# RENAL TRANSPLANTATION: *An Overview*

**OKEWOLE A. O.**
**OSISIOGU C. U.**
*The authors are 2nd year clinical students of the College of Medicine, University of Ibadan.*

## INTRODUCTION: BACKROUND HISTORY

The technique of vascular anastomases was developed in the 1920s by Alex's Carrel. The human allograft attempts of David Hume and Joseph Murray in the early 1950s were possible based on this great surgical breakthrough. Dialysis techniques and machinery fashioned by Willen Kolff set the stage for George Thorn's group at Harvard Medical School to advance clinical dialysis to a viable and familiar therapy. These two sets of achievements eventually synergized, leading to dramatic changes in the management of chronic renal disease.

In th past two decades, organ transplantation has become established as effective therapy for end-stage renal, hepatic, cardiac and pulmonary disease. The combination of dialysis techniques and allograft transplantation has led to kidney transplant operations being vastly greater than other transplant procedures. Patients can freely move back and forth between dialysis and transplantation, so that life does not depend on only one form of treatment.

Other advances include Peter Medawar's description of second set reactions and his insights into cellular immunology. The close collaboration of pharmaceutical companies such as Burroughs-wellcome and clinical researchers such as Roy Calne led to the development of azathioprine, which made possible kidney transplantation in nonrelated individuals.

### *Immunologic Aspects*

Both T and B lymphocytes play a role in kidney allograft rejection. B lymphocytes are responsible for production of circulating antibodies. The role of T lymphocytes is however crucial. These constitute a heterogenous group made up of helper, suppressor and cytotoxic T cells.

In the late 1960's Daussette described the human leukocyte antigen (HLA) system. Also known now as the major histocompatibility complex (MHC), it is found in humans on chrosomosome 6 and codes for two classes of antigens on cell membranes: class 1 (A, B and C) and Class II (OP, OQ, DP). Inheritance of these cell antigen markers is co-dominant. Each parent transmits one set of HLA antigens (haplotype) to his or her child. Nearly all cells, except red blood cells, express class I antigens, while B lymphocytes, monocytes, and endothelial cells express class II antigens.

T-cell mediated rejection is initiated when the recipient's lymphocytes encounter the donor's HLA antigens[2]. It is believed that interstitial dendritic cells carried in the donor organs are the most important immunogens. The host T cells encounter the dendritic cells within the grafted organ or after these cells migrate to the draining lymph node. The CD4+ helper T-cell subset is triggered into proliferation by recognition of the class II specificities. At the same time, precursors of CD8+ CTL (prekiller T cells), which bear receptors for class I HLA antigens, differentiate into mature CTLS. This complex incompletely understood process of differentiation involves interactions of antigen-presenting cells, T-cell subsets, and release of cytokines, such as IL-2, IL-4 and IL-5. Once mature CTLS are generated, they lyse the grafted tissue.

As in delayed hypersensitivity reactions, cytoxines derived from the activated CD4+ Tcells cause increased vascular permeability and local accumulation of mononuclear cells (lymphocytes and macrophages). Some investigators claim that these are the most important mechanisms involved in graft destruction.

In human and animal recepients of kidney allografts, matching for both class I and class II antigens correlates with successful graft outcomes. The source of most human kidney tranplants is however the cadaveric donor, with the result that a good HLA match is more difficult.

### *Indications*

Studies reveal that the most common diseases which result in referral of patients for translantion include

1. diabetes mellitus with renal failure (Kimmelstiel-Wilson disease)
2. hypertensive renal disease
3. glomerulonephritis

These causes of end-stage renal disease were said to account for nearly 75% of candidates.

While no specific cause of intrinsic and irreversible renal failure is considered a contraindication to kidney transplantation, all patients should have reversible causes of renal dysfunction excluded (e.g. incomplete obstruction) prior to consideration of renal replacement therapy. Most patients undergo a period of chronic dialysis prior to receiving an allograft.

