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LONG-TERM OUTCOME OF RENAL TRANSPLANTATION IN CHILDHOOD

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Illustration: John Sandberg

To Erika, Lovisa and Christer

ABSTRACT

The aim of this thesis was to evaluate the long-term results of renal transplantation in children at Huddinge University Hospital, with special reference to outcome.
We therefore evaluated the course of events in children (age 0.1-16 years) transplanted between December 1981 and December 1991 during a 10-20-year period until 2001. Fifty-three children (26 girls) received a renal transplant at median ages of 7.1 (0.5 - 15.6) years in girls and 5.0 (0.4 - 14.4) years in boys. Seventeen children have received a second transplant 7.7 (0.01-14.7) years after the first, and one a third, 1 year after the second. In 79%, the underlying disorders were congenital (malformations and hereditary disorders). Among acquired disorders, glomerulopathies were the commonest. Dialysis was given mean 1.8 months before the first transplantation to 55% of the children.
Living donors (LD) were used in 72% and most were parents. At that time, the standard immunosuppression included cyclosporine, azathioprine and prednisolone. During follow-up, 21 children were switched to tacrolimus 4–12 years after transplantation, and 3 were treated primarily with tacrolimus after a second transplantation.

The overall actual 1-, 5- and 10-year patient survival rates were 91%, 89% and 89%, respectively, and the corresponding graft survival rates after the first graft were 85%, 77% and 66%, respectively. One- and 5-year graft survivals in 18 re-grafted patients were 89% and 89%. We found no difference in patient survival rates between children who received LD kidneys and kidneys from a deceased donor (CD), but the graft survival rates were better in LD (90%, 84% and 74%) than in CD (73%, 60% and 47%) kidneys at 1, 5 and 10 years, respectively (p=0.007). Graft losses were due to acute rejection in 5, chronic rejection in 13 and renal cell carcinoma in 2 cases. Three children died with functioning grafts.
Renal function (GFR) was mean 58 ± 19 mL/min/1.73m^2 body surface area (BSA) at 1 year (N = 42) and 44 ± 16 mL /min /1.73m^2 BSA at 10 (N = 33) years. When we evaluated the renal reserve, transplanted children increased their GFR after a protein-rich meal and retained this capacity during follow-up, which contradicts maximal hyperfiltration.
The height Z-score increased from -1.3 ± 1.7 in girls and -2.7 ± 1.6 in boys at transplantation to -0.6 ± 1.0 and -1.5 ± 1.2 at 5 years in a study of 58 children, transplanted from 1981 to 1994 and followed for at least 5 years. The final adult height Z-score of 16 girls was -0.7 ± 1.2 and of 8 boys -1.8 ± 1.2, who reached adulthood during the study. GFR at 1 and 5 years predicted good growth from transplantation to 5 years.

In conclusion, good long-term patient survival was found after renal transplantation in childhood, even in the youngest age group. Graft survival was better in LD grafts. Good growth and a promising absence of severe long-term effects of immunosuppression were seen 10-20 years after transplantation.

Key words: Adolescent, Adult height, Cadaver donor, Child, Glomerular filtration rate, Growth, Immunosuppression, Infant, Kidney Transplantation, Living Donor, Renal function, Renal reserve, Survival Analysis

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CONTENTS

LIST OF ABBREVIATIONS

BW	Body weight
ARPKD	Autosomal recessive polycystic kidney disease
BA	Bone age
BSA	Body surface area
BW	Body weight
CD	Cadaveric donor
CMV	Cytomegalovirus
CRF	Chronic renal failure
EBV	Ebstein-Barr virus
EPO	Erythropoietin
ERPF	Effective renal plasma flow
ESRD	End-stage renal disease
FH	Final adult height
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HD	Hemodialysis
Ht	Height
LD	Living donor
MMF	Mycophenolate mofetil
NAPRTCS	North American Pediatric Renal Transplant Cooperative Study
NxAg	After nephrectomy or because of agenesis
PAH	Para-aminohippuric acid
PD	Peritoneal dialysis
PTLD	post-transplant lymphoproliferative disorder
PUV	Posterior urethral valve
PUV	Posterior urethral valve
RCC	Renal cell carcinoma
RFR	Renal functional reserve
rhGH	Recombinant human growth hormone
TRF	Terminal renal failure
Tx	Transplant/ transplantation
UNOS	United Network for Organ Sharing
VUR	Vesico ureteral reflux
ΔERPF	Increase in ERPF from baseline to maximal
ΔGFR	Increase in GFR from baseline to maximal

1 INTRODUCTION

1.1 BRIEF HISTORICAL REMARKS

Experimental organ transplantation was reported at the beginning of this century,
mostly between animals. The Hungarian surgeon, Emerich Ullman, performed a
famous transplant in 1902, which he described at a Medical Society Meeting in Vienna.
He removed the kidney of a dog and transplanted it into the neck of another dog, with
the renal artery joined to the carotid artery and the renal vein to the external jugular
vein (Ullmann 1902). Although he did not succeed in human transplantation, he
probably prepared the way for the transplantation era. In 1936, Vorony, a Russian,
performed the first human kidney transplant, probably without success. In the early
1950s, experiments by Simonsen in Denmark, among others, led to a series of human
transplants with cadaver kidneys in Paris and Boston. Since no immunosuppression
was available, these kidneys failed after a few weeks. In 1954, Murray performed the
first successful renal transplantation between identical twins in Boston, and he received
the Nobel Prize in 1990 for this pioneer work (Jansson and Andersson 2002).
At first, the only type of immunosuppression was total body irradiation, which often
resulted in fatal infections due to pancytopenia. In 1959, the immunosuppressive effect
of 6-mercaptopurine was reported and successful kidney transplantations were done in
dogs when this medication was used. A further development was azathioprine, which is
still used in renal transplantation. During the past 30-40 years, developments in this
field of medicine have been rapid. With the advent of cyclosporine, a new potent
immunosuppressive agent, in the beginning of the 1980s, there was a substantial
increase in organ transplantation. Today, new drugs like tacrolimus and mycophenolate
mofetil have been developed, which are also used in pediatric transplantation.
With the introduction of cyclosporine, even infants were accepted for transplantation
and the number of pediatric renal transplantations has therefore gradually increased. In
Sweden today, about 250 pediatric renal transplantations have been performed, 150 of
these in Stockholm. The data from some of them form the basis of this thesis.

1.2 UNDERLYING DISORDERS

1.2.1 Definitions

Chronic renal failure (CRF) is defined as a glomerular filtration rate (GFR) below 30 ml/min/1.73m^2 during 6 months and terminal renal failure (TRF) or end-stage renal disease (ESRD) is defined as a stage when either dialysis or transplantation is required.

1.2.2 Epidemiology

In the European Union (including 15 countries with a total population of 373.3 million people in 1996) the annual incidence of ESRD was 118 per million population in all age groups. The corresponding annual number of transplantations was 30.4 per million population, which shows that the need for renal transplantations far exceeds their availability (ERA-EDTA 2000).

In the latest Swedish survey in this field, for the period 1986-1994, the median annual incidence of CRF in children (6 months to 16 years) was 7.7 and of TRF 6.4 per million children under the age of 16 years (Esbjorner et al. 1997). The prevalence of preterminal renal failure (the period from CRF to TRF) was 21 per million children and the prevalence of TRF 38 per million children in 1994. With a mean annual incidence of primary transplants of 6.5 per million children (below 16 years) in the Nordic countries, probably all Nordic children with TRF receive a renal transplant (Tyden and Berg 1998) unlike in the rest of Europe.

1.2.3 Renal disorders

Renal disorders can be classified in various ways, and we have chosen to classify them as congenital and acquired. Most disorders in children are congenital disorders, unlike in adults who usually have acquired diseases, of these glomerulonephritis and diabetic nephropathy are among the commonest.

Congenital renal disorders in children are malformations, including hypo-and dysplasia with or without obstruction, and hereditary disorders.

Hypo-and dysplastic kidneys, with or without obstruction, are usually detected as small kidneys on ultrasound. Although this condition is congenital, enough renal function may persist for several years. Renal dysplasia is a disturbance in the normal development of the branching ureteric bud and the metanephric blastema resulting in primitive ducts and cartilaginous metaplasia. Dysplasia is often associated with other genitourinary abnormalities. Renal hypoplasia is a reduction in the number of normally developed nephrons with an overall small kidney size.

Obstructive uropathies comprise posterior urethral valves (PUV), prune-belly syndrome and other obstructive malformations. PUV (only in males) are congenital folds in the urethra, which disturbs the outflow or, in the worst cases, induce total obstruction. This condition affects bladder emptying, and leads to pressure in backward direction from the bladder to the kidneys, increases the risk of urinary tract infection and leads to renal damage. Severe cases coexist with renal dysplasia. The natural history of this disease, often detected with prenatal ultrasound may vary, and the primary intervention in the

newborn child is considered important in "rescuing" renal function. The management
may be early vesicostomy followed by delayed valve ablation, primary valve ablation
or bilateral cutaneous nephrostomy drainage until ablation of the valve is performed.
The prune-belly syndrome is characterized by deficiency or absence of the abdominal
wall muscles, elongated, dilated, and tortuous ureters due to replacement of smooth
muscle by fibrous tissue, retentio testis and often an enlarged, non-trabeculated bladder
in combination with renal dysplasia. Mucosal folds in the urethra, "pseudo valves", are
sometimes found.

