THE DEVELOPMENT OF MALIGNANCIES IN RENAL ALLOGRAFT RECIPIENTS WITH SPECIAL EMPHASIS ON KAPOSI'S SARCOMA

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DECLARATION

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously in its entirety or in part submitted it at any university for a degree.

Signature:

Date:
RENAL transplantation is undoubtedly the best treatment for patients with irreversible renal failure. As a prelude to establishing the nature of malignancies in renal transplant patients we sought to determine factors influencing the outcome of renal transplantation. The survival of renal allografts and of recipients is influenced by a number of demographic, clinical and therapeutic factors. Some of these factors have been better studied than others, and we sought to establish the influence of particular factors on our own patients and allografts. The total number and nature of malignancies developing in these patients subsequent to transplantation was also established.

All patients transplanted in our unit between April 1, 1976 and March 31, 1999 were included in the study. In the study period, 542 patients received 623 renal allografts. Demographic details were analysed. Patient and graft outcomes were assessed using Kaplan-Meier survival analysis. The survival curves were compared using univariate analysis; results that were significant were subjected to multivariate analysis. The influence of a number of factors on graft and patient survival were assessed and compared. The impact of a variety of variables on the number and behaviour of malignancies was also established.
Patient and graft survival were superior in recipients who were aged less than 40 years; cyclosporine improved graft survival but not patient survival. Early graft loss was associated with a high patient mortality rate. Contrary to the experience elsewhere, black and white patients had similar outcomes after renal transplantation.

Of the 542 recipients 41 (8.1%) developed malignancies with Kaposi's sarcoma occurring, in 21 patients and skin cancers in 13 patients. The relative risk for the Kaposi's sarcoma development was 235. Kaposi's sarcoma was the most common tumour in non-white patients (accounting for 79% of malignancies in this group) and occurred less than 2 years after transplantation. Kaposi's sarcoma was equally common in male and female recipients. Under cyclosporine the latent period to malignancies was reduced but the frequency remained unaffected. Kaposi's sarcoma skin lesions were present in all the affected patients, with the lower limbs the most common site of involvement. Kaposi's sarcoma responded to reduction of immunosuppression without the need for complete discontinuation, and with preservation of renal function. Extracutaneous involvement occurred in over one quarter of the patients and invariably proved fatal in all patients with visceral organ involvement. The histopathology of posttransplant Kaposi's sarcoma was the same as that described in the other epidemiological forms of the disease.

White male recipients were at the greatest risk of developing skin cancers after renal transplantation. Squamous cell carcinomas were relatively more common and were found in sun-exposed areas. The lesions were treated only by local excision and none metastasized. Malignant lymphoma, breast cancer and lung cancer occurred in individual patients but the relative risk of all these lesions were close to unity. Patients with preexisting cancers did not develop recurrences following transplantation.

SECTION 2
Both immunosuppression and immunostimulation are thought to play a role in the development of Kaposi's sarcoma after renal transplantation. We investigated the quantitative and qualitative aspects of the immune system of patients who had developed Kaposi's sarcoma.
The lymphocyte phenotypes were established using flow cytometry while transformation studies were performed using mitogens. Pokeweed was used as the B-cell mitogen, and concanavalin A and phytahaemagglutinin were the T-cell mitogens. Cell mediated immunity was also tested using delayed type hypersensitivity skin tests and the serum immunoglobulin levels were estimated.

Firstly, with regard to humoral immunity, 2/3 of the patients had normal serum immunoglobulin levels, although the B-cell count was reduced in all the patients on immunosuppression. B-cell transformation tests with pokeweed mitogen revealed that B-cell function was not impaired in patients with Kaposi's sarcoma. The patients with decreased immunoglobulin levels also appeared to be malnourished as evidenced by low albumin levels. Secondly, CD3 and CD4, but not CD8, cell counts were reduced in patients with Kaposi's sarcoma. The transformation analyses revealed significant differences compared to controls, with reduced responses in patients with Kaposi's sarcoma. Thirdly, natural killer (NK) cell numbers were also reduced in patients with Kaposi's sarcoma. There were no significant differences in delayed type hypersensitivity skin reactions that could not be accounted for by racial differences.

Cellular immunity is impaired in patients with Kaposi's sarcoma with a reduction in the number of NK cells. Both of these components of the immune system are important in protection against malignant transformation.

SECTION 3

Kaposi's sarcoma is an important complication of renal transplantation. If the human herpesvirus 8 (HHV-8) causes Kaposi's sarcoma, the virus should be present in all Kaposi's sarcoma lesions and be drastically reduced or cleared from involved tissue on remission of the Kaposi's sarcoma.

Fourteen renal transplant patients with cutaneous Kaposi's sarcoma, including autopsy material from two cases, were investigated for the presence of HHV-8. A second skin biopsy was taken from 11 survivors, after remission of Kaposi's sarcoma, from normal skin in the same anatomical region as the first biopsy.
Remission was induced by reduction or cessation of immunosuppression. A peripheral blood sample was collected simultaneously with the repeat biopsy. A nested polymerase chain reaction assay was used to detect HHV-8 DNA in the biopsy tissue and peripheral blood mononuclear cells followed by direct sequencing of polymerase chain reaction product to detect any nucleotide changes.

HHV-8 DNA was detected in all the cutaneous Kaposi’s sarcoma and all the visceral Kaposi’s sarcoma samples, as well as a number of Kaposi’s sarcoma-free organs including the thyroid, salivary gland, and myocardium that have not been described before. Mutations in the viral DNA could be demonstrated in all patients. The mutations found were related more to that seen in AIDS-Kaposi’s sarcoma cases than that found in African endemic Kaposi’s sarcoma cases. HHV-8 sequences could be detected in follow-up frozen skin biopsies of five patients but were negative in the equivalent formalin-fixed specimens. Viral DNA was also detected in 2 of 11 peripheral blood mononuclear cell samples collected at the time of the follow-up skin biopsies.

Reduction or withdrawal of immunosuppression allows the immune system to recover sufficiently to reduce viral replication with subsequent viral persistence and low-grade viral replication that coincides with clinical remission of the Kaposi’s sarcoma lesions. This provides further evidence for the important etiological role played by HHV-8 in the pathogenesis of posttransplant Kaposi’s sarcoma.

SECTION 4

The recently discovered HHV-8 is an important factor in the aetiopathogenesis of Kaposi’s sarcoma. The reason for the exceptionally high prevalence of Kaposi’s sarcoma in our area, as well as that of other developing countries, remains unexplained. We investigated the seroprevalence of the virus in the different healthy subjects as well as organ donor-recipient pairs.

All recipients were tested at the time of transplantation, as were the paired donors. Control subjects tested were healthy blood donors, Renal Unit staff, and household contacts of patients with Kaposi’s sarcoma. An enzyme-linked immunoassay
(ELISA) to the whole virus was used for screening and all positives were confirmed using ELISA to the latent ORF 73 antigen.

The prevalence of HHV-8 was similar in all groups and averaged less than 6%. After transplantation the seroprevalence increased to almost 20% but neither the transplanted kidney nor blood transfused perioperatively could account for the increase. Kaposi's sarcoma developed in 3 of the 116 patients transplanted. All patients with Kaposi's sarcoma were proven to be HHV-8 seropositive before the development of the disease. Two of the patients who developed Kaposi's sarcoma were seropositive before transplantation. No patient who received a graft from a seropositive donor developed Kaposi's sarcoma.

We refute the notion that a high prevalence of HHV-8 in the general population is responsible for the high prevalence of Kaposi's sarcoma in our population or that the donor organ is a major source of infection in renal transplant recipients. Reactivation, rather than primary infection appears to be the source of the virus after renal transplantation.
OPSOMMINGS

AFDELING 1

Nieroorplanting is ongetwyfeld die beste behandeling vir pasiënte met onomkeerbare nierversaking. As 'n aanloop om die aard van maligniteite in nieroorplantingspasiënte vas te stel het ons gepoog om die faktore wat die uitkoms van nieroorplantings beïnvloed te bepaal. Die oorlewings van oorgeplante niere en van nierontvangers word deur 'n aantal demografiese, kliniese en terapeutiese faktore beïnvloed. Sommige van hierdie faktore is beter ondersoek as ander en ons het gepoog om die invloed van sekere faktore op ons eie pasiënte en oorgeplante niere te bepaal. Die getal en aard van maligniteite wat ontwikkel het in hierdie pasiënte ná nieroorplanting is ook gedokumenteer.

Alle pasiënte in ons eenheid in wie 'n nier tussen 1 April 1976 en 31 Maart 1999 oorgeplant was, is in die studie ingesluit. Tydens die studieperiode het 542 pasiënte 623 niere ontvang. Demografiese detail is ontleed. Pasient- en nieroorplantings uitkomste is beraam deur gebruik te maak van Kaplan-Meier oorlewings analiiese. Die oorlewingskurwes is vergelyk deur gebruik te maak van enkelveranderlike ontleedings; noemenswardige resultate is onderwerp aan meerveranderlike ontleedings. Die invloed van 'n aantal faktore op oorgeplante nier- en pasientoorlewings is ondersoek en vergelyk. Die impak van 'n verskeidenheid veranderlikes op die getal en gedrag van maligniteite is ook ondersoek.
Pasient oorlewing asook oorlewing van oorgeplante niere was beter in ontvangers onder die ouderdom van veertig jaar. Vroeë verlies van 'n oorgeplante nier het verband gehou met 'n hoë pasientmortaliteit. Siklosporien het die oorlewing van oorgeplante niere verbeter, maar nie dié van pasiente nie. In teenstelling met die ervaring elders, het swart en wit pasiente soortgelyke uitkomste uitkoms gehad na 'n nieroorplanting.

Van die 542 ontvangers, het 41 (8.1%) maligniteite ontwikkeld; Kaposi se sarkoom het in 21 pasiënte voorgekom en velkanker in 13 pasiënte. Die relatiewe risiko ("relative risk") vir die ontwikkeling van Kaposi se sarkoom was 235. Kaposi se sarkoom was die algemeenste tumor in swart en gekleurde pasiënte (verantwoordelik vir 79% van maligniteite in dié groep) en het binne twee jaar voorgekom. Kaposi se sarkoom was ewe algemeen in manlike en vroulike ontvangers. Met behandeling deur middel van siklosporien het die latente periode totdat maligniteite ontwikkeld het verkort, maar die insidensie daarvan het onveranderd gebly. Velletsels geassosieer met Kaposi se sarkoom was teenwoordig in alle pasiënte met die vel van die onderste ledemate die mees algemeen betrokke ligging. Die sarkoom het gereageer op vermindering van immuunonderdrukking, sonder die nodigheid vir volkome onttrekking, en met die bewaring van nierfunksie. Ekstrakutane betrokkenheid het in meer as 'n kwart van die pasiënte voorgekom en was altyd noodlottig in pasiënte met viserale aantasting. Die histopatologie van postoorplanting Kaposi se sarkoom was dieselfde as dié wat beskryf is vir die ander epidemiologiese vorms van die siekte.

Wit mans het die hoogste risiko vir die ontwikkeling van velkankers na nieroorplanting gehad. Plaveiselsel karsinoom was betreklik meer algemeen en het in son-blootgestelde areas voorgekom. Die letsels was uitsluitlik met lokale eksisie behandel en geen pasiënte het metastases ontwikkeld nie. Maligne limfoom, borskanker, en longkanker het in enkele pasiënte voorgekom maar die relatiewe risiko van al dié letsels was om en by een gewees. Nie een van die pasiënte met vorige maligniteite het herhaling van die tumore na oorplanting ontwikkeld nie.
AFDELING 2

Die vermoede is dat beide immuunonderdrukking en immuunstimulasie 'n rol speel in die ontwikkeling van Kaposi se sarkoom na 'n nieroorplanting. Ons het die kwantitiewe en kwalitatiewe aspekte van die immuunsisteem van pasiënte wat Kaposi se sarkoom ontwikkel het na 'n nieroorplanting, ondersoek.

Limfosiet fenotipes is met behulp van vloeisitometrie bepaal, terwyl transformasiestudies uitgevoer is deur gebruik te maak van mitogene. "Pokeweed" is gebruik as die B-sel mitogeen, en konkanavalien A en fitaheemagglutinien was die T-sel mitogene. Sel-gemediëerde immuniteit was ook getoets deur die gebruik van vertraagde tipe hipersensitiwiteit veltoetse. Die serum immunoglobulien vlakke was ook bepaal.

Eerstens, met betrekking tot humorale immuniteit, het 2/3 van die pasiënte normale serum immunoglobulienvlakke gehad, alhoewel die B-seltelling verminder was in al die pasiënte op immuunonderdrukking. B-seltellings en B-seltransformasie-toetse met "pokeweed" mitogeen het getoon dat B-sel funksie nie ingekort was in pasiënte met Kaposi se sarkoom nie. Die pasiënte met verminderde serum immunoglobulinvlakke het ook wangevoed voorgekom soos die verlaagde serum albumienvlakke uitgewys het.

Tweedens was CD3 en CD4 seltellings, maar nie CD8 nie, verlaag in pasiënte met Kaposi se sarkoom. Betekenisvolle verskille is ook aangetoon met T-sel transformasietoetse in vergelyking met kontroles, met verminderde response in Kaposi se sarkoom pasiënte. Derdens was natuurlike dodersel (NK) getalle ook minder in pasiënte met Kaposi se sarkoom. Daar was geen noemenswaardige verskille in vetraagde tipe hipersensitiwiteit velreaksies wat nie deur rasseverskille kon verklaar word nie.

Sellulêre immuniteit is ingekort in pasiënte met Kaposi se sarkoom met 'n verlaging in die aantal NK selle. Beide die komponente van die immuunstelsel is belangrik vir beskerming teen maligne transformasie.
AFDELING 3

Kaposi se sarkoom is 'n belangrike komplikasie van nieroorplanting. As die menslike herpesvirus-8 (HHV-8) Kaposi se sarkoom veroorsaak, behoort die virus teenwoordig te wees in alle letsels en as Kaposi se sarkoom remissie ondergaan behoort dit drasties te verminder of te verdwyn in weefsel waarin dit voorkom.

Veertien nieroorplantingspasiënte met Kaposi se sarkoom van die vel, insluitend outopsiemateriaal van twee gevalle, is ondersoek vir die teenwoordigheid van HHV-8. 'n Tweede velbiopsie van dieselfde anatomiese area as die eerste is uitgevoer op 11 oorlewende pasiënte na remissie van die sarkoom. Remissie was deur die verminder of onttrekking van immuunonderdrukking bewerkstellig. 'n Perifere bloedmonster is by dieselfde geleentheid as die tweede biopsie geneem. 'n Geneste polimerase kettingreaksiestoets ("nested polymerase chain reaction") is gebruik om die teenwoordigheid van HHV-8 DNA in die biopsieweefsel en perifere bloed mononukluëre selle te bepaal, gevolg deur direkte volgordebepaling ("sequencing") van die polimerase kettingreaksieproduk om enige nukleotiedveranderings te dokumenteer.

HHV-8 DNA is waargeneem in al die kutane Kaposi se sarkoom en al die viserale Kaposi se sarkoom monsters, sowel as in weefsel waar die Kaposi se sarkoom nie voorgekom het nie en waar die teenwoordigheid van die virus nie tevore beskryf is nie, soos die skilklier, speekselklier, en hartspier. Mutasies in die virale DNA kon in alle pasiënte aangetoon word. Die mutasies wat gevind is, was nader verwant aan dié wat in VIGS-Kaposi se sarkoom beskryf is as dié wat in endemiese Kaposi se sarkoom in Afrika gevind word. HHV-8 volgordes kon waargeneem word in bevrome opvolg-velbiopsies van vyf pasiënte, maar was afwesig in die ekwivalente formalien-gefixeerde monsters. Virus DNA is ook waargeneem in 2 van 11 perifere bloed mononukluëre selmonster wat versamel is tydens die opvolg velbiopsies.

Verminder of onttrekking van immuunonderdrukking laat die immuunsisteem toe om genoegsaam te herstel om virale replikasie te verminder met daaropvolgende teenwoordigheid en laaggraadse virale replikasie wat ooreenstem met kliniese remissie van letsels van Kaposi se sarkoom. Dit verskaf verdere bewyse van die
belangrike oorsaaklike rol wat deur HHV-8 gespeel word in die patogenese van postoorplanting Kaposi se sarkoom.

AFDELING 4

Die onlangs-ontdekte HHV-8 is 'n belangrike faktor in die etiopathogenese van Kaposi se sarkoom. Die rede vir die buitengewone hoë prevalensie in ons gebied, sowel as dié van ander ontwikkelende lande, is nie voor die hand liggend nie. Ons het die seroprevalensie van die virus in verskillende gesonde persone, sowel as orgaan donor-ontvanger pare ondersoek.

Alle nierontvangers en hul gepaarde donors is getoets ten tye van die nieroorplanting. Getoetste kontrole persone was gesonde bloedskenkers, nierenheid personeel en huishoudlike kontakte van pasiënte met vorige Kaposi se sarkoom. 'n Ensiemgekoppelde immuuntoets (enzyme-linked immunoassay; ELISA) vir die volledige virus was gebruik vir sifting en bevestiging is verkry vir alle positiewe toets deur gebruik te maak van 'n ELISA vir die latente ORF 73 antigeen.

Die prevalensie van HHV-8 was vergelykbaar in alle groepe en was gemiddeld minder as 6%. Na oorplanting het die prevalensie gestyg tot byna 20%, maar nóg die oorgeplante nier nóg perioperatiewe bloedoortappings kom die styging verklaar. Kaposi se sarkoom het in 3 van 116 van die pasiënte wat 'n oorplanting ondergaan het, ontwikkeld. Ál die pasiënte met Kaposi se sarkoom was HHV-8 seropositief vóór die ontwikkeling van die Kaposi se sarkoom. Twee van die pasiënte wat Kaposi se sarkoom ontwikkel het was seropositief vóór die oorplanting. Geen pasient wat 'n nier van 'n seropositiewe donor ontvang het, het Kaposi se sarkoom ontwikkeld nie.

Ons weerle die stelling dat 'n hoë prevalensie van HHV-8 in die algemene bevolking verantwoordelik is vir die hoë prevalensie van Kaposi se sarkoom onder ons nieroorplantingspasiënte of dat die donornier 'n belangrike bron van infeksie is. Dit wil voorkom of heraktivering, eerder as primêre infeksie, 'n bron van die virus is na nieroorplanting.
DEDICATION

This work I dedicate to my entire family who sacrificed considerably more than I did during the course of the project. Their love and support was the beacon that guided me during the stormy course of this undertaking. To my parents whose belief in their children was my source of inspiration; to my brother and sisters, and their spouses for understanding when there was no reason to do so; to my wife, Raheme and sons, Tauriq and Mikhail, for their unstinting support but especially their unconditional love even when they were not quite sure who the stranger in their midst was.
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To all the above I wish to thank, as well, for their friendship, which carried me through when the goal seemed to dim.
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ADDENDUM: Publications and Congress Presentations
Science is not a static compendium of eternal truths but a continually evolving body of knowledge and ideas.

_R.S. Schwartz_
THE DEVELOPMENT OF MALIGNANCIES IN RENAL ALLOGRAFT RECIPIENTS WITH SPECIAL EMPHASIS ON KAPOSI'S SARCOMA

Mohammed Rafique Moosa

Dissertation presented for the Degree Doctor of Medicine at the University of Stellenbosch

Volume 1

Promotor: Professor D.F. Du Toit
Co-Promotor: Professor P.A.B. Wranz

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SECTION 1

Alexis Carrell (1873-1944)
INTRODUCTION

Organ transplantation is arguably one of the most impressive medical therapeutic advances of the last century. It has prolonged the survival of countless patients around the world suffering from endstage organ failure. Perhaps, as important, is the often-dramatic improvement in the quality of life that these patients experience following organ transplantation. No other form of treatment has raised as much hope and expectation. The success of organ transplantation has resulted in an increase in the demand for this form of treatment by a public that has become increasingly aware of its benefits, but is often ignorant of its many problems, of which development of malignancies is an uncommon, but serious one.

A successful kidney transplant is undoubtedly the best treatment for the patient with endstage renal failure. For the individual patient, not only is it the most cost-effective option, but it also holds the promise of improved quality of life (Hathaway et al., 1998) and longevity compared to dialysis therapy (Basadonna et al., 1992; Denton et
The success of renal transplantation is dependent on adequate immunosuppression to prevent and treat acute rejection. Adequate immunosuppression, however, represents a fine balance between minimising the toxicity of the drugs and maximising the efficacy (Fig. 1-1). The price that patients pay for long-term immunosuppression can be quite considerable. The commonest causes of morbidity in recipients of renal allografts are infections and cardiovascular disease (Arend et al., 1997; Mazzuchhi et al., 1999; Ojo et al., 2000; Washer et al., 1983) with malignancies accounting for significant mortality in long-term survivors (Sheil et al., 1980). It is well recognised that the longer patients survive the greater the likelihood of them developing malignancies (Disney et al., 1998; Disney et al., 1997; Sheil, 1994b).

![Adequate Immunosuppression](image)

**Fig. 1-1** A delicate balance exists between under-immunosuppression that may result in acute rejection and over-immunosuppression that may produce adverse events.
MOTIVATION FOR THIS STUDY

The idea for this study arose as a result of observations made while collecting data on our renal allograft recipients for the Cincinnati Transplant Tumor Registry (CTTR) (now known as the Israel Penn International Transplant Tumor Registry) at the request of the late Dr Israel Penn, the founder of the Registry. It became clear to us that the pattern of malignancies that we were observing in our transplant patients differed entirely from that reported by other countries that were submitting data to the same registry. While countries such as Australia (Sheil, 1994a; Sheil, 1996) and the United States of America (USA) (Penn, 1994), and even European countries were reporting very high incidences of skin cancers following renal transplantation (Blohme et al., 1990; Coebergh et al., 1991), we were observing a very high incidence of Kaposi’s sarcoma. Our suspicion of an alternative pattern of cancers was supported by the experience of other developing countries with the first reports originating in Saudi Arabia (Qunibi et al., 1988).

Our first approach was to study our renal transplant recipients as a group as this had never been done previously. This involved studying the demography of this population and the outcome of renal transplantation in these patients. We made some interesting observations in this preliminary phase of the study especially with regard to the impact of the immunosuppressive agents. Although we found that infections and cardiovascular disease were the major causes of mortality we did proceed to study the nature of the malignancies that occurred in these patients. These aspects of the study are contained in Section 1 of this dissertation and form the core this study. The various chapters of this section explore the outcome of renal transplantation in our cohort in comparison with local, national and international groups. Our study spans a period of 23 years, which is one of the longest reported but more importantly allows comparisons in different treatment eras. These chapters are also unique because we look at factors influencing graft survival that have never been addressed in this country. The remaining chapters in this section specifically address the problems of transplant malignancies. We recount in detail our experience with Kaposi’s sarcoma and compare it with experience elsewhere. Our treatment of the disease confirms what has been suggested by the literature but never proven until this study. The unique pattern of malignancies in the black
compared to the white patients epitomises the experience of cancers in developing and developed countries respectively.

In Section 2, Chapter 14 of this dissertation we expand on our published study (Moosa et al., 1998). An important aetiological factor of Kaposi's sarcoma is postulated to be the human herpesvirus type 8 (HHV-8). In this chapter we describe the presence of the HHV-8 in the Kaposi's sarcoma tissue of all our patients with the posttransplant form of the disease, as have some other authors. Unique to this study is our observation that when the disease remits, the virus can no longer be detected locally.

In Section 3, Chapter 15, we investigate the role of the immune system in the development Kaposi's sarcoma. Since some degree of immunosuppression is present in most if not all the forms of Kaposi's sarcoma, we attempt to establish the immune status of posttransplant patients who had developed Kaposi's sarcoma. Although, immunosuppression has been recognised to contribute to the development of the disease, the exact nature of the immune defect that allows Kaposi's sarcoma to occur remains unknown. We also discuss the known mechanisms of action of the immunosuppressive agents that we used and explore the influence of these agents on the development of malignancies in Chapter 16.

Finally, with growing acceptance of an important aetiological role for HHV-8 in the development of Kaposi's sarcoma, the question of the epidemiology of the virus becomes an issue. The virus belongs to the herpesvirus group and the question that remains to be answered is whether HHV-8 behaves like other viruses in the group. We attempt to answer the question by investigating the presence of antibodies to the virus in different groupings including transplant recipients, Renal Unit staff, healthy blood donors, relatives and contacts of Kaposi's sarcoma patients. Also unique to this project is the study of organ donor-recipient pairs and the assessment of the risk for the development of Kaposi's sarcoma.

An important thread that runs through this dissertation is the fact that we are reporting our experience from a developing country. Most of the data that exist today has been reported from countries with developed economies. We show that
the experience from these first world countries cannot and should not be extrapolated to countries with emerging market economies. Differences between the two economic extremes have a profound impact on the disease patterns in these countries including malignancies (Jones, 1999), and this theme is exploited throughout.

For the sake of convenience, the references have been included at the end of each chapter. An extensive review of the literature has been undertaken with the citations included mainly in the Introductory and Discussion portions of the chapters, where it was easier to place our own experience in perspective. Extensive use has also been made of Tables and Figures to aid in the illustration of important points.

Most of the surgical and other principles applied in organ transplantation today evolved over time, and the successes we enjoy today and the techniques we take for granted is a tribute to the hard work and astute observations of our predecessors. In honour of their illustrious achievements, a brief review of the History of Renal Transplantation has been undertaken in Chapter 2. In honour of the amazing contributions to medicine generally and dermatology specifically, a brief biography of Moritz Kaposi is presented in Chapter 7.

LITERATURE CITED


Chapter 2

AN HISTORICAL PERSPECTIVE OF RENAL TRANSPLANTATION

It is often enough to know that a thing is possible

Marius Barnard

The replacement of a diseased, malfunctioning organ with a healthy one removed from a living or dead donor is an attractive solution to the problem of end-stage organ failure. Man's fascination with transplantation dates back several millennia and began as the medicine of mythology (Kahan, 1991). Greek and Egyptian mythologies are rich in examples of metamorphoses and other fantastic events portraying man's earliest thoughts and imaginings about transplantation and grafting. In Ovid's Metamorphosis Diana transforms Actaeon into a stag as punishment for his voyeurism. He is then set upon and ripped to pieces by his own dogs who fail to recognise him. Nagy (1999) suggests that (sic) this could be considered the first literary evidence of transplantation and rejection. . !" This rich mythological world has served to foster the imaginations of many
painters including Picasso. In Picasso's *Guernica* the Minotaur's head is replaced with that of a bull's. However, the ancient civilisations of India and China have legends specifically relating to transplantation, which pre-date the Greek mythology. Some of these myths date back at least 3 millennia in the medicine of mythology (Bhandari *et al.*, 1997; Kahan, 1991). Although it is impossible to test the rationality or authenticity of these myths, they emerged from deep-seated religious beliefs. These fantastic stories in no way undermine the achievements of modern researchers in the last 100 years but by the same token, there can be little doubt of the conceptual contributions made by these seemingly impossible legendary feats (Bhandari *et al.*, 1997).

**INDIAN MYTHOLOGY**

**The legend of Lord Ganesha**

The Hindu scriptures contain accounts of transplantation that are reputedly 5000 years old. The *Vedas* are the main religious scriptures of Hinduism but it is the *Pur'ānas*, a collection of verses composed by Vedavyasa that vividly describes the nefarious activities of the gods Brahma the creator, Vishnu the preserver and Siva the destroyer. The disputes between the gods result in the mythical xenogeneic transplantation on the sage Daksha and the Indian god Ganesha that are performed

![Fig.2-1](http://scholar.sun.ac.za/pic.png)  
*Fig.2-1* Upper left: *Depiction of the legendary tale of Judge Lu performing a heart transplant.* Lower right: *The Lord Ganesha after his reincarnation.* From Bhandari *et al.* (1997).
by Siva. The legend of Daksha has it that the latter had 60 daughters, one of who, Sita, was married to Siva the destroyer. Daksha had a great dislike of his son-in-law and deliberately failed to invite him and Sita to a large religious ceremony. Sita attended the function uninvited, which resulted in her father humiliating her and insulting her husband in front of the invited guests. Disgraced, Sita killed herself by jumping into the fire. Upon hearing of the fate of his wife, Siva became furious and ordered two monsters under his control to disrupt the festivities, which they promptly did killing all the guests and beheading the hapless Daksha. The head was thrown into the same fire that had consumed his ill-fated daughter. At the request of all the gods, Siva however later called off his monsters and was ordered to bring Daksha back to life. However, the head was nowhere to be found and it was replaced with that of a ram with the help of Brahma the creator (Moore et al.,1984; Wilson,1961).

The legend of Ganesha (Fig. 2-1)
This legend is even more popular and well documented in Indian mythology. Parvati, another wife of Siva, created Ganesha to act as her sentry to forewarn of the god’s untimely visits. On the fateful day, Siva decided to pay Parvati, who was taking a bath, a visit, but was confronted by the trustworthy and reliable Ganesha, who making no exceptions refused him entry. He severely assaulted Siva and his companions and a heated battle ensued. Realising that her pride was at stake, Parvati endowed Ganesha with supreme powers and weapons, which made him invincible. Realising this, Siva stealthily crept up on Ganesha and in the heat of the battle decapitated him with his trident. Parvati was furious when she learnt of her loyal servant’s fate and threatened to destroy the universe. She only relented when Siva agreed to reincarnate Ganesha and to endow him with divine powers. However, Ganesha’s head could not be found and Siva sent his allies to bring back the head of the first living creature found to be committing an error against nature. This happened to be an elephant that was found to be sleeping facing the north. They removed the head of the elephant and attached it to the headless body of Ganesha who was thus restored to life (Kahan,1989b; Mackenzie,1978).

Xenotransplantation: acts of repentance
It would appear that most instances of xenotransplantation in Hindu mythology are related to the god Siva who decapitates human beings in a fit of rage. He then uses
animals as donors when he performs the transplants as penitence for his brash actions. These accounts are reputedly 5000 years old and probably represent the oldest accounts of transplantation in history (Bhandari et al., 1997).

**CHINESE MYTHOLOGY**

**Judge Lu** (Figs. 2-1 and 2-2)

The Chinese legends are less gruesome and are acts of kindness rather than acts of retribution and include two popular stories. The story of Judge Lu tells of a brave but simple man, Zhu Ertan, who was encouraged by his mischievous companions, in the middle of the night, to bring the Infernal Judge back to them. To their surprise he returned with a full-length effigy of the Judge. Zhu proceeded to invoke the image and invited it to drink with him whenever he felt the fancy to do so. He then returned the image to its rightful place. The following evening the judge walked into Zhu’s humble abode and the poor man pleaded for his life. But the good Judge did not intend to punish the imbecile and instead accepted the offer of the drink. The judge became a regular visitor thereafter stopping by 2 to 3 days a week. One evening Zhu awoke with a throbbing pain in his chest to find the judge at his bedside. The judge had cut open his chest and was about to remove his heart. Zhu pleaded for

*Fig. 2-2 Another depiction of Judge Lu at work. From Lerut (2000).*
his life but the judge reassured him and informed Zhu that he was replacing his heart with a smarter one. He completed his operation and not only was Zhu fine after the procedure but he became a famous writer with a faultless memory. He was most grateful to the Judge for his wonderful gift but pleaded for one more favour. He argued that if the Judge could exchange his heart he surely could perform his craft on Zhu's ugly wife. The Judge was delighted to comply and a few days later he returned with the head of a beautiful young woman that he successfully transplanted to Zhu's wife (Zhuangzi, 1991).

Doctor Pien Ch'iao The other classical Chinese legend describes the story of the Chinese doctor Pien Ch'iao. Kung He and Ch'i Ying were two men from the province of Po-Hai in China who sent for Pien Ch'iao when they both took ill. The doctor diagnosed a domination of "yin" in one and a domination of "yang" in the other patient. Pien Ch'iao recommended an exchange of hearts to restore equilibrium of the two men's energy. Not only did the two men accept the diagnosis but also they agreed to the treatment. Pien Ch'iao cut open their chests and exchanged their
hearts. More importantly he used a strong narcotic to render the patients unconscious and postoperatively applied potent drugs. Both patients made a full recovery (Wong et al., 1973).

CHRISTIAN ERA (FIG. 2-3)

Miracles
The arrival of the Christian era saw the emergence of miracles based on acts of faith. The most famous miracle was recorded in the 13th century in the Leggenda Aurea of Jacopo da Varagine who recounts the "miracle of the black leg" performed by twin brothers Saint Cosmas and Saint Damian in 348 A.D. In this account the holy men grafted the leg of a deceased Ethiopian Moor gladiator to replace the gangrenous limb of Deacon Justinian, the sacristan of the Roman basilica. (Kahan, 1983; Nagy, 1999)

These myths and miracles were the product of man's fertile imagination. However, for several centuries, transplantation remained the domain of eccentric painters and imaginative writers until the early part of the last century (Nagy, 1999). Renal transplantation has now become routine treatment for end-stage renal failure but its path to clinical acceptance was a rocky one fraught with difficulties that often appeared to be insurmountable. However, developments along three major areas set the stage for the success of the procedure. These developments occurred in the surgical technical aspects of the procedure that were mastered relatively early, the appreciation of the immunological nature of rejection and lastly the development of immunosuppressive drugs.

1. PERFECTING THE SURGICAL TECHNIQUES OF RENAL TRANSPLANTATION

THE EARLY PIONEERS
In the second century BC the Indian surgeon Sushruta performed the first skin autotransplants for rhinoplasty (Susruta, 1907). This skill was rediscovered by famous Bolognese surgeon and anatomist Gaspare Tagliacozzi in 1596, to reconstruct noses destroyed by syphilis and other diseases (Gnudi et al., 1950).
Tagliacozzi was also the first physician to appreciate the relevance of biological individuality when he stated: "The singular character of the individual entirely dissuades us from attempting work (tissue transplantation) on another person" suggesting that he had a notion of the barriers to allotransplantation (Converse et al., 1968). Hunter (1935) was however successful at engrafting a human tooth to the comb of a cock in the 18th century which led him to conclude that "...transplantation is founded on a predisposition in all living substances to unite when brought into contact with each other".

**Early animal experiments**

In 1804 Baronio successfully grafted skin both allogeneically and xenogeneically (Baronio, 1804). Paul Pert (1863), successor to Claude Bernard disputed this claim in 1863 in his doctoral dissertation De la Greffe Animale. In his thesis he outlined animal experiments using skin and tissue, allo- xeno- and rat parabiont "Siamese" grafts. He concluded that autografts would be successful but that allografts and xenografts would predictably fail.

**Surgical advances**

In the last quarter of the 19th century advances in suturing techniques were made by Murphy (1897), Payr (1900) and Jaboulay (1906). Animal experiments were performed intermittently in the early years of the 20th century to address the issues of transplantation. The kidney emerged as the best experimental model. The reason for this was that the kidney was paired, had a relatively simple blood supply, and the flow of urine through the ureter served as an instant marker of function.

**Ullman's contribution**

In 1902 Emerich Ullman made a major breakthrough when he reported the first successful experimental renal transplant (Fig. 2-4) (Ullman, 1902). He removed a kidney from a dog and transplanted it into the neck of another dog. The graft functioned for 5 days. He proceeded to experiment with auto-, alio- and xenotransplants and even attempted to transplant the kidney of a pig into a uraemic woman in 1902 (Nagy, 1999; Ullman, 1914). However, although he failed to report his attempts at human transplant until 1914, he is credited with the initiating the transplant era (Hamilton, 1994; Nagy, 1999)
Inhalt:


IV. Aus verschiedenen Zeitungsblatt.

V. Vornemliche Nachrichten.

VI. Vereinigungskundige Mitteilungen und Veranstaltungen.

Expérimenle Nierentransplantation.

Verlaßt die Mitteilungen

Von Dr. Ernesti Ullmann, Privatdozenten für Chirurgie in Wien.

Meine Herren! Gelegentlich meiner Versuche über Derm-tranplantation, über welche ich vor Jahren dieser Gesellschaft zu berichten die Ehre hatte, dachte ich daran, ob es nicht möglich wäre, nach die Niere zu transplantieren. Die ersten einheimischen Versuche mißlangen aus dem Grunde, weil ich als Versuchsobjekt das Schwein wähle, dessen Venen untersuchten sich nicht für die Transplantation an Handen ausgeführt habe, gelangen sie vollständig. Ich will vorerst benennen, dass es sich bei meinen Versuchen und als solchen wählte ich erst die Jäginalgegen, später auf Herrn Hofrat Exner's Empfehlung den Hals, weil an der letzteren Stelle die Thiere sich nicht leiden können und eine Veranlassung um ebenso vermieden werden kann — wird durch einen Schacht Arterie und Vene, am Halse also Carotis und Vene jugularis auf eine weise Strecke bis freigesagt; dieselben werden peripherwärts ligirt und centralwärts mit je einem arumischen Schieber — armirt, damit kein Verlust der Gefässe aussteht — von der. Nun werden die Gefässe durchschritten und sowohl Carotis als Jugularis zur Gefässverknüpfung, wie von Payr angewogen wurde, vorbereitet. Die Gefässe werden durch kleine Mageninnehräume, welche ich mir auf die Weise herstellen liess, dass die eine Hälfte der Brust gart, die andere Hälfte zwei

Fig. 2-4 Publication of Ullman's first series of experimental transplants in 1902. The obituary of M. Kaposi who described Kaposi's sarcoma also appeared in this issue of the journal.
Historical Aspects

Fig. 2-5 Nobel laureate Alexis Carrel pioneered a number of surgical techniques many of which are still in use today. The Carrel patch was a major advance in vascular surgery and is still used today.

produced urine for one hour before they failed. The failure of the grafts was attributed to vascular thrombosis. Although the grafts failed this is considered the first technically successful xenotransplant in humans (Jaboulay, 1906).

Alexis Carrel (Fig. 2-5)

Working with Jaboulay was his protégé Carrel, who in 1902, under Jaboulay's guidance started developing the suturing techniques that are still in use a century later. With fine silk suture material he used his newly developed triangulation technique to perform renal autotransplants in animals and noted that they produced urine. Infection ultimately destroyed all the grafts. Carrell (1902) also performed experimental transplants of blood vessels, thyroid, parathyroids, heart and other organs. In 1906 Carrel, in collaboration with Guthrie described his famous "patching method" for anastomosing small blood vessels (Carrel et al., 1906). This was one of the most useful techniques to be developed in surgery and contributed immensely to the technical success of organ transplantation surgery. He also developed the internal vascular shunt and reported aortic patching using inert foreign materials.
For his invaluable contributions Carrel received the Nobel Award in Physiology and Medicine in 1912 (Kahan, 1991).

**Ernst Unger**

The second attempt at human transplantation was better documented than the first one. In 1909 Ernst Unger attempted to transplant a kidney from a pig ape to the thigh vessels of a young girl dying from renal failure. The kidney failed to produce urine and together with his extensive experience in animal studies he concluded with some foresight that there had to be a "biochemical" barrier to transplantation (Unger, 1909). These early experiments established that renal transplantation was technically possible (Table 2-1) but lack of simple tests to monitor renal function as well as uncertainty of mechanisms underlying graft rejection led to a decline in interest in transplantation until well after the Second World War (Hamilton, 1994).

**Table 2-1 Early experimental renal transplantation**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1902</td>
<td>Kidney allograft and xenografts in dogs and goats</td>
<td>Ullman, 1902</td>
</tr>
<tr>
<td>1902</td>
<td>Kidney autografts in dogs</td>
<td>Carrel, 1902</td>
</tr>
<tr>
<td>1905</td>
<td>Kidney allografts to groin, neck, renal fossa in dogs</td>
<td>Floresco*</td>
</tr>
<tr>
<td>1906</td>
<td>First human kidney transplant (xenograft)</td>
<td>Jaboulay, 1906</td>
</tr>
<tr>
<td>1906</td>
<td>Improved technique for vascular access</td>
<td>Carrel et al., 1906</td>
</tr>
<tr>
<td>1909</td>
<td>Second human kidney transplant (xenograft)</td>
<td>Unger, 1909</td>
</tr>
<tr>
<td>1910</td>
<td>Kidney allografts in dogs</td>
<td>Villard*</td>
</tr>
<tr>
<td>1924</td>
<td><em>En bloc</em> kidney xenografts: cats to dogs in cold preservation</td>
<td>Avromovici*</td>
</tr>
<tr>
<td>1923</td>
<td>Kidney autografts in dogs and goats</td>
<td>Williamson, 1923</td>
</tr>
<tr>
<td>1926</td>
<td>Kidney autografts in dogs and goats</td>
<td>Williamson, 1926</td>
</tr>
<tr>
<td>1926</td>
<td>Kidney allografts in dogs</td>
<td>Holloway*</td>
</tr>
<tr>
<td>1934</td>
<td>Kidney auto/allografts in dogs</td>
<td>Win and Mann*</td>
</tr>
<tr>
<td>1948</td>
<td>Kidney allografts could clear urea</td>
<td>Oudet*</td>
</tr>
<tr>
<td>1950</td>
<td>Biology of renal transplantation (neck) in dogs</td>
<td>Dempster, 1950</td>
</tr>
<tr>
<td>1953</td>
<td>Biology of renal transplantation (abdomen) in dogs</td>
<td>Simonsen, 1953</td>
</tr>
</tbody>
</table>

These references were cited by Lerut (2000).
The intermediate period (Table 2-2)
The highlight of this period was a dramatic but little known event that took place in the Ukraine province: Soviet surgeon Yu. Yu. Voronoy performed the first human renal allograft in 1936. He published his report in an obscure Spanish medical journal under the title, which translated into English, read "On the blockage of the reticulo-endothelial system in some kinds of corrosive sublimate poisoning and the transplantation of the kidney from the cadaver as method of treatment of that anuria" (Fig. 2-6). Not only does the title convey the fact that he performed a renal transplant from a cadaver, but also clearly shows his insight into the immunological characteristics of graft rejection (Voronoy, 1936). Voronoy was an experienced investigator who worked under Shamov, a respected surgeon. Their main area of interest was blood transfusion and testicular transplantation, then in vogue for its potentially rejuvenating ability (Hamilton et al., 1984). Voronoy turned his attention to kidney transplantation in dogs using Carrel's vascular suture methods (Fig. 2-7). He was technically successful but took the experiments further by measuring the level of complement fixing antibodies using the Bordet-Gengou reaction in the dogs on which he had performed autotransplantation (vide infra) (Voronoy, 1929; Woronoy, 1930).
### Table 2-2 Early clinical renal transplantation

<table>
<thead>
<tr>
<th>Year</th>
<th>Comments</th>
<th>No. of patients</th>
<th>Site of kidney placement</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1936</td>
<td>First human cadaveric transplant. No function.</td>
<td>6</td>
<td>Groin</td>
<td>Voronoy, 1936</td>
</tr>
<tr>
<td>1946</td>
<td>No function</td>
<td>1</td>
<td>Renal fossa</td>
<td>Hume¹</td>
</tr>
<tr>
<td>1951</td>
<td>Functioned 19 days</td>
<td>1</td>
<td>Pelvis</td>
<td>Servelle et al., 1951</td>
</tr>
<tr>
<td>1951</td>
<td>No function</td>
<td>2</td>
<td>Pelvis</td>
<td>Dubost et al., 1951</td>
</tr>
<tr>
<td>1953</td>
<td>Questionable function</td>
<td>6</td>
<td>Pelvis</td>
<td>Küss et al., 1951</td>
</tr>
<tr>
<td>1953</td>
<td>First living related transplant</td>
<td>1</td>
<td>?</td>
<td>Michon et al., 1953</td>
</tr>
<tr>
<td>1954</td>
<td>Successful transplant between identical twins</td>
<td>-</td>
<td>Iliac</td>
<td>Merrill et al., 1956</td>
</tr>
<tr>
<td>1955</td>
<td>4 functioned 35 - 188 days</td>
<td>9</td>
<td>Groin</td>
<td>Hume et al., 1955</td>
</tr>
<tr>
<td>1962</td>
<td>First use of tissue typing to select recipient</td>
<td></td>
<td>Iliac</td>
<td>Hamburger et al., 1962</td>
</tr>
<tr>
<td>1963</td>
<td>First renal transplant in UK</td>
<td></td>
<td>Iliac</td>
<td>Woodruff et al., 1963</td>
</tr>
<tr>
<td>1966</td>
<td>First renal transplant in RSA</td>
<td></td>
<td>Iliac</td>
<td>Myburgh et al., 1983</td>
</tr>
</tbody>
</table>

¹Cited by (Moore, 1964)

---

**Fig. 2-7** The surgical method used by Voronoy for renal grafting in the dog. From Woronoy (1929).
The first human-to-human kidney transplant

The first human renal allograft transplant took place on April 3, 1933 and was described in detail in a recent Soviet review (Mirskii, 1973). The patient was a 26 year-old female who had developed acute renal failure following a suicide attempt using mercuric chloride. When the patient failed to improve on conservative measures and remained anuric, Voronoy decided to proceed to perform a cadaveric transplant. The donor was a man who had sustained a base of skull fracture and had died in the emergency room. The donor nephrectomy was performed 6 hours later. The blood groups of the patients were also incompatible: The patient was blood group O while that of the cadaver was B. Voronoy decided to proceed with the transplant despite the difference in blood groups because he felt that the blood of the recipient would dilute the blood in the graft. Perhaps more importantly, there was no other potential donor kidney available. The surgery was performed under local anaesthesia and the graft was implanted in the right upper thigh and anastomosed to the femoral vessels, while the ureter was brought out onto the skin. In spite of a modest exchange transfusion the graft never worked. The patient died 2 days later. At autopsy the blood vessels were patent.

Success and failure

The operation was technically a success and reasons the graft failed to work are obvious now: the prolonged warm ischaemia time and the blood group incompatibility. From his experience in dogs the non-functioning of the graft did not perturb Voronoy. He was not discouraged by the poor outcome and proceeded to perform a further 5 transplants none of which functioned (Voronoy, 1950).

The second group to attempt renal allotransplantation

In 1946 Hufnagel, Hume and Landsteiner undertook the second documented human renal allograft transplant in Boston. The operation was also performed under local anaesthesia and the kidney was grafted onto the brachial artery and cephalic vein of a young woman with acute renal failure. The graft functioned transiently but fortunately the patient's own kidneys started recovering a few hours after the transplant and the graft was removed after 2 days (Moore, 1964).
Haemodialysis

In 1944 a remarkable development took place in Holland that was to have a profound impact on the transplantation of kidneys. Kolff (1944) had invented the artificial kidney that was to provide patients with end-stage renal failure with support while awaiting transplantation and a refuge for those whose grafts failed. The first patients were placed on a chronic haemodialysis program at the Peter Bent Brigham Hospital in Boston in 1949 under the supervision of Thorn and Merrill (Merrill et al., 1950). It soon became apparent that this form of treatment was capable of sustaining the life of a patient with end-stage renal failure for almost indefinite periods. The success of chronic haemodialysis was crucial to the development of clinical renal transplantation. This life support system allowed the development of a pool of transplant recipients and prevented the diagnosis of chronic renal failure being equated with death. Chronic dialysis provided patients (and still does so) with a dimension of safety not enjoyed by patients with other vital organ failure (Banowsky, 1983).

European developments of the 1950s

In 1951, 3 teams under Servelle et al. (1951), Dubost et al. (1951) and Küss et al. (1951) respectively, all working independently in Paris reported their experience with renal allografts in small number of patients. None of the grafts functioned for any length of time. The Parisian teams all placed the grafts in the pelvis, anastomosed the kidneys to the iliac vessels and made cutaneous ureterostomies. The patients were all transplanted without immunosuppression. The Boston group under Hume embarked on a kidney transplant trial in 1952. They placed the renal allografts in the upper thigh, which had many anatomical disadvantages but gave them an opportunity to observe the behaviour of the graft. Many of the grafts worked for varying periods of time and one graft functioned for a remarkable 175 days without immunosuppression (Hume et al., 1952; Hume et al., 1955). All allografts used up to this point were from unrelated donors but in 1953 Michon and his group reported the first kidney transplant from a healthy living-related donor. The patient was 16-year-old male who lost his solitary kidney, which had been damaged in a scaffolding accident. The mother was the donor. The graft functioned immediately but abruptly rejected on the 22nd day. The young man died shortly thereafter (Michon et al., 1953).
The insurmountable barrier
Up to this point the surgical techniques were standardised and the short-term results acceptable but the problem of the immunological barrier that resulted in acute rejection remained to be broached. Interest in clinical and experimental transplantation again waned, although knowledge of basic immunological mechanisms in the laboratory was steadily increasing (Hamilton, 1994; Toledo-Pereyra et al., 1999).

The late period: the barrier overcome?
The barrier breached
With the pioneering work of Medawar and others (Billingham et al., 1954) involved in the successful transplant of skin graft in human identical twins and syngeneic
animals to encourage them, the team of Murray, Merrill and Harrison performed the first long-term successful renal transplant (Fig. 2-8). They overcame the problem of the immunological barrier by applying the concept of genetic similarity (Brower et al., 1977; Toledo-Pereyra et al., 1999). The operation was performed in Boston on December 23, 1954 when a kidney was transplanted into a patient from an identical twin (Merrill et al., 1956; Murray et al., 1958). Harrison removed the left kidney of the healthy twin brother while Murray was performing the dissection in the patient. The graft was placed retroperitoneally and anastomosed to the iliac vessels with the ureter implanted into the bladder. The graft started functioning immediately and the donor made a full recovery (Merrill et al., 1956). The patient returned to work and raised a family, after marrying one of the nurses who cared for him in hospital. The patient developed proteinuria two years later and biopsy confirmed that he had a recurrence of glomerulonephritis in his graft. However, he died of an acute myocardial infarct 8 years later, with the graft still functioning (Merrill et al., 1956). From then on a number of similar transplants were performed with great success with many patients achieving long-term survival. The successes were however tempered by failures caused by the recurrence of glomerulonephritis in the transplanted kidney (Hamilton, 1994).

2. HISTORY OF THE IMMUNOLOGICAL ASPECTS OF RENAL TRANSPLANTATION

The early pioneers
The greatest barrier to renal allotransplantation once the technical aspects of the surgery were mastered was overcoming the problem of acute rejection. All transplants done up this point had been undertaken without the benefit of immunosuppression. Over the years many observers had a notion that there were biological reasons for the failure of grafts to function. As mentioned above, Tagliacozzi (Gnudi et al., 1950) and Pert (1863) made pertinent observations that suggested that they appreciated the barrier to allotransplantation (Converse et al., 1968).
Landmarks in renal transplant immunology
The most important immunological landmarks in the early part of the 20th century were the discovery of the ABO blood groups by Landsteiner (1900). The other major event of this era was the discovery by Gorer (1937) of the genetic system controlling histocompatibility that provided the basis for further genetic studies in animals and man on histocompatibility. In 1944 Medawar demonstrated the actual immunologic basis of allograft rejection using skin grafts in rabbits and thus established the basis of transplantation research (Medawar, 1944; 1945; 1946). Sir Peter Brian Medawar was therefore the first to recognise that rejection was an immune reaction and all subsequent contributions to the field of organ transplantation sprang forth from this sentinel observation. Sir Medawar received the 1960 Nobel Prize in Medicine for his remarkable work. In 1952 Dausset and Nenna described the presence of antibodies to leucocyte antigens in patients who had received multiple blood transfusions. They further showed that these antibodies recognised cell surface antigens on leucocytes that were distributed in a group fashion in man. Dausset named the first group MAC, subsequently renamed HL-A2, and that later was found to be part of the major histocompatibility complex in man (Dausset, 1958). Parenthetically, Voronoy had also shown the presence of antibodies in his dogs that had undergone renal transplantation (Fig. 2-9).

Recognition of acute rejection
As early as 1910 Da Fano had observed the presence of lymphocytes in rejected allografts (DeFano, 1910). Many others later described histological changes that would subsequently be recognised as those of acute rejection (Toledo-Pereyra et al., 1999). This included Carrell, and his observations prompted him to state that, "... the technical aspects of the organ grafting are solved but from a biological standpoint no conclusions has thus far been reached, because the interaction of the host and the new organ are practically unknown" (Converse et al., 1968). Carell may have failed to recognise the immunological basis of acute rejection but Guthrie, a one-time associate of Carrell suggested that "The outlook is by no means hopeless and the principles of immunity, which yield such brilliant results in many other fields would seem to be worthy of being tested in this case" (Converse et al., 1968). In 1923 and 1926 Williamson was able to confirm Carrel's finding that in dogs and goats renal autografts lasted much longer than allografts.
Voronoy observed that antibodies to kidney antigens measured by the Bordet-Gengou reaction resulting from autotransplantation of the kidney to the neck of dogs. The antibodies were most marked in the animals (marked with crosses) that died because of infection or infarction of their grafts. In one successful graft no immune response occurred (Voronoy, 1930).

(Williamson, 1923; 1926). He described the histological changes following renal allotransplantation as acute atypical glomerulonephritis with lymphocytic infiltration. He concluded that the failure of the renal allografts was due to biological incompatibility between the donor and the recipient (Williamson, 1926). His suspicions were proved correct following the work of Simonsen (1953) in Denmark and Dempster (1950) in London. Both of them working independently showed that
immunological mechanisms were involved in the destruction of the renal allograft. Both considered that a humoral mechanism was involved in rejection. Together with the pioneering of Medawar (1944), it became self-evident that successful transplantation would depend on weakening or otherwise altering the immune response of the host. Dempster (1950) found that radiation, but not cortisone delayed rejection.

**Tolerance demonstrated**

The difficulties encountered in the attempts at transplantation appeared to support Loeb’s concept of the biological uniqueness of individual characteristics as a prohibitive barrier to transplantation (Loeb, 1945). The possibility of inducing tolerance to alloantigens seemed impossible until the brilliant contributions of Billingham, Brent and Medawar (Billingham et al., 1953; Billingham et al., 1956). They elegantly demonstrated that tolerance could be induced in mice by the injection of viable cells from the prospective graft donor strain *in-utero* into embryos of a different strain. After birth the inoculated recipients were fully tolerant to skin grafts from the donor strain. It was this observation among others (Bauer, 1927; Little et al., 1916) which encouraged Murray to successfully undertake the first renal allograft transplantation between identical twins (Merrill et al., 1956). However, allograft transplantation remained a problem.

