observed recurrence in the graft after transplantation in the following diseases: nephronophthisis (29 cases), cystinosis (15 cases), congenital nephrotic syndrome of Finnish type (2 cases), Bartter's syndrome (1 case), Alport's syndrome (1 case), acroosteolysis with nephropathy (1 case) and Nail Patella syndrome (1 case).

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RENEAL TRANSPLANTATION IN CHILDREN

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Diagnosis and treatment of rejection

Three forms of allograft rejection are well recognised in paediatric as well as adult renal allograft recipients. Hyperacute rejection occurs immediately after allograft revascularisation and is associated with the presence of preformed lymphocyto-
toxic antibodies in the recipients directed against HLA antigens. No treatment is effective in reversing this form of rejection; however, recently, the incidence has diminished markedly with the development of the long incubation time cross-match technique.

Acute rejection usually occurs within the first three post-transplant months and is usually reversible with increased corticosteroid therapy. Non-compliance with immunosuppressive therapy or concomitant infection processes should be considered with the occurrence of late acute rejection episodes.

Chronic rejection is usually manifest after the sixth post-transplant month and is characterised by a slow progressive deterioration of allograft function, which ultimately results in allograft failure. To date, no specific therapeutic intervention has been effective in reversing the phenomenon. However, allograft function may remain stable for many years following the development of chronic rejection with adequate function sufficient to sustain life without dialysis.

Recently, an additional form of rejection has been identified which may occur with increased frequency in paediatric recipients. Acute accelerated rejection [1] occurs during the first post-transplant week following an initial period of allograft function. The clinical manifestations are more severe and the duration more prolonged than acute rejection. Treatment is ineffective, with ultimate allograft failure. In our experience with 10 recipients of primary allografts (5.6% of total primary allografts during an 11-year period), none of the recipients had pre-formed lymphocytotoxic antibodies and all allografts were lost. Typical light microscopic findings in each allograft included haemorrhagic infarction or fibrinoid necrosis of the renal cortex [1]. The precise mechanism of acute accelerated rejection has not been identified; however, antibodies directed against the vascular endothelium require serious consideration [2].

Recipient responsiveness

It is likely that one of the major factors determining the outcome of renal transplantation in children as well as adults is individual immunological responsiveness. Previous factors which have been proposed as indicators of immunological responsiveness in adult recipients have been:

1) development of lymphocytotoxic antibodies following blood transfusion [3];
2) ‘T’ cell blastogenesis to PHA stimulation [4];
3) active ‘T’ cell levels [5];
4) persistence of HBs antigenaemia [6];
5) low response to 2,4-dinitrochlorobenzine [7]; and total ‘T’ cell levels [8].

Uittenbogaart et al [8] have evaluated the pre-transplant recipient total ‘T’ cell levels as a predictor of allograft outcome in 50 paediatric allograft recipients. The 17 recipients with low pre-transplant total ‘T’ cell levels had significantly improved (94%) 18 month allograft survival rates when compared with the recipients
with medium (41%) or high (53%) levels. Obviously, segregation of potential recipients into groups with different anticipated allograft survival rates would permit more aggressive immunological manipulation of the group at greater risk for rejection.

Additional factors affecting the incidence and severity of rejection

*HLA A and B antigen matching* Although Professor Broyer and his colleagues at des Enfants Malades [9] have shown improved allograft survival with better HLA A and B antigen matching, we (Robert B Ettenger, personal communication) have been unable to demonstrate any salutary effect of such matching in primary cadaver donor renal allografts. However, it should be noted that the number of 3 or 4 antigen matches is small (5 out of 178 primary cadaver donor renal allografts).

Conversely, our experience with HLA A and B antigen matching in multiple cadaver donor renal allografts is encouraging. The 10 year allograft survival rate for 14 of 91 recipients of multiple transplants with a 3 or 4 HLA A and B antigen match was 70%, whereas the survival rate of the remaining 77 allografts with lesser matches was 20 to 30%. Therefore, HLA A and B antigen matching is probably important in all cadaver donor transplants in children and our inability to demonstrate any beneficial effect in primary allografts is probably related to the small number of primary ‘matched’ allografts in our experience.

*HLA DR antigen matching* To my knowledge, no previous study has evaluated the effect of DR antigen compatibility on renal allograft survival in paediatric patients. We (RB Ettenger, personal communication) have evaluated the effect of DR matching in 63 paediatric renal allograft recipients. The 17 recipients of cadaver donor allografts with zero DR incompatibilities had a 63% 18 month allograft rate compared to a 42% survival rate in those recipients receiving an allograft with 1 or 2 DR incompatibilities. It is still too early to advocate transplantation solely on the basis of DR antigen compatibility; however, the preliminary data are encouraging.