Hereditary disorders comprise: 1) familial juvenile nephronophthisis (an autosomal
recessive disorder that usually becomes clinically evident during childhood or early
adolescence, when the renal pathology is dominated by changes in the tubular basement
membrane and medullary cysts and the disorder is sometimes accompanied by liver and
eye abnormalities); 2) autosomal recessive polycystic kidney disease (ARPKD, with
congenital hepatic, periportal, fibrosis among other associated abnormalities); 3)
congenital nephrotic syndrome (usually the Finnish type, but other forms are also seen);
4) Laurence Moon Biedl syndrome, or Bardet Biedl syndrome (an autosomal recessive
disorder characterized by obesity and several other abnormalities such as retinal
dystrophy, polydactyly, and renal malformations); 5) other hereditary disorders. Drash
syndrome is a disorder characterized by nephropathy (diffuse mesangial sclerosis),
male pseudohermaphroditism, and Wilms' tumor and often presents as congenital or
infantile nephrotic syndrome.

Acquired renal disorders include glomerulopathies (IgA-nephritis, crescentic
glomerulonephritis, membranoproliferative glomerulonephritis, focal segmental
glomerulosclerosis and others), vascular nephropathies (renal damage due to neonatal
asphyxia, hemolytic uremic syndrome with or without preceding diarrhea) and others.
In some children with ESRD, the primary renal disease may be difficult to establish due
to chronic disease with long-standing changes.

1.3   RENAL FAILURE IN CHILDREN

1.3.1   Clinical consequences of renal failure

Manifestations of renal failure include disorders of fluid and electrolyte balance, acid-
base balance, and abnormalities related to hormonal dysfunction.

Fluid and electrolyte balance. Children with obstructive uropathy (and reduced GFR)
and/or tubular disorders can often not reabsorb sodium and water effectively and a salt-
and water-losing state occurs, which contributes to poor growth.

Fluid retention (due to reduced GFR and increased activity of the renin-angiotensin-
aldosterone system) on the other hand, is a factor that is common in acquired diseases.
The kidneys' capacity to excrete potassium is often preserved and severe hyperkalemia
is not usually present until late stages of renal failure.

In CRF, *metabolic acidosis* develops when the kidneys are unable to secrete enough
endogenous acid into the urine in the form of ammonia and/or to reabsorb filtered
bicarbonate.

Hormonal dysfunction.
Reduced *erythropoietin* (EPO) production leads to decreased red blood cell production
by the bone marrow, which is the primary cause of anemia in CRF (Wassner and Baum
1999). Recombinant human EPO is now available.

Another hormone produced by the kidneys is *calcitriol* (1,25-dihydroxycholecalciferol or active vitamin D), a hormone that stimulates calcium uptake by the intestine. CRF is associated with several events that affect the mineral metabolism and may cause renal osteodystrophy, including rickets and secondary hyperparathyreoidism (Sanchez et al. 1999; Hruska 2000). With the reduction in GFR in renal failure, hyperphosphatemia develops from the inability of the kidneys to excrete enough phosphate and results in hypocalcemia (Kates et al. 1997). Hypocalcaemia, reduced renal synthesis of calcitriol and phosphate retention stimulate the release of parathyroid hormone which all are factors implicated in the pathogenesis of renal osteodystrophy. Renal osteodystrophy has different histological features - i.e., osteitis fibrosa, osteomalacia and adynamic bone disorder (Hruska 2000). Clinical manifestations of renal osteodystrophy in children may include bone pain, slipped epiphyses, bone deformities (in young children similar to those due to vitamin D-deficient rickets - i.e., rachitic rosary, metaphyseal widening leading to wrist and ankle enlargement, craniotabes and frontal bossing), muscle weakness and growth retardation (Sanchez et al. 1999).

Hypertension, common in CRF, is closely related to renal function and the type of underlying disorder, such as various kinds of glomerulopathies. It has several causes including volume expansion, increase in the activity of the *renin*-angiotensin and in the sympathetic nervous systems, among others (Gruskin et al. 1999). Hypertension is one of the determinants of progression of CRF. Cardiovascular complications are the main cause of mortality in CRF and hypertension is the main risk factor for left ventricular hypertrophy (Daniels et al. 1998).

Among other features of CRF are:
*Hyperlipidemia*is also a frequent finding in CRF, - i.e., both hypertriglyceridemia and hypercholesterolemia. In addition some changes occur in the distribution of lipids within the lipoprotein fractions, the commonest defect being a reduction in high-density lipoprotein cholesterol (Zacchello et al. 1987; Silverstein et al. 2000). Atherosclerosis begins during childhood (Strong et al. 1999) and children with CRF presumably undergo years of accelerated atherosclerosis as they mature. CRF is associated with several cardiovascular risk factors (hypertension, dyslipidemia, hyperphosphatemia, hyperhomocysteinemia and chronic inflammation) and the effects of these risk factors probably accumulate with the duration of the disease.
Neurological disturbances. Twenty years ago, there was an alarming report by Rotundo, who described encephalopahy with developmental delay, microcephaly and EEG abnormalities in 20/23 children with renal failure in infancy (Rotundo et al. 1982). He therefore recommended early transplantation to protect the development of the brain. Recent data show that infants and children with renal failure and after transplantation have more satisfactory neurodevelopment than previously reported by Rotundo (Warady et al. 1999; Brouhard et al. 2000; Qvist et al. 2002).

1.3.2 Growth in renal insufficiency

Growth impairment, one of the most troublesome complications of renal failure (Chantler et al. 1977; Broyer 1982; Rizzoni et al. 1984; Mehls et al. 1992), is in some cases the clinical manifestation that brings the child to a medical investigation that

leads to the diagnosis of renal failure. Severe growth impairment is associated with renal failure in some syndromes, cystinosis and other tubular disorders.

Many children with renal insufficiency early in life have retarded growth (Rees et al. 1989; Schaefer et al. 1996), loses growth potential during puberty and finally have an adult height below normal (Haffner et al. 2000). Various conditions arising from, or related to, inadequate renal function may interfere with normal growth, such as malnutrition (Betts et al. 1977), metabolic acidosis (Hanna et al. 1996), renal osteodystrophy (Sanchez et al. 1999) and dialysis effectiveness (Broyer 1982). Disturbances in the somatotropic hormone axis play an important pathogenetic role in growth retardation in children with CRF (Tonshoff et al. 1997; Kuizon and Salusky 1999). The levels of growth hormone (GH) are normal or elevated, depending on the extent of renal failure, which would suggest end-organ GH resistance (Tonshoff et al. 1997). Treatment with GH is recommended early in the preterminal phase in growth retarded children with CRF, since it may improve their final height (Haffner et al. 1998; Haffner et al. 2000).

1.4 TREATMENT OF ESRD

Today's management of CRF includes early treatment of acidosis and prevention of renal osteodystrophy (Rigden 1996; Salusky and Goodman 1996). Dieticians are involved in care at an early stage and nutrition in the form of enteral feeding is often required (Kari et al. 2000; Ledermann et al. 2002) as also are recombinant human growth hormone (rhGH) if growth retardation is marked and EPO in case of anemia. Renal transplantation is the optimal therapy for children with ESRD despite advances in dialysis therapy (Fine 1985; Holtta et al. 1997; USRDS 2001).

1.4.1 Dialysis

Two kinds of dialysis are available – i.e., peritoneal (PD) and hemodialysis (HD). PD is frequently used at our unit, especially in the youngest children (Holtta et al. 1997; Ledermann et al. 2000). Children on dialysis are chronically ill and this life-sustaining method obviously restricts their own and their families' lives. Parents learn how to manage the PD treatment at home, and most children receive overnight continuous cycling PD. The complications arising from PD include catheter malfunction, exit-site/tunnel infection and peritonitis. Peritonitis occurs more commonly in the youngest children (Lerner et al. 1999). There is also a risk of sclerosing peritonitis with long-term PD (Hoshii et al. 2000).

Hemodialysis, the often preferred method in older children at our unit, require use of a vascular access, - i.e., either as an external double-lumen catheter into a central vein or as an internal arteriovenous fistula or graft (lower arm). The complications with HD include infections, clotting and malfunction of the access (Warady et al. 1997). Children in HD may be absent from school for long periods, which may seriously affect their school work (Brouhard et al. 2000). PD, however, permits children to have their days free from dialysis in order to attend school. This is reflected by NAPRTCS data, which shows that full-time studies are more common in PD treated than HD treated students (Lerner et al. 1999).

1.4.2 Renal transplantation

1.4.2.1 Brief immunological background
Pre-emptive transplantation - i.e., transplantation without prior dialysis - is performed in about 20-45% of cases (Englund et al. 1993; Offner et al. 1993; Mahmoud et al. 1997; Vats et al. 2000).

In general, renal transplantation can be successfully performed if the donor and the recipient's blood group is compatible, according to the AB0-blood group system, using the same principles as with blood transfusions. Recently, in living donor transplantation, AB0-incompatible renal transplantations have been successfully performed (with special pre- and posttransplant management), even in children (Shishido et al. 2001).
Rejection of the graft is the response by the recipient's immune system against antigens on the graft, - i.e., proteins that vary from individual to individual and are thus perceived as foreign by the recipient. The recognition of an antigen by helper (CD4+) and cytotoxic (CD8+) T-lymphocytes is the primary event that leads to the cascade of events in the cell-mediated immune response causing cell death and rejection of a transplanted organ (Holgersson et al. 2002).

1.4.2.2 Immunosuppression

Since one can not suppress specifically the immunological response to the graft, generalized immunosuppression of the recipient is necessary. A combination of various immunosuppressive drugs is usually given, thereby reducing the doses and consequently the side effects of each drug. Children are more immunoreactive than adults, and therefore require larger doses of immunosuppressive medications.

The calcineurin inhibitor, *cyclosporine,* is of fungal origin and *tacrolimus* is a macrolide antibiotic; they both inhibit production and release of IL-2 and IL-2-induced activation of resting T-lymphocytes. They produce their effect by binding to immunophilins in the cytosol. The immunophilin: drug complexes inhibit the phosphatase activity of a Ca^{2+}-activated enzyme, calcineurin (an enzyme that transmits signals from the T-cell receptor to the nucleus), which then inhibits the clonal expansion of activated T-cells.

