C J Mieny, U Mennen: Principles of Surgical Patient Care - Volume II

Chapter 13: Organ Transplantation

Principles of Organ Transplantation

J R Botha and L P Margolius

Introduction

In this chapter special reference will be made to kidney transplantation which has become the accepted modality of treatment for most patients with end-stage renal disease. Its success relies on many fields of expertise such as medicine, surgery, immunology and not least of all, dialysis. The first renal allograft in man was done by Voronoy, a Russian surgeon. This patient died within 48 hours. Eighteen years were to pass before the surgeons at the Peter Brent Brigham Hospital in Boston performed the first successful graft. Their surgical technique was based on autotransplantation experiments done in dogs, where kidney grafts were anastomosed to the iliac vessels and with a simple ureterovesicle anastomosis for the ureter. It was only later that Politano and Leadbetter reported their antireflux submucosal procedure. Many other modifications have been reported, but their technique is still practised by many centres today. The last decade has witnessed many advances such as adequate immunosuppressive drugs, better patient selection, tests of recipient reactivity, post-op monitoring and more recently the promise of specific immune tolerance by the use of total lymphoid irradiation (TLI). Predictions based on worldwide estimations of previous years hold that in excess of 20000 transplants will be performed annually of which 1% will be performed in South Africa. In spite of this, the number of patients on dialysis are increasing at an alarming annual rate. It is of note that the results of kidney transplantation worldwide are improving and the mortality rate is decreasing. This chapter addresses the common issues facing a surgical transplant registrar and consultant.

Definitions

Graft: A graft or transplant does not include synthetic, prosthetic or artificial devices, but it may consist of tissues, cells or organs.

Allograft (homograft): An allograft is a graft between two genetically dissimilar individuals of the same species.

Autograft: An autograft is a graft where the donor and the recipient is the same individual.

Isograft (syngeric): An isograft is done between two genetically identical individuals.

Xenograft (heterograft): The donor and the recipient belong to different species.

Histocompatibility: The varying ability of an individual to accept tissues from another individual.

Transplantation antigens: The human leukocyte antigens (HLA) or the major histocompatibility complex (MHC) antigens are the molecules expressed on the surfaces of human cells. There are three groups: MHC class I, II and III antigens. Donor MHC class I and II antigens are capable of provoking an immune response in the immune competent recipient.

Tissue typing: This is the technique of identifying the HLA antigen in a recipient. This is usually done by the use of an antisera.

Crossmatching: The process of matching donor cells with recipient sera, to identify antibodies against recipient antigens. A positive crossmatch is an antibody reaction against the donor cell antigen.

The Immune System

The immune system (IS) is a highly flexible specific defence mechanism, which is responsible for the recognition and elimination of invading pathogens and foreign substances. This system also has the ability of distinguishing between "self" and "non-self" with elimination of only only "non-self". It also has the power of responding against an infinite variety of antigens during an individual's life time and to retain the memory of such antigenic encounters. The first exposure to a given antigen will elicit a primary response which is less effective in magnitude and time taken to eliminate the antigen, than the subsequent encounters of the secondary immun response. This memory is retained by circulating long-living small lymphocytes.

The defensive functions of this system are performed by white blood cells and a number of accessory cells which are found throughout the body but tend to cluster in lymphoid organs. Accumulation of these cells are also found in tissues where contact with pathogens would be likley, such as gut and lung. The IS is artificially divided into humoral and cellular arms of immunity, but this distinction belies the intricate and close interaction between these subsystems.

The principal effector cells in the IS are:

- T lymphocytes (thymus dependent) which are responsible for cell-mediated immune activity and regulatory functions within the IS.

- B lymphocytes (bone-marrow dependent) which are responsible for the production of antibodies and thus humoral immunity.

- The accessory cells (antigen-presenting cells or APC) are present in all tissues but are in their highest concentration in lymphoid organs.

These cells comprise a heterogeneous group including macrophages, monocytes, histiocytes, dendritic cells and Langerhans cells. They have the ability of taking up micro-organisms and soluble antigen and presenting fragments (epitopes) on their cell surface for reaction with receptors on immune competent cells.

- Other cells such as the large granular lymphocyte (LGN) with natural killer activity, inflammatory cells such as neutrophils and eosinophils, and soluble protein factors also play imporftant non-specific roles in the immune response.

T-cells are derived from bone marrow precursor cells which mature in the thymus. During maturation, various antigens are expressed on their cell surfaces, such as OKTII, OKT3, OKT6 and OKT4 or OKT8. Mature T cells express OKT3 and OKT4 or OKT8. They also express Class I MHC (major histocompatibility antigens) and when activated, Class 2 MHC antigens. With regard to function and surface antigens, the following T cells subsets are known:

- T helper (Th)/T inducer cells which express the OKT4 and OKT3 on their cell surfaces. They use Class 2 MHC antigens expressed on the APC as restriction elements, and this subset of T cells will only recognise antigen in the presence of Class II antigens. Th cells also help B-cells to recognize antigen and stimulate them to differentiate and proliferate and thereby lead to the production of antibody.

- T-suppressor (Ts)/T-cytotoxic (Tc) cells express OKT8 and OKT3 on their cell surfaces. Once they recognize APC presented antigen in association with Class I antigen, they are activated and are capable of destroying allogeneic cells as well as virally infected cells. Suppressor T cell (Ts) modify down and regulate the activity of T helper cells. This suppression can be specific or non-specific.

- Delayed hypersensitivity T cells (Td) cause other inflammatory cells such as macrophages, leukocytes and monocytes to enter the area. These Td cells are probably a subset of T helper cells.

B cells or bone-marrow dependent cells, when mature, express immunoglobulin on their cell surface which acts as antigenic receptors. Class I and II MHC antigens are also expressed; the latter is needed for Th/B cell interaction. The mature B cells leave the bone marrow and travel to lymph nodes, spleen and lymphatic tissues in other organs. The generation of millions of different B cell clones, their initial maturation and migration from the bone marrow to the spleen, are all antigen independent events. When specific B cells meet up with specific antigen they are activated. B cell activation and differentiation requires Th activity and as a consequence of this process, B cells differentiate into plasma cells which produce antibody and small long-lived memory cells. The specific antigen, after binding to the surface receptor, is internalized and partially digested. The antigen fragments are then recycled to the B cell surface and expressed in association with Class II MHC molecules (16 in Cooper). The Th cell requires interaction with both specific antigen and the Class II MHC molecules before lymphokines are secreted that activate B cells. B cells are thus induced to divide and undergo terminal differentiation into plasma cells that can produce thousands of antibody molecules per second, before their death a day or so later. The unstimulated B cells will also demise within days of reaching the spleen.

The immune response has been capsulized by Nossal into six key words:

- encounter
- recognition
- activation
- deployment
- discrimination
- regulation.

Encounter between antigen and immune competent lymphocytes is theorized as follows: the accessory cells capture antigen by breaking down micro-organisms or by absorption of circulating antigen. These fragments or epitopes are presented on the cell surface where they can be retained for long periods. Schwartz has shown that some accessory cells have got immune activation (Ia) glycoproteins on their cell surface which are important in the activation of T cells. A given antigen is thus presented to circulating T cells and B cells with appropriate specific receptors. The PB recognition phase between antigen and immune competent cells is a difficult concept which fundamentally differs from all biological recognition between macromolecules. For example enzyme/substrate or hormone/receptor recognition requires a precise "fit" or high-affinity binding. The initial antibody/antigen "fit" is usually poor and of low affinity. It is the subsequent complex process of specific activation which leads to higher affinity and more specific recognition (binding). Both B and T cells undergo gene translocations that ultimately give rise to unique antigen receptor specificity. There is a difference between the T cell receptor and the B cell antigen receptor. The T cell receptor usually recognizes the antigen or epitope in a loose association with Class II self-antigens, the so-called restriction elements or glycoproteins. The B cell recognizes a different part of the antigen.

