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HANDBOOK of TRANSPLANTATION MANAGEMENT

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CHAPTER THREE 3

The Organ Transplanted Patient--- Immunological Concepts and Immunosuppression

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- II. Modulation of the Immune Response
- III. Maintenance Immunosuppressive Therapy
- IV. Rejection Therapy
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Introduction. The first unsuccessful attempt to transplant a human kidney was done in 1936 by the Russian surgeon Yu. Yu. Voronoy.⁷¹ In the early 1950s several other attempts were made but without long term success.^{21, 26, 38, 39, 57} Finally in 1954 the first successful human kidney transplant was performed with an identical twin donor⁴⁵ confirming that if the problem of immunosuppression could be overcome, renal transplantation was a cure for uremia. Total body irradiation was employed as a means of immunosuppression^{25, 42} but quickly abandoned as a consequence of its prohibitive morbidity and mortality.

Two basic concepts related to organ transplantation of today were not obvious when clinical organ transplantation started in the early 1960s. Based on available data from animal experiments many immunologists advised against clinical organ transplantation at that time. They were:

1. It is possible to suppress the immune response to a foreign organ without suppressing immune responses to microorganisms to an unacceptable degree.
2. It is possible to reverse a transplant directed immune response that has already reached the point of production of effector cells and antibodies.

In order to understand how these goals have been attained, a basic knowledge about the human immune system is mandatory. Obviously it is necessary to interfere with the capacity to evoke immune responses in a selective way and to develop methods to diagnose the presence of such responses. Still, in a situation when a life threatening infection is present, it is often necessary to stop transplant directed immunosuppressive measures to save a patient's life. However, often a catabolic state of such a degree is then present that the discontinuation of the immunosuppressive treatment does not result in immediate rejection of the transplant.

The human immune response system is described in detail in every textbook of basic immunology. (See *Glossary* at the end of this chapter.) The transplant antigens belonging to the MHC (Major Histocompatibility Complex) are the molecules on the cells of the transplanted organ that challenge the immune defense system of the host. The antigens are mainly present on lymphoid cells that leave the graft by the transplant vein or by lymph channels. MHC antigenic structures on the parenchymal and endothelial cells of the transplanted organ are the targets of the resulting (or any preexisting) immune response.

I. The Rejection Process.

The transplant antigens that reach the host are first phagocytosed into macrophages. After processing they are presented to antigen sensitive T and B cells with the help of a messenger substance (lymphokine) called interleukin-1 (IL-1). A burst of mitotic activity ensues in the activated cells and, after maturation, a number of cells able to recognize and destroy cells carrying the challenging antigens are produced. The system is outlined in Fig. 1. Cytotoxic lymphocytes (sometimes referred to as "killer cells") are produced as a result of the T cell (thymus dependent) response to the antigen, and a number of plasma cells capable of producing antibodies specific to the challenging antigen is generated as a consequence of the B cell (bursa dependent) response. The resulting attacks on the target cells are initiated by these cells and antibodies with specificity against the foreign cell surface

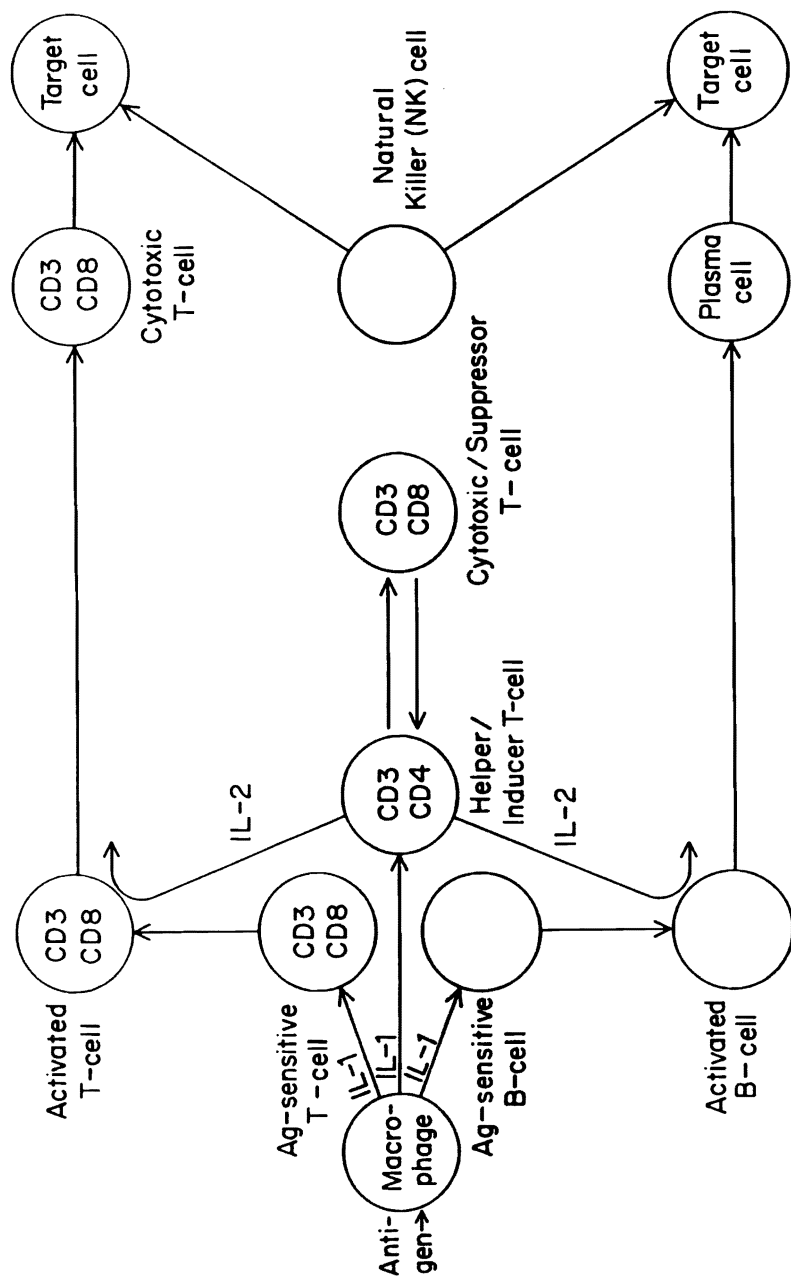


Fig. 1. The human immune response system. CD numbers inside cells designate surface antigens that are present on different subclasses of lymphoid cells.

antigens. However, once the cells begin to suffer they leak intracellular components that attract other host lymphoid cells by nonspecific chemotaxis. This population of "natural killer" (NK) cells participates in the attack without having a preexisting antigen directed specificity. Further damage attracting more cells occurs, and soon the NK cells vastly outnumber the initiating "specific" cells. Thus the system has a built-in fast acting amplifier once a reaction is initiated.

The antibodies produced belong to different immunoglobulin subclasses called IgM, IgG, IgA, IgD and IgE. IgM antibodies are the first to be produced after an antigenic challenge. They are highly agglutinating and cytotoxic together with complement and have the highest molecular weight among the subclasses. Later in the immune response, IgG antibodies are produced, and they then decrease the IgM antibody production by feedback inhibition. IgG antibodies can be cytotoxic with complement or can block (protect) the target cell surface antigenic structures. IgA, IgD and IgE antibodies are not thought to have a primary role in transplant rejection processes. The working units of all antibodies are made up of two identical light (lambda or kappa type) and two heavy protein chains. A structurally different kind of heavy chain exists for each of the five classes of immunoglobulin. Antibody molecules can also be fractionated in such a way that the complement binding (Fc) portions, but not the antigen binding (Fab) parts, are lost. Such antibody fragments retain their ability to bind (and block) the target antigens, but cannot initiate the target cell lysis. As a general rule, although with numerous exceptions, the antibody mediated branch of the immune response is of major importance in immune responses against infectious agents (particularly bacteria) while the cell mediated branch is of primary interest during rejection processes.

