TRANSPLANTATION IMMUNOLOGY

Transplantation: It may be reffered to as the act of transferring cells, tissues or organs form one site to another and some times from one individual to another.

Graft: The tissue or organ being transferred is called a graft or a transplant.

Donor: The individual donating graft.

Recipient: The individual receiving graft.

Transplantation Immunology: It is the study of the response of the immune system when a graft is implanted on an individual.

The first human kidney transplant was conducted in 1935 by a Russian, but the transplant was rejected due to mismatch of blood groups. The first successful transplantation of kidney was done in 1954 in Boston. It is a kidney transplant between identical twins. Today transplantations are being performed among non-identical individuals also. It includes kidney, pancreas, heart, lung, liver, bone marrow and cornea transplantations. They use immunosuppressive agents during grafting. New methods are also being developed to induce specific tolerance to the graft.

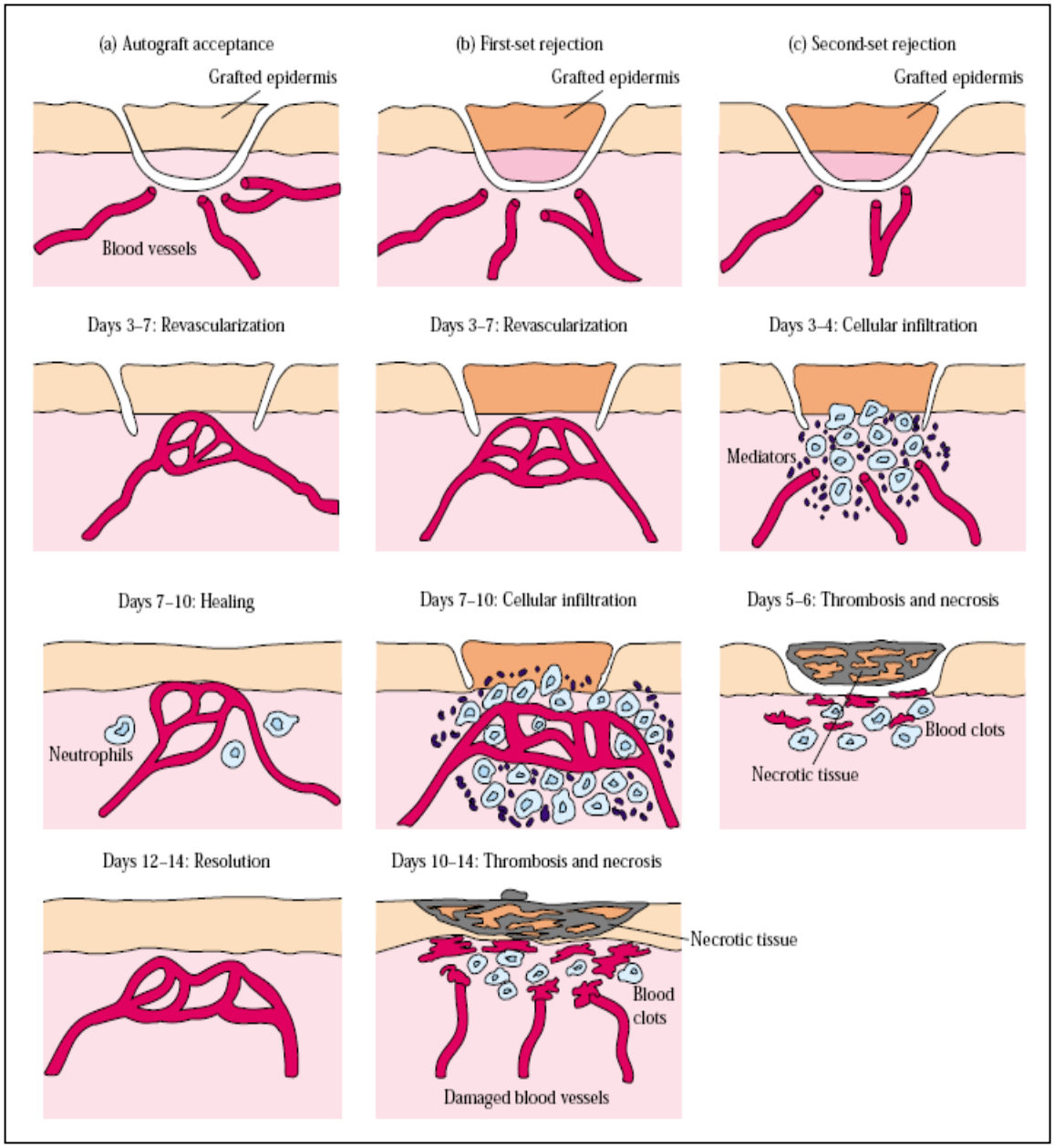
Types of grafts: There are four types of grafts.

