Transplantation Immunology

Transplantation refers to the act of transferring cells, tissues, or organs from one site to another.

The first accounting of tissue transplantation comes from India, in the fifth century B.C. The legendary surgeon Sushruta (or Susruta) describes nose reconstruction that required collection and transfer of skin from one site to another. Although there is no documentation of success rates, today we know that this type of transfer, called an autograft, is the most likely to succeed.

It was not until 1908 that **Alexis Carrel** produced a systematic study of kidney transplantation in cats, some of which maintained urinary output for 25 days, establishing that a transplanted organ could carry out its normal function in a new recipient.

Then, in 1954, **Joseph Murray** and colleagues in Boston successfully transplanted a kidney between identical twins.

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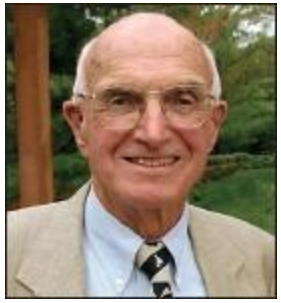
1890: Alexis Carrel reported the first systematic study of transplantation. He interchanged Kidneys in a series of nine cats.
The transplanted kidneys remained functional for 25days.

Nobel Prize: 1912
Alexis Carrel
Born: 28 June 1873, Sainte-Foy-lès-Lyon, France
Died: 5 November 1944, Paris, France
Affiliation at the time of the award: Rockefeller Institute for Medical Research, New York, NY, USA
Prize motivation: "in recognition of his work on vascular suture and the transplantation of blood vessels and organs"
Field: **transplantation**
Prize share: 1/1

1954: **Joseph Edward Murray** conducted first successful transplantation of human kidney between two identical twins at Peter Bent Brigham Hospital in Boston.



Dr. Joseph E. Murray, an extraordinary plastic surgeon, opened a new era of medicine with the first successful human organ transplant. He suffered a stroke at his suburban Boston home on Thanksgiving and passed away on 26 November 2012, at the Peter Bent Brigham Hospital (later Brigham and Women's Hospital) in Boston at the age of 93. It was in this same institution that he performed the first successful kidney transplant on 23 December 1954.

The donor was an identical twin. Murray later wrote, “There was a collective hush in the operating room as blood began to flow into the implanted kidney and urine began to flow out of it. It was a moment I can never forget.”

For this great path-breaking achievement, he was awarded the **Nobel Prize for medicine in 1990.**

The Nobel citation read: “He has given the gift of life to hundreds of thousands of people destined to die young. His success did not come easily. How many people do we know try to achieve something that no one has ever before even attempted, because it was judged to be impossible? He kept trying; he kept failing, but still kept trying for a decade! His attempts were severely criticised by his peers. But he did not give up.”

A team of surgeons led by Dr. Samuel Kountz, an African American transplant surgeon at Stanford, completed the first nontwin, living human transplant in the year 1961: a kidney, from mother to daughter. Their pioneering work with immune suppressants and a new kidney perfusion technique heralded a leap forward in the ability of physicians to imagine transplantation as a cure for disease.

Dr. Samuel Kountz, Stanford University. Along with colleagues, Kountz performed the first transplant between individuals expressing different MHC molecules, a kidney from mother to daughter.

The degree and type of immune response to a transplant varies with the type and source of the grafted tissue.

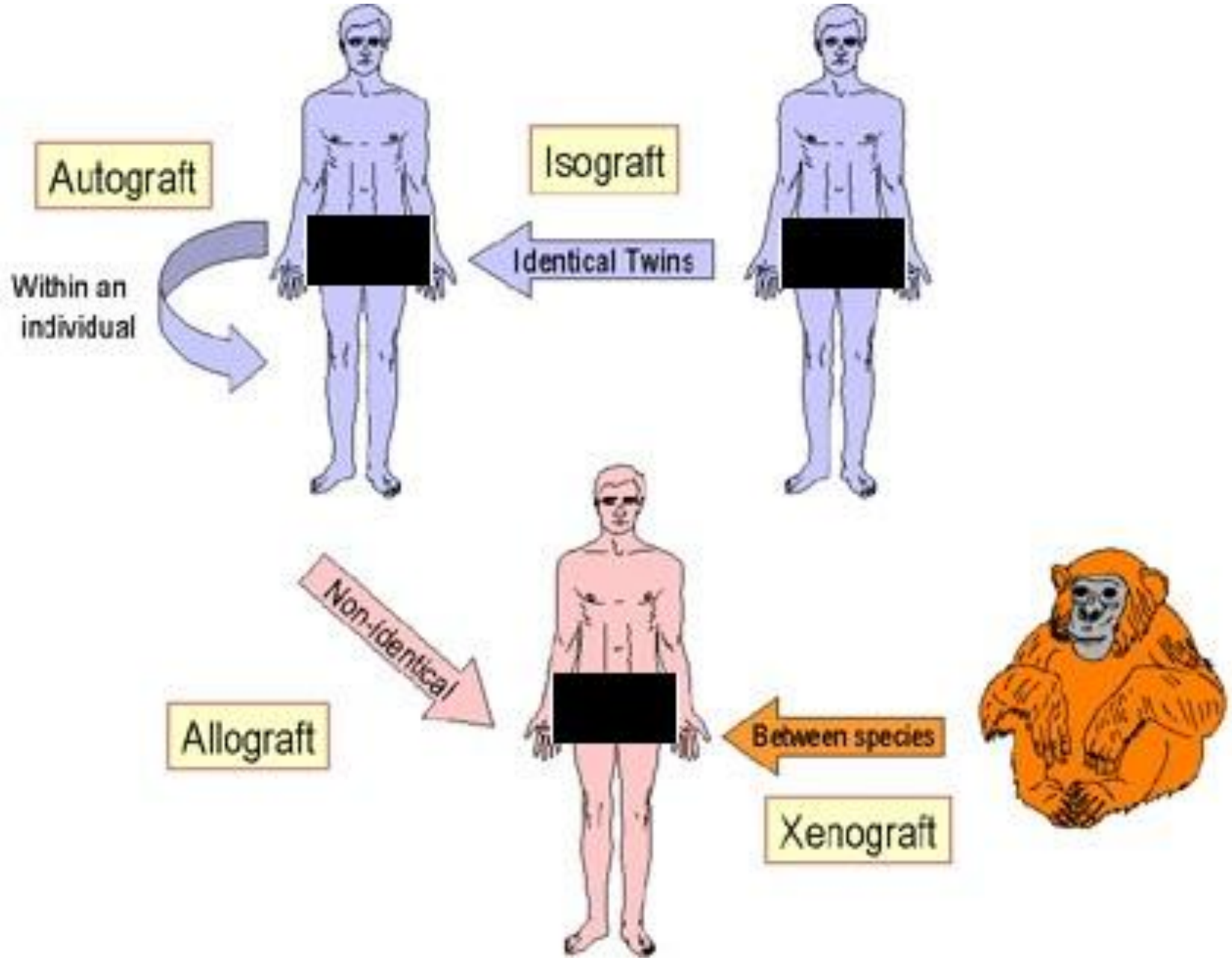
The following terms denote different types of transplants:

Autograft: When tissue is transplanted from one site to another in the same individual, the transplant is referred as "auto graft" or "autogenic graft" (From Greek Auto=Self).
Immune system of recipient accepts the auto graft very easily, because antigens of recipient cells and the transplanted tissue are alike.

Isograft: The graft taken from a genetically identical person is known as Isograft or Syngraft or Syngentic graft. This kind of transplantation is possible between two genetically identical twins. Since development of identical twins takes place from a single zygote, identical twins share same genes that are responsible for the production of antigens.

Allograft: Tissue transferred between genetically different members of the same species.
This is the most common type of tissue graft, occurring between nonidentical humans or different strains of mice. The histo compartbility antigens of allograft are dissimilar with the host histo compartbility antigens. Hence immune system of recipient/ host identifies the graft as foreign and induces an immune response against to it, resulting rejection of graft.

Xenograft: Tissue transferred between different species. Since the histocompatibility genes are quite different, hosts body rejects the graft more vigorously.


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

Graft rejection occurs based on immunologic principles

Autograft s and isograft s are usually accepted, owing to the genetic identity between donor and recipient .

Because an allograft is genetically dissimilar to the host and therefore expresses unique antigens, it is oft en recognized as foreign by the immune system and is therefore rejected.

Obviously, xenograft s exhibit the greatest genetic and antigenic disparity, engendering a vigorous graft rejection response.

