The Kidney:
Understanding It From Development to Disease to Therapy

“Superficially, it might be said that the function of the kidneys is to make urine; but in a more considered view one can say that the kidneys make the stuff of philosophy itself.”

Homer Smith

Peter V. Hauser
Today

- Kidney Transplantation
Transplantation

Transplantation is the treatment of choice for ESRD!
- Restoration of “normal” renal function

Higher quality of life compared to HD or PD.
- Freedom from dialysis
- Return to “normal” life

Only restrictions is transplant availability.

Still just a treatment *not a cure!*
Transplantation

Disadvantages

- Life long medications
- Multiple side effects from medication
- Increased risk of tumor
- Increased risk of infection
- Major surgery
ESRD Patients

- Diabetic nephropathy accounts for 40% of the diseases resulting in renal transplantation. This group of patients is also more prone to complications after renal transplantation.

- The spectrum of diseases in transplant patients is different from the general population.

- The classical presentation of common medical disorders may be modified by immunosuppressive medication.
Statistics of Organ Transplantation

- There are more than 91,500 people on the organ transplantation waiting list.
- Each day 74 people receive an organ transplantation, but 18 people on the waiting list die because a donor is not available.
- There are 55,000 people waiting for a kidney, 17,000 waiting for a liver and 3,000 waiting for either a heart or liver transplant.
Between 1880 and 1930 there was a rapid surge in experiments with tissue transplantation (thyroid, parathyroid, testicles, ovary, adrenals) with the aim of replacing endocrine function.

Emerich Ullmann (1861-1937), born in Pecs, Hungary and a surgeon in Vienna, Austria was the first to perform transplantations of solid organs.

During 1899 and 1900 he conducted several experiments with intestinal transplantation and must be regarded as the father of intestinal transplantation. Then he moved to kidney transplantation.

On March 7, 1902 he demonstrated a dog with a functioning kidney graft anastomized to the collar vessels with urine dripping off the ureter sutured to the skin of the neck in the lecture hall of the Society of Physicians in Vienna.
Ullmann was the first to perform kidney auto-, homo- and heterotransplantations and in 1902 tried to perform the first human kidney transplantation using a pig kidney which he anastomized into the cubital region of a women with end stage renal disease.

With the obvious immunologic barriers to transplantation, the first "technical surgical period" of transplantation came to an end around the times of Ullmann's death and clinical transplantation was not to be revived before effective means of immunosuppression became available in the 1950s.

Druml, 2002
1936
Dr. Voronoy, a Russian, reports the first human-to-human kidney transplant, when a kidney from a deceased donor is transplanted to a recipient with a different blood type.

1947 Dr. David Hume transplanted a kidney to arm vessels

1954
Surgeons Joseph E. Murray and John Hartwell Harrison, in collaboration with nephrologist John P. Merrill, perform the first successful kidney transplant -- between identical twins -- at the Peter Bent Brigham Hospital in Boston.

1967
Dr. Christiaan Barnard performs the first heart transplant at Groote Shuur in Cape Town, South Africa.
Definitions

**Allograft:** graft between genetically dissimilar individuals of the same species

**Autograft:** graft in which donor and recipient are the same individual

**Xenograft:** Donor and recipient belong to different species.
Self vs Non-Self

Immune system differentiates between Self and Non-Self

Self: cells and tissue of the body

Non-Self: foreign material (tissue, snake venom, dust, pollen, viruses, microorganisms)

If the immune system identifies a substance as foreign, the activated immune system aims to remove the material before it causes harm.
The HLA system

Human leukocyte antigens otherwise known as MHC (Major Histocompatibility Complex) molecules
Highly polymorphic Glycoprotein complexes
~ 200 genes on chromosome 6
3 clusters:
**MHC class I** – HLA-A, HLA-B, HLA-C
**MHC class II** – HLA-DR, HLA-DP, HLA-DQ
**MHC class III** – Soluble components
In the early time, people carry out the transplantation surgery without HLA typing and then the rejection occurs very often.

Just as the case before.
The photo here shows necrotic kidneys.