### 3. HISTORY OF IMMUNOSUPPRESSIVE TREATMENT IN RENAL TRANSPLANTATION (Table 2-3)

**Irradiation**

Irradiation was the first form of immunosuppression to be employed in an attempt to control the immunological response to allografts. The immunosuppressive capacity of radiation was discovered in 1908 by Benjamin and Sluka who noticed that total body irradiation (TBI) impaired the ability of rabbits to produce precipitating antibodies to bovine serum (Benjamin et al., 1908). The first attempts at immunosuppression for renal allografts were with TBI between 1959 and 1962 (Hamburger et al., 1959; Küss et al., 1960; Murray et al., 1960). However, results were
Historical Aspects

**Table 2-3** Summary of immunology landmarks in that contributed to renal transplantation

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900</td>
<td>Discovery of ABO blood groups</td>
<td>Landsteiner, 1900</td>
</tr>
<tr>
<td>1937</td>
<td>Discovery of histocompatibility genes</td>
<td>Gorer, 1937</td>
</tr>
<tr>
<td>1944</td>
<td>Immunological basis of allograft rejection</td>
<td>Medawar, 1944</td>
</tr>
<tr>
<td>1948</td>
<td>Congenic line of mice produced</td>
<td>Snell, 1957</td>
</tr>
<tr>
<td>1952</td>
<td>Describe leucocyte antibodies</td>
<td>Dausset, 1958</td>
</tr>
<tr>
<td>1953</td>
<td>Induce immunological tolerance in mouse experimental model</td>
<td>Billingham et al., 1953;</td>
</tr>
<tr>
<td>1954</td>
<td>Identical twin donors - first successful long-term survival</td>
<td>Merrill et al., 1956</td>
</tr>
<tr>
<td>1955</td>
<td>Apply irradiation to induce tolerance in mouse model</td>
<td>Main et al., 1955</td>
</tr>
<tr>
<td>1959</td>
<td>Immunosuppressive properties of 6-mercaptopurine discovered</td>
<td>Schwartz et al., 1959</td>
</tr>
<tr>
<td>1961</td>
<td>First clinical use of azathioprine</td>
<td>Caine et al., 1962</td>
</tr>
<tr>
<td>1963</td>
<td>First large series of successful renal allografts; use of high doses of steroids to reverse acute rejection</td>
<td>Starzl et al., 1970</td>
</tr>
<tr>
<td>1964</td>
<td>Description of mixed lymphocyte reaction (MLC)</td>
<td>Bach et al., 1964</td>
</tr>
<tr>
<td>1966</td>
<td>Describe humoral basis for hyperacute allograft rejection</td>
<td>Kissmeyer-Nielsen et al., 1966</td>
</tr>
<tr>
<td>1967</td>
<td>Describe class II HLA antigens</td>
<td>Bach et al., 1967</td>
</tr>
<tr>
<td>1969</td>
<td>Describes microchimerism</td>
<td>Starzl et al., 1992</td>
</tr>
<tr>
<td>1973</td>
<td>Blood transfusion effect described</td>
<td>Opelz et al., 1973</td>
</tr>
<tr>
<td>1974</td>
<td>Demonstrate MHC restriction of immunological reactivity</td>
<td>Doherty et al., 1974</td>
</tr>
<tr>
<td>1976</td>
<td>Discovery of cyclosporine</td>
<td>Borel et al., 1976</td>
</tr>
<tr>
<td>1977</td>
<td>Clinical use of cyclosporine</td>
<td>Calne et al., 1978</td>
</tr>
<tr>
<td>1987</td>
<td>Discovery of tacrolimus</td>
<td>Kino et al., 1987</td>
</tr>
<tr>
<td>1989</td>
<td>Clinical use of tacrolimus</td>
<td>Starzl et al., 1989</td>
</tr>
<tr>
<td>1993</td>
<td>Attempts at humanising the pig</td>
<td>Cozzi et al., 1995; Galili, 1993</td>
</tr>
</tbody>
</table>

generally poor and mortality high. Strober (Levin et al., 1985) applied the method of radiation as refined by Kaplan (Kaplan, 1980) who used total lymphoid irradiation to renal transplantation while Myburgh used the wide-field method (Myburgh et al., 1986; 1987). However, despite these refinements the propensity toward unpredictable side-effects and high mortality from infection remained a major problem (Kahan, 1991).
Pharmacotherapy: the early days
The pharmacological era of immunosuppression began in the early part of the last century when Murphy (1914) and Hektoen (1916) observed the effects of the simple organic compounds toluene and benzene on tissue grafts and antibody production respectively. Baker (1952) was the first to prolong the survival of experimental renal allografts by the use of nitrogen mustards. Schwartz and Dameshak (1959) initiated the modern era of pharmacological immununosuppression when they reported the prolonged survival of rabbit skin allograft using 6-mercaptopurine.

Azathioprine
Hitchings and Elion (1954) developed the anti-proliferative agent 6-mercaptopurine as a competitive inhibitor of purine salvage pathways. In 1960 Hitchings and Elion provided Calne with new derivatives of 6-mercaptopurine of which BW57-322 proved to be the most successful at prolonging survival of dog renal allografts and was less toxic than 6-mercaptopurine (Calne et al., 1962). Azathioprine, as the compound came to be known, became available for clinical use in 1961 with Murray (1963) reporting the first successes with extended renal allograft survival. Although initial results with azathioprine alone were disappointing, Starzl (1963) and Goodwin (1962) working independently were able to prolong graft survival by combining it with prednisilone and the combined use of the two agents became conventional immunosuppressive treatment. Using the combined conventional therapy and with live-related donors, remarkably good results were reported by Starzl (1963) and Hume (1963) which did much to encourage renal transplantation.

Therapeutic antibodies
Another development that had an impact on therapeutic options was the rediscovery of antilymphocyte globulin. This agent was initially produced by Metchnikoff (1899) and rediscovered by, among others, Medawar (Levey et al., 1966a; 1966b). Starzl and Machioro adopted this powerful immunosuppressive agent into the clinical transplant setting (Starzl et al., 1967) while Najarian and Simmons refined its use (Najarian et al., 1970). Its potent non-specific attack on T-cells was associated with many serious adverse events and required great care in its use. Monoclonal antibody development saw the birth of more selective agents capable of neutralising cells bearing specific antigens. OKT3 was one of the first of this generation of
agents to become available for clinical use. However, the non-specific effect of the antibody as well as the high incidence of serious adverse events has seen OKT3 falling into disuse (Cosimi et al., 1981). A number of other monoclonal agents with much better safety profiles have now become available for clinical use (Kahan, 1991).

Cyclosporine
The next major development in transplantation after the implementation of conventional treatment was the discovery of cyclosporine. Cyclosporine was isolated in 1969 from a fungus *Tolypocladium inflatum Gams*, present in the soil from the plains of southern Norway. Jean-Francois Borel (1976) discovered the potent immunosuppressive properties of cyclosporine in transplantation and autoimmune diseases. The first use of the drug in animals was by White et al. (1981) who showed that the short-term administration markedly prolonged allograft survival in animals. Calne (1978) was involved in the initial clinical trials of cyclosporine reviving his earlier triumph with azathioprine. Graft survival improved by up to 15-30% under cyclosporine compared to conventional treatment (Banowsky, 1983). Despite its potency it posed an amazingly low immunosuppressive hazard. However, its nephrotoxic side effects limited its use in doses that exploit its full immunosuppressive potential (Kahan, 1989a). However, the success of cyclosporine in renal allotransplantation resuscitated interest in all other forms of transplantation that had been waning because of the poor results obtained with conventional treatment. The result was an ever-increasing demand for transplantable organs. The success of cyclosporine also stimulated the search for alternative agents that were to make their appearances later.

Tacrolimus
In 1987 the highly potent tacrolimus was discovered by Kino (Kino et al., 1987) expanding the available armamentarium of immunosuppressive agents available. The drug was introduced into the clinical arena by Ochiai et al. (1987) and Starzl et al. (1989) who confirmed its efficacy. Since that time several other drugs have entered the transplant pharmacopoeia including mycophenolate mofetil and rapamycin (Rapaport, 1999).
Other important developments in transplantation

Blood Transfusion effect

Opelz et al. (1973) demonstrated that blood transfusions, which had been avoided during regular dialysis up to this time, were in fact beneficial to the outcome of renal transplantation. This may explain the initial failure of cadaveric renal transplantation survival to improve in the 1970s, as immunosuppressive regimens were perfected and patient survival increased. Following these observations by Opelz, many centres liberalised their transfusion policies with consequent improvement in graft outcomes (Belzer, 1988). Salvatierra et al. (1980) deliberately applied donor-specific blood transfusions to mismatched siblings and other living-related donors and was able to show results comparable to that of HLA-identical siblings.

Discovery of HLA antigens

Rapaport did extensive work on skin allografts and was able to demonstrate the existence of tissue groups in man (Rapaport et al., 1962). Rapaport et al. (1968) working with Dausset et al. (1965) was able to show that the histocompatibility groups detected by skin graft experiments were the same as the leucocyte groups that had been identified serologically by Dausset. They also showed that these were part of a major human histocompatibility complex first named Hu-1, later renamed HLA. Bach and Hirschhorn (1964) described the mixed lymphocyte culture (MLC) test while the class II HLA antigens were identified by Bach and Amos (1967). Ting and Morris (1978) reported the first successful application of HLA-DR typing in 1978. Another important development was the description of the lymphocyte microcytotoxicity test that was to form the basis of HLA typing (Terasaki et al., 1964). Tissue typing was introduced into routine use in 1962 (Hamburger et al., 1962; Dausset, 1980) and allowed the selection of a recipient and donor to be made. Kissmeyer-Nielsen et al. (1966) documented the humoral basis of hyperacute renal allograft rejection that was greatly reduced by the direct cross-match between donor cells and recipient serum.

Xenotransplantation

Man's preoccupation with xenotransplantation has enjoyed a revival with the prospect of transplantologists having an unlimited supply of organs available for treatment. The current interest focuses on xenotransplantation with intense efforts to
humanise the pig by selective genetic engineering techniques. One approach has been to breed animals that do not express the -GAL epitope (Galili, 1993). Another approach has been to insert into the porcine genome genes that code for the inhibitors of the human complement cascade (Cozzi et al., 1995). The challenges facing the transplant community with respect to xenotransplantation are large and no doubt many of the frustrations that we experience in this regard probably reflect the same frustration that our predecessors experienced a century ago with regard to allotransplantation.

Chimerism
Starzl reported the persistence of numbers of donor cells (which he termed microchimerism) in the tissues of long surviving liver transplant recipients. He believed that these cells of graft donor origin, present in the graft and lymph nodes of the host constituted the basis for long-term allograft acceptance by the host and suggested that this may be the ultimate form of inducing tolerance (Starzl et al., 1989; Starzl et al., 1992), although others felt that chimerism was not a feasible clinical strategy to employ in renal transplantation (Kahan, 1991). However, the search is on for the most effective method of inducing tolerance, which is thought to be the ultimate way of ensuring graft survival.

THE SOUTH AFRICAN TRANSPLANT SCENE
The pioneering years
South Africa stole world centre-stage in 1967 when the late Christiaan Barnard performed the world’s first human heart transplant at the Groote Schuur hospital in Cape Town. Although there was remarkable interest shown in this historic event in the lay press, the response from the more objective scientific community was somewhat muted (Barnard, 1968). Tom Starzl and Bert Myburgh performed the first renal transplant in South Africa in Johannesburg in June 1966. The same team undertook a second transplant a month later. Both were living-related donor transplants with siblings being the donors in both cases. Both patients were treated with conventional therapy. The first patient died of sepsis after 2 months. The second died after 10 months of metastatic calcification and other complications
arising from severe hyperparathyroidism (Meyers, A.M., personal communication). By 1982 the Johannesburg group had performed 525 renal transplants, both cadaveric and living-related donor, over the 17-year period and was achieving results that were comparable to centres elsewhere in the world (Myburgh et al., 1983). The group used azathioprine and steroids between 1966 and 1968. They then introduced equine anti-lymphocyte globulin, which in true pioneering spirit they produced themselves from 1968 to 1973. From 1973 the group used irradiation, pioneering the technique of wide field low-dose total lymphoid irradiation (Myburgh et al., 1986; Myburgh et al., 1987).

Cape Town
A little known fact is that Christiaan Barnard also performed the first kidney transplant in Cape Town in 1967, several months before his historic heart transplant (Uys et al., 1970). This patient (and all subsequent patients) received conventional immunosuppressive treatment consisting of steroids and azathioprine. This patient survived for over 2 decades with a well-functioning graft and died of ischaemic heart disease (Pascoe, M.D., personal communication). In 1983 the group converted to cyclosporine but pioneered the discontinuation of the drug at 3-12 months after the transplant (Jacobson et al., 1988), a practice continued successfully to this day. As elsewhere in the world, the liberalisation of blood transfusion protocols and the introduction of cyclosporine markedly benefited graft survival (Jacobson et al., 1988; Myburgh et al., 1983).

National Registry
Furman undertook a national annual audit of renal transplantation and dialysis in South Africa starting in 1974. This effort culminated in the formation of the South African Dialysis and Transplant Registry (SADTR) in 1984 (Furman, 1974; Furman, 1977; Furman, 1978). The registry, the only one of its kind on the African continent, continues to document the details of all patients who enter any of the renal replacement programs in South Africa and their outcomes. It surveys all the units in the country involved in renal replacement treatment and documents their number and various activities. The registry reports on its results annually. Since 1984, the number of transplants has steadily grown and currently 5 state centres and a
A growing number of private hospitals offer renal transplantation as a therapeutic option. Since the establishment of the SADTR in 1984, almost 5000 renal transplants have been done. The source of the kidneys is largely cadaveric although more living (both related and unrelated) are being done (Fig. 2-10). In 1994, the one-year graft survival was 70% and patient survival 97% (Du Toit et al., 1994).

**LITERATURE CITED**


Baronio, G. (1804) Degli innesti animati. Milan


Historical Aspects


Murphy, J. B. (1897). Resection of arteries and veins injured in continuity, end to end suture: experimental and clinical research. *Med.Record.* 51, 73.


Chapter 3

AIMS AND METHODS

PART 1

Cancer remains one of the major scourges to afflict humankind. There is evidence that cancers are not new diseases. The earliest drawings and writings from ancient civilisations in all parts of the world have provided descriptions of cancer. Bone and urinary bladder cancers have been identified in Egyptian mummies, while the writings of Hippocrates contained descriptions of, and even recommended treatment for, cancers. The writings of the ancient physicians make it obvious that they appreciated that cancers exhibited spatial and temporal characteristics that ultimately proved fatal (Bryan et al., 1999). However, the cause of cancers was never really fully understood nor investigated, and it was generally assumed that cancers were an inevitable accompaniment of the aging process. This led to the belief that there was little that could be done except to diagnose the disease early when it was amenable to surgery or radiotherapy. However, a change in attitude occurred following the Second World War and it was increasingly realised that certain environmental factors, genetic factors, and viruses all contributed to the development of malignancies. Many iatrogenic factors were also implicated in cancer development. Among these was the use of immunosuppressive agents. It therefore came as no surprise when the first cases of lymphomas following a renal


<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>High incidence area</th>
<th>Low incidence area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Australia</td>
<td>India</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Iran</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Bronchus</td>
<td>England</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Stomach</td>
<td>Japan</td>
<td>Uganda</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>Colombia</td>
<td>Israel</td>
</tr>
<tr>
<td>Liver</td>
<td>Mozambique</td>
<td>Norway</td>
</tr>
<tr>
<td>Prostate</td>
<td>USA</td>
<td>Japan</td>
</tr>
<tr>
<td>Breast</td>
<td>USA</td>
<td>Uganda</td>
</tr>
<tr>
<td>Colon</td>
<td>USA</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>India</td>
<td>Denmark</td>
</tr>
<tr>
<td>Rectum</td>
<td>Denmark</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Bladder</td>
<td>USA</td>
<td>Japan</td>
</tr>
<tr>
<td>Ovary</td>
<td>Denmark</td>
<td>Japan</td>
</tr>
<tr>
<td>Uterus</td>
<td>USA</td>
<td>Japan</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>Singapore</td>
<td>England</td>
</tr>
<tr>
<td>Pancreas</td>
<td>New Zealand</td>
<td>Uganda</td>
</tr>
<tr>
<td>Penis</td>
<td>Uganda</td>
<td>Israel</td>
</tr>
</tbody>
</table>

Modified from Doll (1977).

What has been interesting in looking at the epidemiology of cancer is that the incidence of cancers varies widely not only in different geographical regions but that the incidence of certain cancers differ between different ethnic groups residing in the same geographical locality. These observations have contributed much to the understanding the process of carcinogenesis (Doll,1977). A generalisation is that the poor and the rich in this world are at high risk for different kinds of cancer (Table 3-1). Cancers of the upper gastrointestinal tract such as oesophageal cancers are digestive cancers of the poorest populations, as seen in our black patients. When caloric intake increases because of greater starch intake, stomach cancer becomes
the dominant cancer, as is the case in the Western Cape. The most affluent groups replace carbohydrates with animal fat and protein and by doing so substitute colonic cancer for stomach cancer. Affluence also increases the risk of cancer of the breast, prostate, and endometrium suggesting that dietary factors may contribute to the enhanced risk of these cancers (Willett, 2000; Lee et al., 2000; Larking, 1999). By contrast, cervical cancer is mainly a cancer of poverty and poor hygiene (Berg, 1977).

Malignancies are the second only to cardiovascular disease as the most common cause of death in industrialised countries, especially with the increasing age of the population in these countries (Balducci et al., 2001). In developing countries cancers become important causes of mortality as infectious disease are increasingly brought under control. It is estimated that by 2020, new cancer cases will double to 20 million a year (Sikora, 1999); over 50% of all new cancers arise in people from developing countries but by 2020 the proportion will reach a staggering 70% (Murray et al., 1996).

The causes of cancer vary worldwide. In developed countries tobacco is a major culprit, causing 1 cancer death in 3 (Jones, 1999). The effect of the widespread use of tobacco over decades in developed countries is starting to wane because of public resistance to its use resulting in the reduction of tobacco-related cancer deaths (Levi, 1999; Smith et al., 2000). Sadly, however, the epidemic is now being propagated globally with devastating effects in developing countries (Pandey et al., 1999). In developing countries chronic infection plays a major role in the development of cancer and is responsible for 1 in 4 cancer deaths (Jones, 1999). The human papillomavirus causes uterine cervical cancer; Helicobacter pylori, has been implicated in stomach cancer; and hepatitis B and C viruses are major causes of hepatocellular cancer. Together these agents account for over 90% of infection-related cancers (Pisani et al., 1997). Variations in cause are reflected in the differences in cancers that predominate in different parts of the world (Fig. 3-1) (Parkin et al., 1999).

The theme of this dissertation revolves around the ideas developed in this introduction: with this brief perspective of the global situation with regard to cancers, the question arises as to the nature of cancers following organ transplantation. The
experience with malignancies following renal transplantation is still rather limited but preliminary evidence suggests that geographic and ethnic differences may exist (Penn, 2000; Qunibi et al., 1988). The role of chronic infections remains uncertain. The objective of this study was to formally investigate whether there were indeed any differences in the pattern of posttransplant malignancies and if these in anyway followed the patterns seen in cancers in general.

The study was designed to answer the following questions in relation to the patients who had undergone renal transplantation in the Renal Unit, Tygerberg Hospital:

1. What was the incidence of malignancies in renal allograft recipients with a minimum of 2-year follow-up?
2. What was the pattern of malignancies?
3. Were there any racial differences in the malignancies?
4. What was the influence of the introduction of cyclosporine on the incidence and pattern malignancies?

5. What happened to patients with pre-existing malignancies in remission who received renal allografts?

Our experience was then compared with that of both developed and developing countries.

We found that the experience of posttransplant malignancies in developing countries differs remarkably from industrialised countries and in many ways reflects the global cancer experience.

However, in order to be able to address these questions, a full review of the transplant program of the Tygerberg Hospital first had to be undertaken.

**PART 2**

Kidney transplants have been performed in South Africa since the pioneering days of this form of treatment (see Chapter 2, History of Transplantation). Since the initiation of the transplant program in South Africa there have been few single centre reports of the outcome and successes of this form of treatment. One of the most comprehensive reviews of the subject appeared in 1983, before the introduction of cyclosporine (Myburgh et al., 1983). This study reviewed the Johannesburg experience of 525 renal transplants over a 17-year period and found graft survival rates of 52% in cadaveric donor renal transplants. Myburgh et al. (1983) report a steady attrition over 10 to 15 years in both graft and patient survival with infection and myocardial infarction as the main causes of mortality. There have been subsequent reports from Myburgh’s unit and other South African units (Bauling et al., 1989; Botha et al., 1988; Modiba et al., 1989); others have looked at a particular aspect of renal transplantation (Meyers et al., 1988) but none as comprehensively as the earlier report of Myburgh and his colleagues. However, the transplant centres in this country have been submitting their data to the South African Dialysis and Transplant Registry (SADTR) since the inception of this body. The SADTR uses this data to generate a report that includes details of patient and graft survival, as well as
other important information, for the country as a whole. Individual unit data are not generally available for evaluation. Limitations of registry data are discussed below.

A vast body of experience with regard to renal transplantation now exists which reflects the world experience of this treatment modality, but in many developing countries renal transplantation is still in its infancy and the experience is different from that in developed countries, as are the results (Moosa et al., 2001).

The Renal Unit attached to the Department of Medicine of the Faculty of Medicine of the University of Stellenbosch commenced its renal transplant program in 1976. Detailed records of all transplants have been maintained on a computerised database. An initial report was generated from this Unit looking specifically at racial differences in transplant outcome (Moosa et al., 1992). A very large database of renal transplant patients has been built up since the inception of the transplant program and the large number of patients has allowed us to study various aspects of renal transplantation, including the factors that influence patient and graft survival. Our experience in renal transplantation is documented here. It is hoped that it will add to the South African and developing countries experience and give a perspective of the population from which our cohort of patients, who developed posttransplant malignancies, are derived.

METHOD

DATA COLLECTION

This was a single centre retrospective cohort study. All patients transplanted between April 1st 1976 and 31st March 1999 were included. Data were obtained from several sources to establish a complete database including:

1. Computerised patient records: The details of all patients transplanted have been computerised and date back to the inception of the renal transplantation program.
2. **Registry Data:** All details of patients who received renal transplants have been recorded by the SADTR based in Cape Town. The SADTR has been collecting information since 1984.

3. **Anatomical pathology reports:** The names of patients obtained from the previous sources were reconciled with histology reports. All pathology reports generated on transplant patients were also reviewed.

4. **Postmortem reports:** All reports on postmortem examinations on transplanted patients were reviewed.

All malignancies recorded in the pathological records were reviewed and confirmed. In the absence of pathological confirmation, clinical diagnoses of malignancies were accepted only if there was sufficient evidence from the available clinical data to support the diagnosis. The details of patients with confirmed malignancies were recorded. Data included demography, nature of the transplant (cadaveric or living-related), primary renal disease, type of immunosuppression, number of transplants, duration of graft survival, and reason for graft failure or death. The relevant information of all the renal transplants that were performed in our unit over the 23 years between 1976 and 1999 were also collected to provide an epidemiological basis for this study. All data were recorded on Microsoft Excel Office 97 spreadsheet.

**DATA ANALYSIS**

Statistical analysis was performed using software package Statistica for Windows, (Release 5.5, 2000; Stat Soft Inc, Tulsa, OK).

For the first part of the study, the date of study entry was the date of the first kidney transplantation. The closing date was March 31, 1999 or the date of graft loss, whichever occurred first. Patient death was considered graft failure. The variables considered were the patients' age at transplantation, race, sex, primary renal disease and immunosuppressive therapy.
**Continuous data**
Continuous data were compared by Student's t-test that has been designed to deal with the problem of working with small samples of 30 or less (provided that the population from which it is derived has a normal distribution) (Mould, 1998d). The conditions to be fulfilled before the Student's t-test can be used are listed in Appendix Table 3-2. When faced with small numbers many authors use the more robust non-parametric Mann-Whitney U test which does not require the data to be analysed to follow any sort of distribution (Mould, 1998d). In most cases the Student's t-test was used but where there was uncertainty about the distribution of data the Mann-Whitney U test was also applied.

**Categorical data**
Categorical data were analysed using the $\chi^2$-test. The test was applied with Yate's correction if the population was less than 20 or if any value entered was less than 5. Alternatively, if the value entered was less than 5, or the sample size less than 20 the 2x2 table was not used and Fisher's exact test was applied. In all cases the null hypothesis was assumed unless otherwise stated. All tests performed were two-tailed.

**Multivariate vs. univariate analysis**
Multivariate as well as univariate analyses of graft survival were performed using the following variables: sex, race, age less than and equal to 40 years, and greater than 40 years, immunosuppressive therapy and primary renal disease. Multivariate analyses were also used to compare the influence of variables on the incidence of malignancies, skin carcinoma and Kaposi's sarcoma. Univariate analyses such as the use of contingency tables ignore the fact that variables may influence each other, and were therefore avoided. The main advantage of multivariate analyses is that several variables can be studied simultaneously with attention to the analysis of the correlations that reflect the extent of the relationship among three or more variables. Analysis of variance (ANOVA) is used very extensively in the current literature to compare several variables but in this study multiple regression analyses was used because it provided a mathematical model of the linear relationship between a
dependent and two or more independent variables (Weintraub et al., 1985). The superiority of multivariate analyses is discussed below.

**Survival analysis.**

The Kaplan-Meier method of calculating the survival of allografts in this cohort was used mainly because it is the conventional method of reporting graft survival in the transplantation literature currently. The technique was originally used by actuaries in the 19th century and modified by Greenwood in 1926 (Greenwood, 1926), Berkson and Gage in 1950 (Berkson et al., 1950), Wood and Boag also in 1950 (Wood et al., 1950), Merrell and Shulman in 1955 (Merrell et al., 1955), Kaplan and Meier in 1958 (Kaplan et al., 1958) and finally by Ederer (Ederer, 1961) in 1961. The technique is also called the actuarial method and product-limit method. Prior to the introduction of the technique patients who were lost to follow were assumed to either have all been alive or died. Neither of these assumptions was correct and the result was that this led to the over- or underestimation of the survival rate respectively. In the Kaplan-Meier method the individual survival times are used and there is no withdrawal group. Patients who fail to reach the endpoint (graft failure in the case of our patients) were censored. Censored data implies that the endpoint has not been reached as would be the case in patients whose grafts are still functioning at the end of the observation period. The main disadvantage of the method is that if there are too many withdrawals of alive patients or too many patients lost to follow-up, the results can be affected by the poor quality of data (Mould, 1998c).

**Life table method**

An alternative method of calculating the survival of patients is to use the life table method for grouped data where for a large series of patient data the survival times can be grouped and the calculations thus made easier. The assumption made by this method is that patients withdrawn (alive or lost to follow-up) in a time interval are alive on average for half the interval. The question of which of the above two tests to choose, is not entirely clear. The factors to be taken into consideration are the length of follow-up available, on how many grafts have already failed, and also on the pattern of graft loss that are grouped together in the early months following transplantation. With small samples the Kaplan-Meier is the better test while with large numbers grouping can take place. In practice the two tests often yield results
that differ very little from each other. For the purposes of this study the Kaplan-Meier method was used but the life table method for grouped data has also been calculated and, as expected, shows curves which are virtually identical (Appendix Fig. 4-13b) (Mould, 1998c).

Comparisons of survival curves
The tests that are most commonly used for the comparison of survival curves are the logrank and Mantel-Haenszel tests. The logrank method is capable of comparing two or more curves while the Mantel-Haenszel method is restricted to two. The two tests are in fact related and both are approximated by the $\chi^2$-statistic. It has been shown that significance by the logrank will always be confirmed by the more exact but also more complicated Mantel-Haenszel method. It is therefore unnecessary to use the Mantel-Haenszel method unless the logrank is on the borderline. For the purposes of this study, the logrank test was used (Schwartz et al., 1980).

Cox proportional hazards method
The logrank test performs a univariate analysis. In practice the results of renal allograft survival is influenced by a number of prognostic variables and therefore a multiple regression model such as the Cox proportional hazards method is more appropriate (Cox, 1972). Multivariate analysis gives a series of hazard ratios each one of which indicates the magnitude of the effect on outcome of that particular variable, if all the other variables are assumed to held constant. However, the Cox regression model requires care in its application and may not be appropriate in all circumstances. The underlying assumption of the model is that the ratio of the risks of graft loss in two subgroups is constant over time (hence proportional hazards) (Mould, 1998a). This is certainly not true for the graft loss following transplantation where the loss of graft occurs initially and there are a number of long term survivors (Appendix Fig. 3-12). It is in fact not reasonable to assume that the hazard ratio is independent of time. This problem with the Cox regression model has been experienced previously and commented upon (Langlands et al., 1979). In the case of our patients, the logrank test was used initially and any results that were significant were then subjected to multivariate analysis as well. Both results are reported.
In the second and subsequent parts of the study dealing with the malignancies, all patients were included and considered at risk from the date of the first transplant to the patient's death or March 31, 1999. This approach has been adopted by several authors (Bloehme et al., 1985; Hoshida et al., 1997). The variables that we considered were the age of the patients at the time of the diagnosis of malignancy was made, race, sex, immunosuppressive therapy and number of transplants. In addition the interval between the first transplant and the diagnosis of the first malignancy (called the latent period) was documented. The incidence rate of malignancies in the transplanted cohort was over the study period of 23 years was calculated. The definition of incidence rate:

\[
\text{No. of new cases of malignancy arising in a defined population over a given time period} = \frac{\text{Total person-time at risk during that period}}{\text{Number of new cases of malignancy arising in the defined population over the given time period}}
\]

The measure of disease frequency also called the incidence density (dos Santos Silva, 1999) that in the case of this study was expressed as the number of lesions per 1000 patient-years of follow-up. By this method the time that each individual is at risk is taken into account and the denominator is the sum of each individual's time at risk. This approach is known as the subject-years or person-years method and it is widely used in epidemiology especially in the analysis of incidence and mortality of cancer (Armitage et al., 1987). The shortcomings of this method have been highlighted by Windeler and Lange (1995) who have suggested alternatives. However, their main criticism was directed at the use of the concept in the osteoporosis literature although some of the comments would be relevant to our data as well (Windeler et al., 1995). Care has been taken in the interpretation of our data to avoid the limitations of the technique.

Multivariate analyses using the multiple linear regression model included the following variables: age (below and above 40 years), race, sex, immunosuppressive treatment and number of grafts. The latent periods were compared using the Student's t-test (see comments above). The study group was compared with the general population (South African National Cancer Registry) by using the expected
numbers of cancers obtained by applying the age, sex and race specific incidence experienced by the general population. The expected numbers of cases were then summed to obtain the total number of expected, of the various forms of cancer. These values were compared with the observed number of cases by means of the risk ratio (observed/expected). The test of significance is the usual one of comparing an observed random variable with its expectation under the Poisson assumption. The expected number of malignancies in this population was calculated from the 1985-1995 South African National Cancer Registry incidence rates. The relative risk is the ratio between the number of cancer cases in the transplanted population to the number of cases expected in the general population. The relative risk was calculated because the absolute incidence of the malignancies was not known with certainty. The relative risk or odds ratio (odds of developing a disease among transplanted and non-transplanted patients) are commonly employed when the denominator is not known in population studies of cancer risks (Mould,1998b). The relative risk was used as a measure of the magnitude of the risk of Kaposi’s sarcoma and other malignancies compared to the general population with a 95% confidence interval. Significance was set at the 5% level and all tests were two-tailed.

DETAILS OF SURGICAL TECHNIQUE USED
The surgical team was responsible for the harvesting of donor organs from heart-beating donors after in-situ cooling through a catheter placed in the common iliac artery. Renal preservation was by means of flushing and simple cold storage in ice slush for periods generally not exceeding 24 hours. The kidney was implanted extraperitoneally with the renal artery anatomised end-to-side with a cuff of aorta to the external or common iliac artery in most cadaveric donor transplants. Ureteroneocystostomy to a submucous tunnel in the bladder dome was the preferred technique in the majority of cases. In living donor transplants a similar technique was used except that no aortic cuff was taken.

DETAILS OF PREPARATION OF PATHOLOGICAL SPECIMENS
All tissues were fixed in 10% formaldehyde in phosphate buffered saline (PBS) pH 7.4 for 6-12 hours and processed overnight, through ascending concentrations of
ethyl alcohol (70%, 2x 96% and 3x 100%) (Merck, Darmstadt, Germany), xylene (Merck, Darmstadt, Germany) and molten paraffin wax (Histowax, Leica, Nussloch, Germany). Sections of 5-7 μm were cut from wax-embedded tissue. Sections were mounted on Silane coated glass slides (Fluka, Buchs, Switzerland). Haematoxylin and eosin staining was performed on dewaxed and rehydrated sections by staining with Mayer’s haematoxylin for 10 minutes and counterstaining with 1% eosin for 1 minute. Sections were then rinsed in running tap water, dehydrated through ascending concentrations of ethyl alcohol (70%, 96% and 2x 100%), cleared in xylol and coverslipped with DPX mountant.

Immunocytochemistry was performed on hydrated formaldehyde fixed paraffin sections. Endogenous peroxidase was blocked with 3% hydrogen peroxide in methanol for 10 minutes. Sections were then washed in PBS pH 7.6 at room temperature. Non-specific binding was blocked with normal goat serum (DAKO, Glostrup, Denmark, cat. no. X0907) diluted 1:10 with PBS. Excess normal serum was drained from the slides and the primary antibodies applied which included, Von Willebrand factor (DAKO code A0082, Denmark, Glostrup) diluted 1:200, CD31 (DAKO code 0823, Glostrup, Denmark) diluted 1:500 and CD34 (DAKO code M7168, Glostrup, Denmark) diluted 1:500 in PBS pH 7.6. The sections were incubated with the relevant primary antibodies for 60 minutes. Following incubation slides were washed in three changes of PBS of 5 minutes each. The excess buffer was drained and the biotinylated goat anti-mouse and rabbit immunoglobulin LSAB2 kit link-antibody (DAKO, Glostrup, Denmark, cat. no. K0609) applied and incubated for 30 minutes. Thereafter, the sections were washed as previously described and incubated with horseradish peroxidase conjugated streptavidin-biotin complex (ABC) LSAB2 kit (DAKO, Glostrup, Denmark cat. no K0609), and allowed to incubate for 30 minutes. Sections were washed as before. Positive labelling was demonstrated by 0.05% 3,3-diaminobenzidine tetrachloride (DAB) in PBS, pH 7.6, to which hydrogen peroxide was added immediately prior to incubation in the substrate for 3-5 minutes. After washing in running tap water, sections were counterstained with Mayer’s Haematoxylin, dehydrated, cleared and mounted in DPX.
REFERENCES


Appendix

**Table 3-2** Conditions to be met for the appropriate use of the t-test.

1. The observations must be independent in order to avoid bias.
2. The observations must be drawn from normal populations.
3. These normal populations must have the same variance.
4. The variables involved must have been measured in an interval scale, so that it is possible to use arithmetic operations.

*From Mould, R. F. (1998b).*
Chapter 4

RESULTS

(1) ALL PATIENTS UNDERGOING RENAL TRANSPLANTATION

DEMOGRAPHIC DETAILS

Since the commencement of the renal transplant program in April 1976 at the Tygerberg Hospital, 542 patients had received 623 renal allografts by the end of March 1999. The demographic details of the patients are shown (Table 4-1). Fewer females than males were transplanted, but this reflects the slightly greater proportion of males on dialysis in our renal replacement program.

<table>
<thead>
<tr>
<th>Table 4-1. Demographic details of renal allograft recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Mean Age (yrs)</td>
</tr>
</tbody>
</table>
Age distribution (Fig. 4-1)
The mean age of the patients at the time of transplant was 37.0 years, with no significant difference in the age of males and females or between the race groups (Student's t-test). The youngest patient transplanted was 8 years old and the oldest 64 years. The accompanying figure indicates the number of transplants done in the various age groups.

Race (Fig. 4-2)
The racial distribution of the patients who received renal allografts corresponded with that of the population of the Western Cape Province. There was a slight relative predominance of white patients transplanted but this difference was starting to even out as the racial laws were repealed allowing more blacks into the Western Cape Province. The lower numbers of black patients was the result of bias against blacks by virtue of their poorer social circumstances that resulted in their exclusion from the renal replacement program. In addition, blacks were largely confined to the "homelands" and freer population movement only occurred after 1985.
Immunosuppression

Conventional  The standard immunosuppression until October 1983 was azathioprine at 1-2 mg/kg per day and methylprednisolone at doses varying 1-2 mg/kg per day over the years. A total of 123 patients received conventional treatment over the 7-year period.

Cyclosporine  From October 1983, cyclosporine was included as part of triple therapy and was administered to 419 patients. Patients were maintained on cyclosporine for the life of the graft. The dose of cyclosporine was regularly monitored and the dose adjusted to maintain whole blood trough levels between 250-350 ng/l. The dose of cyclosporine was reduced at 3-6 months and whole blood trough levels were maintained between 150-250 ng/l. Cytochrome P450 inhibitors such as ketoconazole and diltiazem were not used routinely to allow the reduction in the dose of cyclosporine. Under the triple immunosuppressive regimen oral methylprednisolone dose was reduced at 3-6 months to maintenance of 8 mg per day. Azathioprine was administered at doses of 50-100 mg per day with the majority receiving the lower dose.

Acute rejection  This was treated with intravenous pulses of methylprednisolone 250-500 mg per day for 3 consecutive days. Polyvalent anti-thymocyte globulin or anti-lymphocyte globulin as well as OKT3 monoclonal antibodies were used individually (and occasionally sequentially) to treat steroid-resistant rejection as part of rescue therapy.
Fig. 4-2 Comparison of the population of the Western Cape and the racial profile of the transplant patients at the Tygerberg Renal Unit.

Population of the Western Cape
Census 1996

- Black: 22%
- White: 21%
- Coloured: 56%
- Asian: 1%

Racial Distribution of Renal Transplant Recipients
1976-1999

- Black: 10%
- White: 34%
- Coloured: 56%
Results

Table 4-2  Number of renal grafts transplanted
in this cohort until March 31st 1999.

<table>
<thead>
<tr>
<th>No. of patients transplanted</th>
<th>542</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of kidneys transplanted</td>
<td>623</td>
</tr>
<tr>
<td>No. of patients with single grafts</td>
<td>470</td>
</tr>
<tr>
<td>No. of patients with two grafts</td>
<td>64</td>
</tr>
<tr>
<td>No. of patients with three grafts</td>
<td>7</td>
</tr>
<tr>
<td>No. of patients with four grafts</td>
<td>1</td>
</tr>
</tbody>
</table>

Multiple Grafts (Table 4-2)
Multiple grafting was performed in 72 patients who between them received 153 renal allografts. The immunosuppressive treatment was not increased for subsequent grafts and patients received the treatment in use at the time of their subsequent transplants. Induction therapy using polyvalent serum or monoclonal antibodies for highly sensitised patients was not routinely used. On occasion, plasmapheresis was used in this situation for the first week following the transplant.

Primary Renal Disease (Fig. 4-3):
The most common disease leading to end-stage renal failure in our cohort of patients was chronic glomerulonephritis, which accounted for 42% of all the causes of chronic renal failure. The diagnosis of chronic renal failure was confirmed histologically in 36% of these cases while in the rest the diagnosis was made clinically.

Racial differences  Hypertension was the second most common cause of renal failure especially in the non-white patients. In the latter it accounted for 27% of all-cause end-stage renal failure compared with only 5.4% of the white patients. Autosomal dominant polycystic kidney disease, by contrast, was more common in the white patients in whom it accounted for 19% of all-cause end-stage renal disease compared with 4.7% in the non-white patients.

Diabetes  In our experience diabetes was an uncommon cause of primary renal disease in our cohort because the majority of patients with diabetic nephropathy and
**Fig. 4-3** Racial differences in primary renal diseases resulting in end-stage renal failure.

AN = analgesic nephropathy; CGN is chronic glomerulonephritis; CPN is chronic pyelonephritis; Cystic is autosomal dominant and other hereditary forms of cystic kidney disease; Hereditary is other hereditary forms of kidney disease; SLE is systemic lupus erythematosis.
**Fig. 4-4a** Renal Allograft Recipients
Factors Influencing Patient Survival

- **Overall Patient Survival - 1976 to 1999**

- **Influence of Graft Failure in First Year**
  - Graft retained first year (n = 341)
  - Graft lost in first year (n = 201)

- **Influence of Age**
  - Age <= 40 years (n = 325)
  - More > 40 years (n = 214)

- **Influence of Donor Source**
  - Cadaver Kidney (n = 528)
  - Living-related Kidney (n = 14)
end-stage renal disease were not offered renal replacement treatment, usually because of associated co-morbid factors. Less than 4% of all patients transplanted were diabetics.

Other causes  Analgesic nephropathy was seen in both white and non-white patients but is now uncommon with the last case being diagnosed in 1985. Of the 10 cases that were transplanted, 8 were female patients. Although the Western Cape has a high incidence of systemic lupus erythematosis (SLE) less than 2% of patients transplanted had end-stage lupus nephritis and all, except one, were female.

PATIENT AND RENAL ALLOGRAFT SURVIVAL

Patient Survival (Fig. 4-4a and Appendix Fig. 4-12b)
Over the study period 542 patients received first grafts. The actuarial one-year patient survival was 81% with the highest mortality occurring in the first year. Univariate and multivariate analyses revealed that patient survival was related to patient age, with patients older than 40 years having a much worse outcome; patients who received cadaveric kidneys and patients whose grafts failed within the first year did much worse. Patient survival was not significantly influenced by the race, gender or duration of dialysis prior to transplantation. The most common cause of death was sepsis, which accounted for 38% of all patient deaths; acute myocardial ischaemia resulted in 6.7% of deaths. Of the patients who died in the first year 43% succumbed to infective complications and 6.7% to acute myocardial ischaemia. In subsequent years infections continued to be the main cause of mortality with cardiovascular disease remaining an important second cause. Malignancies accounted for 8 (2.5%) of all deaths. One-half of all cancer deaths were due to disseminated Kaposi's sarcoma with all 4 deaths occurring within the first year and either within days of the diagnosis or with the confirmation at postmortem examination. Two patients succumbed to lung cancer long after their grafts had failed, while there was one case each of malignant lymphoma and hepatocellular carcinoma. All the non-Kaposi's sarcoma malignancies occurred after one year. Of the 8 cancer patients who died 5 were male and 3 female. Neither patient survival nor graft survival correlated with the duration of pre-transplant dialysis. Lack of data did not allow us to determine the effect of other factors such
Results

**Fig. 4-4b** Survival of Primary Renal Allografts (n = 542)
April 1976 - March 31, 1999

Note: The numbers within the graph represent the number of surviving patients who were still at risk for the development of malignancies. See Appendix Table 4-12a for the linear hazard model. For a life-table analysis of the same data see Appendix Fig. 4-13a.

as type of dialysis, donor gender, cold ischaemia time, and tissue matching on patient or graft survival.

**Graft Survival (Fig. 4-4b)**
The overall one-year graft survival rate was 62% while just over one third of grafts survived 5 years. Patient death was also considered graft failure for the purposes of this study. Of the 542 patients transplanted until March 31 1999, 321 had died. Of these 180 (56%) died with functioning grafts. There were 200 patients whose grafts failed before they died. Patient death therefore accounted for 47.3% of all grafts lost. The remaining patients lost renal function progressively over months to years with chronic allograft nephropathy being the most likely cause. Acute rejection due to lack of compliance and chronic cyclosporine nephrotoxicity may have contributed but these were not objectively documented. Some 27 patients survived for more than 20
**Fig. 4-5** Factors Influencing Primary Renal Allograft Survival

Influence of Age

- Azathioprine vs Cyclosporine

Survival (Years)

Note: All comparisons were done using the logrank test. All significant results were repeated using Cox proportional hazards model.
years with functioning grafts, all under azathioprine. The number of patients at risk of malignancies is indicated on the survival curve. The number represents the patients with functioning grafts on immunosuppressive therapy as well as patients who were previously exposed to immunosuppression for more than 28 days and continued receiving dialysis therapy. For the purposes of this study these patients were considered permanently at risk for the development of malignancies.

Factors influencing primary renal allograft survival (Figs. 4-5 and 4-6)
The factors that could have an impact on graft survival were evaluated. These included the type of immunosuppressive therapy (azathioprine compared to cyclosporine), the patient's race, sex and age. Our data supports the benefit of cyclosporine on graft survival with over 20% improvement in graft survival compared to azathioprine at one year. Patients aged 40 years or less at the time of transplantation had a significantly better outcome compared to older recipients. However, when death with a functioning graft was corrected for, graft survival in the older patient was as good as, if not better than in the younger patient. There was no
difference in graft survival among the 3 race groups studied nor was there a gender difference in graft survival. An unexpected finding was the importance of the underlying disease in the outcome of the grafts. Patients with undiagnosed primary renal disease or diseases that could not be placed in one of the other specified categories fared the best. The diabetic group did surprisingly well but the careful selection of patients with uncomplicated disease for the renal replacement program undoubtedly accounts for the good initial results. The patients with systemic lupus erythematosis (SLE) and hypertension fared the worse of all the patients although the number of SLE patients was very small.

**Graft survival with regrafting**

The outcome of re-grafting in 72 patients is shown (Appendix Fig. 4-13b). The overall one year graft survival of second and subsequent transplants was 58% and 31% at 5 years compared to the 65% and 35% in the primary graft survival of this cohort.
(2) Patients Who Developed Malignancies

OCCURRENCE OF MALIGNANCES

Incidence of malignancies (Fig. 4-7)
In 542 patients receiving renal allografts over the 23-year study period, 44 (8.1%) malignancies developed in 41 patients. The mean follow-up period was 6.3 years (95% confidence interval: 5.8 - 6.7) with the longest being 22 years. However, if only the patients who were exposed to immunosuppressive agents for a period exceeding 28 days are taken into consideration then the number of patients at risk decreases to 460 (Fig. 4-4b) and the incidence of malignancies rises to 9.6%. The mean follow-up period of this group was 6.4 years (95% confidence interval: 5.9 - 6.9). For the purposes of this study, however all calculations requiring estimations of relative incidence were done using the entire cohort of patients.

Fig. 4-7 Cumulative No. of Post-Renal Transplant Malignancies

[Graph showing the cumulative number of post-renal transplant malignancies by year intervals following transplantation]
All malignancies that manifested within 28 days of transplantation were considered to have developed before the transplant and were therefore excluded. Only one case of transitional cell carcinoma of the bladder was thus excluded when the diagnosis was made on cystoscopy done at two weeks because of persistent post-operative haematuria. The majority (61%) of patients developed their first malignancies within the first five years following renal transplantation. Only one patient developed a malignancy after 15 years (Fig. 4-7). A major reason for this is the progressive decrease in the number of surviving patients at risk for the development of malignancies (Fig. 4-4a).

**Incidence rate**

Another method of representing the incidence of malignancies in this cohort of patients who have been followed up for varying periods of time is the incidence per number of patient-years (also called the incidence density) that takes into consideration the period that the patients survived. The total patient-years at risk in this cohort were 3450.28. The incidence rate of malignancies in this cohort was 12.8 per 1000 patient-years.

**Lesions (Table 4-3)**

Kaposi's sarcoma was by far the most common malignancy that developed and accounted for 47.7% of all lesions followed by non-melanoma skin malignancies. However there were marked racial differences in the pattern of the malignant lesions (see below). Of the tumours commonly seen in the general population, only lung and breast malignancies were represented.

**Comparative demography (Table 4-4)**

The mean age of the patients at the time of renal transplantation was 42 years compared to 45 years at the time of the diagnosis of the first malignancy. The incidence of malignancies was comparable in the patients who were transplanted after the age of 40 years to younger patients. In patients aged over 40 years the rate of malignancies was 20.9 per 1000 patient-years and 9.6 in the younger patient. The differences were not significant. The male to female ratio of the patients with malignancies (1:0.84) corresponds with that of the transplant population (1:0.78).
Results

**Table 4-3.** Type and frequency of posttransplant malignancies ($n = 44$).

<table>
<thead>
<tr>
<th>Lesion</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi’s sarcoma</td>
<td>21 (47.7%)</td>
</tr>
<tr>
<td>Non-melanoma skin</td>
<td>12 (27.2%)</td>
</tr>
<tr>
<td>Lung</td>
<td>3 (6.8%)</td>
</tr>
<tr>
<td>Breast</td>
<td>2 (4.5%)</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>2 (4.5%)</td>
</tr>
<tr>
<td>Liver</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Renal Cell</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>1 (2.2%)</td>
</tr>
</tbody>
</table>

The 19 malignancies occurring in the 248 female patients represents a 7.6% incidence of malignancies which was not significantly different from the 25 (8.5%) that was detected in the 294 male patients ($\chi^2$ - test). The number of malignancies in male patients was 11.1 per 1000 patient - years and comparable to the 13.1 per 1000 patient - years in female patients.

**Table 4-4.** Incidence and demographic details of patients who developed malignancies

<table>
<thead>
<tr>
<th></th>
<th>Black (n = 56)</th>
<th>Coloured (n = 301)</th>
<th>White (n = 185)</th>
<th>Total (n = 542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of malignancies (%)</td>
<td>4 (7.1)</td>
<td>21 (7.0)</td>
<td>19 (10.3)</td>
<td>44 (8.1)</td>
</tr>
<tr>
<td>Incidence (per 1000 pat-yrs)</td>
<td>12.1</td>
<td>12.1</td>
<td>13.6</td>
<td>12.8</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>9</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>11</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Total no. of patients (%)</td>
<td>4 (7.7)</td>
<td>20 (6.6)</td>
<td>17 (9.1)</td>
<td>41 (7.5)</td>
</tr>
<tr>
<td>Mean age(^1) (yrs)</td>
<td>50</td>
<td>43</td>
<td>42</td>
<td>45</td>
</tr>
</tbody>
</table>

\(^1\) Age at the diagnosis of the first malignancy
Table 4-5. Racial\(^1\) differences in the number of patients who developed malignancies.

<table>
<thead>
<tr>
<th>Race</th>
<th>White (n = 17)</th>
<th>Non-white (n = 24)</th>
<th>P-value(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi's sarcoma</td>
<td>2</td>
<td>19</td>
<td>0.03</td>
</tr>
<tr>
<td>Skin</td>
<td>13</td>
<td>0</td>
<td>0.0000</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Basal cell</td>
<td>7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>0</td>
<td>3</td>
<td>0.21</td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
<td>1</td>
<td>0.64</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>1</td>
<td>1</td>
<td>0.64</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td>0</td>
<td>0.16</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
<td>0</td>
<td>0.16</td>
</tr>
<tr>
<td>Renal Cell</td>
<td>0</td>
<td>1</td>
<td>0.47</td>
</tr>
</tbody>
</table>

\(^1\) The total number of non-white patients was 357 and the number of white patients 185.

\(^2\) Multiple linear regression analysis. The same results were obtained with ANOVA.

Table 4-6. Comparative incidence of malignancies in different groups of renal allograft recipients.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of malignancies diagnosed (%)</th>
<th>Group</th>
<th>No. of malignancies diagnosed (%)</th>
<th>P-value(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (n = 294)</td>
<td>25 (8.5%)</td>
<td>Females (n = 248)</td>
<td>19 (7.7%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Black (n = 357)</td>
<td>25 (7.0%)</td>
<td>White (n = 185)</td>
<td>19 (10.2%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Age &lt; 40-years (n = 329)</td>
<td>24 (7.3%)</td>
<td>Age &gt; 40-years (n = 213)</td>
<td>20 (9.4%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Conventional (n = 123)</td>
<td>9 (7.3%)</td>
<td>Cyclosporine (n = 419)</td>
<td>35 (8.4%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Single graft (n = 470)</td>
<td>39 (8.3%)</td>
<td>Multiple grafts (n = 72)</td>
<td>5 (6.9%)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

\(^4\) Multiple linear regression analysis. The same results were obtained with ANOVA.
Racial differences

The incidence of malignancies was not significantly different in the white and non-white patients (Table 4-4). The number of black patients was too small to allow meaningful analysis, and they were therefore included with the coloured patients as the non-white group for purposes of statistical analysis. The number of lesions per 1000 patient-years was 13.6 in both the white patients and 12.1 in the non-white patients. The pattern of malignancies between the races (Table 4-5) was however strikingly different but there were differences in other comparative groups (Table 4-6).

Main differences Of note in the racial differences in the pattern of posttransplant malignancies was the absence of any primary skin malignancies (excluding Kaposi's sarcoma) in the non-white patients and the significantly higher incidence of Kaposi's sarcoma in the non-white patients. There was no difference in the incidence of the other malignant lesions. Using multivariate analyses there was no difference in the incidence of malignancies between the race groups, the gender groups or patients...
who had received multiple compared to single grafts. Of note was that there was no significant increase in malignancies under cyclosporine (Table 4-6).