a) **Autograft:** Transfer of self tissue from one body site to another. Eg: Skin grafts during burns. Healthy arteries are transferred to replaced blocked coronary arteries.
b) **Isograft:** Tissue transfer between genetically identical members twins (homozygous twins or homozygotic twins). These grafts survive.
c) **Allograft:** Tissue transfer between genetically different members of same species. These grafts are rejected,
d) **Xenografts:** Tissue transfer between different members of different species. These grafts are rejected vigorously.

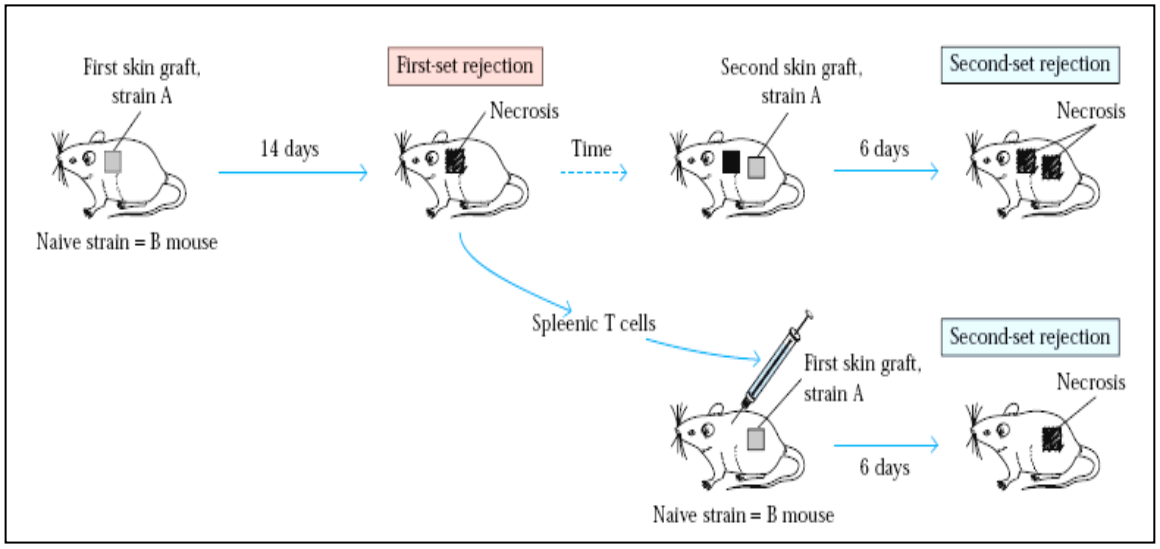
Incases of autografts and isografts, the acceptance and revascularization of the graft takes 3-7days. Healing at the site of grafting completes in 7-10 days and complete resolution occurs in 12-14 days. In allografts, skin grafts are rejected faster than other tissues such as kidney or heart.

Eg: If skin from strain B is transplanted to strain A, primary graft rejection occurs and it is known as first set rejection. The events include, revacularization which occurs between

3-7days. Infiltration of lymphocytes, monocytes, neutrophils and other inflammatory cells occur which start damaging the graft. Visible necrosis of graft occurs by 10th day and complete graft rejection occurs by 12-14 days.