Two other cell types are of importance for the development of the immune response to a foreign antigen (Fig. 1). The "helper/inducer" cell and the "suppressor/cytotoxic" cell both belong to the T cell family and influence both the T cell and B cell mediated arms of the immune response. The helper/inducer cells send a signal to the precursors of the cytotoxic T cells and plasma cells in order to allow them to mature. This signal is conveyed by the lymphokine "interleukin-2" (IL-2). The suppressor/cytotoxic cells are thought to interact with the helper/inducer cells and can prevent the maturation of both B and T cells into effector cells. However they cannot be differentiated with certainty from the cytotoxic T cell population by cell surface markers. Nor has it been possible to identify a gene for the development of specific suppressor cell activity with DNA clone techniques. Their "suppressive" effect can be studied with ease *in vitro* but not *in vivo*, and suppressor cells from *in vitro* experiments can even help nude mice to mount an *in vivo* immunoresponse.⁴³ These facts have led several reputable immu-

nologists to doubt that there is a structural difference between suppressor and cytotoxic T cells.¹⁶ This is the reason behind the somewhat contradictory name "suppressor/cytotoxic" cell.

Clinically, hyperacute, acute and chronic rejection processes can be differentiated from each other. The hyperacute rejection may occur after kidney, pancreas, heart and probably also liver transplantation as a consequence of a reaction between preformed complement binding cytotoxic antibodies in the recipient and antigenic structures (mainly situated on the vascular endothelium) in the transplant. The organ is destroyed within minutes. Acute rejection is mainly mediated by killer cells generated in the grafted patient 5 to 15 days after transplantation. Chronic rejection is a slow process with few clinical symptoms. It gradually diminishes the transplant function and is microscopically recognized by a pattern of fibrosis, parenchymal cell death and intimal thickening. Both cellular and antibody mediated immune responses play a role in chronic rejection. Of the three types of rejection, only the second can be treated with a good long term outcome.

II. Modulation of the Immune Response.

Tools that are capable of dealing with subgroups of cells involved in an immune response are obviously highly desirable. The first prerequisite for such tools is that markers enabling us to identify the different subsets of cells have to be at hand. Such markers are now available to some degree, and the different cells can thus be made into targets for manipulations of the immune responses. The nomenclature involved in the surface markers has been far from unified, and attempts are being made to create a logical and universally accepted system. The nomenclature that is used at the present time divides the different T cell subsets into "clusters of differentiation" (CD). The CD numbers given to different T lymphoid cells are shown in Fig. 1. An analogous B cell subset nomenclature is under development.

The system now outlined can be influenced so as to accept a foreign organ transplant in several ways.

1. The immune system of an organ transplant recipient can be taught to consider the foreign transplant antigens as "self" creating a "tolerance".
2. A class of antibodies capable of blocking the transplant antigens rather than attacking them can be produced as the result of the antigenic challenge ("enhancement").
3. Donor selection can be made to ensure that the antigenic determinants specific to the cells of a given individual donating an organ are as similar as possible to the corresponding antigens of the person who receives the transplant.
4. The mitotic activity eventually resulting in the production of immuno-

competent effector cells can be blocked by antimetabolic agents, e.g., by azathioprine [Imuran].

5. The effector cells resulting from an antigenic stimulus can be removed, killed or defunctionalized, e.g., by glucocorticoid.

6. The IL-2 conveyed message from the helper/inducer cell to the activated T cell can be blocked. This results in a suppressive effect directed at the cytotoxic T cells, e.g., by cyclosporine A (CyA) and FK506 treatment.

7. The surface markers that are specific to cells providing a key function in the immunological reaction against the transplant can be destroyed or inactivated by antibodies directed against these markers, e.g., by monoclonal antibodies.

Ad 1 and 2: The concepts of *tolerance* and *enhancement* are of great interest and can be made to work in an impressive way in standardized and inbred animal models. However a treatment failure can result in sensitization and so far no reproducible human treatment strategies have been presented. At one time blood transfusions pretransplantation were thought to induce an enhancement-type host unresponsiveness following organ transplantation.⁵⁰ This effect appears not to exist in cyclosporine/steroid treated patients.³³

Ad 3: This represents the well-known and thoroughly studied concept of *tissue typing*. Its overall importance in the age of CyA and monoclonal antibodies is somewhat controversial^{33,49} but, as it still governs the clinical transplant practice in more centers, it is important for transplant surgeons and physicians to be familiar with the system.

Major Histocompatibility Complex (MHC) antigens are known in all vertebrate species studies. The MHC antigenic structures are often divided into two classes called I and II. The antigens of the former class are present on nearly all nucleated cells, while the antigens of the latter class predominantly exist on the cells that present the transplant antigens to the host immune system, namely, monocytes, macrophages and B lymphocytes. The class I antigens primarily create a cellular immune response while class II antigens mainly stimulate the plasma cell antibody immune sequence. Class I molecules consist of two parts, one larger polypeptide chain and a smaller chain called B₂-microglobulin. Class II molecules consist of two polypeptide chains of about the same size. Both class I and class II molecules resemble immunoglobulins. The human MHC system is called HLA (Human Leucocyte Antigen). All the genes controlling class I and II antigens are situated on different loci on chromosome 6 (except those controlling B₂-microglobulin). Every human being has two alleles on each of the A, B and C loci governing the class I antigens. These genes constitute the basis for serological HLA-A and B tissue typing. Also on chromosome six are the DP, DQ and DR loci which direct the production of class II antigens and constitute the basis

for clinical *DR typing*. In clinical everyday practice the A, B and DR loci are used to define a patient's *tissue type*.

The different human antigens belonging to the HLA-A, B and DR systems have been identified by the collection of a vast number of sera from multiparous women and multitransfused men and women. The persons of interest are those that have developed antibodies against MHC antigens present on white blood cells and other nucleated cells. After absorptions and cross testing between panels of antisera and lymphocytes from blood donors, it has been possible to identify antisera that are monospecific, that is, directed against *one* HLA antigen. Today more than 50 HLA A and B, as well as at least 13 DR antigens, are known. Each individual should have three identifiable antigens on each chromosome for a total of 3-6 HLA A-B and DR designations depending on whether homozygosity on the loci exist or not. An individual's HLA pattern can be determined by the addition of aliquots of viable lymphocytes and complement to trays with multiple micro wells each containing a specific HLA anti-serum. The detection of the pattern is based on the complement dependent cytotoxic reaction which results in a number of wells containing dead cells. The total reactivity then determines a person's tissue type.

As all human A, B, C, DR, DP and DQ genes are linked on the same chromosome, a simple "Mendelian" heritage pattern is present among siblings for each group of haplotypes. Twenty-five percent of siblings are HLA identical to each other. Such individuals constitute excellent organ-recipient pairs. However since such transplant recipients need transplant protective immunosuppression it is obvious that some genes not residing on chromosome six also control non-HLA histocompatibility antigens.

Although the degree of histoincompatibility does not have major influence on the results of organ transplantation with cyclosporine A treatment in many centers, two recent discoveries have made it clear that MHC antigens are of major physiological and pathophysiological importance.

First, there are clearly associations between certain HLA types and specific diseases.⁶⁷ The correlation is most obvious between HLA type B 27 and ankylosing spondylitis, but several other associations have been discovered. They mainly involve diseases where autoimmune processes have been considered. That is, for instance, type I diabetes mellitus, rheumatoid arthritis, Reiters disease and SLE.

Second, it has been shown in mice and more recently in man that virtually all T cell mediated immune reactions are regulated by MHC gene products (so called "MHC restriction").⁵⁶ Thus an immunocompetent cell, with its specificity directed against a certain microorganism, can only attack the foreign antigens if those are in close contact with Class I MHC structures of the same

kind as the attacking cell. This means that the combination of "self MHC + foreign antigen" is recognized. The validity of the principle can be demonstrated in vitro where virus particles having infected a monolayer of human cells only can be attacked by lymphoid cells sensitized to the appropriate viral antigens if the lymphoid and monolayer cells have class I MHC determinants in common.

Pretransplant crossmatch. The pretransplant crossmatch is of undisputed and paramount importance in the efforts to reduce the incidence of hyperacute rejection after kidney and heart transplantation. It is of less significance when liver transplantation is performed. The crossmatch is done with fresh serum from the intended recipient which is mixed with complement and donor lymphoid cells isolated from blood, spleen or lymph nodes. In multitransfused patients peripheral blood might not contain enough representative lymphoid cells. Also if the donor patient has received steroid treatment, this induces lymphocytopenia in peripheral blood. Splenic cell preparations are often contaminated by neutrophils and macrophages to the extent as to make the reading of any reactions more difficult. A relatively pure preparation of B and T cells can be prepared from lymph nodes.