The following diseases, while not contraindications to transplantation, require special prior consideration as the outcome for patients may be less satisfactory with them:

1. Hemolytic Uremic Syndrome: as the disease can recur and cause graft failure rapidly. Cyclosporine may increase the risk of recurrence.
2. Sickle cell disease: Improved haematocrit can result in increased incidence of sickle crises.
3. Scleroderma: Long-term vascular and gastrointestinal problems of scleroderma can limit rehabilitation.
4. Oxalosis: recurrence of stone disease can be severe.
5. Cystinosis and Faber's disease. Disease activity continues.
6. Focal glomerulosclerosis: Graft loss from recurrence is common.

### *Evaluation of Donor and Recipient*

Evaluation is best done at the centre where the transplantation will be done, before the actual transplantation date. The team should include a transplant surgeon, nephrologist, urologist, social worker and psychiatrist.

Donor evaluation (in the case of live donors) focuses on

1. General medical assesment - to ensure that there are no medical problems that would increase the risk of surgery.
2. Renal function and the anatomy of the donor's renal arteries.
3. Psychological status, including motive for organ donation.

Evaluation of the recipient focuses on

1. Overall medical status, bearing in mind that the recipient may face both major surgery and marked immunosuppression in

the future. Emphasis should be placed on the recipients cardiovascular and urologic status.
2. The original disease - often important in the post-transplant management of the patients;
3. The recipient's socio-economic circumstances and ability to arrange follow-up;
4. Also, the patient's awareness of the risks and benefits of the transplant should be assessed.

***Transplant Precedure; During and After***

During the procedure for transplantation, the surgeon places a kidney allograft in the recipient iliac fossa. An anastomosis is created between the donor renal artery and the hypogastric artery. The donor renal vein is connected to the Iliac vein while the ureter is implanted into the recipient's bladder. These three connections all have variations.

After the procedure, three issues face the team:

1. If the kidney is not working immediately ("immediate non-function") the reason (or reasons) need to be identified.
2. If the kidney is working, careful observation for possible rejection or infection begun.
3. Immunosuppression.

Immediate non-function is due, most often, to an acute tubular necrosis (ATN) - like syndrome in which there is reversible ischemic damage to the allograft that will heal, given time. Obstruction, vascular thrombosis, and ureteral compression from haematoma should be considered in cases on primary non-function.

Rejection could be hyperacute, accelerated, acute or chronic.

Hyperacute and accelerated rejection both occur before the end of the first week. The former is rare with current crossmatch techniques. The latter is less well understood though more common. They often do not respond to therapy.

Acute and chronic rejections are more common. Acute rejection episodes, occuring usually after the first week up to as much as years after the transplant, are recorded in most kidney tranplant patients. They are moderated by T lymphocytes and are often associated with marked cellular infiltration of the allograft with oedema. Vascular lesions also occur and suggest a poor prognosis. Most episodes, if diagnosed early, will respond to increased dosages of immunosuppressive agents.

Chronic rejection is less understood. Most cadaveric allografts eventually show histologic changes of rejection. These changes are mostly vascular and similar to the histology of nephrosclerosis. Ultimately, the allograft develops fibrosis and glomerular lesions that appear secondary to ischemia. There is neither a good understanding of chronic rejection nor an accepted effective therapy.

Immunosuppression improves the chances of graft survival. From the 1960s through the early 80s. Azathioprine and prednisone were the two drugs employed. Cyclosporine was approved for use in 1983, and since then different immunosupressive protocols have been developed. Other drugs in use include antilymphocyte globulin (ALG) and OKT3, a monoclonal antibody.

Cyclosporine has revolutionized organ transplantation, being associated with as much as 10 to 15% improvement in initial and long-term allograft survival rates. It acts by inhibiting synthesis of IL-2 and gamma interferon. It however has such side effects as nephrotoxicity, potentiation of nephrotoxicity due to other substances, and slowing of recovery from ATN. It also commonly causes tremor, palmar and plantar paresthesia, hyperglycemia, hepatotoxicity, hypertrichosis, gingival hypertrophy, and hyperkalemia.

Infections could occur from wound site, intravenous line, catheter, or opportunistic infections, such as cytomegalovirus.