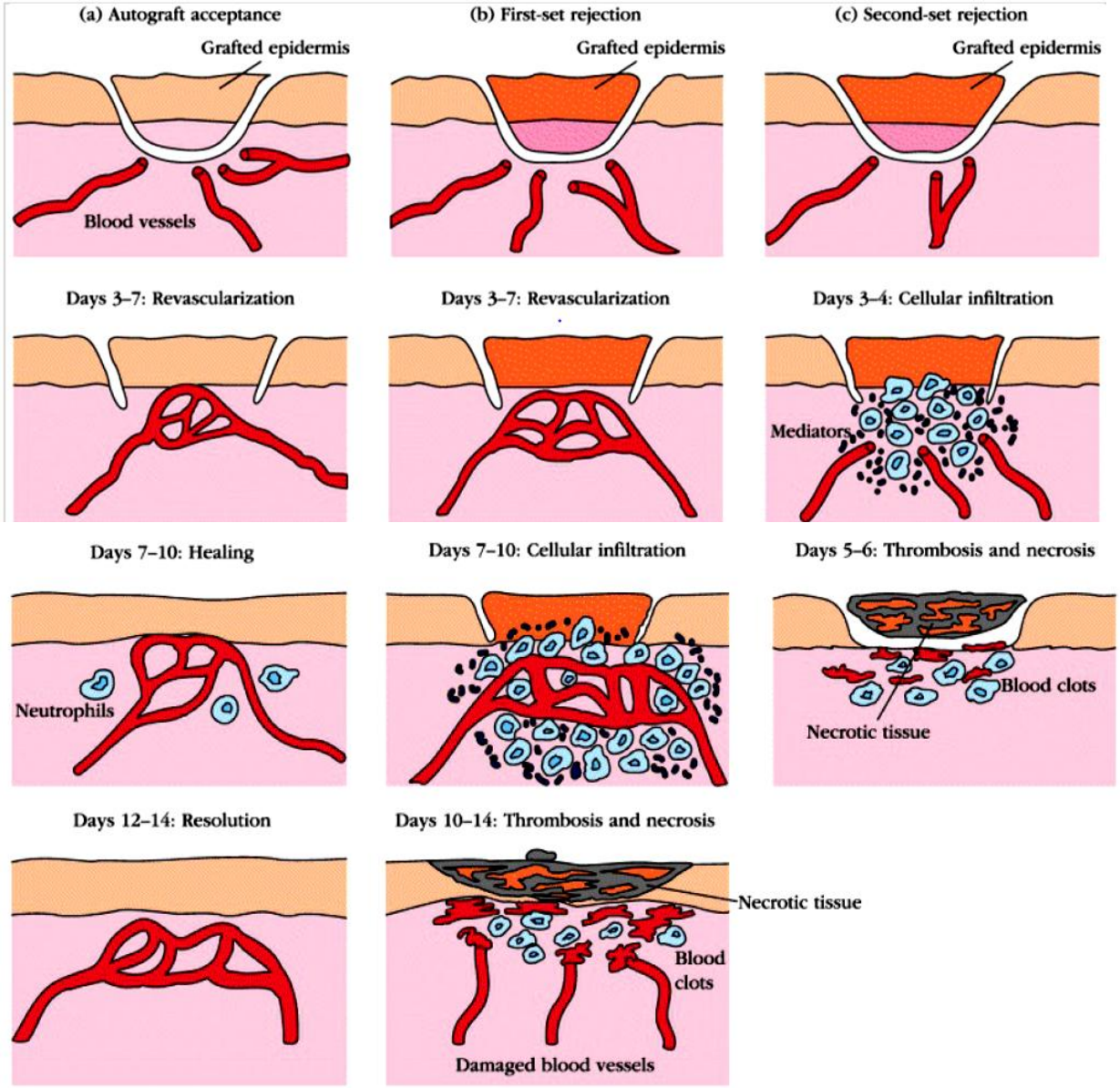
Specificity and memory in allograft rejection

The rate of allograft rejection varies according to the tissue involved; skin graft s are generally rejected faster than other tissues, such as kidney or heart.

Despite these time differences, the immune response culminating in graft rejection always displays the attributes of specificity and memory. If an inbred mouse of strain A is grafted with skin from strain B, primary graft rejection, known as first-set rejection, occurs.
The skin first becomes revascularized between days 3 and 7. As the reaction develops, the vascularized transplant becomes infi ltrated with inflammatory cells. There is decreased vascularization of the transplanted tissue by 7 to 10 days, visible necrosis by 10 days, and complete rejection by 12 to 14 days.

Immunologic memory is demonstrated when a second strain-B graft is transferred to a previously engrafted strain-A mouse. In this case, the anti-graft reaction develops more quickly, with complete rejection occurring within 5 to 6 days.

This secondary response is called second-set rejection . Specificity can be demonstrated by grafting skin from an unrelated mouse of strain C at the same time as the second strain-B graft . Rejection of the strain-C graft proceeds according to the slower, fi rst-set rejection kinetics, whereas the strain-B graft is rejected in an accelerated second-set fashion.



Schematic diagrams of the process of graft acceptance and rejection.

(a) Acceptance of an autograft is completed within 12 to 14 days.

(b) First-set rejection (based on a primary response) of an allograft begins 7 to 10 days after grafting, with full rejection occurring by 10 to 14 days.

(c) Second-set rejection (based on a secondary response) of an allograft begins within 3 to 4 days, with full rejection by 5 to 6 days.

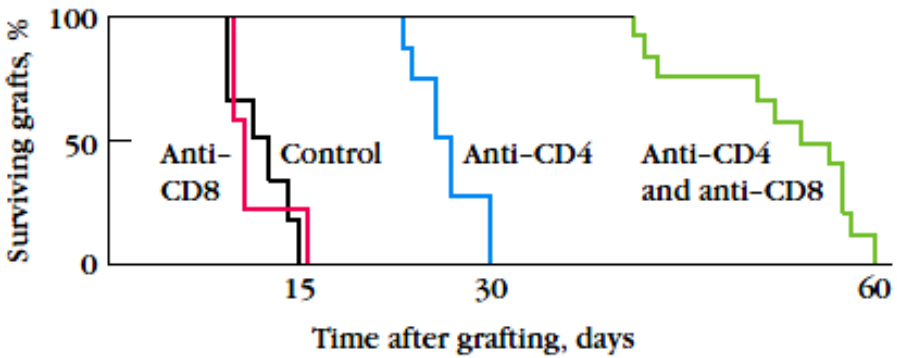
The cellular infiltrate that invades an allograft (b and c) contains lymphocytes, phagocytes, and other inflammatory cells.

Acceptance of an autograft within 12 to 14 days.
Rejection of an allograft 1st: 7-10days; 2nd: 5-6days

Involvement of T cells during graft rejection

Analysis of the T-cell subpopulations involved in allograft rejection has implicated both $CD4^+$ and $CD8^+$ populations. In one study, mice were injected with monoclonal antibodies to deplete one or both types of T cells and then the rate of graft rejection was measured. Removal of the $CD8^+$ population alone had no effect on graft survival, and the graft was rejected at the same rate as in control mice (15 days). Removal of the $CD4^+$ T-cell population alone prolonged graft survival from 15 days to 30 days.

However, removal of both $CD4^+$ and $CD8^+$ T cells resulted in long-term survival (up to 60 days) of the allograft s. This study indicated that both $CD4^+$ and $CD8^+$ T cells participated in rejection and that the collaboration of the two subpopulations resulted in more pronounced graft rejection. These data are supported by human studies showing $CD4^+$ and $CD8^+$ T cells infiltrating human kidney allorafts.



The role of CD4 and CD8 T cells in allograft rejection is demonstrated by the curves showing survival times of skin grafts between mice mismatched at the MHC. Animals in which the $CD8^+$ T cells were removed by treatment with an anti-CD8 monoclonal antibody (red) showed little difference from untreated control mice (black). Treatment with monoclonal anti-CD4 antibody (blue) improved graft survival significantly, and treatment with both anti-CD4 and anti-CD8 antibody prolonged graft survival most dramatically (green).

Matching donor and recipient involves prior assessment of histocompatibility

three important pretransplantation tests must be completed prior to transfer:

(1) blood group matching (also called blood typing),

(2) MHC matching (also known as tissue typing), and

(3) cross-matching.

The results of these tests are used to determine compatibility, and can predict subsequent graft success rates.

ABO Blood Group Matching

The first human kidney transplant, attempted in 1933 by a Russian surgeon, failed because a mismatch in blood type between donor and recipient caused almost immediate rejection. In fact, the most intense graft rejection reactions are frequently due to ABO blood group differences between the donor and recipient. Blood group antigens are expressed on red blood cells (RBCs), epithelial cells, and endothelial cells, requiring the donor and recipient to first be screened for ABO compatibility.

If the recipient carries antibodies to any of the donor's blood-group antigens, the transplanted tissue will undergo rapid **antibody-mediated lysis** in a process known as hyperacute rejection . For this reason, most transplantations are conducted between individuals with a matching ABO blood type.

MHC Matching

Either serologic or molecular tests can be used to determine the HLA compatibility, collectively called **tissue typing.**

The choice is somewhat dependent on the organ or tissue in question, and the time available. Molecular assays using sequence-specific primers to establish which HLA alleles are expressed by the recipient and potential donors have become more common in recent years, especially in bone marrow transplantation. Molecular assays provide greater specificity and higher resolution than assays that characterize MHC molecules serologically, using antigen-antibody interactions alone.