If a direct cytotoxic effect is recorded, usually by a vital staining technique, the crossmatch is "positive" due to the presence of antibodies that are capable of destroying the transplant. Such antibodies in the prospective recipient are indicative of a high likelihood of a hyperacute antibody-mediated rejection within minutes after revascularization. The crossmatch should be carried out with recipient serum added to different subclasses of the donor lymphoid cell population and at different temperatures. Thus recipient serum is usually tested against donor B cells, T cells and monocytes. B and T cell crossmatches are carried out at room temperature and at 30°C. T cell crossmatch activity is also checked at +4°C. If a T cell cytotoxic reaction takes place at any of these temperatures, the crossmatch is reported as "positive". It is generally accepted that a positive T cell crossmatch predicts a substantial risk for a hyperacute rejection at least after kidney, heart and pancreas transplantation. An isolated positive B cell crossmatch has been reported by some to predict a favorable outcome of the planned transplantation. Others have found that preexisting B cell mediated immunity predicts a transplant course with frequent rejections. The monocytes are thought to share antigens with endothelial cells. A positive monocyte crossmatch has been reported to predict a risk for an acute antibody mediated attack directed at the graft vasculature. A full crossmatch test takes about six hours to perform.

The number of HLA specificities among the preexisting antibodies can be tested against a panel of lymphocytes from blood donors at routine intervals before transplantation. A *panel reactive antibody (PRA)* percentage

figure is thus established. A low number predicts a good chance to obtain a negative crossmatch when an organ is offered. The uremic patients with *high PRA* percentages will thus have to wait longer for their kidneys as compared to those with *low PRA*s. In all kidney procurement areas, sera from patients with high PRA's are collected on "high reactor trays". Lymphoid cells from organ donors and complement are added to these trays before kidney recipients are selected. A negative reaction, i.e., lack of donor cell killing, then constitutes priority to one of the kidneys at hand.

Blood groups. Blood group identical transplantation is sought even if organs can be transplanted according to the standard compatibility rules for red cell transfusion. If an uremic patient with a high PRA percentage has a negative crossmatch with a blood group nonidentical but compatible kidney, the patient will be offered this organ. Obviously in the long-run, this will have the consequence that a pool of uremic nontransplanted O patients will accumulate. At the same time, all AB kidneys cannot be placed. The use of A₂ kidneys in O patients has been proposed as a partial solution to this problem. Persons of blood type A can be subdivided into A₁ (approximately 80%), and A₂ (approximately 20%). The A₂ antigen is considered to be so weak as to allow a blood type incompatible transplantation. A substantial patient material showing promising results was published,⁹ but after further clinical studies the procedure is generally felt to create an increased risk for acute and hyperacute rejection processes. In liver transplantation, blood type nonidentical and even incompatible combinations are possible in emergency situations. Hyperacute rejections generally do not occur; however, a price in decreased statistical graft survival has to be paid.

Ad 4-7: The mode of action of most immunosuppressive agents used today falls under these categories. They, therefore, represent the current standard immunosuppressive therapy.

The major immunosuppressive agents currently employed by us for long term maintenance therapy in solid organ transplantation are corticosteroids, azathioprine, cyclosporine, cyclophosphamide and the new (still experimental) drugs FK506 and RS61443. Corticosteroids, OKT3 antibodies and ALG/ATG are the most commonly used agents in the therapy of rejection processes. The new drugs FK506 and RS61443 may also have a role in rejection treatment.

III. Maintenance Immunosuppressive Therapy.

A. Corticosteroids. Adrenocortical steroids were the first pharmacologic agents tried for immunosuppression on rodents in the early 1950s.^{7,44} Despite extensive investigation, the precise mechanism of the immunosuppressive effects of corticosteroids has not yet been elucidated.^{2,15,19,20,66} What

is known is that these compounds penetrate lymphocyte cellular membranes. Corticosteroids are believed to act intracellularly to reduce production of both interleukin-1 from antigen presenting cells and interleukin-2 from activated lymphocytes.

There are four major corticosteroid compounds which are used clinically: hydrocortisone, prednisone, prednisolone and methylprednisolone (see Table 1). The side effects of each of these steroid compounds are related to the dose and duration of therapy. Hydrocortisone is available only for intravenous administration. In addition this compound possesses significant mineralocorticoid activity which must be taken into consideration in clinical immunosuppressive regimens.

Methylprednisolone, prednisolone and prednisone are the three steroid compounds used most frequently for both the prophylaxis and treatment of graft rejection. These drugs have been selected because they possess a high antiinflammatory potency in conjunction with low mineralocorticoid activity.^{3,66} Methylprednisolone, which has the least mineralocorticoid effect, is available for both oral and intravenous administration; however the high cost of the oral form of this steroid has limited its utility for chronic patient immunosuppression though it is used extensively in most standard early post-operative immunosuppressive regimens.

Prednisone is rapidly absorbed from the gastrointestinal tract; however hepatic metabolism to prednisolone is required for biologic activity.¹ The resultant bioavailability of administered prednisone is approximately 80% as a consequence of this required metabolism. In the case of methylprednisolone, the intravenous form possesses a succinate moiety which must be hydrolyzed by the liver for steroid activity. In addition this compound has multiple active metabolites which prolong its biologic half-life. As the oral and intravenous dosages of prednisolone are equivalent and no hepatic metabolism is required for steroid activity, we prefer this steroid agent to both prednisone and methylprednisolone.

Steroid compounds are primarily inactivated by hepatic metabolism through reduction and conjugation and are then excreted in the urine.^{2,3} Thus changes in the status of the patient's hepatic function may markedly influence the inactivation of steroid drugs (and in those cases where hepatic metabolism is required for activity, can alter their bioavailability). In patients with cirrhosis the half-life of steroid compounds may even be doubled.⁴⁰ A similar alteration in steroid metabolism is probably seen during acute hepatic allograft rejection. This should be considered in planning a standardized therapeutic postoperative steroid regimen.

Many commonly employed antiepileptics, including phenytoin and phenobarbital, as well as other clinically important drugs, such as rifampin,

TABLE 1. Corticosteroids Used in Organ Transplantation.

Generic Name	Trade Name	Equivalent Dose	Comments	Half-life (est.)
Hydrocortisone	Solu-cortef	20 mg	Immediately biologically active. Significant mineralocorticoid activity.	90 min
Prednisone	Deltasone	5, 7 mg	Inactive until metabolized to active form, prednisolone, by the liver.	60 min (to prednisolone)
Prednisolone	Deltacortef	5 mg	IV and po forms are approx. equivalent.	200 min
Methylprednisolone (succinate for IV)	Solumedrol	4 mg	The succinate must be split off by the liver for activity; multiple active metabolites.	8 hr

act to induce the hepatic P450 enzyme system. This dramatically shortens the biologic half-life of steroid compounds in patients taking these medications²⁰ resulting in a decreased allograft survival⁷² unless adequate additional steroid is given to compensate for this increased turnover. We have found that a 50% increase in the standard protocol steroid dose to patients receiving prednisolone and azathioprine successfully ameliorates the problems with increased incidence of rejection.

The majority of immunosuppressive protocols begin with a high-dose burst of steroid therapy followed by a stepwise dose reduction. When not used in conjunction with cyclosporine, prednisolone is started at 150-200 mg daily and tapered slowly to reach a dosage of approximately 30 mg daily at one month and 10-20 mg daily at one year. Cyclosporine has been referred to as a steroid sparing drug allowing a more rapid taper of the steroid dosage. This may be due to the stronger immunosuppressive effects of CyA in comparison to azathioprine, or a synergism in their action, but may also reflect an interference between CyA and steroid metabolism.^{36, 52}

Our present prednisolone protocol when used in combination with CyA is summarized in Table 2. In triple drug regimes including azathioprine, we employ even lower steroid doses (Table 3). Daily doses of less than 10 mg are usually not used in the adult patient. In the pediatric recipient, efforts are often made to convert to alternate day therapy in an effort to minimize the side effects. This should not be attempted until the long term maintenance dose has been reached and only then with considerable caution.

1. Side Effects. i. Infections. Incidence is directly related to the steroid dose. A time correlation is seen with rejection therapy. The patients are sensitive not only to normal pathogens but also to opportunistic infections such as *Pneumocystis carinii*, *Listeria monocytogenes*, cytomegalovirus, herpes simplex virus, herpes zoster, *Candida albicans*, *Aspergillus*, *Nocardia asteroides* and reactivation of *Mycobacterium tuberculosis*. Thus do not order rejection therapy lightly.

ii. Poor wound healing. Staples and sutures should be left undisturbed for three weeks.

iii. Muscle weakness. Seen particularly in the knees. It manifests primarily after rejection therapy.

iv. Osteonecrosis. Particularly in hips and knees, it can effect other joints, often bilaterally. It has no clear-cut dose relationship. The symptom is localized pain. Only symptomatic therapy is available. Joint replacement may be required.

v. Cataract. It occurs in less than 10% of patients. Seen as a posterior pool lenticular cataract. It results in variable degree of impaired vision; 10% to 20% of affected patients need cataract surgery.

