Section One

TRANSPLANT DERMATOLOGY: AN EVOLVING DYNAMIC FIELD

1

Introduction to Transplant Dermatology

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INTRODUCTION TO TRANSPLANT DERMATOLOGY

Forty years ago, the world marveled at the news of the first heart transplant and was saddened by the transplant recipient's not unexpected death 18 days later. Today it is not uncommon to see a cardiac transplant recipient living well 15 or more years after transplantation. Unfortunately, it is also common to see that patient plagued with multiple skin cancers. When solid organ transplantation was in its infancy in the 1960s and 1970s, surviving the immediate transplant period was the most pressing concern. Today, patients leave the hospital quickly after transplantation, and the challenges involve managing the complications of years of illness and immunosuppression: diabetes, hypertension, coronary artery disease, peripheral vascular disease, and skin cancer.

SOLID ORGAN TRANSPLANTATION AND SKIN CANCER

Over many years, solid organ transplantation has evolved into a commonly practiced, successful life-saving medical intervention. An intersection of advances in physiology, immunology, pharmacology, surgical technique, and critical-care medicine has made solid organ transplantation the standard of care for many instances of kidney, heart, lung, and liver failure. Initial attempts at organ transplantation were disappointing in terms of both allograft and patient survival. Although there were widely publicized successes in living related kidney transplants in the 1950s, it was not until 1962 that a long-term successful cadaveric renal transplant was performed in the United States. Surviving a transplant for more than a brief time was accomplished with the use of potent immunosuppressive agents. By the end of the 1970s, azathioprine, in combination with prednisone, provided 1-year overall survival rates around 50% for cadaver kidney transplants and near 80% for living related transplants. Unfortunately, 5-year allograft survival rates for cadaver transplants hovered around 35%. With the widespread use of cyclosporine in the 1980s, 5-year cadaver allograft survival rates doubled.[1] This success led to a dramatic increase in transplantation, which was constrained only by donor organ availability. With increased transplantation and increased survival, the number of living transplant recipients in the United States more than doubled from 81,873 in 1995 to 168,761 in 2004.[2]

Recipient survival past the immediate transplant period allowed the observation of the consequences of transplantation and long-term immunosuppression. Aside from mortality from other causes, end-stage renal disease patients on hemodialysis were noted to have malignancy rates about twice the normal population. Transplant recipients were soon observed to have a much more significant increase. In 1969, Penn and Starzl reported lymphomas in five renal transplant patients and theorized that the malignancies were related to the use of immunosuppressants.[3] By 1971, Schneck and Penn reported a 6% chance of developing a malignancy within 4 to 8 years after transplantation.[4] The association between solid organ transplantation and an increased risk of skin cancers was first described by Walder and colleagues in 1971.[5] This relationship has now been confirmed by multiple centers with a documented 65-fold increased risk of SCC [6[, 10-fold increase in BCC [7], 3.6-fold increased risk of malignant melanoma [8], and 84-fold increase in Kaposi's sarcoma.[6] These tumors are also more aggressive in behavior when compared to those in the general population and demonstrate increased rates of metastasis.[9] Occasionally, patients will develop tremendous numbers of tumors, having 100 or more distinct skin cancers in a year.[10]

Most of the early demographic data regarding the high incidence of skin cancer in organ transplant recipients came from transplant physicians collecting outcomes data on transplant survivors. Much of the awareness of the problem of increased malignancy in transplant recipients originated with Dr. Israel Penn. As noted in the preceding paragraph, Dr. Penn was the first to report on the increased incidence of malignancies following transplantation. He established the Cincinnati Transplant Tumor Registry, now the Israel Penn International Transplant Tumor Registry (www.ipittr.uc.edu/Home.cfm), which has tracked data on over 15,000 malignancies in transplant recipients. He also disseminated this information throughout the medical community via hundreds of publications. Dr. Penn is widely recognized as having laid the cornerstone of transplant oncology (Figure 1.1).