Immunosuppression
Under azathioprine the number of malignancies was 7.4 per 1000 patient-years compared with 13.9 under cyclosporine (also see Table 4-6). The difference was not statistically different. However, when the latent period between renal transplantation and development of the first malignancy was established, there was a significant difference in the intervals under cyclosporine as compared to conventional immunosuppressive treatment using azathioprine ($P = 0.017$, Student’s T-test). The mean interval under azathioprine was 86.9 months (95% confidence intervals: 34.1 - 140.5) compared to 41.3 months cyclosporine (95% confidence interval: 27.9 - 54.7) (Fig. 4-8). The shortest interval to the development of a malignancy was 2.8 months to the diagnosis of Kaposi's sarcoma in a patient under cyclosporine. The shortest interval under azathioprine was 8.4 months also for the development of Kaposi's sarcoma although the lesion was disseminated in this patient. Patients who received multiple renal allografts and were thus exposed to multiple courses of immunosuppressive therapy did not have an increased propensity to develop malignancies (Table 4-6).
(3) THE MALIGNANCIES IN THE TRANSPLANTED PATIENTS: KAPOSI’S SARCOMA

DEMOGRAPHY AND CLINICAL ASPECTS (Table 4-7)

Incidence and racial distribution
Kaposi’s sarcoma was the single most common malignancy and accounted for 21/44 (47.7%) of all malignancies. Of the 41 patients who developed a tumour 21 (51.2%) developed Kaposi’s sarcoma. Kaposi’s sarcoma occurred in 21/542 (3.9%) of all patients receiving renal allografts. Kaposi’s sarcoma was significantly more common in non-white patients accounting for 19/357 (5.32%) of all malignant lesions in this group. In contrast, only 2 (1.08%) of 185 white transplant patients developed Kaposi’s sarcoma (p = 0.032, multiple linear regression analysis). Of the 17 white patients who developed a malignancy 2 (11.7%) developed Kaposi’s sarcoma but among the 24 non-white patients with malignancies 19 (79.2%) developed Kaposi’s sarcoma (p = 0.0000, Fisher’s exact). The number of Kaposi’s sarcoma lesions was 1.4 per 1000 patient-years in the white patients and 9.2 per 1000 patient-years in the non-white patients. None of the patients were of Jewish or Mediterranean origin.

Age
The mean age of patients at the time of diagnosis of Kaposi’s sarcoma was 42 years (range: 27-54 years). The mean age of patients at the time of the primary transplant was 39 years (range: 24-50 years) compared to the mean of 37 years (range: 8-64) for the transplant cohort. Patients who were aged over 40-years also did not have a higher incidence of Kaposi’s sarcoma compared to the younger patients [10/213 (4.7%) vs. 11/329 (3.3%), P = 0.78, multiple linear regression analysis].

Relative risk of Kaposi’s sarcoma (Table 4-8)
The risk of developing Kaposi’s sarcoma in our cohort of patients was increased by a factor of 235 when compared to the lesions expected in the non-transplant population.
## Table 4-7 Demographic and clinical data on the cohort of patients with Kaposi's sarcoma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>Treatment</th>
<th>Distribution of lesions</th>
<th>Latency (mo.)</th>
<th>Treatment Discontinued</th>
<th>Outcome</th>
<th>Patient/Lesions</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>38</td>
<td>Male</td>
<td>Caucasian</td>
<td>Azathioprine</td>
<td>Visceral</td>
<td>8.4</td>
<td>All</td>
<td>Died of disseminated disease</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>JM</td>
<td>45</td>
<td>Male</td>
<td>Coloured</td>
<td>Azathioprine</td>
<td>Cutaneous</td>
<td>228.3</td>
<td>Cyclosporine</td>
<td>Lesions improved</td>
<td>Maintained</td>
<td></td>
</tr>
<tr>
<td>JA</td>
<td>53</td>
<td>Male</td>
<td>Coloured</td>
<td>Azathioprine</td>
<td>Cutaneous</td>
<td>24.0</td>
<td>All</td>
<td>Lesions improved</td>
<td>Graft loss</td>
<td></td>
</tr>
<tr>
<td>KM</td>
<td>49</td>
<td>Male</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Cutaneous</td>
<td>21.2</td>
<td>All + DXR + Chemo (M)</td>
<td>Lesions improved</td>
<td>Graft loss</td>
<td></td>
</tr>
<tr>
<td>JW</td>
<td>39</td>
<td>Male</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Visceral</td>
<td>11.2</td>
<td>All</td>
<td>Died of disseminated disease</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MO</td>
<td>29</td>
<td>Female</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Cutaneous</td>
<td>2.9</td>
<td>All</td>
<td>Lesions improved</td>
<td>Graft loss</td>
<td></td>
</tr>
<tr>
<td>IM</td>
<td>54</td>
<td>Male</td>
<td>Black</td>
<td>Cyclosporine</td>
<td>Mucocutaneous</td>
<td>56.3</td>
<td>Cyclosporine + DXR (M)</td>
<td>Lesions improved after DXR</td>
<td>Maintained</td>
<td></td>
</tr>
<tr>
<td>LF</td>
<td>49</td>
<td>Male</td>
<td>Black</td>
<td>Cyclosporine</td>
<td>Cutaneous</td>
<td>26.8</td>
<td>All</td>
<td>Lesions improved</td>
<td>Maintained</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td>44</td>
<td>Female</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Cutaneous</td>
<td>64.1</td>
<td>Cyclosporine + DXRx1</td>
<td>Lesions improved</td>
<td>Maintained</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>31</td>
<td>Male</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Cutaneous</td>
<td>34.4</td>
<td>All</td>
<td>Lesions improved</td>
<td>Maintained</td>
<td></td>
</tr>
<tr>
<td>GN</td>
<td>35</td>
<td>Female</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Mucocutaneous</td>
<td>22.2</td>
<td>Cyclosporine</td>
<td>Lesions improved</td>
<td>Maintained</td>
<td></td>
</tr>
<tr>
<td>WB</td>
<td>27</td>
<td>Male</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Cutaneous</td>
<td>4.1</td>
<td>All</td>
<td>Lesions improved</td>
<td>Maintained</td>
<td></td>
</tr>
<tr>
<td>GO</td>
<td>41</td>
<td>Male</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Cutaneous</td>
<td>17.5</td>
<td>Cyclosporine + Chemo (S)</td>
<td>Lesions improved</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MB</td>
<td>43</td>
<td>Female</td>
<td>Caucasian</td>
<td>Cyclosporine</td>
<td>Visceral</td>
<td>4.1</td>
<td>All</td>
<td>Died of disseminated disease</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CM</td>
<td>50</td>
<td>Female</td>
<td>Black</td>
<td>Cyclosporine</td>
<td>Cutaneous</td>
<td>8.9</td>
<td>All</td>
<td>Lesions improved</td>
<td>Graft loss (advanced renal failure)</td>
<td></td>
</tr>
<tr>
<td>SG</td>
<td>53</td>
<td>Female</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Cutaneous</td>
<td>61.4</td>
<td>Cyclosporine</td>
<td>Lesions improved</td>
<td>Maintained</td>
<td></td>
</tr>
<tr>
<td>RJ</td>
<td>40</td>
<td>Female</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Visceral</td>
<td>8.3</td>
<td>Nil</td>
<td>Died of disseminated disease</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>LJ</td>
<td>48</td>
<td>Female</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Cutaneous</td>
<td>13.9</td>
<td>Cyclosporine</td>
<td>Lesions improved</td>
<td>Graft loss (advanced renal failure)</td>
<td></td>
</tr>
<tr>
<td>RB</td>
<td>36</td>
<td>Female</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Visceral</td>
<td>13.3</td>
<td>Cyclosporine + DXR (M) (after 3mo.)</td>
<td>Lesions improved, relapse after 2 years</td>
<td>Maintained</td>
<td></td>
</tr>
<tr>
<td>ML</td>
<td>44</td>
<td>Female</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Cutaneous</td>
<td>31.5</td>
<td>Cyclosporine</td>
<td>Lesions improved</td>
<td>Maintained</td>
<td></td>
</tr>
<tr>
<td>DI</td>
<td>37</td>
<td>Male</td>
<td>Coloured</td>
<td>Cyclosporine</td>
<td>Visceral</td>
<td>10.6</td>
<td>Mycophenolate</td>
<td>Lesions improved</td>
<td>Maintained</td>
<td></td>
</tr>
</tbody>
</table>

1 Patient with clinical visceral Kaposi's sarcoma organ involvement. Postmortem examination not obtained. DXR is radiotherapy; Chemo is chemotherapy.
Table 4-8  Relative risk for the development of Kaposi’s sarcoma in various groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative risk</th>
<th>95% CL$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>235.1</td>
<td>146.0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>540.5</td>
<td>279.3</td>
</tr>
<tr>
<td>Female</td>
<td>118.3</td>
<td>54.0</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 45 yrs</td>
<td>510.9</td>
<td>279.0</td>
</tr>
<tr>
<td>&gt; 45 yrs</td>
<td>113.0</td>
<td>102.8</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>174.4</td>
<td>36.0</td>
</tr>
<tr>
<td>Coloured</td>
<td>308.4</td>
<td>168.6</td>
</tr>
<tr>
<td>Black</td>
<td>149.8</td>
<td>4.8</td>
</tr>
</tbody>
</table>

$^1$Confidence limits

The risks were calculated for the different race, gender and age groups (Table 4-8) (also see Appendix Table 4-16). Males, those below the age of 45 and coloured patients had the greatest relative risk of developing Kaposi’s sarcoma.

Gender

There was no significant male predominance in the incidence of Kaposi’s sarcoma. The number of male patients who developed Kaposi’s sarcoma was 11/294 (3.7%), not significantly from the 10/248 (4.0%) of females who acquired the lesion ($\chi^2$- test). The male to female ratio was 11:10 (1:1), which was the same as the gender ratio of the renal transplant population. Kaposi’s sarcoma was therefore equally common in the 2 sexes.

Immunosuppression

Of 419 patients under cyclosporine, 18 developed Kaposi’s sarcoma, compared with 3 of the 123 patients receiving azathioprine. The difference was however not statistically significant ($P = 0.37$, multiple linear regression analysis). Patient JM developed Kaposi’s sarcoma 10 months after commencement of cyclosporine, having previously received azathioprine and methylprednisolone for 18 years after
transplantation. The azathioprine was being replaced by cyclosporine to allow the introduction of allopurinol to control severe gout. The skin lesions of Kaposi's sarcoma regressed when cyclosporine was discontinued.

**Cutaneous involvement**

The skin was involved in all patients diagnosed with Kaposi's sarcoma. Details of the skin lesions were not available for two patients (JA, AL). In the remaining 19 patients the lower limbs were involved in 16 (84.2%) of cases. No particular area of the leg was favoured with lesions being reported from the buttock to the sole of the foot. The upper limbs were affected in 6 (32.6%) of the patients. The torso was involved in 5 (26.3%) patients and the hard palate in only 2 (10.6%) patients (these patients are identified as having mucocutaneous involvement in Table 4-7).

**Extra-cutaneous involvement**

Lymph node and/or visceral organ involvement by Kaposi's sarcoma was present at initial presentation in 6 (28.6%) patients. Bilateral inguinal lymph node disease occurred in two patients (RB, DI) and was associated with skin involvement. Three patients with visceral organ involvement also had deep lymph node disease (AL, MB, RJ). Four patients had extensive visceral organ disease (AL, JW, MB, RJ) at the time of the initial diagnosis of Kaposi's sarcoma. One patient (RB) who did not have visceral organ involvement was found to have disease of her bronchial tree when Kaposi's sarcoma relapsed almost two years after the initial presentation (see page 4-26 for further details).

**Latent period**

The mean interval between renal transplantation and the diagnosis of Kaposi's sarcoma was 32.0 months (95% confidence intervals: 9.96 - 54.16). If patient JM who developed Kaposi's sarcoma only after the secondary introduction of cyclosporine is excluded from the analysis, the mean interval is 22.25 months (95% confidence intervals: 13.44 - 31.05). The shortest interval was 2.9 months (patient MO) and the longest (excluding patient JM) was 64.1 months (patient LC). The mean interval to the diagnosis of Kaposi's sarcoma under azathioprine was 86.9 months (95% confidence intervals: 2178 - 391.6) compared with 22.9 months (95% confidence intervals: 22.9 - 13.2) under cyclosporine (P = 0.03, Student's t-test).
Results

The data must however be interpreted with caution because of the small number of patients in the azathioprine group and the very wide standard deviation. If patient JM is excluded from the analysis then there is no difference in the latent intervals in the two treatment groups. There was no difference in the mean latent intervals of males and females (23.0 months compared to 21.4 months). However, there was a significant difference in the time interval between the diagnosis of local disease compared to disease with lymph node and/or visceral organ involvement with the latter occurring 16.5 months earlier (Fig. 4-9).

![Fig. 4-9 Latency Period](image)

Kaposi's Sarcoma: Visceral vs Cutaneous disease

Mann-Whitney U test: $p = 0.014$

Management

Treatment of the patients who developed Kaposi's sarcoma was primarily either withdrawal or reduction of immunosuppression. The policy in our Renal Transplant Unit until 1989 was the complete withdrawal of immunosuppression. From 1989, the immunosuppression was reduced by the withdrawal of cyclosporine and the maintenance of the patient on azathioprine and methylprednisolone. The cyclosporine was selected for withdrawal because it was considered to be the most
potent immunosuppressive agent. In the majority of cases the cyclosporine dose was tapered over several weeks rather than abruptly discontinued. The exceptions were patient MB who had visceral organ involvement and in whom the cyclosporine was abruptly stopped when it became apparent that the patient had extensive disease; the other exception was patient RJ who died before the diagnosis of Kaposi's sarcoma could be confirmed. Patient DI received mycophenolate mofetil as part of a phase 2 clinical drug trial. With the development of the Kaposi's sarcoma, the trial drug was withdrawn as required by trial protocol but the cyclosporine was maintained at standard doses.

**Adjunctive radiotherapy**

Four patients (GO, LF, RB, JM) with localised disease underwent either single or multiple courses of radiotherapy in an effort to control certain aspects of the disease. Whereas 3 patients received treatment for focal skin disease, patient RB received radiotherapy for a non-cutaneous lesion. This patient had very painful bilateral inguinal lymphadenopathy and required irradiation when the pain became unbearable despite the withdrawal of cyclosporine and attempts at pain control failed. A single patient (KM) with isolated skin involvement received chemotherapy as well. Patient MB who had very aggressive and extensive visceral disease also received chemotherapy pre-terminally but with little benefit.

**Prognosis**

**Visceral organ** involvement at presentation was an important determinant of patient outcome. All four patients presenting with visceral organ involvement died within days of the diagnosis being made or the diagnosis was confirmed at postmortem examination (RJ). The 2 patients (RB, DI) with bilateral inguinal lymphadenopathy but no apparent visceral organ involvement responded well to reduction in immunosuppression although the former required local irradiation after 3 months to control pain over the enlarged lymph nodes on one side as mentioned earlier.

**Skin lesions** generally responded to the reduction or withdrawal of immunosuppressive therapy. Occasionally some lesions required local irradiation
(see above). The lesions healed over several months often leaving behind pigmented or hyperkeratotic lesions.

The renal prognosis of patients who did not succumb to disseminated disease was directly related to the strategy employed with regard to the immunosuppressive treatment. All three patients in whom the immunosuppression was withdrawn had functioning grafts at the time when Kaposi's sarcoma was diagnosed but all grafts were lost to acute rejection. Dialysis had to be re-instituted in these patients at a mean of 5 weeks after withdrawal of the immunosuppressive agents. In contrast, the only patients to lose their grafts with the elimination of cyclosporine from their immunosuppressive regimen were two patients (CM, LJ) who already had advanced renal failure (plasma creatinine values > 800 µmol/l) when Kaposi's sarcoma was diagnosed. The difference in the outcomes of these two management strategies was highly significant (P = 0.014, Fisher's exact, two-tailed). In the treatment reduction group, the 12 patients had reasonably well preserved renal function when treatment was reduced. None developed acute rejection.
At one year 11 of the 12 patients in whom immunosuppression had been reduced and who had plasma creatinine values below 500 \( \mu \text{mol/l} \) had survived and all had functioning allografts. The mean plasma creatinine was 165.2 \( \mu \text{mol/l} \) (95% confidence intervals: 80.7 - 249.7) at the time of the diagnosis of the Kaposi’s sarcoma. One year after the diagnosis and discontinuation of cyclosporine (mycophenolate mofetil in the case of patient DI) the mean plasma creatinine value was 142.2 \( \mu \text{mol/l} \) (95% confidence intervals: 84.8 - 199.6). The difference was not significant (Student’s paired t-test, \( P = 0.248 \)) (Fig. 4-10). Patient JM died of septicaemia 9 months after the diagnosis of Kaposi’s sarcoma. He had a functional graft at the time of his demise. Patients GN and LF died of septicaemia and heart failure respectively both with functioning grafts 5 years after the diagnosis of Kaposi’s sarcoma. In both Kaposi’s sarcoma was in remission at the time of their final illnesses.

Relapse (See Fig. 9-5)
A single patient (RB) experienced relapse of Kaposi’s sarcoma. This occurred 22 months after the initial diagnosis and after the original lesions had resolved. The relapse involved lesions on both legs but with no involvement of the inguinal lymph nodes as had been the case with her original disease. Her relapse was, interestingly enough, preceded by repeated episodes of cellulitis affecting both legs over a period of 3 months. At the time of her presentation with relapse of Kaposi’s sarcoma she had severe ulcerating infections involving both legs. She was only on azathioprine 50 mg and methylprednisolone 8 mg daily. An endoscopic examination of the stomach and duodenum was normal but bronchoscopic examination revealed a lesion very suspicious of Kaposi’s sarcoma. A biopsy was not considered to be safe. The lesion was still present when the bronchoscopic examination was repeated 2 months later but no new lesions were seen. The patient was treated for her septic lesions on her legs with antibiotics and local dressings. The dose of the azathioprine was further reduced to 25 mg per day. Her renal function deteriorated by 30% before the reduction in the azathioprine dose but remained stable thereafter. Withdrawal of immunosuppression was not an option in this patient because she was not considered to be a suitable candidate for the local renal replacement program.
Other investigations
Patients DI, RB, ML and SG all underwent routine gastroscopy to establish the presence of upper gastrointestinal disease. All the patients had normal examinations. Routine chest X-rays were also available on most of the patients. Two patients (MB, RB) had abnormal findings and both were subjected to bronchoscopic examination. In all the other patients with focal skin disease no suspicious abnormalities were found. The X-rays of patients AL, JW and JA had were not available for review.

Human immunodeficiency virus (HIV) test
All the patients tested negative for the human immunodeficiency virus (HIV) with two exceptions. One patient (JA), a coloured male tested positive for the human T-lymphotrophic virus III (HTLV III) in 1985 before routine testing for HIV became available. Another patient (AL), a white male was diagnosed with Kaposi's sarcoma in 1978 before the HIV had been described.

HLA profiles
The HLA antigen frequencies in renal transplant patients with and without Kaposi's sarcoma were compared. Partial antigen profiling was available for 518 (98.9%) of the patients and full profiling (including DR antigens) was available in 457 (84.3%) of all the patients. The HLA antigen profile was available in 19 (90.5%) of the 21 Kaposi's sarcoma patients. No single HLA antigen occurred with significantly increased frequency in Kaposi's sarcoma patients compared to the Kaposi's sarcoma negative patients. The HLA-A2 antigen was the one most commonly encountered in the Kaposi's sarcoma patients occurring in 5 (26%) of 19 patients but it also occurred in 144 (28.9%) of the 499 non-Kaposi's sarcoma patients. The HLA-A2 antigen was the most frequently encountered class I antigen in this cohort occurring in 149 (28.8%) of the patients. HLA-DR2 was the most frequent class II antigen and occurred in 121 (28.9%) of the patients. HLA-DR2 also occurred in 4 (26.6%) of the 15 Kaposi's sarcoma patients who had full HLA-antigen typing available.
PATHOLOGY OF THE KAPOSI'S SARCOMA LESIONS

The original pathological material was reviewed in all except two patients. The tissue of patients AL and JA was no longer available for examination. The tissue of the remaining 19 patients was re-examined and the diagnosis of Kaposi's sarcoma confirmed. Postmortem examinations were performed on 3 of the 4 patients (AL, MB, RJ) who succumbed to the disease. In patient RJ the diagnosis of Kaposi's sarcoma was only confirmed at postmortem examination.

Skin disease (Table 4-9)

Cutaneous Kaposi's sarcoma was present in all 19 patients. The skin lesions were classified morphologically into macules-patches, papules-plaques and nodules-tumours according to Safai (1981). Seventeen (71%) of the 24 skin lesions biopsied fell into the second category, 5 (21%) were nodules and only 2 (8.3%) in the macule-patch category. Fifteen of the patients had multiple cutaneous lesions of which the most advanced were selected for biopsy. The 21 skin biopsy specimens that were available for examination were histopathologically classified according to Harawi et al. (1989): 3 (14.2%) were early type; 11 (52.3%) were mixed type lesions, 6 (25.5%) were spindle type lesions and only 1 (4.8%) lymphangiomatous type lesion. There were no angiomatous, inflammatory or pleomorphic type lesions present in this cohort.

In the two patients with disseminated disease in whom tissue was available for examination it was found that patient MB had the mixed variant of Kaposi's sarcoma in the skin but spindle type lesions in the visceral tissue. Patient RJ had the spindle variant of Kaposi's sarcoma in the skin as well as all involved tissue examined at postmortem examination. Patient RB who had sequential skin biopsies showed progressively early, spindle and mixed lesions. Patient DI had mixed type lesions in both the skin and the lymph node, which were biopsied contemporaneously. All 4 solitary lesions were of the mixed type. There was a comparable distribution of the lesion types between males and females. There were no discernible differences in the pattern of the histological type of lesions that occurred on the legs compared with those lesions elsewhere.
# Results

Table 4-9 Distribution and pathological aspects of Kaposi's sarcoma lesions

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>Tissue</th>
<th>Distribution</th>
<th>Number</th>
<th>Morphology</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>WB</td>
<td>30</td>
<td>Male</td>
<td>Coloured</td>
<td>Skin</td>
<td>Face, arms</td>
<td>Multiple</td>
<td>Nodules</td>
<td>Spindle</td>
</tr>
<tr>
<td>LC</td>
<td>44</td>
<td>Female</td>
<td>Coloured</td>
<td>Skin</td>
<td>Arms</td>
<td>Multiple</td>
<td>Macules, papules</td>
<td>Early</td>
</tr>
<tr>
<td>LF</td>
<td>53</td>
<td>Male</td>
<td>Black</td>
<td>Skin</td>
<td>Leg, arm, trunk</td>
<td>Multiple</td>
<td>Papules, plaques</td>
<td>Early</td>
</tr>
<tr>
<td>LJ</td>
<td>48</td>
<td>Female</td>
<td>Coloured</td>
<td>Skin</td>
<td>Shoulder</td>
<td>Solitary</td>
<td>Nodule</td>
<td>Mixed</td>
</tr>
<tr>
<td>IM</td>
<td>56</td>
<td>Male</td>
<td>Black</td>
<td>Skin</td>
<td>Legs, palate, nose</td>
<td>Multiple</td>
<td>Papules, nodules</td>
<td>Lymphangiomatous</td>
</tr>
<tr>
<td>CM</td>
<td>51</td>
<td>Female</td>
<td>Black</td>
<td>Skin</td>
<td>Leg</td>
<td>Multiple</td>
<td>Papules, plaques</td>
<td>Spindle</td>
</tr>
<tr>
<td>KM</td>
<td>60</td>
<td>Male</td>
<td>Coloured</td>
<td>Skin</td>
<td>Leg</td>
<td>Multiple</td>
<td>Plaque, papules</td>
<td>Mixed</td>
</tr>
<tr>
<td>GN</td>
<td>38</td>
<td>Female</td>
<td>Coloured</td>
<td>Skin</td>
<td>Leg, palate</td>
<td>Solitary</td>
<td>Plaque</td>
<td>Mixed</td>
</tr>
<tr>
<td>MO</td>
<td>39</td>
<td>Female</td>
<td>Coloured</td>
<td>Skin</td>
<td>Leg, arm</td>
<td>Multiple</td>
<td>Papules</td>
<td>Mixed</td>
</tr>
<tr>
<td>GO</td>
<td>42</td>
<td>Male</td>
<td>Coloured</td>
<td>Skin</td>
<td>Leg</td>
<td>Multiple</td>
<td>Papules, plaques</td>
<td>Mixed</td>
</tr>
<tr>
<td>RT</td>
<td>43</td>
<td>Male</td>
<td>Coloured</td>
<td>Skin</td>
<td>Leg, trunk</td>
<td>Multiple</td>
<td>Papules, nodules</td>
<td>Spindle</td>
</tr>
<tr>
<td>JW</td>
<td>49</td>
<td>Male</td>
<td>Coloured</td>
<td>Skin</td>
<td>Trunk, abdomen</td>
<td>Multiple</td>
<td>Papules, nodules</td>
<td>Mixed</td>
</tr>
<tr>
<td>MB</td>
<td>46</td>
<td>Female</td>
<td>Caucasian</td>
<td>Skin</td>
<td>Liver, Lung</td>
<td>Multiple</td>
<td>Papules</td>
<td>Spindle</td>
</tr>
<tr>
<td>RJ</td>
<td>41</td>
<td>Female</td>
<td>Coloured</td>
<td>Skin</td>
<td>Lymph-node</td>
<td>Multiple</td>
<td>Papules</td>
<td>Spindle</td>
</tr>
<tr>
<td>MB</td>
<td>46</td>
<td>Female</td>
<td>Caucasian</td>
<td>Skin</td>
<td>Lymph-node</td>
<td>Multiple</td>
<td>Papules</td>
<td>Spindle</td>
</tr>
<tr>
<td>RB</td>
<td>36</td>
<td>Female</td>
<td>Coloured</td>
<td>Skin</td>
<td>Legs 5/97</td>
<td>Multiple</td>
<td>Plaque</td>
<td>Early</td>
</tr>
<tr>
<td>SG</td>
<td>53</td>
<td>Female</td>
<td>Coloured</td>
<td>Skin</td>
<td>Legs 10/97</td>
<td>Multiple</td>
<td>Papules, plaques</td>
<td>Spindle</td>
</tr>
<tr>
<td>DI</td>
<td>38</td>
<td>Male</td>
<td>Coloured</td>
<td>Skin</td>
<td>Legs 7/00</td>
<td>Multiple</td>
<td>Nodules</td>
<td>Mixed</td>
</tr>
<tr>
<td>ML</td>
<td>45</td>
<td>Female</td>
<td>Coloured</td>
<td>Skin</td>
<td>Buttock</td>
<td>Solitary</td>
<td>Nodule</td>
<td>Mixed</td>
</tr>
<tr>
<td>JM</td>
<td>45</td>
<td>Male</td>
<td>Coloured</td>
<td>Skin</td>
<td>Legs, arms</td>
<td>Multiple</td>
<td>Macules, papules</td>
<td>Spindle</td>
</tr>
</tbody>
</table>
Table 4-10. Postmortem findings in 3 patients with disseminated Kaposi’s sarcoma.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Visceral Organs / Lymph nodes Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stomach</td>
</tr>
<tr>
<td>AL</td>
<td>Yes</td>
</tr>
<tr>
<td>RJ</td>
<td>Yes</td>
</tr>
<tr>
<td>MB</td>
<td>No</td>
</tr>
</tbody>
</table>

Postmortem findings

The range of organ involvement in the 3 patients who underwent postmortem examination is shown (Table 4-10). Of note is the observation that Kaposi’s sarcoma affected the lungs and deep lymph nodes in all three patients. One patient (RJ) had extensive disease including renal allograft and bone involvement. In the two patients (MB, RJ) in whom Kaposi’s sarcoma tissue was available for review, the histological features indicated the spindle variety of Kaposi’s sarcoma according to Harawi et al. (1989).
(4) The malignancies in the transplanted patients: Non-Kaposi's sarcoma malignancies

Skin malignancies and pre-malignant lesions (Table 4-11)

Incidence
Malignant skin lesions exclusively affected white patients. In no instance did a single black or coloured patient develop a skin malignancy despite the fact that non-white patients formed the bulk of the transplant population and despite the prolonged follow-up period. All 13 (7.0%) skin malignancies occurred among the 185 white patients. Of the 20 malignancies detected in the white group 13 (65%) were skin malignancies. Basal cell carcinoma occurred in 7 patients and squamous cell carcinoma in 5 patients. Two male patients had both basal cell carcinoma and squamous cell carcinoma. Both these patients had pre-malignant lesions as well: one had solar keratosis, Bowen's disease and in situ squamous cell carcinoma lesions of the skin; the other patient had multiple solar keratosis lesions. In addition, one patient with basal cell carcinoma had multiple in situ squamous cell carcinoma lesions. All non-melanoma skin lesions with the exception of one squamous cell malignancy, occurred in male patients. The incidence of non-melanoma skin malignancies was significantly greater in white males developing in 11/96 (11.4%) compared to white females 1/88 (1.1%), \( p = 0.0046, \chi^2 \) test). The mean age of patients at the time of diagnosis of the first non-melanoma skin malignancy was 41 years (range: 34-60). A single case of malignant melanoma was recorded and this in a white female patient under azathioprine.

Of 101 skin biopsies for suspected skin tumours, 98 lesions were either malignant or pre-malignant (Table 4-11). Of the total number of skin biopsies, 83 (83%) were from 2 patients (LM and NvdW). Squamous cell carcinoma was the most frequently encountered lesion accounting for 59% of the 63 malignancies and 38% of all suspicious skin lesions. The number of squamous cell carcinoma lesions exceeded the basal cell carcinoma lesions by a factor of 1.7. Solar keratosis
Table 4.11 Details of the discrete malignant and premalignant skin lesions in white renal transplant patients.

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of biopsies</th>
<th>SQ CA</th>
<th>BCCA</th>
<th>Carcinoma-in-situ</th>
<th>SK</th>
<th>Other lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM</td>
<td>43</td>
<td>65</td>
<td>27</td>
<td>16</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Metatypic carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Basosquamous (X2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Keratoacanthoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Verruca vulgaris (X2)</td>
</tr>
<tr>
<td>NvdW</td>
<td>50</td>
<td>18</td>
<td>7</td>
<td>1</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bowen's disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Verruca vulgaris</td>
</tr>
<tr>
<td>JB</td>
<td>60</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anaplastic carcinoma</td>
</tr>
<tr>
<td>MG</td>
<td>53</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>AM1</td>
<td>31</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MN1</td>
<td>41</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>34</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DL</td>
<td>55</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CV</td>
<td>36</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FvdW</td>
<td>40</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FIR</td>
<td>39</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>101</td>
<td>37</td>
<td>22</td>
<td>14</td>
<td>19</td>
<td>-</td>
</tr>
</tbody>
</table>

Female patients. SQ CA is squamous cell carcinoma; BCCA is basal cell carcinoma; SK is solar keratosis.

was the most common pre-malignant condition followed closely by in-situ carcinoma. Single cases of Bowen's disease of the leg, anaplastic carcinoma most probably of sweat gland origin and a metatypic carcinoma involving a nasal ala, were diagnosed. The two patients (LM and NvdW) with the most abundant skin lesions also had verruca vulgaris on the penis and shoulder respectively. For the purposes of this study, different types of lesions were only counted once, irrespective of the number of lesions that appeared.

Latent period The mean time interval to the development of the first basal cell carcinoma lesion was 63.4 months (95% confidence interval: 27.2 - 99.5) compared to the 82.1 months (95% confidence interval: 2.4 - 166.6) to the first squamous cell carcinoma (data not shown). The difference was not statistically significant (p = 0.6; Student's t-test).
Influence of sun-exposure (Fig. 4-11) Of the 104 cancerous and pre-cancerous lesions 87 (83.7%) occurred in sun-exposed areas of the body which included the face, the head, the neck and the dorsum of the hands. Each of the more common type of lesion also occurred predominantly in sun-exposed areas. Whereas invasive squamous carcinoma of the skin occurred almost exclusively in sun-exposed skin, in the case of in situ squamous carcinoma the proportion of lesions in the two areas approached unity: this difference in the number of lesions in the two areas was significant (p = 0.0006; $\chi^2$ test). No lesions were described in the groin or in the axillae.

Influence of immunosuppression In the 69 white patients transplanted under azathioprine, 4 (5.8%) non-melanoma skin malignancies and 1 (1.4%) malignant
Table 4-12  Comparison of types of malignant skin lesions in white renal transplant patients under two immunosuppressive treatment regimens.

<table>
<thead>
<tr>
<th></th>
<th>Azathioprine</th>
<th>Cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients at risk</td>
<td>69</td>
<td>116</td>
</tr>
<tr>
<td>No. of lesions</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Incidence(^1)</td>
<td>5.8%</td>
<td>8.6%</td>
</tr>
<tr>
<td>• Squamous cell carcinoma(^1)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>• Basal cell carcinoma(^1)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>• Malignant melanoma(^1)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>• Anaplastic carcinoma(^1)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>• Metatypic carcinoma(^1)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Mean latent period in mo. (95% CL)(^1)</td>
<td>95.1 (3.4 - 186.8)</td>
<td>55.7 (18.35 - 93.0)</td>
</tr>
</tbody>
</table>

\(^1\)P = NS, comparing malignant skin lesions in patients under azathioprine and cyclosporine.

melanoma were detected. The incidence of non-melanoma skin malignancies under cyclosporine was not statistically different in the 116 white patients with 8 (6.9%) malignancies in this group (p = 0.83, \(\chi^2\) - test). No malignant melanomas occurred in the cyclosporine group. The latent period to the development of the first skin malignancy was not significantly different under cyclosporine compared to azathioprine (Table 4-12). All the skin tumours were adequately treated with excision biopsies. None of the patients developed metastatic lesions or died as a direct result of the skin malignancy.

Carcinoma of the bronchus (Table 4-13)
Carcinoma of the bronchus was diagnosed in 3 patients. The details of the patients are shown. All three patients were cigarette smokers and had received triple immunosuppressive therapy including cyclosporine. Both male patients had failed grafts and had received haemodialysis treatment for approximately 10 years after failure of the renal allograft, before developing the bronchial lesion. Neither of these two patients was therefore on immunosuppressive therapy at the time of the diagnosis of the lung. Both patients presented with advanced lesions which
### Table 4-13. Details of renal transplant patients diagnosed with carcinoma of the lung.

<table>
<thead>
<tr>
<th></th>
<th>Patient PT</th>
<th>Patient JM</th>
<th>Patient DJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>Coloured</td>
<td>Black</td>
<td>Coloured</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age at transplant (yrs)</td>
<td>30.6</td>
<td>36.7</td>
<td>44.5</td>
</tr>
<tr>
<td>Age at malignancy (yrs)</td>
<td>42.0</td>
<td>46.2</td>
<td>51.4</td>
</tr>
<tr>
<td>Haemodialysis recommenced</td>
<td>5-Aug-87</td>
<td>12-Oct-89</td>
<td>-</td>
</tr>
<tr>
<td>Duration of immunosuppression (mo.)</td>
<td>17.4</td>
<td>6.67</td>
<td>71.82</td>
</tr>
<tr>
<td>Cigarette use (pack yrs)</td>
<td>27</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>Latency period (mo.)</td>
<td>139.2</td>
<td>119.4</td>
<td>83.3</td>
</tr>
<tr>
<td>Histology of carcinoma</td>
<td>-</td>
<td>Undifferentiated</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Treatment</td>
<td>Radiotherapy</td>
<td>Radiotherapy</td>
<td>Surgery</td>
</tr>
<tr>
<td>Outcome/survival (mo.)</td>
<td>Mortality (3)</td>
<td>Mortality (4)</td>
<td>Alive (March 00)</td>
</tr>
</tbody>
</table>

were considered inoperable and both underwent palliative radiotherapy. In patient JM, the diagnosis of malignancy was made on cytological examination of the sputum which showed poorly differentiated malignant cells. A formal biopsy was not undertaken. In patient PT, cytological examination of the sputum was unhelpful and a histological diagnosis of a malignancy could not be confirmed because material obtained was inadequate. However, the clinical and radiological evidence was sufficiently strong to warrant radiotherapeutic intervention. Tests for tuberculosis and fungal infections were repeatedly negative. Patients PT and JM survived 3 and 4 months respectively following the diagnosis with both succumbing to complications arising from the primary malignancy.

Patient DJ developed her lesion while on immunosuppressive treatment. She presented with a discrete lesion in the upper lobe of the right lung and the malignant nature of the lesion was proven on fine needle aspiration. In the absence of any metastases the lesion was considered curable and she underwent surgical resection. Post-operative sputum examination also revealed the presence of acid-alcohol fast
bacilli; the patient was commenced on a course of anti-tuberculous treatment and is doing well 6 months after surgery.

The relative risk of the development of lung cancer was compared to the incidence in age- race- and sex-matched subjects in the general South African population. The risk of lung cancer among renal allograft recipients was not increased in the white patients but was doubled in coloured patients and increased 2.4 fold in black patients (see Appendix Table 4-17).

Breast carcinoma
Two female patients, both under cyclosporine, developed carcinoma of the breast. The first patient, who was coloured and aged 51 years, was diagnosed with infiltrating ductular adenocarcinoma of the right breast at a peripheral hospital 16 months after renal transplantation. She underwent radical mastectomy and died 2 years following the surgery of an unrelated cerebrovascular accident.

The second patient, a white recipient aged 53 years was also diagnosed with an infiltrating duct carcinoma 53 months after renal transplantation. She was treated with radical mastectomy and tamoxifen. Fifty-seven months later she presented with relapse of the malignancy in regional lymph nodes. The patient was referred for local irradiation. The patient continues to do well one year after the treatment with a well-functioning graft.

The risk for the development of breast cancer was compared to age- race- and sex-matched South African controls (see Appendix Table 4-18). The risk of this lesion was reduced in all race groups.

Malignant lymphoma
Two patients, both receiving cyclosporine-based triple therapy, developed malignant lymphomas. The first patient was a white female who was 16 years old at the time of her primary renal transplant. This graft never functioned and was lost as the result of acute rejection and rupture. The second transplant was performed 20 months later. The patient again suffered acute rejection that was treated with conventional pulses of methylprednisolone and the graft maintained some function. Two months after the
second transplant the patient presented with biopsy-proven acute cellular rejection and this time the patient received a 7-day course of OKT3 monoclonal antibodies. The patient died 18 days after this admission with the cause of death at postmortem examination being established as disseminated mucormycosis. An unexpected finding at postmortem examination was that of a large cell lymphoma with involvement of lymph nodes, the spleen, tonsils, gastric mucosa and the renal allograft. Both native kidneys had been removed before the first transplant because the patient had had severe ureteric reflux with ongoing sepsis. The patient was also found to have cytomegalovirus pneumonitis. Another incidental finding in this patient at postmortem examination was the presence of papillary carcinoma of the thyroid gland, which manifested as a solitary nodule that had not been clinically detectable.

The second patient was a coloured female aged 44 years at the time of renal transplantation. The patient had an uneventful course following the transplant. She was never treated for acute rejection and never received OKT3 monoclonal antibodies. She presented 8 years after transplantation with a 9-month history of a painless annular ulcer on the left lower leg measuring 30 mm in diameter associated with dermal nodules. Biopsy of the lesion showed infiltration by malignant lymphoma cells that predominantly had the B-cell phenotype. The diagnosis of a diffuse large B-cell lymphoma (REAL classification)\(^1\) was made. The patient did not have cytomegalovirus infection. The only therapeutic intervention undertaken was the reduction of the patient's immunosuppression by withdrawing azathioprine. She was maintained on conventional doses of cyclosporine and methylprednisolone. A repeat skin biopsy done 4 months later showed features of a chronic ulcer but no evidence of the lymphoma. The patient's renal function remained stable and the azathioprine was permanently withheld. However, the patient subsequently had to have a below-knee amputation because of uncontrollable sepsis of the left leg.

No other renal transplant patient exposed to OKT3, used to treat steroid-resistant acute renal allograft rejection, developed malignant lymphoma. The relative risk for the development of non-Hodgkin's lymphoma (NHL) is increased in the white and coloured patients by 2.9 and 1.5 respectively while black patients had no increased

\(^1\) Revised European-American classification of lymphoid neoplasms
risk of developing NHL (Appendix Table 4-19). Initially, patients were treated with OKT3 for 7-10 days but over the years the duration of therapy was reduced to 5 days and on occasion 3-day courses were given. On no occasion was treatment continued for longer than 14 days. No patient received more than one course of OKT3 for fear of the reaction to anti-murine antibodies.

Hepatocellular carcinoma.
A single patient developed hepatocellular carcinoma. The patient was a white male, aged 22 years at the time of renal transplantation. The patient was initially hepatitis B-virus negative but seroconverted 4 months following the transplant. The graft functioned for 4 years before dialysis was re-initiated. The patient developed intractable ascites 3 years after the transplant. Extensive investigations were undertaken. Two years later a visceral angiogram showed a large vascular lesion in the liver in keeping with hepatocellular carcinoma. No biopsy was undertaken because of the vascularity of the lesion and the serum α-fetoprotein levels remained normal. He succumbed to complications related to the hepatocellular carcinoma 2 months later. A postmortem examination was not performed.

Renal cell carcinoma
The diagnosis of renal cell carcinoma was suspected in one coloured male patient. He was 58 years old when he received his renal allograft. Investigations undertaken 30 months after the transplantation to diagnose the renal lesions included ultrasound and computerised axial tomography. These showed large cystic lesions related to the kidney. Surgical intervention was planned to confirm the diagnosis but the patient died unexpectedly soon afterward of unrelated causes. At postmortem examination the macroscopic appearance of the lesion was in keeping with renal cell carcinoma but the tissue was too autolytic to allow an histological diagnosis to be made.
Results

(5) PRE-EXISTING MALIGNANCIES IN RENAL TRANSPLANT PATIENTS

Introduction
Malignancies were documented in 6 patients prior to renal transplantation. The details of these patients and their lesions are shown in Table 4-14. In 4 patients the diagnosis was made before they received their grafts. In the other two cases the diagnosis was made within two weeks of the transplant suggesting that the lesions must have been present before the transplant. In the first group of patients, single cases of a seminoma, skin carcinoma, breast carcinoma and renal cell carcinoma were diagnosed.

Case studies
Seminoma The patient (MM) who was diagnosed with this lesion was a phenotypic female who had been on dialysis for 49 months. The patient was a true hermaphrodite who presented with ascites and an abdominal mass. At surgery the uterus and an adnexal seminoma were removed. No further treatment was given for the malignancy. The patient was transplanted and received triple

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Race</th>
<th>Site</th>
<th>Histological Type</th>
<th>Treatment</th>
<th>Interval (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>25</td>
<td>Female</td>
<td>Black</td>
<td>Gonad</td>
<td>Seminoma</td>
<td>Surgery</td>
<td>73</td>
</tr>
<tr>
<td>BC</td>
<td>44</td>
<td>Male</td>
<td>White</td>
<td>Skin</td>
<td>Squamous cell CA</td>
<td>Excision</td>
<td>15</td>
</tr>
<tr>
<td>LC</td>
<td>36</td>
<td>Female</td>
<td>Coloured</td>
<td>Breast</td>
<td>Intraducal CA</td>
<td>Surgery and Iridium rods</td>
<td>33</td>
</tr>
<tr>
<td>JA</td>
<td>37</td>
<td>Male</td>
<td>Coloured</td>
<td>Kidney</td>
<td>Renal cell CA</td>
<td>Surgery</td>
<td>90</td>
</tr>
<tr>
<td>JC</td>
<td>46</td>
<td>Male</td>
<td>Coloured</td>
<td>Thyroid</td>
<td>Papillary CA</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>CvdH</td>
<td>37</td>
<td>Male</td>
<td>White</td>
<td>Bladder</td>
<td>Transitional cell CA</td>
<td>Fulguration</td>
<td>0</td>
</tr>
</tbody>
</table>

1 This is age at the diagnosis of the malignancy
2 This refers to the time from the initial diagnosis of the malignancy to the primary renal transplant.
3 These patients received multiple grafts
4 This patient subsequently developed Kaposi's sarcoma
5 This patient was under azathioprine. The rest were transplanted under cyclosporine
CA is carcinoma
immunosuppressive therapy. At 8 years follow-up the patient remains free of disease with a well-functioning graft.

**Squamous cell carcinoma of the skin** Only one white male patient (BC) had evidence of a malignant skin lesion before transplantation. The dermis surrounding the lesion exhibited features of severe solar keratosis. The patient had been on dialysis for less than 1 month when the lesion was detected. The lesion was excised and the patient subsequently transplanted under triple therapy including cyclosporine. The patient received his first graft 16 months after the initiation of dialysis. The first graft was lost after only 4 days and a second graft was transplanted 8 months later, which functioned for 2 years before it was lost to chronic rejection. Of note is that when the patient died 15 months later of cardiovascular disease, he had developed no new malignant skin lesions.

**Breast carcinoma** One female patient (LC) underwent a mastectomy with clearance of the regional lymph nodes for breast carcinoma. She also had adjunctive radiotherapy to the lesion. At the time of the surgery the patient already had moderately impaired renal function and was commenced on dialysis 32 months after the diagnosis of the malignancy. She was transplanted one month later under triple immunosuppressive therapy including cyclosporine. She had no further recurrence at 94 months follow-up. She did however develop Kaposi's sarcoma at 64 months after the transplant (see above for further details).

**Renal cell carcinoma** A nephrectomy was performed in a male patient (JA) for a renal cell carcinoma 8 years before he was commenced on dialysis. The disease had not infiltrated the inferior vena cava or the regional lymph nodes. He had no further treatment for the lesion. He received a renal allograft 8 weeks after the initiation of dialysis and was maintained on triple immunosuppressive treatment. The first graft failed after 39 months but the patient received a second allograft 6 months later. At the time of his demise 10 months later the patient had no evidence of recurrence of the renal cell carcinoma.

**Other lesions** One patient (JC) was found to have an incidental papillary cell carcinoma of the thyroid at postmortem examination. The patient had died within 24
hours of complications arising from the transplant surgery. One other patient (CvdH) was found to have a transitional cell bladder carcinoma at cystoscopy done 2 weeks after the transplant for persistent haematuria. The patient required repeated treatments to fulgurate the lesion. This patient was the only one to receive azathioprine treatment. The patient died 14 years later of causes unrelated to the malignancy.

LITERATURE CITED


Appendix

Fig. 4.12a  Graft Loss over time expressed as Probability Density

Model: Linear Hazard
Appendix

**Fig. 4-12b** Renal Allograft Recipients  
Factors influencing Survival

- **Patient Survival**  
  Influence of Immunosuppressive Therapy

- **Patient Survival**  
  Influence of Primary Renal Disease

- **Duration of Dialysis Prior to Transplantation**

- **Influence of Race**
Appendix

*Fig. 4-13a*  Survival of Primary Renal Allografts

Life Table Model: Linear Hazard

![Graph showing cumulative proportion surviving over time](image-url)
Appendix

**Fig. 4-13b Graft Survival**

*Multiple Transplants (n = 72)*

Cumulative Proportion Surviving

Survival (Years)
### Table 4-16: Relative risk of the development of Kaposi's sarcoma in the race groups

<table>
<thead>
<tr>
<th>Age group</th>
<th>Total cancers</th>
<th>No. of cases</th>
<th>Sum of O</th>
<th>Proportion of total cancers</th>
<th>No. of cases</th>
<th>Sum of E (O/E)</th>
<th>Relative Risk</th>
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1 Excludes non-melanoma skin malignancies.
Table 4-17  The relative risk for the development of lung cancer in renal allograft recipients.

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<th>Age group</th>
<th>Total cancers</th>
<th>No. of cases</th>
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<th>Proportion of total cancers</th>
<th>No of cases</th>
<th>Sum of E</th>
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<th>95% CL</th>
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### Table 4-18 Relative risk for the development of breast cancer in renal allograft recipients.

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### Table 4-19 Relative risk for the development of non-Hodgkin's lymphoma (NHL) in renal transplant patients.

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<th>Relative Risk</th>
</tr>
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<td>Proportion of total cancers</td>
<td>No. of cases</td>
<td>Sum of E</td>
</tr>
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Chapter 5

THE OUTCOME OF RENAL TRANSPLANTATION

The results of kidney transplantation have improved remarkably during the past 25 years (Cecka, 1998). Some of the developments that have influenced improvements are indicated in Fig. 5-1. The paradoxical benefit of pre-transplant blood transfusions was recognised in 1973 (Opelz et al., 1973) and during the subsequent years the majority of patients were given blood transfusions as an extension of the immunosuppressive regimen. The use of deliberate blood transfusions was discontinued in the late 1980s because the survival rates for patients not transfused had improved to the point that little advantage was gained by continuing this practice (Opelz, 1987). Patient survival rates also improved between 1975 and 1986 with better patient selection and the development of better treatment modalities (Cecka, 1998). The introduction of OKT3, a monoclonal antibody capable
of inhibiting T-cell activity added a powerful tool for the treatment of acute rejection when it was introduced for clinical use in the early 1980's (Cecka, 1998). However, it was the introduction of cyclosporine into routine clinical practice in late 1983 that changed the field of organ transplantation forever. Graft survival rates improved on average by 15% over the subsequent 2 years in the USA (Cecka, 1998). The recent introduction of a new generation of drugs may lead to further improvements in graft survival.

THE RENAL REPLACEMENT PROGRAM

The Tygerberg Unit

The renal transplant program was established at our institution in 1976 as the prime modality of treatment for end-stage renal failure. This was preceded by the initiation of a dialysis program and the two have from the outset remained complementary and non-competitive modalities of therapy in this unit. A multidisciplinary team is responsible for the renal transplants. The surgical team is responsible for the implantation of the graft and attends to all surgical problems. The medical team is responsible for the manipulation of the immunosuppressive protocol and long-term follow-up of these patients. Efficient radio-isotope radiology, biochemistry and anatomical pathology services have contributed to the success of the program.
Single centre study: Advantages
This institution has been submitting its statistics to the South African Dialysis and Transplant Registry (SADTR) since the inception of this body in 1984 and all our data were reported as part of the national registry. While this method of study clearly has statistical advantages, results differ widely in individual units and the pooling of data obscures the variations in a single unit. This study is therefore a single centre cohort study with the advantage of having complete data on the majority of patients.

Rates
The number of transplants performed in our unit and in the centres in South Africa is woefully inadequate to meet the needs of a growing nation. It has been estimated that the annual incidence of end-stage renal failure in South Africa is 250 patients per million population (pmp) (Meyers, 1995). In 1994 the number of new patients entering renal replacement therapy was 17 patients pmp, and even this figure is an overestimation because no allowance for the increase in the population since 1991 was made (SADTR, 1994). In this respect the number of patients receiving treatment lags far behind the figures for new patients not only in Europe and the United States of America but also developing countries with similar gross national products (GNP) as South Africa (Moosa et al., 2001). The number of renal transplants performed in South Africa is 8.7 patients pmp (SADTR, 1994), which is in the same range as countries with a similar GNP (Moosa et al., 2001).

The influence of events that occur early following renal transplantation such as delayed graft function/acute rejection on long-term graft survival, has been widely reported, but its association with patient survival has received less attention especially in developing countries. We evaluated the factors that influenced patient and graft survival and found, among other factors, that age was an important determinant of outcome and that the graft survival in the first year had a major impact on patient survival.
(1) PATIENT SURVIVAL

Rates
Present study
In the present study, actuarial patient survival was 81% at one year, 58% at five years and 36% at 10 years. This is somewhat poorer than that reported by Washer et al. (1983) who found 85% and 72% 1-year and 5-year patient survival rates and more recently by Troppman et al. (1995) 93% and 79% at the same time intervals, while Gorlén et al. (1992) reported 48% and 45%, 5-year and 10-year patient survival rates. More recently excellent patient survival rates exceeding 95% at 1 year and approaching 85% at 5 years have been reported (Arend et al., 1997). The present study was not designed to compare patient survival between the different forms of renal replacement treatment, but recent evidence suggests that although initial mortality may be higher after transplantation, long-term patient survival was clearly superior compared to dialysis (Fig. 5-2) (Wheeler, et al., 2000).

Other developing countries
Comparison with other developing countries is more difficult because the majority perform living-related donor renal transplantation whereas all but 13 of our cases were cadaveric donor transplants. Our results are comparable to those few countries that have a cadaveric donor transplant program (vide infra). The higher mortality in our patients compared with those in developed countries is almost certainly related to the very high infective complication rate that we continue to experience. Whereas in developed countries infections remain the main cause of mortality in the first year, cardiovascular deaths become more important thereafter (vide infra). In our experience infections remains the main cause of patient mortality throughout.

Causes of patient mortality
Infections
The mortality rate was highest in the first year, with sepsis being the main cause of patient death. Septicaemia and pulmonary infections together accounted for almost 70% of all infections. After the first year sepsis remained the major cause of death followed by myocardial ischaemia. This is in agreement with many studies,
Fig. 5-2 Adjusted relative risk of death among 23,275 recipients of a first cadaveric transplant, in comparison to the mortality in all patients on dialysis awaiting transplantation. From Wheeler et al. (2000).

consisting of earlier series, which have reported infection as the leading cause of death in a mix of patients with and without graft function (Hill et al., 1991; Karakayali et al., 1995; Kim et al., 1994; Kirkman et al., 1982; Najarian et al., 1979; Salvatierra et al., 1976; Sato et al., 1994; Scroggs et al., 1987; Tilney et al., 1978; Washer et al., 1983). In more recent reports (Dlugosz et al., 1989; Gorlen et al., 1992; Hiess et al., 1997; Matas et al., 1993) including a series by Lindholm et al. (1995) ischaemic heart disease was the overwhelming cause of death accounting for 53% of deaths with graft function (vide infra). The discrepancy in the leading cause of death among studies can be explained by several differences including the transplant era (pre- vs. cyclosporine), patient selection, posttransplant interval under observation, nosological definition of terms and the source of mortality statistics (Ojo et al., 2000).

High patient mortality
In our population almost 60% of the patients died within 10 years of receiving their first renal transplant. This surprisingly high figure is explained by the high
prevalence of sepsis and cardiovascular disease in this population and by the inclusion of patients who died after their grafts had failed, this group accounting for a large proportion of the deaths. Previous reports have excluded or censored this group of patients in their analyses (Arend et al., 1997) which may have been misleading because our study demonstrates that graft loss correlates with an increased risk of death. A Turkish report on 1021 patients transplanted between 1975 and 1994, found that 48% of patients who died within 4 years succumbed to infections, with the pulmonary infections being the most prevalent, followed by septicaemia complicated by multi-organ failure (Karakayali et al., 1995). A similar finding was made by Sato et al. (1994) who report that infections accounted for 51% of deaths in their cohort of 316 patients transplanted between 1972 and 1990. Pulmonary infections and septicaemia were again the most common types of infection.