Once the T and B cells have recognized the antigen, activation takes place. B cell activation requires collaboration between presented antigen on the APC and helper T-cells. The Th-cells (OKT4) require class II antigens and antigen on the APC for activation. Antigen antigen-receptor recognition stimulates the release of interleukin 1 (IL-1) by the accessory cell (macrophage). The activated Th cell in turn secretes a family of lymphokines, in particular IL-2. B cells also require antigen presented by the APC; however, such B cells require Th cells for further differentiation. Thus the activated B cells will differentiate into plasma cells and produce specific antibody, initially IgM then IgG and IgA. Lymphokines produced by Th can induce the B cell to differentiate into plasma cells that will produce IgG or IgA or IgE instead of IgM. Both stimulated T and B cells ultimately give rise to subpopulations of small recirculating long-living memory cells with specific receptors of high affinity for specific antigen. Cytotoxic T cells (Tc or OKT8) require antigen on APC together with Class I MHC antigen on the Th cells, to become activated. How suppressor T cells (Ts) become activated is not clear.

Deployment of the immune message takes place via a variety of lymphokines secreted by Th cells, granulocytes and macrophages. Via gamma Interferon, eosinophils and mastcells are stimulated and complemented, and other non-specific inflammatory proteins are mobilized.

There are several mechanisms whereby the IS is able to recognize self as "self". This is collectively known as "immunological tolerance". Burnet's clonal deletion theory is an

oversimplification of this mechanism. T and B cells in early neonatal life meeting up with antigen are regulated down or receive a negative signal causing clonal anergy. Suppressor T cells may play a role in this immunological tolerance. Further regulation of the immune response may be due to insufficient antigen to cause T cell activity, immune complexes inhibiting lymphocytes and/or anti-idiotype antibodies.

Graft Rejection

Transplant rejection serves as an example to illustrate the above mechanisms. Two of the mechanisms by which acute graft rejection is initiated are:

- by circulating donor antigen processed by recipient APC cells and presented to Th cells. These APC cells process recipient Class II antigens needed for stimulation of Th cells.

- Donor AP cells express both Classes I and II antigens, and if these differ from the recipient, this can stimulate the IS without the necessity of complexing with Class 2 self-antigens.

Thus both donor and recipient AP cells can "switch on" the immune response. The interaction between Th cells and the APC cells (donor or recipient) causes the APC cells to liberate IL1. The three signals, IL1, donor antigen and recipient Class II antigens stimulate the Th cells via the T3 Ti receptor and via a calcium mediated signal that causes gene alteration which activates the interleukin cascade. The activated Th cell will proliferate and secrete IL2 and B cell growth factor (BCGF or IL 4) and B cell differentiation factor (BCDF or IL 5). The Th cell-derived IL-2 will stimulate cytotoxic T cells to differentiate and proliferate and thus mount the cellular attack on the graft. At the same time other lymphokines such as gamma-interferon is liberated by the Th cell causing macrophages to migrate to the area and to become activated producing a variety of factors such as leukotrienes, thromboxane, platelet activating factor, tumour necrosis factor, oxygen radicals and proteolytic enzymes which further damage the graft. Th cell liberated colony stimulating factor (CSF) will cause other non-specific cells like granulocytes and natural killer cells (NK) to migrate to the area; this will cause an intense inflammatory response. The cytotoxic T cells will damage the graft by the production of perforin, lymphocytotoxins and macrophage activating factors. The above series of events amplifies the immune response so that more antigen is processed and more cells are activated and drawn into the area, culminating in graft destruction.

Cadaver Kidney Procurement

The acquisition of suitable cadaver donors has become a major problem to transplantation centers the world over. This shortage of suitable organ supply is the limiting step in cardiac, liver and kidney transplantation and unfortunately the gap between supply and demand is rapidly growing. The problem in South Africa is even more acute, as we rely on cadavers for more than 80% of our kidney supply. Furthermore, there seems to be apathy with regard to the primary care physician and nurses becoming involved in the desperate struggle of meeting the demand for suitable kidneys and organs. Most of them are reluctant to become involved or forget to inquire about organ donation. Many suitable donors are thus lost, and it has been estimated that only 10% of potential donors are utilized. Although various

systems, such as the drivers licence endorsement, the living will and the carrying of donor cards are in use in the Western World, this does not stimulate the willingness of the attending physicians to become involved. Thus doctors' and nurses' apathy or forgetfulness leads to a lack of opportunity for the family or the next of kin to exercise their right to donate organs. Obviously preoccupied by their own loss, they will seldom think to volunteer, unless repeatedly informed of such options. The participation of the primary care medical, nursing and paramedical personnel attending victims with total irreversible brain destruction is central and critical to facilitate an adequate organ procurement program, so much so that Barry et al were able to increase the number of kidneys obtained by recruiting community retrieval teams.

The results with cadaver renal transplantation, although not as good as with related living transplantations, have recently improved dramatically. This is in part due to the routine use of pre-operative blood transfusions, better matching, and HLA-DR locus matching. Furthermore, the use of low-dose steroids, Cyclosporine and more recently total lymphoid irradiation (TLI) have improved graft as well as patient survival. As such, transplantation has become the modality of choice in the treatment of most cases of chronic end-stage renal failure. As a result of this, the demand for kidneys and other organs now far outstrips the supply. This has led to commercialization of transplantation in some of the European centres. We deplore the buying and selling of human organs and agree with the guidelines as put forward by the Council of the Transplantation Society which are summarized in table 13.1.

Table 13.1. Guidelines for Cadaver Organs

--> The best possible use to be made of organs.
--> Most appropriate recipient to be selected.
--> Organs should never be wasted.
--> Recipients not chosen on basis of politics, payment, gifts or favourism.
--> Transplant doctor not to adverttise regionally, nationally or internationally.

The following report outlines our experience with cadaver kidney procurement, with reference to removal, storage of kidneys and the diagnosis of brain stem death (BSD).

Who is a suitable donor?

Any patient who sustains brain stem death (BSD), whether from direct trauma to the brain, cerebro-vascular accident, intracranial tumour or from severe anoxia following a cardiorespiratory arrest, is a potential donro. Ideally the potential donor should be adequately resuscitated, on a ventilator, well perfused and passing good volumes of urine. Normal haemodynamics and blood biochemistry are ideal but not essential. The age of these patients arbitrarily should be between 6 months and 60 years, but younger and older patients should be considered. A definite history or diagnosis of extracranial cancer, systemic sepsis, severe hypertension and renal disease will all militate against a given potentialdonor being used. It is important that if uncertainty exists with regard to the above diagnosis, cultures and/or histology should be obtained at the time of donor take, in theatre. The evaluation of these results can be made after the organs have been removed and preserved.

What is brain stem death?

The concept of brain death is not a new one and in fact over 30 sets of criteria have been proposed for the diagnosis of brain death. These criteria were designed to distinguish those patients with severe coma that may recover partially or fully from those with no such possibility. Irreversible damage to the brain stem is accepted as brain death as is total destruction of the brain and brainstem. Damage to the higher centres (cortical mantle) alone is as yet not accepted as brain death, as these cases may have spontaneous respiration andintact brainstem reflexes. In some cases of BSD the spinal cord can be totally normal and retain or regain spinal reflexes.

How do we diagnose brain stem death?

There are three essential steps to making the diagnosis of BSD:

- certain preconditions must be obtained
- reversible causes of apnoeic coma must be excluded
- tests must be carried out to confirm brain-stem areflexia.

Preconditions and Exclusions

The two preconditions that must be met are:

--> the patient must be in apnoeic coma, unresponsive to all stimuli and on mechanical ventilatory support and
--> the cause of the coma must be known.

Severe head injury, cardiorespiratory arrest, cerebrovascular accident, drowning, strangulation and suffocation are all acceptable causes of irreversible coma. Drugs, alcohol, hypothermia, electrocution (struck by lightning), metabolic and endocrine causes are not unconditionally acceptable. However, some of these may well ultimately lead to irreversible damage. A potential donor should not be tested for BSD until all the preconditions have been satisfied. Trauma, intracranial bleeding and drowning can be tested within a few hours as the cause is obvious. On the other hand drugs, endocrine and/or metabolic causes may need longer periods of observation before testing brainstem reflexes. The timing before testing for BSD is the time it takes to establish an unequivocal diagnosis of irreversible coma. To this end an unhurried approach is the best precaution against premature suspicion of BSD. It is the responsibility of the primary care physician to decide whether longer periods of observation are necessary.

Tests to confirm BSD

Only once the cause of apnoeic coma has been established as irreversible, and the patient is adequately resuscitated and not hypothermic (temp > 35 °C), can the testing of his brainstem start.