HISTORY OF TRANSPLANT DERMATOLOGY

Dermatologists became involved in the field of transplant oncology as transplant patients presented for diagnosis and treatment of their cutaneous malignancies, as well as infectious and inflammatory skin diseases. As larger numbers of transplant

Figure 1.1. Israel Penn, M.D., 1930–1999, the father of transplant oncology. (Used with permission from Steven Woodle, MD, Israel Penn International Transplant Tumor Registry.)

patients presented with multiple, aggressive tumors and some succumbed to metastatic disease, dermatologists found it increasingly important to focus on defining the nature and magnitude of the problem and exploring its etiology. As early as 1977, the incidence of skin cancer in renal transplant recipients was being reported in the mainstream dermatologic literature when Hoxtell and colleagues detailed a 36-fold increase in cutaneous squamous cell carcinoma in a Minnesota renal transplant cohort.[11] Abel in 1989, provided a CME review of cutaneous problems in organ transplant recipients in the *Journal of the American Academy of Dermatology* solidifying the importance of transplant oncology in dermatology.[12] Berg and Otley updated the dermatologic community on transplant cutaneous oncology with another *Journal of the American Academy of Dermatology CME* article in 2002.[13] An issue of *Dermatologic Surgery* in April of 2004 was devoted to transplant oncology. A visible affirmation of the importance of transplant cutaneous oncology in dermatology can be seen in the March 2006 issue of the *British Journal of Dermatology*. The issue contains four original articles and an editorial pertaining to the field. The timeline of development of transplant dermatology is outlined in Table 1.1.

Over the same period of time, transplant cutaneous oncology and transplant dermatology began to be discussed in presentations at regional and national meetings. Through the interaction between speakers and the audience, it gradually

Table 1.1 A timeline of transplant cutaneous oncology

1969	Penn reports increased risk of lymphoma
1971	Walder reports increased risk of skin cancer
1977	Hoxtell reports increased risk of skin cancer in Archives of Dermatology
1982	Penn establishes the Cincinnati Transplant Tumor Registry
1989	Abel publishes CME article in JAAD on transplant dermatology
2000	SCOPE formed
2001	First ITSCC organizational meeting
2002	First joint ITSCC/SCOPE meeting
2004	Transplant Oncology supplement to Dermatologic Surgery
2006	AT-RISC Alliance formed

became clear that a more systematic approach was needed to care for this unique set of patients and that this approach would require a collaborative effort by physicians involved in transplant cutaneous oncology around the world. In addition, because cutaneous carcinogenesis in transplant patients is accelerated and accentuated, understanding the details of the disease process in transplant recipients might provide insight into the mechanisms that underlie the development of skin cancer in the general population.

ORGANIZATIONS IN TRANSPLANT DERMATOLOGY

In attempting to define the course of metastatic SCC in transplant recipients, in 2000, Dr. Clark Otley and Juan Carlos Martinez recruited participation by interested dermatologists via email and internet invitations. This effort defined a multi-institutional group of dermatologists with similar interests in better understanding skin cancer in transplant patients and improving patient care. Under the guidance of Dr. Otley and Dr. Stuart Salasche, a preliminary meeting of these physicians was held in October 2001, in conjunction with the American Society of Dermatologic Surgery and the American College of Mohs Micrographic Surgery and Cutaneous Oncology Combined Annual Meeting in Dallas, Texas. A collaborative organization was envisioned to improve the care and quality of life for transplant patients and the North American Transplant-Skin Cancer Collaborative was formed. After membership grew to include professionals from Central and South America and Australia, the name was changed to the International Transplant-Skin Cancer Collaborative (ITSCC). Meetings are held annually in conjunction with the annual meeting of the American Academy of Dermatology.

The European counterpart to ITSCC, Skin Care in Organ Transplant Patients, Europe (SCOPE) was forming about the same time. Its initial goal was to establish an internet-based database of skin cancer in transplant patients. It rapidly expanded its vision to include not only epidemiology, but also basic research and patient care on transplant dermatology issues. SCOPE meets annually in the Spring. SCOPE includes

national organizations in its membership structure. One national organization, Skin Care in Organ Recipients, United Kingdom, has been particularly active with a separate yearly scientific meeting.