***Medical Complications following kidney Transplantation***

**I. Cardiovascular Events**
1. Myocardial infarcition
2. Cerebrovascular accident

**II. Hypertension**
1. Stenosis of transplant renal artery
2. Native kidney induced
3. Drug induced
4. Renal impairment of the allograft
5. Polycythaemia/ post transplant erythrocytosis

**III. Malignancies**
1. Skins carcinomas
2. Lymphomas
3. Kaposi's sarcoma

**IV. Erythrocytosis**
1. Induced by native kidneys
2. Thromboembolic disease

**V. Bone Disease**
1. Osteoporosis
2. Aseptic bone necrosis
3. Persistent hyperparathyroidism

**VI. Gastrointestinal**
1. Peptic ulcer
2. Pancreatis
3. Diverticulitis
4. Nepatitis

**VII. Infections**
1. *Listeria monocytogenes*
2. *Pneumocystis carinii*
3. Cryptococcus
4. Aspergthus
5. Nocardia
6. Toxoplasma
7. Mycobacteria
8. *Legionella pneumophila*
9. Cytomegalovirus (CMV)
10. Herpes Simplex virus (HSV)
11. Varicella zoster virus (VZU)
12. Hepatitis viruses
13. Papovaviruses
14. Human immunodeficiency virus (HIV)
15. Epstein-Barr virus (EBV)

**VIII. Glucocoticoid - induced Complications**

1. Obesity
2. Cataracts
3. Hyperglycemia
4. Myopathy

**IX. Endocrine and Metabolic Disorders**

1. Secondary hyperparathyroidism
2. Proximal and distal types of renal tubular acidosis
3. Asymptomatic hyperuricemia and gout
4. Mild hyperkalemia
5. Glycosuria without an increased serum glucose concentration

**X. Miscellaneous**

1. Idiopathic polyarthrides
2. Hirsutism
3. Lymphocele
4. Warts
5. Psychiatric affectivedisorders

**RECENT ADVANCES IN RENAL TRANPLANTATION**

Since the first successful renal transplant performed by Hume et al (1952), there has been an elusive search for agents that can render the immune mechanism unresponsive to the specific alloantigen stimulus of the engrafted organ, while sparing non-specific host resistance. The introduction of cyclosporin A (CyA) in the early 1980s and the new and very potent immunosuppressants have contributed their share in reducing acute allograft rejection though with their attendant side effects.

The immunologic barrier remains the major obstacle to widespread use of tranplanstation as replacement therapy for terminal organ failure. Recent immunosuppressants are designed to focus their action selectively on T and/or B cells by inhibiting cytokine synthesis (cyclosporin, FK506), cytokine action (rapamycin), or cell differentiation (15-deoxy-spergualin) pathways, rather than act on immune systems in a non-selective way.

Mycophenolate mofetil results in lymphocyte-selective arrest of cell division with little effect on other tissues thus reducing acute rejection episodes especially in conjunction with steroids and cyclosporin. Clinical trials have established its safety and efficacy with its principal toxicity being gastrointestinal and some increase in cytomegaloviral infection.

**PROBLEMS FACING RENAL TRANSPLANTATION IN NIGERIA**

Till date there is yet to be established a renal transplant centre/ programme in the country. Work on this had taken off at a time with a proposal to set up one in the Univeristy College Hospital as far back as 1992. A team consisting a nephrologist, surgeon, nurse and social worker had been sent in late 1992 to understudy renal transplantation in a developing country - in this case India - along with its successes and problems so as to relate it to this country and based on the experiences, to propose some recommendations for the kick-off of this programme. Till date logistic difficulties have hampered the start of this.

On a general note for renal transplantation in Nigeria to succed some problems would have to be fully addressed. These include:

1. **Funds/Operating Costs**

So far funds have been a major obstacle to the setting up of the Renal Transplant programme in UCH. This could be attributed to a lack of commitment to this programme from successive adminsitrations.

On the other hand, funds would act as the greatest drawback to the patient. A greater percentage of CRF patients in UCH cannot afford the minimum dialysis course as a form of renal function replacement therapy. These are the same who require the kidney transplants being proposed.