Even at this stage the examiner should remain alert to certain signs which may be an indication that he is not dealing with BSD. An abnormal posture (decorticate or decerebrate),

trismus, focal or generalized seizures and the presence of an oculocephalic reflex (doll's-eye movement), should indicate that the brainstem is intact. The following reflexes should be tested:

--> The oculocephalic reflex - this is done by rotating the head slowly through 180° and observing the eyes. In the cadaver the eyes move with the head; if the brainstem is intact the eyes will be out of phase or lag for a short while, and deviate away from the side to which the head is being rotated. Both eyes usually move and must be examined.

--> The pupillary reflex to light - there should be no pupillary response of any nature to a very bright light shone in the eyes. This test should preferably be done in a darkened room. Beware of eye drops and/or drugs that can affect the pupils.

--> The corneal reflex - stimulation of both corneas, with a cotton bud rather than with a wisp of cotton, should produce no observable response, such as blinking or other movements.

--> Painful stimuli in the head and neck region should not produce a response.

--> Neither should there be any gag reflex on pharyngeal or tracheal stimulation.

--> No vestibulo-ocular reflexes on stimulating a clear external auditory canal with saline at 4 °C should be elicited. The test is done by irrigating the tympanic membrane with 20 to 50 mL of cold water. Both sides should be tested and a wax-free external meatus is essential. It should be noted that if a large tympanic perforation is present in the face of an intact brainstem, a fall in blood pressure or a bradycardia may occur.

By using these few tests the brainstem can be thoroughly evaluated and a firm diagnosis made. Testing of the brainstem reflexes is a simple procedure and is reproduceable; it does not require elaborate equipment or machinery. If done meticulously it will yield unambigous results.

Tests for apnoea

A preoxygenated patient is taken off the ventilator for 10 minutes. During this time oxygen is delivered to the lungs via an intratracheal catheter with a flow of 6 L/min. This ensures that adequate oxygenation takes place and that PCO_2 builds up in order to achieve maximal stimulation by carbon dioxide. The PCO_2 should be > 60 mm Hg (8.0 kPa). Preoxygenation with a mixture of 95% O_2 and 5% CO_2 is helpful in rapidly achieving the correct partial pressure of carbon dioxide. The patient must show no signs of or any effort to breathe, and should there be any attempt at breathing, this is an indication of a functioning brainstem. If no response is detected the diagnosis of BSD can be made and no further tests are necessary. Retesting of the patient after a short time is customary. This can vary from four to twenty four hours. This practice will exclude observer error and confirm the persistence of findings. If, however, the cause of coma (head injury, gunshot) is quite clear, then retesting will serve no purpose. The criteria are summarized in table 13.2.

Table 13.2. Diagnosis of Brain Death

--> **Respiration**

Is the $PaCO_2$ more than 45 mm Hg?

Is there spontaneous ventilation after 10 min?

--> **Brain stem reflexes**

Do pupils react to light?

Is there nystagmus after ice water in either ear?

Any response stimulating the corneas?

Doll's eyes movement or other in head and neck?

Gag or tracheal reflex?

--> **Body temperature**

Is the core temperature over 35 °C.

--> **Drugs**

Any drugs that may affect respiration or CNS?

--> **Any metabolic or endocrine factors?**

If in the examiner's opinion there is no doubt

--> about the primary diagnosis

--> there being no reversible causes or factors

and

--> the adequacy of the clinical examination, he can declare the patient dead.

Furthermore, it is important to inform the family and nursing staff that by stopping therapy or disconnecting the patient, the doctor is not allowing the patient to die, but is in fact ceasing to treat someone who is already dead. These facts and the deteriorating condition of the patient must be frequently communicated to the family. The ultimate objective as well as the concept of BSD must be clearly and frequently explained to them. Once the diagnosis has been made and the family understands the futility of further treatment, only then can the possibility of organ donation be raised. This is obviously a delicate matter and must be handled tactfully and with understanding. It cannot be delegated to an inexperienced person.

The reliability of the diagnosis of BSD is clearly established in the literature and its discussion beyond the scope of this publication.

Removal of Kidneys

Consents Required

The following legal documentation is required before organs can be removed from a BSD donor:

- Written consent from the next of kin.

- Certification of BSD by two registered doctors, one of whom must have been qualified for longer than five years. These doctors must not be members of the transplant team.

- Telephone consent is obtained from the government pathologist.

Although these documents are prescriptive, it is also important that the hospital superintendent be informed. Only once these documents become available may organs be removed.

Donor Pretreatment

Adequate hydration with balanced saline solutions is of prime importance. Fluid losses, specifically water loss, can at times present problems. If diabetes insipidus develops, the fluid should be changed to half strength saline or 5% dextrose water. Under these conditions pitressin snuff has proved to be helpful. In controlling the blood pressure it may become necessary to use vaso-active drugs such as dopamine, isoproterenol or metraminol. The use of bolus injection of diluted metraminaol have also been helpful in controlling falling agonal blood pressures.

The Donor Operation

Standard surgical preparation and toweling procedures are used as for any laparotomy. The donor receives full ventilation and is positioned on his back. Muscle relaxants are given to overcome the agonal spasm that at times can be very irksome. Heparin 10000 units is given with the muscle relaxant. A slow drip of 50 mg of phenoxybenzamine in 150 mL of saline is started; this must have run in by the time the aorta is cross-clamped. With this drug maximal vasodilatation of the kidneys is achieved. Other drugs like adenosine, magnesium-ATP, mannitol, xanthine oxidase inhibitors and oxygen radical scavengers have been proposed by some to improve the quality of the kidneys.

Incision

A longitudinal midline incision is made from the xiphisternum to the pubis. If any difficulty is encountered in getting proper exposure, lateral incisions can be made. Good light and strong assistants are essential.

The Operation

--> By mobilising the caecum and the ascending colon, extraperitoneal exposure of the common iliac vessels and the ureters can be achieved. The right and left common iliac arteries are ligated distally.

--> The right common iliac artery is now securely cannulated by tying a sterile drip set (AFC0917) into the vessel with 0 silk. This is connected to a vacolitre of cold Ringer's lactate (4 °C).

--> The ascending colon mobilisation is now extended up towards the liver. The first assistant holds the medially flopped caecum and small bowel out of the surgeon's way. This exposes the vena cava, the renal veins and the aorta, and the right kidney and its ureter.

--> The structures in the porta hepatis are double clamped and transsected. Thie manoeuvre involves passing the left index finger through the foramen of Winslow and encircling these structures. The clamps are applied with the right hand. The lower clamp, together with the mass containing the pancreas, colon and the small bowel, is retracted by the first assistant towards the midline. At the same time the second assistant controls the upper clamp.

--> The retroperitoneal exposure is now taken across the vena cava to the crus of the diaphragm. This is where the aorta is exposed by cutting into the crus. A haemostat is used to break through the tough tissues behind the aorta. Thereafter the right index finger controls the aorta prior to applying cross clamps with the left hand. The aorta is now transsected and cold ischaemic time begins. The cold perfusion is started through the catheter in the common iliac artery.

--> Next the inferior mesenteric artery is isolated, ligated and transsected. The superior mesenteric artery is now exposed by sharp dissection and firm upward retraction of the pancreas by placing the left index finger between the pancreas and the aorta. This vessel is also ligated and cut. The same procedure is used to deal with the coeliac trunk. Once these structures have been transsected the retroperitoneal area opens like a book.

--> The lower vena cava is encircled and ligated, following this the suprarenal vena cava is clamped and cut. By making an inferior side hole the blood and cold perfusate coming from the kidneys is allowed to escape.

--> Both kidneys are now mobilised by dissection laterally and superiorly. They are flopped medially and held by the assistant.

--> The right index finger is placed behind the cut aorta and tractio downwards and forwards is applied to the aorta and the vena cava clamp. The block of tissue containing the aorta, the vena cava and the kidneys is freed by cutting the crus of the diaphragm and the lumbar arteries as they come off posteriorly. The lower extent of the block is freed by transsecting the ureters and the common iliac vessels where they cross the pelvic brim. Care must be taken not to cut the perfusion catheter, but to incorporate it in the block. This block is now flopped onto the thighs of the donor and dissection of the kidneys can begin.