Dr. Salasche was instrumental in bringing ITSCC and SCOPE together. Representatives of both organizations first met formally in Berlin in January 2002. With an agreement on the need for collaboration on major issues established, annual joint workshops were held in August from 2002 to 2005. These workshops resulted in the publication of guidelines for the treatment of skin cancer in organ transplant recipients [14] and numerous other publications addressing the use of retinoids and reduction of immunosuppression. This international cooperation continues with continued annual joint meetings planned beginning in 2007.

Prevention of skin cancer was quickly established as a primary goal in the care of organ transplant patients at risk for skin cancer. Aggressive sun protection offers the best hope for prevention, and education is the key to sun protection. In addition, because most skin cancer is more easily treated when discovered early, education of transplant professionals and transplant patients is crucial. To this end, ITSCC teamed with the International Transplant Nurses Society and Transplant Recipients International, to form the After Transplant-Reduce the Incidence of Skin Cancer (AT-RISC) Alliance. The Alliance has developed educational materials to educate physicians, nurses, coordinators, and patients about the risks of skin cancer in transplant recipients. At the organization's web site, www.at-risc.org, there are downloadable brochures, posters, fact sheets, and PowerPoint presentations targeted at the various constituencies. Through an aggressive outreach program, especially involving transplant nurses, the Alliance hopes to reach transplant patients with a sun protection and early skin cancer recognition program and improve outcomes.

THE CHALLENGE

Solid organ transplantation has overcome enormous hurdles and made incredible strides in the past 50 years, but the journey is not complete. Organ procurement, patient selection, surgical technique, and immunosuppression are still evolving with the goal of extending life in patients with organ failure. The challenge for transplant cutaneous oncology and transplant dermatology is to play an active role in this process to eliminate skin cancer as a significant cause of morbidity and mortality. Additionally, early diagnosis of cutaneous infectious diseases and management of the cutaneous complications after organ transplantation is a priority. Our goals, as this text will illustrate, include patient education, early skin cancer recognition, understanding the process of carcinogenesis, developing better treatment plans and chemopreventive strategies, and exploring the effects of alterations of immunosuppression. We know well the ravages of skin cancer in organ transplant patients. The challenge now is to lessen the burden of this preventable complication in this special patient population.

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Section Two

TRANSPLANT MEDICINE AND DERMATOLOGY

2

The History of Organ Transplantation

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Solid organ transplantation can yield cures for previously fatal diseases. The concept of transplantation is very old. According to legend, in the fourth century, Cosmas and Damian, twin brothers and physicians from Arabia, were credited with amputating the cancerous leg of the custodian of a Roman basilica and replacing it with the leg from a slain Ethiopian gladiator recently buried in the Church of St. Peter. As a result, the brothers were honored in artist Fra Angelica's painting (Figures 2.1) and recognized as the patron saints of transplantation.[1,2]

In modern times, physicians envisioned replacing diseased organs with healthy ones, but before organs could be transplanted successfully, several technical medical problems had to be overcome (Table 2.1). The solutions included general anesthesia, first used in 1842 by a country doctor, Crawford Long, MD, in Jefferson, Georgia. After this procedure was publicly demonstrated in 1846 by a dentist, William Morton, at Massachusetts General Hospital, the technique of general anesthesia disseminated around the world in months. Next, studies by the chemist Louis Pasteur in Paris defined the role of bacteria in fermentation and putrefaction in wine making. These findings convinced the great surgeon Joseph Lister, of Glasgow, that similar germs in the air were responsible for surgical infections, an idea that led him to develop antiseptic surgery in the 1860s. Finally, in the early 1900s, Alexis Carrel, MD, in Lyon, France, the father of vascular surgery, was the first to suture two blood vessels together (vascular anastomosis), a procedure that made solid organ transplantation possible. Carrel later moved to Chicago and worked with Charles Guthrie, MD, grafting many kidneys, hearts, and other organs, using his blood vessel anastomosis technique (Figure 2.2). Carrel was awarded the Nobel Prize for this work in 1912. More than fifteen Nobel prizes have been awarded to scientists in fields related to transplantation and immunology.