Dutch experience
Arend et al. report on 1002 Dutch recipients of first renal transplants treated between 1966 and 1994, and established that in the first year infection was the most frequent cause of death (34%) but after the first year cardiovascular death was most common (44%) (Arend et al., 1997). Compared with the general population the all-cause standardised mortality ratio (SMR) was 12.1 in the first year and fell to 4.4 in the subsequent years. The largest contribution to the all cause SMR in the first year was non-cardiovascular and non-malignant causes of death, which included sepsis (sepsis was not recorded separately because the Dutch population death rates for infectious causes of death were not available) (Arend et al., 1997). Sepsis continues to be a risk for death even for transplant patients who have survived for more than 5 years.

Other issues
Kirkman et al. (1982) report that sepsis was the cause of death in 18% of recipients of renal allografts who had survived more than 5 years. Despite improved experience with the use of immunosuppressive drugs and decreased risk of sepsis this group of patients remains at high risk of early death (Woo et al., 1999). Although it is beyond the scope of this study to identify the possible mechanisms, it is likely the result of multiple factors including the effect of early return to dialysis, the physical
trauma of major surgery and the increased exposure to immunosuppressive agents in those cases where acute rejection was considered to play a role. Cardiovascular disease remains a very important cause of death in renal transplant recipients in the present study and in most reported series. According to Levey et al. (1998) risk factors for cardiovascular disease in transplant recipients include hypertension, hyperlipidaemia, diabetes mellitus, smoking, menopause, hyperhomocystinaemia, and physical inactivity. These risk factors are based largely on those established for cardiovascular disease in the general population. Exposure to these risk factors may account at least in part for the development of de novo cardiovascular disease in renal transplant patients (Kasiske et al., 1996).

**Malignancies as a cause of mortality**

*Uncommon*

In most reports, including ours, infections and cardiovascular deaths dominate posttransplant mortality (Frisk et al., 1987; McGeown et al., 1988; Murray et al., 1976), while malignancies are an uncommon cause of death. In our cohort only 8 (2.5%) deaths could be ascribed to an underlying malignancy. This contrasts with the findings of Kirkman et al. (Kirkman et al., 1982) who report that malignancies occurred in 14% of 217 long-term renal allograft recipients who had grafts functioning for more than 5 years. Skin tumours were most common with metastatic squamous cell carcinoma caused two deaths, while adenocarcinoma of the oesophagus caused one death. Malignancies accounted for 9% of all patient deaths. None of the patients had lymphomas. Similarly, a Turkish report found that malignancies caused 8.6% of patient deaths in a cohort of 1021 patients followed-up over 19 years. The fatal malignancies were 2 lymphomas, and one case each of a brain tumour, Kaposi's sarcoma and gastric carcinoma (Karakayali et al., 1995). In an early report from the pre-cyclosporine period on 299 patients, only two patients succumbed to malignancies accounting for a mere 4% of patient deaths. The malignant lesions were an undifferentiated sarcoma and malignant lymphoma (Washer et al., 1983).

**Late complication**

Gorlén et al. (1992) found that malignancies were an important cause of patient mortality in the second decade after transplantation, responsible for 20% of all
patient deaths. Arend et al. (1997) report an overall patient mortality rate of 12% but found that malignancies were an uncommon cause of patient mortality in the first year accounting for 2% of deaths. However, malignancies accounted for 18% of deaths after 1 year (Arend et al., 1997). Another important finding was that death due to malignancy was relatively less frequent in men (11%) compared to females (22%) (Arend et al., 1997). The number of cancer deaths in our own cohort was too small to allow a valid conclusion with regards to the gender of patients who succumbed to malignancies (3 females and 5 males). A Japanese study reported a 4.2% mortality in 316 renal allograft recipients transplanted over a 22 year period, with both cancer deaths being due to gastric lesions, a common cause of malignancies in that part of the world (Sato et al., 1994). In Korea, sepsis is the most common cause of mortality as elsewhere in the world, with malignancies only an infrequent cause of death (Kim et al., 1994).

**Long-term survivors**

Long-term survivors who die with functioning grafts most commonly succumb to cardiovascular disease but malignancies were the third most common cause of death in a recent multi-centre American study. Malignancies were responsible for 9% of deaths (Ojo et al., 2000). A similar mortality rate due to cancer was reported recently from a single centre study in the United Kingdom of 589 patients over 9 years (Woo et al., 1999).

**Factors influencing patient survival (Fig. 4-4a)**

**Age**

One of the most significant factors determining the mortality of patients is patient age. In the present study patients aged more than 40 years at the time of the primary transplant, had a mortality rate that was significantly greater than that of younger patients, with the discrepancy increasing with time. At 5 years, only 40% of the older group have survived compared to 62% of the younger group and at 10 years the figures are 18% and 48% respectively. This is in agreement with previous studies that reported increased risk in the older patient throughout the transplant period (Meyer et al., 1996; Perez et al., 1990) and in partial agreement with others. Arend et al. (1997) report that the crude first year mortality rates were roughly the same for all age categories in the first year but increased significantly for patients
aged over 40-years but only after the first year. Hirata et al. (1996) analysed the data reported to the United Network for Organ Sharing (UNOS) Scientific Renal Transplant Registry by participating centres between 1987 and 1995. In the cohort of 46 971 first cadaveric renal transplant recipients there were 5 036 deaths. The relative risk of dying for a patient aged 45 years was double that for a patient age 31-45 years and almost 4-fold greater than patients aged 2-15. Unlike the experience in our group however, the risk remained relatively constant over time (Hirata et al., 1996).

In a single centre study from the United Kingdom of 589 primary renal transplant patients the risk of patient death progressively increased as the age of patients at transplantation increased. The risk of death at 50-59 years was almost double that of patients aged 40-49 and triple that of patients aged 30-40 (Woo et al., 1999). A study of the clinical outcome in elderly patients revealed that the 10-year patient survival was 45% in patients aged ≥ 60 years compared to 68% in patients aged 18 to 59 years (Doyle et al., 2000). The main explanation for the excess mortality in older patients in the present study may be the development or acceleration of co-morbid diseases that resulted in the 3.5 fold greater incidence of ischaemic myocardial events. Ojo et al. (2000) also support a direct mechanistic relationship with premature cardiovascular death in the elderly renal allograft recipient. In the present study there was also more sepsis than in younger patients which may have contributed to the excess mortality (Hirata et al., 1996). The susceptibility to infection may be attributed to the decline in immunocompetence with age, as has been reported (Hirokawa, 1992).

Gender
No difference in patient survival was found in the present study with regard to race or gender. This contrasts with the findings of Arend et al. who report a lower mortality in women both in the first year posttransplant and during long-term follow-up (Arend et al., 1997). In an earlier, smaller study done over a mean observation period of 9.5 years the mortality was higher in female patients than males: 60% vs. 39%, although the difference was not statistically different (Gorlén et al., 1992). Similarly, Troppman et al. (1995) found that the relative risk of mortality was higher in females (1.25) but
the difference was not significant. Woo et al. (1999), reporting on patients treated entirely in the cyclosporine era found that patient survival was much better in women than in men (hazards ratio: 0.66). In another study male patients had a 1.16 greater risk of dying with graft function relative to female patients (Ojo et al., 2000).

Race
In the same study African American and other race group recipients had a lower risk of death with graft function, after controlling for other factors, compared with whites (relative risk = 0.92) (Ojo et al., 2000). According to the USRDS 1999 Annual Report patient survival was virtually identical in white and black. The patient survival at one year was 97.9 and 98.0 for living donor transplants in black and white patients respectively. Among recipients of cadaveric donor allografts the 1-year survival was 96.5 and 95.7 respectively. In the present study we were also unable to find any significant racial differences in patient survival after first renal transplantation, which confirms our earlier report of this observation (Moosa et al., 1992).

Death with functioning grafts
Of note is that over the 23-year period of the present study death with functioning grafts accounted for 44% of grafts lost in patients aged over 40 years. For patients aged less than 40 years 26% of grafts were lost due to death. In a similar analysis done in California over 5 years, death with functioning grafts occurred in 6% of patients aged 30 to 45 years. For patients aged over 45, 13% of grafts were lost as a result of death over the 5 year time period (Hirata et al., 1996). Ojo et al. (2000) have also confirmed the importance of death with functioning graft as a very important cause of graft loss. In their experience almost one-half of all graft-loss was due to death with function (Ojo et al., 2000) making this and chronic rejection the most important causes of graft-loss in developed countries (Morris, 1997). Besides age, the other important determinant of death with function has been found to be end-stage renal failure caused by diabetes. The excess risk of death in these patients can be explained primarily by significantly higher rates from both cardiovascular disease and stroke in the diabetics (Ojo et al., 2000). Because of the small number of diabetics in our cohort we were unable to confirm these findings.
Dialysis prior to transplantation

Controversy surrounds the role of dialysis prior to transplantation in subsequent patient survival. In two recent studies patient survival was significantly worse the longer the period of dialysis prior to transplantation. Cosio et al. (1998a) evaluated 523 patients transplanted at a single centre followed up for a mean of 7 years. The patients who had been transplanted pre-emptively had a mortality of 7% compared with 23% who were dialysed for 1-2 years and 44% of patients dialysed for more than 3 years. The type of dialysis i.e. continuous ambulatory peritoneal dialysis (CAPD) vs. haemodialysis, did not correlate with patient survival. However, graft survival when censored for patient death, was not significantly influenced by the duration of dialysis prior to transplantation. In pre-emptive transplantation of kidneys from living donors, however, graft survival is better if patients receive their grafts before the initiation of dialysis (Mange et al.,2001). Ojo et al. (2000) analysed registry data and studied the causes of death in 18 482 patients among 86 502 recipients. They also found that a history and duration of pre-transplant dialysis treatment (> 6 months) to be associated with an increased risk of death with function. They concluded that the longer exposure to the immunosuppressive effect of both renal failure and dialysis, as well as the greater likelihood of malnutrition contributed to the adverse patient survival posttransplant.

Our own findings indicate that duration of dialysis does not significantly impact on patient survival following renal transplantation. This is in accordance with the results of a study of paediatric patients (Nevins et al.,1991), and another of adult diabetic patients (Ekstrand,1993). Woo et al. (1999) after controlling for the effect of early graft function, age, gender, and primary renal disease found that the influence of time on renal replacement therapy prior to transplantation was not significant. In a cohort of 1002 Dutch recipients of first renal transplants there was no effect of the type or duration of pre-transplant dialysis on posttransplant patient mortality (Arend et al.,1997). O'Donoghue et al. (1992) similarly found no effect of the dialysis modality on patient survival after 10 years follow-up. Arend et al. (1997) have suggested that these findings could be explained by selection bias, because death rates of patients on dialysis are high (Anonymous,1991) and survival of a long period of haemodialysis can be expected "... to select patients with the strongest constitution". The pre-emptive transplantation of kidneys from living donors without
dialysis being initiated is associated with better renal allograft survival. The reduction in the rate of acute allograft rejection suggests that pre-emptive transplantation may modulate immune mechanisms that shorten allograft survival (Donnelly et al., 1996; Mange et al., 2001; Schurman et al., 1997). Patient survival rates were not studied in the latter reports.

Early graft loss

Graft loss within the first year was another important determinant of patient mortality in the present study. Graft loss was used as a surrogate for delayed graft function and acute rejection in the first year. Five years after the primary renal transplant only 30% of patients who lost their grafts within the first year survived as compared to 70% of those recipients whose grafts were retained. Most of the deaths in the former occurred within the first year (see Fig. 4-4a, Chapter 4). The excess patient mortality rate almost certainly reflects the complications of the use of additional immunosuppression to salvage a failing kidney. In addition, the immunosuppressive effects of both renal failure and dialysis treatment, and the greater likelihood of malnutrition may have adversely affected posttransplant patient survival (Cosio et al., 1998a). The majority of the patients died of septic complications, cardiovascular disease and gastrointestinal haemorrhage. Clearly, the price of trying to salvage a failing graft at all costs is very high. The fact that patients with primary non-function or later graft loss have an increased mortality when they return to dialysis is not unexpected, but it is of considerable clinical importance.

Our findings concur with those of Woo et al. (1999) who demonstrated that the mortality of patients whose grafts failed to function was 44% compared with 29% in patients with delayed graft function. They also found a correlation between the serum creatinine levels at 3 months and patient survival. Data from the Canadian Organ Replacement Registry 1990 Report have previously also documented poorer survival in patients following a failed first transplant (Cattran et al., 1993). The highest mortality was in those who lost their grafts within 90 days compared with graft loss after 90 days followed by those who maintained good function. The 4-year patient survival rates were 59% vs. 72% vs. 85% respectively. The most common cause of death (22%) in these patients was sepsis as was the case in our study. In a recent study the combination of delayed graft function and early acute rejection
were associated with an increased relative risk of patient mortality (Troppmann et al., 1995), confirming the findings of other studies (Gorlen et al., 1992; Hirata et al., 1996; Lindholm et al., 1995; Ojo et al., 2000).

Source of kidney

In the present study it was determined that patients who received their grafts from living related donors, also had a better survival than patients whose kidneys are derived from cadaveric donors. The superior tissue matching, fewer rejection episodes and optimal timing of the transplant no doubt contributed to the improved outcome. Myburgh et al. (1983) have made similar observations with regard to patient survival in patients receiving cadaver as opposed to grafts from a related donor. In their experience the main difference was the higher mortality in the first year (78% vs. 93%), which is followed by a steady and parallel attrition thereafter. By far the major cause of mortality in the present study as well as the one reported by Myburgh et al. (1983) is sepsis. They relate this complication to the intensity of immunosuppression during the initial period and were therefore not surprised to find the excess patient and graft mortality. The maintenance immunosuppressive regimen in the two groups is similar after the first year. The South African findings concur with those of other centres confirming the superiority of patient and graft survival of living donor transplants over cadaver donor transplants (Arend et al., 1997; Gorlén et al., 1992; Karakayali et al., 1995; Sato et al., 1994; Tilney et al., 1978; Washer et al., 1983). However, Kirkman et al. (1982) report that there were no differences apparent in survival after 5 years between recipients of living related and cadaver donor allografts nor was graft survival dependent upon donor source during this late follow-up period.

Primary renal disease (Appendix Fig. 4-12b)

Hirata et al. (1996) found that after the age of the patient, the primary renal disease leading to end-stage renal failure was the most important factor influencing the mortality rate, with diabetes mellitus carrying the greatest risk. In our cohort we demonstrated that patients with hypertension fared the worst. The main reason for the failure to confirm the widely held observation of poorer outcome is the small number of diabetics that were transplanted (less than 4%) leading to a type II error.
In addition, the diabetic patients that we selected for transplantation were generally young and had minimal co-morbid disease.

**Immunosuppressive treatment (Appendix Fig. 4-12b)**

The survival of patients receiving azathioprine and cyclosporine was comparable in the first 6 years, but thereafter the mortality rate of patients under cyclosporine was much worse than patients receiving conventional therapy. This is almost certainly related to the cumulative cyclosporine toxicity resulting in hypertension, diabetes mellitus and possibly malignancies. At 10 years, 44% of patients on conventional therapy were still alive compared to 30% of patients on triple therapy. This observation brings into question the long-term safety of cyclosporine. This observation is even more pertinent if one considers that the dose of steroids used in the conventional treatment were generally much greater than is the current practice under cyclosporine. Our observation therefore seems to suggest that it may be worthwhile discontinuing the use of cyclosporine when the risk of graft failure is at its lowest. Randomised conversion from cyclosporine to azathioprine at 3 months was associated with comparable 3-year and improved long-term patient survival (Hollander et al., 1995a; Kootte et al., 1988b). The need for immunosuppression is greatest soonest after renal transplantation and it is generally accepted that it can be cautiously reduced from one year onward. A recent study of randomised conversion at one year was not associated with significant adverse effects on long-term patient or graft mortality. Both blood pressure control and renal function showed improvement (MacPhee et al., 1998). Most studies have compared graft survival under the two treatment regimes and few have compared patient survival as has been done here. In these reports conflicting results have been published with respect to the effect of cyclosporine on long-term patient survival (Hollander et al., 1995a; Kootte et al., 1988b; Kootte et al., 1988a; Paul et al., 1992; Sato et al., 1994; Stiller et al., 1991). The distribution of the causes of death is similar under cyclosporine and conventional treatment with cardiovascular disease being the most common cause of death (Penn, 1993). Hollander et al. (1995b) report a higher incidence of cardiovascular death in patients maintained on cyclosporine. Cyclosporine is known to have an effect on a number of cardiovascular risk factors including the blood pressure (Porter et al., 1990), lipid profile and glucose tolerance (Harris et al., 1986), which all improve if patients are converted to azathioprine.
OTHER CONSIDERATIONS

Previous malignancy
An important observation made by Doyle et al. (2000) who were trying to predict the clinical outcome in the elderly renal allograft recipient was that a history of non-skin malignancy was associated with poor graft and patient survival. Several of their patients aged over 60 years (a group that we would not transplant) died of metastatic disease despite extensive screening to rule out residual or recurrent tumour prior to transplant, and an average disease-free interval of 2.6 years for these patients compared with 10.9 years in patients without recurrent malignancy, suggesting that the elderly patients may require a longer period disease-free interval prior to transplant. The poor survival of the remaining patients suggests that a history of malignancy may predispose to death in other ways such as an increased susceptibility to infection related to prior chemotherapy or radiation treatment (Doyle et al., 2000). In the present study the impact of prior malignancies on patient and graft survival could not be evaluated because the number of patients with cured lesions (6), who were grafted was too small to allow statistical evaluation.

Limitations
One of the limitations of our analyses is that we did not compare the survival rates of our patients with those of patients on the transplant waiting list treated with haemodialysis. Such an study was done by Port et al. (Port et al., 1993) who observed that an initial excess risk of mortality in the posttransplant period but a subsequent decline with the equal cumulative mortality rate being achieved on day 325. A survival advantage brought about by the renal transplant therefore seems to commence 1 year after transplantation. In the analysis by Schaubel et al. (1995) the risk of mortality in patients aged 60 years and over on haemodialysis was approximately double the risk of transplanted patients.

(2) GRAFT SURVIVAL

Rates
The overall actuarial graft survival in the present study was 64% at one year decreasing to 36% at 5 years and 21% at 10 years. A comparative analysis is made
in Table 5-1 (page 5-25) with other developing countries. The fact that our observations are made almost entirely on cadaveric donor transplants and include patients both under azathioprine and triple therapy need to be taken into consideration to explain the apparently poorer results obtained in the present study. In some of the latest reports from developed countries: 1-year and 5-year graft survival rates of 87% and 67%, respectively, are being achieved (Troppmann et al., 1995), and 84% at one year, 68% at 5 years and 55% at 10 years (Woo et al., 1999). By multivariate analysis, the main factors that influenced the outcome of the grafts in the present study were: the age of the patient (less or greater than 40 years), the type of immunosuppression (azathioprine or cyclosporine), the underlying renal disease that led to the renal failure as well as the source of the donor kidney (living related or cadaver).

Factors influencing graft survival (see Fig. 4-5)

**Age**

In the present study graft survival was significantly better in patients aged ≤40 years compared to older patients and this difference increased the longer the follow-up. Patient survival stratified for age reveals a curve that closely follows that of graft survival. Patient death with functioning grafts therefore may explain the discrepancy in the survival of grafts in the 2 age groups. In the older age group 42% died with functioning grafts compared to 27% of the younger age group. This accounted for 47% of grafts lost. In a recent large survey Ojo et al. (2000) report that 38% of their over 18 000 deaths were deaths with graft function and this accounted for 43% of graft loss (Ojo et al., 2000). Most of the patients were over 40 years and sepsis was the commonest cause of death even after the first year. Several factors were identified as predictors of reduced graft survival in the elderly patient: increasing patient age, a pre-transplant history of non-skin malignancy, time on the waiting list of less than 1 year and recurrent tobacco use (Doyle et al., 2000). When graft failure in the elderly was censored for loss due to patient death, there was a decrease in graft failures with increasing age (Doyle et al., 2000). The decrease in graft failures can be attributed to declining immunocompetence with age as has been previously suggested (Hirokawa, 1992).
Immunosuppressive regimens
Cyclosporine had a dramatic impact on 1-year allograft survival and rekindled world interest in organ transplant in the early 1980’s. In the United States the approval of cyclosporine in November 1983 resulted in an improvement in graft survival of 15% in the subsequent 2 years (Cecka, 1998). One-year graft survival in our cohort dramatically improved by over 20%, a difference that was maintained for approximately 8 years. After that period more patients on conventional therapy had functioning grafts. This observation has been confirmed by others who found that despite its initial impact on graft survival cyclosporine, disappointingly has had little beneficial effect on long-term graft survival when compared with conventional immunosuppressive regimen of azathioprine and steroids (The Canadian Multicentre Transplant Study Group, 1986; Calne, 1987; Fischel et al., 1991; MacPhee et al., 1998; Morris et al., 1987). Cyclosporine therefore appears to reduce early graft loss compared to azathioprine. However, as indicated above, cyclosporine is associated with a greater late patient mortality rate. The initial improvement in graft survival in our patients could not be explained by an improvement in patient survival, which was the same under conventional treatment and was almost certainly related to the reduction in acute allograft rejection rates affected by the use of cyclosporine.

Race
Contrary to reports both from this country (Modiba et al., 1989) and elsewhere non-white patients had the same graft survival rates as white patients in the present study. Black patients specifically had the same graft survival rates as the other groups. This confirms an earlier report in which we found that white and non-white patients had the same one-year graft survival (Moosa et al., 1992). The long-term survival of renal allografts in black patients has been reported to lag behind those of all other races (Koyama et al., 1994). The 1- and projected 10-year survival of first cadaver donor transplants were 84% and 47%, respectively, in white recipients compared to 81% and 23% in a similar sized cohort of black recipients in the same age range. After the first year, the rate of graft-loss was more than twice that of white patients (half-life of 10.8 years vs. 4.9 years). Important determinants of outcome may be socio-economic and histocompatibility differences (Butkus et al., 1992), and possibly poorer blood pressure control. However, our previous study has refuted the socio-economic aspect of this argument (Moosa et al., 1992). Also,
Asian patients who have similar difficulties finding histocompatible donors experience graft survival rates superior to those of white patients (Cecka et al., 1992b). Most of the current studies concur that black patients have comparable 1-year survival rates but that the problem seems to be with long-term graft retention (Butkus et al., 1992; Koyama et al., 1994). A higher incidence of late graft rejection among black recipients (Tesi et al., 1997) may be an indication of greater difficulty in maintaining adequate immunosuppression for these patients.

Gender
There is no gender difference in the survival rate of renal allografts in the present study. This contrasts with the findings of others who report better graft survival in women (Perez et al., 1990) but confirms the findings of the majority of others who also found no relationship between graft survival and gender (among other factors) (Cecka et al., 1992a; Cole et al., 1995; Gulani et al., 1992; Troppmann et al., 1995; Troppmann et al., 1996). Troppman et al. (1995) using multivariate analysis could not demonstrate a difference in graft survival. Ojo et al. (2000) found that males patients had a 1.16 greater relative risk of death with graft function compared to females (Ojo et al., 2000). Veller et al. (1987) report that with renal retransplantation female patients fared less well than their male counterparts. It has been suggested that this could be due to the female patients having higher levels of pre-formed lymphocytotoxic antibodies (Koka et al., 1989), but in the study by Veller et al. (1987) the proportion of males and females with levels of pre-formed antibodies was comparable. The effect of parity on graft survival does not appear to have been investigated yet (Veller et al., 1987). However, the degree of pre-sensitisation was not specifically looked at in the present study.

Primary disease
It is recognised that the primary disease leading to end-stage renal failure can have an influence on graft survival (Levey et al., 1966). Hirata et al. (1996) established that patients with hypertension had the highest graft failure rate and of even greater concern was that it was associated with a relatively higher patient mortality. Hypertension was the second most common cause of end-stage renal failure in our patients after chronic glomerulonephritis. Patients who had diabetes did surprisingly well in the short term, but there were few long-term survivors. The diabetic patients
in our cohort were very carefully screened before admission to the replacement program and are not representative of the average patient with diabetic nephropathy. The poor outcome in hypertensive patients almost certainly reflects the damage caused by the disease that affects the patient and the new graft. Hirata et al. (1996) ascribed the poor outcome among hypertensive patients to the fact that more than half the patients transplanted for hypertension were black (Katznelson et al., 1995).

**Donor kidney**

The source of the donor kidney also plays an important role. The number of living-related transplants performed was only 14. Despite this small number, the graft survival was significantly better both by univariate and multivariate analysis. This result is very encouraging and has influenced us to pursue this source of organs more vigorously. Koo et al. (1999) recently investigated the reason for the superior graft survival following living donor kidney transplant. They postulated that part of this result was due to the kidney being obtained under optimal conditions from healthy donors whereas cadaveric kidneys may have been exposed to inflammatory events around the time of brain death. They were able to prove their hypothesis by comparing the expression of inflammatory antigens in biopsy specimens from cadaveric kidneys vs. living related donor kidneys.

**Multiple Grafts**

Despite major advances in immunosuppressive therapy a significant number of renal allografts are lost mainly from rejection, either acute or chronic (Sumrani et al., 1993). The result is that the pool of patients with failed grafts continues to grow and in our population represents a significant source of patients entering the renal replacement program. Retransplantation presents many challenges including recipient sensitisation from the initial graft (Cecka et al., 1988), technical aspects of engraftment (Koyle et al., 1988) and a higher risk of immunologic graft loss (Iwaki et al., 1987b). Kidney retransplantation was performed in 72 of our patients who between them received additional 81 kidneys following the primary grafts. In our study population the retransplant rate of 13.0% is comparable with the values of 11.8 - 15.9% reported in the literature (Fasola et al., 1989; Howard et al., 1984; Jackson et al., 1989; Salmela et al., 1990; Stratta et al., 1988). One year graft survival in patients
undergoing retransplantation has consistently been 10 - 15% lower than those primary transplantation, both before (Howard et al., 1984) and after (Iwaki et al., 1987a) the introduction of cyclosporine. In the present study the overall 1-year graft survival was 7% less than that of primary grafts and at 5 years there was only a 3% difference in graft survival compared to the primary grafts. Veller et al. (1987) reported on a South African experience with 108 renal retransplantation procedures. The actuarial graft survival at 1 and 5 years were 53% and 41% respectively compared to those of our patients in the present study of 58% and 30%. They found that factors that influenced subsequent renal allograft survival included the level of pre-formed antibodies, the use of cyclosporine and the duration of function of the primary graft. Age >40 years was not associated with a detrimental outcome unlike the experience in other centres (Caine et al., 1968; Peters, 1982). Other major determinants of graft survival in renal retransplants are early function among cadaver donor recipients, donor source and the absence of rejection within the first year after engraftment (Sumrani et al., 1993). Controversy still surrounds the influence of race, pre-formed antibody levels and the presence of diabetes on the outcome of retransplants (Stratta et al., 1988; Sumrani et al., 1993). Veller et al. (1987) recommend, and we concur, that regrafting should be considered after failure of the primary transplant, especially if the graft was lost to chronic rejection. Recent studies confirm that kidney retransplantation is associated with diminished overall graft survival (Kountz et al., 1972; Opelz et al., 1976; Schulak et al., 1984; Spees et al., 1983; Stratta et al., 1988) but the discrepancy between primary and second cadaver-donor 1-year graft survival has improved from 8% in 1988 to 2% in 1991 (Kerman et al., 1997). Graft nephrectomy contributes to poorer graft survival and is not recommended (Abouljoud et al., 1995).
GAUTENG PROVINCE EXPERIENCE

The very first renal transplant was performed in South Africa soon after it became a recognised form of treatment for end-stage renal failure \textit{(vide supra)}. The first report of the South African experience was on 159 consecutive first cadaver renal transplants recipients who received renal allografts over an 8-year period in Johannesburg. The actuarial graft survival was 69\% at one year and 59\% at 5 years. This included 16 patients who received grafts from living related relatives and 5 retransplants (Myburgh \textit{et al.},1976). Myburgh \textit{et al.} (1983) detailed the 17-year experience of the Johannesburg group starting in 1966. At the time of their analysis they had transplanted 525 kidneys into 468 patients. They used conventional therapy and for the first half of the period under review used prophylactic graft irradiation. Prednisone in varying doses was used over the years. One-year patient survival was 78\% while graft survival was 52\%. Better results were obtained with living related transplants (Myburgh \textit{et al.},1983). The patients transplanted in Johannesburg were predominantly white patients.

Black patients

Two centres treating exclusively black patients reported results in 1989. Bauling \textit{et al.} (1989) reporting from Medunsa, Pretoria found the actual 4-year patient survival to be 78\% and graft survival 70\% in a group of 59 patients, half of who received cyclosporine. All the organs, bar one, were from cadaveric donors. At the (Chris Hani) Baragwanath Hospital, Johannesburg, 51 patients received renal allografts, of which 88\% were from cadaveric donors. Of the cadaver donors 30\% were black. Actuarial 1- and 5-year patient survival rates were 52\% and 27\% for cadaveric donor transplants. The corresponding graft survival rates were 38\% and 28\% (Modiba \textit{et al.},1989). The majority of the patients received conventional therapy and only 4 were under cyclosporine. According to Meyers \textit{et al.} (1988), reporting from the General Hospital, Johannesburg, graft survival in 60 black renal allograft recipients was comparable to that of white patients provided the former were maintained on
cyclosporine. Actuarial graft survival increased from 30% to 72% when cyclosporine was not discontinued (Meyers et al., 1988).

**WESTERN CAPE PROVINCE EXPERIENCE**

**Tygerberg hospital experience**

A report from our unit established an overall 1-year graft survival rate of 70% under cyclosporine but found no racial difference (Moosa et al., 1992). The introduction of cyclosporine improved graft survival rate by 23% at 1-year compared with conventional therapy.

**Groote Schuur hospital experience**

The group from Cape Town also reported the results of the introduction of cyclosporine and found that the 1-year patient and graft survival rates in 50 recipients were 94% and 88% respectively. The mean follow-up period was only 8 months however, ranging from 1 to 15 months. The complication rate was low probably because cyclosporine was discontinued at 3 months and substituted with azathioprine (Jacobson et al., 1985). This group discontinued cyclosporine at 3 months in order to minimise the long-term toxic effects of the drug (Cassidy et al., 1986). The same group recently reported the results of renal transplants from living-related donors (Kahn et al., 1994). The 1- and 5-year survival rates of HLA-identical donor renal transplantation were 95% and 81% compared to 79% and 64%, respectively, for one-haploype-matched donors. Donor specific blood transfusions (DST) significantly improved graft survival in patients with only one-haploype match but the data are difficult to interpret because DST and cyclosporine were introduced simultaneously. In a follow-up report on their policy of discontinuing cyclosporine at 3 months, Cassidy et al (1986) found that in the 26 patients under review, 35% had acute rejection episodes. The acute rejection episodes were reversed after treatment with methylprednisolone in all patients except one. The practice of discontinuing cyclosporine at varying periods after transplantation still remains controversial but is practised in many developing countries for reasons of economic necessity (Table 5-1, page 5-25). However, it is not widely practised in South Africa.
Centre effect

The marked discrepancy between the results reported by the Cape Town group and our own is cause for great concern. Although the "centre-effect" is well recognised (Benlahrache et al., 1987; Cho et al., 1996; Evans et al., 1991; Gjertson, 1993; Ogura et al., 1991; Shabtai et al., 1991) it is important to try to establish why two centres operating in the same region and serving the same population have such discrepant results (88% vs. 70% 1-year graft survival rate under cyclosporine). One of the main differences between the two units is the policy toward cyclosporine, with the Cape Town group discontinuing the agent at 3-months to 1-year. The greater immunosuppression used in our Unit may result in more graft losses to cyclosporine nephrotoxicity or infective complications. According to South African Registry data the 1-year and 5-year patient survival rates from 1984 to 1994 were 84% and 64% respectively. The corresponding graft survival rates were 70% and 60% respectively (SADTR, 1994).

Malignancies as a cause of mortality

The only other South African single centre (Johannesburg) to determine causes of mortality in renal transplant patients established that 5% of all deaths among 525 patients were due to malignancies and that all the deaths occurred more than one year after transplantation. The fatal malignancies were liver and skin lesions (two cases each), and one case each of lung, rectum and kidney cancer, and malignant melanoma (Myburgh et al., 1983). The SADTR reports that malignant disease caused 3% of all patient deaths in 1994, compared with 4% in 1984 (SADTR, 1994). In the present study 50% of the cancer deaths occurred in the first year. The high mortality rate in our patients in the first year compared to the other reports is due to the nature of the malignant lesion that our patients develop. Kaposi's sarcoma is much more prevalent in our cohort than in any of the other centres that have reported the results of patient survival and it is a malignancy that occurs earlier than the other common forms. Our cohort is relatively younger than the patients treated in the developed countries: the mean age of our patients is 37 years while that of other centres is much higher (Arend et al., 1997; Gorlén et al., 1992; Ojo et al., 2000; Rao et al., 1983; Woo et al., 1999). Our patients would therefore perhaps be less vulnerable to the cancers that afflict recipients in the developed countries.
(4) PATIENT AND GRAFT SURVIVAL: COMPARISON WITH OTHER DEVELOPING COUNTRIES

Comparison with other developing countries is more difficult because in most developing countries living donors form the basis of the renal transplant programs. However, several countries do have cadaver donor programs. The results of our predominantly cadaveric donor-based renal transplant program compares favourably with those recently reported from other developing countries (Table 5-1).

While renal transplantation is the treatment of choice for end-stage renal failure in developed countries, in many developing countries it remains the only viable long-term therapeutic modality. The high cost of setting up and maintaining chronic dialysis programs, the lack of technical expertise and the rural location of the majority of the population places maintenance haemodialysis and continuous ambulatory peritoneal dialysis (CAPD) outside the economic capacity of many developing countries (Arije et al., 1995; Chugh et al., 1995; McLigeyo et al., 1988). This is particularly true of sub-Saharan Africa (excluding South Africa) where very few centres exist which are able to provide any form of renal replacement treatment (Assounga, 1999; Swanepoel, 1999; Were, 1999). Dialysis activity in a developing country is generally related to the gross national product (GNP) per capita. However, South Africa is treating many fewer patients on maintenance haemodialysis compared to countries such as Brazil, Mexico and Argentina that have GNP per capita very similar to our own (Fig. 5-3). Transplant activity is also related to GNP per capita and here South Africa compares very favourable with other developing countries at the same level of economic development (Fig. 5-4). Since the commencement of our Transplant program in 1976, a detailed analysis of outcome has never been undertaken. A report in 1992 compared graft survival in white and non-white groups, but no further analyses have been attempted since.
### TABLE 5-1. Immunosuppressive regimens used in selected developing countries and outcomes

<table>
<thead>
<tr>
<th>Country (Period)</th>
<th>No. Transplants</th>
<th>Donor Type</th>
<th>Immunosuppression</th>
<th>% Survival (at year indicated)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh (1982 - 1992)</td>
<td>68</td>
<td>LRD</td>
<td>Aza</td>
<td>96(1) + 81(3)</td>
<td>Rashid et al., 1992</td>
</tr>
<tr>
<td>Brazil (1970 - 1989)</td>
<td>687</td>
<td>LRD</td>
<td>NS</td>
<td>70(1) + 49(5)</td>
<td>Goldani et al., 1991</td>
</tr>
<tr>
<td>Brazil (1987 - 1989)</td>
<td>239</td>
<td>CD</td>
<td>CsA</td>
<td>76(2)</td>
<td>Sesso et al., 1990</td>
</tr>
<tr>
<td>Egypt (1982 - 1992)</td>
<td>45</td>
<td>LRD</td>
<td>Aza (Good matches)</td>
<td>89(2)</td>
<td>Barsoum, 1994</td>
</tr>
<tr>
<td>India (1985 - 1988)</td>
<td>153</td>
<td>LURD(C)</td>
<td>Aza (low dose)</td>
<td>83(1)</td>
<td>Thiagarajan et al., 1990</td>
</tr>
<tr>
<td>Iran (1989-1994)</td>
<td>16</td>
<td>LURD</td>
<td>CsA</td>
<td>83(1) + 69(3)</td>
<td>Simfuroosh et al., 1992</td>
</tr>
<tr>
<td>Iran (1984 - 1992)</td>
<td>220</td>
<td>LURD</td>
<td>CsA</td>
<td>76(1) + 70(3)</td>
<td>Simfuroosh et al., 1992</td>
</tr>
<tr>
<td>Kuwait (1985 - 1990)</td>
<td>53</td>
<td>LURD (C)</td>
<td>NS</td>
<td>90(2)</td>
<td>Johny et al., 1990</td>
</tr>
<tr>
<td>Mexico (1967 - 1991)</td>
<td>282</td>
<td>LRD</td>
<td>CsA</td>
<td>86(1) + 68(5)</td>
<td>Bordes-Aznar et al., 1992</td>
</tr>
<tr>
<td>Pakistan (1975 - 1998)</td>
<td>200</td>
<td>LRD</td>
<td>CsA</td>
<td>93(1) + 83(5)</td>
<td>Rizvi et al., 1998</td>
</tr>
<tr>
<td>Philippines (1985 - 1994)</td>
<td>1024</td>
<td>LRD</td>
<td>CsA</td>
<td>70(1) + 70(3)</td>
<td>Li and Otsuyama, 1999</td>
</tr>
<tr>
<td>Saudi Arabia (1999 - 1995)</td>
<td>2500</td>
<td>LRD</td>
<td>CsA</td>
<td>96(1) + 95(1)</td>
<td>Al-Khader, 1999</td>
</tr>
<tr>
<td>Singapore (1985 - 1992)</td>
<td>47</td>
<td>LRD</td>
<td>CsA</td>
<td>90(1)</td>
<td>Chaballout et al., 1995</td>
</tr>
<tr>
<td>Slovenia (1986 - 1991)</td>
<td>83</td>
<td>CD</td>
<td>CsA</td>
<td>70(1)</td>
<td>Nauck and Otsuyama, 1999</td>
</tr>
<tr>
<td>Taiwan (1968 - 1992)</td>
<td>1000</td>
<td>LRD</td>
<td>NS</td>
<td>82(1)</td>
<td>Lee, 1992</td>
</tr>
<tr>
<td>Turkey (1985 - 1993)</td>
<td>80</td>
<td>LURD</td>
<td>NS</td>
<td>80(1-3)</td>
<td>Daar, 1991</td>
</tr>
<tr>
<td>Turkey (1975 - 1993)</td>
<td>230</td>
<td>CD</td>
<td>CsA (1955)</td>
<td>Aza: 42(10)</td>
<td>Habel et al., 1995a</td>
</tr>
<tr>
<td>Turkey (1985 - 1992)</td>
<td>391</td>
<td>LRD</td>
<td>DST + Aza or +CsA</td>
<td>92(1)</td>
<td>Hamaloglu et al., 1992</td>
</tr>
<tr>
<td>U.A.E. (1991)</td>
<td>89</td>
<td>LURD (C)</td>
<td>CsA</td>
<td>94(1) + 84(3)</td>
<td>Masri et al., 1993</td>
</tr>
<tr>
<td>U.A.E./Oman (1984 - 1988)</td>
<td>130</td>
<td>LURD (C)</td>
<td>CsA</td>
<td>77(1) + 75(3.75)</td>
<td>Salahu deen et al., 1990</td>
</tr>
</tbody>
</table>

1. Regimen predominantly used.
2. Cyclosporine discontinued at 3 to 12 months.
CD = cadaveric donor; L(R)D = living (related) donor; LURD = living unrelated donor; LURD (C) = commercial living unrelated donor; Aza = azathioprine; CsA = cyclosporin as part of triple or dual therapy; NS = not specified; DST = donor specific blood transfusion.
Modified from Moosa et al. (2001).
**FIG 5-4.** Renal Transplant Activity and GNP per capita in Selected Developing Countries (1996)

Modified from Moosa et al. (2001).
Table 5-2. Demography of renal replacement therapy in developing countries compared with the registry data from the United States and Australia/New Zealand.

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of Patients</th>
<th>Mean Age (years)</th>
<th>Males (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>1563</td>
<td>38 (CAD)(^1)</td>
<td>63</td>
<td>Sesso et al.,1990</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33 (LRD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>India (1)</td>
<td>265</td>
<td>36</td>
<td>80</td>
<td>Kathuria et al.,1995</td>
</tr>
<tr>
<td>India (2)</td>
<td>310</td>
<td>-</td>
<td>93</td>
<td>Chugh et al.,1993</td>
</tr>
<tr>
<td>Kenya</td>
<td>77</td>
<td>30</td>
<td>64</td>
<td>McLigeyo et al.,1988</td>
</tr>
<tr>
<td>Malaysia</td>
<td>37</td>
<td>37</td>
<td>64</td>
<td>Lei et al.,1992</td>
</tr>
<tr>
<td>Morocco</td>
<td>2000</td>
<td>51</td>
<td>59</td>
<td>Bourquia,1999</td>
</tr>
<tr>
<td>Nigeria</td>
<td>368</td>
<td>&lt;40</td>
<td>73</td>
<td>Mabayoje et al.,1992</td>
</tr>
<tr>
<td>Oman/UAE</td>
<td>130</td>
<td>38</td>
<td>62</td>
<td>Salahudeen et al.,1990</td>
</tr>
<tr>
<td>Pakistan (1)</td>
<td>500</td>
<td>32</td>
<td>78</td>
<td>Rizvi et al.,1998</td>
</tr>
<tr>
<td>Pakistan (2)</td>
<td>79</td>
<td>43</td>
<td>61</td>
<td>Kumar et al.,1992</td>
</tr>
<tr>
<td>Qatar</td>
<td>187</td>
<td>41</td>
<td>55</td>
<td>Rashid et al.,1998</td>
</tr>
<tr>
<td>Reunion</td>
<td>767</td>
<td>52</td>
<td>41</td>
<td>Albitar et al.,1998</td>
</tr>
<tr>
<td>South Africa</td>
<td>7331</td>
<td>40-59(^2)</td>
<td>59</td>
<td>SADTR,1994</td>
</tr>
<tr>
<td>Slovenia</td>
<td>151</td>
<td>35</td>
<td>70</td>
<td>Kandus et al.,1992</td>
</tr>
<tr>
<td>Turkey (1)</td>
<td>520</td>
<td>35</td>
<td>77</td>
<td>Yildiz et al.,1998b</td>
</tr>
<tr>
<td>Turkey (2)</td>
<td>562</td>
<td>32</td>
<td>80</td>
<td>Kekec et al.,1992</td>
</tr>
<tr>
<td>US</td>
<td>79 102</td>
<td>61</td>
<td>53</td>
<td>US Renal Data System,1999</td>
</tr>
<tr>
<td>Australasia</td>
<td>1708</td>
<td>58</td>
<td>58</td>
<td>ANZ Data Report, 1999</td>
</tr>
</tbody>
</table>

\(^1\)CAD = cadaveric and LRD = living related donor transplant, \(^2\)peak ages

Demographics (Table 5-2)

In line with the experience in other developing countries, the mean age of patients commencing renal replacement treatment in our unit is considerably younger than in developed countries. In the United States the mean age of patients commencing dialysis is 61 years (US Renal Data System,1999), while the mean age of our patients who received primary renal allografts was 37 years. The main reason for the relative youth in our population is the deliberate exclusion of older patients from the program purely for reasons of economy.
There was a slight male predominance in the number of patients who were transplanted in our unit. Males constituted 54% of the transplant population, compared to 53% in the United States. In other developing countries the proportion of males varied from 41% (Reunion) to 93% (India), with the average being 68%. The SADTR (1994) reported that 59% of the patients in South Africa who were transplanted, were males. It is likely that the overall bias against females reflects social and cultural factors that favour males (Table 5-2).

CAUSES OF CHRONIC RENAL FAILURE

Chronic glomerulonephritis

Chronic glomerulonephritis was the most common cause of end-stage renal failure in our patients. The diagnosis was presumptive in the majority of cases although it was confirmed histologically in 36%. The nature of the underlying glomerulonephritis that leads to renal failure is uncertain. In a large clinicopathological study of 2827 Indian patients with renal disease reported by Date et al. (1987) nephrotic syndrome was found to be the most common clinical presentation, and membranous nephropathy the commonest cause of nephrotic syndrome in adults over the age of 40 years (Date et al., 1987). Renal disease may also present with the nephritic syndrome. Diffuse proliferative glomerulonephritis, crescentic nephritis and mesangial proliferative glomerulonephritis accounted for almost 90% of all cases. In the study by Date et al. (1987) as in our practice, patients with small kidneys and those with classic diabetic nephropathy did not undergo pathological examination. Anti-streptococcal antibodies were elevated in 50% of the patients with nephritis confirming the predisposition of individuals in the topics to infections (Date et al., 1987). The much higher incidence of chronic glomerulonephritis in non-white patients (48%) compared to the white patients in the present study suggests that the poor socio-economic conditions prevailing among the latter may have contributed to increased infections and the higher incidence of acute nephritis.

Zimbabwean experience

Seggie et al (1984) reviewed the Zimbabwean experience and reported that infections with β-haemolytic streptococcal, hepatitis B and syphilitic infections contributed to the development of glomerulonephritis in 46% of patients who
underwent renal biopsies. In this series, 41% of the post-streptococcal infections were complications of scabies infections (Seggie et al., 1984). Glomerulonephritis in Africa is characterised by the high prevalence of proliferative glomerulonephritis in older adults, both idiopathic and postinfectious (Brown et al., 1977; Kung'u et al., 1980; Seedat, 1979). IgA nephropathy, which is estimated to be the most common glomerulonephritis in the world (D'Amico, 1987), is relatively uncommon in black patients in South Africa (Swanepoel et al., 1989).

Hypertension
In sub-Saharan Africa, hypertension is the most common cause of end-stage renal disease in black individuals (Seedat et al., 1984). In South Africa it accounts for 37% of black, compared to 8% of white, end-stage renal disease patients (Seedat, 1999). In the present cohort, 27% of non-white patients and 5% of white patients who were transplanted, had hypertension as the primary cause for their end-stage renal disease, confirming the local and international experience of the high incidence and severity of hypertension in the black population (US Renal Data System, 1999). Hypertension also develops at an earlier age in the black patients than in white patients in South Africa (Seedat, 1999), as is the case in the United States (Weiss et al., 1938). Black females aged 35-40 years have a higher prevalence of hypertension than males in the same age range (Seedat, 1983). Urbanised blacks also have a much higher prevalence of hypertension (Akinkugbe, 1985), possibly related to dietary changes (Seedat, 1999). Another important consideration is that only 10% of black hypertensive patients in South Africa have effective control of blood pressure; blood pressure control is much better in white (22%) and Asian hypertensive (40%) patients (Seedat, 1983), in part perhaps to the better health care available to these racial groups (Seedat, 1999).

Diabetic Nephropathy
Diabetic nephropathy is the single most common cause of end-stage renal disease in United States (Ismail et al., 1999), Japan and industrialised Europe (Raine, 1993). In the United States over 40% of patients receiving treatment for end-stage renal failure have diabetic nephropathy and the number is steadily increasing (US Renal Data System, 1999), as is the experience in Europe (Pirson, 1996; Rodriguez et al., 1997). By contrast it accounts for between <1% - 14% of patients receiving
treatment for end-stage renal disease in developing countries (Albitar et al., 1998; Alzaid et al., 1994). In our cohort less than 4% of patients who received grafts, were diabetics. The sharp contrast between developing and industrialised (Ritz et al., 1999) countries may be due to bias against the selection of these patients for renal replacement therapy rather than the rarity of diabetic nephropathy. In our cohort, diabetics who were aged 50 years or more, who had evidence of either cardiac or vascular disease, were excluded from the program.

**Ethnic groups**

A marked ethnic predisposition to end-stage renal disease and diabetes in some non-white populations has been noted (Ritz et al., 1999). In Australasia diabetic nephropathy was the primary cause of end-stage renal failure in 42% of the Australian Aborigines, 61% of the New Zealand Maoris and 49% of the Pacific Islanders (Disney et al., 1998). This is very similar to differences seen between mainland France and the overseas territories (Albitar et al., 1998; Cordonnier et al., 1993). This pattern is confirmed by the USRDS data that show that diabetes accounts for a larger proportion of incident cases among the non-white races particularly blacks, Asians, and Native Americans (US Renal Data System, 1999). Irrespective of ethnicity, Western lifestyle is also associated with an increase in end-stage renal disease from diabetic nephropathy (Ritz et al., 1999). As our local population becomes increasingly urbanised, we can expect to see an increase in end-stage renal disease due to this disease. If the experience in the United States and Japan are indicative of future trends, then this “silent epidemic” of diabetes mellitus can be expected to wreak havoc among the population and present new challenges for nephrologists in future (Ritz et al., 1999).

**Silent epidemic**

The reasons for the increase in the incidence of type II diabetes in the Western population is the advancing age of the society and it is known that the prevalence of type II diabetes increases with advancing age (Ritz et al., 1999). More importantly, however is the fact that survival of patients with diabetes has continuously improved over the past few decades mainly as a result of improvements in the general care of these patients with anti-hypertensive therapy and treatment of coronary heart disease (Ritz et al., 1996). End-stage renal failure due to diabetic nephropathy is, in
a sense, a disease of medical progress. This can be compared to the situation in 1922 when insulin therapy became available. Whereas before this date most patients succumbed to infections or ketoacidosis, atherosclerosis became the main cause of death 10 years after the introduction of insulin. Similarly today, as patients with diabetes have a greater chance of surviving the cardiovascular complications, they live long enough to develop end-stage renal failure (Ritz et al., 1999).

Treatment of end-stage diabetic nephropathy

The renal replacement treatment of choice for patients with end-stage renal failure is renal transplantation, (preferably with a kidney from an HLA-matched sibling), with the other treatment options being haemodialysis and continuous ambulatory peritoneal dialysis. However, the survival of diabetic patients is still very poor on dialysis. In an early series mean patient survival was 11 months and the authors concluded that "dialysis for such patients...carried little likelihood of long-term survival or improvement in quality of life" (Ghavamian et al., 1972). Survival has improved greatly with mortality decreasing from 46% in 1982 to 29% in 1993 in the United States (Friedlander et al., 1997). However, the diabetic patient continues to fare worse than the non-diabetic patient (Anonymous, 1997; Disney et al., 1998; Port, 1993). The Catalonia registry illustrates the differences: 5-year survival is 30% on haemodialysis for diabetics compared to 60% for non-diabetic renal failure patients (Rodriguez et al., 1997). In a recent study it was found that 32% of diabetic patients died after a mean follow-up of 211 days, mostly from cardiovascular disease (Chantrel et al., 1999). The coronary death rate was estimated to be 10 fold greater in diabetics on renal replacement therapy as compared to their non-diabetic counterparts. Other cardiovascular as well as infectious causes were recorded in a similar proportion of deaths in diabetics as in non-diabetics (Brunner et al., 1988) The poor prognosis of patients referred late and the contribution of iatrogenic, therefore reversible, factors to deterioration in renal function has also been emphasised (Chantrel et al., 1999).

Graft survival

Recent studies have found comparable graft survival rates between diabetic recipients and matched controls as was our own experience (McMillan et al., 1990). Indeed, in the first 5 years after transplantation, renal allograft survival is similar in
diabetic and non-diabetic recipients (Cecka, 1996) but overall mortality in diabetic patients is three times that in non-diabetic group (Hirata et al., 1996). In contrast, other authors have experienced much worse transplant survival in recipients in whom the primary cause of renal failure was diabetes (both type 1 and type) (Morris et al., 1999). The main reason is the greater likelihood of death with a functioning graft as a result of comorbid cardiovascular disease resulting from accelerated atherosclerosis, sudden death related to autonomic neuropathy and infections (Fischel et al., 1991; Morris et al., 1999).

**Simultaneous pancreas-kidney transplantation**

The long-term prognosis of patients with diabetes and end-stage renal failure appears to be better after renal transplantation compared with dialysis. The results of renal transplantation in diabetic patients are acceptable provided macrovascular disease has been excluded (Hirschl, 1995). What has remained controversial is the additional benefit to be gained by a simultaneously transplanted pancreatic graft. Recent studies have however proven that simultaneous pancreas-kidney transplantation prolongs the survival of diabetic patients with renal failure (Smets et al., 1999). In the United States simultaneous pancreas-kidney transplantation is now regarded by many clinicians as the treatment of choice for uraemic diabetic patients (Kumar et al., 1999) in the absence of advanced coexisting vascular disease or after its correction (Pirsch et al., 1996; Schweitzer et al., 1997). However, in other parts of the world including South Africa, pancreatic transplantation has been viewed more critically. Reasons for the controversy are multiple but centre around the following observations: (1) Simultaneous pancreas-kidney transplantation is associated with a higher incidence of surgical complications than kidney transplantation alone (Bruce et al., 1996; Pirsch et al., 1996; Stratta et al., 1993; Sutherland et al., 1997; Sutherland, 1997); (2) although simultaneous pancreas-kidney transplantation improves the patient’s quality of the life (Adang et al., 1996; Bruce et al., 1996; Cosio et al., 1998b; Kiebert et al., 1994) its effect on established diabetic complications is controversial (Pirsch et al., 1996; Remuzzi et al., 1994; Stratta et al., 1993; Sutherland et al., 1997; Sutherland, 1997); (3) it has been suggested that simultaneous pancreas-kidney transplantation increase mortality compared with kidney transplantation alone (Manske et al., 1995); (4) the perceived risk associated
with the requirement for greater immunosuppression to prevent acute rejection (Remuzzi et al., 1994).

