typing)

Used to identify HLA molecules on cells



- Once a set of HLA compatible donors is available (commonly, siblings of the patient), the best donors among them can be chosen by tissue matching
- This is done by the mixed lymphocyte reaction or culture (MLR, MLC)

- It depends on the fact that T lymphocytes in culture, when exposed to HLA incompatible antigens, will undergo blast transformation
- The intensity of the reaction being a measure of the antigenic disparity between the donor and recipient lymphocytes
- The test, as performed, is a one-way test in which the donor lymphocytes are killed and only the recipient lymphocytes are permitted to be transformed in response to the incompatible antigens on the donor cells

Mixed Lymphocyte Reaction:

- Strong Proliferation--->High incompatibility
- Weak proliferation--->Low incompatibility
- No proliferation---> 100% compatibility
- Helps to identify any antigenic differences between donor and recipient

Does MHC (HLA) 'matching' prevent rejection?

- Reduces rejection but there are still 'minor histocompatibility antigens' (MiHA)
- MiHA are probably polymorphisms affecting peptides in the grooves
- But we cannot MHC-match most grafts: *too much polymorphism, too little time, too few donors*
- Therefore need immunosuppression

Immunosuppression

- Clinical transplantation employs a combination of immunosuppressive drugs, including steroids, azathioprene and the fungal metabolite cyclosporin A, which is currently the most effective agent

Privileged sites

- Privileged sites where allografts are permitted to survive, safe from immunological attack
- Fetus can be considered an intrauterine allograft - contains antigens which are foreign to mother
- Though many explanations have been offered- REASONS not clear

Why is fetus not rejected by the mother?

- Fetus has MHC genes inherited from the father that are foreign to the mother
- Many pregnancies from the same mother-father combination that produce offspring of the same MHC haplotypes

A/B

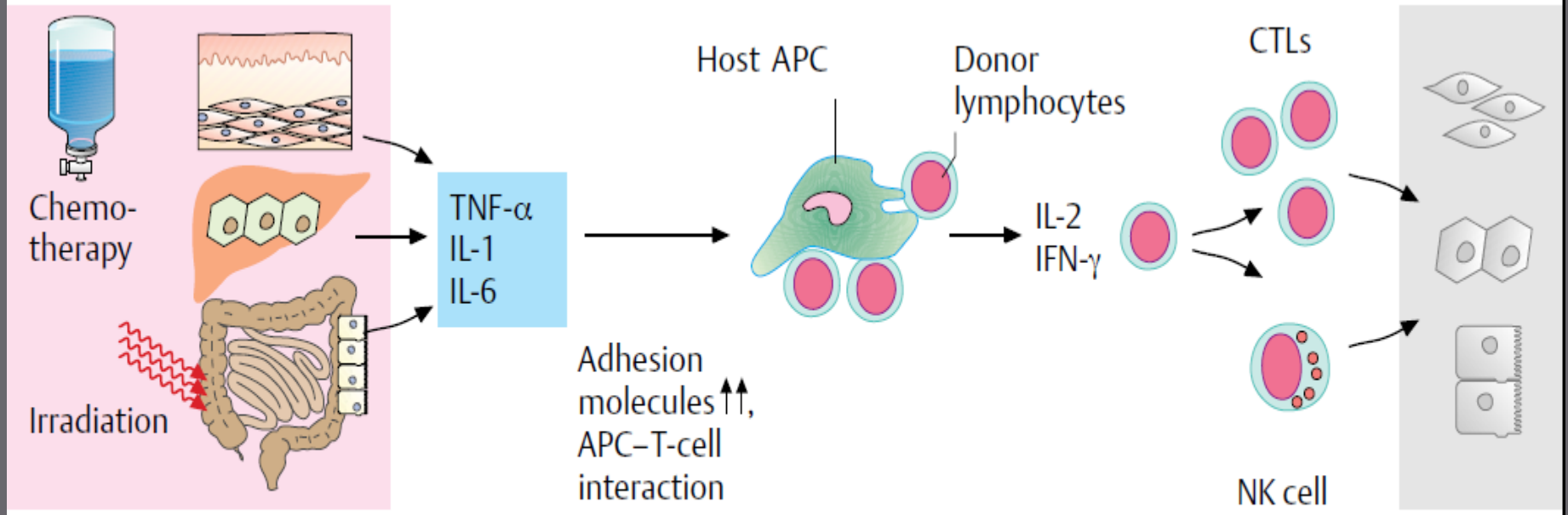
C/D

A/C, A/D, B/C, B/D

Why is fetus not rejected?

- Placenta acts as an immunological barrier:
  - Generates a hormone which is locally immunosuppressive
  - Filters anti-MHC Abs
- Trophoblast (outermost layer)-direct contact with maternal blood
  - MHC antigens-low density- resistant to attack by T cells
- Progesterone---hormone---immunosuppressive
- High concentration of alpha-fetoprotein in fetal blood
  - immunosuppressive properties
  - may protect against immunological damage from maternal leucocytes entering fetal circulation.