TABLE 2. Steroid Protocol When Used in Combination with Cyclosporine. (In double drug regimens)

INTRAOPERATIVE:		Hydrocortisone	1 g IV			
POSTOPERATIVE:		Prednisolone	Day 1	50	mg q 6h	=
			Day 2	40	mg q 6h	=
			Day 3	30	mg q 6h	=
			Day 4	20	mg q 6h	=
			Day 5	20	mg q 12h	=
			Day 6	10	mg q 12h	=
			Day 60	15	mg q 24h	=
			Day 180	12.5	mg q 24h	=
			Day 360	10	mg q 24h	=

200 mg/day
160 mg/day
120 mg/day
80 mg/day
40 mg/day
20 mg/day
15 mg/day
12.5 mg/d
10 mg/d

TABLE 3. Steroid Protocol When Used in Combination with Azathioprine. (In triple drug regimens)

INTRAOPERATIVE:		Hydrocortisone	1 g IV			
POSTOPERATIVE:		Prednisolone	Day 1	60	mg q 12h	=
			Day 2	55	mg q 12h	=
			Day 3	50	mg q 12h	=
			Day 4	45	mg q 12h	=
			Day 5	40	mg q 12h	=
			Day 6	35	mg q 12h	=
			Day 7	30	mg q 12h	=
			Day 8	25	mg q 12h	=
			Day 9	20	mg q 12h	=
			Day 10	15	mg q 12h	=
			Day 11	10	mg q 12h	=
			Day 30	15	mg q 24h	=
			Day 60	10	mg q 24h	=

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mg/day

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30
20
15
10

vi. *Steroid diabetes*. The incidence increases with patient age and with a hereditary trait for diabetes mellitus.²⁴ Etiology is obscure, but increased insulin resistance, increased gluconeogenesis and hyperglucagonemia may contribute.⁴¹

vii. *Cushingoid habitus*. It is more frequent in younger patients and is dose related. It usually improves when the daily dose is reduced to 20 mg/day or less.

viii. *Gastrointestinal*. Pancreatitis, gastric and duodenal ulceration and colon perforations are uncommon but feared complications. They are more commonly seen in rejection treated patients. Symptoms of GI perforations are vague. Accurate and early diagnosis requires a high level of suspicion. Signs of peritonitis are uncommon; usually there is only localized tenderness, even in cases with perforation. If not diagnosed and treated early, perforations in transplant patients carry a grave mortality. Preoperative evaluation of the prospective transplant recipient should include a search for active peptic ulcer disease and diverticulosis coli.

ix. *Hypertension*. Steroids may contribute to hypertension because of their mineralocorticoid effect. Other primary etiologies should be considered, i.e., renal artery stenosis, chronic renal allograft rejection, renin production from native kidneys and cyclosporine A toxicity.

x. *Obesity*. Steroids increase appetite, and with normalization of the patient's diet excessive weight gain is often seen beginning one to two months after transplantation. Patients require dietary counseling during their transplant hospitalization to avoid this complication.

xi. *Central nervous system*. Insomnia and mild euphoria or depression are common. Psychosis is rare. Psychotic reactions usually respond well to haloperidol (Haldol) administration. Chlorpromazine (Thorazine) is hepatotoxic and should be avoided where possible. It should be remembered that insomnia is most commonly caused by beta blockers.

xii. *Growth retardation*. A serious problem in the pediatric transplant population. Alternate day steroid administration may be of benefit and warrants consideration in long term immunosuppressive regimens for the pediatric recipient.

B. Azathioprine. In 1961 azathioprine, the imidazole derivative of 6-mercaptopurine, was studied on dogs¹¹ and subsequently clinically.⁴⁶ The utility of this drug as a single immunosuppressive agent was severely limited by its profound systemic toxicity at high dosages. Ultimately in Denver in 1962 it was demonstrated that, by using maintenance corticosteroids with azathioprine and treating rejections with high dose corticosteroids, rejection could be reversed and a state of graft acceptance established.⁶³ By 1964 this "double drug" immunosuppressive regimen had become the gold standard.

The combination of azathioprine and corticosteroids is usually referred to as conventional therapy, with or without the addition of antilymphocytic⁶² or lymphocyte depleting techniques.²³ Azathioprine is metabolized by the liver to the biologically active compound 6-thioinosinic acid. An important immunosuppressive action of this drug is the inhibition of cellular DNA and RNA synthesis. Azathioprine effects both the humoral and cell mediated immune responses; however, only partial systemic immunosuppression is accomplished with the dosages generally utilized in clinical practice.

The enzyme xanthine oxidase is involved in the metabolism of azathioprine. Accordingly, concomitant therapy with allopurinol, a xanthine oxidase inhibitor, can be hazardous as a consequence of noteworthy increases in both the magnitude of systemic immunosuppression and the drug's hematologic toxicity. If therapy with both of these agents is mandatory, the azathioprine dose should be reduced to 25-30% of that customarily used.^{1,2}

Azathioprine is available in both intravenous and oral forms. Its metabolites are excreted in the urine. Therapy is started prior to transplantation and is initiated at 2-3 mg/kg/day. Oral and intravenous doses are approximately equivalent. After oral administration, a maximum blood level effect is seen after 1-2 hours. Azathioprine should be given daily as a single dose not to exceed 200 mg/day.

The dosage of this agent should be adjusted in accordance with the patient's total white blood cell count. The dose is adjusted down when rapid decreases in WBC count are seen or when the WBC count is less than 5000/ml. The dose should be completely withheld or reduced to 25mg/d with WBC counts of less than 3000/ml.

1. Side Effects. i. Hematologic. Bone marrow suppression is significant. Leukopenia is almost universally seen and often prevents the use of an effective therapeutic dose. Thrombocytopenia may also mandate dose adjustment or cessation of azathioprine therapy. Anemia is an uncommon occurrence. An important consideration is that viral infection, most notably with cytomegalovirus, can also cause leukopenia.

ii. Hepatic. Azathioprine is potentially hepatotoxic. This is seen clinically as an increase in bilirubin and serum transaminases. Before cyclosporine A was available such patients were switched to cyclophosphamide.

iii. Other. Problematic hair loss and skin fragility may improve after exchanging azathioprine for some other immunosuppressant.

C. Cyclosporine A. In 1978 in Cambridge a new immunosuppressive agent was introduced clinically for transplantation.¹³ CyA is a lipophilic metabolite from the soil fungi *Tolypocladium inflatum* GAMS and *Cylindrocarpum lucidum* Booth.⁸ It is a cyclic endecapeptide containing a unique,

previously unknown amino acid. This amino acid is essential for immunosuppressive effect. It is not myelotoxic, and at the time of its introduction it was the most specific immunosuppressive agent known. The clinical introduction of CyA particularly combined with other agents such as prednisone⁶⁵ has resulted in significant improvement in graft and patient survival after all organ transplants, spurring a wider interest in transplantation as a therapeutic modality.

CyA affects primarily the T cell immune response, in particular, interleukin-2 production.²⁷ The prevention of interleukin-2 production seems to include interference with the Ca⁺⁺ signal; possibly by binding between CyA and calmodulin, a cytoplasmic protein involved in Ca⁺⁺ mediated activities.¹⁷ The net effect from the blockage of interleukin-2 production is the failure to react to Class I and Class II antigens expressed by allogeneic cells, thus preventing the cascade of events leading to cytotoxic T lymphocytes.

Orally administered CyA is absorbed from the proximal jejunum, and peak blood levels are seen after 2-4 hours. The half-life varies widely between 16 and 42 hours, averaging 27 hours. The bioavailability of oral CyA is only 34% (range 20- 50%) of the administered dose. Thus when changing a patient from oral to intravenous medication, only 1/3 of the oral dose should be given. The drug's metabolism is hepatic and is complex. At least three metabolites, M1, M17 and M21, are known to be immunologically active. The drug is extremely lipophilic and the renal excretion is negligible, 0.1%. CyA is not dialyzable.^{5, 6, 47}

Clinically important pharmacokinetic and pharmacological interactions are common. Interference with the P450 enzyme system in the liver is a common site of interaction. Ketoconazole and high dose steroids increase the CyA level. Phenytoin, barbiturates and rifampin reduce the CyA level. Other nephrotoxic pharmacologic agents such as the aminoglycosides, amphotericin B, melphalan, trimethoprim and trimethoprim-sulphamethoxazole may cause increased nephrotoxicity when used together with CyA.