Dissection of the Kidneys

A variety of methods have been described for the removal of the kidneys and/or other organs, but basically only two methods apply, depending on the method of storage that will be used. Usually is simple cold storage is to be used, the kidneys are removed from the aorta and vena cava, and placed in separate sterile plastic bags and in melting ice. Should machine storage be the method, then the aorta, vena cava and kidneys must not be separated. We prefer tha latter technique as it can be used for both storage methods. The kidney block is flopped on to the thighs of the donor so that the posterior aspect of the block faces upward. The aorta is cleaned from its bifurcation by upward sharp dissection, always remaining close to the midline, up to and past the origins of the renal arteries. During this process the posterior lumbar arteries are ligated and cut, but care must be taken not to damage accessory renal polar arteries. About 1 cm of the origins of the renal arteries is cleared. The specimen is rolled so that the block faces right side upwards. The vena cava and renal veins are then carefully freed from the underlying tissues. Accessory veins can be ligated with impunity. The renal veins are separated by a longitudinal anterior and posterior splitting of the vena cava, each vein flopped over to its own kidney. The next step is to clear the anterior surface of the aorta from its bifurcation to above the renal arteries. The inferior and superior mesenteric arteries and the coeliac trunk are ligated and divided closer to the aorta. The anterior aspect of the renal arteries is also cleared for about 1 cm. No dissection should be done in the hilar region! The ureters are then freed with a generous sleeve of fat. The adrenals are removed from the specimen and the left adrenal vein tied. Excessive perinephric fat is also removed. The aorta with attached kidneys, renal veins and ureters is placed into a plastic bag or can be attached to the pulsatile machine for perfusion. The kidneys can also be separated at this tage and placed in plastic bags for transport in melting ice.

Kidney Preservation

At present kidney preservation in clinical transplantation is achieved by either machine perfusion or simple flushing of the kidneys with special solution. The latter method using Eurocollins solution has been shown by Squifflet and others, as well as in our own experience, to be a safe and inexpensive method to store kidneys for up to 36 hours. For short cold storage periods (less than 24 hours to 36 hours) there is little difference between the two methods. For prolonged storage (36 hours to 48 hours) and where there is warm ischaemic damage in the donor (low blood pressure, cardiac arrest), pulsatile perfusion is superior. This fact is particularly important in recipients who will receive Cyclosporine. Beltzer and Southard report excellent results in prolonged storage with pulsatile preservation, in that they had no primary nonfunctioning kidneys, and a 75% function rate. Kidneys that require less than 2 hours to 3 hours cold storage, as in the related living recipients, can be flushed with either intracellular or extracellular solutions, and will predictably function well. Barry showed an increased incidence of acute tubular necrosis with increasing storage time. He is of the opinion that flushing with ice-cold intracellular electrolyte followed by simple cold storage, is the most economical and practical way of sharing kidneys between transplant centres. The increasing demand for other organs for transplantation calls for multiple organ harvesting and storage. These methods are reported.

Patient Selection

The increasing safety and good results have affected recipient selection criteria. The goals of selection are:

--> To identify in the recipient associated disease or factors that may adversely affect the transplanted kidney and/or recipient.

--> To restrict the small numbers of available kidneys to those recipients who will maximally benefit from the procedure. One should therefore decide whether, in a given patient, dialysis or transplantation will be the most beneficial for the patient.

In the older patients and in those with serious associated medical or surgical problems, dialysis is preferred. It is clear that transplantation will lead to better rehabilitation, improved survival and better quality of life than dialysis, providing that the correct recipients are selected for this treatment. There are risk factors that affect prognosis and outcome, and these should be considered in each individual patient. These are:

--> Recipient older than 55 years to 60 years.

--> Diagnosis of the renal diseases: diabetes mellitus, membranoproliferative glomerulonephritis type 2 (high recurrence rate), IGA nephropathy, FSH, pyelonephritis, analgesic nephropathy and malignant hypertension.

--> Malignancy.

--> Tuberculosis.

--> Hepatitis.

--> Coronary artery disease.

--> Severe peripheral vascular disease.

--> Severe diverticular disease of the large bowel.

Of these, age, vascular disease and malignancy are serious risk factors that may contraindicate transplantation. The patients should be thoroughly assessed with regard to cardiovascular status, cause of renal disease, urological tract (ureters, bladder and urethra), endocrine status, gastrointestinal tract (foregut and hindgut), lungs, liver, gynaecological status, and for systemic disease. Surgical evaluation with regard to peptic ulceration, diverticular disease, pancreatitis, gallbladder disease, gastroesophageal reflux and a baseline screening for malignant disease, should be done. Peptic ulcer disease should be treated prophylactically, either surgically or medically prior to transplantation, depending on the circumstances. Patients with malignant diseases who are "disease free" two years after treatment, can be considered for renal transplantation. Metastatic disease or untreated primary malignant disease is an absolute contraindication. Patients with malignant hypertension, reflux nephropathy and infected kidneys will be nephrectomised prior to or at the time of

transplantation. Splenectomy for hypersplenism is now rarely performed. Once the patient is found to be suitable for transplantation, the immunological workup is done. This would entail the following:

--> ABO blood grouping

--> HLA A; B; C and DR typing

--> preformed antibodies in the recipient sera measured against a panel of lymphocyte donors

--> blood transfusions are given, either donor specific in related recipients, or third party transfusions in cadaver transplant recipients. Usually three units of blood are given over a few weeks.

The recipient immunological reactivity towards a given potential donor is measured on the day of cadaver transplantation by doing:

--> the dye-exclusion serological microplate crossmatching of donor cells with recipient sera

--> a T-cell-directed crossmatching and

--> the lymphocyte-mediated cytotoxicity assay. The latter assay measures the cellular arm of the recipient's immune response against this donor, whereas the first test measures antibodies directed against donor antigens. Target cells in both assays are labeled with Chromium 51. Chromium 51 release in excess of 5-10% is taken as a positive reaction. Positivity in either one or both of these assays will lead to a high-percentage graft failure from rejection.

Surgery

Preoperative Preparation

The selected recipients are admitted 4 hours to 6 hours prior to the operation. A complete and thorough history and physical examination is done by the renal physician. Dialysis or ultrafiltration is done as required. One or two units of blood are prepared for the procedure. Administration of intravenous, broad-spectrum antibiotics as a single bolus is recommended. The patient receives immunosuppressive drugs (Immuran or Cyclosporine) on the way to the theatre. A standard general anaesthetic is given with endotracheal intubation and muscle relaxation. A central intravenous line is inserted in theatre. The patient is positioned on his back and abdomen cleaned from nipples to the mid thighs with surgiscrub (5-10 min) and Hibicol. The bladder is catheterized and filled with 100-150 mL saline plus an antibiotic and the Foley's catheter clamped.

The Operation

It is beyond the scope of this chapter to describe any of the transplantation operations in detail. As kidney transplantation is the commonest of the procedures performed, a few principles will be discussed.

The kidney is transplanted in a heterotopic position. Usually the renal artery is anastomosed to the external iliac artery using a Carrel patch. The renal vein is anastomosed end-to-side to the external iliac vein. There is some degree of urgency in creating the vascular hookup as the kidney rewarms during this procedure. Longer warm times are associated with an increased incidence of acute tubular necrosis. The anaesthesia should ensure good circulating blood volume and bloor pressure in the recipient. A bolus of steroids (250 mg-500 mg Solumedrol) is given intravenously, and the vascular clamps removed from the artery. The venous clamp remains on until it becomes distended by the inflowing blood. The venous clamp is removed after adequate filling and the kidney and vascular anastomoses inspected for bleeding. Haemostasis is now secured and the wound washed out with warm saline. The ureter is inspected and redundant length removed. The ureteric hookup is done by creating a submucosal tunnel by closing the muscle in a single layer over the ureter which has been anastomosed to bladder mucosa. The kidney and three anastomoses are now inspected, the wound washed out and final haemostasis secured. A suction drain is placed laterally and the wound closed in layers using standard surgical technique.