Advantages Strong arguments are made in support of pancreatic transplantation at the time of renal transplantation to establish a return to normal carbohydrate metabolism (Pirsch et al., 1996; Schweitzer et al., 1997). Quality of life is improved through the abolition of dietary restrictions, freedom of exogenous insulin administration and constant blood glucose monitoring, and the removal of the fear of hypoglycaemia (Kumar et al., 1999). The results of simultaneous pancreas-kidney transplantation are very encouraging. Patient and pancreatic graft 1-year survival rates of 92% and 79%, and 5-year rates of 81% and 67% have been achieved - results which are comparable to cadaveric renal transplantation in non-diabetic uraemic patients (Cecka, 1996; Hirata et al., 1996; Pirsch et al., 1996; Schweitzer et al., 1997). More importantly, when diabetic patients receive renal allografts, changes of diabetic nephropathy recur within 2 years (Najarian et al., 1989), progressing to end-stage disease in 10 years. Successful pancreatic transplantation prevents the recurrence of diabetic nephropathy in the renal allograft (Kumar et al., 1999).

Selection Critical to the success of simultaneous pancreas-kidney transplantation is the careful selection of patients. Diabetic patients have to be free of ischaemic heart disease, cerebrovascular disease and major peripheral vascular disease to be considered candidates for simultaneous pancreas-kidney transplantation. Advances in surgical practice and the introduction of newer immunosuppressive agents have contributed substantially to the success of the procedure (Bartlett et al., 1996; Pearson et al., 1997). The outcome of simultaneous pancreas-kidney transplantation has been found to be comparable to patient and graft survival following living-related kidney transplantation, and considerably better than that following cadaveric transplantation (Rayhill et al., 2000). Simultaneous pancreas-kidney transplantation thus improves the ability of the diabetic patients to live more of their expected lifespan. This suggests that glycaemic control even as a late intervention in a diabetic's lifetime may beneficially affect survival (Becker et al., 2000). Kumar et al. (1999) argue that these developments warrant a reappraisal of the cautious approach taken by centres outside of the United States toward simultaneous pancreas-kidney transplantation.
SUMMARY

Our data has shown that both overall patient and graft survival are better in younger patients, patients under cyclosporine and when a relative donated the kidney. Patient survival in addition is adversely affected by the failure of the graft to remain functional for the first year. Neither gender nor race has any major influence on either patient or graft survival. Diabetic patients fared as well initially but most grafts were eventually lost by 5 years after transplantation from patients dying of cardiovascular disease. Long-term survival of grafts under cyclosporine is less than in patients under azathioprine. Hypertensive patients suffered a poorer outcome compared to patients with other primary renal diseases. In non-diabetic patients death with functioning graft is also a major cause of graft loss.

Recommendations that arise from this survey are that while every attempt should be made to maintain a functioning graft especially in the first year, meticulous care should be taken to avoid sepsis, using less aggressive immunosuppressive strategies as well as adequate chemotherapeutic prophylaxis. In patients with severe rejection that fails to respond to treatment attempts to salvage the graft at all costs should be avoided in order to reduce patient mortality. Also important is that chronic renal failure should be prevented from developing in diabetic patients by good glycaemic control as proven by the Diabetes Control and Complications Trial (1993).

LITERATURE REVIEW


Chapter 6

THE FREQUENCY OF CANCERS FOLLOWING RENAL TRANSPLANTATION

Renal transplantation is accepted as the definitive treatment for end-stage renal failure. A successful renal transplant affords the physician a form of treatment which is superior in terms of patient survival (Port et al., 1993; Schnuelle et al., 1998), the recipient a superior quality of life (Bremer et al., 1989; Evans et al., 1985; Simmons et al., 1984) and the society great savings in the total cost of treatment (Kyllonen et al., 1994; Laupacis et al., 1996; Russell et al., 1992). With improvements in clinical care and advancements in immunosuppressive regimens, patients and grafts are surviving for longer periods of time. Graft survival has increased to 80 - 90%, 1 year and 55 - 70%, 5 years after renal transplantation respectively (Agodoa et al., 1995; Disney, 1995; Mallick et al., 1995; Opelz, 1992; Teraoka et al., 1995). Epidemiological studies that were performed before the availability of cyclosporine failed to demonstrate a substantial survival advantage of transplant recipients over dialysis patients on a waiting list (Burton et al., 1987; Garcia-Garcia et al., 1985; Hutchinson et al., 1984; Vollmer et
al.,1983). However, more recent data from diverse sources have clearly indicated that renal transplantation reduces patient mortality (Agodoa et al., 1995; Disney, 1995; Mallick et al., 1995; Teraoka et al., 1995). As a result of the prolonged survival of grafts and patients, other problems associated with sustained immunosuppression are now becoming evident. A significant cause of morbidity in patients who are recipients of renal allografts is the development of neoplasms, a well recognized, but poorly studied, problem (London et al., 1995).

The increased incidence of malignancies with the prolonged use of immunosuppressive agents was predicted as long ago as 1967 (Swanson et al., 1967) and the first documentation of the occurrence of de novo malignancies in renal allograft recipients was made in 1968 (Doak et al., 1968; Editorial, 1968; Zukoski et al., 1968). It was subsequently realised that these patients are indeed at considerable risk of neoplasia (Penn et al., 1969). Solid organ transplantation is associated with more than a 20-fold increase in the incidence of carcinoma and a 40-fold increase in the incidence of non-Hodgkin’s lymphoma (Gupta et al., 1986a; Kinlen et al., 1979; Kinlen, 1982; Penn, 1989). The difficulty in assessing small numbers of patients in specific centres prompted the creation of multicentre registries. Penn (1987) initiated the Cincinnati Transplant Tumor Registry (CTTR) in the USA and Sheil (1977) started the Australian and New Zealand Dialysis and Transplant Registry that covered the pan-Pacific region. Both multicentre registries act as repositories for data on this important subject. These registries have confirmed the persistent increase in the incidence of malignancies in renal allograft recipients and have also revealed the different patterns of malignancies in these patients compared to the general population (Sheil, 1977; Wehrli et al., 1998).

SINGLE CENTRE vs. MULTICENTRE REPORTS: STRENGTH AND WEAKNESSES

Single Centre Reports
The incidence of malignancies varies in different geographical regions from 0.75% in India to 27% in Australia (Table 6-1, page 6-9). However, the data need to be interpreted with caution. Periods of follow-up that are reported vary widely and some centres report only the most serious lesions while less serious ones such as skin
cancers and carcinomas-in-situ may not be reported. Also, many centres excluded from the denominator the patients who failed to maintain their grafts for minimum periods ranging from 1 to 4 months (Herr et al., 1979; Starzl et al., 1970). Many studies from single centres (Birkeland, 1983b; Gruber et al., 1994) included patients treated in the early era of transplantation when graft survival and patient follow-up was short. Comparing the results of single centres therefore also has to take these limitations into consideration. In Table 6-1, the raw data were used to calculate the incidence of malignancies, in order to allow meaningful comparisons. The total number of patients transplanted irrespective of the outcome of the graft or the patient was used as the denominator. This method underestimates the true incidence of malignancies because patients whose grafts fail or who die are not at risk of developing malignancies. Starzl et al. (1970) illustrated that by excluding the patients who died or whose grafts failed within the first 4 months the incidence of malignancies increased from 5.3% to 7%. In the present study the incidence of skin cancers increased from 8% to 9.5% if the patients who were exposed to immunosuppressive agents for less than one month were excluded.

Renal transplant recipients are at considerable risk of tumours but the difficulty of assessing small groups of patients (Gruber et al., 1991; London et al., 1995; Tokoro et al., 1992) in a specific centre prompted the creation of multicentre registries. The Cincinnati Transplant Tumor Registry (CTTR) and the Australian and New Zealand Dialysis and Transplant Registry have produced ongoing reports on particular tumours associated with transplantation (see Table 6-1 for relevant references).

REGISTRY DATA
The Cincinnati Transplant Tumor Registry (CTTR), currently known as the Israel Penn World Transplant Tumor Registry (IPWTTR) started as the Denver Transplant Tumor Registry and collects data voluntarily submitted by physicians from transplant centres around the world. Credit is due to the late Dr Israel Penn who launched the project in 1968 and regularly reported back to the international community on his findings. Table 6-1 illustrates some of the changes in the pattern of malignancies in the decades since the birth of the Registry. The main observation with regard to the CTTR is the progressive decline in the relative number of patients suffering from lymphomas. In the early period lymphomas accounted for more than one third of all
Fig. 6-1 The exponential increase in the number of posttransplant malignancies.

The exponential increase in the number of posttransplant malignancies. Since then the relative incidence of lymphomas has progressively declined and currently accounts for just over 10% of all malignancies reported to the registry. This decline in the relative incidence of lymphomas is also reflected in the Australian and New Zealand experience.

The CTTR records an exponential increase in the number of malignancies from its inception in 1968 to 2000 as more patients received organs and as patients and grafts survive for longer periods of time (Fig. 6-1).
Although registry and other multicentre studies have contributed greatly to our understanding of the epidemiology of posttransplant malignancies, there are several drawbacks in the analysis and interpretation of such data. These potentially confounding variables include (Gruber et al., 1994):

1. One of the major problems of registry data is that although the number of patients with malignancies is known, the number of patients who received transplants is not. The database also does not include information on the length of follow-up for the patient groups. These limitations preclude the determination of the true incidence of malignancies (Mihalov et al., 1996).

2. Another difficulty in analysing the CTTR data derives from the fact that the large series based on national transplant registries report data referred from centres using different and often non-comparable immunosuppressive regimens (Montagnino et al., 1996).

3. Variation in the intensity and type of immunosuppressive therapy employed by the different transplant centres and within transplant centres depending on transplant source; also certain centres in developing countries withdraw cyclosporine at varying times following transplantation (Montagnino et al., 1996).

4. Variation in the completeness of reporting: certain centres would report all malignancies whereas others only the more lethal or morbid types (Starzl et al., 1970).

5. The grouped data is the analysis of all organ and tissue transplants recipients (Gruber et al., 1994).

6. The difficulty in using actuarial life-table analyses when comparing cancer incidence between conventionally treated patients and cyclosporine treated patients to account for different follow-up periods (Gruber et al., 1994).

7. The difficulty in controlling or analysing for relevant risk factors such as transplant number, donor source, diabetic status and recipient age (Gruber et al., 1994).

8. The CTTR provides a comprehensive description of different type of tumours but fails to give information on the risk of developing these tumours (Gaya et al., 1995).

9. The Australia and New Zealand Transplant Registry does give the relative risk of de novo malignancy but does not indicate if there is a relationship between the relative risks and the duration of immunosuppression (Gaya et al., 1995).
Despite universal recognition of malignancy as an important complication following organ transplantation, there are discrepant views on the importance of the lesion in different parts of the world. In the USA the incidence of lymphoproliferative syndrome is disturbingly high but little recognition is given to squamous cell carcinoma of the skin as a cause of significant morbidity. Greater attention has been paid to Kaposi’s sarcoma which remains rare even in the transplant patient (London et al., 1995). In reality, cutaneous squamous cell carcinoma affects many more renal transplant patients than lymphoproliferative disease especially in countries with sunny climates such as Australia and is becoming a significant cause of mortality (Sheil et al., 1993).

Most studies on posttransplant malignancies have originated from developed countries that have predominantly Anglo-Saxon populations. Reports from Japan (Hoshida et al., 1997; Kishikawa et al., 1998; Yasumura et al., 1997) and from developing countries, excluding South Africa, have indicated that the incidence of malignancies ranges from 0.75% in India (Thiagarajan et al., 1998) to 6.15% in Taiwan (Yang et al., 1998). If allowance is made for the shorter follow-up in these countries then the incidence is comparable to that of countries with a predominantly Anglo-Saxon population. What does differ remarkably between the two groups of countries (Anglo-Saxon vs. non-Anglo-Saxon) is the difference in the type of tumours that occur after organ transplantation.

CLASSIFICATION OF MALIGNANCIES

Following successful renal allografting patients can develop malignancies from 3 potential sources. De novo malignancies are the most common and accounted for all the malignancies in our cohort of patients. Tumors may also be transmitted to the patient with the graft if the donor had an undetected malignancy at the time of the transplant. Indeed, the first indication that immunosuppressed patients were susceptible to malignancies came when apparently normal kidneys were transplanted from donors dying with cancer. It was soon recognised that such organs harbour malignant cells that could proliferate in the recipient with fatal consequences (Martin et al., 1965; McPhaul et al., 1965). Our policy is not to use organs from donors with malignancies except if the lesion is a primary brain tumour,
although there are some centres that even avoid these donors. There are several reports of these types of malignancies and the patients have generally done poorly unless the graft was removed as soon as possible. Finally, malignancies in renal transplant recipients may be recurrences of tumours that were treated in the recipient before the transplant. The policy in our Renal Unit is to wait at least 2 years following treatment of cancers before transplanting patients with previous cancers (Matos et al., 1977; Penn, 1983), and thus far none has developed a relapse of the original tumour.

GEORAPHIC VARIATIONS IN THE INCIDENCE AND DISTRIBUTION OF MALIGNANCIES

In the present study based on a cohort in the Western Cape Province of South Africa, 7.6% of all the patients who received renal allografts developed at least one malignancy. The incidence of malignancies in this study is distressingly high but comparable with the experience of other centres around the world (Table 6-1, page 6-9). The incidence of posttransplant malignancies varies, depending on geographic location, environmental factors and ethnic/racial makeup of the population - indicating a possible genetic basis for the predisposition toward posttransplant malignancies.

Skin cancers

The importance of environmental factors is emphasised by the observation that the incidence of skin cancer among renal allograft recipients varies with the amount of solar exposure. In areas with limited amounts of sunlight there is a 4- to 7-fold increased incidence but in areas with copious sunlight there is a 21-fold increase over the already high incidence experienced in the local population (Bouwes et al., 1991). In an Australian series the incidence of posttransplant malignancies reported was 24% of which 75% were skin malignancies (Sheil et al., 1991). Similarly, in South Africa, 7.3% of renal transplant patients developed malignancies of which 59% were primarily of skin (Disler et al., 1981).
Countries with moderate climate

However, exposure to sunlight is not the only factor because a surprisingly high incidence of posttransplant skin tumours was reported from countries with a moderate climate. In a series of 523 transplant recipients from Toronto, Canada there was an 18.5-fold increase in squamous cell carcinoma of the skin (Gupta et al., 1986b). Similarly, a study of 934 renal transplant patients from a Swedish centre found a 29-fold increase in incidence in comparison to controls (Blohme et al., 1985). A similar increase was reported from Finland where investigators found a 20.1 fold increase in the risk for skin cancer (Kyllonen et al., 1994). Interestingly, and contrary to findings in other countries with moderate climates, Hartevelt et al. (1990) reported that in the Netherlands the incidence of squamous cell carcinoma was increased by a factor of 250, basal cell carcinoma 10 fold, and was therefore on a level with the studies reported from Australia and New Zealand (Hardie et al., 1980; Sheil et al., 1979).

Ethnic/Racial factors

The fact that sun-exposure is not the only factor in the development of skin malignancies is aptly demonstrated by the observation that countries with abundant sunlight but a predominantly non-Caucasian population do not experience a similar increase in skin cancers (Table 6-1). This is further corroborated by the observation in the present study that there is an absence of skin cancers in non-Caucasian patients from the same geographical area as the Caucasian patients. This supports the observations by Disler et al. (1981) who also found that skin cancers occurred in white patients but not the black renal transplant patients; patients from the Middle East are also exposed to an abundance of sunlight but rarely have skin malignancies (Al-Sulaiman MH et al., 1994); among Japanese, Korean and Taiwanese patients skin cancers also occur uncommonly (Hoshida et al., 1997; Kim et al., 1998; Yang et al., 1998). These extensive observations serve to illustrate that beside environmental factors, genetic factors may play a role in the predilection for skin malignancies. The relevance of ethnicity/race/genetics following renal transplantation is further demonstrated by variation in the pattern of malignancies in different race groups in this study as well as that seen in different regions of the world as will become apparent later.
**TABLE 6-1.** Crude incidence of the commonest posttransplant malignancies in countries with predominantly Anglo-Saxon populations compared to other regions in the world.

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>No. of Patients</th>
<th>No. of Malignancies</th>
<th>Incidence</th>
<th>Treatment</th>
<th>Skin (%)</th>
<th>Lymphoma (%)</th>
<th>Kaposi's (%)</th>
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<td>794</td>
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<td>72</td>
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</table>
COMPARISONS WITH OTHER COUNTRIES

The present study has highlighted the disturbingly high risk of malignancies following renal transplantation. The overall risk of 7.6% is quite misleading. If the number of patients who did not receive immunosuppression for more than 28 days are excluded because either the patient or the graft failed to survive, then the incidence rises to 8.9%. Also patients who have been transplanted most recently have not been followed up for a period of time exceeding one year. By 5 years 68% and by 10 years 93% of the malignant lesions had developed in our patients. Of the patients who had survived for more than 15 years with a functioning graft 2 (8.3%) developed malignancies. This is considerably less than the 20% reported from Australia (London et al., 1995) and undoubtedly reflects the differing patterns of malignancies seen in developed countries. The distribution of malignancies that occurs in our population differs very markedly on racial/ethnic grounds. The patients of Anglo-Saxon origin, had patterns of malignancies which closely resemble that reported by developed countries whereas the pattern followed by the non-Caucasian group of our patients reflected that reported by other African and Central Asian centres (Bakr et al., 1997; Qunibi et al., 1988).

Australian and New Zealand experience

Sheil et al. (1991) report from Australasia, which has a sunny climate similar to ours, that skin cancer is the most prevalent malignant lesion in their population of renal transplant patients. It occurred in 18% of posttransplant patients with a mean follow up 6.4 years. Skin cancer was responsible for 74% of all malignancies. Squamous cell carcinoma was the most common form and occurred in almost 75% of those with skin cancer (Sheil et al., 1991). In our patients, who had a mean follow-up period of 6.4 years, the incidence of skin cancer in the white patients was 7.0%, much lower than in their Australasian counterparts, but skin cancer did account for 65% of all malignancies in white patients. Not a single non-white patient in our study developed a primary skin malignancy. Sheil and his colleagues make no mention of the problem of malignancies in Aboriginal Australians (Sheil, 1994a; Sheil et al., 1997; Sheil, 1999). In agreement with the Australian experience (Sheil et al., 1980; Sheil et al., 1987; Sheil et al., 1991; Sheil, 1996) as well as that elsewhere (Cassidy et al., 1982; Gaya et al., 1995; Hiesse et al., 1997; Kyllonen et al., 1994; Mihalov
Cancer Frequency Posttransplantation 6-11

et al.,1996;Montagnino et al.,1996;Ritters et al.,1994;Vilardell et al.,1992) squamous cell carcinoma was the most common skin lesion accounting for 59% of the skin malignancies in our patients. This is a reversal of the usual pattern where basal cell carcinoma predominates. None of our patients had metastatic lesions but metastases occurred in up to 16% of the patients with cutaneous malignancies reported by Sheil et al. (1980; 1994b). While they also experienced a mortality of 3% among patients with skin cancers (Sheil et al.,1987), none of our patients died as a direct result of their skin lesions. A very important observation also made by Sheil et al. (1980, 1991) was that in their population risk of cancer is increasing exponentially with time and they have extrapolated that any of their patients surviving 33 years after renal transplantation must expect to develop some form of cancer.

Fig. 6-2. The risk of developing a malignancy is indicated as the percentage probability each year after renal transplantation. The plots include all cancers, all skin cancers and all non-skin cancers. Modified from Sheil et al. (2001).
Table 6-2. The relative risk of posttransplant malignancies in Japanese patients compared with non-skin tumours in Australian patients and patients in the present study.

<table>
<thead>
<tr>
<th></th>
<th>Stomach</th>
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<th>Breast</th>
<th>Lymphoma</th>
<th>Kidney</th>
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<tbody>
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<td>NS</td>
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<tr>
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<td>1.36</td>
<td>79</td>
<td>1.53</td>
<td>11.1</td>
<td>80</td>
</tr>
<tr>
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<td>-</td>
<td>-</td>
<td>1.3</td>
<td>8.8</td>
<td>4.3</td>
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<tr>
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<td>1.7</td>
<td>-</td>
<td>0.6</td>
<td>1.8</td>
<td>4.8</td>
</tr>
</tbody>
</table>

¹NS is not specified
²This is the risk for all alimentary tract tumours

(Fig. 6-2). Most malignancies are skin cancers and we can perhaps expect a similar pattern in our white patients.

Japan

In Japan, the incidence of posttransplant malignancies is among the lowest in the world ranging between 2.3% and 2.8% (Hoshida et al., 1997; Tokoro et al., 1992; Yokota et al., 1994) compared with 7.6% in the present study and 6-8% reported by Penn (1994). However, more importantly is the tumour types seen compared with that in Western countries. The most common posttransplant malignancy is carcinoma of the stomach (Gunji et al., 1990), while skin carcinoma and lymphomas, the most common lesions in the Western countries are very rare (Hoshida et al., 1997; Tokoro et al., 1992; Yokota et al., 1994). These studies have shown that the pattern of cancer development in renal allograft recipients is similar to that occurring in the general Japanese population. This contrasts with our own experience and that of other developing countries (vide supra), as well as the experience in Western countries where the malignancies common in the general population are not the lesions that occur following organ transplantation (Penn, 1989). Epidemiological studies have suggested that the Japanese population is predisposed to gastric carcinoma due to its dietary habits and hereditary background (Inoue et al., 1994).
Hepatoma is the second most common tumour posttransplant (Tokoro et al., 1992) and this is related to the high prevalence of hepatitis B and C infections (Arita et al., 1992; Tanaka et al., 1991; Yu et al., 1990). Malignancies of the alimentary tract account for almost 60% of all posttransplant malignancies in Japanese patients (Yokota et al., 1994) compared with 20% of all non-skin malignancies in the Australian experience (Sheil, 1994b) and 11% of those reported by the CTTR (Penn, 1993). Several authors (Table 6-2) have reported the relative risk of the various malignancies in transplanted patients compared to the general Japanese population. The other malignancy that has been detected with increased frequency in the Japanese transplant patients is carcinoma of the bladder (Hoshida et al., 1997; Ishikawa et al., 1998). Of all malignancies that occur in Japanese patients following renal transplantation renal cell carcinoma carries the highest relative risk (Table 6-2) (Hoshida et al., 1997). Under cyclosporine the relative risk was 122 compared with 33 under non-cyclosporine immunosuppressive regimens (Hoshida et al., 1997). All but one patient with bladder cancer reported by Ishikawa et al. were receiving cyclosporine (Ishikawa et al., 1998). The Japanese patients who developed malignancies following renal transplantation are much younger than the patients in the general population and were, on average, 40 years old (Hoshida et al., 1997; Yokota et al., 1994), much like their Western counterparts in whom malignant lesions were detected. The median age at diagnosis of malignancy in the general Japanese population is 64 years and fewer than 5% of cancer patients are diagnosed below 40 years of age as having the same type of malignancy as observed in the transplant patients (Hoshida et al., 1997).

Not surprisingly, considering the type of the lesions that these patients were susceptible to, the period between the transplant and the detection of the tumour was relatively long and averaged over 6 years (Table 6-1). In at least 2 reports the latent period to tumor appearance was significantly shorter under cyclosporine compared with azathioprine (Hoshida et al., 1997; Yokota et al., 1994). The prognosis of the patients with posttransplant malignancies was poor with only 43% surviving after follow-up periods ranging from 1 month to 8 years in one study. Most of the deaths were related directly to the underlying malignancy (Yokota et al., 1994).
Table 6-3. Site of the most common malignant lesions in the Western Cape population in order of frequency (from the National Cancer Registry, 1998).

<table>
<thead>
<tr>
<th></th>
<th>White Male</th>
<th>White Female</th>
<th>Coloured Male</th>
<th>Coloured Female</th>
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<th>Black Female</th>
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</thead>
<tbody>
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<td>Cervix</td>
<td>Stomach</td>
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<tr>
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<td>Prostate</td>
<td>Breast</td>
<td>PSU¹</td>
<td>Stomach</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>PSU</td>
<td>Lung</td>
<td>Stomach</td>
<td>Lung</td>
<td>Breast</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Cervix</td>
<td>PSU</td>
<td>PSU</td>
<td>Prostate</td>
<td>PSU</td>
<td>Liver</td>
</tr>
<tr>
<td>PSU</td>
<td>Melanoma</td>
<td>Colorectal</td>
<td>Colorectal</td>
<td>Liver</td>
<td>Lung</td>
<td></td>
</tr>
</tbody>
</table>

¹PSU is site of primary tumour unknown

The reason for the great interest in the Japanese experience is the predisposition of the local community of the Western Cape, in common with the former, to carcinoma of the stomach. It is the most common malignancy in the non-white males and after carcinoma of the cervix the most common lesion in the females (Table 6-3). Despite sharing with the Japanese the risk of stomach carcinoma, in contrast to the Japanese renal transplant population, carcinoma of the stomach did not occur in any of our renal transplant recipients. Hepatitis B virus (HBV) infection is a risk factor for hepatocellular carcinoma. In our patients the chronic carrier rate of HBV is 5-10%, comparable to the rate in Far Eastern countries (Robson et al., 1994). Hepatocellular carcinoma is therefore not uncommon in black rural patients who have the highest HBV carriage rate. However, the only renal transplant patient to develop hepatocellular carcinoma was a white patient who had seroconverted soon after renal transplantation. Of note is that no cases of posttransplant Kaposi's sarcoma have been reported in any of the studies from Japan that are available to date (Hoshida et al., 1997; Tokoro et al., 1992; Yokota et al., 1994). This suggests that the correct environmental or genetic factors for Kaposi's sarcoma formation are absent in this ethnic group. This is in stark contrast to the experience in the present series and that of other developing countries (vide infra). The absence of Kaposi's sarcoma in the Japanese patients was noted even in long-term survivors who had functioning grafts for more than 10 years. In a group of 267 patients, 26 (9.7%) developed malignancies but none had Kaposi's sarcoma nor were there any cases of lymphoma noted in these long-term survivors. Interestingly, the most common malignancies in
these patients were of the skin (mostly squamous cell carcinoma). Hepatoma was the next most common lesion with the disease proving universally fatal (Yasumura et al., 1997).

**Other Far East countries**

There are very few reports from other countries in the Far East on their experience with posttransplant malignancies. Kim et al. (1998) documented a 2% incidence of malignancies in 1600 Korean kidney transplant patients. There were 5 cases of Kaposi's sarcoma, which accounted for 15.6% of total malignancies and occurred in 0.3% of all recipients. Yang et al. (1998) reported an incidence of posttransplant malignancies of 6.2% in 390 Taiwanese renal transplant patients. The most common malignancies were transitional cell carcinoma of the bladder and carcinoma of the liver which each accounted for 8/25 (32%) malignancies. Kaposi's sarcoma occurred in 2/25 (8%) patients with tumours (Yang et al., 1998). The high incidence of hepatoma and bladder carcinoma was ascribed to the high incidence of infection. No cases of skin cancer were diagnosed. In an earlier report the incidence of posttransplant malignancies was 8 (4.1%) among 193 Taiwanese renal allograft recipients. The most common lesions were hepatocellular carcinoma and lymphoma, each accounting for 37.5% of all lesions. Kaposi's sarcoma was present in 1 patient thus accounting for 12.5% of all lesions. No skin or bladder cancers were found either (Wu et al., 1992). The absence of any skin malignancies is in keeping with the trend demonstrated by countries that do not have a predominantly Caucasian population. What is surprising is the absence of genito-urinary cancers, which has been commonly reported by other countries in the Far East region and was by far the most common type of malignancy in the later report from Taiwan (vide supra). One explanation for this discrepancy is that the size of their cohort is very small and their observation period was only 10 years.

**Africa and the Central Asian**

The incidence of malignancies in this region (excluding South Africa) is reported to be between 0.75% and 5.87%, which is somewhat lower than that reported by the Western countries. However, if skin malignancies are excluded then the cancer incidence of 4.7% is very comparable (Penn, 1991). In many of these countries renal transplantation is still in its infancy. The patients are comparatively young and
the follow-up period short. Another explanation for the lower incidence is that most transplants in these countries are from living-related donors and consequently patients received less immunosuppressive treatment (Bakr et al., 1997). However, most striking is the distribution of types of reported posttransplant malignancies. With a single exception, one of the most common malignancies in all of these countries is Kaposi’s sarcoma, which accounted for 24% to 76% of all malignancies (Table 6-1). The single exception was an Indian report that failed to detect a single case of Kaposi’s sarcoma (Thiagarajan et al., 1998). The other observation is the relatively higher incidence of lymphomas in this group of countries. In the most recent CTTR report lymphomas comprise 11% of all reported malignancies (Penn, 2000). In developing countries, the incidence ranges from 8.6% in Saudi (Al-Sulaiman MH et al., 1994) to 50% in Pakistan (Askari et al., 1999). However, the incidence of lymphomas in the West also used to be very high when transplant programs were launched but decreased over time as experience was gained with the use of immunosuppressive drugs (Rao, 1998). This may well be the case in the developing countries, many of which have transplant programs that are in their infancy. In the present study lymphomas comprised 4.9% of all the malignancies that we detected.

Skin cancers were very uncommon in these countries and in several reports none were documented. The lower incidence of skin cancers partially explains the lower overall incidence of cancers in these countries. The only African country outside South Africa to report its experience with posttransplant malignancies in detail is Egypt (Bakr et al., 1997). In agreement with other developing countries in the region, Kaposi’s sarcoma accounted for 50% of all malignancies. Bladder carcinoma, not surprisingly for an area in which schistosomiasis is endemic, constituted 14% of all malignancies and was as common as lymphomas. All the patients who had carcinomas of the bladder following renal transplantation had a history of urinary and intestinal schistosomiasis and bilharzial hepatic fibrosis.

Saudi Arabia

In contrast to the Australian experience, Qunibi and his colleagues (1988; 1993) report that Kaposi’s sarcoma is the most common malignancy to occur in renal transplant patients in Saudi Arabia. In 630 renal allograft recipients transplanted
over a 17-year period, 26 cases of Kaposi's sarcoma were identified, an incidence of 4.1% compared with the reported incidence of 0.4% among recipients from developed countries (Penn, 1979). Kaposi's sarcoma represented 68% of tumours in their renal transplant population. In our non-white population of renal transplant recipients the risk of developing Kaposi's sarcoma was 5.32% and accounted for almost 80% of all malignancies. By contrast, Kaposi's sarcoma although considerably more common in renal transplant patients still accounted for only 4.3% of all malignancies in the latest reports by Penn (2000) and 0.73% in the reports by Sheil (1996)! The shorter follow-up period may well account for the Saudi patients having a lower incidence of other malignancies compared to our own group. In a larger cohort of 950 patients from neighbouring Egypt transplanted over an 18-year interval, Bakr et al. (1997) report a 2.3% incidence of posttransplant malignancies. Kaposi's sarcoma accounted for 50% of the lesions. None of the de novo malignant lesions described by either Qunibi et al. (1988; 1993) or Bakr et al. (1997) were primary skin cancers.

Other countries
Ecder et al. (1998) report that 68% of the posttransplant malignancies among the 557 Turkish patients followed over 14 years was Kaposi's sarcoma. They report only a single case of skin cancer in their cohort and 2 cases of lymphoma. In contrast, Mexico that is situated on a similar latitude as South Africa but has a predominantly Anglo-Saxon population, the most common posttransplant malignancy in 318 patients followed for 24 years was carcinoma of the skin and it was responsible for 63% of all lesions while lymphomas accounted for 9%. No cases of Kaposi's sarcoma were diagnosed (Bordes-Aznar et al., 1992).

SOUTH AFRICAN EXPERIENCE
Johannesburg
The very first South African reports of posttransplant malignancies originated from Johannesburg in 1981. Disler and colleagues reported 14 (7.2%) malignancies in 193 patients transplanted since 1966. The most common malignancies were those of the skin, which occurred in 9 patients. The predominant lesion was squamous cell
carcinoma, which occurred in 8 patients and basal cell carcinoma in 2 patients with one patient having both types of lesions. They observed that 63% of patients with squamous cell carcinoma of the skin originally had analgesic nephropathy and postulated a causal relationship. They noted a single case of Kaposi’s sarcoma and 2 cases of in-situ carcinoma of the cervix. They also reported the first case of Philadelphia chromosome positive chronic myeloid leukaemia in a transplant patient. The mean interval between transplantation and the diagnosis of malignancy was 32.6 months with the earliest lesion being diagnosed at 4 months. No cases of lymphomas were diagnosed. The race of the patients was not specified in this report. However, from other reports originating from the same group at that time, it is known that the majority of the patients were white with very few non-white patients receiving grafts at this time despite the latter forming the bulk of the population of the region (Myburgh et al., 1983). This explains the high incidence of skin cancer in the renal transplant population and essentially confirms the findings of the current study that Anglo-Saxon patients in South Africa, like their counterparts in other parts of the world (Liddington et al., 1989) are predisposed to skin cancers following renal transplantation.

The race of the patient who had Kaposi’s sarcoma was also not specified. The patient was treated with radiotherapy but died later of septicaemia, with no evidence of Kaposi’s sarcoma at the post-mortem examination. The dose of immunosuppression was not reduced in this patient. Another important observation made by Disler et al. (1981) and one that confirms those of this study was that the patients who developed neoplasms had better graft survival and are less likely to have acute rejection than the other patients. They suggested that these patients had a "... generally poor immunosurveillance mechanism allowing them to better tolerate the foreign antigens of the allograft and the altered antigens of the neoplastic cells." (Disler et al., 1981).

Johannesburg update
Margolius et al. (1996) updated the Johannesburg experience of posttransplant malignancies recently. Of 1374 patients receiving renal allografts over a 30-year period 106 (7.7%) patients developed 134 malignancies. The transplanted recipients
were overwhelmingly white and therefore, not surprisingly, the most common malignancy was that of skin, which accounted for 61% of the malignancies. Kaposi's sarcoma comprised 7% of all patients with posttransplant malignancies. Five of 7 patients with Kaposi's sarcoma were non-white (Margolius et al., 1994; Margolius, 1996) while both white patients to develop Kaposi's sarcoma were of Mediterranean origin.

Margolius et al. (1996) observed as we did that Kaposi's sarcoma occurred predominantly in non-Caucasians: of 297 non-white renal recipients 1% developed Kaposi's sarcoma compared with 0.19% of the white patients. The incidence of Kaposi's sarcoma was higher by a factor of over 5 in our patients with 5.32% of the non-Caucasian patients and 1.08% of our Caucasian patients developing the malignancy following renal transplantation. The reasons for the marked geographical difference in the incidence are not immediately apparent (Table 6-4). One reason for the difference may that our region (the Western Cape) has a predominantly coloured population that may be at greater risk compared to all the other race groups. Genetic factors and/or the higher prevalence of certain viral infections such as HHV-8, may be responsible. Table 6-4 summarises the main features of Kaposi's sarcoma in the two South African centres. Other major differences are evident in data from the two regions. Kaposi's sarcoma in its classical form is considerably more common in males than in females. This male predominance is lost in other forms of the disease as aptly demonstrated by our own data and confirmed by other centres around the world. In our cohort, slightly more males received renal allografts than females and once this was corrected for there was no gender difference in the incidence of Kaposi's sarcoma. Since Margolius et
Cancer Frequency Posttransplantation

al. (1996) do not specify the number of females who received renal allografts, it is not possible to exclude the fact the many more males may have been grafted than females. Also the number of cases is very small and it is possible that as more cases are diagnosed the discrepancy may become less pronounced.

Although no cases of malignant lymphoma were identified in the early reports from South Africa, Margolius et al. (1996) reported 4 cases (3% of all non-cutaneous malignancies) compared to 2 cases (6.4%) in the present series. The Tumour Registries reported that malignant lymphomas (Penn et al., 1988; Sheil et al., 1991) constituted 12% of all non-cutaneous malignancies (Sheil, 1994b). The relative incidence of malignant lymphomas, for reasons that are unclear, therefore is considerably less in South Africa than reported elsewhere, especially other developing countries where lymphomas constitute up to one in three posttransplant neoplasms (Askari et al., 1999) (Table 6-1).

Because Margolius et al. (1996) did not report the differential incidence of malignancies under azathioprine and cyclosporine, or the effect of race on the incidence of malignancies in their cohort further comparisons between their study and ours is not possible. Of note in our study is the observation that unlike other studies (Mihalov et al., 1996) patients aged more than 40 years at transplantation, and male sex were not associated with an increased incidence of malignancies. Cyclosporine was not associated with a greater incidence of malignancies compared to conventional therapy and this finding has been widely confirmed by others (Montagnino et al., 1996) although the time to the first neoplasm was reduced by more than one-half in agreement with Mihalov et al. (1996). Importantly, patients under cyclosporine were not more prone to develop Kaposi’s sarcoma, although others have suggested that there is an increased risk of Kaposi’s sarcoma due to the increased degree of immunosuppression (Montagnino et al., 1996).

Cape Town

Cassidy et al. (1982) reported the first Cape Town experience with de novo post-renal transplant malignancies. Of 209 patients transplanted between 1967 and 1979, 8 (3.8%) developed malignant tumours. This is almost one-half the incidence reported from Johannesburg by Disler and his colleagues one year earlier (Disler et
In the Cape Town series skin malignancies occurred in 3 patients, all of who were white renal allograft recipients. Kaposi's sarcoma was diagnosed in 2 patients. The race of patients with Kaposi's sarcoma was not specified in the report but in comparing the difference in the incidence of malignancies with the Johannesburg group the authors do emphasise that over 50% of their patients were non-white. Cassidy and his colleagues also state that unlike the Johannesburg experience less than 3% of their patients suffered from analgesic nephropathy, a disease known to be prevalent among white females (Cassidy et al., 1982). The mean duration of immunosuppressive treatment was 35 months with the shortest intervals being in two patients who had developed Kaposi's sarcoma at 16 and 18 months respectively. In contrast to Disler et al. (1981), Cassidy et al. (1982) withdrew all immunosuppressive treatment in the two patients with Kaposi's sarcoma. One patient died of disseminated disease 19 months later while the disease was cured in the second patient although she lost her graft to acute rejection when the immunosuppressive treatment was withdrawn. Neither centre reported any cases of lymphomas. Cassidy et al. (1982) in agreement with Disler et al. (1981) and the current series report the incidental finding of carcinoma of the thyroid. Cassidy et al. (1982) report a single case of sclerosing undifferentiated carcinoma of the thyroid diagnosed at autopsy in a patient dying of septicaemia 44 months after transplantation. The case of papillary carcinoma of the thyroid reported by Disler et al. (1981) was discovered when the patient underwent a parathyroidectomy 2 months posttransplant. Our own case has been described in detail above (see Results). Cassidy et al. (1982) observed that 80% of the patients in whom malignancies were diagnosed and in whom tissue typing was available had the HLA-A28 antigen in common, compared to 9% and 7% in the general population and transplanted patients.

The present study is unique in the South African setting in reporting in detail the various factors that influence the development of malignancies in renal allograft recipients over a prolonged period of time. It has identified the importance of race in determining the distribution of the type of malignancies and highlighted the risk of Kaposi's sarcoma in the non-Caucasian population. This is also the first study in South Africa to determine the relative risks of the various malignancies.
OTHER MEASURES OF THE FREQUENCY OF CANCERS

Relative Risks
The relative risks in the current study were determined using the expected number of tumours based on the National Cancer Registry statistics and the actual numbers of cases observed in the study. The national statistics relate to the general population although it would be more appropriate to compare renal transplant recipients and non-transplanted dialysis patients with each other. However, no registry of cancers in dialysis patients exists. There are some reports of an increased incidence of malignancies in uraemic patients (Matas et al., 1975) but these have found an excess of non-Hodgkin’s lymphoma (Kantor et al., 1987) and renal tumours (Port et al., 1989). The racial mix of our population also differs somewhat from that of the National Cancer Registry. There is a greater proportion of coloured patients in our series because our patient profile is that of the Western Cape in which this race group predominates (Fig. 4-2.) More importantly however is that the Western Cape has a relatively greater proportion of white patients, which should increase the overall risk of skin cancers. However, although these factors could alter the overall

<table>
<thead>
<tr>
<th>Country</th>
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<th>Skin</th>
<th>KS</th>
<th>Lymphoma</th>
<th>Reference</th>
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</tr>
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<td>-</td>
<td>300</td>
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</tr>
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<td>162</td>
<td>-</td>
<td>-</td>
<td>London et al., 1995</td>
</tr>
<tr>
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<td>4.2</td>
<td>-</td>
<td>33</td>
<td>Hoover et al., 1973</td>
</tr>
</tbody>
</table>

¹ Australia and New Zealand
calculated relative risk, they would not affect the subgroup comparisons made within the current series. No detailed risk ratios are available for comparison with other South African transplant units. Disler et al. (1981) report that the incidence of skin cancer was 41.5 cases per 1000 transplanted patients, which was a 16-fold increase over the predicted number for the general population. In view of the unreliability of the reported data on skin cancer, the National Cancer Registry of South Africa, like many other tumour registries, excludes skin cancers from its tumour statistics. The relative risk of skin cancers therefore could not be calculated for the present cohort of transplant recipients. The calculation of relative risks requires access to national or regional tumour registries that are seldom available in developing countries. Comparison with other developing countries was not possible because of the lack of this information. Data were available from some Western countries and is shown in Table 6-5.

The overall risk of cancer in transplanted patients is increased by between 2.5- to 27-fold in various populations. The excess risk was greatest in the case of Kaposi's sarcoma, which is extremely rare in the general population in developed countries (Sheil et al., 1987; 1994b). In some of the early reports, the risk of lymphomas was 30 to 40 times that expected with certain subtypes being 350 times more common (Hoover et al., 1973; Sheil et al., 1980). In an early multicentre report the risk of lymphoma was increased early after transplantation and the risk remained uniform at various times after transplantation. The risk ratio (observed/expected) of lymphoma was 33 within the first year, the same in the next four years and 40 for patients transplanted for longer than 5 years (Hoover et al., 1973). In contrast, the risk of other cancers increased with longer follow-up. The risk ratio of skin cancers increased from 1.8 within the first year, to 2.8 within the first 5 years posttransplant, to 4.3 beyond 5 years (Hoover et al., 1973). The same report was one of few to compare the risk ratio of the genders. The relative risk of lymphomas was comparable with the risk ratio being 32.1 in males and 38.1 in females. The risk of cancers other than lymphomas was 2.5 greater than expected in males but in females the risk of other cancers was not increased. Subsequent studies have failed to make the same comparisons as this early study (Hoover et al., 1973).
The current report is unique in comparing the relative risk of various malignancies on the basis of age, sex and race. Although there are some reports of comparisons between the genders (Gaya et al., 1995; Hoshida et al., 1997; Tokoro et al., 1992) there are a few age-matched (Hoshida et al., 1997; Montagnino et al., 1996) and no race-matched comparative studies that could be found in the English literature. The risk of non-skin malignancies was increased by a factor of 3.8 in our patients followed up for a maximum of 23 years or a total of 3450 patient-years of observation. This compares with a relative risk of 3.4 for non-cutaneous tumours from New Zealand and Australia (Sheil, 1994b) and 6.2 reported from the United Kingdom, with the latter having accumulated 2622 patient-years of follow-up (Gaya et al., 1995). The only country with a predominantly non-Caucasian population to report its results was Japan. In the first report of a small number of patients the overall relative risk was 7.41 (Tokoro et al., 1992). The 257 patients were followed up over 24 years. In a second, much larger study, the reported relative risk was 2.78. A total of 12 982 patient-years of observation had been accumulated. The 1744 patients had been followed up over 29 years (Hoshida et al., 1997).

In studies that have compared posttransplant malignancies between the genders, the excess risk is greater in men than in women. In an early report from the USA, the relative risk of malignant lymphomas was 38.1 in females compared with 32.1 in males. However, the other non-cutaneous malignancies were 2.5 times more common than expected in men only. In females the risk of other cancers was not increased (Hoover et al., 1973). In a report from the United Kingdom the relative risk of all malignancies was 7.3 in males (n = 165) and 4.9 in females (n = 109) (Gaya et al., 1995). However, if only non-cutaneous lesions were considered the excess risk was 4.9 in males and 4.5 in females (Gaya et al., 1995). In the two Japanese studies the relative risks were 2.91 (males: n = 1155) and 2.46 (females: 589) (Hoshida et al., 1997), and 7.94 (males: 205) and 5.56 (females: 52) (Tokoro et al., 1992) respectively. In the current study the excess risk of non-cutaneous malignancies was 4.3 in the 294 males and 3.4 in the 248 females. The reasons for the lower excess risk of malignancies could include the smaller number of females receiving grafts, the smaller cumulative doses of immunosuppressive administered to females by virtue of their lower body mass. Hormonal and genetic factors may also play a role. In the current study the most striking difference was in the relative risk of
Kaposi's sarcoma, which was more than 5-fold greater in females than in males. This contrasts with the reports by Montagnino et al. (1996) who found the excess risk was similar in men and women.

The current study is unique in its ability to compare the risk of cancer in different populations in the same geographical area. The non-white patients had a much greater risk of non-skin cancer than the white patients. This excess was largely due to the increased incidence of Kaposi's sarcoma in the former. White patients have double the risk of malignant lymphomas while the risk of breast carcinoma was reduced in all race groups. The non-white patients were also at increased risk of developing lung cancer but other malignancies that occur commonly in the non-white population, such as stomach and liver carcinomas, were not seen. The relative youth of the transplant recipients may be one explanation for the rarity of these common tumours. Hepatitis B infected patients are seldom accepted for renal replacement treatment, providing a possible explanation for the rarity of hepatocellular carcinoma. Changes in the patients' life-style habits and diet following the onset of chronic renal failure and the institution of renal replacement therapy may also play a possible role in the reducing the risk of malignancies of the stomach among the current cohort. Among the Japanese who also have a high incidence of gastric carcinoma in their general population the excess risk of this lesion in the transplant recipients is 1.4 while that of liver carcinoma is 1.36 (Hoshida et al., 1997).

**Incidence density of posttransplant malignancies**

The incidence density is another tool for looking at the incidence of malignancies which corrects for varying periods of follow-up. It is therefore perhaps more accurate than the raw incidences which are commonly quoted. It is also more accurate than the risk ratios because these require an accurate knowledge of the incidence of malignancies in the underlying general population. With very few tumour registries in developing countries, risk ratio is unlikely to be a useful comparative measure. In addition, the relative risk does not give the absolute incidence and the frequency of individual lesions will influence the value of others even if the absolute incidence of the other lesions remains constant (dos Santos Silva, 1999; Rosner, 2001).
TABLE 6-6. Incidence density of posttransplant malignancies in various countries.

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of Patients</th>
<th>Cumulative Patient-years</th>
<th>Overall (pyr)</th>
<th>KS (pyr)</th>
<th>Lymphoma (pyr)</th>
<th>Skin (pyr)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>2090</td>
<td>12055</td>
<td>7.8</td>
<td>0.17</td>
<td>0.6</td>
<td>1.0</td>
<td>(Kyllonen et al., 1994)</td>
</tr>
<tr>
<td>Italy</td>
<td>854</td>
<td>5874</td>
<td>12.9</td>
<td>2.2</td>
<td>0.5</td>
<td>3.4</td>
<td>(Montagnino et al., 1996)</td>
</tr>
<tr>
<td>Japan</td>
<td>1744</td>
<td>12982</td>
<td>3.5</td>
<td>0</td>
<td>0.38</td>
<td>0</td>
<td>(Hoshida et al., 1997)</td>
</tr>
<tr>
<td>S'Bosch</td>
<td>542</td>
<td>3450</td>
<td>12.7</td>
<td>6.1</td>
<td>0.6</td>
<td>3.4(8.5)</td>
<td>Current study</td>
</tr>
<tr>
<td>Sweden</td>
<td>934</td>
<td>4547</td>
<td>7.2</td>
<td>0</td>
<td>2.0</td>
<td>Excl.</td>
<td>(Blohme et al., 1985)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>274</td>
<td>1659</td>
<td>15.0</td>
<td>1.2</td>
<td>0.6</td>
<td>0</td>
<td>(Yang et al., 1998)</td>
</tr>
<tr>
<td>UK</td>
<td>274</td>
<td>2622</td>
<td>27.0</td>
<td>0.38</td>
<td>3.8</td>
<td>7.2</td>
<td>(Gaya et al., 1995)</td>
</tr>
<tr>
<td>USA</td>
<td>6297</td>
<td>11224</td>
<td>5.3</td>
<td>NS</td>
<td>2.2</td>
<td>1.9</td>
<td>(Hoover et al., 1973)</td>
</tr>
</tbody>
</table>

1pyr is per 1000 patient-years at risk.
2The incidence of skin cancer in white patients.

Many studies have corrected for varying periods of follow-up in patients by using the cumulative number of years since the patients were transplanted and estimating the number of malignancies in terms of patient-years (Birkeland, 1983b; Blohme et al., 1985; Gaya et al., 1995; Hoover et al., 1973; Kyllonen et al., 1994; Montagnino et al., 1996). However none have used this figure to estimate the number of malignancies. Using the data supplied by Blohme (1985), we calculated that the incidence of malignancies was 7.2 per 1000 patient-years in the Swedish cohort compared to that of the current study of 12.8. They however excluded all skin cancers from their estimates and the comparable value of the current study is 9.3 non-cutaneous malignancies per 1000 patient years. In an earlier study from Maryland, USA the total patient-years of observation were 11 224 and the incidence of all malignancies following renal transplantation was 5.3 per 1000 patient-years. When skin cancers were excluded, the incidence was 3.4 per 1000 patient-years. The study was one of few to look at gender differences. Using the data supplied the incidence of malignancies could be calculated and were 4.4 and 3.0 per 1000 patient-years in male and female recipients respectively (Hoover et al., 1973).

In a recent study from the United Kingdom (UK), the cumulative follow-up was 2 622 patient-years. Using the data supplied, the incidence of all cancers was 27.0 per 1000 patient-years but was only 14.1 per 1000 patient-years if skin malignancies were excluded (Gaya et al., 1995). In a recent Japanese report the incidence...
densities of all posttransplantation was the lowest reported with both skin and malignant lymphomas being very uncommon (Hoshida et al., 1997). The incidence densities of cancers from various countries and periods are summarised in Table 6-6 for comparison with that of the current study. Skin cancer among white patients in the present series is the highest in terms of incidence density. What is surprising is the very high incidence density of skin cancers in the UK patients. In the Nordic countries the incidence densities of skin cancers is lower but it still remains the most common posttransplant malignancy in these patients (Blohme et al., 1985; Kyllonen et al., 1994). Patients from the Mediterranean region are recognised to have a higher incidence of posttransplant Kaposi's sarcoma (Penn, 1997) and therefore the high incidence density of the lesion in Italy is not unexpected.

SUMMARY

The frequency with which malignancies occur following renal transplantation has been investigated using several techniques. What is clear is that there is a marked increase in these lesions in our patients as well as in most units that have reported their data. The risk of these tumours was recognised soon after the establishment of renal transplantation as a clinical option for the treatment of end-stage chronic renal failure (Penn et al., 1969).

The pattern of malignancies has changed. In the initial period, lymphomas were the most commonly encountered lesions to be replaced by skin lesions. Whether this represented a true decrease or was a function of the relative increase in the number of skin cancers is difficult to be certain because most of the available registry data, the only source of continuous data over the years, fails to record the number of patients at risk. The Australian and New Zealand registry also records a decrease in the proportion of lymphomas as the number of skin malignancies rapidly escalated but it remains uncertain whether the absolute incidence has changed over the years (Sheil, 1994b). What has been observed is that the relative risk of lymphomas increases to a maximum within a few months of transplantation but remains constant thereafter (Hoover et al., 1973). In contrast, the relative risk of skin cancer increased with time (Gaya et al., 1995). It is unclear why there should be an increase in skin

cancer but not other tumours the longer a patient receives immunosuppressive treatment, although some hypotheses have been offered (Gaya et al., 1995).

What should be noted is the difference in the type of cancers in cancers in the Western countries compared to the rest. In all countries with a predominantly Anglo-Saxon population even those with temperate climates skin cancers are the most common malignant lesions to occur following renal transplantation. This is in stark contrast to countries in Africa and the Middle-East where Kaposi's sarcoma is the predominant lesion. Among the Japanese neither skin cancers nor Kaposi's sarcoma occur and the malignant lesions that occur in the general population occur most frequently in the transplant patients as well. This contrasts with the experience in all areas including our own, where the most prevalent malignancies in the general population occur with similar or lower frequency in the renal transplant recipients (Yang et al., 1998).

LITERATURE CITED


Chapter 7

A BRIEF HISTORY OF KAPOSI: THE MAN AND THE DISEASE

Moritz (Moritz) Kaposi first described the disease that today bears his name in 1872. Before embarking on the historical aspects of the disease, it is appropriate to sketch briefly the biography of the man himself who made such a major contribution to the field of dermatology. He was one of the few who experienced the Golden Age of the Viennese School and transmitted its essence to succeeding generations.

HIS LIFE

Dr Moriz Kaposi (Fig. 7-1) was born Moritz Kohn on October 23, 1837 (Fig. 7-2) in Kaposvár, a small town with a population of 20,000 situated on the river Kapos (Safai, 1984) in Southern Hungary, to an orthodox Jewish family of limited material means (Holubar et al., 1981). The family did not have any intellectual pretensions or any outstanding achievements. The young Kohn was a bright student who excelled
at the local Gymnasium, and moved on to Pressburg (now known as Bratislavia) where he completed the last four years of his secondary schooling in the German Gymnasium (Frankl, 1971; Frankl, 1975). He matriculated at the University of Vienna in 1856. He qualified *cum laude* from the University earning the degree of Doctor of Medicine in 1861, a Doctor of Surgery in 1862, and a Master of Obstetrics in 1866. His main interest however was in dermatology, which was stimulated by his 2-year stint in Sigmund's Department of Syphilology at the Allgemeines Krankenhaus around 1864. He successfully applied for the post of Privatdozent (Associate
Fig. 7-2 The entry recording the birth of Moritz Kohn in the Mosaic birth registry. Interestingly the birth record on page 62, number 43, contains a postscript in Hungarian by Rabbi Emanuel Herzog in 1902 that reads: "meghalt mint Professor Kaposi Bécsben 1902 márc 6" (died as Professor Kaposi in Vienna (on) March 6, 1902). Adapted from Holubar et al. (1981.)

Professor in 1866 and was subsequently transferred to Ferdinand von Hebra's department of dermatology (Weidenfeld, 1981).