Azathioprine, an imidazolyl derivative of 6-mercaptopurine, antagonizes purine metabolism and inhibits the synthesis of DNA, RNA, and proteins. It was developed originally to treat cancer, but was found to be cytotoxic to dividing lymphocytes and therefore immunosuppressive as well. The use of azathioprine is limited because of its many toxic effects on tissues that have in common the property of inhibiting continuous cell division (reduces immune function, causes anemia, leukopenia, thrombocytopenia, hair loss and damages the intestinal epithelium). Because of its toxicity, lower doses are given in combination with other drugs, such as corticosteroids (Tufveson 2002).

Mycophenolate mofetil, MMF, reduces purine synthesis in T- and B-lymphocytes, thereby inhibiting lymphocyte proliferation and antibody production.

Prednisolone, a corticosteroid, suppresses the immune system by regulating the expression of several genes (coding for a number of cytokines) that have an anti-inflammatory effect. Corticosteroids inhibit the synthesis of almost all known cytokines. In doses of 5-20mg/d, steroids are known to down-regulate the expression of MHC II on antigen-presenting cells (Tufveson 2002). Another immunosuppressive effect is peripheral lymphopenia (Ferraresso and Kahan 1994).

1.4.2.3 Rejection

In organ transplantation, the principal targets of the immune response to the graft are the MHC molecules expressed on the surface of donor cells. The immune system of the graft recipient considers the graft "non-self" and therefore initiates an immune response against the graft. If not treated, the graft will be destroyed by the immunological response.

Rejection episodes can occur despite immunosuppression, and rejections are classified as acute and chronic. The Banff 97 classification (which is based on the 93 Banff classification of kidney transplant pathology) is an internationally agreed standard for histological grading of renal allograft biopsies defining various acute rejections and chronic allograft changes (Solez et al. 1993; Racusen et al. 1999).

Hyperacute rejection can occur if the recipient is pre sensitized, - i.e., has antibodies against the donor's tissues. This can occur after pregnancies, blood transfusions or previous transplantations. It occurs within minutes of transplantation.

Acute rejection can occur at any time, although most patients have had their first rejection within 3 months of the transplantation. By the end of the first year, 45-60% have had at least one rejection episode (Tejani and Emmett 2001). With improved immunosuppression, the incidence of acute rejection episodes has been markedly reduced during the past few years, as compared to the 1980s (McDonald et al. 2001). Many cases of *late acute rejections* (after the first year) are due to inadequate compliance (Tejani et al. 1998).

Chronic rejection or chronic allograft nephropathy is characterized by a slowly increasing graft dysfunction, which ultimately leads to chronic renal failure. Histopathological examination shows various combinations of lesions, such as vascular changes, glomerulopathy, interstitial fibrosis and tubular atrophy (Kasiske et al. 1991; Racusen et al. 1999). Chronic transplant dysfunction is usually associated with previous early and late acute rejection episodes (Matas 2000; Tejani and Sullivan 2000).

1.4.2.4 Donors

The kidney donor is either a living related or unrelated donor, or a so-called cadaveric donor - i.e., a person who has been diagnosed as having a total brain infarction with no brain function, but is kept on a ventilator to maintain breathing and circulation (SOSFS 1996:5).
The advantages of using a live donor include: reduced waiting time for the transplant, the avoidance or shortening of pretransplant dialysis, which is of value for graft survival (Mahmoud et al. 1997; Vats et al. 2000), the timing of transplantation under the best conditions is possible, and especially the better results obtained from living donor transplantation (Englund et al. 1993; Offner et al. 1993; McDonald et al. 2000; Seikaly et al. 2001). A donated kidney from a live donor is also of benefit to others on the waiting list, since the overall pool of recipients waiting for a kidney is increasing. Live-related donors are usually members of the family - e.g., most commonly parents, but also grandparents or other relatives. In the Scandinavian countries, grafts are frequently obtained from living donors, however, in some countries the use of live donors is debated and most organs are therefore taken from cadaveric donors. Living kidney donation is possible because enough renal function is maintained by a single kidney. As in other fields of medicine, the ethical principle is that one should do no harm, which, in this context, means that the donor should be exposed to little, if any, risk (Fehrman-Ekholm et al. 1997; Fehrman-Ekholm et al. 2001).
Un-related living donation requires special considerations and has rarely been used in the pediatric transplant program in our department. In adults and in many other countries, the number of unrelated donors is increasing because of the shortage of donors (Foss et al. 1998; USRDS 2001).

1.4.2.5 Surgical technique

The surgical technique for pediatric renal transplantation in children >20 kg body weight (BW) is similar to that used in adults, although placement of the vascular anastomoses depends on the size of the child and its vessels. The approach is extraperitoneal, and the venous anastomosis is done to the common or external iliac vein and the arterial anastomosis is to the common, external or internal iliac artery. The ureterovesical anastomosis is done with the Leadbetter-Politano technique. A ureteral stent is placed between the pelvis of the kidney and the urinary bladder.

In children < 20 kg BW, the kidney is usually placed intraabdominally through a midline incision. The renal vein is anastomosed to the vena cava and the renal artery to the aorta (Miller et al. 1983), see illustration.

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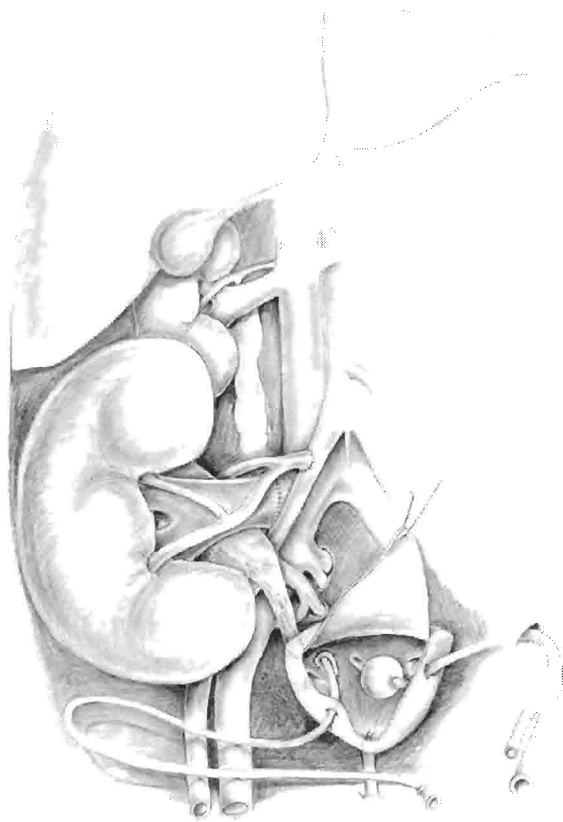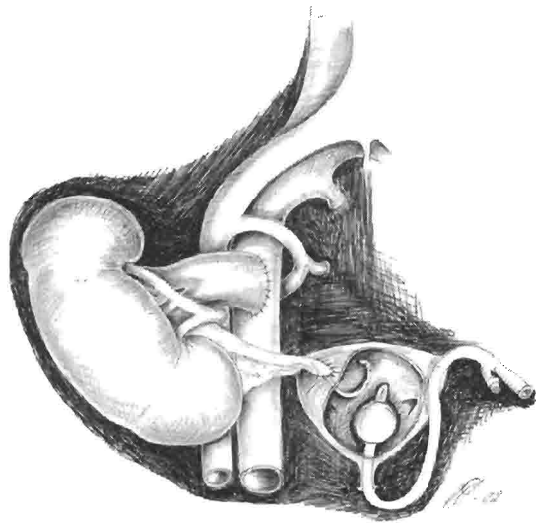
The upper illustration shows the surgical technique for pediatric renal transplantation in children >20 kg BW, and the lower the technique used for children < 20 kg BW.

1.4.2.6 Complications

Typical early complications include technical problems, acute tubular necrosis, allograft rejection, infections, hypertension and neurological and gastrointestinal disorders. The complications that may occur later include recurrent and de novo renal disease, chronic allograft rejection, cataract, skin diseases, malignancies, osteoporosis, hyperlipidemia and atherosclerotic disease. Infections could remain a problem and hypertension may even become more severe if graft function decreases. In children, growth failure is a special problem before and after transplantation, despite an increase in the rate of growth when steroids are switched to alternate days (Potter et al. 1975; Turenne et al. 1997).
The problems that are especially related to immunosuppression include hypertension, nephrotoxicity, neurotoxicity, gastrointestinal disorders, hepatotoxicity, hirsutism, gingival hyperplasia, diabetes and an increased risk of infection (Gaston 2001).

Infections

In the first month after renal transplantation, the major infectious complications include post-surgical bacterial and fungal infections that are similarly present in the nonimmunosuppressed population, - e.g., wound infections, catheter-related infections, pneumonia and urinary tract infections (Fishman and Rubin 1998). After the first month, the pattern of infections changes to that of an immunosuppressed patient - i.e., pneumocystis carinii (before prophylaxis became available) and viral infections becoming more frequent. Bacterial infections still occur more frequently than in those who are not on immunosuppressive therapy. After the first 6 months, most transplant recipients have infectious-disease problems similar to those of the general community - i.e. primarily respiratory infections. Chronic or progressive viral infections could cause morbidity (Fishman and Rubin 1998). The viral infections of particular importance after transplantation include: herpes viruses (cytomegalovirus, CMV, Ebstein-Barr virus, EBV, varicella and herpes simplex), hepatitis viruses and BK virus, belonging to the polyomavirus.

