The first successful kidney transplant was performed 25 years ago. Since then in many centers throughout the world, renal transplantation has become the preferred alternative for patients with end-stage renal disease. While many transplant patients (whether they received kidneys from living relatives or cadaveric donors) have enjoyed a very active and productive life, others have been less fortunate and have experienced organ rejection, despite administration of massive amounts of immunosuppressants. These patients have had to suffer troublesome side effects such as sepsis.

The phenomenon of rejection is initiated by the immune system of the body, by which the body protects its integrity against foreign agents or substances. At best, the immune system is partially understood and many aspects remain baffling. This article reviews the multiple facets of rejection and the serious problems encountered by patients whose bodies reject the organ grafts.\textsuperscript{5,6}

**Mechanisms of rejection**

*Transplantation antigens:* The concept that the rejection of foreign tissues is the result of an immune response to cell surface antigens, termed *transplantation antigens*, emerged in the early part of the century from the work of Sir Peter Medawar, P. Gorer, and G. Snell. (Medawar and Snell both won Nobel Prizes for their research on antigens.) Today, we know that the biological uniqueness of an individual is determined at the time of conception, with each chromosome from the parents carrying markers for cell surface antigens.

More than 50 human lymphocyte antigens (HLA) have already been identified. The HLA system consists of four major genetic loci designated HLA-A, B, C and D (Figure 1). These loci are located on chromosome 6. Typing for antigens is generally performed by cytotoxicity testing with anti-sera; thus, these antigens are frequently referred to as being serologically determined (SD). A recently defined system of DR antigen (D-related) can now be determined by serologic technique.\textsuperscript{5,1}

The antigens of the HLA-D loci are determined by the mixed leucocyte reaction and are referred to as I.D antigens (lymphocyte-defined).

Siblings from the same parents can either be two halotype identical, one halotype identical or two halotype distinct. In organ transplantation, the importance of HLA antigens rests in the fact that the highest rate of success is between HLA identical siblings.\textsuperscript{1}

Rejection by the patient of foreign tissues is the major problem blocking the widespread clinical application of organ and tissue transplantation.

*Clinical aspects of the immunologic phenom-
Hyperacute rejection occurs within minutes to hours. The circulation through the graft comes to a standstill as a result of plugging of the capillaries with platelets and polymorphonucleocytes. Eventually, the formation of the thrombin with necrosis of the graft occurs.⁵

Today, scientists and surgeons are aware that hyperacute rejection of the solid organ grafts occurring within minutes to hours of their implantation is basically mediated by humoral factors. Moreover, the specific union of antigen and antibody recruits other mechanisms which are the final mediators in bringing about the damage to the grafted tissue. The complement system triggered into activity by the antigen-antibody complex leads to the production of an agent that causes damage to the cell membrane, producing holes in it and making it leaky. Similarly, the immune complex, formed by the combination of antigens with a specific antibody, brings about the activation of Hageman factor (factor XII), thus triggering the intrinsic pathway of thrombin formation.¹

Histocompatibility matching: The importance of the ABO antigens has been recognized for a quarter of a century in the field of blood transfusion, the most common clinical transplantation. These antigens are "transplanted antigens" and are extremely important in solid organ transplants. A donor recipient, therefore, has to be compatible with regard to ABO antigens. Rhesus antigens, on the other hand, are not important for solid organ transplant.