Ferdinand von Hebra was the founder of dermatology in Vienna. Von Hebra had worked as an assistant to Skoda and had been strongly influenced by Rokitansky's ideas of pathology. He achieved international recognition with his publication
Versuch einer auf pathologische Anatomie gegründeten Eintheilung der Hautkrankheiten (Attempt at a Classification of Skin Diseases on Basis of Pathological Anatomy), which appeared in 1845. Following this, von Hebra's clinic achieved great popularity as a training centre of excellence in dermatology (Holubar, 1981). Professionally, Kohn and von Hebra complemented each other very well. Von Hebra was a skilled observer and experienced diagnostician but had limited skills at microscopy. Kohn on the other hand, trained in the post-Virchow era, had the skills that his mentor lacked. Together, they undertook the revision of von Hebra's opus Hautkrankheiten that appeared in 1860.

They collaborated well together and undoubtedly also socialised together because Moritz met and fell in love with von Hebra's daughter, Martha. There was however a major obstacle to their engagement: the difference in their religious beliefs. The von Hebra's were Roman Catholics while Kohn was Jewish. The problem was solved when Kohn embraced Roman Catholicism in 1869. The couple were married on February 6, 1869. The union was a satisfactory one with Kohn and Martha von Hebra having 5 children, 3 sons and 2 daughters (Holubar et al., 1981). By all accounts Kohn (Kaposi) was a devoted husband and loving father. In 1871 he applied for and was granted the legal right to change his name to Kaposi, after the river Kapos of his birthplace in Hungary (Fig. 7-3). The reason he offered for changing his name was that he wished to avoid confusion with other members of the teaching faculty who were also named Kohn. Whether this was the only reason or whether it had anything to do with his recent conversion to Catholicism has been questioned (Dirckx, 1988). The Jewish community of Vienna probably held him in disdain for his action but did not ostracise him professionally, continuing to refer patients to him because of his competence as a dermatologist.

Kaposi worked as his father-in-law's faithful and accomplished associate until von Hebra's death in 1880. Kaposi was unanimously chosen as his successor, bypassing the standard procedure that required the submission of 3 names (Fig. 7-4). For Kaposi this was a major achievement because, in Vienna, at the time, Jews were barred from professional preferment, suggesting that his religious conversion and thoughtful choice of bride had paid professional dividends. Hans von Hebra, Kaposi's brother-in-law, was also a dermatologist working as a lecturer in the same
department but there seems to have been little love between them as Hans was passed over for promotion for 20 years (Ober, 1988). Kaposi headed the department for 20 years and made enormous contributions to the literature. He was a prolific writer and published on a range of subjects: erythema multiforme, rhinoscleroma, dermatitides in diabetics, lichen rubra moniliformis, impetigo herpetiformis, scleroderma, the pathogenesis of pigmentation and depigmentation, acne, sarcomatosis cutis and totaled 115 publications (Spiegler, 1902). He also published the famous "Textbook of Skin Diseases" that first appeared in 1880. Its worldwide popularity is reflected by the fact that it reached its fifth edition and was translated into several languages (Weidenfeld, 1981). In 1872, the same year that he described his Pigmentsarkom, he also published a detailed treatise on lupus erythematosus "New Contributions to the Knowledge of Lupus Erythematosis", one of his first works under the name Kaposi (Breimer, 1994; Weidenfeld, 1981). Well known was Kaposi's unique position on lupus which, unlike his contemporaries who considered it a special form of skin tuberculosis, he considered as a clinical condition
**Fig. 7-4.** The letter of appointment (in German Gothic) of Professor Moriz Kaposi to the chair of the Department of Dermatology founded by his father-in-law Ferdinand von Hebra by imperial resolution dated February 8, 1881. The right column relates to the pertinent report to the emperor by the minister of "Cultus and Unterricht". The details of the appointment are spelt out in the left column and the document is signed by Emperor Franz Joseph I (1830 - 1916). Adapted from Holubar et al. (1981).
Fig. 7-5. Kaposi's tomb in Vienna. The figure on the tomb was created by Kundman who used Kaposi's wife Martha as a model. Adapted from Holubar et al. (1981).
sui generis because he had found a unique form to be a true form of tuberculosis which he characterised as tuberculosis cutis propria (Weidenfeld, 1981). He was internationally respected as a dermatologist, recognised for his astute observations and respected as a gifted albeit dogmatic teacher (Breimer, 1994). Together with Unna in Hamburg and Hutchinson in London, Kaposi is considered one of the leading dermatologists of his era. Beside his description of Kaposi's sarcoma, he is also credited with the first description of xeroderma pigmentosum (Kaposi, 1882).

On October 24, 1900 one day after celebrating 25 years as the head of one of the leading Dermatology Institutes in Europe, he suffered a minor stroke from which he made a full recovery (Weidenfeld, 1981). He was to suffer another stroke one year later, but this time his recovery was incomplete. Despite his handicap, he continued with his professional activities and lectures refusing to be parted from what was the essence of his life. Even in the hours before his death he stubbornly refused to take to bed. He died quickly and painlessly on March 8, 1902, "after a life replete with fruitful activity enriched by success, as proved by the all the honours which can be bestowed on an academic teacher . . . . With him died a great spirit, a restless worker and a good human being" (Weidenfeld, 1981) (Fig. 7-5).

HIS WORK

In 1872 Kaposi published an account (Fig. 7-6) of 5 cases of a lesion which he labeled Idiopathisches multiples Pigmentsarkom der Haut (Idiopathic multiple-pigmented sarcoma) (Kaposi, 1872). He described 5 patients, all men over 40 years of age from all corners of the Habsburg empire (Breimer, 1994), who had multiple cutaneous red-blue nodules, mainly on the extremities. One patient died and underwent a postmortem examination while a second patient had a biopsy. Follow-up data is unfortunately not given for this patient or the others. Kaposi shared his experience with Virchow who informed him of a case of a ten-year old boy who had presented to him with similar nodular lesions on the leg that had proliferated and proved fatal within a year. The histopathological appearance of Virchow's case resembled that of Kaposi's cases. From these limited observations Kaposi made some generalisations and summarised the nature of the problem as follows:
Idiopathisches multiples Pigmentsarkom der Haut.

von

Dr. Kaposi,
Docent an der Universität in Wien.

Mit Recht hebt Köbner in einem über Sarkome der Haut handelnden Aufsatze*) hervor, dass diese Neubildung auf der Haut an und für sich selten vorkommt, und bisher mehr Object anatomischer als klinischer Aufmerksamkeit gewesen ist. Dasselben werden zwei Krankheitsfälle mitgetheilt, in deren erstem Hautsarkome in grosser Anzahl als metastatische Bildungen, wahr scheinlich von den Lymphdrüsen der Leistengegend her, ent standen waren, während im zweiten Falle die allgemeine Sarkomatosis von einem seit Kindheit bestandenen Naevus des linken Zeigefingers ausgegangen war, der primär in ein pigmentirtes Spindelzellensarkom sich umgewandelt hatte. Beide Fälle endigten innerhalb drei Jahren tödtlich. Die Section war in einem derselben gestattet worden.

Ich glaube eine Form des Pigmentsarkoms der Haut als eine typisch-klinische von denjenigen absonndern zu können, welche unter allen Umständen als consecutive (metastatische) Eruptionen und demnach von den verschiedensten Primärherden ausgehen können, und deren Beispiele in den Fällen von Köbner ge geben sind.

Ich will die hier zu beschreibende Form deshalb als idiopathisches multiples Pigmentsarkom der Haut bezeichnen.

Als Grundlage für die Aufstellung dieser Form dienen mir fünf einschlägige Beobachtungen; dieselben sollen hier speziell mitgetheilt werden, nicht nur weil der Gegenstand neu, und Form und Verlauf der Krankheit von der grotztßen Wichtigkeit

*) Dieses Archiv 1869, 3. Heft, pag. 369.
"Nodules ranging from the size of a peppercorn to that of a pea or a hazelnut . . . brown-red to blue-red in colour develop in the skin without a known . . . cause. Their surface is smooth, their consistency elastic; they sometimes swell like an angioma. They are either isolated and then protrude, after growing larger, in a peripheral shape, or else they form clusters and remain flatter . . . . They usually appear first on the sole of the foot and the instep, . . . also on the hands . . . where they are accompanied by diffuse thickening of the skin and deformity of the feet and the hands.

During the further progress . . . isolated nodules and groups of nodules also appear on the arms, legs, face, and trunk . . . . Some of the nodules may atrophy and regress . . . . They ulcerate later on . . . . The lymph nodes do not enlarge significantly . . . . Finally, identical nodules appear in the larynx, trachea, stomach, intestines, and other nodules form in the liver." His description of the disease is remarkably accurate and can hardly be improved upon. Even his histological observations were remarkably accurate: "The histological structures consists of foci of fusiform spindle cells and a rich network of capillaries".

However, contrary to our current understanding of the prognosis of classical Kaposi's sarcoma, he wrote "Die Krankheit führt zum Tode und zwar innerhalb einer kurzen Frist von 2-3 Jahren . . . . Die Krankheit muss nach den vorliegenden Ermahnuungen von vornherein nicht als unheilbar, sondern auch als lethal gelten." (The disease leads to death and it does so within the short span of two to three years . . . . The disease must, according to our existing experiences, be considered a priori not only incurable but also lethal). Indeed, three of his 5 patients were dead within 12 -16 months after the initial diagnosis. On the basis of postmortem findings of characteristic lesions everywhere, not only on the limbs, trunk and face but also in the gastrointestinal tract and the liver, Kaposi suggested that the disease was disseminated from the start rather than a local tumour that later metastasised: "muss fur dieses Unbel eine bereits von Anfang her vorhandene allgemeine Erkrankung (Dyskrasie) angenommen werden" [(one) must postulate, for this scourge, that there is a generalised disease (dyscrasia) pre-existing from the beginning] (Breimer,1994). This controversy remains unresolved to this day.
**Fig. 7-7** Earliest chromolithographs of Kaposi's Idiopathisches multiples Pigmentsarkom. The top frame depicts lesions on the right foot and the lower frame lesions on the hands. From Hebra et al. (1856).
Table 7-1 Some names applied to the tumour since its initial description.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1872</td>
<td>Kaposi</td>
<td>Idiopathic multiple pigmented sarcomas of the skin</td>
</tr>
<tr>
<td>1878</td>
<td>Tanturri</td>
<td>Sarcoma idiopathicum telangiectoides</td>
</tr>
<tr>
<td>1883</td>
<td>Hardaway</td>
<td>Sarcoma cutis</td>
</tr>
<tr>
<td>1884</td>
<td>Babes</td>
<td>Angiosarcoma peritheliae fusocellulare</td>
</tr>
<tr>
<td>1889</td>
<td>Funk</td>
<td>Sarcomatous gummatoides</td>
</tr>
<tr>
<td>1894</td>
<td>Kaposi</td>
<td>Sarcoma idiopathicum multiplex haemorrhagicum</td>
</tr>
<tr>
<td>1894</td>
<td>Unna</td>
<td>Acrosarcoma multiplex cutaneum telangiectoides</td>
</tr>
<tr>
<td>1898</td>
<td>Tommasoli</td>
<td>Primitives hemorrhagisches acrosarcoid</td>
</tr>
<tr>
<td>1899</td>
<td>Bernhardt</td>
<td>Sarcomata idiopathica multiplica pigmentosa cutis</td>
</tr>
<tr>
<td>1899</td>
<td>Gilchrist</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>1899</td>
<td>Pospelow</td>
<td>Acroangioma hemorrhagicum</td>
</tr>
<tr>
<td>1901</td>
<td>Radaeli</td>
<td>Angioendothelioma cutaneum</td>
</tr>
<tr>
<td>1902</td>
<td>Pelagatti</td>
<td>Acrosarcoma</td>
</tr>
<tr>
<td>1910</td>
<td>Sequeira</td>
<td>Granuloma angiomatoides</td>
</tr>
<tr>
<td>1912</td>
<td>Sternberg</td>
<td>Kaposi’s sarcoma</td>
</tr>
</tbody>
</table>

Adapted from Ober, (1988)

There were other criticisms of his otherwise brilliant description. Despite his reputation as a keen clinical observer and an astute histopathologist of cutaneous diseases, Kaposi failed to illustrate his article with chromolithographs of either the gross appearance of the lesions or drawings of the histopathologic sections. Fortunately, a chromolithograph of outstanding quality appeared contemporaneously in the publication Atlas der Hautkrankenheiten edited by Hebra, Elfinger and Heitzman (1856) (Fig. 7-7). Kaposi remained silent on the subject until 1894 when he proposed that name of the condition be changed to Sarcoma Idiopathicum Multiplex Haemorrhagicum because the word pigmentsarkom had created confusion with melanoma (Kaposi, 1894). Kaposi later embellished his original description of the disease and finally had 16 patients, all men, who he noted still had an unfavourable prognosis (Kaposi, 1895).
What's in a name (and the contribution of others) (Table 7-1)
The name change made by Kaposi (1894) was to be one of many name changes that the condition was to undergo over the following decades. Following Kaposi's original description, other observers added their anecdotal experiences and many tried to develop more precise vocabulary that would take account of the feature that they felt was most distinctive. There was general consensus that the condition was a sarcoma as illustrated by the list of names ascribed to the lesion over the years and most authors added Kaposi's name in parenthesis or quotation marks to the tumour. Sternberg's eponymous label largely settled the issue in 1912 but this did not prevent subsequent authors like Hamdi and Halil from suggesting the unwieldy label of "perithelioma mutiplex nodulosum cavernosum lymphangiectoides cutaneum" in 1927. When this title did not find favour with the scientific community, Hamdi and Resat proposed the equally unwieldy "acroepithelioma idiopathicum multiplex cavernosum lymphangiectoides cutaneum" in 1932.

Cell of origin
The multiplicity of names (there have been over 40) given to this disorder highlights one of the enigmas of this disease faced by the early authors - and that still remains a challenge for modern investigators, namely, the cell of origin of the tumour (Hutt,1984). Most investigators favoured (as do most current researchers) vascular endothelium, either dermal capillaries or perivascular lymphatics but a minority believed that the tumour arose from the adventitia. Sternberg (1912) felt that the lesion arose from smooth muscle cells in the adventitia. Pautrier and Diss (1929) developed the idea that the tumour arose from vascular neuromuscular annexes and schwannian elements, and presented the concept of a pseudosarcoma arising in neurovascular dysgenesis. Involvement of the reticuloendothelial system was invoked by Dörffel (1932) who suggested some relation to the lymphoblastic tumours, an opinion shared by many others (Lane et al.,1953; Nicholas et al.,1928; Puhr,1931). Lane and Greenwood (1953) reported the first case of Kaposi's sarcoma to be associated with a confirmed lymphoproliferative disease, mycosis fungoides.

In an exceptional review of the subject by Becker and Thatcher in 1938, observations from tissue culture were added that showed that the spindle cells did
not have the cytological features of either fibroblasts or smooth muscle cells. They
discounted the reticuloendothelial hypothesis but failed to commit themselves to a
position with regard to the cell of origin. Despite this groundbreaking work, only 3
years later, Symmers, in a detailed clinicopathological study, asserted that the
tumour unequivocally arose from fibroblasts (Symmers, 1941). The nature of the
cell of origin continued to be debated even into the era of the electron microscope.
In 1962 Pepler and Theron published a series of electron photomicrographs that
fairly convincingly showed that the tumour arose from Schwann cells. However, the
later arrival of immunoperoxidase techniques have demonstrated that factor VIII is
present in many of the proliferating cells, with the result that current opinion favours
the simple endothelial cell as the origin of the tumour as initially proposed by Gilcrest
and Ketron in 1916.

Other Reports of the Tumour
It was the accumulation of anecdotal cases that was to outline the nature of the
disease. The most important one was that of Tomasso De Amicis, a Neapolitan
dermatologist whose 1882 monograph was rediscovered by Francesco Ronchese, a
Providence, Rhode Island dermatologist in 1958. In his monograph entitled Dermo-
polimelano-sarcoma Idiopatico, De Amicis describes 12 cases seen in Northern Italy.
All his patients were male, including a 5-year old boy who presented with a lesion on
the nose. The adult patients presented with the conventional nodules on the limbs,
with later development of lesions on the penis, palate, chin, and elsewhere. Biopsies
were obtained in 4 cases and 3 patients were followed up until their demise only
months later. There is no follow-up information given on the remainder implying a
more indolent course. In one of his patients the pigmented nodules on the foot
spontaneously regressed after 4 years (Ronchese, 1958). De Amici subscribed to
the then popular theory expounded by Cohnheim that the tumour arose from
embryonal cells that had lain dormant until an as yet unspecified stimulus triggered
their malignant transformation (Ronchese, 1958). De Amici's detailed drawings of the
histology of the lesions depict the main features of the tumour (Fig. 7-8).

Many other clinical accounts of the disease appeared during the late 19th century
and early 20th century. Some of these reports were accompanied by
histopathological observations while others were not. A summary of these reports by
Dörfell allowed certain misconceptions to be cleared up, including the one that the disease occurred almost exclusively in Italian and Eastern European males. It was also widely recognised that the tumour was rare in childhood and adolescence and that although the cases generally progressed slowly, a number proved rapidly fatal with widely disseminated lesions (Ober, 1988). An early, purely dermatological study by Funk (1889) noted that the early form of the tumour was either a *macula*, "a blotch having a yellowish-red, red, brownish, or bluish-red colour, and the size of a pea" or a flat papule, "the size of a millet seed which may shoot up from the border of the macula". Funk suggested that from the early macules and papules sarcomas later developed as "a nodule . . . a soft spongy tumour . . . a diffuse infiltration of the

![Fig. 7-8](image)

**Fig. 7-8** Drawing of a vascular space surrounded by spindle cells: a, enlarged blood vessels; c, fusiform cells; d, pigment granules; f, highly pigmented sarcoma cells; g, pigmented coil cells. From De Amicis (1882) in Ronchese (1958).
skin . . . (or) subcutaneous nodules" (Funk, 1889). Kaposi's sarcoma begins as a macule and then progresses to tumour stages of plaque, papule-plaque, or nodule-ulcerating tumour.

The accumulation of case reports also allowed the discovery that the classical form of the disease had two different types of natural history very much like that described in the present report of post-renal transplant Kaposi's sarcoma. There was an indolent form that remained confined to the limbs, face and occasionally other parts of the integument, even involving mucous membranes; and a more aggressive form with visceral involvement. Postmortem reports showed involvement of lymph nodes, lungs and liver but particularly of the gastrointestinal tract. Another important observation that was evident from these studies was that the disease was multicentric in origin and that the "secondary" lesions were not true metastases. This prompted Lang and Haslhofer (1935) to suggest that the disease should perhaps be considered a systemic angiomatosis.

Many reports on Kaposi's sarcoma appeared in the 1950's. It is stated that no disease comes of age until it is the subject of a monograph. For Kaposi's sarcoma this was to be in 1957, 87 years after the original description and was undertaken by Bluefarb (1957). It neatly condensed the knowledge of Kaposi's sarcoma available up to that time and was well illustrated. Just prior to the appearance of the monograph, the report of McCarthy and Pack (1950) from the United States epitomised the clinical experience of Kaposi's sarcoma. They contrasted 36 cases of Kaposi's sarcoma with 20 cases of angiosarcoma. They noted that the male to female ratio was 92:8, that 78% of their patients were aged over 40 years, that the presenting lesions affected the extremities with 73% on the feet and 14% on the hands, that 83% of their patients were Jewish (44%) or Italians (39%), that the mean survival was 8 years and that 19% were free of the disease 5 years after the initial diagnosis of the disease. Three (8%) of their patients developed lymphoproliferative disease. Treatment of their patients consisted of wide surgical excision of the solitary lesion and radiotherapy if the disease was more extensive.

Cox and Helwig (1959) reported an even larger cohort in that decade. They had 50 patients with Kaposi's sarcoma, 44 of whom had the benefit of longterm follow-up. In
contrast to the earlier report from the United States by McCarthy and Pack (1950), there were no Jews in the cohort reported by Cox and Helwig (1959), but 11 of the 50 patients were black (it had previously been thought that Kaposi's sarcoma was rare in this race group). These authors confirmed that Kaposi's sarcoma was similar in all the racial groups. Although 25 of the patients died, death was directly attributable to the sarcoma in only 11 (22%) of the cases. At the time of their report 19 (38%) patients were still alive, 9 (18%) with residual disease and 10 (20%) were disease-free 8 years after the initial diagnosis. Two of their patients developed a lymphoproliferative disease. They noted that the association with these diseases but concluded "... neither the clinical nor the pathological features justify the classification of Kaposi's sarcoma as a malignant lymphoma or a reticuloendothelial disease" (Cox et al., 1959).

**African Kaposi's sarcoma**

Hallenberger described the first case of Kaposi's sarcoma involving an African patient in 1914. However, the prevalence of the disease was not appreciated until 20 years later when Smith and Elmes (1934) reviewed a series of 500 tumours in African patients and discovered that 10 (2%) were Kaposi's sarcoma. In 1950 Kaminer and Murray (1950) drew attention to fact that the disease was common in "Bantu" men in South Africa. It subsequently became apparent that the disease is endemic on the African continent particularly in the sub-Saharan region, in countries such as Uganda, Tanzania and Congo. Over the subsequent years, several reviews of Kaposi's sarcoma in Africa appeared culminating in a conference that was held in Kampala, Uganda in 1961 and that led to the publication of the monograph by Ackerman and Murray (Ackerman et al., 1963). In the same year Oettle (1962) also observed that Kaposi's sarcoma accounted for 12% of all malignancies in Zaire (now known as the Democratic Republic of Congo). He noted that the disease behaved differently compared to the classical form that was known in Europeans. A second report on Kaposi's sarcoma in South Africa also appeared in the same year (Keen, 1962). At about that time Lothe (1963) published the largest series ever reported consisting, of 211 cases of Kaposi's sarcoma in Ugandan Africans.
Posttransplant Kaposi's sarcoma
It had first been recognised that Kaposi's sarcoma was associated with a breakdown of immune surveillance because of the number of cases described where second malignancies were present. The commonest lesions were malignant lymphomas. In a report of 83 cases of Kaposi's sarcoma, O'Brien and Brasfield (1966) found that 18 (14%) developed a second malignancy, all of which were lymphomas. The association of Kaposi's sarcoma with the use of immunosuppressive agents has also been recognised for some time. Zemek et al. (1964) described Kaposi's sarcoma in a patient with autoimmune haemolytic anaemia treated with steroids, while Mazzaferi et al. (1968) had a patient with multiple myeloma who developed Kaposi's sarcoma after treatment with an alkylating agent.

The very first case of Kaposi's sarcoma following a renal transplant was reported in 1969, a mere 3 years after the first successful renal allograft was performed (Siegel et al., 1969). Subsequent to this, a spate of reports appeared confirming the association between immunosuppression, renal transplantation and Kaposi's sarcoma (Haim et al., 1972; Hardy et al., 1976; Klepp et al., 1978; Meyers et al., 1976; Myers et al., 1974; Stribling et al., 1978). Kaposi's sarcoma has come to be recognised as one of the most common malignancies to occur following solid organ transplantation. Penn (1979) published the first series of cases to occur in allograft recipients, immunosuppressed with azathioprine and prednisone. Kaposi's sarcoma carries the highest relative rate of occurrence of all posttransplant tumours (Harwood et al., 1979) (see Chapter 6).

AIDS-Associated Kaposi's sarcoma
The description of Kaposi's sarcoma in young homosexual males in 1981, heralded the onset of the acquired immunodeficiency syndrome (AIDS) epidemic and drew attention to this uncommon malignancy once again (Borkovic et al., 1981; Gottlieb et al., 1981; Hymes et al., 1981). The role of immunosuppression in the development of Kaposi's sarcoma was highlighted by this epidemic but the exact mechanism whereby the immunosuppression leads to the multicentric proliferation of vascular endothelium remains to be clarified. At one point a third of patients who had AIDS had Kaposi's sarcoma but the incidence has fallen subsequently (Jacobson et al., 1995).
LITERATURE CITED


Chapter 8

KAPOSI'S SARCOMA

EPIDEMIOLOGY

Classic Kaposi's sarcoma described by Moriz Kaposi in 1872 remained the only clinical form of Kaposi's sarcoma to be recognised until the 1960s when the African form of the disease, also known as endemic Kaposi's sarcoma was recognised as an unique entity (Ackerman, et al., 1963; Oettle, 1962). Soon thereafter, the first cases of Kaposi's sarcoma related to immunosuppressed patients appeared in the literature (Mazzaferri, et al., 1968; Zemek, 1964) and the first series of cases related to renal transplant recipients soon confirmed the association between Kaposi's sarcoma and immunosuppressed patients (Penn, 1979b). This iatrogenic form of Kaposi's sarcoma is now associated with all forms of solid organ transplants but especially with renal transplantation. The most recent form of Kaposi's sarcoma heralded the onset of the worldwide acquired immunodeficiency syndrome (AIDS) epidemic in 1981 (Borkovic, et al., 1981; Gottlieb., 1981; Hymes et al., 1981) and is the most common form of malignancy in these patients.

All forms of Kaposi's sarcoma share the same histological appearances (Ackerman et al., 1988) but there are marked differences in the clinical behaviour of the disease among the different epidemiological forms, with marked variations in the prognosis.
between the forms as well (Harawi, 1989). This chapter will compare and contrast the iatrogenic form of the disease with the classical, endemic (African) Kaposi’s sarcoma and AIDS-related Kaposi’s sarcoma. Subsequent chapters will highlight the clinical features, the pathological appearances and management of Kaposi’s sarcoma. Before embarking on the epidemiological description of the disease it is perhaps appropriate to highlight certain problems inherent in this exercise. Research design depends on existing conditions and trends prevailing in populations. As an example, researchers in Africa rely on relative frequency of cancers (as we did) because in most populations the denominator is unknown (Wahman et al., 1991). Clearly, the relative frequency is important in this situation but does not allow for meaningful comparisons with other regions. In addition, rates may be biased by over- or underreporting. Individual risk factors, which will be discussed below, also need to be evaluated with caution because factors may exert an influence on others, and may change over time; ethnicity and geography are closely associated, and different forms of Kaposi’s sarcoma may be difficult to distinguish from each other (Wahman et al., 1991).

EPIDEMIOLOGICAL TYPES (Table 8-1)

Classic (Sporadic) Kaposi’s sarcoma

Incidence

This type of Kaposi’s sarcoma accounts for only a fraction of malignancies among Europeans and North Americans. In the United States of America (USA) the incidence is well below 1%. The estimated annual rate of Kaposi’s sarcoma in the USA before the outbreak of AIDS, from 1973 to 1979 was 0.29 cases per 100 000 population of men and 0.07 cases per 100 000 population of women (Biggar et al., 1984a). The Mayo Clinic experience was reviewed by Reynolds et al. (1965) who reported only 70 cases over a 38-year period and these accounted for 0.06% of malignancies diagnosed at that institution. Others have suggested an even lower incidence of 0.02% in the USA (Oettle, 1962). Before 1980 the prevalence of classic Kaposi’s sarcoma was highest in the countries bordering the Mediterranean, with the rate being 1.8 per 100 000 person-years. These rates are high compared with the rates of less than 0.5 per 100 000 person-years observed in the USA, Northern Europe, Asia, Australia and South America (Biggar et al., 1984a; Dictor et
al., 1988a; Harnly et al., 1988; Oettle, 1962). Although rare in Northern Europe, the incidence of classic Kaposi's sarcoma was increasing among young men in the two decades before the onset of the AIDS epidemic, suggesting an infective aetiology for the disease (Dictor et al., 1988a). Classic Kaposi's sarcoma usually affects Caucasian men, with 75% of cases occurring in patients aged 60 years or older. Although the disease has been described in a variety of countries and ethnic groups, classical Kaposi's sarcoma has a predilection for persons of Mediterranean origin, especially Italians, and Ashkenazic Jews who originate from Eastern Europe (Beral, 1991; Dorffel, 1932; Oettle, 1962).

Clinical features
The classic disease is nodular in 85-90% of the cases and the aggressive clinical pattern is unusual. In a comprehensive study at the Mayo clinic in 1965, only 7 of the cohort of 70 (10%) patients had the aggressive pattern of Kaposi's sarcoma and of these 5 required amputations of the affected limb (Reynolds et al., 1965). However, in a more recent series, of the 41 patients with classic Kaposi's sarcoma 10 (24%) had an aggressive, rapidly progressive course (Friedman-Birnbaum et al., 1993). The patches, plaques and nodules are deep-red to violaceous. The feet and ankles are the most common sites of involvement for the initial lesion and in the series from the Mayo Clinic, the lower limbs were ultimately always involved (Reynolds et al., 1965). The lesions tend to occur first on the one foot and then become bilateral and spread upward (Harawi, 1989). The distal parts of the arms are the next most common site of involvement giving the descriptive "glove-and-stocking" distribution of the lesions (Harawi, 1989). Involvement of the skin of the head and neck occurs in 14% of cases and generally only occurs when there is widespread cutaneous involvement by the Kaposi's sarcoma (Cox et al., 1959; Reynolds et al., 1965).

Prognosis
Although the majority of patients with the classic form have a lifespan that is close to normal (Friedman et al., 1990), there are marked variations in the reported prognosis of patients with the disease and this is vividly illustrated in two series from the USA (Table 8-2). In the Armed Forces Institute of Pathology (AFIP) series, the Kaposi's sarcoma had a more rapid and progressive course than is generally accepted.
Table 8-1. Characteristics of the various epidemiological types of Kaposi's sarcoma.

<table>
<thead>
<tr>
<th>Type</th>
<th>Predominant Lesions</th>
<th>Mucocutaneous Distribution</th>
<th>Population at Risk</th>
<th>Age at Onset (yrs)</th>
<th>M:F Ratio</th>
<th>Clinical Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>Some patches, mostly plaques and nodules, usually rounded</td>
<td>Usually confined to lower extremities; disseminated lesions late in course of disease</td>
<td>Eastern European, Jewish, and Mediterranean backgrounds</td>
<td>50 - 60</td>
<td>10-15:1</td>
<td>Indolent, gradual increase in number of lesions often associated with lymphoedema; visceral lesions occur late, often discovered at postmortem; survival 10-15 years</td>
</tr>
<tr>
<td>Endemic African</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Benign nodular</td>
<td>Papules and nodules</td>
<td>Multiple localised tumours, most commonly seen on the legs</td>
<td>Black African adults</td>
<td>25 - 40</td>
<td>17:1</td>
<td>Indolent, resembles classical type disease; survival 8-10 years</td>
</tr>
<tr>
<td>2. Aggressive</td>
<td>Large exophytic nodules and fungating tumour</td>
<td>Most often located on the extremities</td>
<td>Black African adults</td>
<td>25 - 40</td>
<td></td>
<td>Progressive development of multiple lesions, with invasion and destruction of underlying subcutaneous tissues and bone, survival 5-8 years</td>
</tr>
<tr>
<td>3. Florid</td>
<td>Nodules</td>
<td>Widely disseminated</td>
<td>Black African adults</td>
<td>25 - 40</td>
<td></td>
<td>Rapidly progressive, locally invasive, early visceral involvement; survival 3-5 years</td>
</tr>
<tr>
<td>4. Lymphadenopathic</td>
<td>Rarely manifests lesions</td>
<td>Minimal</td>
<td>Black African children</td>
<td>2-15 (mean 3)</td>
<td>3:1</td>
<td>Rapidly progressive; survival 2-3 years</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Patches, plaques and nodules</td>
<td>Usually localised to the extremities; rarely disseminated</td>
<td>Patients on immunosuppression including renal transplant recipients</td>
<td>30 - 60 (mean 42)</td>
<td>2.3:1</td>
<td>Indolent; occasionally tumour regression after immunosuppression is discontinued</td>
</tr>
<tr>
<td>Epidemic (HIV-associated)</td>
<td>Patches, plaques, nodules often fusiform and irregular</td>
<td>Multifocal, widely disseminated, often symmetric; frequent oral lesions</td>
<td>Homosexual men (95%)</td>
<td>18 - 65</td>
<td>106:1</td>
<td>Rapidly progressive; survival 2 mo. to 5 years</td>
</tr>
</tbody>
</table>

Modified from Drotman et al. (1995) and Tappero et al. (1993).
Table 8-2. Clinical course of classical Kaposi’s sarcoma in two centres in the USA (AFIP and Mayo Clinic).

<table>
<thead>
<tr>
<th></th>
<th>Cox et al., 1959</th>
<th>Reynolds et al., 1965</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>44</td>
<td>53</td>
</tr>
<tr>
<td>Dead</td>
<td>25 (57%)</td>
<td>29 (55%)</td>
</tr>
<tr>
<td>Death due to Kaposi’s sarcoma</td>
<td>11 (44%)</td>
<td>29 (55%)</td>
</tr>
<tr>
<td>Duration of disease (yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long</td>
<td>38</td>
<td>13-32</td>
</tr>
<tr>
<td>Short</td>
<td>2</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Alive with Kaposi’s sarcoma</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Mean duration (yrs)</td>
<td>5.5</td>
<td>13</td>
</tr>
<tr>
<td>Longest duration (yrs)</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>Alive without Kaposi’s sarcoma</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Mean duration (yrs)</td>
<td>8</td>
<td>-</td>
</tr>
</tbody>
</table>

Modified from Harawi (1989).

Unfavourable prognostic features included the occurrence of multiple and rapidly developing lesions, lymph node involvement and visceral involvement, and the young age of the patient (under 45 years) (Cox et al., 1959). In some cases death is associated with the occurrence of a second malignancy that develops in 35% of these patients (Reynolds et al., 1965; Safai et al., 1980; Safai et al., 1981).

Endemic Kaposi’s sarcoma of Africa
As an entity endemic Kaposi’s sarcoma was born at a symposium held at Makerere Medical College in Kampala, Uganda in May 1961 under the auspices of the African Committee of the International Union Against Cancer. Most of the participants were workers from Africa with vast personal experiences and the meeting culminated in the publication of a collection of 23 papers (Ackerman et al., 1963).

Incidence (1)
The greatest concentration of Kaposi’s sarcoma in the world occurs in eastern equatorial Africa where Kaposi’s sarcoma accounted for, on average between 4 and
10%, of all malignancies before the onset of the AIDS epidemic (Harawi, 1989; Oettle, 1962). However, individual reports from various African countries show the percentage to range from less than 1% to more than 90%, depending on the area (Hutt, 1984a; Lothe, 1963; Oettle, 1962; Slavin et al., 1969; Templeton et al., 1973). In some countries Kaposi's sarcoma is the fourth or fifth commonest tumour in men (Hutt, 1984b). The areas that are affected are predominantly hill and open savannah bush country at an altitude of 1200 to 1500 metres in Zaire, Kenya and Tanzania (Safai, 1984), Uganda, Rwanda, Burundi, Malawi, Zambia and Zimbabwe (Desmond et al., 1991). In the AIDS era, the data from central African countries have shown significant alterations in the incidence of Kaposi's sarcoma. In Uganda Kaposi's sarcoma has caused 49% of all malignancies in men and 18% of cancers in women. This incidence in men (30.1 per 100,000 population) represents an increase of more than 10-fold since the 1950s and is about 3 times that in women (11 per 100,000) (Thijs, 1957; Wabinga et al., 1993). Interestingly the countries previously known to have the highest rates of endemic Kaposi's sarcoma are now the African countries reporting the largest number of cases of AIDS to the World Health Organisation (Anonymous, 1990).

Incidence (2)
The areas particularly endemic for Kaposi's sarcoma are northeast Zaire (now called the Democratic Republic of Congo) and northwest Uganda (west Nile district) (Fig. 8-1). From this epicentre the incidence of Kaposi's sarcoma falls radially, gradually to the south, and more precipitously to the north and the western horn of Africa (Templeton, 1981). The tumour is endemic in southern Sudan but not in Khartoum or other parts of North Africa (Hutt, 1984b). Asian and European residents do not share the increased rate that is evident in the native population (Taylor et al., 1972). Another observation made in South Africa was that the incidence of Kaposi's sarcoma was 10 times greater in the black population than among whites of the same region (Oettle, 1962). Several large series of endemic Kaposi's sarcoma have been reported. The most notable among these include those from Zaire, 230 cases (Thijs, 1957) and 299 cases (Kalengayi et al., 1984), Uganda, 339 clinical cases (Taylor et al., 1972) and 37 post-mortems (Templeton, 1972), Tanzania, 117 cases (Slavin et al., 1969), and 220 cases (Schmid, 1973). In all these series the disease...
Fig. 8-1 The proportional frequency (male and female combined) of endemic Kaposi’s sarcoma in the African continent. Modified from Hutt (1984).

exhibits the same basic clinical patterns outlined in Table 8-1. The peak age of afflicted males is one or two decades younger than in patients with classic Kaposi’s sarcoma.

Classification of Endemic Kaposi’s sarcoma
Taylor and his colleagues (1971b) described a clinical classification system for patients with endemic Kaposi’s sarcoma based on their experience in Uganda. The
disease occurs as benign nodular, florid, locally aggressive or disseminated forms (Table 8-1).

**Benign nodular**

The clinical features and prognosis of localised endemic Kaposi's sarcoma are similar to those of classic Kaposi's sarcoma. Like the classic form, endemic Kaposi's sarcoma is predominantly nodular, involves primarily the distal extremities, especially the legs, and is usually associated with lymphoedema (Slavin et al., 1969; Thijs, 1957).

The skin of the head and neck seem to be spared when the cutaneous disease is localised (Thijs, 1957). Skin lesions may occur singly or in crops and occasionally lesions regress spontaneously. The prognosis of this form of Kaposi's sarcoma is generally good with patients surviving for over 10 years after diagnosis (Armes, 1989). Lymph node or bone involvement is rare (Taylor et al., 1971b).

**Locally invasive forms**

Florid Kaposi's sarcoma is also frequently seen in adults who present with fleshy, friable, exophytic masses that often extend through tissue planes to involve periosteum and underlying bone. The closely related locally aggressive Kaposi's sarcoma is less common and presents with swelling and marked induration of the hand or foot, commonly with adjacent bony involvement (Taylor et al., 1971b). Survival in these two forms of Kaposi's sarcoma can be prolonged with chemotherapy, although the prognosis is worse than the local form. Untreated the lesions are locally destructive and may lead to death within a year (Armes, 1989).

**Disseminated Kaposi's sarcoma**

In the pre-AIDS era, disseminated or generalised Kaposi's sarcoma was very rare and occurred most commonly in younger adult and female patients (Kyalwazi, 1981). It is now the form described most commonly in patients with HIV infection. In disseminated endemic Kaposi's sarcoma skin lesions accompany widespread visceral involvement. However, in contrast to patients with AIDS, internal organ involvement (most commonly the liver, lungs, adrenals, and small intestine) in patients with endemic Kaposi's sarcoma was usually silent and discovered only at
postmortem examination (Desmond et al., 1991). The prognosis of this form of endemic Kaposi's sarcoma is poor.

Endemic Kaposi's sarcoma in childhood
The lymphadenopathic form of endemic Kaposi's sarcoma is a variant that occurs in African children. Skin lesions are either absent or sparse and then atypical in site and form. The lymph nodes are however characteristically infiltrated by massive, symmetrical tumour deposits. These children usually succumb to the disease within one year of the diagnosis (Armes, 1989). Kaposi's sarcoma in children therefore has several distinctive features: (1) occurrence of lymph nodes in the absence of skin involvement; (2) predilection for eyelids, lacrimal glands, jaw, parotid, and other salivary glands; (3) poor patient survival; (4) and a lower male-to-female ratio than seen in adult Kaposi's sarcoma (Olweny et al., 1976).

Prognosis
It has been reported that the prognosis in endemic Kaposi's sarcoma depends on the clinical pattern at presentation (Templeton et al., 1975). The age and sex of patients influence the pattern of disease likely to be found but the prognosis for a given clinical pattern was the same in both sexes and at different ages (Harawi, 1989; Templeton et al., 1975). The only deaths among the patients with the nodular form of the disease were due to intercurrent sepsis. The mean 3-year survival of patients with locally aggressive disease was 64%. All patients with generalised Kaposi's sarcoma died of their disease after a mean period of 2 years (Templeton et al., 1975).

Epidemiology of Kaposi's sarcoma in Africa in the AIDS era
The onset of the HIV epidemic has had a profound impact on the epidemiology of Kaposi's sarcoma in Africa. The first cases of Kaposi's sarcoma in black African patients were reported from Belgium. Clumeck et al. (1984) described 3 cases of Kaposi's sarcoma in 22 Zairean patients with AIDS. Another report from Zambia described a group of patients younger than those with endemic Kaposi's sarcoma with atypical lesions such as generalised symmetrical lymphadenopathy, oropharyngeal and gastrointestinal tract lesions, respiratory distress and gross
weight loss. Skin lesions were seen in unusual sites such as the face, trunk and genitalia (Bayley et al., 1985). This group of atypical Kaposi's sarcoma patients compared to those with endemic Kaposi's sarcoma are younger (Armes, 1989), usually are of a higher socioeconomic class, and include a relatively higher number of female patients (Coker et al., 1986). It is also characterised by a poor response to conventional therapy and early deaths (Bayley et al., 1985). Subsequent reports originating from other parts of Africa confirmed that Kaposi's sarcoma was part of the clinical spectrum of HIV-related diseases in Africa and current data suggested that approximately 5-15% of African AIDS patients present with Kaposi's sarcoma (Desmond et al., 1991; Piot et al., 1984; Van de Perre et al., 1984).

Serology in the two forms of Kaposi's sarcoma

Serologic studies have made it apparent that two populations of Kaposi's sarcoma patients now exist in Africa: "atypical" or epidemic Kaposi's sarcoma associated with HIV-1 infection and endemic Kaposi's sarcoma which is not associated with retroviral infection. In the serologic study reported by Bayley et al. (1985), the enzyme-linked immunosorbent assays (ELISA) for HIV were positive in 95% of African patients with epidemic Kaposi's sarcoma. In contrast only 16% of patients with endemic Kaposi's sarcoma were HIV-positive. In other endemic areas serology for HIV-1 was consistently negative (Biggar et al., 1984c; Otu, 1988). As indicated earlier, patients with "atypical" Kaposi's sarcoma had lesions in unusual sites such as lymph nodes, liver, spleen, lungs, and gastrointestinal tract. Kaposi's sarcoma has also been described in HIV-2 infection. In a recent report 4 of 17 (24%) AIDS patients had Kaposi's sarcoma (Clavel et al., 1987). Kaposi's sarcoma in African patients can therefore occur in patients without HIV or in patients with either HIV-1 or HIV-2 infection.

Changes in the epidemiology

In areas with a high prevalence HIV-1 infection, there are now more cases of epidemic than endemic Kaposi's sarcoma and this has been associated with a marked change in the age and sex distribution of Kaposi's sarcoma in these countries. Wabinga (1993) compared Kaposi's sarcoma patients diagnosed by
pathology in Uganda from 1964 to 1968 with those from 1984 to 1987 and found that Kaposi's sarcoma patients in the post-AIDS era were younger and more likely to be women. Interestingly, in 1964-1968 patients who developed generalised disease were more likely to be women but by 1983-1987, men were more prone this form of the disease. Some of the demographic changes in Kaposi's sarcoma in Uganda are shown in Table 8-3. The demographic changes in Kaposi's sarcoma have been noted in other African countries. In Malawi a six-fold increase in Kaposi's sarcoma

### Table 8-3. Changing demography of Kaposi's sarcoma in Uganda

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (no.)</td>
<td>314</td>
<td>407</td>
<td>362</td>
</tr>
<tr>
<td>Peak age (yrs)</td>
<td>40-49</td>
<td>20-29</td>
<td>20-29</td>
</tr>
<tr>
<td>Male:Female</td>
<td>14:1</td>
<td>5:1</td>
<td>4:1</td>
</tr>
<tr>
<td>Disseminated disease (%)</td>
<td>5</td>
<td>47</td>
<td>77</td>
</tr>
</tbody>
</table>

Adapted from Desmond et al. (1991).

### Table 8-4. Endemic vs. Epidemic Kaposi's sarcoma in Zambia

<table>
<thead>
<tr>
<th></th>
<th>Endemic</th>
<th>Epidemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak age</td>
<td>5&lt;sup&gt;th&lt;/sup&gt; decade</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; decade</td>
</tr>
<tr>
<td>Females (%)</td>
<td>5-12</td>
<td>25</td>
</tr>
<tr>
<td>Pattern</td>
<td>Nodular, Aggressive</td>
<td>Disseminated</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>Absent</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>Excellent</td>
<td>Poor</td>
</tr>
<tr>
<td>Course</td>
<td>Indolent</td>
<td>Fatal</td>
</tr>
<tr>
<td>HIV + (%)</td>
<td>25</td>
<td>90</td>
</tr>
<tr>
<td>Relative incidence (%)</td>
<td>1975-1982: 80</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>1983: 50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>1984: 40</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>1985: 25</td>
<td>75</td>
</tr>
</tbody>
</table>

Adapted from Bayley (1991), Downing et al. (1984)
among women has been noted from 1983 to 1988 and the male to female ratio declined from 10:1 to 3:1 (Liomba et al., 1989). In Zimbabwe, the male to female ratio was 4.6:1 with the mean age 34 years in men and 31 years in women (Latif et al., 1989). In Uganda the comparative gender ratio is 2:1 and the peak ages 35-39 years in males and 25-29 years in females (Wabinga et al., 1993). The Zambian experience with Kaposi’s sarcoma is shown in Table 8-4.

**Epidemic (AIDS-associated) Kaposi’s sarcoma**

Since its initial description in July 1981 in association with *Pneumocystis carinii* pneumonia in homosexual men, Kaposi’s sarcoma has remained one of the major hallmarks of AIDS (Friedman-Kien et al., 1981). In 1985 and 1986 Kaposi’s sarcoma occurred in 28-33% of patients with AIDS in the USA (Centers for Disease Control, 1986; Haverkos et al., 1985a). Kaposi’s sarcoma was the primary disease in 25% of the AIDS cases and in 15% it was the only manifestation of the illness (Centers for Disease Control, 1986). On the basis of Kaposi’s sarcoma incidence rates in the USA from 1973 to 1979, the overall risk of Kaposi’s sarcoma in AIDS patients is more than 20,000 times that of the general population and 300 times that of other immunosuppressed patients (Beral et al., 1990). The clinical patterns of epidemic Kaposi’s sarcoma are a combination of noninvasive mucocutaneous lesions and of disseminated disease.

**At risk groups**

**Early reports**

Kaposi’s sarcoma varies markedly in incidence in the different groups at risk for AIDS. Early data from the Centers for Disease Control (CDC) in Atlanta, Georgia in the USA showed that Kaposi’s sarcoma occurred in 36% of homosexual men compared to 10% of Haitians, 4.3% of intravenous drug abusers and 1.4% of haemophiliacs (Haverkos et al., 1985a). Kaposi’s sarcoma occurred in 12.5% of female drug abusers while ethnicity did not alter the incidence of the disease in the various risk groups (De Jarlais et al., 1984). The majority (95%) of Kaposi’s sarcoma cases occur in HIV-infected homosexual men. Other important observations are that the infants of mothers with Kaposi’s sarcoma and perinatally acquired HIV have in no instance developed Kaposi’s sarcoma (Gutierrez-Ortega et al., 1989). There are
some reports, however, of heterosexual couples in which both partners had AIDS and developed Kaposi's sarcoma (Bary et al., 1991; Janier et al., 1990).

Later reports

More recent data, however, show a lower incidence of Kaposi’s sarcoma in homosexual males but it remains the group at greatest risk for Kaposi’s sarcoma (Table 8-5). Male patients account for 98.3% of all HIV-related Kaposi’s sarcoma (Drotman et al., 1995). This unequal distribution of Kaposi’s sarcoma among persons with AIDS provides an important clue to the aetiology of Kaposi’s sarcoma. Remarkably similar distributions of Kaposi’s sarcoma have been reported from the United Kingdom, Italy, Spain, and Australia (Beral, 1991; Serraino et al., 1992).

**Table 8-5.** Number of adult patients with AIDS who develop Kaposi’s sarcoma, by risk group and gender in the USA until 1994.

<table>
<thead>
<tr>
<th>HIV Risk Group</th>
<th>Gender</th>
<th>% with KS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homosexual/Bisexual</td>
<td>Male</td>
<td>19.1</td>
</tr>
<tr>
<td>Homosexual/Bisexual and intravenous drug abuser</td>
<td>Male</td>
<td>15.7</td>
</tr>
<tr>
<td>Born in Caribbean/Africa</td>
<td>Male</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>4.2</td>
</tr>
<tr>
<td>Heterosexual partner of person born in Caribbean/Africa</td>
<td>Male</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2.5</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>Male</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1.6</td>
</tr>
<tr>
<td>Haemophilia</td>
<td>Male</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>Male</td>
<td>14.1</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Adapted from Drotman et al. (1995).
Kaposi's sarcoma in homosexual men

Declining proportion of Kaposi's sarcoma

The proportion of homosexual men who develop Kaposi's sarcoma has been decreasing, possibly as the result of practice of safer sex procedures (Roth, 1991). In 1981 63% of homosexual men with AIDS in San Francisco had Kaposi's sarcoma while in 1985 this incidence was 24% (Drew et al., 1988). The relative incidence of AIDS-associated Kaposi's sarcoma has been decreasing in all patients at risk: Kaposi's sarcoma was the initial diagnosis in 33% of the first 1000 Centers for Disease Control (CDC) reported cases compared to only 10% of 1100 cases reported to the CDC between January and August 1987 (Des Jarlais et al., 1987). At the onset of the epidemic Kaposi's sarcoma occurred in 40% of patients with AIDS (all risk groups) but this was down to 28% by 1985 (Haverkos et al., 1985a). The relative decline using a logistic model has been 26% per year in homosexual men and 20% per year in the other AIDS risk groups (Beral et al., 1990) (Fig. 8-2). However, as more HIV-infected patients are diagnosed with AIDS the actual number of cases and hence the incidence of Kaposi's sarcoma has continued to increase because the latter is calculated from prospectively collected data from cohort

Fig. 8-2 Percentage of AIDS patients with Kaposi's sarcoma by year of diagnosis of AIDS and risk group for period 1983-1988. Modified from Beral et al. (1990).
populations followed up over time with known infection rates (Chow et al., 1989; Jacobson et al., 1990).

Problems with the interpretation of the perceived declining incidence

The variations in the occurrence of Kaposi's sarcoma in AIDS patients may be artifactual due to different analytical approaches, or may be a real reflection of differences in exposure or host susceptibility (Jacobson et al., 1995). A problem in reviewing population rates is that the size of the populations at risk are generally unknown. In addition, inferences based on using the proportion of Kaposi's sarcoma among AIDS cases need to account for the relative increases of other AIDS diagnoses. If, for example the number of other opportunistic AIDS infections increases each year, the relative number of Kaposi's sarcoma among all cases would decrease (Jacobson et al., 1995). Plausible explanations for the observed temporal differences in the occurrence of Kaposi's sarcoma exist. Attenuation of exposure to the aetiological agent may have occurred in specific populations. This together with a fixed latency between agent and disease would result ultimately in a decrease in the number of cases (Jacobson et al., 1995). Also, given the high mortality of Kaposi's sarcoma with more than 50% of patients dying within two years of presenting with an AIDS-defining illness (Bacchetti et al., 1988; Bindels et al., 1991; Friedland et al., 1991; Jacobson et al., 1993; Lemp et al., 1990; Rothenberg et al., 1987), HIV-1 infected individuals presenting with another illness may die prior to developing Kaposi's sarcoma (Jacobson et al., 1995).

Early in the epidemic, AIDS reporting was more comprehensive in that surveillance data were updated with each illness that an AIDS patient developed. Subsequently, for the most part, the only illnesses reported to the public health authorities are those apparent when AIDS is diagnosed. Although underreporting could play a role in the decrease in the reported cases of Kaposi's sarcoma, a study in San Francisco that did extensive follow-up of all AIDS patients failed to confirm underreporting of Kaposi's sarcoma (Rutherford et al., 1989). In the Multicenter AIDS Cohort Study, the decline in the percentage of patients with Kaposi's sarcoma was minimal (Jacobson et al., 1990). Some authors have attributed part of the decline to the shorter incubation period for AIDS when the manifestation is Kaposi's sarcoma.
rather than *Pneumocystis carinii* pneumonia (Lifson *et al.*, 1990a). The first patients to be diagnosed in the AIDS epidemic would be the ones with the shortest incubation periods and the ones most likely to have Kaposi's sarcoma. This phenomenon explains that as persons with the longer incubation periods are diagnosed the percentage with Kaposi's sarcoma would seem to decrease (Drotman *et al.*, 1995). Other authors have suggested additional hypotheses to explain the phenomenon of apparent decline in the proportion of patients with AIDS who develop Kaposi's sarcoma (Beral *et al.*, 1990; Centers for Disease Control, 1987; Haverkos *et al.*, 1985b; Haverkos, 1990; Lifson *et al.*, 1990b; Reynolds *et al.*, 1990; Rutherford *et al.*, 1990; Winkelstein, Jr. *et al.*, 1988). Large decreases in the incidence of Kaposi's sarcoma in AIDS patients have also been reported from other countries such as Italy (Serraino *et al.*, 1992).