Early experimentation with animal and human transplantation was performed in the early 1900s. Emerich Ullmann, MD, a surgeon born in Hungary, performed a famous demonstration before the Vienna Society of Physicians in the Bilroth-haus on March 7, 1902, removing a kidney of a dog and transplanting it into the neck of another dog. The end of the ureter was sutured to the skin and, in the presence of the audience, urine flowed from the ureter. Thus, Ullmann is credited with ushering in the era of solid organ transplantation. He later attempted to transplant the kidney of a pig into the elbow of a young woman with uremia, but the kidney failed to function and he ended his transplantation research.[3] A few years later, in 1906, Mathieu Jaboulay, MD, Professor of Surgery in Lyon, connected the vessels of a sheep kidney to the vessels of one patient and the vessels of a pig kidney to the vessels of another patient, both of whom were dying of renal failure. Neither kidney worked. The first attempts to transplant cadaveric human kidneys were in the 1930s by a Ukrainian surgeon, Yu Yu Voronoy, MD, who transplanted six kidneys into human recipients; all the kidneys failed to function. This result brought an end to the first technical period of transplantation.[3]

The first successful renal transplantation was between identical twins and was performed in 1954 in Boston. The recipient survived for 8 years before dying of heart complications but never had rejection of the kidney. This experience confirmed the benefit of organ replacement in the absence of an immune barrier. Organ transplantation became a reality for the first time.

Allogeneic solid organ transplantation, however, began slowly and in only a few institutions. The early times were referred to as the "dark days" or the "black years" of transplantation because most patients died. These were frustrating and challenging times for the surgical pioneers and their patients. For example, Thomas Starzl, MD (the first to perform liver transplantations), reported that the initial patients receiving liver transplants survived for a maximum of 21 days.[4] In the 1960s, there were only six active kidney transplant programs in the United States. Other organs first transplanted in the 1960s were bones, intestines, and lungs.

Dramatic attention was brought to the field of transplantation in 1967 when Christian Barnard, MD, in South Africa, transplanted the first human heart. The recipient survived for 18 days. The second heart transplant recipient survived for 6 hours, and the third for several years. This experience led to the frenetic transplantation of more than 100 hearts, but recipients had a 3-month survival rate of only 35%. Thus, cardiac transplantation was mostly abandoned until the 1980s.

Why were these transplanted organs failing? It was clear from the studies in Vienna in the early 1900s that autografts were almost always successful and allografts were nearly always unsuccessful. Dr Alexis Carrel stated that these organs failed because of "biological" and not surgical factors. Subsequently, during World War II in the 1940s, the English zoologist Sir Peter Medawar and the plastic surgeon Thomas Gibson, MD, working with skin grafts in burn victims, referred to these biologic factors as a "second-set response."[5] The first time a patient received a skin graft it would be rejected in 7 days. When a second graft was performed on the same person, it would be rejected in 3 days. The body had developed a specific