CMV infection is probably the most important opportunistic infection in renal transplant recipients. It is common and can occur when CMV-negative recipients receive grafts from CMV-positive donors, but it may also be due to a reactivated infection (positive recipient) or reinfection (when a positive recipient is infected by a positive donor's CMV strain). This infection has been reported in up to 2/3 of renal transplant recipients and 6-30% of those with CMV-disease, requiring hospitalization (Bock et al. 1997). The infection manifests in 90% during the first 5 months after transplantation (Bock et al. 1997) and an association has been found between a CMV infection and graft rejection. The clinical findings range from an asymptomatic infection to severe organ (hematological, lung, liver and gastrointestinal) involvement that can result in death. Today, prophylactic treatment with antiviral agents (acyclovir, ganciclovir) is given routinely, and it has markedly reduced complications from CMV infections (Bock et al. 1997; Couchoud 2000).
EBV is an oncogenic virus, which infects most people during childhood. A primary EBV infection, more common in children than in adults, is a risk factor for the development of a posttransplant lymphoproliferative disorder (PTLD) (Cohen 2000).

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Primary varicella, a common contagious disease, may cause fatal infections in immunosuppressed subjects (Fleisher et al. 1981; Lynfield et al. 1992; Kashtan et al. 1997). The youngest children may not have had it before transplant; this poses the risk of a primary varicella infection during immunosuppression since the virus is common in the community. Vaccination is routinely performed in children who are varicella IgG-negative before transplant.

Another family of viruses are the hepatitis viruses A, B and C (among others). Hepatitis B (HBV) and C virus (HCV) infections frequently occur in adult patients undergoing maintenance dialysis, at least in other parts of the world (Lee et al. 2001; Almroth et al. 2002; Breitenfeldt et al. 2002). Both HBV and HCV infections increase patient morbidity and mortality (Hanafusa et al. 1998; Bruchfeld et al. 1999; Lee et al. 2001; Almroth et al. 2002). Liver-related complications affect the HBV- and HCV-positive renal transplant population (Lee et al. 2001).

Among the polyomaviruses are BK virus, which can cause subclinical and persistent infections and can be reactivated in their host during immunosuppression. Ureteral stenosis and nephropathy with progressive graft dysfunction and graft loss has occurred in renal transplant recipients (Nickeleit et al. 1999). Current treatment is supportive and involves reduction of immunosuppression (Randhawa et al. 1996; Randhawa and Demetris 2000). A possible treatment option has emerged in the antiviral agent cidofovir (Andrei et al. 1997; Kwak et al. 2002).

During the first months after transplantation, *hypertension* is common (about 80%) (Broyer et al. 1987; Offner et al. 1992), its causes being drugs (steroids, calcineurin-inhibitors), electrolyte abnormalities, rejection, renal vascular stenosis of the graft and, in case of a reduction in graft function, renal failure (Broyer et al. 1987; Ponticelli et al. 1993). Pathology of the native kidneys, recurrence of the original disease and obesity are other factors that may contribute to hypertension (Gruskin et al. 1999). Hypertension is associated with increased rates of subsequent graft failure (Sorof et al. 1999; Dall'Amico et al. 2001).

Various nonmalignant changes and infections of the *skin* may develop after transplantation, the commonest being hypertrichosis and gingival hyperplasia, induced by immunosuppression, and V*errucae vulgares* and *Condylomata accuminata*, caused by human papilloma viruses (Euvrard et al. 2001; Avermaete et al. 2002).

Ocular changes are also common after transplantation -e.g., changes associated with hypertension and posterior subcapsular cataract. The latter is a side-effect from steroid treatment, and is seen in 24–40% of adults (Pai et al. 2000).

After renal transplantation, most metabolic disturbances that cause renal osteodystrophy are corrected. Nevertheless, bone disease may persist or even become worse (Julian et al. 1991; Boot et al. 1995; Ellis et al. 2000; Delmas 2001; Feber et al. 2001). Bone mineral density loss or *osteopenia* is a complication that affects transplanted children and may increase the incidence of fractures several years later (Ellis et al. 2000).

In transplanted children, other complications of long-term treatment include *malignancies*, with PTLD being the commonest and skin cancer as the second

commonest (Penn 1998). The risk of PTLD increases with: pretransplant EBV seronegativity (Ho et al. 1988), tacrolimus immunosuppression (compared with cyclosporine) (Dharnidharka et al. 2001) and the use of anti-T-cell antibodies (Swinnen et al. 1990). Skin cancer is the second most common malignancy in pediatric recipients (20% of tumors)(Penn 1994). Malignant melanomas were commoner in pediatric than adult recipients (15% v 5% of skin cancers). Skin cancer surveillance and education are important for prevention and transplanted children should be closely followed throughout their lives with respect to skin pathology (Cowen and Billingsley 1999; Kasiske et al. 2000; Harden et al. 2001).

1.4.2.7 Renal function in the transplanted kidney

A successful renal transplantation assumes that the child will have a normally functioning kidney for several years ahead. Measuring the glomerular filtration rate, GFR, is a clinical marker of the functioning renal mass and is an essential part of the evaluation of children with renal disease and after transplantation. Clearance of inulin is the "gold standard" that is used to measure renal function. Other filtration markers are thus compared with inulin. The formula clearance based on serum-creatinine and height (Schwartz, modified by Counahan) is often used, but tends to overestimate GFR (Berg 1991).

We have regularly, since 1981, measured renal function by inulin- and PAH clearances in our children after renal transplantation. In previous studies from our unit, GFR ($mL/min/1.73m^2$ BSA) was approximately 60 at 1 year and declined to 50 at 5 years and the corresponding absolute GFR (mL/min) was 35-40 at 1 and 5 years (Berg and Bohlin 1992). The same study also showed a declining GFR with an increasing number of rejection episodes at 1 year. Studies have also shown a functional adaptation of the adult kidney to the size of the child, reflected in a decreased absolute GFR (mL/min) within the first months after transplantation, whereafter absolute GFR remained stable in the adult donor graft resulting in decreasing GFR related to BSA ($mL/min/1.73m^2$ BSA) (Bohlin and Berg 1991; Berg et al. 1993). A better adaptation of the pediatric donor graft to the growing child (increase in absolute GFR) resulting in a stable GFR related to BSA ($mL/min/1.73m^2$ BSA) has also been reported (Berg et al. 1997; Dubourg et al. 2002).

Studies from other centres have shown GFR at 3-5 years after transplantation of 38-68 $mL/min/1.73m^2$ BSA determined by Schwartz formula (Offner et al. 1989; Hoyer et al. 1990; Flom et al. 1992; Chao et al. 1994; Sorof et al. 1999), and 40-70 $mL/min/1.73m^2$ BSA determined by clearances of inulin, iothalamate or EDTA (Williams et al. 1994; Gellert et al. 1996; Dubourg et al. 1998) in children with similar ages at transplantation.

1.5 RENAL FUNCTIONAL RESERVE

The progression of renal disease is of great concern for every nephrologist. The mechanisms underlying the decline in renal function puzzle clinicians and researchers. In 1948, Addis reported a relation between GFR and protein intake and suggested that patients with chronic renal insufficiency should have a protein-restricted diet to prevent the increase in "workload" and minimize the loss of renal function (Addis 1948). In 1982, Brenner et al. suggested that there is a relation between hyperfiltration and the progression of renal disease (Brenner et al. 1982). In experimental studies, a reduced number of nephrons leads to compensatory hyperfiltration in the remaining nephrons (Hostetter et al. 1981). This compensatory hyperfiltration could cause glomerosclerosclerosis and deterioration in renal function (Brenner et al. 1982). Increased protein intake also induces increase in GFR - i.e., a hyperfiltration. In 1983, Bosch et al. proposed, that a functional renal reserve is responsible for the increase in GFR after a protein rich meal. To determine whether hyperfiltration exists, they suggested a test with a protein load to determine the so-called "renal functional reserve"(Bosch et al. 1983; Bosch et al. 1984). Other stimuli, such as amino acids and dopamine infusion, can be used to increase GFR.

The assumption was made that in disease states a low renal reserve capacity would be the first indication of functional renal impairment before a reduction in glomerular filtration rate would become evident (Bosch et al. 1984; Bosch et al. 1986).

A consequence of a reduced or absent renal functional reserve could be to reduce the protein intake (Brenner et al. 1996) thereby decreasing the workload of the remaining nephrons.

These theories underly the studies reported in Papers 2 and 3.

2 AIMS OF STUDY

Renal transplantation in childhood is a comparatively new method used to treat renal failure in children. It involves various difficulties and risks, the long-term effects of which remain to be seen. The growing child may develop unexpected complications in the future.

The aims of this study were therefore to monitor and evaluate renal transplantation in childhood with reference to:

- Patient and donor data, including underlying diseases of the children
- Patient survival, both short and long-term
- Graft survival and causes of graft failure
- Renal function and reserve
- Growth after renal transplantation
- Short- and long-term complications

3 PATIENTS AND CONTROLS

3.1.1 Patients and controls in Papers I-V

All of these studies were done after the introduction of cyclosporine, which commenced in December 1981.

Table 1
The number of transplanted children, donors and children with a single kidney (NxAg) included in Papers I-V are shown here.

Paper	Tx children	Donors	NxAg
	n (in Paper I)	n (in Paper II)	n
I	53		
II	36 (32)	15	15
III	30 (27)	7 (7)	
IV	65 (53)		
V	53 (53)		

3.1.2 Papers I and V

Fifty-three children, transplanted between 15 December 1981 and 11 December 1991, were studied up to a minimum of 10 and maximum of 20 years. All children, up to the age of 16 years, transplanted during the 10-year period were included. During 1981-1991, 5 children died within 6 months, one 3.3 years after transplantation (Paper I) and 47 were followed for 10 – 20 years (Paper V).