**Geographic variation in incidence: Homo- and bisexual males**

An important observation is that the risk of Kaposi's sarcoma is not geographically uniform in homosexual men with AIDS. Therefore, in the USA and UK, homosexual and bisexual men with AIDS are more likely to have Kaposi's sarcoma if they live in foci of the AIDS epidemic. In the USA, the incidence ranges from 3% in Kansas and 6% in Iowa, to 30% in California and 31% in New York (Beral *et al.*, 1990). It has also been found that homosexual men who resided in either California or New York are at greater risk for the development of Kaposi's sarcoma than are homosexuals residing in other areas (Schechter *et al.*, 1991). Moreover, it was found in Vancouver that men were more likely to have Kaposi's sarcoma if they had had sexual relations with a man from San Francisco, Los Angeles or New York (Archibald *et al.*, 1992). Homosexual men from Baltimore, Pittsburg and Chicago were also more likely to have Kaposi's sarcoma if their partners were from San Francisco (Drotman *et al.*, 1995). In the United Kingdom, homosexual and bisexual men from London are twice as likely to have Kaposi's sarcoma as are men from other areas (Beral *et al.*, 1991). Also in the United Kingdom, homosexual men were also more likely to have Kaposi's sarcoma if their partners were from the USA or Africa (Beral *et al.*, 1991). A similar pattern of Kaposi's sarcoma is also seen in among persons who acquired HIV infection through other routes, such as sharing needles or heterosexual contact, but the relative risks are not as high (Drotman *et al.*, 1995). Geographical
clustering has also been observed in other countries (Pedersen et al., 1990; Selik et al., 1987). Women with AIDS were four times more likely to have Kaposi's sarcoma if their partners were bisexual males rather than intravenous drug abusers (Beral et al., 1990; Biggar et al., 1985; Biggar et al., 1989).

**Geographic variation in incidence: Heterosexual persons**

The risk of Kaposi's sarcoma is especially high in HIV-positive subjects who originate in Africa or the Caribbean countries (Table 8-6). The proportion of heterosexual AIDS patients who are reported to have Kaposi's sarcoma ranges from 8-18% in Africa and 6-9% in the Caribbean (Beral, 1991). This contrasts with the rates in AIDS patients born in the USA or UK, in whom the incidence Kaposi's sarcoma is less than 1% (Beral, 1991). The incidence of Kaposi's sarcoma was high in Africa before the onset of the AIDS epidemic. It may be that African subjects are asymptomatic carriers of the agent that causes Kaposi's sarcoma. The incidence of Kaposi's sarcoma is especially high in HIV-positive subjects who originate in Africa or the Caribbean countries (Table 8-6). The proportion of heterosexual AIDS patients who are reported to have Kaposi's sarcoma ranges from 8-18% in Africa and 6-9% in the Caribbean (Beral, 1991). This contrasts with the rates in AIDS patients born in the USA or UK, in whom the incidence Kaposi's sarcoma is less than 1% (Beral, 1991). The incidence of Kaposi's sarcoma was high in Africa before the onset of the AIDS epidemic. It may be that African subjects are asymptomatic carriers of the agent that causes Kaposi's sarcoma.

| Table 8-6. Kaposi's sarcoma in heterosexual AIDS patients by country of origin |
|---------------------------------|-----------------|-----------------|
| Country of origin               | Incidence of KS (%) | Reference        |
| **Africa**                      |                  |                 |
| Rwanda                          | 18               | Van de Perre et al., 1984 |
| Zaire                          | 16               | Piot et al., 1984 |
| Zaire (Resident in UK)          | 14               | Clumeck et al., 1984 |
| Africa (Resident in Belgium)    | 13               | Beral et al., 1991 |
| Africa (Resident in USA)        | 8                | Beral et al., 1990 |
| **Caribbean**                   |                  |                 |
| Haiti                           | 9                | Beral et al., 1990 |
| Excluding Haiti                 | 6                | Beral et al., 1990 |
| **USA/Europe**                  |                  |                 |
| USA                             | 1                | Beral et al., 1990 |
| UK                              | 0                | Beral et al., 1991 |
sarcoma in the Caribbean before the onset of the AIDS epidemic is largely unknown. In Puerto Rico the incidence of Kaposi's sarcoma was higher than in the rest of the USA (Biggar et al., 1984a) and it may well be that the asymptomatic carrier rate is also higher than in the US population accounting for the high risk in this group (Beral, 1991).

Risk factors for Kaposi's sarcoma in male homosexuals
Kaposi's sarcoma is rarely diagnosed among those who acquired the disease parenterally, haemophiliacs and intravenous drug abusers (Table 8-5) (De Jarlais et al., 1984; Haverkos et al., 1990; Jaffe, 1990; Selik et al., 1987). Concomitant with the AIDS epidemic, Kaposi's sarcoma has been reported in young male homosexuals not infected with HIV-1 (Friedman-Kien et al., 1990). Results from case-control and cohort studies among homosexual men infected with the HIV-1 have provided evidence for behavioural risk factors for the disease (Archibald et al., 1992; Goedert et al., 1987; Haverkos et al., 1985b; Jacobson et al., 1990; Jaffe et al., 1983; Marmor et al., 1982). In the earliest studies there were significant but nonspecific, associations of Kaposi's sarcoma with sexual behaviour including the number of sexual partners, history of sexually transmitted diseases and number of partners from bathhouses. In addition there was an association with the use of recreational drugs (Haverkos et al., 1985b; Jaffe et al., 1983; Klepp et al., 1978). The postulation of nitrite inhalant abuse predisposing to Kaposi's sarcoma arose from its use as a sexual stimulant by homosexual men (Haverkos et al., 1990). Although some investigators have demonstrated an association between nitrite inhalant use and Kaposi's sarcoma (Haverkos et al., 1985b; Marmor et al., 1982), this finding has not been confirmed by subsequent studies of larger well-defined populations (Armenian et al., 1993; Goedert et al., 1987; Jacobson et al., 1990; Lifson et al., 1990a; Polk et al., 1987). Similar associations of Kaposi's sarcoma with other types of recreational drugs such as marijuana and hashish, make this causal hypothesis less plausible (Archibald et al., 1992). It has been suggested, that nitrites, which are vasodilators, may facilitate the transmission of an infectious agent during sexual intercourse (Archibald et al., 1992). Although, the association between Kaposi's sarcoma and increased sexual activity has been demonstrated in most studies, specific risk behaviour has not been consistently identified (Jacobson et al., 1995). Several reports have
demonstrated an association with sexual activity in which exposure to faeces was likely (Beral et al., 1990; Jacobson et al., 1990) but this observation was not consistently corroborated (Archibald et al., 1990; Elford et al., 1992; Lifson et al., 1990a; Matondo, 1992). As an indicator of sexual activity, history of prior sexually transmitted infections was most consistently associated with Kaposi’s sarcoma (Haverkos et al., 1985b). In a recent study the risk of Kaposi’s sarcoma was shown to be additive with the number of sexually transmitted infections (Armenian et al., 1993). In the same study it was found that any partner from the West Coast of America, use of inhaled nitrites, and the number of male sexual partners in the preceding two years also increased the risk of Kaposi’s sarcoma in HIV-1 infected homosexual men (Armenian et al., 1993). These associations with sexual activity and infections are consistent with a putative infective cofactor that is sexually transmitted. In addition to the sexual aspects of Kaposi’s sarcoma transmission, Kaposi’s sarcoma is more frequent in among whites than among black AIDS sufferers (Centres for Disease Control, 1982; Haverkos et al., 1982).

Incubation period of Kaposi’s sarcoma

Kaposi’s sarcoma is usually not a late complication of the immunocompromised state. In 80% of cases in which Kaposi’s sarcoma occurs, it is the presenting symptom (Lifson et al., 1990a). Studies of transfusion recipients (Beral et al., 1990) and homosexual men (Lifson et al., 1990a) indicate that the time between HIV infection and the onset of AIDS is shorter for those with Kaposi’s sarcoma than those with other manifestations of AIDS. When the time between transfusion and the onset of AIDS was compared between those who had Kaposi’s sarcoma and Pneumocystis carinii pneumonia, the incubation period was consistently found to be 6.6 month longer in the latter (Beral et al., 1990).

The initial lesions of AIDS-associated Kaposi’s sarcoma occur in many different sites and systemic spread is common (Hutt, 1984b). The earliest skin lesions are often difficult to diagnose both clinically and histopathologically (Gottlieb et al., 1982).
Iatrogenic Kaposi's sarcoma

The first cases of Kaposi's sarcoma related to the use of immunosuppressive agents were reported soon after renal transplantation became clinically accepted as a form of renal replacement treatment (Hardy et al., 1976; Siegel et al., 1969). Approximately 15% of cases of Kaposi's sarcoma seen in Europe and North America prior to the onset of the AIDS epidemic were due to immunosuppressive treatment (Harwood et al., 1979a; Klepp et al., 1978). The very first case of Kaposi's sarcoma in a renal transplant recipient provides some clues as to the epidemiological nature of the disease that was to unfold subsequently.

The first case

The first case of Kaposi's sarcoma to occur following renal transplantation was a 35-year old black female patient suffering from chronic renal failure due to chronic pyelonephritis (Siegel et al., 1969). The patient received a renal allograft that functioned well initially but was complicated by the development of mild acute rejection, which responded to local irradiation and high-dose steroids. She had a second rejection episode 4 months after the transplant. This proved to be more resistant to treatment requiring 3 successive doses of cactinomycin, and two courses of local irradiation before the renal function stabilised at a creatinine clearance of 35 ml/min. The patient had several infective complications and pre-terminally she developed a serious Pseudomonas and Aerobacter sinus infection that induced her physicians to withdraw all immunosuppression and resume haemodialysis. She developed acute and severe respiratory distress eight months after the transplant and died despite aggressive attempts at resuscitation. At postmortem examination she was found to have extensive visceral Kaposi's sarcoma involving the lungs, oesophagus, bladder, stomach, mediastinal and retroperitoneal lymph nodes. Unusually, no skin lesions were noted either ante- or postmortem (Siegel et al., 1969).

Siegel and his colleagues (1969) recognised the uniqueness of their case because they knew Kaposi's sarcoma to be a disease of elderly men of Caucasian origin with a benign course in general. In this instance, the patient was young, female and black while the disease followed a very aggressive course. The authors made the astute suggestion that the tumour was related "... to the alterations in the immune
status of the host". They observed that Kaposi's sarcoma not uncommonly occurred with other malignancies (Bluefarb, 1957) that were associated with "... reduced or abnormal immune response, similar in many ways to that produced by the use of immunosuppressants ..." (Smith, 1968). Another important association that they made was that between viral infection and certain tumors. Siegel et al. (1969) stated "... virus-like particles have been reported in the plasma of patients with reticulum cell sarcoma, Hodgkin's disease, lymphomas, and a variety of leukaemias, ..." (Newell et al., 1968). In addition they noted that Henle et al. (1968) had demonstrated the presence of high titres of anti-Epstein Barr Virus (EBV) in 100% of Burkitt's lymphoma patients. They predicted, "If there are oncogenic viruses with pathogenicity in man, it seems very likely that we will see an increasing incidence of neoplasia associated with homograft rejection in patients undergoing immunosuppressive therapy" (Janier et al., 1990). And how correct they were in their predictions!

Two other early reports
Other cases of Kaposi's sarcoma were described in the early and mid-1970's. In the earlier report 2 cases were described (Myers et al., 1974), both patients were young and had Kaposi's sarcoma soon after transplantation (the 36-year old female patient developed the disease at 9 months after transplant and the 27-year old male at 7 months); the race/ethnicity of the patients was not mentioned. The female patient had non-Hodgkin's lymphoma of the brain but was free of Kaposi's sarcoma when she died of Pseudomonas aeruginosa septicaemia 31 months after transplantation. Azathioprine was discontinued but she maintained renal function albeit impaired until her death. In the male patient, the skin lesions of Kaposi's sarcoma eventually disappeared but only after all immunosuppressive treatment was discontinued. Hardy et al. (1976) described a 48-year old Puerto Rican patient who developed Kaposi's sarcoma 9 months after renal transplant. Azathioprine was discontinued which led to complete regression of the lesions.

First series
Penn compiled the first series of cases of de novo Kaposi's sarcoma to occur following organ transplantation in the late 1970s. This series highlighted the high
incidence of Kaposi's sarcoma in organ transplant recipients in whom it comprised 3% of all \textit{de novo} malignancies (Penn, 1979a), giving rise to the description of this epidemiological type of Kaposi's sarcoma. The Denver Transplant Tumor Registry that was initiated by the late Dr Israel Penn collected information on malignancies in organ transplant recipients from transplant centres around the world. By 1978 the Registry had collected details on 630 \textit{de novo} malignancies that had occurred in 604 organ transplant recipients, most of whom had received renal allografts. Of these, 20 (3.2%) were Kaposi's sarcoma. In comparison the incidence of Kaposi's sarcoma in the general population in the USA was less than 0.6% of all cancers (Caro, 1975). It was also noted that the average age of 42 years (range: 23 to 59) in these patients was considerably less than that of patients who had classic Kaposi's sarcoma in whom the peak incidence was in the seventh decade but comparable to those patients who had African (endemic) Kaposi's sarcoma in whom the disease peaked in the fourth decade (\textit{vide supra}) (Caro, 1975). Penn (1979) also noted that the male preponderance of iatrogenic Kaposi's sarcoma (with a ratio of 2.3:1) was considerably less than that of the classic type (with a ratio of 15:1) (Templeton, 1981). In this initial report a spectrum of ethnic and racial groups, including black patients, were found to be affected. However, of the 20 cases in this report, 2 were white South Africans of Portuguese descent. Also noted, were concomitant malignancies in two patients with non-Hodgkin's lymphoma and colonic cancer, respectively. The patients were all heavily immunosuppressed.

\textbf{Steroids and Kaposi's sarcoma}

Although Kaposi's sarcoma has been associated with a spectrum of patients receiving chronic immunosuppressive therapy, beside that for organ transplantation (Gange \textit{et al}., 1978; Kapadia \textit{et al}., 1977; Klein \textit{et al}., 1974; Leung \textit{et al}., 1981), the number of cases of steroid-induced Kaposi's sarcoma reported in the literature only totaled 18 by 1987 (Schulhafer \textit{et al}., 1987). The male to female ratio in the latter report was 4:1 and all the patients, but 2, were aged more than 60 years. The majority of these patients presented with lesions on the legs typical of sporadic Kaposi's sarcoma. The course of the disease was benign with only 2 deaths directly due to the Kaposi's sarcoma. A study from Israel of patients on steroids demonstrated a genetic susceptibility in persons of Italian and Mediterranean
descent (Trattner et al., 1993). The number of patients on steroid immunosuppression who have Kaposi's sarcoma is very small if the extent of the use of steroids for a variety of medical conditions is taken into consideration.

**Organ transplant recipients**

Most of the patients on prolonged immunosuppressive therapy at present are recipients of organ transplants (Harwood et al., 1979a; Myers et al., 1974). It has been estimated that approximately 16% of these patients develop *de novo* malignancies at an average of 37 months after transplantation. If non-melanoma skin malignancies and *in-situ* carcinoma of the cervix are excluded, then malignant lymphoma accounts for 25% of these cancers and Kaposi's sarcoma some 5%. Kaposi's sarcoma is the first malignancy to appear, presenting, on average, 16 months after transplantation. Malignant lymphomas are the next neoplasms to appear, presenting at a mean of 32 months (Harawi, 1989). Considering the number of patients receiving immunosuppressive therapy, the overall risk of developing iatrogenic Kaposi's sarcoma is very small (Klepp et al., 1978). Other factors, including genetic susceptibility and the prevalence of human herpesvirus 8 (HHV-8) in the community, are likely to potentiate the effect of the immunomodulating drugs (Harawi, 1989). The genetic susceptibility is supported by the data of Harwood et al. (1979b) who report 7 cases of iatrogenic Kaposi's sarcoma among 44 cases of Kaposi's sarcoma. All 7 patients with iatrogenic Kaposi's sarcoma were either Jewish or of Mediterranean ancestry, as were 40 of the 44 patients with all types of Kaposi's sarcoma. There were four patients with Kaposi's sarcoma following renal transplantation in a cohort of 100 recipients of similar ethnic background *i.e.* Jewish or Mediterranean ancestry. This represented a 400- to 500-fold increase in the incidence of Kaposi's sarcoma in renal allograft recipients compared with a control population of the same ethnicity (Harwood et al., 1979b).

**Highest incidence**

Saudi Arabia currently has the highest incidence of iatrogenic Kaposi's sarcoma ever reported (Akhtar et al., 1984; Qunibi et al., 1993). The incidence of Kaposi's sarcoma in renal allograft recipients was 5.3% of 283 patients transplanted over 11 years (Qunibi et al., 1993). This is much higher than the 0.18% - 0.3% in recipients in the
USA (Penn, 1986) or the 1.6% in a recent Italian study (Montagnino et al., 1994). In the series of renal transplant recipients from Saudi Arabia, Kaposi's sarcoma accounted for 87.5% of all malignancies! (Qunibi et al., 1993). In Britain, the USA and Australasia Kaposi's sarcoma is far less common than transplant-associated lymphoma (Kinlen et al., 1981; Penn, 1988). If the crudely calculated incidence of 28 per 100 000 population of Kaposi's sarcoma in the Saudi population is correct, Kaposi's sarcoma may be more common in this population than in other Mediterranean people. The male to female ratio was 1.5:1, which was similar to the ratio of patients receiving renal allografts (Qunibi et al., 1993). The mean interval after transplantation to the occurrence of the Kaposi's sarcoma was 15.6 months.

Epidemiological variables
The mean age of patients with iatrogenic Kaposi's sarcoma is 42 years and the male to female ratio 2:1. This ratio is similar to the gender ratio of the patients undergoing renal transplantation. Unlike the endemic or classic Kaposi's sarcoma there is no marked male excess of iatrogenic Kaposi's sarcoma. Lesions tend to occur soon after transplantation and the disease process can be reversed or at least halted by the withdrawal of the immunosuppressive therapy (Penn, 1988). This suggests that there may be symptom-free carriers of the causal agent and that immunosuppression results in clinical expression of the disease in carriers. Thus, an individual's immunological status probably determines whether Kaposi's sarcoma is expressed clinically and also the severity of the disease as well as the anatomical distribution of the associated lesions (Beral, 1991). Of the 68 cases of post-organ transplantation Kaposi's sarcoma recently reported, 72% had involvement limited to the skin and mucosa, while the remaining had visceral organ involvement. The outcome of the two groups was also markedly different with 51% of the former going into remission on therapy, compared to only 16% of those with visceral organ involvement (Penn, 1986). The mean duration of the therapy was 61 months if the patients received combination therapy (Gange et al., 1978). This is almost double compared to the 32 months in the present study.
**Table 8-7** A comparison of the largest series of posttransplant Kaposi's sarcoma reported with the experience in the present study.

<table>
<thead>
<tr>
<th>Year Reported</th>
<th>No. of Patients</th>
<th>Incidence (Range) mo</th>
<th>Latency (Range) 1 year</th>
<th>M:F Ratio</th>
<th>Mean Age (Range) yrs</th>
<th>Mucocutaneous Disease</th>
<th>Benign Disease¹ (%)</th>
<th>% of all Cancer²</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saudi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>12</td>
<td>3.4%</td>
<td>13.6 (4-48)</td>
<td>NS</td>
<td>2:1</td>
<td>36.9 (16-23)</td>
<td>91%</td>
<td>42</td>
<td>NS Al Sulaiman et al., 1987</td>
</tr>
<tr>
<td>1988</td>
<td>14</td>
<td>5.30%</td>
<td>12.5 (1-37)</td>
<td>67%</td>
<td>1.8:1</td>
<td>38.6 (25-55)</td>
<td>93%</td>
<td>64</td>
<td>87.5 Qunibi et al., 1988</td>
</tr>
<tr>
<td>1993</td>
<td>25</td>
<td>4%</td>
<td>15.6 (1-63)</td>
<td>62%</td>
<td>1.5:1</td>
<td>39 (18-56)</td>
<td>92%</td>
<td>77</td>
<td>70 Szende et al., 1997</td>
</tr>
<tr>
<td>1994</td>
<td>35</td>
<td>4.7%</td>
<td>15.9 (3-69)</td>
<td>NS</td>
<td>2:1</td>
<td>40 (11-63)</td>
<td>86%</td>
<td>76</td>
<td>76 Al Sulaiman MH et al., 1994</td>
</tr>
<tr>
<td>1997</td>
<td>39</td>
<td>4.8%</td>
<td>15.9 (3-69)</td>
<td>NS</td>
<td>2.5:1</td>
<td>40 (11-63)</td>
<td>87%</td>
<td>76</td>
<td>76 Shaheen et al., 1997</td>
</tr>
<tr>
<td>CTTTR</td>
<td></td>
<td></td>
<td>16 (4-53)</td>
<td>NS</td>
<td>2.3:1</td>
<td>42² (43-67)</td>
<td>90%</td>
<td>55</td>
<td>4.9 Penn, 1979b</td>
</tr>
<tr>
<td>1997</td>
<td>356</td>
<td>-</td>
<td>21 (1-225.5)</td>
<td>46%</td>
<td>3:1</td>
<td>43 (4.5-67)</td>
<td>84%</td>
<td>60</td>
<td>5.7 Penn, 1997</td>
</tr>
<tr>
<td>Stellenbosch</td>
<td></td>
<td></td>
<td>32 (2.9-228)</td>
<td>38%</td>
<td>1:1⁴</td>
<td>42 (27-54)</td>
<td>100%</td>
<td>71</td>
<td>65.6 Present Study</td>
</tr>
</tbody>
</table>

¹ Benign disease is limited to the skin and/or lymph nodes
² Excludes non-melanoma skin malignancies and in-situ carcinoma of the cervix.
³ NS is not specified
⁴ Corrected for the number of females transplanted
⁵ Age at transplantation

**COMPARATIVE EPIDEMIOLOGY**

The largest series of cases of Kaposi's sarcoma in organ transplant recipients are compared to the present study (Table 8-7). The Saudi's have the largest single centre experience while Dr Penn has accumulated the largest collection of cases from around the world.

**Saudi experience.**

Contributions to the Saudi experience have been made by several authors. Al-Sulaiman *et al.* (1987) were the first to report the unusually high incidence of Kaposi's sarcoma in the native Arab population treated at the Armed Forces Hospital in Riyadh. Among 350 renal transplant patients, 12 (3.4%) developed Kaposi's sarcoma. The mean age of patients who had Kaposi's sarcoma was 36.9 years and of the 12 patients, 4 were females giving a gender ratio of 2:1. In the following year, Qunibi *et al.* (1988) of the King Faisal Specialist Hospital also in Riyadh, reported on
their experience. Among 263 renal transplant patients treated over 11 years, 14 cases of Kaposi’s sarcoma were identified, an incidence of 5.3% with the lesion accounting for 87.5% of all tumours in this cohort. On the other hand the overall incidence Kaposi’s sarcoma in renal transplant recipients in Western countries has been reported to be 0.4% (Odajnyk et al., 1985). In a subsequent report, 5 years later, Qunibi et al. (1993), confirmed the exceptionally high incidence of Kaposi’s sarcoma in his patients. In the updated report, there were 25 (4%) patients who had Kaposi’s sarcoma after renal transplantation in a cohort of 630 recipients. Both cadaveric and living donor renal allograft recipients were affected. Triple therapy and azathioprine were used as immunosuppression.

In a follow-up report from the Riyadh Armed Forces Hospital, Al-Sulaiman and Al-Khader (1994), found that the incidence of Kaposi’s sarcoma among their renal transplant patients was 4.7% (35 cases out of 750 renal transplant recipients). In their patients the tumour accounted for 76% of all malignancies. A further update by the same group reported 4 additional cases giving an incidence of 4.8% among 800 recipients (Shaheen et al., 1997). Saudi patients who had Kaposi’s sarcoma included both living donor and cadaver donor organ recipients. Beside the high incidence, the other epidemiological features of the Saudi experience are comparable to that reported by Penn.

Our own data compare well with that of the Saudis. The proportion of our renal transplant patients who have Kaposi’s sarcoma appears to be lower than that reported by the Saudis, in whom almost all the patients were of Arab origin. Our cohort of patients is not as homogenous as the Arab population. If only the non-white patients in our cohort are considered then of the 357 transplanted over 23 years, 19 had Kaposi’s sarcoma, giving an incidence of 5.32%! one of the highest in the world. Kaposi’s sarcoma accounted for 79.1% of malignancies in the non-white patients. Among the 185 white recipients of renal allografts Kaposi’s sarcoma occurred in 2 patients, an incidence of 1.08%, which is significantly less than that of the non-white group. Kaposi’s sarcoma comprised only 11.8% of all malignancies in the white patients. Further demographic data are given in Table 8-7. The marked difference in the incidence of Kaposi’s sarcoma in the two racial groups in the same
geographical area is emphasised by the present study. The racial difference in the incidence of Kaposi's sarcoma in persons residing in the same geographical region has been appreciated for African Kaposi's sarcoma. Interestingly, these observations were made in South Africa where it was established that the incidence of Kaposi's sarcoma was ten-fold greater in blacks than white in the same region (Oettle, 1962). However, our study is the first, we believe, to demonstrate this discrepancy in iatrogenic Kaposi's sarcoma.

The minor differences in the gender ratios between our report and that of the Saudis is almost certainly related to the differences in the relative number of males and females transplanted. Our male-to-female ratio of 1:1 has been corrected for the slightly greater number of males transplanted.

Penn Reports
Penn (1997) updated the original experience with Kaposi's sarcoma almost 2 decades after his first report (vide supra) (Penn, 1979b). The average ages (Table 8-7) at which patients developed Kaposi's sarcoma remained unchanged despite the progressive increase in the age of the patients receiving dialysis. The only differences that were noticeable in the two reports were that Kaposi's sarcoma accounted for more posttransplant malignancies in the latter period (4.9% vs. 5.7%) and that the disease was followed a more malignant course in the earlier period (Table 8-7). The main criticism against the Penn reports is the failure to establish an incidence of Kaposi's sarcoma in organ transplantation. The reports can only allow comparisons with other forms of cancers. Compared to both the Saudi experience and our own, Kaposi's sarcoma rarely accounted for more than 5% of all malignancies in developed countries (Table 8-7, and Chapter 6); the latter also contains further discussion on the topic. It is interesting to note that the incidence of Kaposi's sarcoma among the white patients in our cohort was comparable to that of the transplant patients from developing countries, whereas the non-white patients suffered the same risk for Kaposi's sarcoma as their counterparts in developing countries.
Explanation of differences
Since it has been established that the putative cause of Kaposi's sarcoma is the HHV-8 (Martin et al., 1998), it may be that the virus is considerably more prevalent among the poor, as many infections are. It could also be that the immunity of the less privileged allows the greater expression of the virus. The other possibilities are that there are genetic/ethnic differences that predispose to either the viral infection and/or the occurrence of Kaposi's sarcoma. However, although there have been some suggestions that certain HLA antigens may occur more frequently than others in Kaposi's sarcoma (Alamartine et al., 1995; Hutt, 1984b; Myskowski et al., 1997; Shepherd et al., 1997; Strathdee et al., 1996), no consistent relation to an HLA antigen has been demonstrated so far (Krown, 1997; Sheil et al., 1997).

EPIDEMIOLOGICAL VARIABLES: THE HOST AND THE ENVIRONMENT

Age Distribution

Classic Kaposi's sarcoma
The incidence of Kaposi's sarcoma varies with age, depending on the type of disease. The mean age of the five adult patients described by Kaposi (1872), was 54 years, and since then the age of onset of classic Kaposi's sarcoma has changed very little. Classic Kaposi's sarcoma occurs in the elderly patient, the average age being 63 years with the highest incidence being in the sixth through to eighth decade of life (Safai, 1984). However, although the mean age remains high, review of the descriptive studies (Table 8-8) reveals that the classic form can occur in children much younger, as noted by Kaposi himself in his initial report.

Epidemic Kaposi's sarcoma
The epidemic form of Kaposi's sarcoma is seen in younger patients with the mean age of 39 years (Haverkos et al., 1982). Among homosexual men with AIDS in the USA, the percentage with Kaposi's sarcoma is higher among 25- to 44-year-old men than among those who were older or younger (Beral et al., 1990). The risk of Kaposi's sarcoma among homosexual and bisexual men with AIDS decreases rapidly with age to levels one third of those seen among 25- to 44-year-old men.
Table 8-8. Age at presentation of classic Kaposi's sarcoma

<table>
<thead>
<tr>
<th>Country</th>
<th>Period of study</th>
<th>No. of cases</th>
<th>Age (yrs) Mean</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany/USA</td>
<td>1920's</td>
<td>15</td>
<td>54</td>
<td>22-83</td>
<td>Dorffel, 1932</td>
</tr>
<tr>
<td>USA</td>
<td>1965</td>
<td>70</td>
<td>64</td>
<td>26-90</td>
<td>Reynolds et al., 1965</td>
</tr>
<tr>
<td>USA</td>
<td>1954-1975</td>
<td>49</td>
<td>74</td>
<td>28-92</td>
<td>DiGiovanna et al., 1981</td>
</tr>
<tr>
<td>Norway</td>
<td>1970-1975</td>
<td>10</td>
<td>&gt;60</td>
<td></td>
<td>Klepp et al., 1978</td>
</tr>
<tr>
<td>Greece</td>
<td>1984</td>
<td>12</td>
<td>69</td>
<td>57-78</td>
<td>Contu et al., 1984</td>
</tr>
<tr>
<td>Sardinia</td>
<td>1984</td>
<td>529</td>
<td>74</td>
<td>9-101</td>
<td>Dictor et al., 1988a</td>
</tr>
</tbody>
</table>

Modified from Wahman et al. (1991).

(Beral et al., 1990). The typical finding for classical Kaposi's sarcoma of an increase risk with age is therefore not evident in men with AIDS - indeed the reverse is true with the risk being lowest of all in men with AIDS who are over 55 years of age. The age pattern has changed over time in the USA with the younger men showing the greater proportionate decline in risk of Kaposi's sarcoma than older men (Beral, 1991). Some of the recent generation of young men would not have been sexually active until after the onset of the AIDS epidemic, and their relatively lower risk of Kaposi's sarcoma may reflect the declining incidence of venereal diseases and hence the likelihood of exposure to the causative agent (Beral, 1991).

Endemic African Kaposi's sarcoma

The African form of the disease as analysed by Davies and Lothe (1934) has a peak incidence in the first decade, rare cases in the second decade and then a progressive increase in incidence throughout adult life (Davies et al., 1934) (Fig. 8-3). Subsequently, endemic Kaposi's sarcoma was classified into 4 categories (Taylor et al., 1971b) (vide supra). Kaposi's sarcoma was recognised in two distinct age groups: young adults, with a mean age 35 years who generally had benign nodular disease, but occasionally aggressive or florid disease that was fatal within 5 to 8 years; and young children with a mean age of 3 years with fulminant lymphadenopathic disease, fatal within 2 to 3 years (Olweny, 1984).
**Iatrogenic Kaposi's sarcoma**

Among iatrogenically immunocompromised patients with Kaposi's sarcoma, age is less strongly correlated with onset of the disease than is duration from initiation of immunosuppression (Penn, 1979b; Stribling et al., 1978). The disease like the epidemic form tends to occur in younger patients with the mean age of around 40 years. The mean age of 42 years in our own group of Kaposi's sarcoma patients is in line with the experience elsewhere (see Table 8-7). The forms of Kaposi's sarcoma therefore associated with severe degrees of immunosuppression appear to behave in a similar fashion. Classic Kaposi's sarcoma is therefore the only form of Kaposi's sarcoma that has a predilection for the elderly.
Table 8-8. Variation in the gender ratio of classic Kaposi’s sarcoma.

<table>
<thead>
<tr>
<th>Year Reported</th>
<th>Male: Female</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1872-1895</td>
<td>15:1</td>
<td>Kaposi,1895</td>
</tr>
<tr>
<td>1932</td>
<td>13:1</td>
<td>Dorffel,1932</td>
</tr>
<tr>
<td>1965</td>
<td>11:1</td>
<td>Reynolds et al.,1965</td>
</tr>
<tr>
<td>1968-1972</td>
<td>3:1</td>
<td>Dictor et al.,1988a</td>
</tr>
<tr>
<td>1970-1975</td>
<td>2:1</td>
<td>Klepp et al.,1978</td>
</tr>
<tr>
<td>1981</td>
<td>3:1</td>
<td>DiGiovanna et al.,1981</td>
</tr>
<tr>
<td>1984</td>
<td>4:1</td>
<td>Papaevangelou et al.,1984</td>
</tr>
<tr>
<td>1985</td>
<td>3:1</td>
<td>Ross et al.,1985</td>
</tr>
</tbody>
</table>

Gender Distribution

All the patients described by Kaposi in his initial report were males and the early male-to-female ratio was reported to be 15:1 (Hutt,1984a). Over the years there has been decrease in the ratio as indicated in Table 8-8. The decrease may be the result of an increasing prevalence of an agent cofactor in women or in heterosexual populations in general. If a sexually transmitted agent is indeed responsible, the sexual revolution of the 1960s may have contributed to the decrease in the sex ratio of Kaposi’s sarcoma (Wahman et al.,1991). The number of women with classic Kaposi’s sarcoma remains small and most of the observations of the gender differences in the behaviour of the disease have been made in women with endemic African Kaposi’s sarcoma.

Differences and possible explanations

African Kaposi’s sarcoma is ten times or more common in men as in women (Table 8-9); what is also striking here is the lack of significant variation of the sex ratio over the years. In a study of 34 women with Kaposi’s sarcoma in Uganda, the mean age was 36.6 compared to 48 years in men (Templeton,1972). Among African women, the disease shows a different distribution of types with an increase in the generalised pattern, which behaves more aggressively. In all endemic areas the tumour occurs mainly in men, but the male-to-female ratio increases with age from 1.7:1 in the first
Table 8-9. Occurrence of African Kaposi's sarcoma by gender.

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of cases</th>
<th>% Males</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uganda</td>
<td>12</td>
<td>96</td>
<td>Hardy et al., 1976</td>
</tr>
<tr>
<td>Uganda</td>
<td>624</td>
<td>95</td>
<td>Hoxtell et al., 1977</td>
</tr>
<tr>
<td>Uganda</td>
<td>37</td>
<td>94</td>
<td>Holecek et al., 1978</td>
</tr>
<tr>
<td>Uganda</td>
<td>339</td>
<td>93</td>
<td>Herr et al., 1979</td>
</tr>
<tr>
<td>Tanzania</td>
<td>117</td>
<td>92</td>
<td>Sheil et al., 1980</td>
</tr>
<tr>
<td>Tanzania</td>
<td>11</td>
<td>100</td>
<td>Birkeland, 1983a</td>
</tr>
<tr>
<td>Tanzania</td>
<td>200</td>
<td>80</td>
<td>Birkeland, 1983b</td>
</tr>
<tr>
<td>Zaire</td>
<td>14</td>
<td>93</td>
<td>Huang et al., 1995</td>
</tr>
<tr>
<td>South Africa</td>
<td>18</td>
<td>83</td>
<td>Lebbe et al., 1995</td>
</tr>
<tr>
<td>South Africa</td>
<td>117</td>
<td>90</td>
<td>Mihalov et al., 1996</td>
</tr>
<tr>
<td>Kenya</td>
<td>425</td>
<td>88</td>
<td>Buccianti et al., 1996</td>
</tr>
<tr>
<td>Nigeria</td>
<td>27</td>
<td>100</td>
<td>Foreman et al., 1997</td>
</tr>
</tbody>
</table>

decade to 15:1 or more in those over 60 years (Kalengayi et al., 1984). These observations suggest that some modifying factor, probably hormonal rather than chromosomal in nature, protect women (Templeton, 1981). The X-chromosome is unlikely to bear a protective gene because it should also protect female children. Oestrogens have been used to treat males with Kaposi's sarcoma (Hurlbut et al., 1949), but with no success in patients with established disease (Templeton, 1981). Relatively few cases of Kaposi's sarcoma have been observed in pregnancy and during oral oestrogen therapy, but there does appear to be an acceleration of tumour nodule formation (Taylor et al., 1971a). This may be due to the immunosuppression that occurs at this time, that abrogates any hormonal influences. Only scanty information is available on the relative frequency of the disease before and after the onset of the menopause. Available data do not give an indication whether resistance to disease was afforded by the hormonal milieu of an active menstrual cycle or by some other aspect of female physiology (Templeton, 1981). Trauma has been suggested as playing a possible role in the aetiology of Kaposi's sarcoma. Blue-collar workers are more prone to the disease than office workers. Barefoot
Fig. 8-4 The prevalence of Kaposi's sarcoma in the different AIDS risk groups by sex. Modified from Beral et al. (1990).

populations are more prone to the disease than those who wear shoes. It has been suggested that men are more likely to sustain repeated trauma to the extremities than women. While this is probably true for Europeans and Americans, this is not the case in many African tribes where women do the bulk of the manual labour. In these areas men are still much more prone to the disease at an age when life is sedentary and rather protected (Templeton, 1981). In Africa, Kaposi's sarcoma in the AIDS era is a disease of heterosexual males. Kaposi's sarcoma occurs in only 3-8% of women with AIDS compared to 35% of men with the syndrome (Harawi, 1989). No studies have compared the natural history of Kaposi's sarcoma in males and females but anecdotal evidence reports suggest that the clinical course of the disease may be worse in women than in men (Myburgh et al., 1987; Templeton et al., 1975; Templeton, 1981).
**Epidemic Kaposi's sarcoma in developed countries (Fig. 8-4)**

In contrast to the African experience, 95% of all cases of Kaposi's sarcoma in patients with AIDS in Europe and North America are homosexual men (Harawi, 1989). Gender differences in the risk of epidemic Kaposi's sarcoma are more difficult to determine because of the confounding by route of transmission. The groups with the highest risk (homosexual men) and the lowest risk (persons with haemophilia) are essentially men (Drotman et al., 1995). The risks among transfusion recipients or intravenous drug abusers can be compared but the higher risk among men may be caused by misclassification of men who deny homosexual contact. If heterosexual men and women are compared, there would appear to be no major differences in risk of Kaposi's sarcoma by age or sex: among Caribbean-born people with AIDS living in the USA, 7% of males and 5% of females were reported to have Kaposi's sarcoma, while among African heterosexuals with AIDS 14% of both men and women had Kaposi's sarcoma (Beral et al., 1990; Beral et al., 1991). However, in a study from Puerto Rico, it was reported Kaposi's sarcoma occurred in 4.5% of heterosexual females and 14% of heterosexual males, compared to 18% of homosexual males (Beral et al., 1990). Women exposed to different risks for AIDS, have varying risks of developing Kaposi's sarcoma as discussed above.

**Iatrogenic Kaposi's sarcoma**

The male-to-female ratio is the least in patients with iatrogenic Kaposi's sarcoma (Table 8-7). In all the larger series the ratio is ≤ 3:1, and in our experience the incidence in males and females is the same once the correction is made for the number of patients who were transplanted. The reason for the almost equal sex distribution in the iatrogenic form of the disease is difficult to explain. The influence of the hormones that have been postulated to play a role (Templeton, 1972), may be lost when patients become uraemic. Since the majority of patients who are reported with iatrogenic Kaposi's sarcoma are from developing countries, it may be that the agent responsible for Kaposi's sarcoma is more prevalent in these populations and that the infection is equally common in women and men. Although other forms of Kaposi's sarcoma are more common in men, females tend to have more severe disease (Wahman et al., 1991); however, none of the reports including the present
study corroborate this observation for the posttransplant form of the disease. Since most of the observations are in African women with Kaposi's sarcoma it may be that they present later because of poorer access to health care facilities.

Geographical Variation

Classic Kaposi's sarcoma is found primarily in people of Mediterranean and Southern European countries and in people with ancestors from these regions. Reports from Greece and Italy have indicated the high prevalence of the disease in these regions (Contu et al., 1984; Papaevangelou et al., 1984; Papasteriades et al., 1984; Robbins et al., 1986). Sardinia in Southern Europe has a prevalence of 1.8 cases per 100 000 persons per year (Contu et al., 1984), compared to 0.27 cases per 100 000 persons per year in Sweden (Blohme et al., 1984) and 0.32 cases per 100 000 persons per year in the USA (Ross et al., 1985).

Kaposi's sarcoma appears to be more common in sub-Saharan Africa than in the rest of the world (Fig. 8-1). The incidence peaks in central Africa and diminishing from there. Eastern Congo-Kinshasa (formerly Zaire) is the epicentre of high frequency of Kaposi's sarcoma where the tumour accounts for over 10% of all malignancies (before the onset of the AIDS epidemic) (Hutt, 1984b). From there the proportional frequency declines to the west and the south. In most countries in the equatorial belt of Africa the tumour accounted for 3% of all malignancies and in some it is the fourth or fifth most common tumour in men (Hutt, 1984b). In South Africa, Kaposi's sarcoma accounts for ~1% of all malignancies among blacks (Hutt, 1984a; Hutt, 1984b). Within the geographic areas there are further regional/ethnic differences. In Asia and the Far East Kaposi's sarcoma occurs only sporadically and in most areas is extremely rare even in countries ecologically similar to sub-Saharan Africa (Hutt, 1984b). Less than 3 cases had reported each from South America, Australia, and Asia by 1962 (Oettle, 1962).

Although techniques for the collection of data, accessibility to medical care and the completeness of reporting undoubtedly vary between countries, the differences in rates between the regions are believed to be true (Collier et al., 1988). Speculations to explain these differences have emphasised variations in climate (Taylor et
al., 1972), altitude (McHardy et al., 1984), and exposure to insects or parasites (McHardy et al., 1984; Williams et al., 1966) as risk factors for the disease. There are interesting similarities in the geographic distribution of endemic Kaposi’s sarcoma and the African form of Burkitt’s lymphoma. However, despite the high concordance between the two diseases in regions, there are many epidemiological differences in patterns of disease (Hutt, 1981; McHardy et al., 1984; Templeton, 1981), and the parallels frequently drawn between these entities may be misleading.

**Epidemic Kaposi’s sarcoma**

Geographic variations in the frequency of Kaposi’s sarcoma among homosexual and heterosexual men with AIDS have been discussed in detail above. Fig. 8-5 serves to emphasise the geographic variability of the disease in the USA with the highest rates occurring on the East coast and New York, both areas with very high rates of HIV infection.

![Geographic variation in the prevalence of Kaposi's sarcoma in white homosexual and bisexual men in the USA. Note the very high rates on the western seaboard and the New York region. Modified from Beral, (1991).](image)
### Table 8-10. Frequency of Kaposi's sarcoma in renal transplant recipients

<table>
<thead>
<tr>
<th>Country and city/region</th>
<th>Patients with KS (%)</th>
<th>No. of renal recipients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia: Sydney</td>
<td>0.17</td>
<td>4241</td>
<td>Sheil et al., 1987</td>
</tr>
<tr>
<td>Canada: Toronto</td>
<td>0.54</td>
<td>1300</td>
<td>Shepherd et al., 1997</td>
</tr>
<tr>
<td>England: London</td>
<td>0.31</td>
<td>1304</td>
<td>Webb et al., 1997</td>
</tr>
<tr>
<td>France: Ile de France</td>
<td>0.45</td>
<td>6229</td>
<td>Farge, 1993)</td>
</tr>
<tr>
<td>Lyon</td>
<td>0.48</td>
<td>2500</td>
<td>Touraine et al., 1996)</td>
</tr>
<tr>
<td>Germany: Hanover</td>
<td>0.06</td>
<td>1497</td>
<td>Behrend et al., 1997</td>
</tr>
<tr>
<td>Italy: Milan</td>
<td>1.5</td>
<td>854</td>
<td>Montagnino et al., 1996</td>
</tr>
<tr>
<td>Rome</td>
<td>3.3</td>
<td>302</td>
<td>Lesnoni La Parola et al., 1997</td>
</tr>
<tr>
<td>Egypt: Cairo</td>
<td>1.2</td>
<td>950</td>
<td>Bakr et al., 1997</td>
</tr>
<tr>
<td>Israel: Petah Tiqva</td>
<td>2.4</td>
<td>330</td>
<td>Shmueli et al., 1989</td>
</tr>
<tr>
<td>Saudi: Riyadh</td>
<td>4.1</td>
<td>630</td>
<td>Qunibi et al., 1993</td>
</tr>
<tr>
<td>South Africa: Jo'Burg</td>
<td>0.5</td>
<td>989</td>
<td>Margolius et al., 1994</td>
</tr>
<tr>
<td>S'bosch</td>
<td>3.9</td>
<td>542</td>
<td>Present study</td>
</tr>
<tr>
<td>Spain: Madrid</td>
<td>0.5</td>
<td>609</td>
<td>Gomez dos Santos et al., 1997</td>
</tr>
<tr>
<td>Santander</td>
<td>0.23</td>
<td>431</td>
<td>Portillo Martin et al., 1992</td>
</tr>
</tbody>
</table>

**Iatrogenic Kaposi's sarcoma**

In common with the other forms of Kaposi's sarcoma, the iatrogenic form also has areas of geographical predilection (Table 8-10). The reports from Saudi Arabia (Al-Sulaiman MH et al., 1994; al Suleiman et al., 1987; Qunibi et al., 1988; Shaheen et al., 1997; Szende et al., 1997), Egypt (Bakr et al., 1997) and Israel (Shmueli et al., 1989) clearly suggest that the Middle East is an area of high risk for posttransplant Kaposi's sarcoma. By contrast the incidence in developed countries is very much lower. Even within these geographical areas, there are regional/ethnic variations. In Saudi Arabia, the majority of the patients who have Kaposi's sarcoma are from the southwestern region of the country (Al-Sulaiman et al., 1994; Qunibi et al., 1988). In the report by Al-Sulaiman and Al-Khader (1994), 200 (27%) of their 730 transplant patients originated from the southern region of the Arabian Peninsula, whereas 22 (64%) of the 35 patients with Kaposi's sarcoma were from that area.
The other group in Riyadh, Saudi Arabia reported an incidence of 63% in people from the south (Qunibi et al., 1988).

The experience in South Africa also suggests a geographical difference with a incidence of iatrogenic Kaposi’s sarcoma higher in the south than in the north. Margolius et al. (1994) report that 0.5% of their renal transplant patients developed Kaposi’s sarcoma compared to the 3.9% of the patients in the present study. However, there are major differences in the renal transplant populations. The majority of Johannesburg patients were white, whereas our patients were predominantly non-white. Nevertheless, the incidence of Kaposi’s sarcoma was 1.08% even in our white patients which is double the overall incidence reported by the Johannesburg group.

Posttransplant Kaposi’s sarcoma seems to occur more frequently in less developed countries. A notable exception is India. The first case of Kaposi’s sarcoma in India was reported in 1998 despite the large number of kidney transplants performed in the country. Both sporadic and AIDS-related Kaposi’s sarcoma are very rare in India and by 1998 only one case of the latter had been reported (Ajithkumar et al., 1998). The reason for the exceptionally high incidence in our cohort and in the Saudi patients may be related to our use of treatment regimens that result in relative over-immunosuppression. In general, protocols used around the world are derived from the West and have been tested on patients who have better states of nutrition (Hutt, 1984b) and who may tolerate immunomodulation much better. If the AIDS-related Kaposi’s sarcoma is any guide, it can be predicted that when developing countries start transplanting on a larger scale, those who have a high background incidence of Kaposi’s sarcoma in the population can be expected to have a higher incidence of posttransplant Kaposi’s sarcoma (Wahman et al., 1991).

**Ethnicity and race**

Until the onset of the AIDS epidemic Kaposi’s sarcoma was widely considered to be a disease of a specific ethnic or racial group. There is predominance of Kaposi’s sarcoma among Ashkenazic Jews and among people of Mediterranean (especially Italian) heritage (Brownstein et al., 1973; DeWys et al., 1982; DiGiovanna et
Epidemiology of KS

al.,1981; Feuerman et al.,1973; O’Brien et al.,1966; Reynolds et al.,1965) and among African blacks (Wahman et al., 1991). The disease appears to be rare in Asians and people from South America (Hutt, 1984b). In a large survey of cancers in Los Angeles, it was found that based on all-site distribution of cancer cases with both religion and birthplace known, the number of Jewish males born in eastern Europe with classic Kaposi’s sarcoma was six times the number expected (Ross et al., 1985).

Endemic Kaposi’s sarcoma

Among black African people there are regional differences in the incidence of Kaposi’s sarcoma. In Kenya, the tribes that live in the high cool areas with moderate rainfall have the highest incidence of Kaposi’s sarcoma (Laor et al., 1979). In Tanzania, there is considerable variation in Kaposi’s sarcoma incidence rates in different districts and analysis of incidence shows that geographic rather than ethnic or sociocultural factors accounted for these differences (Rothman, 1962). In Uganda, the disease is more common in the west than other regions of the country (Tedeschi, 1958). These observations would suggest that environmental factors might be playing a role (Beral, 1991). In South Africa, the overall incidence of cancer between 1949 and 1953 was approximately equal in whites and blacks, but the crude rate of endemic Kaposi’s sarcoma was ten-fold higher among blacks than among whites (Oettle, 1962). Possible explanations for this discrepancy included genetic predisposition, an inherent metabolic defect, contact of certain ethnic groups with a limited environmental factor or spread of an agent within a relatively closed intermixing population (Hutt, 1984b).

Epidemic Kaposi’s sarcoma

In epidemic Kaposi’s sarcoma it has been found that Haitian-born heterosexual AIDS cases had Kaposi’s sarcoma more commonly than did heterosexual patients of other ethnic origins (Selik et al., 1987). Based on the study of the race, drug use, and sexual preference it was concluded that race or ethnic group influences the frequency of Kaposi’s sarcoma independently of homosexuality (Selik et al., 1987). In an analysis of all the cases reported to the Centers for Disease Control by 1989, Kaposi’s sarcoma was in fact not found to be consistently related to race (Beral et al., 1990); rather risk was correlated with being located in the initial foci of the AIDS
epidemic. Other studies corroborated that ethnicity did not alter the incidence of Kaposi's sarcoma in the various risk groups (De Jarlais et al., 1984). The controversy regarding the influence of race may be explained by other intervening factors that work differently in different populations (Wahman et al., 1991).

Postrenal transplantation

In a study of renal transplant patients reported from Toronto, Canada, Harwood et al. reported that of 44 patients with Kaposi's sarcoma 40 (91%) were of Jewish or Mediterranean heritage (Harwood et al., 1979b). The present study is epidemiologically unique in demonstrating conclusively that the incidence of Kaposi's sarcoma in two populations of renal transplant patients, one Caucasian and the other, non-Caucasian (but predominantly Coloured) residing in the same geographic area can differ markedly. This observation has never been made before although Margolius alluded to it in his report on Kaposi's sarcoma in renal transplant patients at the Johannesburg Hospital. In the latter series 4 (66%) of 6 patients in whom Kaposi's sarcoma occurred were non-Caucasian, an unusually high frequency considering that non-white patients constituted only 30% of the renal transplant recipients (Margolius, 1996). As mentioned earlier, George Oettle was the first to note the profound racial differences in the susceptibility to the disease: blacks were considerably more prone to Kaposi's sarcoma than the whites, Coloureds and Indian living alongside them (Oettle, 1962). Oettle (1962), very pertinently, found no cases of Kaposi's sarcoma in Coloured or Indians in his study confirming observations made in Cape Town and Durban that indicated that the disease was rare in these race groups in South Africa. Parenthetically, the first case of Kaposi's sarcoma in Cape Town was described by Uys and Bennett (1959). Oettle (1962), with great foresight speculated on the role of viruses in the aetiology of the disease but considered the failure to transmit the disease by inoculation into humans and animals an obstacle to the infectious aetiology of the disease. A very interesting observation, is that Kaposi's sarcoma was thought to be rare in full-blooded African-Americans, which is in striking contrast to the experience in South Africa (Kaminer et al., 1950). Kaminer et al. (1950) speculated that anthropological differences accounted for the difference. African-Americans are descendant from West African blacks of unique tribal origins, while the South African blacks are mainly of Hamitic
origin. However, in a later report of 50 patients with Kaposi's sarcoma from the USA, 11 (22%) were black and the authors confirmed that the clinical features were the same in all racial groups (Cox et al., 1959). This was confirmed in a recent report that showed that African-American did not have an increased incidence rate of Kaposi's sarcoma compared to whites (Biggar et al., 1984a).

Our unique finding of the differential incidence rate in Caucasian compared to non-Caucasians would suggest that genetic factors rather than environmental factors may account for the increased risk of Kaposi's sarcoma in our non-white population. Early studies of histocompatibility loci in persons with the disease indicated a link between classic and epidemic forms Kaposi's sarcoma, and HLA-DR5 (Friedman-Kien et al., 1982). However, careful analysis of those reports suggests that the association of HLA-DR5 with Italian or Ashkenazic Jewish descent may explain the apparent association between Kaposi's sarcoma and HLA-DR5 (Papasteriades et al., 1984; Pollack et al., 1983a; Pollack et al., 1983b; Pollack et al., 1985). In Caucasian populations in which the HLA-DR5 is less common, no association between the antigen and Kaposi's sarcoma is found (Dalgleish, 1991). Extensive genetic studies using sex- and tribe-matched controls have also been performed in patients with endemic Kaposi's sarcoma. As was the case in the classic form these revealed no definite association between any of the HLA antigens, including HLA-DR5 and HLA-DR3 with Kaposi's sarcoma (Melbye et al., 1987). Even in endemic areas familial cases of the disease are interestingly, very rare (Epstein, 1972; Lothe, 1963; Oettle, 1962; Palmer, 1972) (although clustering has been observed) (Lulat, 1989). Between 1908 and 1955 only six instances of families with multiple cases of Kaposi's sarcoma had been reported (Oettle, 1962) and since then only two other familial cases have been reported (Brownstein et al., 1973; Epstein, 1972). This argues against an autosomal dominant or recessive mode of inheritance unless penetrance is very incomplete. In postrenal transplant patients an association between Kaposi's sarcoma and HLA-DR2 has been suggested by Qunibi et al. (1988). However, our observations and those of others have failed to corroborate this association (Al-Sulaiman et al., 1994). Neither Qunibi et al. (1988) nor we found an increased frequency of HLA-DR5 in postrenal transplant Kaposi's sarcoma patients compared with the rest of the transplant cohort.
THE ORGANISM: SERO-EPIDEMIOLOGY

Cytomegalovirus (CMV) Infection

Before it was recognised that the HHV-8 was the aetiological agent responsible for Kaposi's sarcoma, the cytomegalovirus (CMV) was causally linked to the disease. Sero-epidemiological studies had shown higher prevalences and antibody titres to CMV in Europeans and American patients with the Kaposi's sarcoma than in appropriate controls (Giraldo et al., 1975; Giraldo et al., 1978). No association has been found for antibody to other herpesviruses, including Epstein-Barr virus or herpes simplex-1 or -2. After renal transplantation, as well as in other conditions which require iatrogenic immunosuppression, infection with CMV occurs almost universally (Fiala et al., 1975; Neiman et al., 1977). Similarly, the prevalence of antibody to CMV is virtually 100% in all areas of Africa with a high incidence of Kaposi's sarcoma (Giraldo et al., 1975; Giraldo et al., 1978). These observations, by their very nature, preclude the demonstration of an association between the two phenomena. Although CMV antibody titres were not formally tested in this study our experience is that more than 80% of dialysis patients have antibodies to CMV (unpublished data). Most researchers have now concluded that CMV is not directly involved in Kaposi's sarcoma tumour onset or maintenance (Ambinder et al., 1987; Dictor et al., 1988b; Roth et al., 1988; Selik et al., 1987).