The reconstruction of the urinary tract is somewhat controversial and remains the Achilles' heel of this operation. No single method has proved superior in reconstructing the urinary tract. Whether an internal or external ureteroneocystostomy is used, 7% of these will develop anastomotic complications with an associated graft loss of 20-29% and a 9-16% mortality rate. Alternate methods are ureteroureterostomy or pyeloureterostomy.

Most transplant centres regard pyeloureterostomy as an inferior form of ureteric reconstruction. In theory pyeloureterostomy ensures a viable anastomosis by utilizing the well vascularized donor pelvis, but ureteric fistulae remains the commonest complication of pyeloureterostomy. The major objections to pyeloureterostomy are its alleged high complication rate and the necessity to perform a host nephrectomy. This has been obviated by using fine polypropylene sutures in the form of a "microvascular" anastomosis. Currently the collective complication rate is 6.7% in 464 pyeloureterostomies. Only 3.5% of our pyeloureterostomies developed complications. There was an avoidable underlying problem in each case: iatrogenic injury to the renal pelvis, an undetected stricture of the host ureter, and an anastomotic stricture that developed after ureteroureterostomy. The pyeloureterostomy complications may be avoided by routinely testing the patency of the host ureter and performing a true pyeloureterostomy whenever possible. Uretero-ureterostomy, even with a spatulated oblique anastomosis has a definite risk of stricturing.

Ipsilateral host nephrectomy is a disadvantage of pyeloureterostomy because it unquestionably makes the operation longed and slightly more difficult. Sepsis rates after ureteroneocystostomy and pyeloureterostomy as a whole are equal (6%). It appears therefore that the only disadvantage of pyeloureterostomy is a slightly longer and more difficult operation because of the host nephrectomy. Pyeloureterostomy is of unquestionable value

when the donor ureter is short, damaged or devascularized, and as a secondary procedure when a ureteroneocystostomy is complicated by ureteric necrosis.

Postoperative Care

Following surgery the patient is managed in a specialized unit. Special care should be taken with regard to respiration and fluid status, as the patient is often overloaded intraoperatively, and can recurarize in the immediate postoperative period. Pain control is with intravenous morphine titration 1-3 mg IV/hourly prn. Venous capacitance increases postoepratively and to maintain adequate plasma volume it may be necessary to give boluses (200-300 mL) of plasma or saline. Urinary output is replaced 1 hourly with 1/2 dextrose/saline solution. If the output is 0-150 mL, a 100% is replaced, for 151-300 mL 80%, and more than 300 mL only 50% is replaced. Maintenance is given as 400-500 mL of 10% dextrose water over a 24 hour period. Until the urinary output stabilizes, serum potassium levels are monitored 4-6 hourly. Intravenous lines and the bladder catheter are removed after 48 hours. The suction drain is taken out within 24 hours unless there is persistent drainage. Sutures are removed after 2 weeks. In the first 48 hours, a renal scan and ultrasound studies are done of the transplanted kidney. Severe bleeding, unexplained severe local pain, sudden cessation of urinary output or urinary leakage from the wound will necessitate urgent re-exploration of the patient.

Immunosuppression

Although a variety of different immunosuppressive regimen are employed by different transplant centers, they essentially can be divided into 3 phases:

--> Induction therapy
--> Antirejection therapy
--> Maintenance therapy.

Currently the drugs that are employed are: Cyclosporine (CYA), azathioprine (AZA), prednisolone (pred), antilymphocyte globuline (ALG) and monoclonal antibody (OKT3). Cyclosporine (CYA) interferes with lymphocyte proliferation and activation. Macrophage-liberated Interleukin-1 (IL-1) is blocked and the T-Helper cell (Th) is prevented from liberating IL-2, thus preventing cytotoxic lytphocyte (CTL) proliferation and preventing B-cell help. Graft survival has been significantly increased by the use of CYA. Azathioprine is an imidazole derivative 6-mercaptopurine. It inhibits the synthesis of purine, RNA and DNA, and thereby protein, and the proliferation of lymphocytes. Prednisolone inhibits nucleoside incorporation, DNA and TNA synthesis and the liberation of IL-1 by the macrophage and IL-2 by the Th cells. Macrophage activation is also inhibited. Prednisolone also has an anti-inflammatory action and numerous side effects. Antilymphocyte globulin (ALG) induces a marked lymphopenia and affects all cell lines. Monoclonal antibody, directed at the T3Ti receptor on the T-cell (OKT3), eliminates most of these cells.

Induction Phase

Cyclosporine by virtue of its efficacy as a selective inhibitor, has largely replaced azathioprine. The following regimens are now available:

--> dual therapy (CYA and prednisolone) or

--> triple therapy (CYA, prednisolone and AZA)

--> quadruple therapy (CYA, prednisolone, AZA and ALG). Most centres use a combination of prednisolone and CYA in a dosage of 10 mg/kg/day orally, rapidly reducing to 6 mg/kg daily by about 24 weeks postoperatively.

We use the following regimen:

--> CYA 12 mg/kg per os is given 1-2 hours prior to anaesthetic induction, and 250 mg of prednisolone IVI intraoperatively just prior to release of vascular clamps. Thereafter CYA is given orally 12 mg/kg daily in two divided doses for three days, decreasing to 10 mg/kg daily in two doses to the fourteenth postoperative day. From day 14 CYA is given as a single daily oral dose of 10 mg/kg. The dosage is decreased every second week until a dose of 6 mg/kg is achieved. This reducing scale takes 3-4 months. CYA levels are monitored 3-4 times weekly, and maintained at less than 200 nanog/mL using serum by the RIA method. Prednisolone 50 mg IVI is given twice daily for the first day, 50 mg IVI day 2, 40 mg orally for 3 days, 30 mg daily for 3 days, 25 mg for 3 days and then 20 mg daily for 1 month, 17.5 mg daily until the 3rd month, 15 mg daily from the 4th to the 6th month and then 12.5 mg daily up to the 9th month. Thereafter 10 mg daily is given up to 2 years, after which 7.5 mg is given daily.

This tapering off depends on the patient's renal function and tolerance of the decreasing dose. At 3 months a decision is taken based on renal function, rejection episodes and previous graft outcome to either:

--> maintain on the above regimen or

--> to swop to AZA plus prednisolone or

--> to swop to triple therapy. The change to the AZA and prednisolone combination is started by adding AZA 2.5 mg/kg for the first dose and then 2 mg/kg/day thereafter. Prednisolone is increased to 30 mg/day for 4 days and the CYA is tapered at a rate of 1.5 mg/kg/week until the patient is carefully monitored at least twice weekly for signs of deteriorating renal function. The prednisolone is then decreased by 5 mg/day at weekly intervals until the prechange level is reached. The change to triple therapy also depends on the renal function and the previous transplant history. Again AZA is added at a 2.5 mg/kg initial dose and then 1.25-1.5 mg/kg/day maintenance dose. The CYA dose is decreased by 1-2 mg/kg/day at weekly intervals until a dose of 3 mg/kg/day is reached. Thereafter prednisolone is decreased by 2.5 mg/day at monthly intervals until the 10 mg/day level is achieved. During this period the patient should be seen regularly.

Maintenance Phase

This is the long-term therapy on which the patient will remain and can be either:

--> dual therapy (CYA + pred) or a swop to AZA and prednisolone, usually at 3-4 months, or

--> triple therapy (CYA + pred + AZA), or

--> monotherapy, CYA alone.

Antirejection Therapy

During episodes of rejection a bolus dose of 250 mg of methylprednisolone is given IVI for 3 days, thereafter tailing off with oral doses of 100 mg, 80 mg, 60 mg, 40 mg, 30 mg for 1 week, and then down to the previous maintenance dose. Recently OKT3 has become available, and this therapy can be used in cases of refractory rejection episodes. Many centres would use OKT3 as their first line of antirejection treatment. Conventionally a course of OKT3 consists of 5 mg per day given as a slow IVI infusion for 10 days to 14 days. The efficacy of this drug is excellent, but it is very expensive.