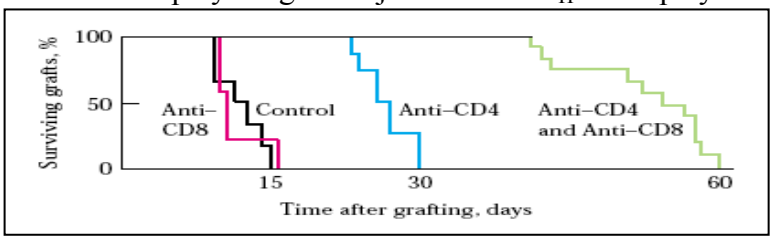
Immunological memory is demonstrated in graft rejection. If a graft of allotype is given for the 2nd time, a second set rejection is seen. The rejection occurs within 5-6 days.



Role of T cells in allograft rejection: In 1950, Avrion Mitchison showed that serum Abs have no role in graft rejection. Only lymphocytes could transfer allograft immunity.

Eg: In nude mice which lack us thymus, both allografts and xenografts are accepted. Thymus is the site for T cell development and maturation. Since thymus is not there, no Tcell development is there and hence grafts are accepted.

Injecting primed Tcells can transfer the graft rejection. Among the T cell population,, both $CD4^+$ and $CD8^+$ cells are identified to be involved in graft rejection. When monoclonal antibodies raised against $CD8^+$ Tcells were given, decline in Tc cells resulted in graft survival for 15days which was very much close to the control. When monoclonal Abs against $CD4^+$ T_H cells were given, the graft survived for 15 to 30 days. But when mAbs against both the receptors were given the graft survived for 60days, which indicated that both the receptors had role to play in graft rejection and T_H cells play important role in graft rejection.



Role of MHC in allograft acceptance: For any grafting, histocompatibility is checked. Tissues that are antigenically similar are said to be **histocompatible**. If antigenic differences are exhibited, it will lead to tissue rejection. There are 40 different loci which are responsible for allograft rejection reactions. But all these are located at the HLA complex in human and H-2 complex in mice. These loci are closely linked, hence inherited as a complete set called a haplotype from each parent. Within an inbred strain, all animals are homozygous at each MHC locus.

In outbred populations, a high degree of polymorphism is exhibited at each MHC locus and hence heterozygosity. There is only 25% chance that two offsprings will inherit identical MHC haplotypes.

Tests to avoid graft rejection: Tissue typing, microcytotoxicity tests and mixed-lymphocyte reactions are carried out to prevent graft rejection and see the tissue compatibility. In kidney transplantations matching of MHC class I has little effect than that of MHC class II. HLA compatibility is very important in kidney and bonemarrow transplantations. Liver and heart may survive even with greater mismatch.

Cell mediated graft rejection: this is primarily due to MHC molecules (alloantigens) expressed on cells of the graft. The process of rejection occurs in two stages.

1. Sensitization phase: In this phase Ag-reaction lymphocytes of the recipient proliferate in response to MHC present on the graft.
2. Effector stage: In this phase, immune destruction of the graft will take place.

1. Sensitization phase: T cells recognize the alloantigens expressed on the foreign graft via their $CD4^+$ and $CD8^+$ receptors and proliferate. The immune response involves recognision of peptides associated MHC. The proteins associated with class I molecules are the ones synthesized within the allogenic cells, where as the peptides presented by MHC class II moleucels are those which are taken up by endocytosis and processed.

Antigen presenting cells are involved in presenting Ags to T_H cells can be

a. Dendritic cells, which express high levels of MHC class II molecules
b. Host APC's , which migrate into grafts, endocytose the foreign MHC molecules and present processed peptides together with self MHC molecules.

Some dendritic cells migrate form tissue grafts like kidney, thymus and pancreas islets. These are called passenger leukocytes. They can migrate to regional lymphnodes of

recipients. These dendritic cells express high levels of class II MHC molecules along with normal levels of class I molecules. These are recognized as Ags and they stimulate T cells in the lymphnodes of the recipient. Other cells which are involved in stimulating immune systems are langerhans cells and endothelial cells lining blood vessels.