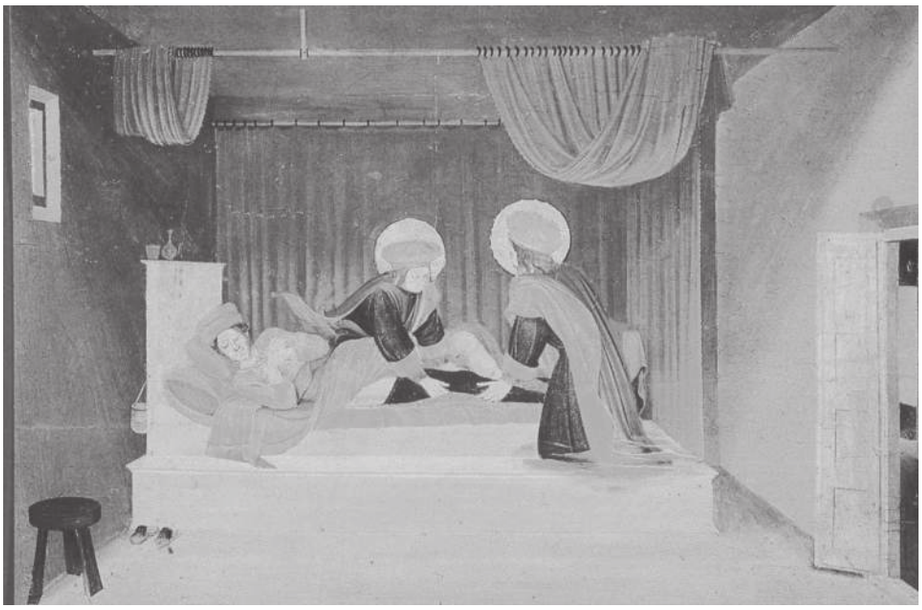

Figure 2.1. Cosmas and Damian, the patron saints of transplantation, replacing the cancerous leg of a man with the leg of a recently slain gladiator. (Used with permission of the Minister of Works and Cultural Activities.)

Table 2.1 Solid organ transplantation and skin cancer: a timeline

Date	*Event*
4th century A.D.	Cosmas and Damian transplant leg
1842	1st ether anesthesia for surgery
1900–1910	Blood vessel anastomosis
1902	1st public demonstration of solid organ transplantation
1954	1st successful renal transplantation
1959	1st use of immunosuppressants in organ transplant recipients
1968	1st report of increased malignancies in transplant recipients
1971	1st report of skin cancer in organ transplant recipients

response to the foreign tissue. This is now recognized as rejection, an immunologic event. The immunologic barrier was greater than the technical ability of the surgeons. The renowned heart surgeon Denton Cooley, MD, explained, "I have done all that I can do as a surgeon. It remains for the immunologists and biologists to unravel the mysteries that have limited our work."[6] Successful transplantation without immunosuppression was doomed to failure and would have to await an effective means of immunosuppression.

Early attempts at immunosuppression to enhance survival of organ transplants began in 1959 with total body irradiation designed to cripple the immune system. The side effects from radiation included susceptibility to overwhelming infections and death. That same year, chemical immunosuppression with the anticancer drug 6-mercaptopurine was introduced to more selectively modify the immune response. In 1960, azathioprine (the imidazole derivative of 6-mercaptopurine) was used with prednisone for immunosuppression. A combination of immunosuppressants (the cocktail approach), including prednisone, appeared to be more successful than the use of one drug alone. With the advent of effective multiagent immunosuppressive regimens, organ transplantation began to provide a realistic alternative to dialysis for kidney failure.

In 1978, a calcineurin inhibitor, cyclosporine, a natural earth fungal by-product discovered by a Swiss microbiologist, led to marked improvement in liver transplant viability. By the late 1970s, the chance of survival was 18% in patients with liver transplants who did not receive cyclosporine and 68% in those who did.

Unfortunately, with long-term immunosuppression using more potent medications, malignant disease was noted to be

a hazard of organ transplantation and immunosuppressive therapy. This association was first reported in 1968 by Dr Thomas Starzl at the Swiss Society of Immunology and the American Surgical Association. In 1969, Israel Penn, MD, and other colleagues of Starzl at the University of Colorado published the first paper on the development of malignancy (lymphomas) in five recipients of renal transplants. The malignancies were thought to be an indirect complication of organ transplantation and the measures taken to prevent rejection.[7] It soon became clear that the frequency of tumors in transplant recipients could not be due to chance alone. Penn and colleagues determined that 11 (6%) malignancies developed in 184 recipients 4–8 years after transplantation. In order to learn about transplant-associated malignancies, Penn began an informal registry, the Denver Transplant Tumor Registry, subsequently known as the Cincinnati Transplant Tumor Registry. Over several decades, Penn recorded data on thousands of transplant-related malignancies. After Penn's death in 1999, the registry was renamed the Israel Penn International Transplant Tumor Registry (http://www.ipittr.uc.edu/Main/main.cfm).