Total Lymphoid Irradiation

Total lymphoid irradiation (TLI), as used for the treatment of lymphoma, has extraordinary ability to supress T-cell activity. It maintains this T-cell suppression for about 6 months, and is associated with an inability to reject allografts. The worldwide experience with clinical TLI has been rather limited, but 5 groups (Minneapolis, Leuven, Rome, Stanford and Johannesburg) have reported their experience. All groups have used TLI in conjunction with other immunosuppressive drugs. Actuarial graft survival in patients receiving TLI is significantly better than in those that do not. The methods used differ between the various centres. At our unit a mean cumulative dose of irradiation of 884+91 cGy (760 to 1220 cGy) from a 60Co source is given. This dose is fractionated and 60 to 100 cGy twice weekly is given alternatively anteriorly and posteriorly as a wide field. TLI therapy has permitted the use of lower doses of immunosuppressive drugs, with improved function. Patients are usually transplanted 7-10 days following completion of their TLI. If this is not possible, then booster doses are given at intervals of 2-4 weeks. The immunosuppressive regimen post transplant now followed is: CYA 6 mg/kg with induction, and then daily for 1 month, thereafter decreasing by 1 mg/kg down to 3 mg/kg. Further reduction is then based on the individual patient's response, number of rejection episodes, degree of presensitization and other factors. Prednisolone is given at a dose of 20 mg IVI wityh release of clamps and then 20 mg daily for 2 weeks, followed by 17.5 mg daily for 2 weeks, 15 mg for 2 months, 12.5 mg for 3 months and then 10 mg daily. Further reductions will depend on the response of the individual patient.

Complications After Transplantation

Rejection

This is the major cause of graft failure. If the immune injury to vessels, tubules and glomeruli is sufficiently severe, the kidney may never recover any useful function. As a rule one should suspect, diagnose and treat any rejection as soon as possible.

Hyperacute Rejection

This is due to the presence of preformed antibodies directed at the graft. Pretransplant crossmatching, tissue typing and blood grouping is done to detect and prevent this event. Nevertheless, non-HLA antibodies and low levels of pre-existing antibodies may occasionally not be detected, leading to hyperacute rejection. The manifestation of this is initial perfusion followed by rapid deterioration as the kidney becomes ischaemic. The graft loses turgor and

becomes blue or black. Sometimes the kidney will perfuse normally and the changes will only occur later. The patient will becomes systematically ill, with high fever and a "serum sickness" like reaction. Thrombocytopaenia may be noted. Under these cricumstances the graft should be removed. The kidney is enlarged and soft blue-black with macroscopic evidence of haemorrhage. Treatment is of little avail and cannot reverse hyperacute rejection.

Accelerated Rejection

This occurs 2-3 days posttransplant, and is due to the presence of activated, already circulating cytotoxic T-cells and preformed antibodies. This condition should be detected by doing crossmatching and tests for lymphocyte-mediated cytotoxicity (LMC), against the donor. It can be diagnosed clinically by a decrease of urine output on the second or third day after the day of the transplant, systematic symptoms and tenderness over the graft. Confirmation can be sought by doing a renal biopsy, renal scan, intrarenal pressuire measurement or the use of cytology (fine-needle aspirate or urine cytology). There is virtue in treating such patients with bolus intravenous immunosuppression, but it should be limited, as the prognosis is poor.

Acute Rejection

This occurs from 7 to 21 days after transplant. It is due to the development of T-cell and B-cell immunity, against the kidney. Many patients will experience such rejection episodes. It usually responds well to increased immunosuppressive therapy. In most cases graft function will return to normal, but if the rejection episodes are multiple and severe, residual renal damage may occur and the graft may be lost.

Chronic Rejection

This is usually apparent from 3 months on wards. It is due to chronic immunologic activity against the graft. It ius detected clinically by a gradual deterioration in graft function. This can be a very slow insidious process over weeks, months or even years. Renal biopsy will show interstitial fibrosis, endothelial swelling with vascular occlusion, transplant glomerulopathy and glomerular sclerosis. Patients may have hypertension and proteinuria. Increasing immunosuppression rarely helps.

Acute Tubular Necrosis (ATN)

This remains a major problem, and it may be due to a variety of factors, such as donor hypotension, long storage time of the kidney, or instability of the recipient caused by hypotension or dehydration. The major problem is to distinguish ATN from delayed hyperacute rejection or accelerated rejection. Clinically the patient with ATN is rarely completely oliguric (though this can happen) and urine output and graft function is poor from the start. Systemic features like pyrexia or graft tenderness are not present. Isotope scanning unfortunately does not really help, as it is difficult to distinguish rejection from ATN, and moreover, rejection frequently causes ATN. In both instances there will be perfusion, some accumulation and poor excretion of the isotope (although with rejection accumulation is usually poorer). Biopsy and the newer techniques of intragraft pressure monitoring, fine-needle aspiration cytology and urine cytology looking for immunologically active cells, may

help distinguish between the two. Ultrasound may show oedema and swelling with rejection episodes.

Cyclosporine Toxicity

Since the advent of CYA a new dimension has been added to the problem. CYA causes both acute and chronic nephrotoxicity. Acute vasospasm and graft ischemia with a decreased glomerular filtration rate may occur acutely, glomerulosclerosis and intestinal fibrosis may be demonstrated chronically. The only way to differentiate this condition from rejection, is to do intrarenal pressure measurements (normal with CYA toxicity), ultrasound cross sectional measurements of the kidney area (increased with rejection) and the measurement of serum levels of CYA. Urine cytology may also help.

Surgical Complications

Surgical complications arising after transplantation can be divided into: vascular problems, urinary complications, local infections, fluid collections around the graft, endocrine and gastrointestinal problems.

Vascular Complications

The incidence of vascular complications is small compared to rejection and sepsis. Louridas et al reported the incidence of vascular complications in 909 kidney transplants into 773 patients. Their findings were similar to that reported previously, apart from an unusually low incidence of thromboembolic disease. The incidence of pulmonary embolism in this series was 1.1%, with a mortality rate of 40%, which is similar to that reported in the general population. The siting of the kidney, haematoma and lymphocoele formation, all can reduce the venous return of that leg and predispose to an ileofemoral DVT. Steroids may also have a thrombogenic effect. It is not surprising that the time period for a transplant patient to develop thrombotic complications is delayed. Von Kaulla et al have shown that the coagulation profile in the post transplant patient usually corrects itself at 3 weeks, and may even become hypercoagulable. Most patients are up and about within a few days postoperatively, and discharged home by day 14.

The incidence of renal artery thrombosis variues from 0.33% to 2%. Renal artery thrombosis is most probably related to rejection. It is important to exclude a technical cause for the condition in the immediate post-operative period, as it may be correctable at this stage, and for this reason we routinely perform radionuclide scans to assess renal blood flow. Unfortunately, it is often only diagnosed at the time of transplant nephrectomy.

Renal artery stenosis has an incidence of 3% to 12%. Our incidence was 0.33%. This low incidence may be due to the fact that the majority of our anastomoses have been end-to-side between the renal and external iliac artery, with the routine use of a Carrel patch of aorta on the donor artery. Tilney has described 4 types of stenosis.

Type 1 is localised stenosis at the site of anastomosis or else due to local atherosclerosis.

Type 2 is a postanastomotic stenosis involving the donor artery, which is found to be encased in dense scar tissue. The exact cause of this is uncertain, but factors implicated are:

--> a response of the periadventitial arterial tissue to the generalised homograft reaction.

--> arterial injury at the time of donor nephrectomy and perfusion preservation injury.

Type 3 is a diffuse stenosis of multiple secondary and tertiary intrarenal arterioles noted on angiography. They may also have discrete proximal stenoses. This is always associated with chronic rejection.

Type 4 is related to a stenosis of the host vessel proximal to the anastomosis, secondary to atherosclerotic disease. The types of surgical procedures used for correction of the stenosis are vein angioplasty, vein bypass graft, resection with primary anastomosis and percutaneous transluminal angioplasty. Chronic patients present with deteriorating renal function and hypertension.

Anastomotic aneurysms do not occur commonly, and should be repaired surgically. Sepsis is the usual cause. Uncontrolled bleeding following such graft sepsis should be treated by ligation of the external iliac artery. This procedure has been reported in at least 20 patients with no loss of limb, although some patients have required bypass procedures to improve claudication. The external iliac artery might have to be prophylactically ligated in cases of severe sepsis to prevent this complication.