2. Effector phase: It involves cell mediated reactions. Influx of Tcells and macrophages into graft occurs and it resembles that seen in Delayed type hypersensitivity response. If Tc cells are stimulated it leads to CTL-mediated killing. If T_H cells are stimulated it leads to cell mediated graft rejection. In this mechanism cytokines secreted by T_H cells play important role.

-IL-2: Promotes T cells proliferation. It is important for effector CTL's.

-IFN-γ: Promotes influx of macrophages into grafts and activates them into destructive cells. It induces increased expression of Class II molecules by vascular endothelial cells and monocytes.

-TNF-β: Has direct cytotoxic effect on cells of a graft.

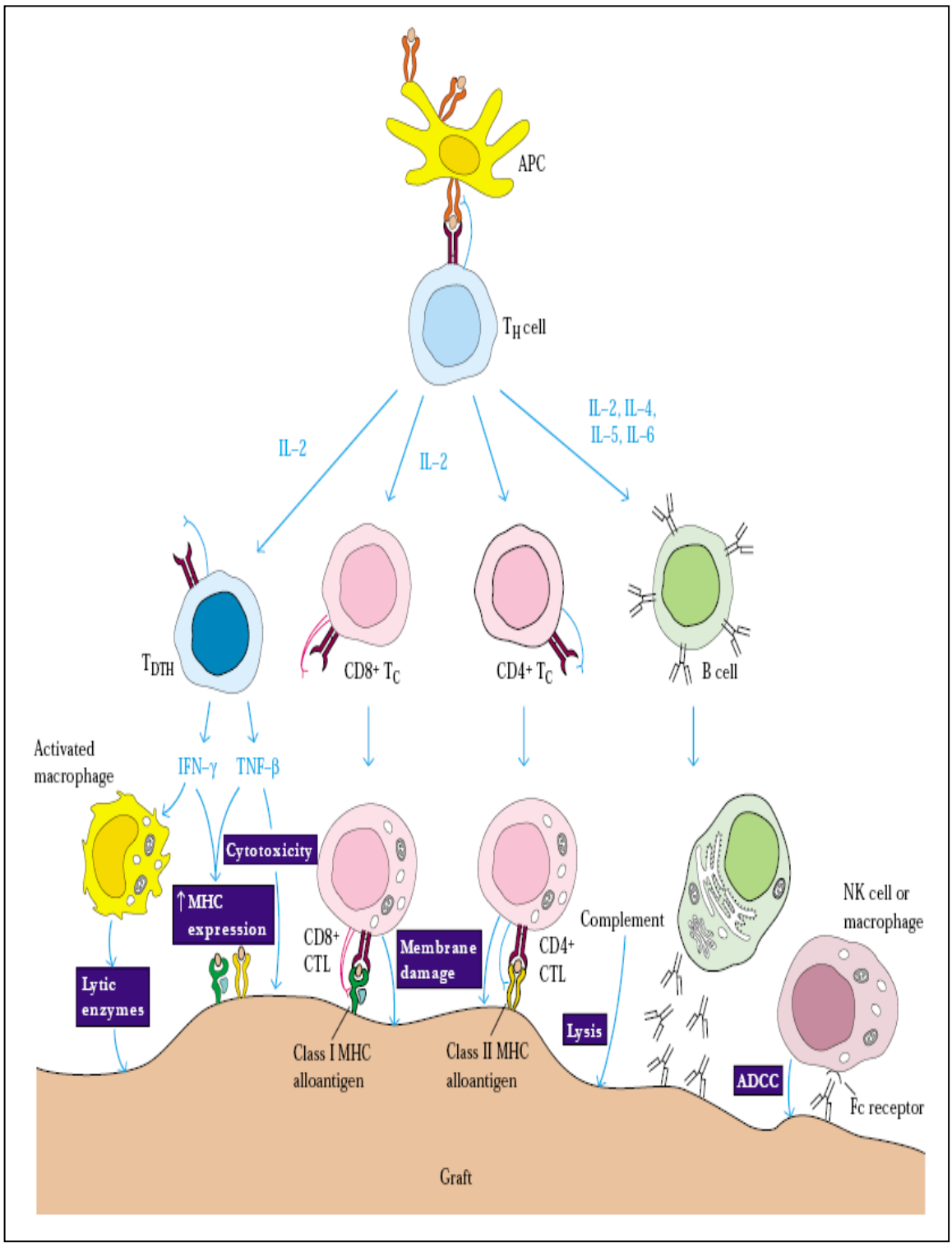
-TNF-α: Increases expression of Class I and class II molecules.