3.1.3 Papers II and III

Renal function and renal functional reserve were evaluated in 36 transplanted children, 32 of these reported in Paper I and another 4 adolescents, transplanted after the age of 16 years (paper II). In Paper II, we included 15 kidney donors and 15 children with single kidneys because of nephrectomy or renal agenesis (NxAg).
In the agenesis group, 5 children had renal agenesis, and 1 nonfunctioning multicystic dysplasia. The reasons for nephrectomy were multicystic dysplasia in 2, small, scarred or rudimentary kidneys in 6 and in 1 the kidney did not function because of iatrogenic damage to a ureter during previous antireflux surgery. The nephrectomies were performed median 3.2 years before the study (min. 0.1 and max. 16.7 years).

The 30 transplanted children studied in Paper III were also included in paper II.

In 14 recipient-donor pairs, simultaneous studies were done (Paper II). One recipient had 2 living donors investigated, but only the second in the pair-comparison (the first graft failed 0.1 year after transplantation and the other parent donated the second kidney). Eight of the 15 kidney donors in Paper II did not participate in the second study (Paper III).

3.1.4 Paper IV

We assessed growth after the renal transplantation in 58 of 65 children (6 had died and 1 had lost 3 grafts immediately afterwards; they were therefore excluded). All children in Papers I and V are included, with an additional 12 children who were consecutive children transplanted from 1991 until 1994. The children in Paper IV had been followed for at least 5 years after transplantation.

3.2 ETHICS

Approval by the Ethics Committee of Karolinska Institutet at Huddinge University Hospital, Stockholm, Sweden and patient and parental consent were obtained in all studies.

4 METHODS

4.1 IMMUNOSUPPRESSION

The immunosuppressive protocol consisted of cyclosporine and prednisolone in the first 15 patients, and of cyclosporine, azathioprine and prednisolone in the following cases.
Since 1995, 15 children with a primary transplant have been switched to tacrolimus instead of cyclosporine, 3.9 - 12.0 years after transplantation. Following the second transplantation, 6 children were switched to tacrolimus 4.3-11.4 years after transplantation and 3 have been primarily treated with this immunosuppressive agent.

Cyclosporine
The initial cyclosporine dose was 15-20 mg/kg/d orally or 10 mg/kg/d intravenously (in patients receiving intra abdominally-placed grafts) aiming at a whole-blood trough level of 300 ng/ml at 1 month, 200 ng/ml at 2 months and 100 ng/ml at 3 months.

Tacrolimus
The initial tacrolimus dose, about 0.3 mg/kg BW, was tapered to approximately 0.1 mg/kg BW, aiming at a trough level of 10-20 ng/ml the first month and 5-10 ng/ml thereafter.

Prednisolone
The initial prednisolone dose in the first 27 patients was 100 mg daily, tapered to 20 mg daily during 1 week and to 10 mg daily for 3 months. In the other patients (since 1988), the dose of prednisolone in children less than 40 kg body weight was 75 mg/ m^2 body surface area (BSA)/d tapered to 7.5 mg/m^2 BSA/d at 3 months. In all patients, the dose of prednisolone treatment was gradually reduced to alternate-day treatment from 3-4 months after transplantation.

Azathioprine
Azathioprine 2 mg/kg BW/d was given during the first month and 1 mg/kg BW/d thereafter.

Mycophenolate mofetil (MMF)
Mycophenolate mofetil was not used after the first transplant in these studies, but 3 of the retransplanted children received this drug in accordance with the actual local policy for such patients. The recommended MMF dose is 15-30mg/kg/d (up to 1200 mg/m^2) divided in 2 doses.

4.2 RENAL FUNCTION

The glomerular filtration rate, GFR, was assessed by the clearance of inulin in Papers I-V, and also by the modified Schwartz formula clearance in Paper I (Counahan et al. 1976; Schwartz et al. 1976). In Paper II, the clearance of creatinine was determined as well. In Papers II and III, effective renal plasma flow, ERPF, was determined with the clearance of para-aminohippuric acid (PAH).

Clearances (C) were calculated using the formula: C=U x V/P where
U= urinary concentration of the substance (mg/mL), V=diuresis (mL/min) and P= plasma concentration of the substance (mg/mL).

4.2.1 GFR and ERPF determined by clearances of inulin and PAH

Inulin clearance

Inulin, a fructose polymer, is solely excreted by the kidneys by free filtration of the glomeruli. Inulin is not reabsorbed, secreted, synthesized or metabolized by the kidney. The method of measuring clearance of inulin includes the intravenous administration of a prime dose of inulin followed by a constant infusion of inulin. Plasma inulin concentration reaches a constant level.
The test begins with an equilibration period of 1 hour, whereafter repeated samples of urine- and venous blood are taken.
The concentration of inulin was determined by the anthrone method (Hilger et al. 1958) until 1994, whereafter an enzymatic method was used for the determination of inulin in plasma, serum and urine (Kuehnle et al. 1992). The coefficient of variation was about 10% among clearance periods in a single test during baseline conditions. The clearance measured (mL/min) was corrected for a standard body surface area (BSA) of 1.73 m^2. BSA was calculated according to Haycock et al (Haycock et al. 1978).

PAH-clearance

PAH is filtered by the glomeruli and secreted by the tubular cells. The clearance of PAH is termed the ERPF to indicate that it represents the plasma flow from which PAH can be extracted. The extraction of PAH in one passage through the kidney of a normal man is, on average, 90%. Therefore, the true renal plasma flow exceeds the PAH clearance by about 10%. PAH in blood and urine is determined by a modified Smith technique (Smith et al. 1945; Brun 1951).

Method of determining inulin and PAH clearance

Two intravenous (iv) lines were inserted, one in each arm.
After a prime dose of inulin, 64mg/kg BW (Inutest, 25% Laevosan, Gesellshaft, Vienna, Austria), and PAH, 9mg/kg BW (PAH, 20% MSD, West Point, USA), a continuous i.v. infusion of 1-2 mg/kg BW/min inulin and 0.15-0.3mg/kg BW/min PAH was given i.v. After the prime dose, a 60-minute equilibration period was allowed to elapse.

To ensure adequate diuresis and emptying of the bladder (without a catheter in the bladder), the child was given water to drink (20 mL/kg during the first hour, followed by 5 mL/kg every 30 minutes in an amount not exceeding 1200mL and 300 mL, respectively).

Timed urine collections were obtained by spontaneous micturition every 30 minutes, starting 1 hour after the equilibration period. Blood samples were taken in the middle of every 30-minute urine collection period. The test was terminated after four 30-minute periods. Clearance was calculated as the mean of the 4 clearance periods.

The prime dose and the infusion rate were reduced when the GFR was expected to be below 40, to avoid reaching too high a PAH level and thereby exceeding the maximal tubular secretion capacity.

4.2.1.1   *Inulin- and PAH-clearance with the single injection technique*

A single injection of inulin and PAH was given, after which blood samples were drawn regularly during the next 180 minutes. From the plasma disappearance rate thus obtained, the clearances of inulin and PAH were calculated by the 2-compartment method (Jereb et al. 1973).

4.2.2 Clearances of inulin and PAH with a protein-rich meal

In Papers II and III testing of the renal reserve included prolonged inulin and PAH clearance tests with a protein-rich meal (oral protein load, OPL) in the following manner:

The prime dose is given 60 min. before the 3 baseline periods starts.

After 3 baseline clearance periods, the child was given an oral protein load of 1.5 g protein/kg BW to be eaten during a 30 min period. The test was then continued for another 6 clearance periods (Figure 1).
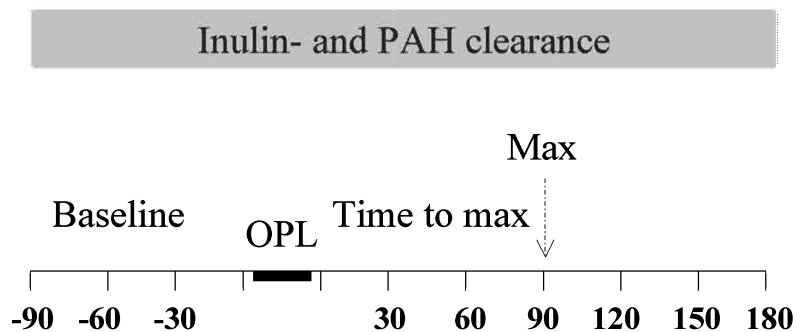

Figure 1. Renal function test with Inulin-PAH and an oral protein load OPL.

OPL= 1.5 g protein/kg BW
Max: maximal stimulated GFR

Baseline GFR and ERPF: The mean values of the 3 periods before the OPL.
Stimulated GFR and ERPF: The peak values after the OPL.
Filtration fraction at baseline and after OPL: The quotient of the mean value of baseline GFR and ERPF and the mean stimulated GFR and ERPF.
Renal functional reserve (RFR) or Δ GFR and Δ ERPF: Baseline GFR and ERPF subtracted from the maximal stimulated GFR and ERPF. RFR was also expressed as the fractional increase (%) from the baseline values.

4.2.3 GFR determined by the clearance of creatinine
In Paper II, the clearances of creatinine were determined simultaneously with the clearances of inulin in the 3 baseline periods before OPL and during 2 sampling periods after OPL (Paper II). Clearance was calculated from the urine and serum concentrations of creatinine and diuresis. The method used to measure creatinine was a modified Jaffé reaction (Masson et al. 1981).

4.2.4 GFR determined by the formula clearance
The Schwartz formula modified by Counahan (Counahan et al. 1976) is
GFR (ml/min/1.73m^2 BSA) = Height (cm) x K / S-creatinine (μmol/l) where K=38.