Immune rejection
Rejection

Fig. 1. The growth of bone marrow (right) and whole organ transplantation (left) from the seed planted by Peter Medawar during World War II. GVHD, Graft versus host disease.
Rejection

HvGD: Host versus graft disease:
Cells of the body attack the implanted organ.

GvHD: Graft versus host disease:
Transplanted cells attack the organs of the host.
We express two alleles at each loci: one inherited from either parent.

- Co-dominant expression
- <0.5% recombination frequency
A well-matched donor is important to the success of your transplant. You inherit half of your HLA markers from your mother and half from your father, so each brother and sister who has the same parents as you has a 25% chance of matching you.
Pre-transplant tests

• %PRA (Panel Reactive Antibody): Percentage of the population a person will react against via pre-existing antibodies. Recipient serum screened for antibodies towards HLA antigens

• ABO blood typing

• HLA tissue typing

• Serum cross-matching
Donor

**HLA type:** A1, -, B8, 39, DR1, 3.
Homozygous at the A locus for A1
Heterozygous at the B locus for B8 and B39
Heterozygous at the DR locus for DR1 and DR3

Recipient

**HLA type:** A1, 24, B39, 44, DR1, 11.
Heterozygous at each loci
1 mismatches for the B locus
1 mismatch for the DR locus
Role of HLA typing

1. Improves the chances for a successful transplant
2. Promotes engraftment.
3. Reduces the risk of a post-transplant complication.
<table>
<thead>
<tr>
<th>Immunization for Kidney Transplant Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended</strong></td>
</tr>
<tr>
<td>• Influenza types A and B (yearly)</td>
</tr>
<tr>
<td>• Pneumovax (every 3-5 years)</td>
</tr>
<tr>
<td>• Diphteria-Pertussis-Tetanus</td>
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<tr>
<td>• Haemophilus influenza B</td>
</tr>
<tr>
<td>• Hepatitis A and B</td>
</tr>
<tr>
<td>• Inactivated polio</td>
</tr>
<tr>
<td>• Meningococcus</td>
</tr>
<tr>
<td><strong>Not Recommended</strong></td>
</tr>
<tr>
<td>• Varicella zoster</td>
</tr>
<tr>
<td>• Intranasal influenza</td>
</tr>
<tr>
<td>• BCG</td>
</tr>
<tr>
<td>• Live oral typhoid</td>
</tr>
<tr>
<td>• Measles, Mumps, Rubella</td>
</tr>
<tr>
<td>• Oral polio</td>
</tr>
<tr>
<td>• Yellow fever</td>
</tr>
<tr>
<td>• Smallpox</td>
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<tr>
<td>• Live Japanese B encephalitis vaccine</td>
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</table>
The Surgical Procedure

- Wet ischaemia time (time from cessation of circulation to removal of organ and its placement in cold storage) should not exceed 30 mins.

- Transplanted kidney is placed in the R or L lower quadrant of the abdomen in an extraperitoneal position. On examination, the transplant is easily palpable.

- The transplant renal artery is anastomosed to the ipsilateral internal or external iliac artery, the renal vein to internal or external iliac vein and the transplant ureter to the bladder.
Generally a single kidney is transplanted.

Small, paediatric or older cadaveric donor kidneys with age-related loss of renal functional are transplanted, both kidneys from the donor might be placed in a single recipient to provide adequate functional renal mass.
Principle of Kidney Transplantation
The Surgical Procedure

- Living donor transplants function immediately after transplant, +/- 30% of cadaveric transplants have delayed graft function because of more prolonged ischaemic cold preservation. These patients need continued dialysis support until the kidney starts to function.
Care of the Recipient
- Major surgery with general anesthesia
- Assessment of renal function
- Assessment of fluid and electrolyte balance
- Prevention of infection
- Prevention and management of rejection

Prevention of Infection
- Major complication of transplantation due to immunosuppression
- HANDWASHING
- Crowds, Kids
- Patient Education
## Varieties of Rejection

<table>
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<tr>
<th>Type of Rejection</th>
<th>Time course</th>
<th>Cause</th>
</tr>
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<tbody>
<tr>
<td>hyper-acute</td>
<td>minutes - hours</td>
<td>pre-formed antibodies (humoral)</td>
</tr>
<tr>
<td>acute</td>
<td>days - weeks</td>
<td>cell mediated</td>
</tr>
<tr>
<td>chronic</td>
<td>months - years</td>
<td>humoral and cell mediated</td>
</tr>
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</table>
Rejection