The MHC makeup of donor and recipient is not the sole factor determining tissue acceptance. Even when MHC antigens are identical, the transplanted tissue can be rejected because of differences at various other loci, including the **minor histocompatibility locus.**

Nonself MHC molecules can be recognized directly by TCRs on T_C and T_H cells, a phenomenon termed **alloreactivity.**

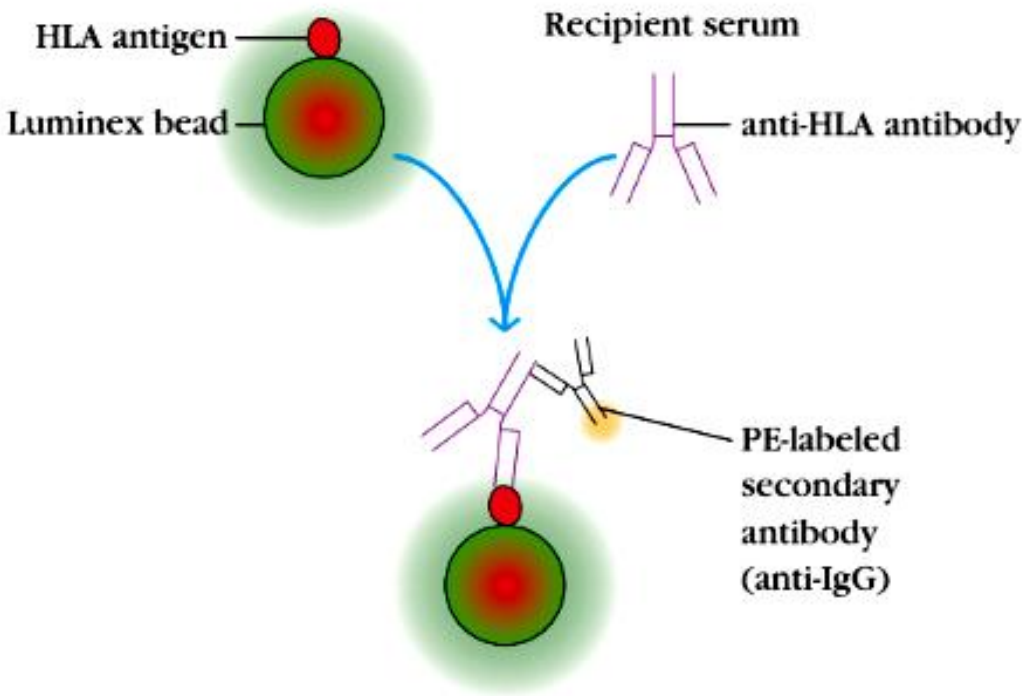
Rejection based only on minor histocompatibility differences is usually less vigorous, but can still lead to graft rejection. Therefore, even in cases of HLA-identical matches, some degree of immune suppression is usually still required.

Cross-Matching

The presence of any preformed antibodies against potential donor alloantigens must also be evaluated in the recipient. Generation of antibodies against non self HLA proteins for a number of reasons, but transplant recipients who have received prior blood transfusions or allografts are especially likely to possess them.

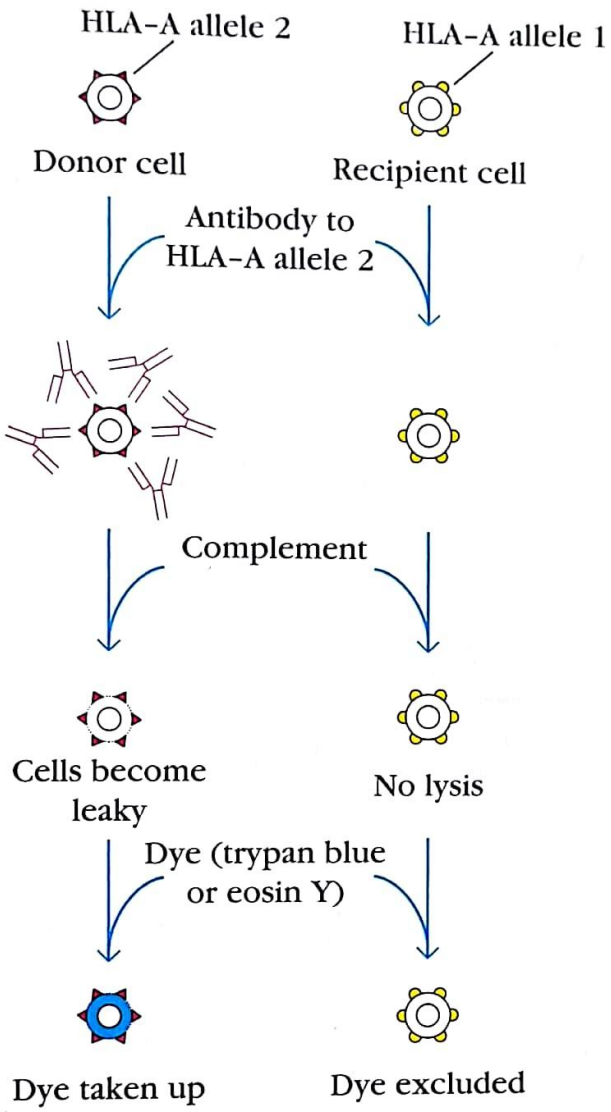
This type of testing is called **cross-matching and is the most** important level of compatibility testing that occurs prior to solid organ transfer; a positive crossmatch means that the recipient has antibodies against HLA proteins expressed by the donor and that these are likely to lead to rapid (hyperacute) rejection.

The most common technique used today for cross-matching is the **Luminex assay**. This employs fluorochrome-labeled microbeads impregnated with specific HLA proteins, where each HLA protein is associated with a fluorochrome of a different intensity. These HLA-impregnated beads are mixed with recipient serum, allowing clinicians to determine more precisely which donor-specific anti-HLA antibodies are present in the recipient prior to transplantation.



The Luminex cross-matching assay.
Microbeads impregnated with fluorochromes of different intensity each carry a different HLA protein.
Recipient serum is incubated with these beads, and any antibody binding is detected using p hycoerythrin (PE)-labeled secondary anti-human immunoglobulin.
Laser excitation and detection are used to determine the fluorochrome intensity of bound beads, and therefore the associated HLA molecule(s) with which the serum reacts.

Other methods of tissue matching



HLA typing by microcytotoxicity

White blood cells from the donor and recipient are added to separate wells in a microtiter plate.

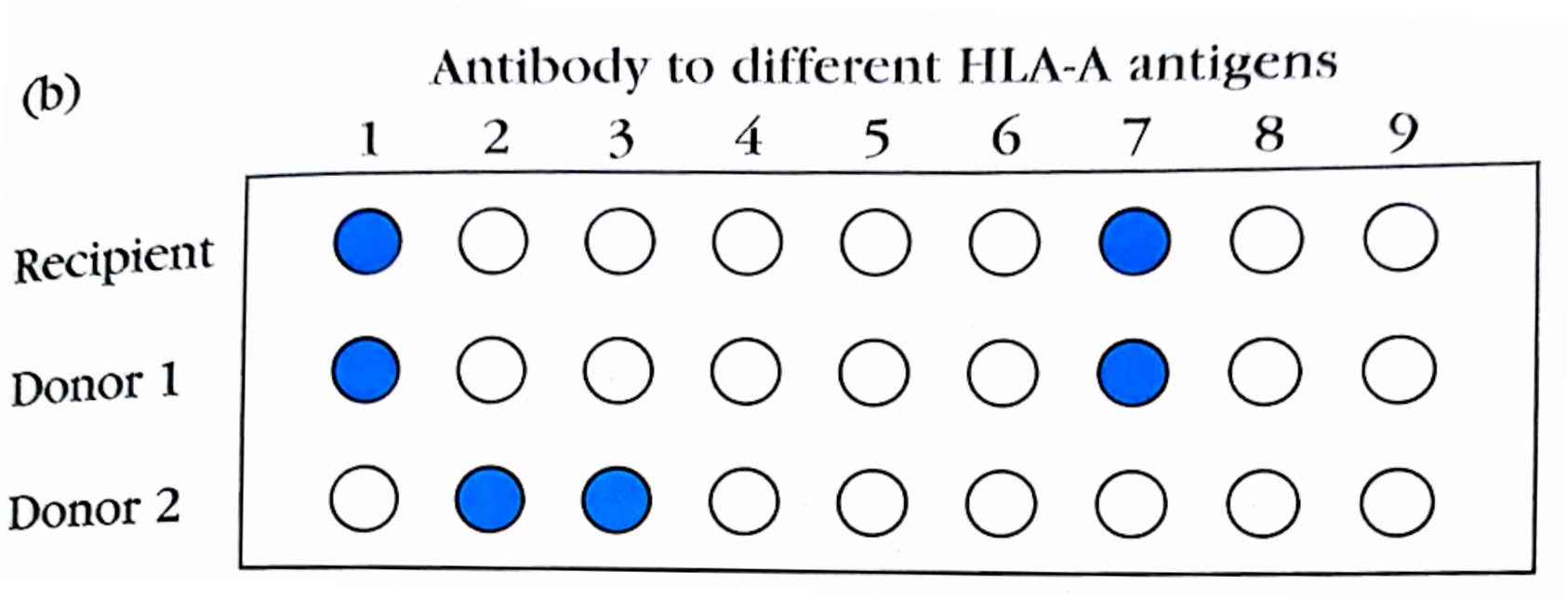
Antibody against one antigen is added to well.

If binding takes place, complement binds to the complex.

Cells become leaky.

Take up dye.