In whole blood 50% of the CyA is found in the blood cells with only 30-40% in plasma, 90% of which is protein-bound.⁵ CyA's affinity for red blood cells varies with temperature. Thus the CyA concentration measured in whole blood is totally different from that measured in plasma. Unlike whole blood concentration, CyA is dependent on the temperature of the plasma at the time of plasma separation.⁴⁷ When plasma concentrations are performed in a standardized fashion, they are as reliable as whole blood for the purpose of patient monitoring.

Three techniques exist for the determination of CyA concentration: radioimmunoassay (RIA) using polyclonal or monoclonal antibodies, high pressure liquid chromatography (HPLC) or polyclonal fluorescent polariza-

tion immunoassay (FPIA). The polyclonal RIA is approximately similar to the RIA kit previously supplied by Sandoz. The polyclonal RIA has a high degree of cross-reactivity with CyA metabolites (up to 60%) whereas the monoclonal RIA and the HPLC measure only the parent compound A. The HPLC results are approximately 10% higher than those obtained by monoclonal RIA. The FPIA technique is very sensitive and measures most of the metabolites, which can be problematic. During good liver function the proportion of the mother compound (HPLCO, monoclonal RIA) is 50-60% of the measured FPIA level. In poor liver function, this can go down to 10-15%. When the liver function deteriorates, i.e., in liver transplants, the liver is less able to excrete the metabolites which accumulate. This gives an impression of too much CyA resulting in a lowered CyA dose and the level of mother compound, which is mainly responsible for the immunosuppressive effect, becoming too low, triggering a rejection. We have seen this happen several times in patients monitored with the FPIA assay and consequently advise against its use in patients with poor or deteriorating liver function.

Standards for both the recommended dose and for the optimum therapeutic levels of CyA have been dramatically reduced since the introduction of this drug. This is primarily a consequence of increased understanding of the drug levels necessary in vivo and an increased awareness of the drug's chronic nephrotoxic side effect. The maximum clinical utility of cyclosporine is achieved by a successful admixture of scientific knowledge and clinical acumen.

Important nuances in cyclosporine management include:

- a. Cyclosporine is always a nephrotoxic agent, even at minimal doses.
- b. One should never react to a single laboratory determination of cyclosporine level. If the blood level suddenly increases without evidence of a change in renal function, repeat the assay; do not change the cyclosporine dose. The most sensitive laboratory value indicative of cyclosporine nephrotoxicity is a rising BUN. Corresponding changes in serum creatinine occur but manifest more slowly. Once a long term maintenance CyA dose has been established, only very rarely should the dose be increased as a response to a decrease in measured blood (or plasma) levels. The optimal therapeutic level for long term patient management has not been conclusively established. Again, the current trend has been to lower recommended maintenance CyA levels.
- c. When dose changes are indicated, add or subtract 20% of the previous dose in 25 mg/dose steps.
- d. Because of CyA's long half-life, several days are required to achieve steady state blood levels after any dose adjustment. Remember this and act

accordingly!

e. Even the best laboratories have a variation of $\pm 10\%$ in their measured results using RIA technique.

f. Blood levels must be drawn just before the morning dose. For longterm management the patient can safely delay ingestion of the morning dose until the blood work has been drawn on the day of an office/clinic outpatient visit.

g. Remember the aforementioned clinically important drug interactions.

h. The intravenous dose is approximately one-third of the oral dose.

i. Side Effects. i. Nephrotoxicity. Nephrotoxicity is seen in two forms, an acute reversible form which is most likely caused by increased sympathetic nervous tone and a chronic irreversible form. Interstitial fibrosis is seen in the chronic form. The etiology of the chronic form is obscure. Acute and the chronic nephrotoxicity may have different underlying mechanisms.^{4, 34}

ii. Electrolyte imbalance. Potassium retention and magnesium wasting are common as a result of acute nephrotoxicity. Hyperkalemia may, in the rare case, be severe enough to mandate the withdrawal of CyA for azathioprine. Hypomagnesemia may result in muscle cramps and weakness, paresthesia and even seizures. Magnesium supplementation is often required.

iii. Hypertension. Elevated blood pressure can often be attributed to CyA. Increased sympathetic tone with sodium and water retention is the likely mechanism; however, concomitant steroid medication may also be the cause. High blood pressure caused by CyA frequently appears to be dose related and may be secondary to the dose related nephrotoxicity of this drug.

iv. Hirsutism. Increased hair growth is common. It is most striking on the face, but is in fact, generalized. The hair also darkens thus becoming more noticeable. This problem is four times as common in young patients as opposed to the elderly (more than 55 years old); the incidence being 32% versus 8%, respectively. No correlation with dose has been demonstrated.

v. Tremor. A fine tremor is seen in 25% of the patients and is dose related. This tremor is most marked approximately two hours after intake when the peak blood level of CyA is found.

vi. Gingival hyperplasia. Gingival hyperplasia is related to oral hygiene. It is unusual in bone marrow transplant patients who routinely use antibiotic containing toothpaste for decontamination purposes. It is only seen in patients who have their own teeth. Improved oral hygiene should be recommended. Occasionally gingivectomies are required.

vii. Hepatotoxicity. The incidence of hepatic dysfunction is clearly dose related and is seen in less than 10% of patients with the dosages presently employed. In renal recipients, bilirubin seems to be the most sensitive parameter, but serum measurements of ALT (GPT), AST (GOT), alkaline phosphatase and glutamyl transferase also increase.³⁵ No clearcut morphol-

ogic changes can be seen on liver biopsy. Accordingly, in liver transplant recipients, this diagnosis may be very difficult to establish, and the only way is by exclusion. This complication responds readily to dose adjustment.

viii. Sinus congestion. Runny or congested nose is often seen with cyclosporine toxicity. It is dose related and responds quickly to dose adjustment.

ix. Tumors. A high incidence of lymphoproliferative disorders were initially seen in the CyA trials.¹² We now regard tumors in immunosuppressed individuals as a general response to excessive immunosuppression. With aggressive dose reduction or total withdrawal of immunosuppression, two-thirds of these tumors have completely regressed.⁶⁰

D. Cyclophosphamide. Cyclophosphamide² is an alkylating agent. Its absorption is incomplete and variable. Cyclophosphamide must be metabolized for biologic activity. This normally occurs in the liver microsomes. The metabolites are excreted in the urine. Cyclophosphamide is one of the most potent suppressors of the humoral immune system. Its activity on B lymphocytes is more pronounced than on T lymphocytes. The initial recommended dose is 2-3 mg/kg/day, but often this must be rapidly reduced due to toxicity of the drug.

i. Side Effects. i. Leukopenia. Close monitoring of the white cell count is necessary.

ii. Alopecia and cystitis. Alopecia is probably caused by the compound itself. The cystitis is caused by the drug metabolites. Both are commonly seen in bone marrow transplants but not with the doses used for solid organ transplantation.

iii. Infection. Because of its B cell immunosuppressive activity and general leukopenic effect, this is a serious concern.

E. New developments: FK506, RS61443. The last two years have seen an increase in the efforts to develop new immunosuppressive agents. Two of these are presently in clinical evaluation. FK506 (Fujisawa, Osaka, Japan) has seen the longest and the most extensive use, primarily at the University of Pittsburgh where already well over 1000 patients have received the drug. All kinds of solid organ recipients, as well as bone marrow transplants and patients with autoimmune disorders, have been treated. Randomized multicenter trials are presently underway in the United States as well as in Europe.

The other drug, a mycophenolic acid, which is now commencing its clinical evaluation, is RS61443 (Syntex, Palo Alto, California). The experience of RS61443 in transplantation is very limited at the present time with fewer than 20 patients being treated for rescue from rejection.

Probably the next drug which will shortly enter into Phase I clinical trials is Rapamycin (Wyeth-Ayerst, Philadelphia, Pennsylvania). This agent, like FK506, is a macrolide but works through a different pathway.