- Hyper-acute - preformed antibodies to donor antigen
  - function ceases within 24 hours
- Accelerated - same as hyper-acute but slower, 1st week to month
Rejection

Acute - generally after 1st 10 days to end of 2nd month
- 50% experience
- must differentiate between rejection and cyclosporine toxicity
Rejection

Chronic - gradual process of graft dysfunction
  – Repeated rejection episodes that have not been completely resolved with treatment
  – Rx = return to dialysis or re-transplantation
Immunosuppressive Therapy

- Renal transplant patients require lifelong immunosuppression to prevent rejection.
- Current “triple” regimes include cyclosporine-microemulsion or tacrolimus, mycophenolate mofetil or azathiopine and corticosteroids.
- Sicrolimus became available in 1994 and has become incorporated into protocols.
# Immunosuppressant Drugs

<table>
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<tr>
<th>Drug</th>
<th>Function</th>
<th>Side Effects</th>
</tr>
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<tr>
<td><strong>Prednisone</strong></td>
<td>- Prevents infiltration of T lymphocytes</td>
<td>- GI disturbances, Diabetes, infection, risk of tumor</td>
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<tr>
<td><strong>Azathioprine</strong></td>
<td>- Prevents rapid growing lymphocytes</td>
<td>- bone marrow toxicity, hepatotoxicity, hair loss, infection, risk of tumor</td>
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<tr>
<td><strong>Cyclosporin</strong></td>
<td>- Interferes with production of interleukin 2 necessary for growth and activation of T-cells</td>
<td>- Nephrotoxicity, Hepatotoxicity, Gingival hyperplasia, Infection</td>
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<td><strong>Tacrolimus</strong></td>
<td>- Newer macrolide compound that binds to lymphocyte proteins and inhibits cytokine synthesis. Used as either primary or rescue therapy for allograft rejection.</td>
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Graft Prognosis

- Directly related to source of donor kidney
- Recipients of cadaveric kidneys have more episodes of rejection and lower graft survival rates
- Graft survival rates for kidneys from living donor is
  - 95% at 1 yr and
  - 76% at 5 yrs
- cadaveric donor is
  - 89% at 1 yr and
  - 61% at 5 yrs
Graft Survival
Post-transplant diabetes mellitus (PTDM) is a complication which takes place after a solid organ transplant, and its incidence is widely variable, ranging from 2 to 53%.

Risk factors for PTDM are:
- age
- ethnicity
- cadaver-donor kidney presence of the hepatitis C virus and cytomegalovirus
- overweight and obesity
- immunosuppression scheme in the immediate post-transplant period

High doses of tacrolimus and corticosteroid represent the highest risk for developing PTDM.

PTDM is associated with a higher risk of posttransplant infections and cardiovascular disease.
Cumulative incidence of post-transplant diabetes


USRDS ADR 2012
Infection and graft failure occur.

Hypertension occurs in 75-85% of all renal transplant recipients

Hyperlipidaemia 60%

CVS disease 15.8 – 23%

DM 16.9 – 19.9% (more likely to be present before transplantation and new onset DM after transplantation is related to corticosteroid use.)

Osteoporosis 60%
Transplant recipients are at significantly higher risk for cancers than the general population because of:

1. chronic immunosuppression
2. chronic antigenic stimulation
3. increased susceptibility to oncogenic viral infections
4. direct neoplastic action of immunosuppressants

Male and female transplant recipients have a significant higher risk to develop cancers of the colon, larynx, lung, and bladder. Male recipients in addition also for cancers of the prostate and testis.
Post-transplant Malignancy

- risk is 4X to 100X compared rates of malignancy in the general population
- no comprehensive reporting system
- strongly under reported = precise rate is unknown
- accounts for 10% of deaths in kidney recipients with functioning graft
- SCREENING is KEY!
Two Types of Transplantation

- **Deceased Donor:** UNOS Waiting list, Local Waiting List

- **Live Donor:** can be related or non-related
  - related by blood or marriage
  - non-related directed donation
  - humanitarian non-directed donor donation
  - National Kidney Paired Exchange Program
It is unlikely that extended family members will match you. However, your parents and/or children may also be tested to confirm your HLA typing and to make sure no possible donors are overlooked.