*Adverse effects of anti-convulsant medications* Wassner et al [10] have shown that recipients receiving concomitant anti-convulsant medication following transplantation have exceedingly poor allograft survival rates. The stimulation of microsomal liver enzymes which enhance the metabolism of corticosteroids, thereby reducing effective blood levels with resultant inadequate immunosuppression, probably accounts for the deleterious effect of the anti-convulsant drugs.

Currently, either discontinuing the anti-convulsant medications, if possible, prior to transplantation or, if continued treatment is mandatory, increasing the corticosteroid dosage for a prolonged period of time post-transplant is advocated.

*Non-compliance with immunosuppressive medications* Non-compliance with prescribed medications is a major problem following transplantation in adult [11] and paediatric recipients [12]. Negrete, Fine and Korsch [13] evaluated the post-transplant course of 110 paediatric allograft recipients who had a functioning
renal allograft for longer than six months in order to determine the incidence and outcome of non-compliance. Non-compliance was suspected by a reduction in allograft function coincident with a modulation in the patients cushingoid appearance. Twenty-one (19%) recipients admitted non-compliance. In most instances the admission was made to allied health professional members of the health care team and not to the physicians. Two-thirds of those admitting non-compliance were females and 18 (88%) were more than 11 years of age at the time of transplantation. Allograft loss occurred in 14 recipients and chronic rejection resulted in an additional three recipients. Of the six recipients who lost an initial allograft consequent upon non-compliance and then received a subsequent allograft, three non-complied following the second transplant. The latter phenomenon indicates that intensive psychological support may be inadequate to prevent non-compliance in susceptible individuals.

Infectious complications

The major infectious complications affecting primarily paediatric recipients are caused by the herpes group of viruses. Infectious complications following transplantation lead to significant morbidity and are the principal cause of death in paediatric allograft recipients [14]. As with adult allograft recipients, unusual bacterial (listeria monocytogenes, serratia marcescens), viral (herpes group), fungal (cryptococcus, nocardia) and parasitic (pneumocystis carinii) organisms are frequently encountered in paediatric recipients.

Information regarding varicella infection is somewhat limited in paediatric recipients. The development of varicella in children receiving immunosuppressive agents has been associated with increased morbidity and mortality [15]. Low-dose corticosteroid therapy is not hazardous in patients with varicella if the primary disease does not compromise the immune system [16]. In this circumstance, abrupt withdrawal of steroid therapy is contraindicated because of the potential for the development of adrenal insufficiency.

In 1969, we reported [17] the benign course of varicella in an 8-year old allograft recipient who was receiving 5mg of prednisone and 50mg of azathioprine daily. Subsequently, numerous recipients under our care have developed varicella infection and none have required hospitalisation. If the lesions were haemorrhagic and systemic symptoms developed, azathioprine was discontinued.

The potential hazard of varicella infection is emphasised by the fact that one of our patients, not under our care, died as a result of disseminated varicella, and there are two recent reports detailing complications from varicella infection in paediatric renal allograft recipients. Hurley et al [18] reported two cases of varicella in 76 paediatric recipients during a 5-year period. One child died with massive upper gastrointestinal bleeding.

Feldhoff et al [19] detailed 19 episodes of varicella in 160 paediatric recipients who were followed over an 11-year period. Eight of the 19 children had severe infection and one died. Second episodes of varicella were documented in three recipients. The authors correlated the continuation of azathioprine following the onset of varicella with increased severity of the disease and recommended discontinuation of azathioprine with the onset of symptoms. Although the authors also
recommended the use of zoster immune globulin or plasma upon exposure, the
data were insufficient to validate the efficacy of such therapy.

Malignancy

There are no previous reports detailing the incidence of malignancy in paediatric
allograft recipients. Preliminary analysis of data from the Tumor Registry (I Penn,
MD, personal communication), indicates that the types of tumours affecting
younger patients is similar to that seen in the entire registry.

The incidence and type of malignancy observed in seven reports detailing the
long-term outcome of renal transplantation in paediatric recipients is shown in
Table III. Except for our experience (RN Fine, personal communication) the
incidence is rather low with either none or one malignancy observed in each report.