Clinical manifestations of graft rejection:

a. Hyperacute rejections: They are caused by preexisting host serum Antibodies specific for Ags of the graft. Ag-Ab complex activate complement system and intense neutrophil infiltration occurs. It causes massive blood clots and prevents vacularization of the graft. These Abs are specific for allogenic MHC Ags. If the graft recipient has been receiving repeated blood transfusions, his blood has Abs against MHC Ag's on WBC. These Abs can be involved in acite graft rejection.

A women with repeated pregnancies, develops Abs against paternal alloAgs present on the fetus. Some Abs may be specific for the blood group Ags.

These can be detected during tissue typind and ABO blood group typing.


APC
T_H cell
IL-2
IL-2
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IL-5, IL-6
T_{DTH}
CD8+ T_C
CD4+ T_C
B cell
Activated
macrophage
IFN-γ
TNF-β
Cytotoxicity
↑MHC
expression
Lytic
enzymes
CD8+
CTL
Membrane
damage
CD4+
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Complement
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Lysis
ADCC
Fc receptor
Class I MHC
alloantigen
Class II MHC
alloantigen
Graft

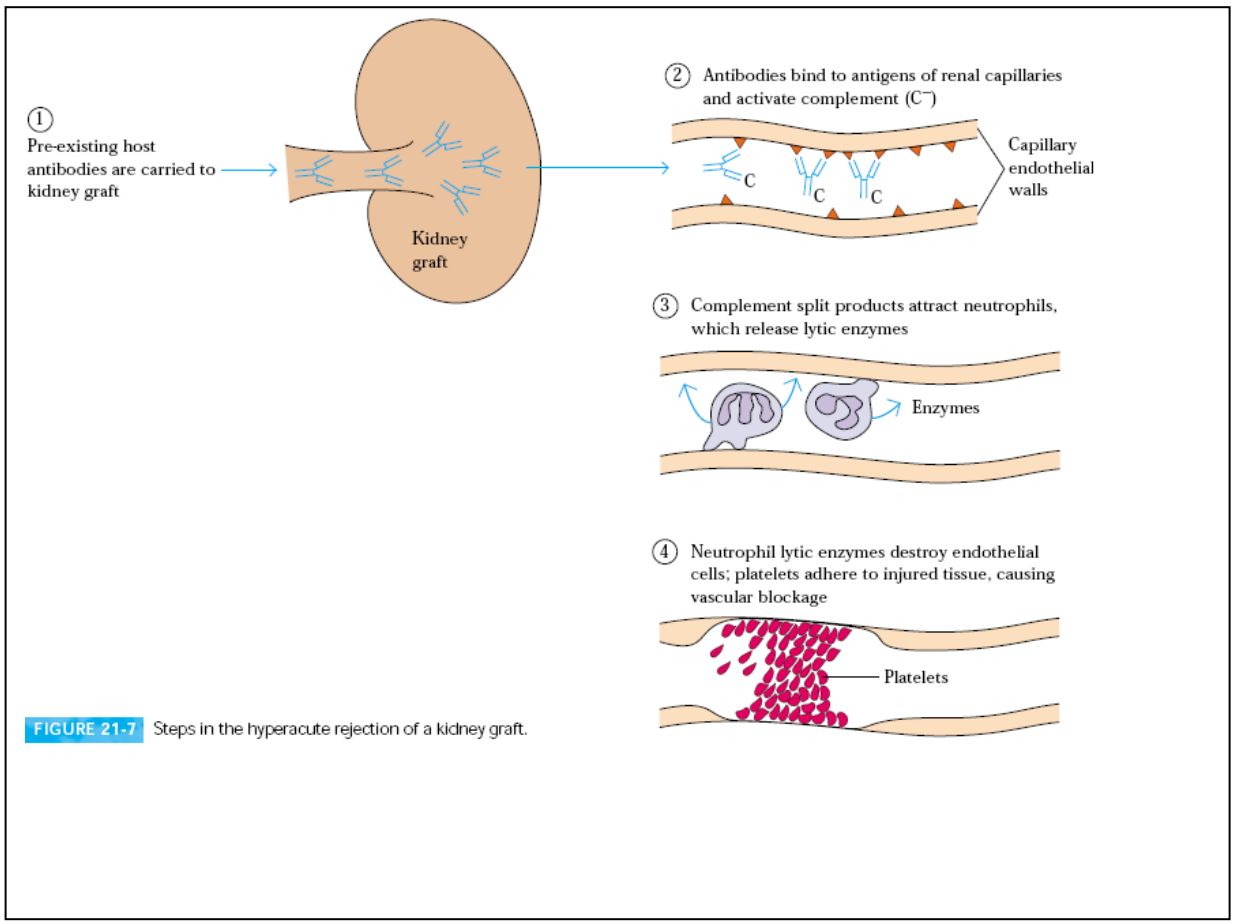

FIGURE 21-7 Steps in the hyperacute rejection of a kidney graft.

2. Acute rejection: Within 10days graft is rejected. Massive infiltration of macrophages and lymphocytes by T_H cells takes place. Their activation and proliferation leads to graft rejection.

3. Chronic rejections: It develops in months or years. It includes both humoral and cell mediated responses by the recipient.

General Immunosuppressive therapy: During allogenic transplantation, some degree of immunosuppression is essential for the graft survival. The therapy ismainly aimed at suppression Tcell proliferation. But it also effects other cells division and causes risk of infections and sometimes life threatening complications. The common agents used are,

1. Mitotic inhibitors:

a. Azathioprine: Blocks the synthesis of inosinic acid, the precursor of the purines adenylic and guanylic acid.

b. cyclophosphamide: Alkylating agent. Gets inserted into DNA double helix and becomes cross linked. It is effective against dividing cells.