HLA typing by microcytotoxicity



As cells express many HLA antigens, they are tested separately with a battery of antibodies. Donor shares HLA antigens for both lane1 and 7. Donor two has none of the antigens in common.

Hyperacute Rejection

In rare instances, a transplant is rejected so quickly that the grafted tissue never becomes vascularized.

These hyperacute rejection episodes are caused by pre-existing host serum antibodies specific for unique antigens found on the graft, sometimes also called antibody mediated rejection (AMR).

The most common targets are ABO blood group antigens or MHC alloantigens.
Pre-existing recipient antibodies bind to foreign antigens on the endothelial cells lining graft capillaries, leading to accumulation of neutrophils, deposition of complement, and a severe inflammatory reaction.

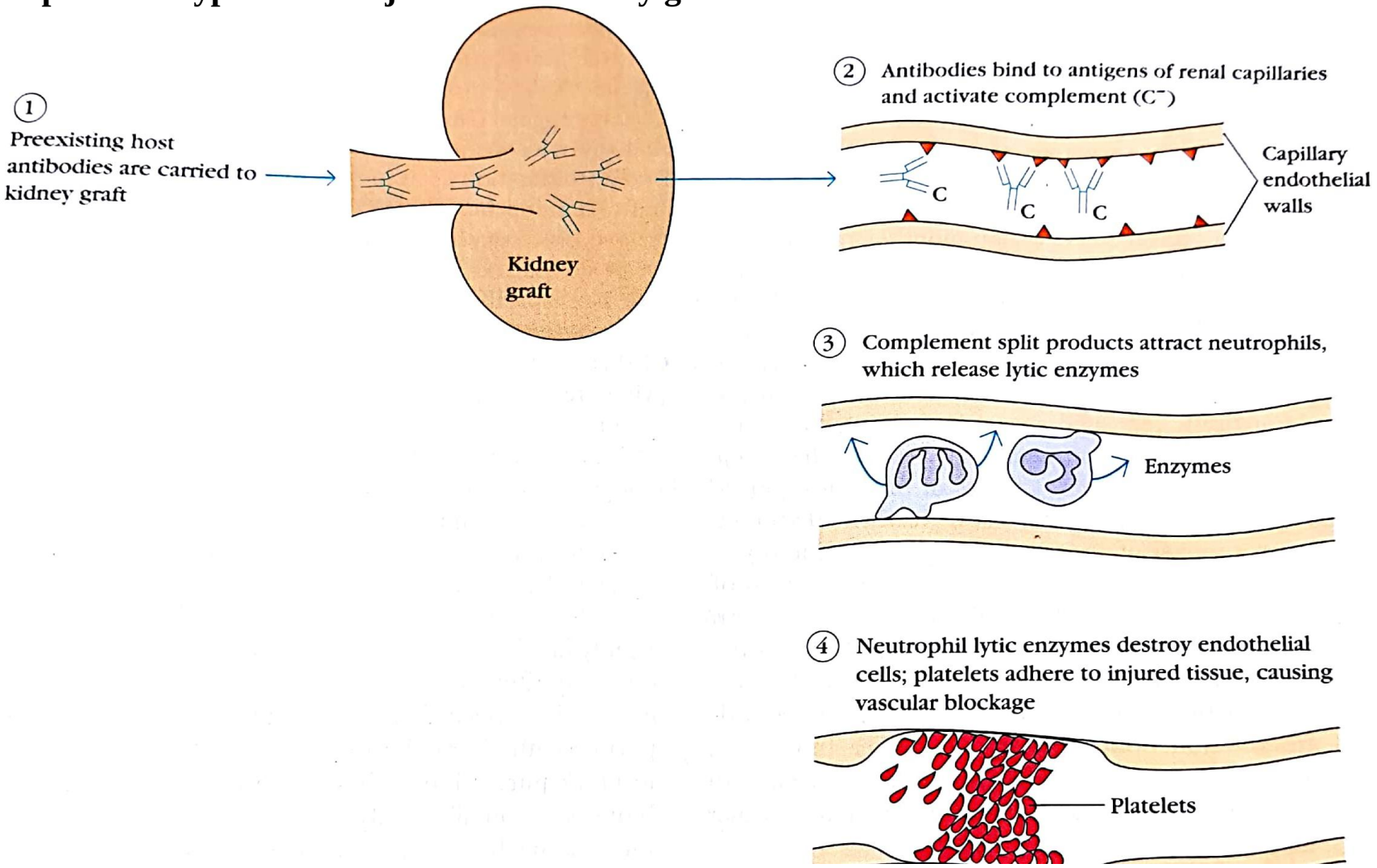
This results in endothelial damage that obstructs capillaries, preventing vascularization of the graft **.**
Antibody mediated rejection (AMR), although most associated with hyperacute rejection, can occur at any time during the clinical course of allograft rejection.

Why do we have pre-existing antibodies against these nonself components?

Antibodies for A or B antigens on blood cells are believed to arise from exposure to cross-reactive oligosaccharides in nature, including their presence on many gut commensals.
Several mechanisms can account for the presence of antibodies specific for MHC alloantigens, including past blood transfusions that induced antibodies to MHC antigens expressed on allogeneic white blood cells in the blood; past pregnancies, in which women develop antibodies against paternal alloantigens of the fetus; exposure to infectious agents, which can elicit MHC cross-reactive antibodies; or a previous transplant, which results in high levels of antibodies to the allogeneic MHC antigens present in that graft.

However, careful pretransplantation testing can all but eliminate hyperacute rejection.

Steps in the hyper acute rejection of a kidney graft.



In rare instances, pre existing serum antibodies specific for antigen of the graft bind to antigens on renal capillary. Complement split products attract neutrophils which destroy endothelial lining.

Acute Rejection

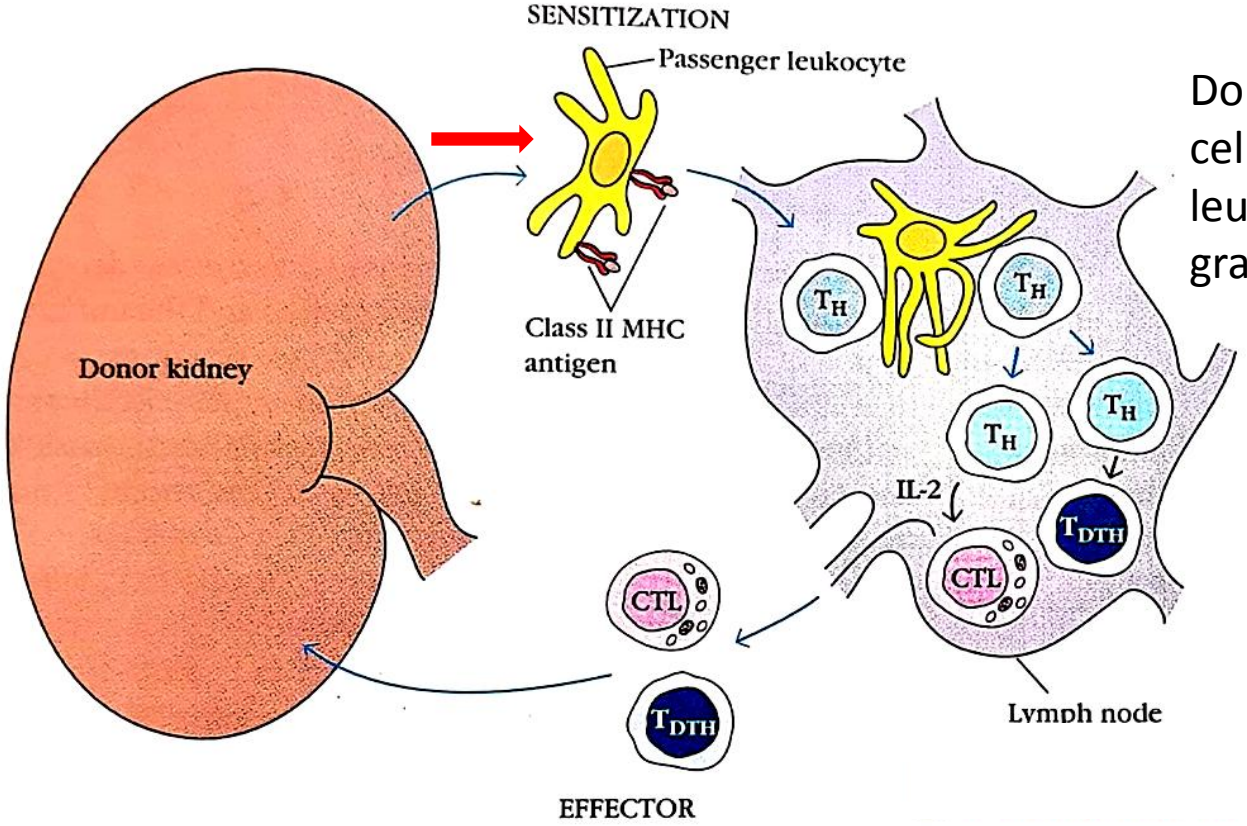
When graft rejection occurs in the absence of pre-existing antibodies it is called **acute rejection, and occurs in two stages, similar to hypersensitivity** responses:
a sensitization phase and an effector phase.