1. FK506. i. Action. The drug is a metabolite produced by *Streptomyces tsukubaensis*. It is a macrolide with a molecular weight of 822 and is lipophilic.^{30, 31, 48, 61} FK506 inhibits the mixed lymphocyte reaction and can prevent the generation of cytotoxic cells. In fact both FK506 and CyA inhibit the Ca⁺⁺ dependent cell activation. This is accomplished through an inhibition of IL-2 release and diminution of IL-2 receptors on activated cytotoxic lymphocytes.^{22, 48}

ii. Metabolism. FK506 is rapidly absorbed, and maximum plasma concentration is found 1-2 hours after administration. The half-life ranges from 5.5 to 16.6 hours with a mean of 8.7. The plasma clearance ranges from 87 to 269 L/hour, with a mean of 143 L/hour. The distribution of the drug is extensive, volume of distribution of 1342:1, with tissue concentrations in decreasing order: lungs, spleen, heart, kidney, pancreas, liver. The bioavailability is estimated at 25%. The presence of bile is not necessary for absorption. However, with deteriorating liver function the bioavailability rapidly increases (21-51%, mean 36%) and is accompanied by a decreased clearance, 12.9-70 L/hour, average 39.8 L/hour.^{28, 70} These changes can result in dramatic increases in FK506 levels, necessitating resolute dose adjustment. FK506 is demethylated and hydroxylated into nine metabolites, some of them with weak immunosuppressive properties.¹⁴ Less than 1% of a given dose is excreted into the urine, and FK506 is not dialyzable.⁷⁰

iii. Drug interactions. Drug interactions are still mostly uncharted, but they appear to be very similar, if not identical, to those seen with CyA. CyA and FK506 strongly interact, preventing their metabolism and elimination resulting in acute toxic drug levels. Other drugs involving hepatic P450 metabolism will affect the FK506 levels. Barbiturates, antiepileptics and anti-tuberculars will increase the elimination of FK506. Ketokonazole, CyA and erythromycin will decrease elimination. At this time it is advisable to exert the same precautions for potential drug interaction as with CyA.

iv. Measurement. The available technique for the measurement of FK506 levels is an immunoassay technique. And since the plasma/blood ratio is temperature dependent, the plasma has to be separated under temperature controlled conditions. The assay also uses overnight incubation.⁶⁴ In our experience, the therapeutic range seems to be 0.4 ng/ml to 3.0 ng/ml with the patients that do well running levels between 0.4 to 0.7 ng/ml. The present technique of measuring levels can be expected to undergo much improvement and consequently also the recommended FK506 levels.

v. Side effects. a. Nephrotoxicity. The mechanism for nephrotoxicity is probably different from that seen during CyA treatment since hypertension is less common in FK506 treated patients. Hyperkalemia can be a problem with both drugs and can be treated effectively with the mineralocorticoid Fluor-

inef®.

Renal function as judged by serum creatinine, BUN and glomerular filtration rate seems to be similarly affected by FK506 and CyA at different postoperative time points. Early nephrotoxicity posttransplant is seen as a sudden drop in urine output accompanied by a rise in BUN, later followed by a serum creatinine increase. This toxicity is readily treated with a FK506 dose adjustment, usually in the range of 30-40%. Long term renal dysfunction is manageable with fine dose adjustments with an eye to the FK506 level.

b. Neurotoxicity. This is seen in two divergent forms. One is hyperactivity, tremulousness, paresthesia, sleeplessness, dreams and/or hallucinations. These symptoms can be a litmus test for FK506 dose adjustment. Hyperactivity can be seen even at therapeutic levels. It is easily managed by fine decreases in the FK506 dose.

The other form of neurotoxicity is more serious and normally is seen when FK506 levels become high, 5 to 10 ng/ml and higher. Patients first become hypoactive and then somnolent. This requires sharp and rapid dose adjustments without waiting for FK506 levels, if daily levels are not available. The dose should be temporarily stopped or reduced in the order of 80%. Further adjustments should be made as soon as a response can be read on levels received. This condition is usually seen in patients with cholestasis when FK506 pharmacokinetics are altered (see above).

The neurotoxicity profile of FK506 is similar to that of CyA, and the delineation of its subtle aspects was facilitated by years of prior experience with the later drug. It is realized now that the binding sites of these two drugs are part of an ubiquitous network of related small molecular weight proteins whose activation or inactivation affects a wide range of metabolic processes. The binding sites are different for the two drugs, but the processes influenced are the same. Appreciation of this concept has been a major advance in the field of signal transduction apart from the immunologic system and helps in understanding the related toxic as well as therapeutic profiles of this class of drugs.^{48, 56} The immunophilin binding sites are densely represented in the central and peripheral nervous system.

vi. Miscellaneous. Both FK506 and CyA have a certain diabetogenic effect. However, since most patients also receive concomitant steroids this is still a side effect that is not fully elucidated.

Lipid metabolism which is seriously affected by conventional immunosuppression is less affected by FK506.¹⁰ However unpublished animal studies suggest that cholesterol synthesis in animals is significantly increased. The lower cholesterol levels seen with FK506 treated patients compared to those in the past may reflect the much lower (and often absent) steroid doses that are required to prevent rejection.

vii. *Dosing.* The presently recommended starting dose when given intravenously is 0.05 mg/kg every 12 hours as a continuous infusion. The oral starting dose is 0.15 mg/kg every 12 hours. Further dose adjustment needs to be done with a view to recorded effects, side effects and reported FK506 levels.

viii. *Conclusion.* FK506 is a very powerful immunosuppressive drug that has increased graft and patient survival in liver and heart recipients.⁶⁸ A window has also been opened to new, hitherto "untransplantable" organs.⁵⁸ Fewer and more easily treated rejections are seen in FK506 treated patients than in patients receiving CyA. Our knowledge of the drug will rapidly increase allowing us to use it more safely and efficiently. Only then can the full benefit of this drug be realized.

IV. Rejection Therapy.

A. **Steroids.** With a double drug CyA-steroid maintenance protocol, 1 gram solumedrol methylprednisolone intravenous, followed by an oral "recycling" of the patient's initial steroids can be used as rejection treatment; i.e., 200 mg/day on day 1; 160 mg/day on day 2; 120 mg/day on day 3; 80 mg per day on day 4; 40 mg/day on day 5; and back to maintenance immunosuppression 20 mg per day. For patients on triple drug immunosuppressive protocol, (CyA - azathioprine - steroids), 0.5 gram solumedrol methylprednisolone intravenously for four consecutive days can be used.

Remember there are as many steroid protocols as there are transplant centers!

B. **OKT3 (orthoclone).** With the development of monoclonal antibodies directed against the CD3 antigen on T-cells,¹⁸ an important step was taken toward selective and effective immunosuppression. What developments will be seen in future immunosuppressive preparations using monoclonal techniques¹⁷ can only be speculative.

Five mg/day is given intravenously for 10 to 14 days. In the pediatric recipient, the daily dose is 1 mg per day. It is imperative that the patient not have any signs of pulmonary congestion before the start of therapy, otherwise the risk of acute cardiopulmonary collapse is significantly increased.

1. *Side effects. i. Acute cardiopulmonary collapse.* This presents as an anaphylactic-like reaction and responds to the same therapy, i.e., epinephrine, corticosteroids, cardiopulmonary resuscitation. It is only seen after the first, or sometimes after the second dose.

ii. *Diarrhea.* This is a frequent complaint. Patients should be given dietary yogurt in order to recolonize the gastrointestinal tract with nonpathogenic lactobacillus. Diphenoxylate hydrochloride (Lomotil) and atropine sulphate (Lomotil) and other anticholinergics should be withheld until

infectious etiologies for the patient's diarrhea have been excluded. It is very commonly seen shortly after injection for the first few days of therapy. It must be differentiated from infection.

iii. *Tingling of hands and feet.* It requires no therapy.

iv. *Headache.* This can be severe. It requires symptomatic therapy after meningitis has been ruled out.

v. *Meningitis.* It is seen as a sterile meningitis. Lumbar puncture may show increased cell count. CT of the head is unremarkable, and the development of meningitis does not require discontinuation of the drug.

C. **ALG/ATG.** The use of antilymphocytic agents such as antilymphocyte globulin/serum (ALG/ALS) or antithymocyte globulin (ATG) has been plagued by problems such as heterogeneity of the product with batch-to-batch variation and unpredictable side effects. Dose differs depending on source (horse or rabbit) and manufacturer. Some titrate out the dose attempting to keep the T cell count down below 10% of pretreatment levels. Others only give a fixed standard dose regimen.

1. *Side effects.* Anaphylactic reaction, serum sickness, chills, fever, erythema, thrombocytopenia and viral infections, especially cytomegalovirus.