c. Methotraxate: Folic acid antagonist, these block purine biosynthesis. All these inhibit mitosis non-specifically, how ever a decrease onn T and B cell population is observed.

2. Corticosteroids- Prednisone and dexsmethasone are potent anti-inflammatory drugs.

3. Fungal metabolites-

Cyclosporin A and Tacrolinus: Block activation of resting T cells and inhibit transcription of genes encoding IL-2 and the high-affinity IL-2 receptor.

Rapamycin: Inhibits proliferation and differentiation of T_H cells in G_1 phase of cell cycle. These are successfully used in kidney, liver, heart and bone marrow transplantations. Grafts survival is increased.

4. Total lymphoid elimination: Lymphocytes are sensitive to x-ray irradiation. If a person receives x-ray irradiation to the thymus, spleen and lymphnodes as per a typical protocol i.e., around 200rad/day for few weeks until 3400radiations were administered and then grafted. The bone marrow which is not irradiated will form new lymphocytes which appear to be more tolerant to the Ags of the graft.

5. Specific immunosuppressive therapy: using mAbs against surface molecules of Tcells and to block costimulatory signals.

Graft versus Host reaction: In x-ray irradiation transplantations, the lymphocytes of the recipient migrate into host. They begin to proliferate in response to the MHC of the Host. Their proliferation causes influx of host cells into circulation and they bind to the donor Tcells. Finally all these will lead to proliferation of $CD4^+$ and $CD8^+$ populations. This inturn leads to release of lymphokine secretions by the stimulated lymphocytes of the graft, which leads to polyclonal Bcell activation of host. These Bcells are autoreactive. Tc cell activation leads to CTLs formation which kill host lymphocytes.

Clinical Symptoms- Skin rash, person becomes thin, diarrhea, hepatomegaly, splenomegaly, increase in bilirubin production, bileduct gets damaged, anaemia, general immunosuppression.

Important questions: Definitions of all graft types.

Write an account on graft rejection by host. Add a note on immunosuppression.-14.