During the **sensitization phase**, CD4 and CD8 T cells recognize alloantigens expressed on cells of the foreign graft and proliferate in response.

This sensitization phase takes some time, which is why the **effector phase** of acute rejection typically manifests 7 to 10 (or more) days later, depending on the immune suppression regimen. The hallmark of the effector phase is a large influx of leukocytes, especially CD4 T cells and macrophages.

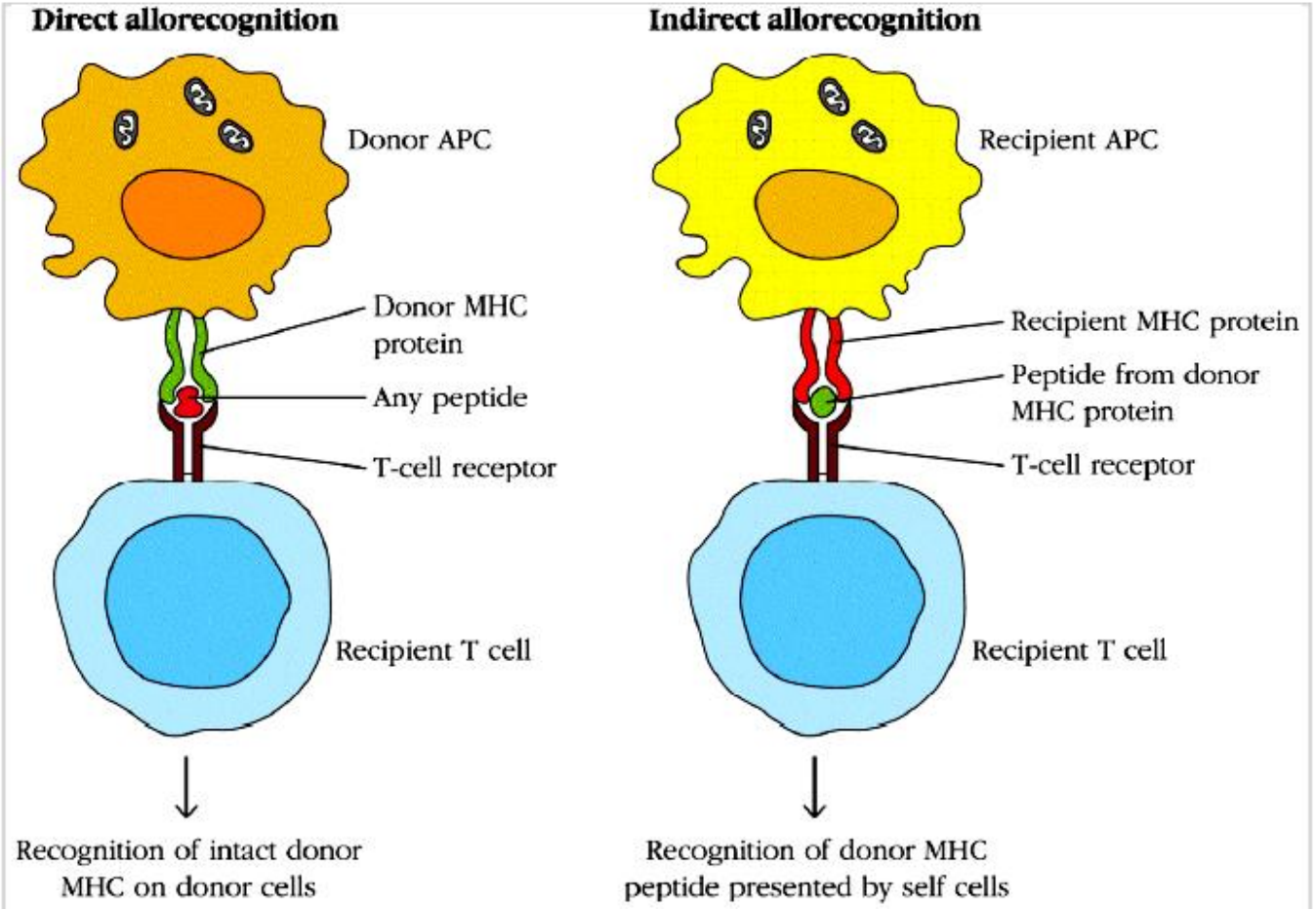
Both major and minor histocompatibility alloantigens can be recognized. In general, the response to minor histocompatibility antigens is weak, although the combined response to several minor differences can be quite vigorous.

The response to MHC antigens can involve recipient T cell recognition of donor MHC molecules expressed on the surface of cells in the transplant (**direct presentation)** or recognition of processed peptides from donor HLA proteins presented in the cleft of the recipient's own APCs via self MHC molecules (**indirect presentation**).



Donor antigen presenting cells called passenger leucocytes migrate from graft to lymph node.

Migration of passenger leukocytes from a donor graft to regional lymph nodes of the recipient results in the activation of T_H cells in response to different class II MHC antigens expressed by the passenger leukocytes. These activated T_H cells then induce generation of T_{DTH} cells and/or CTLs, both of which mediate graft rejection.



Direct versus indirect presentation of allogeneic MHC. During foreign tissue recognition, donor APCs transferred during the operation and bearing foreign MHC molecules can engage directly with host T cells (direct allorecognition, left), or donor cells and cellular debris can be taken up by host APCs and processed, allowing fragments of foreign MHC peptides to be presented by recipient APCs bearing self MHC (indirect allorecognition, right).

T cells are crucial for acute rejection from transplant studies in model animals. For instance, nude mice, which lack a thymus and consequently lack functional T cells, were found to be incapable of allograft rejection; these mice even accept xenografts. In other studies, T cells derived from an allograft-primed mouse were shown to transfer second-set allograft rejection to an unprimed syngeneic recipient as long as that recipient was grafted with the same allogeneic tissue.

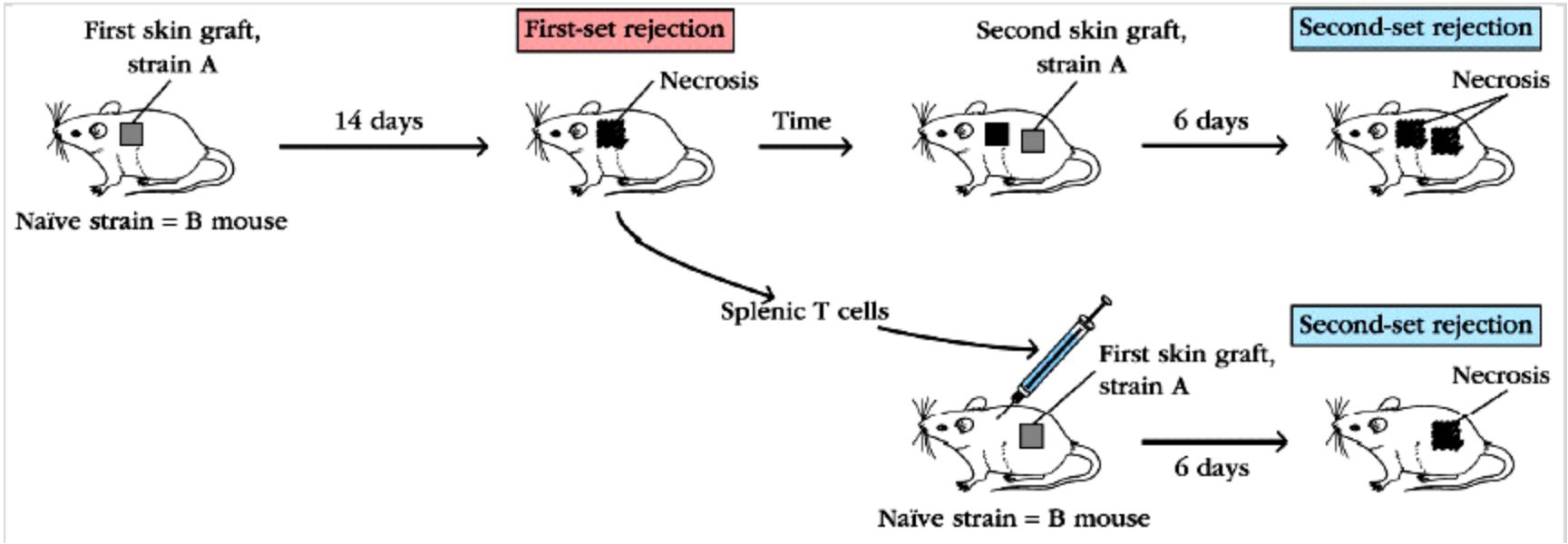


Fig. Experimental demonstration that T cells can transfer allograft rejection. When T cells derived from an allograft primed mouse are transferred to an unprimed syngeneic mouse, the recipient mounts a second-set rejection to an initial allograft from the original allogeneic strain.

Cytokines secreted by T cells play a central role in acute rejection.

For example, IL-2 and IFN-γ produced by T 1 cells have been shown to be important mediators of graft rejection.

These two cytokines promote T-cell proliferation (including CTLs), DTH responses, and the synthesis of IgG by B cells, with resulting complement activation.