The frequency of cancer in patients receiving dialysis is twice that in the general population; but in Starzl's first 483 patients who received transplants, the frequency was several times normal. It became clear that the frequency of tumors that were common in the general population (lung, prostate, breast, and colon) was not increased in transplant recipients but that the frequency of various uncommon tumors (lymphomas, squamous cell carcinomas of the lip, Kaposi sarcoma, and carcinoma of the vulva, kidney, and liver) was higher in transplant recipients. The average time to the first cancer was 61 months, and the increased incidence compared with the general population ranged from 4 to 65 times for skin cancer, 28 to 49 times for lymphoma, 100 times for vulvar carcinoma, and 20 times for liver cancer.

Transplant-associated cancers could be classified as being of three origins: those inadvertently transmitted with the organ from the donor to the host (donor-derived), the relapse of previous cancer in recipients (recurrent), or development of new tumors, such as skin cancer and lymphoma (*de novo*), after transplantation. The cumulative risk for development of at least one malignancy (excluding nonmelanoma skin cancer) was approximately 30% after 20 years. Several common posttransplantation malignancies were thought to be virus-related. Calcineurin inhibitors and azathioprine were linked with posttransplantation malignancy, whereas newer agents such as mycophenolate mofetil and sirolimus were not and were thought to have antitumor properties.

By 1971, neoplasms of the lymphoreticular system were the only malignancies known to be associated with the use of immunosuppressive medications. That year, Brien Walder, MD, and colleagues from New South Wales, Australia, reported that 7 (14%) of 51 renal transplant recipients had a total of 20 malignant skin tumors 4 to 45 months after transplantation.[8] All patients had been treated with prednisone and azathioprine. In the investigators' regular dermatological clinics, basal cell carcinomas were 11 times more common than squamous cell carcinomas, but in this series of transplant patients, the basal cell:squamous cell carcinoma ratio was reversed to 1:16. The seven patients had 16 squamous cell carcinomas, 1 basal cell carcinoma, and 3 keratoacanthomas. They were primarily found on sun-exposed skin (hands, arms, neck), in young patients (average age, 36 years), and in those who had not been previously treated for skin cancer. This report was the first to indicate a link among transplantation, immunosuppressive drugs, and an increased risk for the development of skin cancer.

These findings have since been confirmed by numerous reports.[9–11] Compared with the general population, transplant recipients have an increased risk of skin cancer (squamous cell carcinomas, basal cell carcinomas, malignant melanomas, Merkel cell carcinomas, atypical fibroxanthomas, and Kaposi's sarcoma) depending on a patient's history of sun exposure, duration since transplantation, and the number and dosages of immunosuppressive drugs. Skin cancers now represent one-third to one-half of *de novo* tumors in transplant recipients. Characteristic of transplant-associated skin cancers include a reversal of the basal cell:squamous cell carcinoma ratio, an increased incidence of skin cancer up to several hundredfold, and a worse prognosis compared to cancers in non-immunosuppressed patients, including a greater tendency to recur after treatment and to metastasize.[12]

In an excellent book on the history of transplantation by Nicholas Tilney, MD, published in 2003, a single sentence was devoted to skin cancer, referring to it as "an important epidemiological problem."[2] We now appreciate from numerous reports that skin cancer is one of several malignancies that may be a considerable hazard after organ transplantation as a result of long-term immunosuppressive therapy. The history of solid organ transplantation is fascinating and replete with lessons. As this book will demonstrate, the history of transplant dermatology is young, but holds a sense of excitement to tackle the challenges that transplant patients experience with cutaneous disease.