The most important histocompatibility parameters are the ABO red cell antigens, the direct crossmatch, mixed lymphocytes, culture whenever possible and the degree of HLA antigen matching. The first two parameters are indispensable and the latter two are desirable. In the case of living related kidney donors, ABO compatibility, HLA matching and mixed lymphocyte culture are all performed and are considered essential. The direct crossmatch is always performed prior to carrying out the transplant procedure.⁵

Control of infection

The therapeutic modalities available to suppress the immune mechanisms in a non-specific way are placed under the broad category of immunosuppression. In an attempt to control the rejection process, the following immunosuppressive agents are employed:

Corticosteroids: Glucocorticoids and their synthetic analogs function as "the cortisone of immunosuppressive therapy in transplants." Corticosteroids are catabolic to the lymphoid cell and in given doses will cause lympholysis. They have antiproliferative activity and suppress the multiplication of lymphocytes, thereby checking the numbers of the specifically committed immune cells.
Steroids have several non-specific effects which interfere with the expression of immunity; these may be categorized as non-specific anti-inflammatory effects. The beneficial effects of steroids are a combination of many discrete effects on the immune system. Adverse effects of steroid therapy include susceptibility to infection, sodium retention, Cushing's Syndrome, osteoporosis, skin fragility, hyperglycemia and hypertension.

Azathioprine (Imuran®), an analog of 6-mercaptopurine (6-MP) with less toxicity, is widely used as an immunosuppressive agent in organ transplantation. Interference with nucleic acid synthesis will affect the rapidly proliferated lymphoid cells. In addition, azathioprine may also have a non-specific anti-inflammatory effect by virtue of its effect on neutrophils and macrophages.

Cyclophosphamide (Cytoxan®) is the only radiomimetic agent that has been gainfully employed in clinical and experimental immunosuppression. In renal transplantation, it has been shown to be interchangeable with azathioprine and is preferable when azathioprine liver toxicity is manifested or if the patient develops hepatitis. In leukemia, one of the major indications for bone marrow transplantation today, lower doses of total body irradiation would be required when cyclophosphamide is used.

Antilymphocyte or antithymocyte globulin is well known in reducing the number of immunocompetent cells (small circulating lymphocytes). In clinical renal transplantation, multi-center cooperative trials are still underway to evaluate the effectiveness of antilymphocyte globulin (ATG). Current evaluations reveal it to be an effective immunosuppressive agent in combination with other immunosuppressive drugs and steroids.\(^2\)

**Anesthetic management**

Immunosuppressant drugs such as corticosteroids, azathioprine, cyclophosphamide and antilymphocyte or antithymocyte globulin must be continued on a scheduled basis for all chronic renal failure patients who have had a kidney transplant or are scheduled to have transplantation.

When oral administration is difficult or unreliable, parenteral preparation must be given or the oral dose be administered via nasogastric tube.\(^6\)

Many factors determine the choice of anesthesia, such as repeated exposure to many surgical procedures, shunts, fistulas, grafts, thrombectomy, removal of rejected kidneys, and other surgical procedures for diseases unrelated to renal failure. The following are of primary importance in the choice of anesthesia: the medical status, length of surgical procedure, and the psychological condition of the patient.\(^9\)

**Regional anesthesia:** Spinal or epidural anesthesia is considered safe for kidney transplantation. Spinal and epidural techniques offer good muscle relaxation. Surgical exposure is also improved by bowel constriction secondary to sympathetic blockade. (Patients anesthetized with nitrous oxide may have bowel distension due to nitrous oxide accumulation in the bowel.)\(^16\)

Regional anesthesia has essentially no metabolic effect and will not increase electrolyte imbalance.\(^15\) Regional anesthesia is contraindicated in end-stage renal failure patients who frequently have coagulopathy due to thrombocytopenia associated with the suppressive chemotherapy or platelet dysfunction.\(^15\) Visceral blockade of the afferent impulses prevents arrhythmias because endotracheal intubation is not required and the risk of respiratory infection is reduced. Patients who receive regional anesthesia must be adequately sedated with a tranquilizer of choice.\(^9\) Innovar® (droperidol/fentanyl) has been shown to be effective as adjunct to regional anesthesia.\(^15\)

**General anesthesia:** Hemodialysis has improved the medical status of patients for renal transplantation. Electrolyte imbalance is a possibility following dialysis, therefore, the serum potassium level must be 5 mEq/L or less and hemoglobin not less than 5 gms.\(^9\)

Halothane, enflurane, isoflurane and intravenous narcotics are employed with nitrous oxide when general anesthesia is chosen. Barbiturates are not used intraoperatively because they decrease the effect of corticosteroids.\(^15\) Enflurane liberates inorganic fluoride ions, thus, it is not the first agent of choice. Halothane forms an insignificant amount of fluoride ions and its use is well established in anesthetizing end-stage renal failure patients. Isoflurane appears to be the most ideal of the inhalational agents because it produces only a minute amount of inorganic fluoride ions. Nitrous oxide does not diminish the oxygen carrying capacity of anemic patients.