Renal vein thrombosis may be classified as primary, or secondary to an iliac vein thrombosis. The incidence has been reported to be up to 3%. Primary renal thrombosis is difficult to diagnose as its presenting features of deteriorating renal function, proteinuria, haematuria and a congested kidney may all be indicative of rejection as well. If these features are associated with a swollen leg (in the postoperative period), secondary renal vein thrombosis is a possibility, and a venogram should be done to confirm the diagnosis. The cause is still obscure. It has also been reported after ileofemoral vein thrombosis following acute rejection when it is secondary to immune-complexes, and as a result of technical complications of the operation. Kidneys had been salvaged after renal-vein thrombosis when this occurs secondary to ileofemoral thrombosis. The primary type is most probably due to rejection but this still needs to be proved conclusively.

Although cyclosporine has been implicated as a cause of renal allograft thrombosis, this is not a common finding.

Urinary Tract Complications

The overall urological complication rate reported in 8000 ureterneocystomies (5000 internal and 3000 external) is 7%; 29% of the grafts were lost as a consequence thereof, and 16% of the cases died directly because of these complications. It is quite clear that a cafeful harvesting technique, reimplantation of lower pole arteries, and a restriction of ureteric length have improved results. The use of fine polypropylene or polydioxanone have improved results further.

Urinary Fistula

This is not uncommon and may arise from renal, pelvic or ureteric necrosis. The commonest site of urine leakage is at the implantation of the ureter into the bladder. Most urinary fistulae present within 6 weeks of transplantation. Calyceal fistulae follow a segmental renal infarct, usually in grafts with multiple renal arteries, and constitute 5% of all fistulae. Ureteric fistulae are most common and arise from ureteric anastomosis, whether pyeloureterostomy or ureteroneocystostomy. The pathogenesis includes rejection, ureteric devascularization, poor healing and unrecognised ureteric injury. Vesicular fistulae constitute 5-30% of urine leaks, and may arise from either of the two cystostomies performed during an internal ureteroneocystostomy. They are commoner in bladders that have been previously operated upon. These cases present with suprapubic pain, poor renal function, and oliguria. The diagnosis is confirmed by the use of ultrasonography and cystography. Retrograde pyelography is usually of little benefit, since the ureteric orifice is not able to be cannulated. The treatment of these cases is urgent surgical repair of the urinary tract, by either reimplantation, pyeloureterostomy or a Boari flap.

Ureteric Stenosis

This may occur at the lower end of the ureter, and is due to poor blood supply, ureteric rejection, or a technically narrowed anastomosis. Late obstruction has been reported many years after transplantation, and is attributed to fibrosis as a result of chronic ischemia, rejection or trauma. Early obstruction is usually a dramatic event with acute oliguria, and may resemble acute rejection, whereas late obstruction has an insidious presentation which may be indistinguishable from chronic rejection. The diagnosis is made by ultrasonography showing an obstructed system. Percutaneous prograde pyelography with insertion of a pigtail catheter is diagnostic and therapeutic. Once the creatinine values are in the normal range, correction of the urinary tract can be achieved by reimplantation or pyeloureterostomy. Early urinary obstruction is treated as a surgical emergency.

Urinary-Tract Infections

This is the most frequent infection complicating the postoperative period, the incidence varying from 26-60%. Early urinary-tract infections are most likely related to urological surgery and indwelling catheters in the bladder. Posttransplant urinary infection should be treated aggressively. Wound infections are common in patients with urinary tract infections, and usually the same micro-organism will be responsible for both. The postoperative transplant patient who remains on catheter drainage for longer than 5 days, has a greatly increased incidence of urinary tract infection, because of immunosuppression and the azotemic state. Other factors such as vesicoureteric reflux, the female sex, rejection episodes, and a previous diagnosis of chronic pyelonephritis, diabetes mellitus and analgesic nephropathy, may all predispose to an increased incidence of urinary-tract infections. Early recognition and treatment will decrease the likelihood of septicaemia and complications.

Lymphocoeles

Lymphocoeles may occur in 1.2-18.1% of all transplants. Many will lead to a mistaken diagnosis of rejection, peri-nephric collection or urinoma. Symptoms can parallel those of

rejection, and include abdominal swelling, oedema over the graft, ipsilateral leg oedema, graft enlargement, fever of undetermined origin, weight gain, and ileofemoral thrombosis. These symptoms may be accentuated further by urethral obstruction. The formation of lymphocoeles are avoided by careful ligation or clipping of the lymphatic, which cross the external iliac vessels. The treatment of lymphocoeles is either internal or external marsupialization. We favour external marsupialization.

Wound Infections

Sepsis in the transplanted wound is the second major cause of graft loss. The type of anastomosis, the addition of bilateral host nephrectomy, and the cause of renal failure (diabetes, pyelonephritis or analgesic nephropathy) can all influence the sepsis rate. Wound infections can be superficial, involving only the skin and subcutaneous tissue, or it may be deep. Deep wound infections are usually associated with haematomas surrounding the kidney. Such wound sepsis, especially staphylococcal infections, are directly related to the duration of the operation and a lack of aseptic technique. Wound sepsis can also occur secondary to urological complications, haematomas and lymphocoeles. Superficial wound sepsis is usually caused by staphylococcal or streptococcal infections, and heals without complication, whereas deep sepsis is usually caused by gram-negative bacilli, or staphylococcal infections, and graft loss is common. The incidence of wound infections were high, but recent reports record rates of 1-2%. Wound infection rates after renal transplantation should be no higher than any clean surgical operation, ie, less than 1%. Careful aseptic technique, reduced immunosuppression, improved urological techniques and the use of prophylactic preoperative antibiotics, are all important factors in preventing postoperative wound infections. With deep sepsis graft loss occurs in 50-60% and is associated with a high mortality rate (20%).

Malignancies

There is an increased incidence of *de novo* malignancies in renal transplant recipients. In our series the incidence is 7%. Penn has suggested that transplant recipients are 100 times more likely to develop a malignant disease than the aged-matched general population.

Sixty nine percent are skin carcinomas. Squamous carcinoma of the skin account for 69% of such tumours, basal cell carcinoma 27% and malignant melanoma 4%. These tumours metastasize to regional lymph nodes in 24% of cases, and systemically, causing death of the patient, in a further 11%. Visceral and lymphoreticular malignancies accounted for 31% of tumours. There were 3 colorectal carcinoma, 3 bladder carcinomas, 3 cervical carcinomas, 3 Kaposi sarcomas, 2 lung carcinomas, 2 non-Hodgkin luymphomas, 2 anaplastic tumours, and one each of liver, anal verge, ovarian and chronic myeloid leukaemia. The mortality in this group was significantly higher with 63% of patients dying from their tumours. Multiple malignancies are common with 8 patients having 2, and 3 patients having 3 malignancies. The tumours occurred at a mean of 72 months posttransplant, with an increasing prevalence over time, so that fully 1/3 of patients surviving with a functioning graft from more than 17 years have, or have had, a malignancy. The majority of such patients have been treated with azathioprine and prednisolone. Since the advent of cyclosporine some 4.5 years ago, a different spectrum of tumours has been seen. Tumours are occurring earlier, there is an increased incidence of lymphomas and Kaposi sarcoma. However, numbers are still small.

Lymphoreticular tumours account for only 4% of tumours in Johannesburg, whereas they constitute 18% of tumours in the Denver Tumours Registry, and 8% of tumours in Australia.

Hyperparathyroidism

Although all patients with chronic endstage renal disease on maintenance dialysis suffer from hyperparathyroidism to a greater or lesser degree, the prevalence of posttransplant hyperparathyroidism is only 1-4%. Following successful renal transplantation, the hyperparathyroidic state resolves in the majority of patients. In some patients, however, the large hyperplastic glandular mass fails to involute and surgery is necessary. About half of the patients with posttransplant hyperparathyroidism will present early (within five years), whereas the rest will present early (within the first year), whereas the rest will present years later. Indications for surgery are: persistent hypercalcaemia, severe bone disease, increased parathyroid hormone levels, and in some patients, deteriorating renal function. Complications associated with posttransplant hyperparathyroidism are bone disease, skin necrosis, peptic ulceration, malignancies, bladderstones, vascular calcifications and acute pancreatitis. It is noteworthy that 52% of these patients had interstitial renal disease (analgesic nephropathy or pyelonephritis). As a group the posttransplant HPT have an increased mortality rate and a tendency to develop malignancy. Our surgical approach is to remove 3.5 glands. Recurrent and persistent disease was found in 9%.