4.3 ULTRASOUND

Yearly renal ultrasound examinations of the transplanted and native kidneys were done (Paper V) with a 3.5 or 5 MHz sector scanner. The length and volume of the transplanted kidney was determined at the same time as the RFR tests (Paper II and III) (Dinkel et al. 1985).

4.4 GROWTH

We evaluated the children's growth (height and weight) at transplantation and yearly thereafter (Papers I, IV, V).
Height was measured with a Harpenden stadiometer or a recumbent infant length board in children < 2 years of age. Data on height were converted to a standard deviation score with the following formula, using the growth curve for Swedish children (Karlberg et al. 1976):
Z-score = (patient's height – mean height for age) / SD of height for age.

4.5 BONE AGE

Bone age (BA) was determined on radiographs of the hand–wrist and knee with the Tanner Whitehouse method (Tanner et al. 1983). The same radiologist evaluated all radiographs.

4.6 STATISTICAL ANALYSES

Survival analyses of patients and grafts were performed with the Kaplan-Meier survival plot and the survival curves were compared by the log rank test.
Survival rates for the first 10 years were given as actual survival rates, but for 10–20 years, the predicted survival rates were calculated by the actuarial method. Graft loss was defined as return to dialysis, transplant nephrectomy or retransplantation. Grafts of children who died with a functioning graft were considered as graft losses at the time of death (noncensored for death). All causes of death were included in the analysis.
ANOVA, repeated measurements, or the paired t-test was used to compare normally distributed data from the same children at various times.
Unpaired t-test or ANOVA (factorial) was used when comparing groups. The Sheffe post hoc test was used.
The Mann-Whitney U-test was used to compare 2 groups with nonparametric data.
The sign test was used to test the change in GFR from the first to the last examination in Paper III.
A value of $p < 0.05$ was considered statistically significant.

We used StatView 5.0.1 software for statistical analyses.

5 RESULTS AND DISCUSSION

5.1 PAPERS I, IV AND V

From the start of renal transplantations in small children and infants 1981 at Huddinge University Hospital, the aim at our unit has been to give a renal transplant to all children with ESRD. Some of the first children referred for ESRD treatment were severely affected by long-standing renal failure with renal osteodystrophy and severe growth retardation in some cases. No child with ESRD was denied active treatment during these years.

5.1.1 Results

Seventy-nine percent of the children suffered from congenital disorders including malformations (34%), hereditary disorders (43%) and others. Glomerulonephritis (13%) was the commonest acquired renal disease, Table 2.

Table 2. Primary renal diseases in 53 children transplanted 1981-1991

	n
CONGENITAL DISEASES (42)	
Malformations	
- Hypo-and dysplasia	9
- Obstructive uropathies [a]	9
Hereditary disorders (23)	
- Polycystic kidney disease [b]	6
- Familiar juvenile nephronophthisis [c]	8
- Congenital nephrosis [d]	7
- Heredit. Glomerulonephritis	1
- Primary hyperoxaluria	1
Others	1
ACQUIRED DISEASES (11)	
- Glomerulopathies	7
- Vascular nephropathies	2
- Neonatal acute renal failure	2

[a] Including 3 with Prune Belly syndrome [b] including 1 with glomerulocystic disease [c] including 1 with Jeunes syndrome [d] including 1 with focal segmental glomerulosclerosis and 2 with Drash syndrome.

Forty-five per cent of them received a preemptive transplant at first transplantation, and 28 % were preemptively transplanted at retransplantation. PD was the commonest (75%) dialysis modality before transplantation and the median dialysis time was 1.8 months before the first transplant. Sixty-three percent of the kidney grafts were obtained from living related donors (72% at primary transplant and 39% at retransplant).

5.1.1.1 Patient survival

The patients have been followed from 1981-1991 (I) and 1991-2001 (V).
The overall actual patient survival was 91%, 89% and 89% at 1, 5 and 10 years of follow-up, while the actuarial patient survival at 15 and 20 years was 89% and 89%. In the age group < 2 years at transplantation, the 1-, 5- and 10-year patient survival was 67%, 67% and 67%. Six children died, 5 within 6 months of transplantation and 1 after 3.3 years. Four died of severe infections and 1 probably because of electrolyte disturbances during dialysis. Two of the children who died had lost their grafts and were on dialysis. A third with congenital nephrotic syndrome never had primary graft function since she had a thrombosed inferior vena cava and the kidney circulation never functioned. No child has died since 1989. The Height Z-score of the children who died was median –5.5 (min –10, max –4.7). Patient survival was almost identical in children with or without pretransplant dialysis.

5.1.1.2 Graft survival and rejections

The overall actual graft survival at 1, 5 and 10 years after the index transplant was 85%, 77% and 66%, respectively, while the actuarial graft survival at 15 years was 44%. One-, 5- and 10-year graft survival was 67%, 67% and 67% in children transplanted <2 years of age, 88%, 82% and 53% in children transplanted at age 2.1-7.0 years and 92%, 79% and 75% in children transplanted at age 7.1-16.0 years (Figure 2). When the children were divided into age groups, those transplanted before 2 years of age lost no grafts after the first 6 months during the follow-up (Figure 2). The 1- and 5-year graft survival in 18 retransplanted children was 89% and 89%, respectively.
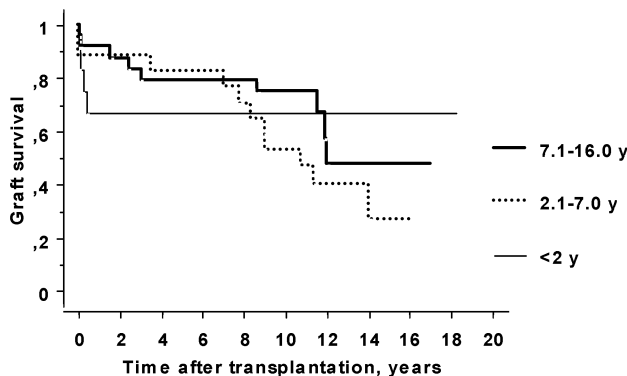
Time	Age <2.0 years	Age 2.1-7.0 years	Age 7.1-16.0 years
	n	n	n
Transplantation	12	17	24
1 year	8	15	22
5 years	8	14	19
10 years	8	9	18
12 years	2	5	6

Figure 2. Graft survival according to age group at primary transplantation
The figure table shows the number of patients at risk at various times.

Graft survival was better in LD (90%, 84% and 74% at 1, 5 and 10 years) than CD recipients (73%, 60% and 47% at 1, 5 and 10 years) after primary transplantation (p=0.007).

The 5-year graft survival was 78% and 94% and the 10-year survival was 56% and 83% in children with or without late rejection episodes after primary transplantation, respectively (p=0.05).

Graft survival at 5 years was similar in children with a possible bladder dysfunction (6 with previous PUV and 3 with the prune belly syndrome) as in the other children. Causes of graft loss are shown in table 3.

Table 3. Causes of graft loss during the two periods of follow-up

	1981-1991	1991-2001	*1981-2001 %*
Acute rejection	5		*19*
Chronic rejection	2	11	*50*
Vascular /technical	1		*4*
Other	1		*4*
Death with functioning graft	3		*12*
Recurrent disease	1		*4*
Malignancy		2	*8*
	13	13	

Rejections
Acute rejection was defined as the use of rejection therapy. The graft losses due to acute rejections occurred at 0.4-1.4 months after transplantation. 72% of the 71 transplants were treated for acute rejections and 58% of all rejection treatments occurred within 1 month and 16% after 1 year (late rejections). Late acute rejections occurred in 2 children within 5 and 7 months from initiation of rhGH-treatment, about 2 and 4 years after transplantation, (Tyden et al. 1997).

5.1.1.3 Growth (IV)

Boys were more growth-retarded than girls at transplantation, probably as a consequence of a higher frequency of long-standing congenital diseases among boys. Children with the severest growth retardation increased most in height after transplantation and the height increment in height Z-score (Ht Z-score) was most marked during the first 3 years (Figure 3) followed by a "plateau" at, or just below, about –1 Ht Z-score. Not only children transplanted before 7 years of age, but also those transplanted at ages 7-12 years increased their Ht Z-scores during the first years. A high GFR at 1 year predicted good growth from transplantation to 5 years later. The most growth-retarded children at transplantation (below –2 Ht Z-score) increased their height Z-score from transplantation to 5 years, despite a reduced GFR at 1 and 5 years (with exception of the 2 extremely growth retarded children).
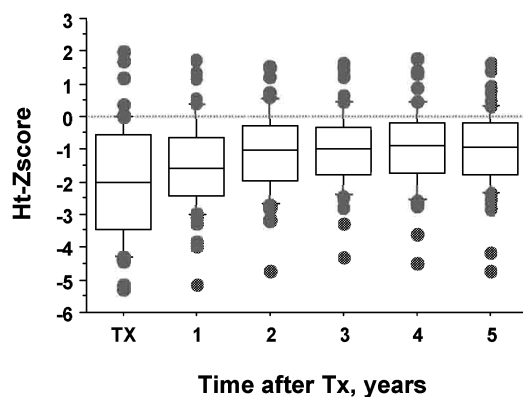
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Figure 3. Height Z-score at transplantation and 1-5 years in 58 children examined at all occasions. Boxes show medians, 25th and 75th percentiles (p=0.0001, ANOVA repeated measures)

Twenty-four children reached final adult height (FH), which was median −1.2 Ht Z-score, but 25% had a FH Z-score below -2.

A longer period (% of time from transplantation to FH) with a reduced GFR (<40 mL/min/1.73m^2) seemed to affect FH negatively (R: -0.53, p=0.01).

5.1.1.4 Complications (I, V)

Most of the early complications after transplantation were related to surgery, infections and acute rejections while the latter ones were mainly graft losses, infections, growth retardation and hypertension.