Inhalation agents are preferred to fixed agents because they are easily eliminated. Fixed agents block the compensatory automatic activity essential to the maintenance of the delicate homeostatic balance in very ill patients. Halothane and regional anesthesia decrease the afterload in renal failure patients with anemia, thereby reducing the myocardial work and in turn reducing the oxygen requirement to the myocardium.\(^15\) The hyperten-
Anesthesia and the immune response: The ability of anesthetic agents and surgery in general to inhibit the immune response is controversial. End-state renal failure patients undergoing surgery may demonstrate the inhibition of the immune response. This may not be due to anesthesia, but could be partly related to the stress of surgery.

Drug interactions occur with volatile anesthetic agents, carcinomatosis, muscle relaxants, mycin antibiotics (tobramycin, gentamycin) and the osmotic diuretic mannitol. Pancuronium bromide and d-Tubocurarine are often administered in the presence of end-state renal failure because hepatic biotransformation and biliary excretion provide an alternate pathway for their elimination.

Reversal of muscle relaxants presents no problems, however, the breakdown products of pancuronium bromide in the anephric patient cause a rebound neuromuscular blockade requiring prolonged intubation. Thus, pancuronium is not considered the ideal muscle relaxant. Immunosuppression medications given to anephric patients have been suspected of depressing cholinesterase synthesis, though the evidence is not convincing.

Succinylcholine used to facilitate tracheal intubation has been reported to cause significant hyperkalemia in the presence of renal failure but subsequent studies have not demonstrated that the potassium increase differs from that seen in normal patients.

Anesthetic techniques: Cadaveric kidney transplantations are emergency surgical procedures. Because of the unpredictable operating time and the psychological condition of the patient, the use of regional anesthesia is often excluded. The potential to transmit microorganisms to the lower respiratory tract exists with tracheal intubation despite the use of surgically clean and sterile equipment. Postoperative pneumonias are common following tracheal intubation. The clinical signs can easily be confused with the early signs of kidney rejection.

The principles of airway management and problems of full stomach and drug interactions are extremely important to this group of patients—just as they are in patients with normal kidney function who require emergency surgical procedures.

Fluid therapy: Intraoperative fluid administration is restricted, thus volumes are given to replace insensible water loss. Patients who have been dialyzed within the last 48 hours frequently have decreased circulating blood volumes, a condition which is often encountered. This is corrected by administering appropriate amounts of normal saline as indicated by blood pressure, pulse and urinary output. Lactated Ringer's solution should be used judiciously as it contains 4mEq of potassium, which tends to accumulate in patients with renal disease. Normal saline solution may be used to replace the estimated volume of sequestrated fluids. Dextrose 5% in water is used to replace water loss. Blood volume expanders are administered to treat hypotension.

Summary
The morbidity of transplantation is considerably decreased and the mortality of cadaver transplants from sepsis has been reduced to 5% or less as the result of excessive immunosuppression therapy and reduced infection. There is uniform agreement that renal transplantation has the best potential for restoring a patient with end-stage renal failure to his normal state of physical, mental, and psycho-social health.

Both regional and general anesthesia have their drawbacks in kidney transplants. However, by combining the practice of safe anesthesia, improved surgical techniques, and better knowledge of the immunosuppressant drugs, there is near perfect control over the possibility of kidney rejection in kidney transplantation between identical twins.

REFERENCES
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