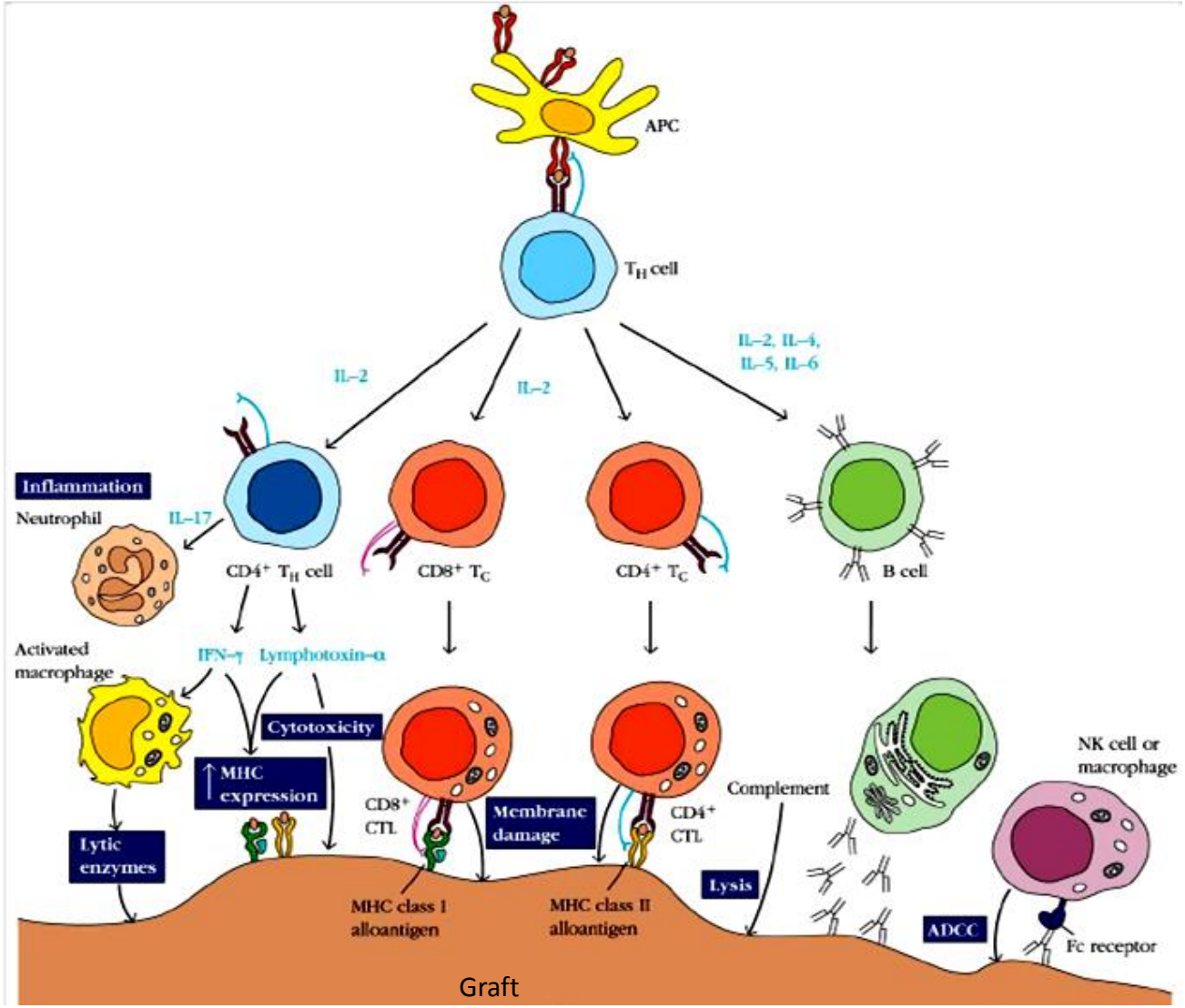
A number of cytokines that encourage the expression of MHC class I and class II molecules (e.g., the interferons and TNFs) increase during graft rejection episodes, inducing a variety of cell types within the graft to increase surface expression of these proteins.

Many of the cytokines most closely associated with T_H2 and T_H17 cells have also been implicated in graft rejection.

Elevations in IL-4, -5, and -6, responsible for B cell activation and eosinophil accumulation in allografts, along with increases in IL-17, have all been linked to transplant rejection.

Recent studies showing that neutralization of IL-17 could extend the survival of cardiac allografts in mice have generated much interest in this cytokine and in the role of T_H17 cells in graft rejection.

Finally, (antibody mediated rejection)AMR, although less frequent, is still a major issue in the acute phase of rejection and is sustained by T-cell-dependent maintenance of alloreactive B cells.



Effector mechanisms involved in allograft rejection. The generation or activity of various effector cells depends directly or indirectly on cytokines (blue) secreted by activated T H cells. ADCC *antibody dependent c ell-mediated cytotoxicity.*

Chronic rejection can develop months or years after acute rejection reactions have subsided.

The mechanisms include both humoral and cell-mediated responses.

Although immunosuppressive drugs and advanced tissue-typing techniques have dramatically increased survival of allografts during the first years, less progress has been made in chronic rejection, or late stages of transplant failure.

Generalized Immunosuppressive Therapy

In 1959, Robert Schwartz and William Dameshek reported that treatment with 6-mercaptopurine suppressed immune responses in animal models. Joseph Murray and colleagues then screened a number of its chemical analogues for use in
human transplantation. One, azathioprine, when used in combination with corticosteroids, dramatically increased survival of allograft s.

Joseph E. Murray received a Nobel prize in 1990 for this clinical advance, and the developers of the drug, Gertrude Elion and George Hitchings, received the Nobel prize in 1988.

The Nobel Prize in Physiology or Medicine 1988

Photo from the Nobel Foundation archive.
Sir James W. Black
Prize share: 1/3

Photo from the Nobel Foundation archive.
Gertrude B. Elion
Prize share: 1/3

Photo from the Nobel Foundation archive.
George H. Hitchings
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1988 was awarded jointly to Sir James W. Black, Gertrude B. Elion and George H. Hitchings "for their discoveries of important principles for drug treatment."

The Nobel Prize in Physiology or Medicine 1990

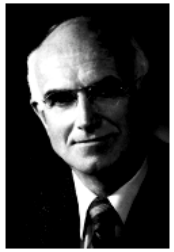


Photo from the Nobel Foundation archive.
Joseph E. Murray
Prize share: 1/2

Photo from the Nobel Foundation archive.
E. Donnall Thomas
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 1990 was awarded jointly to Joseph E. Murray and E. Donnall Thomas "for their discoveries concerning organ and cell transplantation in the treatment of human disease."

Immunosuppressive therapy can be either general or target-specific

Allogeneic transplantation always requires some degree of immunosuppression if the transplant is to survive. Most immunosuppressive treatments are nonspecific, resulting in generalized suppression of responses to all antigens, not just those of the allograft .

This places the recipient at increased risk of infection and cancer. In fact, infection is the most common cause of transplant-related death.

Many immunosuppressive measures slow the proliferation of activated lymphocytes, thus affecting any rapidly dividing nonimmune cells (e.g., gut epithelial cells or bone marrow hematopoietic stem cells), and leading to serious or even life-threatening complications.

Patients on long-term immunosuppressive therapy are also at increased risk of hypertension and metabolic bone disease.

General immunosuppressive therapy

1. Total lymphoid irradiation eliminates lymphocytes: 200rds per day till 3400 rads has been administered.

2. Mitotic inhibitors: Azathiopurine (Imuran) acts on cells in S phase. Cyclophosphamide, an alkylating agent inserts in to DNA helix and becomes crossedlinked, leading to disruption of DNA chain.

2. Corticosteroids (prednisone, dexamethasone) suppress inflammation.

3. Fungal metabolites: cyclosporine A, tacrolimus, rapamycin block activation of resting T cells by inhibiting transcription of genes coding for IL-2 and high affinity IL-2 receptor.

All above therapies are not specific

So, the alternative is specific immunosuppressive therapy.

Total lymphoid irradiation to eliminate lymphocytes

Because lymphocytes are extremely sensitive to x-rays, x-irradiation can be used to eliminate them in the transplant recipient just before grafting.

Although not a part of most immunosuppressive regimens, this is oft en used in bone marrow transplantation or to treat **graft -versus-host disease (GVHD), in which the graft rejects the host.**

In total lymphoid irradiation, the recipient receives multiple x-ray exposures to the thymus, spleen, and lymph nodes before the transplant, and the recipient is engrafted in this immunosuppressed state. Because the bone marrow is not x-irradiated, lymphoid stem cells proliferate and renew the population of recirculating lymphocytes.

These newly formed lymphocytes appear to be more likely to become tolerant to the antigens of the graft .

Mitotic inhibitors and corticosteroids

Azathioprine (Imuran) is a potent mitotic inhibitor often given just before and after transplantation to diminish both B- and T-cell proliferation.

Other mitotic inhibitors that are sometimes used in conjunction with immunosuppressive agents are cyclophosphamide and methotrexate. Cyclophosphamide is an alkylating agent that inserts into the DNA helix and becomes cross-linked, leading to disruption of the DNA chain. It is especially effective against rapidly dividing cells and is therefore sometimes given at the time of grafting to block T-cell proliferation. Methotrexate acts as a folic-acid antagonist to block purine biosynthesis.