TABLE III. Malignancy in paediatric allograft recipients

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Follow-up (years)</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Shanzo</td>
<td>1974</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>Weil</td>
<td>1976</td>
<td>57</td>
<td>13</td>
</tr>
<tr>
<td>Martin</td>
<td>1979</td>
<td>77</td>
<td>12½</td>
</tr>
<tr>
<td>Arbus</td>
<td>1980</td>
<td>78</td>
<td>10</td>
</tr>
<tr>
<td>Chantler</td>
<td>1980</td>
<td>64</td>
<td>10</td>
</tr>
<tr>
<td>Potter</td>
<td>1980</td>
<td>145</td>
<td>15</td>
</tr>
<tr>
<td>Fine</td>
<td>1981</td>
<td>257</td>
<td>14½</td>
</tr>
</tbody>
</table>


Children with prior or concurrent malignancies require end-stage renal disease
care. The principal primary renal malignancy necessitating end-stage renal disease
care in paediatric patients is Wilm’s tumour. Penn [20] reviewed data from 20
patients with Wilm’s tumour who received renal allografts. In 80% of the recipients,
the tumour was bilateral. Those patients who received a renal allograft less than
one year following treatment of the tumour had a 47% incidence of recurrence
or metastasis following transplantation, whereas there was no recurrence or meta-
stasis if transplantation was delayed for more than one year following treatment
of the Wilm’s tumour. Patient survival at two years after transplantation was
superior with unilateral (75%) compared with bilateral (38%) involvement. The
primary cause of death following transplantation in patients with bilateral Wilm’s
tumour is overwhelming sepsis. Previous chemotherapy and irradiation has been
causally related to the latter [21].

Reports of renal transplantation in children with prior non-renal malignancies
are minimal. Fine et al [22] have transplanted two children (rhabdomyosarcoma,
neuroblastoma) and Makker and Kirson [23] have transplanted one child (Burkitt’s
lymphoma) with primary non-renal malignancies. No recurrence of the primary tumour was observed.

**Allograft outcome**

The initial outcome with cadaver donor renal allografts in children indicates that the actuarial survival rate at five years is similar (+50%) for first, second and third allografts [24]. Results with fourth and fifth cadaver donor allografts are quite dismal with no allografts in our experience surviving longer than one month.

The long-term outcome of live-related and cadaver donor allografts in children reported from six centres [25-30] is shown in Table IV. Our more recent experience with 127 children who received 165 renal allografts between February 1967 and August 1975, and followed for 5 to 13½ years, indicates a 5-year actuarial survival rate for parental live-related donor allografts of 73%, for first cadaver donor allografts of 38% and for second cadaver donor allografts of 59% (Figure 3).

To date, all 10 HLA identical sibling allografts are functioning one to 10 years post-transplant.

As shown in Figure 3, allograft survival at five years does not guarantee continued allograft function. Allograft loss from chronic rejection or patient death results in subsequent attrition despite adequate function at five years.

Of the 257 children whom I have cared for since 1967, 47 (18%) died following transplantation. Death was attributable to a complication related to transplantation in 30 and 17 patients died following return to dialysis. The cause of death is shown in Table V.

**Pregnancy**

I have followed 16 female allograft recipients who have had 24 pregnancies. Nine of the pregnancies ended in an abortion; 8 therapeutic and 1 spontaneous. Twelve
TABLE V. Cause of death following transplantation. Thirty patients

<table>
<thead>
<tr>
<th>Cause</th>
<th>Count</th>
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<tbody>
<tr>
<td>Sepsis</td>
<td>20</td>
</tr>
<tr>
<td>Bacterial</td>
<td>13</td>
</tr>
<tr>
<td>Candida</td>
<td>1</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>1</td>
</tr>
<tr>
<td>CMV</td>
<td>3</td>
</tr>
<tr>
<td>Varicella</td>
<td>1</td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
<td>1</td>
</tr>
<tr>
<td>Seizure</td>
<td>3</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>2</td>
</tr>
<tr>
<td>Intracerebral haemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
</tbody>
</table>

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recipients delivered 16 (1 set of twins) live-born infants.

Prematurity (birth weight < 2500gm) occurred in 5 of 15 single birth pregnancies. The only neonatal complication was respiratory distress syndrome in one 1200gm infant. There were no neonatal deaths and all 16 infants are currently surviving and are 3 months to 10 years of age. Previously reported [31] developmental evaluation of six of these offspring revealed no differences from that expected from a population of normal children.

Two recipients manifested reduced allograft function during pregnancy which persisted post-partum. Both recipients had impaired allograft function (serum creatinine level 1.8 and 1.9mg/dl) prior to pregnancy and currently have persistently reduced function (2.5 and 2.6mg/dl). Of the 12 mothers, three returned to dialysis at some time following delivery, one of whom died while undergoing dialysis.

Four male allograft recipients have had six children. All of the offspring are normal. However, one father died eight years following transplantation leaving three children to be reared by his wife.

The potentially adverse effect on allograft function from pregnancy in a female recipient with already impaired function and the potentially shortened life expectancy of allograft recipients are the major issues confronting young allograft recipients who wish to become parents.

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