Human herpesvirus 8 (HHV-8) infection

HHV-8 was initially detected in AIDS-associated Kaposi's sarcoma but was subsequently demonstrated to be present in all epidemiological forms of Kaposi's sarcoma (Chang et al., 1994). Epidemiological data suggest that a high prevalence of HHV-8 in the general population is correlated with a high frequency of Kaposi's sarcoma after renal transplantation. Seroprevalence is high in some African countries (>50%), moderate in Italy and lower in other Western countries (Gao et al., 1996). Most transplant patients have anti-HHV-8 antibodies before immunosuppression is started, suggesting that the subsequent Kaposi's sarcoma results from reactivation of the virus (Parravicini et al., 1997). HHV-8 may be sexually transmitted but there is evidence that the virus can be transmitted from the donor graft to the recipient (Parravicini et al., 1997). This could explain the rare occurrence of Kaposi's sarcoma simultaneously in two recipients of grafts from the
same donor (Bottalico et al., 1997). Viral, bacterial, parasitic, and fungal infections are possible factors in the aggravation of Kaposi's sarcoma. The relapse of Kaposi's sarcoma in one of our own patients (RB) following the onset, of serious local sepsis supports this contention. Admittedly, the evidence in this regard are all from anecdotal reports because controlled prospective trials on the prevalence of infections following transplantation are not available (Siegal et al., 1990). (Further discussion on HHV-8 appears in Chapter 17.

SUMMARY
Epidemiology is a study of disease as it pertains to the community rather than the individual. A classic epidemiological approach to a disease is to look at the host, the environment and the agent. Four epidemiological forms of Kaposi's sarcoma are now recognised and each of these has been described in detail here. For each form the host and environment has been described. The morphology of lesions of classic Kaposi's sarcoma, African (endemic) Kaposi's sarcoma, epidemic (AIDS-associated) Kaposi's sarcoma and iatrogenic Kaposi's sarcoma are similar. However, the reasons for the variations in the type and severity have not been established. It is almost certain that all types of Kaposi's sarcoma are caused by the same transmissible agent (HHV-8) and that the clinical expression of the disease is determined by the individual's immune state. The clustering of cases in the AIDS epidemic provided a very important clue that the disease was sexually transmitted; the strange coincidence that the HHV-8 is spread in a similar way to HIV and the HIV-associated immunosuppression resulting in the clinical expression of Kaposi's sarcoma explains why the disease is so extraordinarily common in people with AIDS. The importance of immunosuppression in the development of Kaposi's sarcoma was appreciated by the widespread use of immunosuppressive agents in organ transplantation. Review of the world experience with posttransplant Kaposi's sarcoma suggests that non-Caucasians are particularly susceptible to the disease, and the current study confirms that this is the case even if the non-Caucasians reside in the same geographical area as Caucasians. The present study has demonstrated that the non-Caucasian population of the Western Cape as an ethnic group has the highest incidence of posttransplant Kaposi's sarcoma in the world.
Epidemiology of KS

Our data also suggests that geographic variation therefore does not seem as important as ethnic variation.

The very young and the very old, perhaps two age groups associated with immunosuppression tend to have a higher incidence of the disease. Children, AIDS patients and, possibly, women tend to have more virulent disease. Males tend to get Kaposi's sarcoma at higher rates than women. Jewish and Mediterranean men have the highest incidence of classic Kaposi's sarcoma and African males of endemic Kaposi's sarcoma. Male homosexuals have a higher incidence of Kaposi's sarcoma than male heterosexuals do, but since the middle 1980s its incidence has been decreasing dramatically. There is no unequivocal association with a particular HLA haplotype. In iatrogenic Kaposi's sarcoma, the male-to-female ratio is reduced to less than 3:1 compared to classic Kaposi's sarcoma where the ratio is 9-15:1. The age of onset of Kaposi's sarcoma in transplant recipients is also much younger than the classic form, but corresponds to certain forms of endemic Kaposi's sarcoma.

Many epidemiological questions concerning Kaposi's sarcoma remain unanswered. These include: the reason for the male predominance of the disease; the explanation for the geographic and ethnic variations (including our observation of the difference between white and non-white patients in the same geographic area); the route of transmission of the virus other than the sexual one; the prevalence of HHV-8 infection in our community (see Chapter 17). Further investigations into the epidemiology of Kaposi's sarcoma as well as HHV-8 would contribute to the knowledge of other oncogenic viruses and in this way may have great public health significance.

LITERATURE CITED


Bluefarb, S. M.


Epidemiology of KS


"... nodules ranging from the size of a peppercorn to that of a pea or hazelnut, and brownish or bluish red in colour...". *Moritz Kaposi*

Although the histological appearance of the various forms of Kaposi's sarcoma varies little, there is a wide spectrum of clinical manifestations. *Classic* Kaposi's sarcoma is predominantly a disease of the legs, although involvement of the lymph nodes and viscera may also occur. It is humbling to consider that since its discovery by Moritz Kaposi over a century ago, there has yet to be an improvement on the clinical description of the disease (Kaposi, 1872). *African-endemic* Kaposi's sarcoma presents in one of 4 clinically distinct patterns:

1. Benign nodular cutaneous disease mimicking classic Kaposi's sarcoma
2. Aggressive localised cutaneous disease invading soft tissue and bone
3. Florid mucocutaneous and visceral disease
4. Lymphadenopathic disease rapidly disseminating to lymph nodes and visceral organs, usually in the absence of cutaneous lesions.

Iatrogenic Kaposi’s sarcoma is primarily a cutaneous complication of immunosuppressive therapy, although lymph nodes and viscera can also be involved. Acquired immunodeficiency disease (AIDS) associated - Kaposi’s sarcoma is characterised by a broad clinical spectrum of disease with overlapping features encompassing all varieties of non-AIDS Kaposi’s sarcoma (Friedman-Kien et al., 1990; Harawi, 1989; Tappero et al., 1993).

CLASSIFICATION

Prior to onset of the AIDS epidemic, four clinical patterns of Kaposi’s sarcoma were recognised (Templeton, 1981). These were the nodular, aggressive cutaneous, lymphadenopathic and systemic generalised. With the advent of the AIDS epidemic, a fifth pattern, referred to as the early pattern was recognised (Harawi, 1989). Nodular Kaposi’s sarcoma is the predominant clinical pattern seen in all types of the disease. The aggressive variety, however, seems to be much more common in Africa. The generalised forms of Kaposi’s sarcoma are seen mainly in

<table>
<thead>
<tr>
<th></th>
<th>Cutaneous</th>
<th>Generalised</th>
</tr>
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<tr>
<td></td>
<td>Early</td>
<td>Nodular</td>
</tr>
<tr>
<td>Classic</td>
<td>+</td>
<td>85%</td>
</tr>
<tr>
<td>Endemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult men</td>
<td></td>
<td>60%</td>
</tr>
<tr>
<td>Adult women</td>
<td></td>
<td>40%</td>
</tr>
<tr>
<td>Young adults</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Epidemic</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Iatrogenic¹</td>
<td>+</td>
<td>89%</td>
</tr>
</tbody>
</table>

Compiled with data from Blumenfeld et al. (1985); Embrey et al. (1988); Kalengayi et al. (1984); Reynolds et al. (1965); Templeton (1972).

¹Stellenbosch experience
African children and young adults. In AIDS all clinical patterns of the disease occur with the exception of aggressive cutaneous disease (Harawi, 1989; Templeton, 1981). Our own experience with iatrogenic Kaposi’s sarcoma is also reflected in Table 9-1. Nodular skin involvement was the most common manifestation of cutaneous Kaposi’s sarcoma. The early lesion occurred as the only cutaneous manifestation in only 1 (5%) patient in our cohort.

**CLINICAL FEATURES**

**Mucocutaneous Disease**

The skin is the organ most commonly afflicted by Kaposi’s sarcoma. In our study as well as the report from Johannesburg (Margolius et al., 1994), all patients with posttransplant Kaposi’s sarcoma had skin involvement. In reports by other authors skin involvement also occurred in the majority of patients, ranging from 87% to 93% (Al-Sulaiman et al., 1994; Qunibi et al., 1988; Qunibi et al., 1993; Shaheen et al., 1997). Of note, is the observation by Shaheen et al. (1997) that 4 of the 5 patients in their study without skin involvement were children. This experience concurs with that in African Kaposi’s sarcoma where affected children have minimal skin lesions and the disease is characterised by generalised lymphadenopathy associated with an aggressive course (Dutz et al., 1960; Olweny et al., 1976; Slavin et al., 1970). The experience reported by Cincinnati Transplant Tumor Registry (CTTR), which largely represents developed countries, is somewhat conflicting. In the initial report (Penn, 1979a) 90% of the patients had skin involvement but in the later report, Penn (1997) found that 27% of patients with visceral involvement did not have skin involvement. This may reflect an underreporting of posttransplant Kaposi’s sarcoma confined to the skin. Notwithstanding this, the occurrence of Kaposi’s sarcoma in the absence of skin lesions is extremely rare (Penn, 1979a).

**Distribution**

In our experience, the most common sites of skin involvement were the lower extremities with 12 (63%) of our patients being affected (associated with variable degrees of oedema), followed by upper limb involvement in 6 (32%). Kaposi’s sarcoma lesions occurred on the extremities of 17 (89%) of our patients. Less commonly affected were the trunk 5 (26%) and hard palate 2 (10%). Some reports
Clinical Aspects of KS

of posttransplant Kaposi's sarcoma fail to mention the location of skin involvement (Al-Sulaiman et al., 1994; Qunibi et al., 1988; Qunibi et al., 1993; Shaheen et al., 1997) but other reports concur with our observation of lesions being localised predominantly on the legs (Frances, 1998; Gotti et al., 1997; Harwood et al., 1979). In classic Kaposi's sarcoma the lower limb is the initial site of involvement in the some 75% of cases, with the hand or forearm as the primary site in 5% of cases, and in the remainder the head or trunk (Lothe, 1963).

In our experience there were no unusual sites that were affected, unlike the situation in epidemic Kaposi's sarcoma. In AIDS patients the tip of the nose is a common site of occurrence (Tappero et al., 1993), possibly as the result of nitrite inhalation (Mirvish et al., 1987). In addition, in epidemic Kaposi's sarcoma, penile and plantar involvement are common while palmar lesions are rare (Safai et al., 1985; Volberding, 1986). However, we have noted the Koebner phenomenon, i.e. the appearance of the lesions in scars. In a single patient in our series it involved the transplant surgery scar and the laparotomy scar that resulted from the insertion of the Tenckhoff catheter (Fig. 9-4b). The Koebner phenomenon has been observed previously in iatrogenic Kaposi's sarcoma (Harwood et al., 1979; Kemeny et al., 1997; Mural, 2000; Seckin et al., 1998). Other features of posttransplant Kaposi's sarcoma in comparison with other sub-types of Kaposi's sarcoma are summarised in Table 9-2. Iatrogenic Kaposi's sarcoma is clinically less aggressive than epidemic Kaposi's sarcoma, but it has been claimed that the disease is generally more severe than the classic form (Gotti et al., 1997).

Skin lesions (See Figs. 9-2 to 9-5)

Kaposi's sarcoma is generally believed to be a multifocal disease and manifests initially with either single or more frequently macules, papules and/or nodules (Safai, 1984). With time there is progression from the macule and patch stage to the papule and plaque stage. The lesions may coalesce to form large plaques or tumours that may become eroded, ulcerating or fungating (Safai, 1984). Lesions have a dark blue or purplish colour on white skin and often appear pigmented on black skin (Cook, 1962; Reynolds et al., 1965; Taylor et al., 1971). Aged or regressing lesions become brownish-blue (Gotti et al., 1997). The lesions seen in our patients
### Table 9-2 Mucocutaneous lesions in the different subtypes of Kaposi's sarcoma

<table>
<thead>
<tr>
<th></th>
<th>Classic</th>
<th>Epidemic</th>
<th>Iatrogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At onset</td>
<td>Localised</td>
<td>Widespread</td>
<td>Localised</td>
</tr>
<tr>
<td>Usual sites</td>
<td>Peripheral:</td>
<td>Central:</td>
<td>Peripheral:</td>
</tr>
<tr>
<td></td>
<td>Distal extremities</td>
<td>Trunk, arms, neck, head,</td>
<td>Distal extremities</td>
</tr>
<tr>
<td>Unique sites</td>
<td></td>
<td>Tip of nose</td>
<td>Surgical Scar</td>
</tr>
<tr>
<td>Symmetry</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Visible mucosa</td>
<td>+</td>
<td>+++ (palate)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common stage</td>
<td>Nodular</td>
<td>Early</td>
<td>Nodular</td>
</tr>
<tr>
<td>Usual size</td>
<td>Up to 3 cm</td>
<td>&lt; 1 cm</td>
<td>Varies</td>
</tr>
<tr>
<td>Colour</td>
<td>Deep purple</td>
<td>Light purple</td>
<td>Deep purple</td>
</tr>
<tr>
<td>Shape</td>
<td>Round</td>
<td>Oval</td>
<td>Various</td>
</tr>
<tr>
<td>Special features</td>
<td></td>
<td>Follows cleavage lines</td>
<td>-</td>
</tr>
<tr>
<td>Associated oedema</td>
<td>Extremities</td>
<td>Fingers, eyelids</td>
<td>Lower limbs</td>
</tr>
</tbody>
</table>

Data from our study and Cox et al. (1959); Reynolds et al. (1965); Safai et al. (1985); Volberding (1986).

varied in size from less than 1 cm to some that were over 5 cm (See Figs. 9-2 and 9-4). Macular lesions are not very common and are usually seen in the early stages of Kaposi’s sarcoma or when the lesion is regressing (McCarthy et al., 1950). Macules are subsequently infiltrated and may form nodular and fungiform tumours. Leg oedema often precedes the development of skin lesions by months (Frances, 1998). In our experience the lymphoedema may not resolve as the skin lesions regress (Fig. 9-4). In some of our patients, acral lesions had marked overlying hyperkeratosis, superficially resembling psoriasis (Fig. 9-3C). This has also been described in epidemic Kaposi’s sarcoma (Tappero et al., 1993). Initially lesions in Kaposi’s sarcoma may be unilateral but with progression bilateral disease occurs. Pruritus of the affected areas has been reported as a symptom by some authors (Dörffel, 1932; Huang, 1983; Symmers, 1941) but the others have considered pruritus to
be distinctly unusual (Bluefarb, 1957; Safai, 1984). In none of the patients examined by us was pruritus a prominent feature. In epidemic Kaposi's sarcoma the lesions are also elongated and oval shaped following the lines of cleavage. In contrast to the skin lesions in classic and iatrogenic Kaposi's sarcoma, the lesions in epidemic Kaposi's sarcoma tend generally to be smaller than 1 cm (Harawi, 1989; Tappero et al., 1993), pink and located on the upper trunk, and head and neck areas.

Course of skin lesions
In classic Kaposi's sarcoma the skin lesions have an indolent course and usually take years to grow. In contrast, in the epidemic form of the disease, the skin lesions behave aggressively, enlarge and become widely disseminated usually within a few weeks to a few months (Friedman-Kien, 1981). In iatrogenic Kaposi's sarcoma the course of the disease is generally benign. In a single patient in our study, progressive lesions on the legs formed exophytic friable tumours that became secondarily infected, while lesions on the sole progressed to confluence with ulceration, both well recognised complications (Tappero et al., 1993). None of our patients developed the aggressive form of skin involvement seen in epidemic Kaposi's sarcoma. However, both Al-Sulaiman et al. (1994) and Shaheen et al. (1997) describe this aggressive pattern in over one quarter of their renal transplant patients who developed Kaposi's sarcoma. With aggressive skin involvement the lesions have "a malignant appearance and behaviour" mimicking that seen in epidemic Kaposi's sarcoma, characterised by rapid growth within a few weeks and widespread dissemination often with visceral involvement (Al-Sulaiman et al., 1994; Shaheen et al., 1997). This aggressive cutaneous form of iatrogenic Kaposi's sarcoma has not been reported outside of Saudi Arabia (Harwood et al., 1979; Margolius et al., 1994).

Oral lesions
Two (10%) of our patients had lesions on the hard palate. These lesions are usually purple in colour and are asymptomatic. These lesions are also described in patients with AIDS, in whom they may form friable tumours resembling bacillary angiomatosis or pyogenic granuloma (Berger et al., 1989; Tappero et al., 1993). Gingival hyperplasia, although not seen in our study, is another manifestation of the disease and it needs to be differentiated from cyclosporine-induced hyperplasia (Qunibi et
The oral lesions are often associated with gastrointestinal disease (Frances, 1998). Involvement of the urogenital tract or conjunctivae is less frequent. In patients with AIDS-associated Kaposi’s sarcoma, lesions occur on the hard palate of 50% of cases (Ficarra et al., 1988) while ocular adnexal involvement occurs in up to 20% (Shuler et al., 1989).

**Unusual forms**

In AIDS patients unusual forms of Kaposi’s sarcoma have been described. Telangiectatic Kaposi’s sarcoma is a rare variant (Snyder et al., 1982), while more recently the disease has been seen to present as generalised lymphoedema, ecchymotic Kaposi’s sarcoma and keloidal Kaposi’s sarcoma (Frans et al., 1994; Schwartz et al., 1994; Schwartz et al., 1995). These forms have yet to be described in iatrogenic Kaposi’s sarcoma.

**EXTRACUTANEOUS KAPOSI’S SARCOMA**

Kaposi’s sarcoma has traditionally been considered an indolent cutaneous disease. However, in his original paper, Kaposi alluded to the fact that the disease does have the propensity to involve extracutaneous sites. Of the five cases he described, a postmortem examination performed on one patient showed very extensive visceral involvement including the lungs, gastrointestinal tract and liver, although the lymph nodes appeared to be spared macroscopically (Kaposi, 1872).

Extracutaneous involvement occurred in 29% of our patients. However, it is likely that visceral involvement is much more common but that it is asymptomatic as in epidemic Kaposi’s sarcoma. There are no postmortem studies in iatrogenic-Kaposi’s sarcoma patients but the experience in epidemic Kaposi’s sarcoma has shown that the disease is limited to the skin in less than 25% of AIDS-Kaposi’s sarcoma cases (Lemlich et al., 1987; McKenzie et al., 1991; Welch et al., 1984). Visceral involvement has been reported to be present in 45% of iatrogenic-Kaposi’s sarcoma in the CTTR (Penn, 1979a; Qunibi et al., 1988). An early report of four renal transplant recipients found no clinical evidence of visceral Kaposi’s sarcoma (Harwood et al., 1979) and contrasts with a study from South Africa that reported disseminated disease in 4 of 5 patients with posttransplant Kaposi’s sarcoma.
Extracutaneous involvement in other subtypes of Kaposi's sarcoma
In a review of 356 cases of classic Kaposi's sarcoma, it was found that 10% of cases had associated extracutaneous disease (Dörffel, 1932). Epstein (1957b) later reviewed 35 cases of Kaposi's sarcoma with symptomatic extracutaneous disease. Between these two studies, visceral Kaposi's sarcoma involved the following organs in decreasing frequency: gastrointestinal tract, liver, lungs and lymph nodes. In a review of primary extracutaneous Kaposi's sarcoma reported in the literature, Anthony et al. (1960) found that organ involvement occurred in the following order of frequency: lymph nodes, heart, gastrointestinal tract, liver and lungs. Visceral involvement is common in AIDS patients with Kaposi's sarcoma. Postmortem studies of patients with AIDS-associated Kaposi's sarcoma suggest that less than 25% have disease limited to the skin or mucous membranes. (Lemlich et al., 1987; McKenzie et al., 1991; Welch et al., 1984). The most common sites of visceral involvement are the gastrointestinal tract, liver, spleen, and lungs. Involvement of these sites accounts for death in approximately 10% - 20% of patients with AIDS-Kaposi's sarcoma (McKenzie et al., 1991). AIDS-Kaposi's sarcoma may also affect the pharynx, bone marrow, urogenital tract, brain, kidney, and adrenal glands (Ahluwalia et al., 1991; Bordelon et al., 1990; Kaul et al., 1991; Kuhlman et al., 1991; Marcusen et al., 1985). Interestingly, in a postmortem study from Paris, the thymus was involved in 55% of AIDS patients with Kaposi's sarcoma (Harawi, 1989).

Nodal Kaposi's sarcoma
In our series of iatrogenic Kaposi's sarcoma lymphadenopathy was detected in 5 patients clinically or at autopsy. The two patients with clinically detectable Kaposi's sarcoma both had inguinal lymphadenopathy, associated with skin lesions. The three patients on whom postmortem examinations were performed, all had deep lymph node involvement that was not suspected clinically. In these patients the disease was disseminated. The diagnosis of lymph node Kaposi's sarcoma was
confirmed by histology in all our cases. In the series reported from Saudi Arabia (Al-Sulaiman et al., 1994), 13 of the 35 patients had lymph node enlargement by clinical examination and/or computerised axial tomography (CT) scanning of the abdomen and chest, although the diagnosis was not histologically confirmed. The inguinal lymph nodes were the only superficial lymph nodes that were involved in our experience. The experience of the Johannesburg group is similar to ours with 2 of their 5 patients having inguinal lymphadenopathy (Margolius et al., 1994). On the other hand, Al-Sulaiman et al. (1994) report enlargement of, mainly, the cervical and less commonly, the axillary lymph nodes. Whereas in our patients the deep lymph nodes involved were the mesenteric, mediastinal and hilar glands, in the Saudi series the paraaortic and peritracheal nodes were mainly affected (Al-Sulaiman et al., 1994).

Nodal involvement in other subtypes of Kaposi's sarcoma
Symptomatic lymphadenopathy is rare in classic Kaposi's sarcoma. In one series, the lesion was proven on biopsy in 11% of cases. In two cases there was regional lymph node involvement while the remaining had generalised lymphadenopathy (Cox et al., 1959). However, at postmortem examination nodal Kaposi's sarcoma was present in 86% of cases (Cox et al., 1959). In another study involving 47 postmortem cases, generalised lymphadenopathy was present in 6% and localised disease in 38% of cases (Templeton, 1972). In a study of African Kaposi's sarcoma involving 156 cases, 10% were found to have lymph node involvement (O'Connell, 1977). Another study from Africa of 48 consecutive patients from Uganda lymph node involvement was present in 33% of the patients. However, in the latter study the nodes were sectioned into 4 mm slices and examined microscopically in their entirety (Bhana et al., 1970). In three postmortem series in patients with AIDS, lymph node involvement occurred on average in 56% of patients and was usually generalised (Lemlich et al., 1987; Niedt et al., 1985; Welch et al., 1984). Kaposi's sarcoma with generalised lymphadenopathy is usually indicative of an aggressive course irrespective of the presence of skin disease (Harawi, 1989).

Outcome
In iatrogenic Kaposi's sarcoma the lymph nodes tend to regress with improvement of the Kaposi's sarcoma elsewhere in the body on treatment (Fig. 9-1). Since there are
**Fig. 9-1** The response of Kaposi’s sarcoma lymph nodes of patient DI to treatment are shown.

several other causes of lymphadenopathy in renal allograft patients on immunosuppression, it is advisable to confirm the diagnosis by biopsy of the node (Massarelli et al., 1982; Rywlin et al., 1983; Ulbright et al., 1981). In a recent series of 356 organ recipients with Kaposi’s sarcoma, it was found that 8 (1.7%) of the patients had associated lymphomas (Penn, 1995).

**Gastrointestinal Kaposi’s sarcoma**

In our series 2 patients who had disseminated disease at postmortem examination had involvement of the stomach while 3 had liver involvement. Routine endoscopy was performed in only 5 patients, none of whom had upper gastrointestinal Kaposi’s sarcoma. None of the patients with disseminated disease had endoscopic examination prior to death. In the Saudi series (Al-Sulaiman et al., 1994), the gastrointestinal tract was the second most commonly involved organ after skin. They, however, routinely studied patients with upper gastrointestinal endoscopy and/or colonoscopy. Of the 26 patients who had gastroscopy, 50% appeared to
have Kaposi's sarcoma lesions, while 45% of the 22 patients who had colonoscopy were suspected of having Kaposi's sarcoma lesions (Al-Sulaiman et al., 1994; Hanid et al., 1989). However, despite several biopsies from multiple sites the histological diagnosis of gastrointestinal was confirmed in only one-half of the cases.

**Symptoms**

Gastrointestinal Kaposi's sarcoma is a well-recognised occurrence in patients with organ transplants (Hanid et al., 1989; Myers et al., 1974; Qunibi et al., 1988; Siegel et al., 1969; Stribling et al., 1978) as well as in patients with AIDS (Gottlieb et al., 1981; Gottlieb et al., 1983; Rose et al., 1982). In the classic form of the disease, gastrointestinal Kaposi's sarcoma occurred in an estimated 10% of patients (Tedeschi et al., 1947), although in one review of classic Kaposi's sarcoma gastrointestinal disease was found to be as high as 66% (Epstein, 1957a). In AIDS patients with Kaposi's sarcoma about 50% have gastrointestinal involvement (Wall et al., 1984). Although lesions of Kaposi's sarcoma may occur anywhere in the gastrointestinal tract, the most common locations are the stomach and duodenum. Gastrointestinal Kaposi's sarcoma rarely cause symptoms (Hanid et al., 1989; Hanno et al., 1979) and are usually detected by finding infiltrated red spots on routine endoscopy of an asymptomatic patient (Frances, 1998). Kaposi's sarcoma may present with non-specific upper gastrointestinal symptoms or with gastrointestinal bleeding (Friedman et al., 1985; Stribling et al., 1978); rarely other presentations have been reported, including perforation (Mitchell et al., 1949), intestinal obstruction (Coetzee et al., 1967), intussusception (Houghton et al., 1988; White et al., 1964), protein losing enteropathy (Laine et al., 1987; Novis et al., 1974; Perrone et al., 1981), or septicaemia (Bieluch et al., 1988; Glaser et al., 1983). None of our patients had any gastrointestinal symptoms, while only 3 of the 26 Saudi patients with gastrointestinal disease had symptoms that included nausea, vomiting, malaena and rectal bleeding (Al-Sulaiman et al., 1994).

**Investigations**

The most effective technique for investigation of the gastrointestinal tract is endoscopy rather than radiological studies, which are useful for filling defects but may miss macular lesions (Ahmed et al., 1975). The endoscopic findings of gastrointestinal Kaposi's sarcoma were first described in 1968 (Rajan et al., 1969).
and three distinct appearances were recognised: a maculopapular, a polypoid and an umbilicated nodular lesion (Ahmed et al., 1975). The mucosa over the lesion may have a strawberry appearance (Ahmed et al., 1975) or a reticulated pattern giving it an appearance of elephant skin (Bernal et al., 1985). The colonic lesions may have a similar appearance but in additional may resemble segmental colitis endoscopically (Bernal et al., 1985). The differential diagnosis of the gross lesions include haemangiomas (Shepherd, 1953), nodules of metastatic melanoma (Willbanks et al., 1970), or endometriosis (Kinder, 1953). It is also important to take several biopsies of suspected Kaposi’s sarcoma lesions (Hanid et al., 1989) because these may be submucosal and may therefore be easily missed (Bernal et al., 1985). In one series only 23% of endoscopic biopsies of Kaposi’s sarcoma were positive histologically (Friedman et al., 1985).

**Histology**

On histological examination the findings are those expected of Kaposi’s sarcoma (see Chapter 10). However, the early stages of Kaposi’s sarcoma in the gastrointestinal tract are not as easily recognised as in the skin or lymph nodes. The submucosal vessels in the gastrointestinal tract are often dilated and have irregular or jagged cross-sections. Plasma cells are found normally in abundance in the mucosa and submucosa. These findings make an early lesion of Kaposi’s sarcoma difficult to recognise in the gastrointestinal tract (Amazon et al., 1988).

**Management**

An aggressive management approach is probably not justified because Kaposi’s sarcoma of the gut does not alter the prognosis of the patient and the lesions regress as the disease regresses after therapeutic intervention (Al-Sulaiman et al., 1994).

**Other organs in gastrointestinal system**

Liver involvement is relatively uncommon but is usually associated with lesions elsewhere in the gastrointestinal tract (Amazon et al., 1988). Diagnosis can be made by computerised tomography (CT) scan of the abdomen and biopsy of suspicious lesions. Whereas all our patients with liver involvement came to postmortem examination, Al-Sulaiman et al. (1994) report that in two of their patients who had
confirmed liver involvement, the lesions regressed in concert with lesions elsewhere. The oral lesions associated with Kaposi's sarcoma have been discussed above.

Pulmonary Kaposi's sarcoma

Involvement of the respiratory tract is uncommon, but well documented in all types of Kaposi's sarcoma. Dörfell (1932) analysed 365 cases of classic Kaposi's sarcoma and found that the lungs followed the lymph nodes and the gastrointestinal tract in frequency of involvement of internal organs. Subsequent reports confirm the occurrence of lung disease in classic Kaposi's sarcoma (Hanno et al., 1979; Loring et al., 1965a), and in African Kaposi's sarcoma (Lothe et al., 1962; Templeton, 1972), but it is in AIDS patients that pulmonary Kaposi's sarcoma has been best studied (Meduri et al., 1986; Ognibene et al., 1985; Pitchenik et al., 1985; Purdy et al., 1986). Pulmonary involvement has also been described in iatrogenic Kaposi's sarcoma (Gunawardena et al., 1988; Penn, 1979b), although, as in our experience, the diagnosis is often made postmortem (Siegel et al., 1969).

Distribution

Any part of the respiratory tract may be affected. Upper respiratory tract involvement may produce hoarseness (Al-Sulaiman et al., 1994), or obstruction whereas pulmonary parenchymal involvement is associated with haemoptysis, dyspnoea, or exsanguinating haemorrhage. Pleural lesions cause pleuritic pain. As in other visceral organ involvement, pulmonary disease may, rarely, occur in the absence of skin disease (Dantzig et al., 1974; Misra et al., 1982).

Diagnostic procedures

Radiological examination of the chest can range from normal to reticulonodular shadowing or alveolar opacities with hilar adenopathy with or without pleural effusions (Davis et al., 1987; Gunawardena et al., 1988; Kramer et al., 1987; Naidich et al., 1989; Nyberg et al., 1987; Ognibene et al., 1988; Sivit et al., 1987). Bronchoscopy is the investigation of choice revealing a violaceous endobronchial Kaposi's sarcoma lesion; a transbronchial biopsy may also be performed (Ciment et al., 1983; Fouret et al., 1987; Gunawardena et al., 1988; Kornfeld et al., 1983). However, these procedures may fail to provide the diagnosis in up to 30% of cases (Hanson et al., 1987; Lau et al., 1986; Meduri et al., 1986; Pitchenik et al., 1985; Purdy et al., 1986). It has recently
been demonstrated that Kaposi's sarcoma lesions are thallium avid (Lee et al., 1988; Lee et al., 1990). Using sequential thallium and gallium scanning in AIDS patients with pulmonary infiltrates, it has been shown that a positive thallium scan with a negative gallium scan is suggestive of Kaposi's sarcoma (Lee et al., 1991), as opposed to lymphoma of the lungs where both gallium and thallium scans are positive (Hamada et al., 1988; Waxman et al., 1996); in Pneumocystis carinii pneumonia the thallium scan is negative while the gallium is positive (Lee et al., 1991). This might be a useful non-invasive technique for the investigation of pulmonary infiltrates in renal transplant patients.

Clinical presentation
Among our 21 renal transplant patients with Kaposi's sarcoma, four (19%) had lung involvement. Of these, 3 died and the lung involvement was confirmed at postmortem examination. Dyspnoea was the most common presentation with bilateral reticulonodular pattern on radiological examination of the chest. Two of the deceased patients had antemortem bronchoscopic examinations that showed the presence of endobronchial lesions. One patient was found to have endobronchial Kaposi's sarcoma when she presented with a relapse of Kaposi's sarcoma several years after the primary disease. A similar number of Saudi renal transplant patients (19%) had pulmonary Kaposi's sarcoma. These patients presented with low-grade fevers, dyspnoea, nonspecific chest pain, and haemoptysis (Al-Sulaiman et al., 1994). Radiologically, the typical finding, as was our experience, was the bilateral reticulonodular pattern, although one patient had an haemorrhagic pleural effusion. All patients were hypoxaemic and had restrictive patterns on lung function testing (Al-Sulaiman et al., 1994). Our experience, shared by Al-Sulaiman (1994), is that there is little correlation between the extent of skin disease and the severity of pulmonary involvement. With pulmonary disease the mortality is very high, usually due to respiratory failure (Al-Sulaiman et al., 1994).

Pathology
The macroscopic appearance of pulmonary Kaposi's sarcoma varies from a single large mass to innumerable small nodular lesions. The lesions vary in colour from deep red to white depending on the degree of vascularity and sclerosis. Large nodules may undergo haemorrhagic necrosis (Amazon et al., 1988). Histologically,
small lesions of the lung parenchyma are perivascular or peribronchial, and infiltrate the surrounding lung. Macrophages containing haemosiderin are numerous within the alveolar spaces adjacent to the tumour (Amazon et al., 1988). Atypia of alveolar lining cells adjacent to the Kaposi’s sarcoma lesion has been reported (Loring et al., 1965b). Early lesions of Kaposi’s sarcoma may resemble granulation tissue and differentiation from organising pneumonitis or fibrosing alveolitis may be very difficult. Fully developed lesions may resemble fibrous mesothelioma or a variety of spindle cell neoplasms (Dail et al., 1983).

Other organ involvement
Kaposi’s sarcoma may occur in any organ in the body (Amazon et al., 1988). Indeed, we have now described the lesions as occurring even in the renal allograft! The involvement of bone marrow has also been described in other forms of Kaposi’s sarcoma but not in iatrogenic Kaposi’s sarcoma, to the best of our knowledge, making our case the first one to be described. Splenic involvement is also rare and was present in the same patient who had bone marrow and allograft disease.

Bone and bone marrow involvement
Bone disease occurs in 20% of African patients with aggressive cutaneous Kaposi’s sarcoma (Templeton, 1981). Most of the bone disease results from an extension of the infiltrative cutaneous Kaposi’s sarcoma (Taylor et al., 1971). The disease may be localised to the bone in endemic Kaposi’s sarcoma and occur in the absence of skin disease (De Jarlais et al., 1984). Bone marrow involvement is extremely rare in classic and even epidemic Kaposi’s sarcoma (Little et al., 1986).

Heart involvement
None of our patients or those in the series reported by Al-Sulaiman et al. (1994) suffered cardiac Kaposi’s sarcoma. Cardiac involvement usually occurs as part of generalised disease and occurs in 16% of the various epidemiological forms of Kaposi’s sarcoma (Harawi, 1989). Interestingly, it appears more likely to occur in the absence of skin disease (Anthony et al., 1960). In classic and endemic Kaposi’s sarcoma the pericardium is more commonly involved than the myocardium (Templeton, 1972). In a postmortem study of nine AIDS-Kaposi’s sarcoma patients, five were found to have cardiac involvement with the subepithelial adipose tissue
adjacent to the coronary arteries being especially affected (Silver et al., 1984). The myocardium and endocardium were free of disease. The patients were all free of symptoms of cardiac disease. In another postmortem study of 41 AIDS patients, 21 had Kaposi's sarcoma of whom four had epicardial and myocardial disease (Cammarosano et al., 1985).

**Central nervous system involvement**

The rarity of brain involvement is ascribed to its lack of lymphatics and its the immunologically privileged status (Templeton, 1981). None of our patients nor those reported from Saudi Arabia (Shaheen et al., 1997) had any overt central nervous system involvement. In the few cases that have been reported in classic and endemic Kaposi's sarcoma (Gonzalez-Crussi et al., 1969; Loring et al., 1965b) the disease occurred as part of generalised disease (Rwomushana et al., 1975). Despite the frequency with which the brain is involved in AIDS, very few cases of Kaposi's sarcoma of the brain have been reported (Gorin et al., 1985; Welch et al., 1984). Of note is the observation that the other immunologically privileged site, the gonads are also generally spared by Kaposi's sarcoma (Malliwah et al., 1985; Templeton, 1972; Templeton, 1981).

**Miscellaneous**

In the series reported from Saudi Arabia (Al-Sulaiman et al., 1994; Shaheen et al., 1997), additional sites affected were the vocal cords, nasal mucosa and penis as part of generalised disease. None of the Saudi patients or ours had any eye, or gonadal involvement.

**Laboratory findings**

Abnormal laboratory findings in patients with Kaposi's sarcoma include microcytic anaemia from chronic disease or blood loss from ulcerated lesions (Hogeman, 1953). Cases of both autoimmune haemolytic anaemia (Reidy et al., 1982; Zemek et al., 1964) and microangiopathic haemolytic anaemia (Ziegler et al., 1988) have also been reported. Other findings usually include monocytosis and occasionally eosinophilia (Gotti et al., 1997).
STAGING OF POSTTRANSPLANT KAPOSI’S SARCOMA

A four-stage classification was suggested by Al-Khader et al. (1988) to assist in the management and prognostication of iatrogenic Kaposi’s sarcoma:

**Stage I** - Localised skin lesions involving only one limb
**Stage II** - Widespread lesions involving more than one limb, but disease confined to the skin
**Stage III** - Involvement of one or more viscera or lymph nodes
**Stage IV** - Any of the above categories plus either a life threatening infection or another neoplasia.

In a later modification of the classification (Shaheen et al., 1997) Stage IV was changed to be generalised Kaposi’s sarcoma involving the skin, viscera and/or lymph nodes and each group was further substaged into:

- **A** - No associated malignancy or life threatening infection and,
- **B** - Associated malignancy or life threatening infection.

Our own opinion is that this classification is of limited value in terms of management and prognostication. Our experience is that categorising the disease into either (a) cutaneous with or without lymph node involvement, or (b) visceral disease with or without skin disease, is far more useful, both as regards management and as well as prognostication, as will be shown in Chapter 11. A different staging has been proposed for AIDS-Kaposi’s sarcoma, which has the propensity for the development of chronic and progressive disease (Tappero et al., 1993). For patients with AIDS-Kaposi’s sarcoma immunologic findings were shown to be most important in predicting survival (Myskowski et al., 1988; Spornraft et al., 1988). For this reason the newer classifications now include an appraisal of the immunologic function. The AIDS Clinical Trials Group (ACTG) have a developed a classification that provides a useful approach to the practical management of AIDS-Kaposi’s sarcoma patients (Table 9-3) (Krown et al., 1989). It must be stated however, that this is but one of many staging classifications that has been suggested, alluding to the fact that a satisfactory one has yet to be proposed (Chachoua et al., 1989; Krigel et al., 1983).
### Table 9-3. A staging classification for AIDS-Kaposi’s sarcoma

<table>
<thead>
<tr>
<th>Good Risk (0)</th>
<th>Poor Risk (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(All of the following)</td>
<td>(Any of the following)</td>
</tr>
<tr>
<td><strong>Tumour (T)</strong></td>
<td><strong>Tumour-associated</strong></td>
</tr>
<tr>
<td>Confined to the skin and/or lymph node and/or minimal oral lesions</td>
<td>oedema or ulceration; extensive oral Kaposi’s sarcoma or Kaposi’s sarcoma in other non-nodal viscera</td>
</tr>
<tr>
<td><strong>Immune System (I)</strong></td>
<td><strong>Systemic Illness (S)</strong></td>
</tr>
<tr>
<td>CD4 cells ≥ 200/μl</td>
<td>CD4 cells &lt; 200/μl</td>
</tr>
<tr>
<td>No history of opportunistic infection or thrush; no &quot;B&quot; symptoms, performance status ≥ 70 (Karnofsky)</td>
<td>History of opportunistic infection or thrush; &quot;B&quot; symptoms, performance status &lt; 70 (Karnofsky); other HIV-related illness</td>
</tr>
</tbody>
</table>

Modified from (Krown et al., 1989)

1 "B" symptoms: unexplained fever, night sweats, > 10% involuntary weight loss, or diarrhoea for more than 2 weeks.

This classification differs completely from that proposed by Al-Khader et al. (1988), and generally supports our view that the extent and distribution of skin involvement is relatively unimportant and that disease isolated to the skin and/or lymph nodes has a good prognosis.

Yet another clinical classification, this for classic and endemic Kaposi’s sarcoma, has been proposed by Templeton (1981) based on the African experience (Table 9-4). **Nodular** disease is the most common and occurs in the subcutaneous tissue of the peripheries; the typical picture is readily recognisable by the clinician. Aggressive lesions are usually associated with nodular disease and in many cases appear to arise from preexisting nodules. The greater the duration of the nodular disease the greater the likelihood of aggressive behaviour (Templeton, 1981). **Aggressive** disease can follow one of two patterns. It may either present as an
Table 9-4. Clinical patterns of Kaposi's sarcoma in African (Endemic) Kaposi's sarcoma and classic Kaposi's sarcoma with the relative frequencies.

<table>
<thead>
<tr>
<th></th>
<th>Endemic (%)</th>
<th>Classic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular</td>
<td>60</td>
<td>85</td>
</tr>
<tr>
<td>Aggressive</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>Exophytic (Ulcerative)</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Generalised</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Lymphadenopathic</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Lymphadenopathic and systemic</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>


Exophytic ulcerating lesion that often penetrates the fascia or less commonly it may produce a diffuse infiltration of the subcutaneous tissue giving the affected limb a "woody" appearance (Templeton,1981). Generalised pattern is the least common variety and it also has two patterns of presentation; it may take the lymphadenopathic form that occurs exclusively in children and rarely involves the skin or viscera. It has to be distinguished from malignant lymphoma by biopsy. The least common pattern of the disease occurs in young adults who initially present with widespread cutaneous, nodal and systemic involvement. The disease runs a fulminant course and is rapidly fatal within a matter of weeks. Templeton (1981) includes transplant patients in the generalised pattern although the generally benign behaviour of the disease, we feel, makes it inappropriate for placement in this category.

CLINICO-PATHOLOGICAL CORRELATION

Our experience has revealed a major discrepancy between the clinical disease and the findings at postmortem, where the extent of the disease is much greater than is suspected clinically. This may be because the disease is indeed silent and that the clinical manifestations of visceral disease are unusual. This is supported by the observation of others that in a large number of patients with Kaposi’s sarcoma who have routine endoscopic examinations, there are lesions in the gastrointestinal tract.
that are clinically occult (Al-Sulaiman et al., 1994; Shaheen et al., 1997). Alternatively, it may be that the patients with more extensive Kaposi’s sarcoma disease are the ones who succumb and come to postmortem examination. Our own opinion is that the disease is probably more extensive than suspected clinically but that certain areas, such as the gut, are more likely to be involved with asymptomatic disease. The best way to resolve the matter would be to actively search for disease elsewhere when the skin disease is diagnosed, and to encourage postmortem examinations in these patients. Other authors concur with us that the involvement of internal organs is more frequent than clinically appreciated with estimates ranging from 10 to 70% of patients showing internal organ involvement (Cox et al., 1959; Ecklund et al., 1962).

ASSOCIATED MALIGNANCIES

None of our patients had second malignancies associated with the Kaposi’s sarcoma but it has been reported that 6% of allograft recipients who develop Kaposi’s sarcoma have a second malignancy (Penn, 1997), most commonly malignant lymphoma (Myers et al., 1974; Penn, 1995; Touraine et al., 1989). In the CTTR series 2% of patients with Kaposi’s sarcoma had malignant lymphomas (Penn, 1997). There is also a well-established association between classic Kaposi’s sarcoma and the development of a second malignancy (Piette, 1987). In a recent report, a second primary malignancy was present in 37% of patients with classic Kaposi’s sarcoma (Safai et al., 1980b) with 58% of lesions being lymphoreticular tumours. By comparison, in a similar study of double primaries in the general population, lymphoreticular malignancies only occurred in 8% of all patients with a primary malignancy other than Kaposi’s sarcoma (Safai et al., 1980b). Other studies have confirmed the association between Kaposi’s sarcoma and second malignancies (Moertel, 1966; O’Brien et al., 1966; Reynolds et al., 1965; Safai et al., 1980a; Safai et al., 1980b). Malignancies associated with Kaposi’s sarcoma include malignant lymphomas, leukaemias, myelomas, mycosis fungoides or thymomas (Ulbright et al., 1981). These malignancies may precede, occur simultaneously with or follow Kaposi’s sarcoma (Safai et al., 1980b; Ulbright et al., 1981). Some 42% of malignancies in classic Kaposi’s sarcoma are of epithelial origin, which may occur in any organ but most commonly the skin (Safai et al., 1980b). Whether this represents
a real association with Kaposi's sarcoma or whether it is a reflection of an accumulated risk of developing tumours in an elderly population, is uncertain (Templeton, 1981). Patients with AIDS are also at risk of dual malignancies. In one study 26% of patients with non-Hodgkin's lymphoma also had Kaposi's sarcoma (Safai et al., 1992). Interestingly, an association between Kaposi's sarcoma and second malignancies is not seen with endemic Kaposi's sarcoma (Slavin et al., 1969).

**REGRESSION**

Kaposi's sarcoma lesions usually regress when treatment is instituted, although spontaneous regression may occasionally occur. With regression, the Kaposi's sarcoma nodule gets smaller, harder, and eventually leaves a hyperpigmented scar. Pathologically the scar consists of dense fibrous tissue with haemosiderin deposition and obliteration of the blood vessels (Templeton, 1981). Regression is more evident in iatrogenic Kaposi's sarcoma than in the other subtypes of Kaposi's sarcoma. In a review of 19 studies of the iatrogenic form of this disease regression occurred in 84% of the cases on discontinuation of the immunosuppressive therapy and in 62% on reduction of the doses of the drugs (Brooks, 1986). It has however also been reported that Kaposi's sarcoma regressed in up to one-third of the cases in whom the immunosuppression was maintained (Schulhafer et al., 1987). Classic and endemic Kaposi's sarcoma may show partial regression while complete regression occurs in a mere 2% of cases (Templeton et al., 1975; Templeton, 1981). In a study of 159 AIDS patients with Kaposi's sarcoma regression occurred only in 6 (4%) (Real et al., 1985). In addition, of the 6 patients only one had complete regression with all the other patients having only partial regression; most patients had active lesions with the regressing ones (Real et al., 1985).

**RELAPSE**

There is growing evidence that iatrogenic Kaposi's sarcoma can relapse under certain circumstances (Al-Sulaiman et al., 1994; Penn, 1997; Poch et al., 1992; Qunibi et al., 1993). In a report of their experience and review of the limited number of cases identified from the literature, Doutrelepont et al. (1996) have shown universal recurrence of iatrogenic Kaposi's sarcoma after renal transplantation. The recurrence seems to occur irrespective of the waiting period after the initial disease:
one subject developed Kaposi's sarcoma after renal transplantation despite 19 years of clinical remission; Doutrelepont et al. (1996) also noted that the pattern of the recurrent disease was similar to the first, with no life-threatening disease. Remission of the recurrent disease could be induced by reduction of immunosuppression albeit at the cost of the graft in some cases. Al-Sulaiman et al. (1992) describe recurrence and remission twice in the same patient following discontinuation and reintroduction of cyclosporine; the Kaposi's sarcoma relapsed and remitted when azathioprine was introduced and withdrawn. Considering the high potential risk of relapse of Kaposi's sarcoma the policy in our Unit has been to avoid retransplantation in patients who have had the disease, irrespective of the period of remission.

The single renal transplant recipient, who experienced a relapse in our series, did so at the time of severe local sepsis (Fig. 9-5). The patient had developed severe necrotising cellulitis of both lower limbs 3 years after clinical remission of the primary Kaposi's sarcoma. The patient, who initially had skin and inguinal lymph node involvement, had a recurrence of the skin disease but not of the lymphadenopathy. At the time of the relapse the patient was only receiving small doses of steroids and azathioprine. The patient was later discovered to have pulmonary Kaposi's sarcoma and she eventually died. To the best of our knowledge, this is the first case of relapse of posttransplant Kaposi's sarcoma associated with an intercurrent infection to be described. AIDS-Kaposi's sarcoma has also been described to flare after intercurrent illness such as *Pneumocystis carinii* pneumonia (Tappero et al., 1993).

**DIFFERENTIAL DIAGNOSIS**

The clinical diagnosis of Kaposi's sarcoma is, as a rule, not very difficult if it occurs in a renal allograft recipient on the distal parts of the lower limbs several months after the transplant. Nevertheless, in certain circumstances, it can be difficult to differentiate patch or plaque lesions of Kaposi's sarcoma from ecchymoses, stasis changes, or even inflammatory changes such as lichen planus. The papular, nodular stages of Kaposi's sarcoma may be clinically similar to several different conditions such as haemangiomatas, venous lakes, glomus tumours, pyogenic granulomas, and malignant tumours such as squamous cell carcinomas, malignant lymphomas, angiosarcomas and malignant melanomas (Mooney et al., 1995; Nielsen...
et al., 1994; Schwartz, 1996). Most of these lesions are discussed in detail in Chapter 10. Another important clinical differential diagnosis is bacillary angiomatosis (Brenner et al., 1993; Cotell et al., 1994; Levell et al., 1995; Raoult et al., 1994; Schwartz et al., 1997; Tompkins et al., 1993), a relatively new bacterial infection caused by Bartonella henselae or Bartonella quintana (Brenner et al., 1993; Raoult et al., 1994) that has a predilection for patients with human immunodeficiency virus infection or others with compromised immunity. It commonly presents with multiple red skin lesions and visceral involvement may occur. The dermatological lesions resemble those of Kaposi's sarcoma.

COLOUR PHOTOGRAPHIC IMAGES (Figs. 9-2 to 9-5)

A series of photographic images of individual patients follow that demonstrate some of the key features of clinical Kaposi’s sarcoma as seen in our cohort of renal transplant recipients.
Fig. 9-2 Patient SG.

(A) The typical appearance of Kaposi's sarcoma lesions on the legs is shown. Some macules are seen but most of the deep violaceous lesions are papular. The white arrow shows lesions along the course of a superficial vein, a pattern well recognised in Kaposi's sarcoma (Safai, 1984).
Fig. 9-2 Patient SG.
The concentration of Kaposi’s sarcoma lesions on the distal part of the legs is clearly demonstrated in these photographs (B, C) taken at the time of diagnosis. This patient had no inguinal lymph node involvement or lymphoedema.
Fig. 9-2 Patient SG.

These series of photographs show the healing of papular-plaque Kaposi’s sarcoma lesions over time. The images were taken at the following times: (C) At diagnosis, (D) at 6 months (E) at 9 months (F), and at one year following the initial diagnosis. Note that the active lesions are deep purple in colour and give rise to healed lesions that are brownish in colour.
**Fig. 9-3 Patient ML.**

This series illustrates the behaviour of a large tumour on the right buttock of the patient situated on a large plaque with two satellite lesions. The subsequent photographs document the remission of the lesions. The photographs were taken at the specified times after diagnosis: (A) and (B) 0 months (C), 3 months, (D) 5 months, (E), 8 months and (F) 12 months after diagnosis. Note the hyperkeratosis resembling psoriasis in (C).
Fig. 9-4. Patient DI.

This series illustrates the Koebner phenomenon quite clearly with Kaposi's sarcoma lesions in the region of the surgical graft implantation site as well as the site of surgical insertion of a Tenckhoff catheter. The associated inguinal lymphadenopathy is illustrated, as is the oedema of the right leg. The timing of the photographs in relation to the primary diagnosis of Kaposi's sarcoma is as follows: (A, B, C), 0 months; (D,E,F,G,) 2 months; (H,I), 4 months; (J,K,L), 6 months; (M,N), 9 months. Note the resolution of the large patch of Kaposi's sarcoma with minimal staining and scarring. Note the persistence of the lymphoedema of the right leg.
Fig. 9-5 Patient RB.

This patient suffered a relapse of Kaposi's sarcoma after the onset of severe cellulitis of both lower limbs. Histological proof had been obtained of the initial diagnosis of Kaposi's sarcoma, the resolution and the subsequent relapse. The photographs (A,B) illustrate the healed Kaposi's sarcoma lesions (black arrow) and the new lesions (white arrows). Beside the skin disease, the patient also had pulmonary Kaposi's sarcoma disease with the relapse but no involvement of the inguinal lymph nodes that were affected by the initial disease.
SUMMARY
Postrenal transplant Kaposi's sarcoma is a disease primarily of the skin, where it produces lesions that are fairly easily recognisable clinically. The lower parts of the legs are the characteristic sites to be affected and lesions are usually violaceous rashes that can be macules but are more commonly papules or nodules. The disease may also occur in the lymph nodes with the inguinal nodes the ones that appear to be most commonly affected clinically. Gastrointestinal involvement is the visceral site most often involved by the disease followed by pulmonary Kaposi's sarcoma. The diagnosis of Kaposi's sarcoma in renal transplant patients should be confirmed by histological examination of tissue because the disease can be mimicked by a large number of other conditions, which clinically resemble Kaposi's sarcoma.

With appropriate management the disease usually remits, although patients with visceral disease, especially lung involvement, are less likely to do so. The disease predictably relapses when immunosuppression is reintroduced, making the question of retransplantation of uraemic patients in Kaposi's sarcoma remission, a very vexed one. We also describe an unusual case of relapse of posttransplant Kaposi's sarcoma following severe intercurrent infection.

LITERATURE CITED


Bluefarb, S. M.


Clinical Aspects of KS


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