Because mitotic inhibitors act on all rapidly dividing cells, they cause significant side effects, especially affecting the gut and liver, in addition to their target, bone marrow-derived cells.

Most often, these mitotic inhibitors are combined with immunosuppressive drugs such as **corticosteroids** (e.g., prednisone and dexamethasone).

These potent anti-inflammatory agents exert their effects at many levels of the immune response and therefore help prevent acute graft rejection.

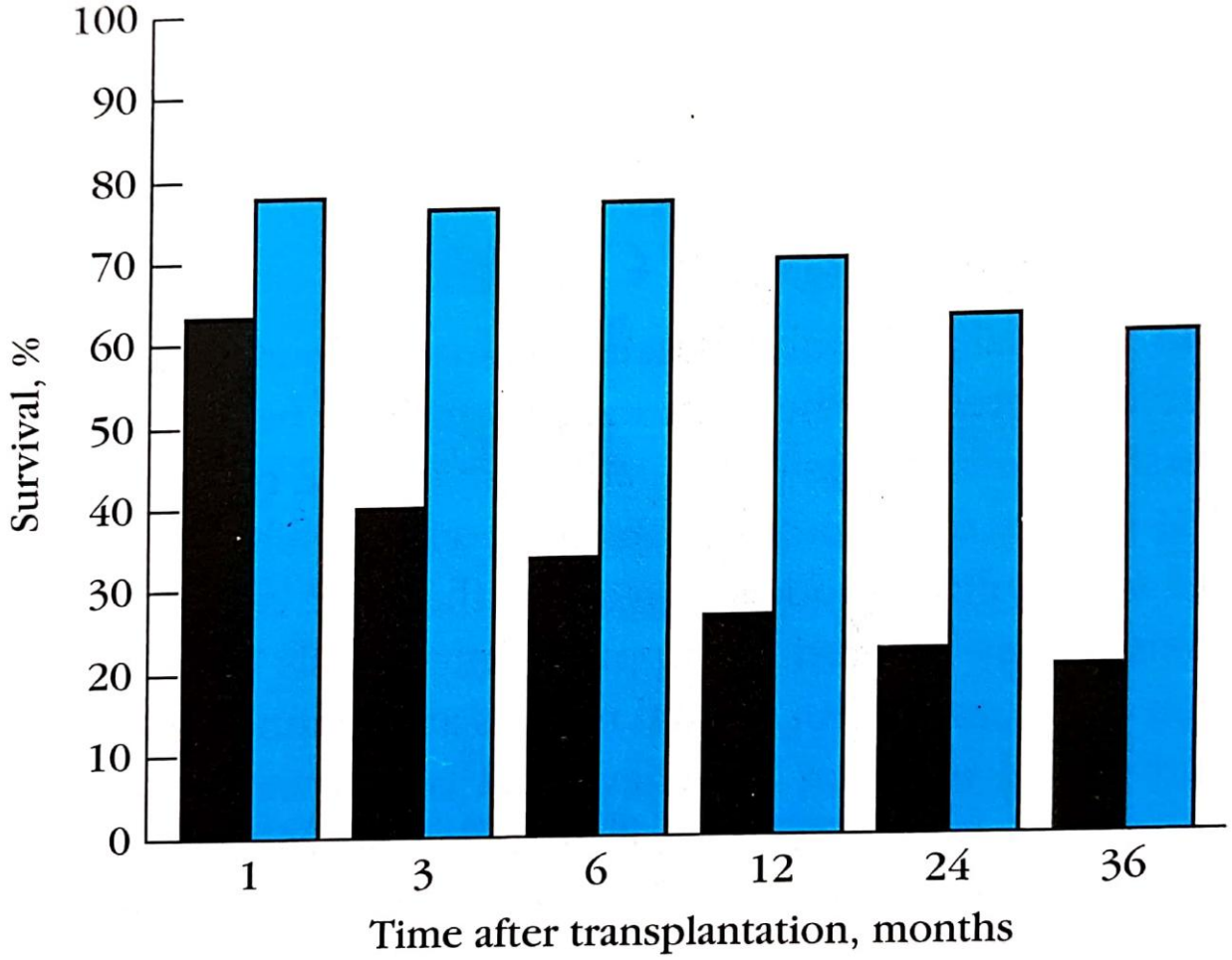
Fungal metabolites help immune suppression

1. *cyclosporin A (CsA),*
2. *FK506 (tacrolimus), and*
3. *rapamycin (also* known as sirolimus).

Some fungal metabolites bock the activation and proliferation of resting T cells.
Some of these also prevent transcription of several genes encoding important T-cell activation molecules, such as IL-2 and the high-affinity IL-2 receptor (IL-2R).
By inhibiting T_H-cell proliferation and cytokine expression, these drugs reduce the subsequent activation of various effector populations involved in graft rejection, making them a mainstay in heart, liver, kidney, and bone marrow transplantation.

In one study of 209 kidney transplants from deceased donors, the 1-year survival rate was 80% among recipients receiving CsA and 64% among those receiving other immunosuppressive treatments. Similar results have been obtained with liver transplants.

Despite these impressive results, CsA does have some side effects, most notably toxicity to the kidneys.
FK506 and rapamycin are 10 to 100 times more potent immunosuppressants than CsA and therefore can be administered at lower doses and with fewer side effects.



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).

Specifi c Immunosuppressive Therapy

The ideal immunosuppressant would be antigen-specific, inhibiting the immune response to the alloantigens present in the graft while preserving the recipient's ability to respond to other foreign antigens.

Although this goal has not yet been achieved, several more targeted immunosuppressive agents have been developed. Most involve the use of *monoclonal antibodies* (mAbs) or soluble ligands that bind specific cell-surface molecules.

One limitation of most first-generation mAbs came from their origin in animals. Recipients of these frequently developed an immune response to the nonhuman epitopes, rapidly clearing the mAbs from the body. This limitation has been overcome by the construction of humanized mAbs and mouse-human chimeric antibodies.

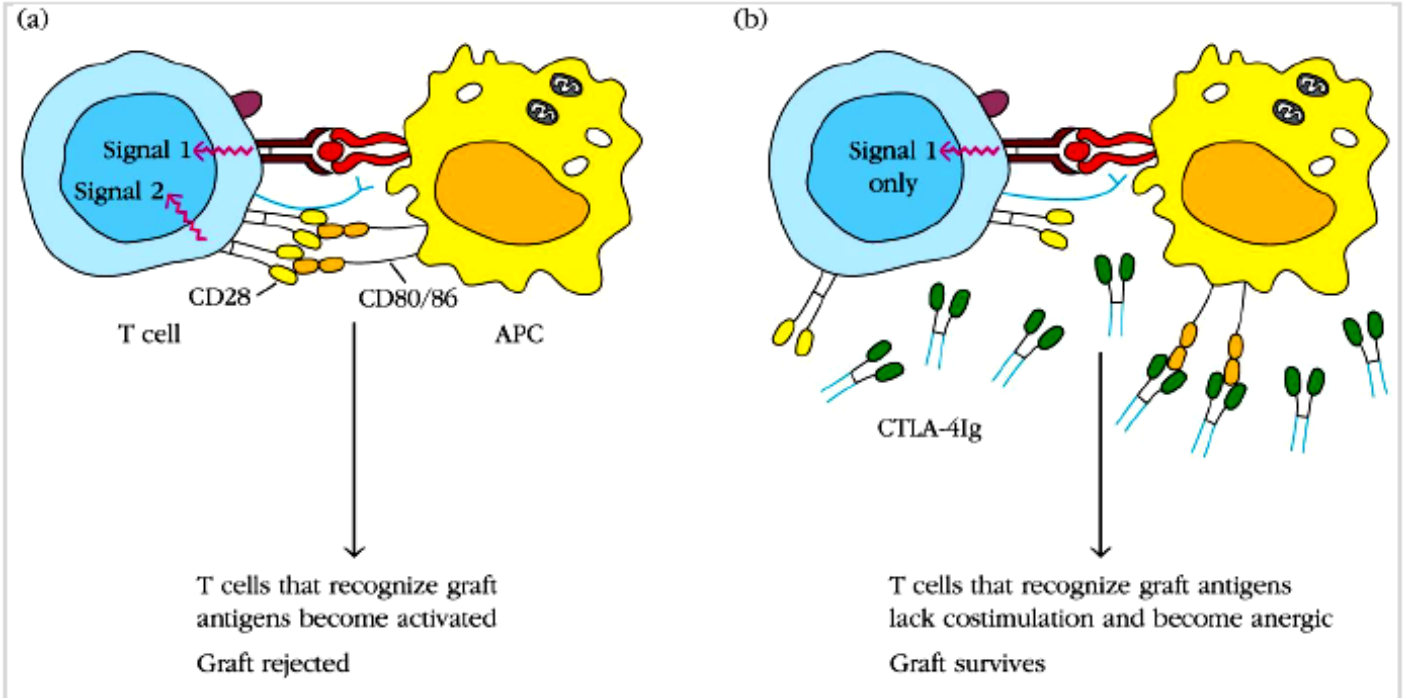
Blocking costimulatory signals

T_H-cell activation requires a costimulatory signal in addition to the signal mediated by the TCR. The interaction between CD80/86 on the membrane of APCs and the CD28 or CTLA-4 molecule on T cells provides one such signal. Without this costimulatory signal, antigen-activated T cells become anergic (unresponsive).