D. **Miscellaneous. 1. X-ray irradiation.** In renal transplantation irradiation has been given for rejection therapy. The usual dose is 150 RAD (deep dose) for three days, totaling 450 RAD. The efficaciousness of this modality has not been established but should not yet be totally discarded.²⁹

2. *Total lymphoid irradiation (TLI).* Total lymphoid irradiation is given at some centers.⁵⁴ With this technique, a donor organ needs to be transplanted as soon as possible after the completion of the irradiation for the maximum benefit. Patients with preformed antibodies are poor candidates for TLI since finding a crossmatch negative donor may take considerable time. The technique can yield good results and is steroid sparing but very cumbersome and is not used by us at the present time.

3. *Thoracic duct drainage (TDD).* This technique, like TLI, is effective⁵⁹ but also unwieldy and thus is falling out of practice. To achieve meaningful results, prolonged hospitalization is required.

V. Organ Specific Recommendations.

A. **Renal transplantation (Table 4). 1. Cyclosporine A.** The high early doses of CyA which were used have been shown to cause interstitial fibrosis.³² Thus today the aim is to avoid the high, early doses to allow the CyA level to build up slowly. No attempt is made to increase a low CyA level achieved by the initial dose during the first week.

B. **Liver transplantation (Tables 5). 1. Cyclosporine A.** CyA is started

TABLE 4. Renal Transplantation. Triple Drug Immunosuppression Regimens.

<i>Cyclosporine</i>	
Preoperative	10 mg/kg po
Postoperative	5 mg/kg q 12h po (2.5 mg/kg q 12h in a nondiuresing pt)
Optimum CyA levels (12h trough, whole blood, monoclonal RIA)	
< 1 month	150-200 ng/ml
> 1 month	100-150 ng/ml
<i>Azathioprine</i>	
Preoperative	3 mg/kg po
Postoperative	2 mg/kg po Adjust according to white cell count
<i>Steroids</i>	
See Table 3	
<i>Transfusions</i>	
No protocol preoperative transfusions are given. Transfusions only given when indicated medically. Leukocyte poor (washed) PRBCs are preferred.	

according to pre- and intraoperative renal function and by the function of the liver graft as assessed intraoperatively.

Postoperatively, as long as renal function is poor, no CyA is given. A low dose is given only after brisk diuresis, >100ml/hr, has been seen for a minimum of 12 hours. The CyA dose is then adjusted to achieve a CyA level (12 hour trough, whole blood, monoclonal RIA) of:

< 1 month	250-400 ng/ml
1-3 months	200-300 ng/ml
> 3 months	180-250 ng/ml

High CyA levels are initially required to achieve adequate immunosuppression because of the preservation damaged liver's inability to excrete CyA and its metabolites. Once the GI tract has begun to function, oral CyA is added to the same intravenous regimen at 15 mg/kg every 12 hours. To ensure that adequate CyA levels are maintained on oral therapy, the intravenous dose is slowly tapered over 7-10 days following daily levels. The oral CyA dose may

TABLE 5. Liver Transplantation. Pre- and Intraoperative Cyclosporine Protocol.

	Renal Function	CyA	Interval	
PREOPERATIVE	Normal	10 mg/kg po	q 12h	
	Impaired	No CyA!		
		Azathioprine 3 mg/kg IV		
INTRAOPERATIVE	1-2 hours after total revascularization			
	Liver Function (as judged by color, softness and bile output) poor	good	1.0 mg/kg	q 12h
		marginal	0 (azathioprine 3 mg/kg IV, repeat dose)	q 12h
		poor	0 (azathioprine 3 mg/kg IV, repeat dose)	q 12h
	medium	good	1.5 mg/kg	q 12h
		marginal	1.0 mg/kg	q 12h
poor		0 (azathioprine 3 mg/kg IV, repeat dose)	q 12h	
good	good	1.5 mg/kg	q 8h	
	marginal	1.0 mg/kg	q 12h	
	poor	0 (azathioprine 3 mg/kg IV, repeat dose)	q 12h	

be as high as 25 mg/kg every 12 hours until the biliary T-tube is clamped (one week after transplantation). When this is done a rapid downward dose adjustment is usually needed to curb soaring CyA levels. When the CyA level increases to more than 600 ng/ml the next (usually evening) dose is withheld and then a reduced, 20%, dose is started 24 hours after the last given dose (usually next morning). It is important to remember that the blood level measured the following day is a 24-hour trough, not a 12-hour trough and accordingly will be lower than one might have anticipated for a 12-hour trough. *Failure of the level to decrease after withholding a dose is an indication of a nonfunctioning liver graft!*

2. *Azathioprine for renal prophylaxis.* In general preoperative azathioprine is given only to patients with impaired renal function. In anuric/oliguric patients a 3 mg/kg dose is given preoperatively and maintained postoperatively, as allowed by the patient's white blood cell count, until the renal function is reestablished. Azathioprine is then discontinued.

3. *Azathioprine for rejection.* Azathioprine is started at 1.0 mg/kg/day after treatment of a first episode of rejection and is maintained indefinitely at 0.5-1.0 mg/kg/day if this is tolerated by the patient.

4. *Steroids.* See Table 2.

C. Heart and heart/lung transplantation. 1. Cyclosporine A. It is presently unclear why heart transplant recipients appear to be more sensitive to the nephrotoxic effects of CyA. This has mandated the use of very low CyA doses beginning early after heart transplantation. One reason may be that the native kidneys of heart transplant recipients are more sensitive to vasospasm and thus to CyA nephrotoxicity than the denervated transplanted kidney. It is not clear how then to explain the disparity between heart and liver recipients in this regard. However, because of the fear of rejection, there is a tendency to use high CyA long term maintenance levels in heart transplantation.

Cyclosporine.

Preoperative: 0
Postoperative: 2.5-5 mg/kg every 12 hours and adjust to maintain a CyA level (12-hour trough, whole blood, monoclonal RIA) of 250-400 ng/ml. Long term 200-300 ng/ml.

Azathioprine.

Preoperative: 4 mg/kg
Postoperative: 2 mg/kg/day for 5 days, then discontinue.

RATG.

Postoperative: 100 mg/day for 5 days.

Steroids. See Table 2.

D. Pancreas transplantation. 1. Cyclosporine A. In the combined transplantation of pancreas and renal allografts, the kidney serves as a marker for rejection. Using this combined method, high success rates have been reported.⁶⁹ To assure that CyA nephrotoxicity mimicking rejection is not confused with true allograft rejection, low CyA dosages and levels are employed.

Cyclosporine.

Preoperative: 0
Postoperative: 3 mg IV over 24 hours. 5 mg/kg q12 hours starting postop day 7. Adjust according to blood levels.

Azathioprine.

Preoperative: 2 mg/kg IV
Postoperative: 2 mg/kg/day for 1 week, then lowered to 1 mg/kg/day.

OKT3.

Preoperative: 5 mg/kg IV
Postoperative: 5 mg/kg IV for 1 week then discontinue.

Steroids. See renal protocol.

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V. Glossary of Terms in the Human Transplant Directed Immune Response

Acute Rejection. Destruction of a transplant by immunological reactions, usually seen five days to two months after grafting. ("Accelerated acute rejection" takes place one to five days postop usually as a result of a pre-existing cellular immune reactivity.)

ADCC. Antibody dependent cell mediated cytotoxicity (see K cells).

Adjuvant. Substance that enhances an immune response when administered together with an antigen.

Agammaglobulinemia. Congenital deficiency of gamma globulins (hereditary or sporadic).

Agglutination. Aggregation of large particles, i.e., red blood cells as a result of antigen-antibody reactions on the surface of the particles.

Allotransplantation (allografting). Transplantation between different individuals of the same species.

Anaphylaxis. Rapid hypersensitivity response of "immediate type" occurring within minutes after the administration of the challenging antigen.

Antibody. Complex protein molecule that combines with antigens in a "lock and key" fashion (as a first step to initiate a sequence of reactions).

Antigen. Molecule(s) that can evoke an immune response when introduced into an individual or when exposed to immunocompetent cells in vitro.

Antilymphocyte Globulin (ALG) or Serum (ALS). Antibodies (serum) directed to lymphoid cell antigens in another species.

Arthus Reaction. Hemorrhagic necrotic skin lesion developing as a result of a reaction between circulating precipitating antibodies and locally injected antigens.