- Any site that is impenetrable to immunocompetent cells (for example, cartilage) is an immunologically privileged site
- Lack of vascularity at the site also prevents graft rejection-reason for success of corneal transplants



3. Immunological complications: GVHD

C. Complications of allogeneic transplantation

GRAFT-VERSUS-HOST REACTION

- Graft rejection is due to the reaction of the host to the grafted tissue
- **Host-versus-graft response**
- The contrary situation, in which the graft mounts an immune response against the antigens of the host, is known as:
- **Graft-versus-host (GVH) reaction**

Essential Components Required for GVHD

- The GVH reaction occurs when the following conditions are present:

1. The graft contains immunocompetent T cells.

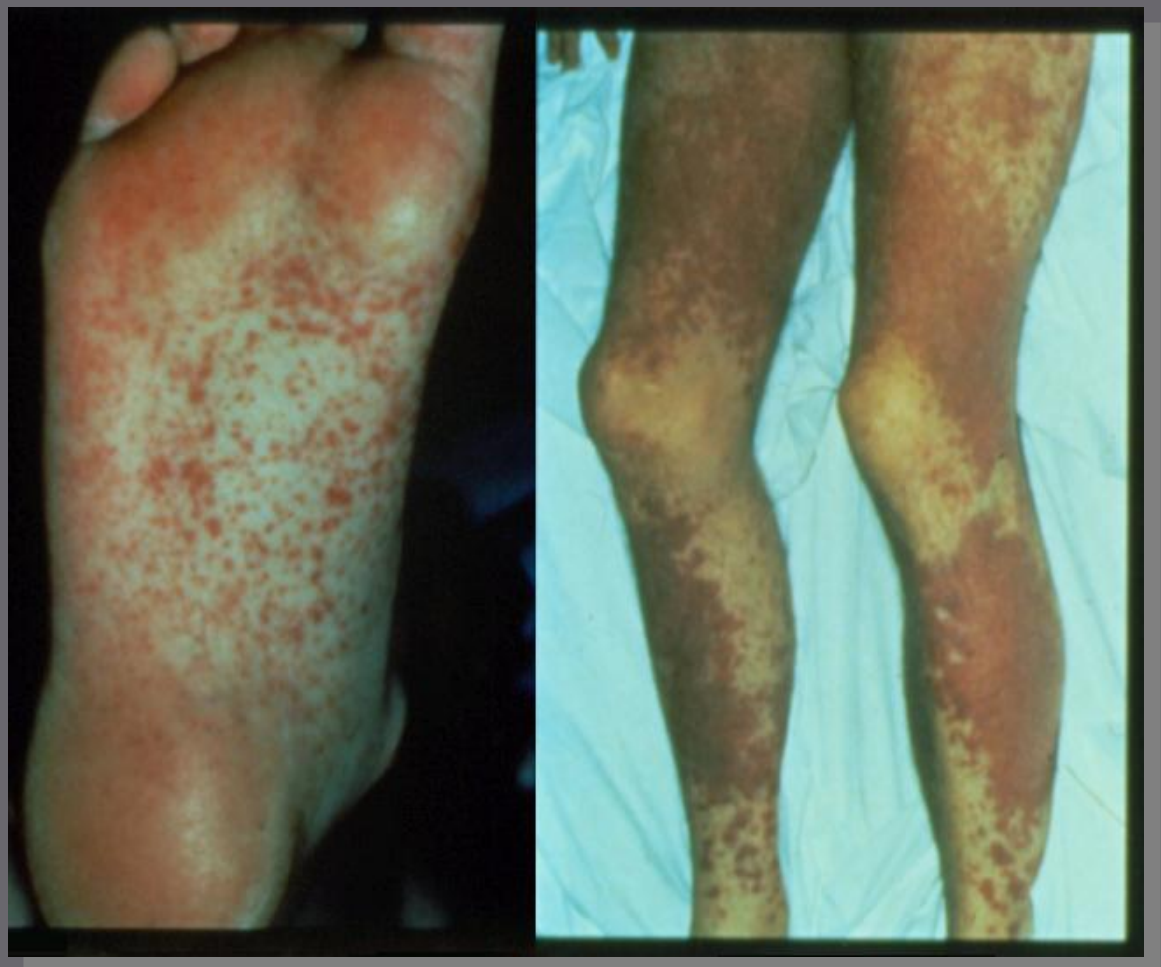
2. The recipient possesses transplantation antigens that are absent in the graft.

3. The recipient must not reject the graft.

Graft versus Host Reaction (GVHR)

- When grafted tissue has mature T cells, they will attack host tissue leading to GVHR.
- Major problem for bone marrow transplant.
- Methods to overcome GVHR:
  - Treat bone marrow to deplete T cells.
  - Use autologous bone marrow.
  - Use umbilical cord blood.

GVH disease in humans



Graft vs. Host Disease

- Caused by the reaction of grafted mature T-cells in the marrow inoculum with alloantigens of the host
- Acute GVHD
  - Characterized by epithelial cell death in the skin, GI tract, and liver
- Chronic GVHD
  - Characterized by atrophy and fibrosis of one or more of these same target organs as well as the lungs