About 70% of patients who need a transplant do not have a suitable donor in their family.
How long does the typical waitlisted patient wait for a transplant?

Source: UNOS/OTPD.net, 4/5/13
Kidney Donor Profile Index (KDPI)

KDPI Variables

- Donor age
- Height
- Weight
- Ethnicity
- History of Hypertension
- History of Diabetes
- Cause of Death
- Serum Creatinine
- HCV Status
- DCD Status
Allocation: Matching Donor Organs With Transplant Candidates

Source: UNOS.org/TransplantLiving.org, 4/5/13
“Match Run”

• Factors affecting ranking may include:
  – tissue match
  – blood type
  – length of time on the waiting list
  – immune status - sensitization
  – donor organ quality
  – distance between the potential recipient and the donor
  – degree of medical urgency (for heart, liver, lung and intestines)

Source: UNOS.org/TransplantLiving.org, 4/5/13
Living vs Deceased Donors

- About 75% of organ donors develop diabetes insipidus due to pituitary necrosis and this leads to hypovolaemia.
- Systemic thermal control is often lost due to hypothalamic ischaemia which results in coagulopathy, hepatic dysfunction and cardiac dysfunction.
Living vs Deceased Donors

Organ donor rates
Per million population, 2010

Spain
Portugal
United States
France
Austria
Italy
Norway
Britain
Germany
Canada
Argentina
Netherlands
Australia
Poland
Sweden
Brazil
Greece
Turkey
Mexico

Source: Council of Europe
The Transplantation Process

- Transplant coordinators should be called early for any patient who may meet brain death criteria in the new future.

- Risk for organ donation include HIV, sepsis, non-CNS malignancy and severe CVS disease.

- Age is also a relative risk (i.e. organs not harvested from pts >75 years of age).

- The pre-transplantation workup of a potential donor includes testing for CMV, HSV, EBV, HIV, Hep A, B, C, D + E and HTLV type 1.
Organ Donor

- Following brain death, a number of physiological changes occur that need to be rectified if donor organ perfusion is to be preserved.

- Increased cerebral oedema after trauma or stroke results in catecholamine release and HT.

- With brainstem necrosis, catecholamine levels drop rapidly resulting in hypotension. This should be corrected with fluid and vasopressors.
Brain Dead – Harvard Criteria

Harvard criteria

A series of 4 parameters delineated by the Harvard Medical School ad hoc committee for irreversible coma

Harvard criteria for brain death
• unreceptivity and unresponsiveness
• no movement or breathing
• no reflexes
• flat electroencephalogram (confirmatory)

In addition, the following must be present
• body temperature ≥32º C
• absence of CNS depressants
Strengthens laws against organ trafficking.

Travel for transplantation may be ethical

For live donor transplantation:
(1) if the recipient has a dual citizenship and wishes to undergo transplantation from a live donor that is a family member in a country of citizenship that is not their residence.
(2) if the donor and recipient are genetically related and wish to undergo transplantation in a country not of their residence.

For deceased donor transplantation:
(1) if official regulated bilateral or multilateral organ sharing programs exist between or among jurisdictions that are based on reciprocated organ-sharing programs among the jurisdictions.
Kidney transplantation is the most cost-effective modality of renal replacement

Transplanted patients have a longer life and better quality of life

Early transplantation (before [pre-emptive] or within 1 year of dialysis initiation) yields the best results

Living donor kidney outcomes are superior to deceased donor kidney outcomes
The most common cause of transplant loss is death with a functional transplant due to

- Heart disease
- Infections
- Malignancies

Success of transplantation results from a delicate balance between the suppression of the immune system to prevent rejection and the long-term side-effects of immunosuppression

Immunosuppressants are essential to prevent immunological loss of the transplant but side effects can also lead to transplant loss
Don’t Take Your Organs to Heaven
Heaven Knows We Need Them Here