Surgical complications and interventions
General surgical complications that can occur in any surgery, such as bleeding (1), vascular complications in the graft (1), ileus (2), bowel perforation (1) and lymphocele (2) occurred. One child developed a bleeding gastric ulcer 2.5 months after the second transplantation. An adolescent with ARPKD, treated with aspirin because of thrombocytosis after splenectomy, underwent neurosurgery for a subdural hematoma after a moderate trauma. Finally, another child, with ARPKD, was operated for a supravalvular aortic aneurysm, 10 years after transplantation.

Urological findings and complications
The early postoperative urological complications comprised urinary outflow obstruction with or without ureteral necrosis and the later ones bladder concrements, ureteric stenosis requiring surgical intervention, urethral stricture in 2 children with primary urethral valves, reimplantation of the ureter in children with vesicoureteric reflux into the graft and frequent infections.

In 10 children, nephrectomies (uni- or bilateral) of the child's native kidneys were performed pre- or peroperatively at transplantation, and in 7 after transplantation. The reasons for nephrectomy are shown in table 4.

One child on dialysis underwent transplant nephrectomy because of severe, drug-resistant hypertension and 2 developed renal cell carcinoma in the transplanted kidney necessitating graft nephrectomy.

Apart from the case whose native kidneys were removed due to cystic transformation (table 4), cysts were found in the native kidneys of more than 10% of the children and in the kidney graft of about 20%.

Table 4. Nephrectomy of the native kidney(s), uni- or bilaterally

Reason for nephrectomy	Pre/preoperatively	After Tx
Nephrotic syndrome	4	
Drash syndrome	2	
Polycystic kidneys	1	
Anatomic reasons	3	
Urinary tract infections		5 *
Hypertension		1
Acquired cystic kidneys		1

* A child with the prune-belly syndrome, had one kidney removed at transplantation while the other was removed after transplantation because of infections.

Infections during the first 6 months

Table 5 summarizes the infections during the first 6 months after transplantation.

Table 5. Infections the first 6 months after transplantation in 53 children

	< 1 m	1 – 2 m	2 - 6 m
Septicemia	8	1	
Pneumonia	1	1	4 *
Peritonitis	1		
Pyelonephritis		1	1
Systemic fungal infection	6		
Clostridium difficile	1	2	
CMV	4	12	
Meningitis			1
Encephalitis	2		1
Herpes zoster	1		1

*) 2 with *pneumocystis carinii* pneumonia

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Infections after 6 months

Bacterial infections
The commonest bacterial infections encountered 6 months after Tx, involved the urinary tract. Sixteen children (8 with dysplasia and/or obstruction as the primary diagnosis) were treated (13 of them more than once) for pyelonephritis and/or urosepsis during this extended follow-up. In 5 children with severe hydronephrosis and dilated native ureters, bilateral nephrectomy was necessary to rid them of bacteriuria. Other bacterial infections included septicemia (1), pneumonia (7), pertussis (4), *Salmonella* enteritis (1), intraabdominal abscess (1), and cholangitis (in a child with ARPKD).

Viral infections
Sixteen children required treatment for a primary CMV infection during the first 6 months after transplantation (Table 5), which was lethal in 2 cases. Of all children who were tested negative (n= 31) for CMV before transplantation, 21 subsequently became CMV-positive. In 8 cases, no data were available on CMV antibodies. About 50% of the CMV-negative children received prophylaxis. Ten years after primary transplantation, 7 of the children were still CMV-negative.
The viral infections after 6 months included: primary EBV infection in 3 children, and 1 of them also had a reactivation after a second transplantation with combined liver and kidney transplant, enterovirus encephalitis associated with seizures in 1 child and 4 children with RS virus infections and 1 with BK virus infection and ureteral stenosis, which was detected during an investigation of impaired graft function.

Ten children (2 of them had been vaccinated) contracted primary varicella and were treated with acyclovir parenterally. One of them developed varicella encephalitis and another developed both primary varicella and 2 episodes of varicella zoster despite one vaccination before transplantation. All of them recovered without sequelae. Five other children had episodes of varicella zoster late after transplantation.

Hepatitis B (HBV) infection was detected in 1 child (1.9%) and hepatitis C (HCV) infection in 2 (3.8%). All 3 were probably infected at or before transplantation, but the infection was found 8 months – 4 years after transplantation and they had probably been infected before 1991. Liver enzymes fluctuated in the child with hepatitis B and in 1 of the 2 with hepatitis C, while the other had normal liver-enzymes during follow-up (11.0 years). A liver biopsy performed in the child with an HBV infection, showed minimal inflammation and moderate fibrosis.

Malignancies
Renal cell carcinomas (RCC) developed in the transplanted living donor kidneys of 2 children, 9 and 11.4 years after transplantation, respectively. Cysts appeared on ultrasound in the graft 4 and 7 years before the diagnosis and the following transplantectomy. Both children were successfully re-transplanted after 6 and 10 months, respectively, on dialysis. The 2 donors' remaining native kidneys were unaffected, as judged by ultrasound examination (Tyden et al. 2000). Both of them had been treated with GH. Apart from the 2 cases of RCC, no malignancies have been found during 10-20 years of follow-up.

Cardiovascular

The commonest cardiovascular disturbance was hypertension, which occurred in 51% of the children before transplantation and then increased to 83% during the first posttransplant year. However, at the 5-year follow-up, 40% were on antihypertensive treatment, which increased to 66% at the 10 year follow-up, at which time 25% of the children had been re-transplanted. When considering only the children with a functioning first graft, the rate was 71% at 10 years (not shown in paper V). Echocardiography showed that, 2 hypertensive children had mild left ventricular hypertrophy 10 years after transplantation and 2 had developed increasing aortic insufficiency. Forty percent of the children had elevated cholesterol levels 5 years after transplantation. We found no other signs of severe cardiovascular disease.

Other

Dermatological examinations were done yearly. Warts were common (in 54 %). A few children developed herpes zoster. One case of condyloma accuminata was found. Nevi were examined and 3 were excised due to a suspicion of malignancy, which not was verified. No carcinomas were found. Some children needed treatment for acne vulgaris.

Among the ophthalmological disturbances, minor posterior subcapsular cataracts without visual disturbance were detected in 45 %. No one was operated on.
Two children developed pseudotumor cerebri in the course of their follow-up. One responded to medical therapy, the other entered spontaneous regression. Both recovered without visual impairment.

The dental examinations revealed gingival hyperplasia in several cases, and in 5 of them immunosuppression was changed because of it.

5.1.1.5 Pregnancies

The 3 pregnancies that occurred during follow-up were terminated prematurely by cesarean sections. One of the mothers (who had been on insulin for diabetes mellitus for a short period in the immediate post transplant period) developed insulin-dependent diabetes mellitus during pregnancy. The 3 children are doing well, as far as we know of.

5.1.1.6 Renal function (I, IV and V)

The day when the creatinine level is lowest after renal transplantation has been used as a measure of primary graft function. We calculated GFR by the formula clearance on this day as well as at 1, 3, 6 and 12 months after transplantation.
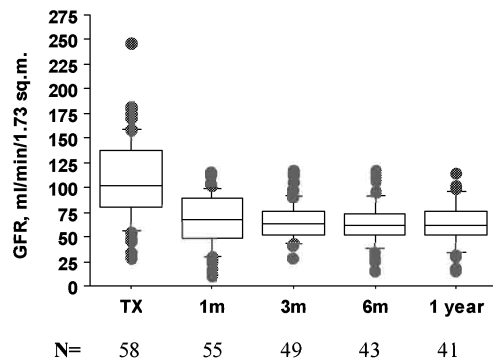
Figure 4. The glomerular filtration rate, calculated with the formula clearance.
TX= the day of the lowest creatinine after transplantation. The numbers of patients investigated at each occasion are shown below the figure.

When evaluating the lowest S-creatinine level after transplantation, we found that the lowest level was reached earlier in LD recipients (median day 3) than in CD recipients (median day 7), p<0.0001(Mann-Whitney U-test), Paper I. The formula clearance declined from TX to 1-12 months, p=0.0001, and from 1 month to 3-12 months p= 0.03 in 40 children investigated at all occasions (ANOVA repeated measures), Figure 4.

The yearly follow-up of children after renal transplantation included determinations of GFR with the clearance of inulin (I-V). GFR at 1 year was higher in children with no or one rejection episode (62±18 mL/min/1.74m^2 BSA) than in with those who had had ≥2 rejection episodes (49±18 mL/min/1.74m^2 BSA) within 1 year (p=0.05), but GFR at the 5- and 10- year follow-up were similar in children with 0-1 or >2 rejections.
GFR at 5 years did not differ between 9 children with disorders where bladder dysfunction could be expected (6 posterior PUV and 3 prune belly syndrome) and children with other underlying disorders.
In 27 children who had been followed yearly for 10 years after primary transplantation, GFR declined from 61 ± 16 to 51 ± 20 mL/min/1.73m^2 BSA and finally to 43 ± 16 mL/min/1.73m^2 BSA at 1, 5, and 10 years, respectively (p = 0.0001, ANOVA repeated measurements), Figure 5.
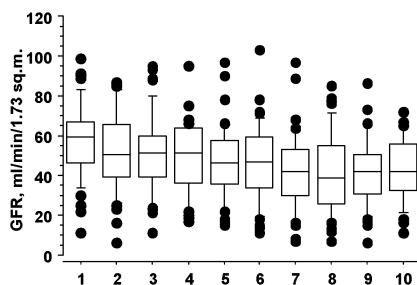

Figure 5. GFR in 27 children who underwent yearly assessments of renal function.