CD28 is expressed on both resting and activated T cells, while Cytotoxic T lymphocyte–associated protein-4 **(CTLA-4) is expressed only on activated T cells** and binds CD80/86 with a 20-fold-higher affinity.

In mice, prolonged graft survival by blocking CD80/86 signaling with a soluble fusion protein consisting of the extracellular domain of CTLA-4 fused to human IgG1 heavy chain (called CTLA- 4Ig) has been demonstrated.

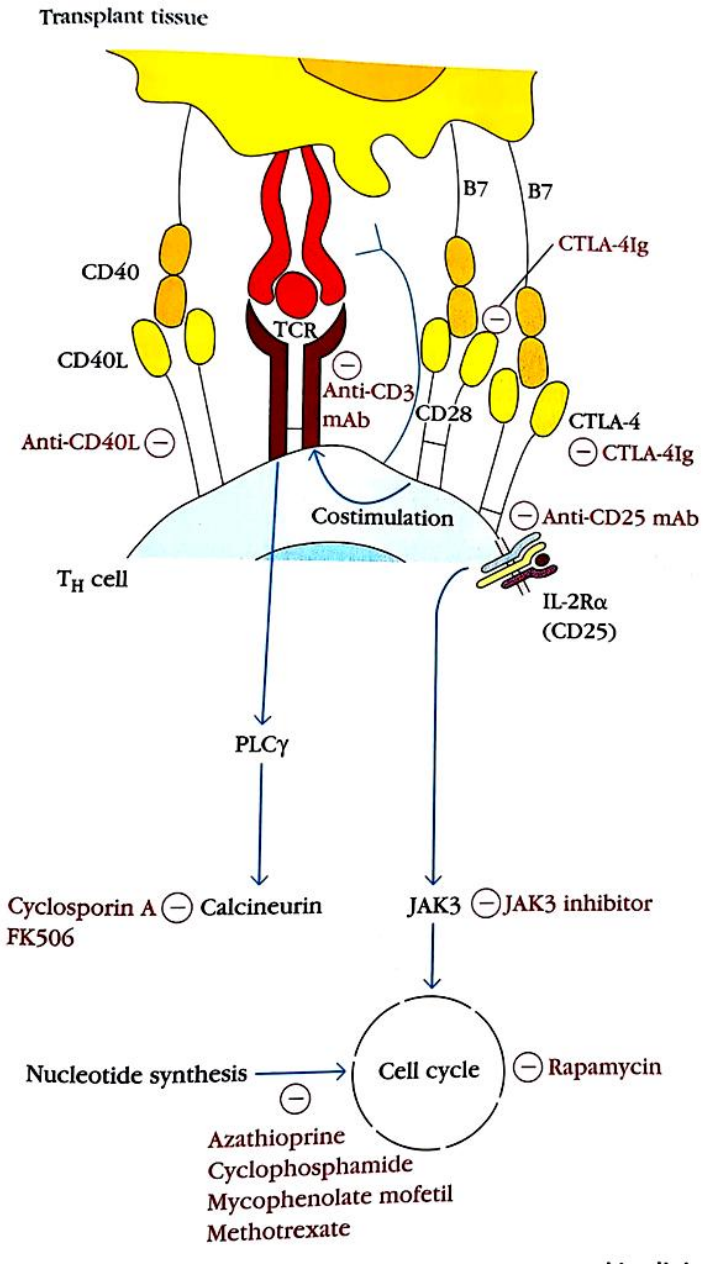
This new drug, belatcept, was shown to induce anergy (unresponsive) in T cells directed against the grafted tissue and has been approved by the FDA for prevention of organ rejection in adult kidney transplant patients.



Blocking costimulatory signals at the time of transplantation can cause anergy (unresponsive) instead of activation of T cells reactive against a graft.

a. T-cell activation requires both the interaction of the TCR with its ligand and the reaction of costimulatory receptors with their ligands.

b. Contact between one of the costimulatory receptors (CD28) on the T cell, and its ligand (CD80/86) on the APC, is blocked by reaction of CD80/86 with the soluble ligand CTLA-4Ig.
The CTLA-4 is coupled to an immunoglobulin heavy chain, which slows its clearance from the circulation. This process specifically suppresses the induction of T cell responses against graft-specific antigens and improves graft survival.



Some of the treatments used to suppress transplant rejection in clinical settings are summarized in Figure along with their sites of action.

Sites of action for various agents used in clinical transplantation

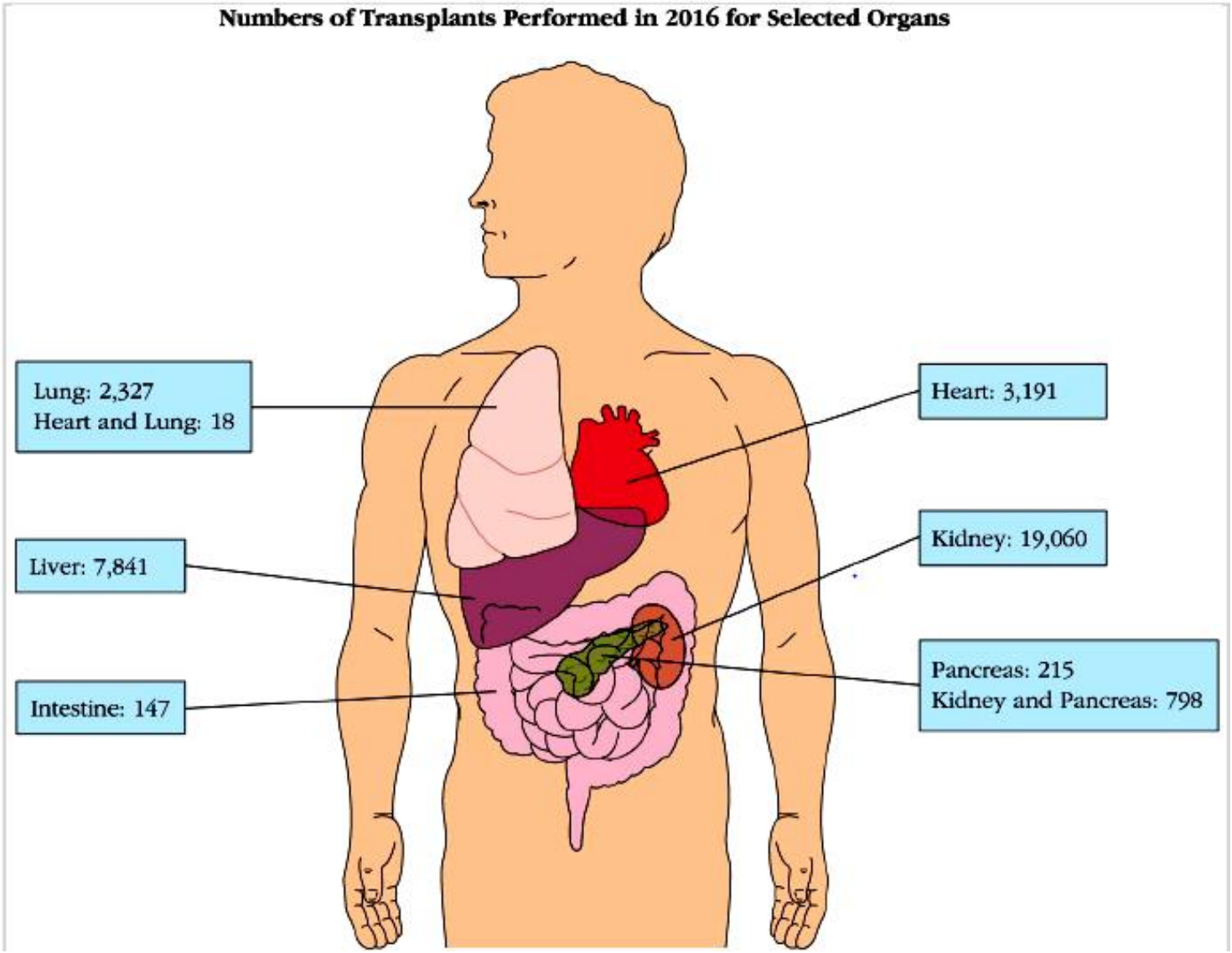
Immunologically Privileged Sites

An allograft placed in an immunologically privileged site, or an area without significant immune cell access (e.g., the anterior chamber of the eye, cornea, uterus, testes, and brain), is less likely to experience rejection.

Each of these sites is characterized by a paucity of lymphatic vessels, and sometimes also blood vessels. Consequently, the recipient's T cells are less likely to become sensitized to the alloantigens of the graft, and the graft has an increased likelihood of acceptance even when HLA antigens are not matched.

The privileged status of the cornea has allowed corneal transplants to be highly successful.

Ironically, the successful transplantation of allogeneic pancreatic islet cells into the thymus in a rat model of diabetes suggests that the thymus is either immunologically privileged or can foster tolerance of antigens found there.



Solid organ transplant numbers for 2016. [Data from https://optn.transplant.hrsa.gov/data/.]