2. Most patients present so late in the disease course that the length of time spent on dialysis sessions is too mimimal to be meaningful. The extras - time and money - to be spent on the transplant make it near impossible for the patient to obtain the maximum benefit from this therapy.
3. Socio-cultural and religious beliefs would pose a hinderance in some way to the actualization of this programme except fully acted on. There are the beliefs as regards the dead, making it difficult for a patient to imagine receiving a cadaver donor kidney. There is also the family protectiveness of their own which would hinder organ harvest for transplants.

3. **Expertise**

A transplant team should, on the minimum, comprise the nephrologists, transplant surgeons, nurses, technicians, social worker and psychologist. These would have to receive the special extras - in terms of training to be able to man a transplant programme. Acceptability in the initial phase for example involves an aggressive post op medical management. The role of a pathologist in tissue HLA typing too cannot be overemphasized.

4. **Logistics**

- Data handling and match grading.

There is the near impossibility of achieving perfect identity. This is best overcome by a competent and near-to-perfect donor and receipent match and selection. Data comprising these have to be handled with utmost care for maximum benefits.

- Staffing
- Communication and transport

To set up a massive network for a transplant programme, these would to be addressed fully. A transplant programme also would have to posses extras in terms of special transplant rooms, transplant theatres for organ havest and transplant and isolation dialysis rooms as minimum for optimum patient care.

- An adequate follow-up programme has to be inculcated into the renal transplant programme itself. This is necessitated by the need for optimum post transplant follow-ups especially when one considers the problems faced with follow-ups of even less severe cases.

***Recommendations***

Recommendations can only border on a increased commitment by the authorities, especially the Government, to the setting up of such a programme. This would cover up for problems with operating costs especially.

An awareness should also be made public on the benefits of such a programme and should aim to counter beliefs that stand in the way of the successful implementation of this programme as stipulated above.

More staff would need to be trained with the proposed setting of such a programme to ensure the presence of expertise enough to handle the programme.

**REFERENCES**


1. Current results and future expectations in Renal Transplantation - Symposium on Renal Transplantation. Urology Clinics of N. America Vol. 10, No.2 May 1983; 337-346.
2. Muway J. E. et al - Renal Transplantation: A twenty-five year experience Ann surg. 184; 564 1976.
3. Monaco A. P. et al - Abstract - Current thinking on recommedations from a 1997 round table discussion (Review). America Journal of Kidney Diseases 33 (1); 150-60, 1999.
4. Sogaolu O. M. - Renal function Replacement Therapy; Owena Dialysis Centre and Prospects for Renal Transplantation in Nigeria - DOKITA 'General Edition' - May 1995.
5. Terasaki P. I. et al: High survival rates of kidney transplants from spousal and live unrelated donors. N. Engl J Med 1995; 333; 333.
6. Opel G. et al; Current status HLA matching in renal transplantation: The collaboration transplant study. Clin Int 1992; 70:767.
7. Muirhead N - Erythropoietin and renal transplantation - Kidney International - supplement 69: S 86 - 92, 1999 March.
8. Walker R: General Managemnt of End-Stage Renal Disease. BMJ 1997: 315:1429.
9. LR. Baker and CRV Tomson. Renal Disease - Clinical Medicine Ed. P Kumar and Mrclarck 3 ed.
10. Zeir in et al - Hypertension in the transplanted patient (Review). Nephron 80 (3); 257-68, 1998.
11. Sabeel A et al - Simultaneous development of Kaposi's Sarcoma and lymphoma in a renal transplant recipient. American Journal of Kidney Diseases 31 (4): 706-9, 1998 Apr.
12. Rodino M.A. Shane E - Osteoporosis after organ transplantation. American Journal of Medicine 104 (5): 459-69, 1998 May.
13. Klemperer J.D. et al - *Mycobacterium tuberculosis* infection in a native polycystic kidney following renal transplantation. Transplantation 66 (1): 118-120, 1998 Jul.
14. Gleiter CH - Post transplant Erythropoiesis: a model for the investigation of the pharmacological control of renal erythropoetin production? Int. J. Clinic Pharm. & Ther. 34 (11): 489-92, 1996.