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3

The Development of Modern Immunosuppressive Medications

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INTRODUCTION

The advent of modern immunosuppressive therapy is arguably the single most important factor in allowing solid organ transplantation to progress from a dubious and dangerous venture to the treatment of choice for end-stage organ failure. During the past two decades, a broad array of immunosuppressants has emerged to expand the armamentarium used by transplant physicians and surgeons for prevention and treatment of organ allograft rejection. The availability of these drugs has resulted in steadily improved outcomes for kidney, kidney/pancreas, liver, heart, lung, pancreas, and intestinal transplants. It has also allowed for the development of clinically feasible protocols for multiorgan transplantation, as well as transplantation of pancreatic islets, gonads, and compound tissues such as limbs. Despite these remarkable successes immunosuppressive drugs continue to lack specificity and are associated with many acute and chronic side effects. Although there has been significant progress in understanding the mechanistic basis of immunological tolerance, consistent clinical application of this knowledge to allow graft-specific tolerance, the ''Holy Grail'' of transplantation, remains elusive. Thus, the large majority of organ transplant recipients in the current era continue to require lifelong immunosuppression. Among the agents in common worldwide use for this purpose are corticosteroids, a select number of small-molecule drugs, and a growing panel of so-called biological agents that includes monoclonal and polyclonal antibodies. In addition to these established agents, a number of novel immunosuppressants have entered preclinical and clinical trials in organ transplant recipients in recent years and show promise for broader clinical use in the near future. In this chapter, the major, currently prescribed immunosuppressive medications, as well as the emerging panel of new agents targeting the immune response to organ allografts are summarized.

OVERALL STRATEGY FOR SOLID ORGAN TRANSPLANT IMMUNOSUPPRESSION

For each of the commonly transplanted solid organs, the general strategy for prevention of graft rejection involves the use of a synergistic combination of immunosuppressive medications designed (usually through a process of trial and error) to maximize efficacy and minimize toxicity. Although the field has begun to change more rapidly in the past five years, these regimens have, most often, involved the combined use of a corticosteroid, an antiproliferative agent, and a calcineurin inhibitor (CNI). Because a high overall level of immunosuppression is generally required during the immediate posttransplant period, frequently the use of a biological agent to further inhibit or deplete functional lymphocytes is required.

Table 3.1 summarizes the drugs and biological agents that are in common current use in the field of clinical transplantation. The corticosteroids most often administered to organ transplant recipients are methylprednisolone, dexamethasone, prednisone, and prednisolone. Typically, high doses of intravenous corticosteroids are prescribed during the first several days after a transplant, followed by a tapering oral schedule. The options for an antiproliferative agent include azathioprine, mycophenolate mofetil, and mycophenolate sodium. These medications are usually prescribed at fixed doses, which remain unchanged unless reductions are necessitated by toxicity or other immunosuppression-related adverse effects. The CNIs in current clinical use are cyclosporine and tacrolimus. More recently, a fourth class of immunosuppressant, inhibitors of the intracellular signaling protein mammalian target of rapamycin (mTOR), has entered the clinical arena in the form of the oral drug sirolimus (formerly referred to as rapamycin). For both CNIs and mTOR inhibitors, the doses are adjusted to achieve specific target trough levels in the blood with higher target levels prescribed during the initial months after the transplantation when rejection risk is highest. For long-term management, the preferred number of drugs and the overall level of immunosuppression required to prevent allograft rejection varies among the commonly transplant organs, being lowest for liver, intermediate for kidney, and highest for heart, lung, pancreas, and intestine. The currently available biological agents include polyclonal antibody preparations (rabbit and horse antilymphocyte antibodies), mouse monoclonal antibody preparations (anti-CD3 antibody (OKT3)) and human/mouse chimeric monoclonal antibody preparations (anti-CD25 antibodies (basiliximab and daclizumab), and anti-CD52 antibody (alemtuzumab)). These agents are typically used as courses of intravenous therapy during the first week after transplantation (induction therapy) or for intervention in the context of acute allograft rejection.

Using this combinatorial approach, transplant physicians have sought out effective prophylaxis against acute allograft rejection while minimizing both the specific medication toxicities, as well as the major direct adverse effects of long-term immunosuppression such as cancer, accelerated cardiovascular disease, and infection.[1–9] It should also be noted that, in addition to the introduction of new antirejection