Autoantibody. Antibody with specificity directed against antigenic structures in the individual producing the antibody ("self" antigens).

Autoimmune Disease. A disease causing, resulting from, or appearing simultaneously with an immune reaction to "self" antigens.

Autotransplantation (autografting). Transplantation of an organ inside the same individual.

B cell (B lymphocyte). "Bursa" equivalent or bone marrow derived lymphocyte concerned with antibody mediated immunity.

Bradykinin. A peptide that can increase vascular permeability, lower blood pressure and contract smooth muscle. The effects are enhanced by prostaglandins.

Bursa Fabricius. Organ in birds where the differentiation of stem cells into B cells takes place.

Cell Mediated Immune Reactions. Expression of immune responses that involve interactions between sensitized cells and antigens.

Cell Mediated Lympholysis (CML). In vitro model of allograft rejection with killing of target cells by lymphocytes. At the present time, more a research tool than a clinical tool.

Chemotaxis. Unidirectional movement by a cell towards an increasing gradient of an attractant.

Chimera. Person or animal with populations of lymphoid cells from two individuals. Tolerance exists between the two populations.

Chronic Rejection. Destruction of a transplant by immunological reactions usually seen months to years after grafting.

Class I and II Antigens. Groups of human transplant (major histocompatibility complex) antigens initiating different kinds of immune responses.

Complement. A group of at least 20 proteins that circulate in plasma in inactive forms. When an antigen/antibody reaction has taken place, they become sequentially activated in order for destruction of the target structures to take place.

Coombs Reaction. "The antiglobulin reaction". The creation of bridging between two antibody coated red cells by the addition of antibodies to the

coating antibodies. A resulting cell agglutination is recorded either "directly" or "indirectly". In the former case, red cells are already coated with antibodies and in the latter, circulating antibodies, if any, are allowed to adhere to the red cells before the test is carried out.

Crossmatch Test. The detection of preformed donor directed cytotoxic antibodies in a patient awaiting organ transplantation. Donor target (lymphoid) cells, recipient serum and complement are brought together.

Cryoglobulin. Immunoglobulin that is insoluble at below body temperatures.

Delayed Hypersensitivity. Manifestation of cell mediated immune reactions.

Dendritic Cell. Interstitial cell with an important role of presenting foreign antigens to the host after transplantation. Sometimes called "passenger leukocyte".

Enhancement. Complex phenomenon where the survival of a graft or tumor is facilitated by the presence of noncytotoxic antibodies with specificity against graft or tumor antigens.

E Rosettes. See Rosettes

F_{ab}, F_c Fragments. Parts of immunoglobulin molecules resulting from cleavage of polypeptide chains and breaking of disulfide bonds.

Gammaglobulin. Immunoglobulin.

Graft-Versus-Host (GVH) Reaction. An immune response to host antigens created by immunocompetent cells from the organ donor.

Granulocytes. Neutrophil, eosinophil and basophil lymphocytes. The former two are phagocytes.

Hapten. A low molecular weight substance that is only immunogenic (antigenic) when coupled to a larger carrier molecule.

Helper Cell. Subclass of T cells interacting with precursors of the cytotoxic T cells and plasma cells allowing them to mature. Also called "helper and inducer cell".

Heterologous Transplantation. Older nomenclature, translates into "xenografting".

HLA Matching. The selection of human donor-recipient pairs with minimal antigenic differences in organ transplantation, HLA= human leukocyte antigens.

Homologous Transplantation. Older nomenclature, translates into allografting.

Humoral Immune Response. Antibody mediated immune response.

Hyperacute Rejection. The destruction of a vascularized transplant within minutes to a few hours after the establishment of blood flow through the organ. Preformed cytotoxic antibodies are instrumental in the process.

Idiotypic. A determinant present on antibodies that appears to represent the antigenicity of the antigen binding site itself.

Immediate-type Immune Response. Antibody mediated immune response.

Immune Complex Disease. "Serum sickness". A generalized disease developing secondary to the formation of circulating antigen-antibody complexes. Vascular, renal, joint and cutaneous lesions occur.

Immunoglobulin. Gammaglobulin.

Immunodeficiency Diseases. Clinical sequelae of impaired function in one or more components of the immune system.

Immunomodulation (Immunopotential or Immunosuppression). Regulation of immune responses. Immunopotential---"up" regulation. Immunosuppression---"down" regulation

Inducer Cell. See "helper" cell.

Interferon. Proteins produced or released by cells following viral infection or after exposure to "inducers". Interferons are mainly antiviral (alpha and beta) or mainly immunoregulatory (gamma).

K Cell. Lymphoid cell of importance in antibody dependant cell mediated cytotoxicity (ADCC). Cytotoxic activity directed toward target cells coated with specific antibodies.

Killer Cell. Lymphoid cell able to lyse target cells. End product of the "T cell response" to an antigenic challenge.

Leucotrienes. Metabolites of arachidonic acid with functions associated with chemotactic activity and smooth muscle contractility.

Lymphocyte. Cell belonging to a family of cells with immune response functions. Can be classified on morphological or functional grounds.

Lymphokines. Effector molecules released from lymphoid cells when reacting with specific antigens in vitro.

Macrophage. Phagocytic cell with a role in antigen recognition and processing.

Major Histocompatibility Complex (MHC). Chromosomal region consisting of a series of genes that code for the cell surface expression of strong transplantation antigens (HLA).

Mast cells. Cells with a reservoir function for vasoactive amines particularly histamine.

Memory Cell. Cells formed following antigenic stimulation of either B or T lymphoid cells that proliferate and differentiate upon reencounter with the antigen in question.

Microglobulin (B₂). 11600 Dalton cell surface protein associated with the Class I HLA system.

Migration Inhibition. The failure of macrophages to migrate from a

capillary tube when the antigen to which the macrophage donor is sensitized is present in the incubation medium. MIF - "migration inhibitory factor".

Minor Antigens. Non-MHC antigens with unclear role in transplantation.

Mixed Lymphocyte Culture Reaction (MLC or MLR). The mitotic reaction within a lymphocyte population when it is mixed with a foreign population of lymphoid cells.

Monitoring. Assessment of host immune response capacity.

Monoclonal Antibodies. Antibodies manufactured by cells derived from one B cell producing antibodies with one specificity.

Monocyte. Mononuclear phagocyte with multiple functions in the immune response. Can differentiate into tissue macrophages after leaving the bloodstream.

Natural Killer (NK) Cell. Cell with no known T or B cell marker that is involved in nonspecific killing of cells with foreign surface markers, i.e., allograft cells, virally transformed cells, tumor cells.

Null Cell. Small population of the lymphocyte pool in a given individual that lacks the antigenic characteristics of T or B cells. Null cells can be divided into NK cells and K cells.

OKT Series. Set of mouse antihuman monoclonal antibodies directed against different T cell surface markers.

Opsonization. Facilitation of phagocytosis by the presence of antigens coated with antibodies.

Passenger Leukocyte. See Dendritic cell.

Phagocytosis. Ingestion of particles into cells. Usually represents the initial host encounter with a foreign substance.

Plasma Cell. Cell producing and secreting immunoglobulins. End product of the "B cell response" to an antigenic challenge.

Thromboxane. Metabolite of arachidonic acid causing smooth muscle constriction and platelet aggregation.

Tissue Typing. Determination of the major histocompatibility complex (MHC) code for a given individual (in preparation for the selection of matched donor/recipient pairs).

Tolerance. A state of immune nonresponsiveness to specific antigen(s) normally capable of inducing immune reactivity.

Total Body Irradiation, Total Lymphoid Irradiation (TLI). The irradiation of an entire transplant recipient or areas of the body housing lymphoid tissues. Administered to achieve immunosuppression in preparation for organ transplantation or infusion of cellular antigens.

Transfer Factor. Substance released following the in vitro interaction between a sensitized lymphocyte and its specific antigen. It has the capacity to transfer the cellular immune reactivity to a nonreactive individual.

Xenotransplantation (Xenografting). Transplantation between individuals belonging to different species.

CHAPTER FOUR 4

Anesthesia for Organ Transplantation

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This chapter is dedicated to Dr. Charles W. Schertz, our beloved friend and an inspiring anesthesiologist, who passed away during his third Mt. Everest expedition.

- I. Heart Transplantation
- II. Heart/Lung Transplantation
- III. Lung Transplantation
- IV. Liver Transplantation
- V. Pediatric Liver Transplantation
- VI. Kidney Transplantation
- VII. Pancreas Transplantation