Peptic-Ulcer Disease

Peptic-ulcer disease occurs in 2.4% to 16% of patients following renal transplantation. The reported frequency of complicating gastroduodenal bleeding varies between 5% and 26%. The death rate from bleeding is high (40%-60%), and most transplant centres employ some kind of prophylaxis to reduce the number of deaths. Peptic ulceration occurred in 5.7% of our patients, with a mortality of 33%. These patients presented with abdominal pain (63%), bleeding (40%), unexplained septicaemia (33%), perforation (20%), or a rejection episode (23%). Recipients with a verified ulcer history or a documented peptic ulcer undergo prophylactic surgery prior to transplantation. Patients with duodenal ulceration will undergo a highly selective vagotomy, those with prepyloric gastric ulceration, an antrectomy and vagotomy, and patients with gastric ulceration, a gastrectomy. Some 5%-15% of transplant recipients develop gastroduodenal bleeding after transplantation.

Acute Pancreatitis

Acute pancreatitis is a devastating complication occurring in 2%-12% of transplant recipients and in patients with chronic renal failure. It poses a formidable threat to the patient it affects, with a high mortality rate. The aetiology of posttransplantation, acute pancreatitis, remains unclear and is probably multifactorial. Immunosuppressive drugs, hyperparathyroidism, viral and bacterial infections, hyperlipidaemia and rejection episodes have all been implicated. Treatment includes intensive fluid replacement, nasogastric suction, and the use of antibiotics. For the less severe oedematous form of acute pancreatitis, this routine treatment should suffice. However, in patients with protracted acute pancreatitis, with the formation of pancreatic abscess and necrosis of the pancreas, surgical intervention, even in the critically ill patient, offers the only hope for survival. The choide of surgical procedures varies between drainage and removal of all infected and necrotic tissues with irrigations of

the cavity, and planned relook laparotomies, and inserting abdominal packs with daily reexplorations.

Perforated Diverticular Disease

Extensive diverticular disease may be a contraindication to transplantation. As with peptic ulceration, these may rupture post-transplant with little warning. Patients with polycystic kidneys seem to be at an increased risk of this complication. There have been 10 such patients in our experience with an 80% mortality. The possibility of prophylactic colectomy for patients with extensive diverticular disease, has been considered. However, because of inadequate data regarding the prevalence of this disease in transplant patients, and in those suffering chronic renal failure, the actual risk of perforation is not known.

Current Results of Kidney Transplantation

Kideny transplantation has become the accepted modality of treatment for most patients with chronic endstage kidney disease. This has happened in less than three decades, in which time maintenance dialysis, improved surgical transplantation techniques and better immunosuppressive drugs, have all become available. In the earlier decades patient mortality and graft rejection were high, as were the complications of transplantation. Mortality rates (at 1 year) of 20%-45% in related and cadaver transplants were reported. Severe uncontrolled systemic infections were the commonest cause of death, and were related to over-zealous use of immunosuppressive drugs. Actuarial one-year graft survival varied from 70% to 80% in related living donors and 45% to 55% in cadaver transplants. Over the last five years there has been a remarkable improvement in patient as well as graft survival. The overall mortality in related living and cadaver transplants is less than 13% and 20% respectively. Banowsky cites the following factors as being responsible:

--> reduced steroid usage
--> fewer rejection episodes
--> decreased frequency of surgical complications
--> the use of perioperative antibiotic prophylaxis to minimise wound infection
--> the use of closed as opposed to open kidney biopsy.

To this should be added:

--> better patient selection
--> preoperative blood transfusions
--> improved immunosuppressive regimens (low-dose steroids, triple therapy)
--> better immunosuppressive drugs (cyclosporin, antilymphocyte globulin)
--> newer modalities of preventing rejection, such as total lymphoid irradiation (TLI).

Currently the one year actuarial graft survival in related living HLA-identical, related living HLA-haplo identical and cadaver transplants on conventional therapy is 95%, 72% and 59% respectively. Patient survival in related living transplants is 93% and in cadaver transplants 78%. Patients receiving cyclosporin therapy have a reported actuarial graft survival at one year in identical, semi-identical, and cadaver donors of 90%-100%, 90% and 78% respectively. Patient survival is obviously better. Myburgh et al reports a graft and patient

survival of 90% and 97% respectively in 32 patients of which 28 were cadaver transplants and 4 semi-identical related living transplants treated with TLI. Diabetes mellitus, retransplants, advances age of recipients and black recipients, have been considered high risk patients for allograft success and patient survival. With the use of cyclosporine there has been an improved graft survival in diabetics, retransplants and in black recipients. Further refinements in total lymphoid irradiation regimens and the advent of newer immunosuppressive drugs and antirejection therapy such as monoclonal antibodies directed against the OKT3 receptor, the IL-2 receptor and other receptors; cyclical peptides other than cyclosporin such as FR900506, may further improve the current results of kidney transplantation. Better selection of patients, better matching and improved monitoring may further improve current results.

Comment

Kidney Transplantation

V Karusseit

The principle discussed in this chapter also apply to transplantation of other organs and tissues. Liver, heart and pancreas transplantation programmes are proliferating. Medical practitioners should be made aware of progress in this field, not only because the patients concerned will be under their care from time to time, but also because awareness of the possibility of organ donation is essential for the success of organ transplantation programmes.

Laws enforcing "required consent" which apply in many states in the USA have greatly assisted in the availability of organs for transplantation. Such laws are not envisaged for South Africa and local transplantation programmes are wholly dependent on the awareness and sympathy of doctors caring for brain-dead subjects.

We differ on very few details from Botha and Margolius in the management of renal transplantation.

It is important to maintain perfusion of the organs in the donor cadaver. This should be accomplished in the first place with large volumes of intravenous fluids. If vasoactive substances are necessary dopamine should be used first because of the beneficial effect on renal circulation. Agents that cause renal vasoconstriction should be used only as a last resort.

An easy way of occluding the aorta during the donor operation is by inflating the balloon of a Foley's catheter introduced into the thoracic aorta via a common iliac artery. We are not at all discouraged by transplantation in diabetics with renal failure. Diabetes mellitus has become a major indication for renal transplantation because so many diabetics now live long enough to require replacement therapy. Especially the blind diabetic is much better off with a transplanted kidney than on dialysis.

We have been satisfied with conservative management of peptic ulceration in the patient awaiting renal transplantation and have not found it necessary to perform prophylactic antiulcer surgery.

The indications for prophylactic native nephrectomy are becoming narrower. We would still perform nephrectomy in the patient with infected kidneys but do not necessarily do so for policystic disease, hypertension or reflux nephropathy. Pathophysiologic mechanisms in the latter are currently undergoing reconsideration.

Cyclosporin A is by far the most effective immunosuppressive agent for maintenance therapy. It would seem that it may make other manoeuvres to improve results such as HLA-typing and pretransplant blood transfusion obsolete. We have suspended our transfusion protocol, especially as some patients become sensitised to donor tissue. On cyclosporin more transplanted kidneys survive, but at the cost of somewhat poorer functioning. What the long-term effect of this nephrotoxicity is, is still uncertain. Because of nephrotoxicity it is important to monitor cyclosporin blood levels. We use FPIA (fluorescent polarising immuno-assay) which is quick and can measure low drug levels.

Because of high cost and concern about nephrotoxicity some units switch from cyclosporin A to azathioprin after 3 months. However, after 5 years use of cyclosporin A, we doubt that this is justified. Kidney and patient survival are probably better on cyclosporin A and it is our policy to continue cyclosporin A as maintenance immunosuppression.

A major problem in the past has been overtreatment of acute rejection causing infectious complications. Previously very high doses of steroids were used. We currently administer 500 mg of methyprednisolone on 3 successive days. Botha and Margolius recommend only 250 mg. The monoclonal antibody OKT3 is still only recommended for steroid-refractory rejection because of high cost, and the development of antimouse antibodies. When human monoclonal antibodies become available, there will be new possibilities.

Total lymphoid irradiation is only used in a few units worldwide at present and cannot be considered to be a practical form of immunosuppression for general application. The promise of creating tolerance with this method in some patients is exciting and should be perused by those units with expertise.