5.1.2 Discussion

End stage renal failure is a condition that untreated is incompatible with prolonged life. The treatment options include kidney transplantation and either peritoneal dialysis or hemodialysis. In children, as well as in adults, renal transplantation is the preferred therapy (Fine 1985; Wolfe et al. 1999; USRDS 2001). This is true despite the promising results from dialysis even in the smallest children (Holtta et al. 1997; Ledermann et al. 1999; Ledermann et al. 2000). In addition to the positive effect on family life, there is a better psychosocial adjustment and school attendance in children with a functioning allograft compared with those on dialysis (Offner et al. 1988; Roscoe et al. 1991).

5.1.2.1 Patients

The hereditary disorders constitute a major part in our children, as opposed to some reports (Mahmoud et al. 1997; Van Damme-Lombaerts et al. 2001) but similar to others (Kashtan et al. 1995; Offner et al. 1999). The majority of congenital and hereditary disorders results in a young age at transplantation and might have an impact on survival and other results. In this cohort, no child had pyelonephritis or reflux nephropathy, a fairly common cause of ERSD in many countries (2.5 per million age-related people in boys and 1 per million age related people in girls according to the EDTAregister (van der Heijden 2002)).

Our high percentage of preemptive transplants is a consequence of the high frequency of living donors. Norway has an equally high, or even higher (72%), frequency of living donors while Finland has the lowest (36%) and Denmark is between (46%) (Tyden and Berg 1998; van der Heijden 2002), among the Nordic countries. Germany and France have reported about 23 and 15% living donors (van der Heijden 2002). The percentages of living donors are 13-23% in Netherlands, France, Belgium and Germany (Mahmoud et al. 1997; Offner et al. 1999; Cransberg et al. 2000; Van Damme-Lombaerts et al. 2001).
In the NAPRTCS (North American Pediatric Renal Transplant Cooperative Study) and UNOS (United Network for Organ Sharing) reports, including 150 and 144 centers, about 50% are living donor transplants and 25% preemptive transplantations.
The percentage of preemtive transplantation is equally high to ours in Norway, in Denmark slightly lower (30%) whereas in Finland only 5% receive a transplant without prior dialysis (Tyden and Berg 1998; van der Heijden 2002). Finnish children with ESRD usually start renal replacement therapy with PD before a transplant (probably due to a high frequency of infants with Finnish nephrosis) (Laine et al. 1994; Tyden and Berg 1998; Qvist et al. 2000; Qvist et al. 2002; van der Heijden 2002).

5.1.2.2 Patient survival

In the early days of pediatric renal transplantation, patient survival was lower in children than in adults, especially of the youngest ones. Later, with the advent of cyclosporine as an immunosuppressant, the survival of patients and grafts increased in infants and children (Najarian et al. 1990; Humar et al. 1998; Qvist et al. 1999; Sarwal et al. 2000; Seikaly et al. 2001).

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The 6 children who died were all severely growth retarded (Ht Z-score –5.5) and in poor condition when referred for treatment of ESRD. This accords with a study by Furth et al., who showed that poor growth in children with ERSD was a marker for a more complicated clinical course (Furth et al. 2002). The patient survival rate did not differ between recipients of LD and CD kidneys, which is in accordance with other reports (Offner et al. 1989; Chavers et al. 1994; Van Damme-Lombaerts et al. 2001), but the number of CD recipients in our study was very low. The equal patient survival rates in preemptive and dialyzed children is in accordance with other reports (Mahmoud et al. 1997; Vats et al. 2000).

5.1.2.3 Graft survival

The graft failure rates were lower for recipients of LD than of CD kidneys, a frequently reported finding (Offner et al. 1989; Briscoe et al. 1992; McEnery et al. 1992; Seikaly et al. 2001; USRDS 2001)
The pretransplant dialysis time was very short (median 2 months) in our children (Papers I and V) and, therefore, we could not expect any difference in graft survival between the preemptively transplanted and dialyzed cases although it has been reported to be better in preemptive LD than in pretransplant dialyzed (Vats et al. 2000) while others found equal or slightly better outcome in preemptively transplanted (Flom et al. 1992; Chavers et al. 1994; Mahmoud et al. 1997; Offner et al. 1999).

Most graft losses were due to acute rejection in the earlier (1981-1991) and chronic rejection in the later (1991-2001) follow-up period (Table 3) which accords with a recent report (Matas 2000). A late acute rejection is associated with a higher risk of graft failure due to chronic rejection (Birk et al. 1997; Tejani et al. 2002). However, we found a better graft survival in those without a late rejection (nearly significant).

The proportion of graft losses due to acute rejection the first year was the same (19%) as in a report on children transplanted from 1984 to 1998 (Matas 2000) and slightly higher than another report (13%) on transplantations between 1984 and 94 (Chavers et al. 1994).
The frequency of acute rejection treatments is fairly high in our children, although it is similar to that of children transplanted during the years 1987-89, reported by Harmon –i.e., 56% of LD and 72% of CD recipients had at least 1 acute rejection (Harmon 2001). Lower incidences of 34% and 35%, respectively, were reported for the years 1999/2000 in the same report. This agrees with our own experience during the later years. Chavers reported 68% (CD 82% LD 62%) biopsy proven acute rejection episodes (Chavers et al. 1994). In the multicenter NAPRTCS report during the years 1987-96, 50% of LD and 65% of CD recipients had had an acute rejection (Feld et al. 1997) and in a report on the years 1984-1997 from another center, acute rejections were reported in 52% the first year after transplantation (Vats et al. 2002).

Chronic rejection is the commonest cause of graft loss after the first posttransplant year and risk factors are acute and late (after 6 or 12 months) acute rejections (Guyot et al. 1996; Birk et al. 1997; Matas 2000; Tejani and Sullivan 2000; Tejani et al. 2002).

Others have reported graft losses due to chronic rejections in 30-50% (Chavers et al. 1994; Offner et al. 1999; Seikaly et al. 2001).

In a recent NAPRTCS report, 32% of the graft losses were due to CR, and the risk of development of chronic graft failure was calculated as an 3-fold increase with 1 acute rejection, and a 12-fold increase with 2 or more acute rejections (Tejani et al. 2002). A late AR (after 1 year) increased the relative risk of chronic rejection 6-fold (Tejani et al. 2002).

It is noteworthy, and in accordance with a recent report, that young recipients (below 2 years) ran a higher risk of graft failure in the short term, but not after 1 year, while the rate of graft loss remained unchanged in the older children (Postlethwaite et al. 2002).

In some reports, recurrent disease is an important cause of graft loss (Gagnadoux et al. 1993; Baum et al. 2002; Patrakka et al. 2002). This occurred in only 1 case in our series – i.e., a girl with focal segmental glomerulosclerosis who developed proteinuria a few days after transplantation. In another child with IgA nephropathy, there was a suspicion of IgA-recurrence, but biopsy was not obtained and her kidney is still functioning. Diseases in children with a high recurrence rate and subsequent graft failure include the focal segmental glomerulosclerosis, primary glomerulo-nephritides, congenital Finnish nephrosis (major type), systemic diseases such as atypical hemolytic uremic syndrome (D-) and metabolic diseases such as primary hyperoxaluria. We had only 5 patients within these categories, which may partly explain why we only lost 1 graft (2%) due to recurrence.

5.1.2.4 Growth

In children, renal transplantation restores growth-promoting conditions, since acidosis is corrected, appetite increased and general well-being is normalized. "Catch up growth" - defined as normalization to the mean standardized height for gender and age-is not common, but an increase in Ht Z-score is often seen. Various factors are responsible for inadequate growth, such as steroid treatment with its well-known growth-suppressing effect, the child's age, growth impairment at transplantation and renal function. In our study, the children were growing well and in some other studies a mean height Z-score at 5 years after transplantation below –2 was reported (Tejani et al. 1993; McDonald et al. 2000). Others have reported similar results as ours (Maxwell et al. 1998; Qvist et al. 2002).

We have also reported better FH as compared to some other studies (Hokken-Koelega et al. 1994; Offner et al. 1999) but others have reported similar findings to ours (Rodriguez-Soriano et al. 2000). However, it deserves to be mentioned, that most of our children who had reached final height were older and less growth-retarded at transplantation, unlike the younger children. It remains to be seen if the youngest, most growth-retarded will grow without losing standardized height until they are adults. The steroid doses given to our children were low and from the 5th month, steroids were reduced to alternate days. This is probably one reason why they have grown so well. Corticosteroid treatment may inhibit IGF-I synthesis and bioactivity by interference with GH secretion. Steroids also interfere with the growth plate and enchondral bone formation among other actions (Schaefer and Mehls 1999).

The finding that the most growth-retarded children at transplantation gain most in height Z-score during the first years has also been reported in the literature (Tejani et al. 1993; Warady et al. 1997). However, several authors have found that children transplanted after 6 or 7 years do not grow as much as those transplanted before 7 years of age (Ingelfinger et al. 1981; Fennell et al. 1990; Warady et al. 1997). This was not the case in our children, since even children in the age-group 7-12 years showed significant increases in Ht Z-score. The children in the oldest age group were not growth-retarded and consequently did not show accelerated growth after transplantation. According to other authors, children transplanted after the age of 12 years have poor growth or even lose standardized height after transplantation (Warady et al. 1997), but some have also reported growth in pubertal children (Maxwell et al. 1998). The increase in appetite in the first months after transplantation often results in overweight, which should decline when the steroid doses are lowered and the child receives alternate-day treatment (Jabs et al. 1996).

5.1.2.5 Complications

Urological findings and complications
The urological complications that we reported are common postoperatively in both children and adults (Baluarte et al. 1994; Ekberg 2002).
Large hydronephroses and vesicoureteric refluxes (VUR) necessitated nephrectomy of the native kidneys at, or after (13%), transplantation in cases with pyelonephritis in order to spare the graft from infections. We report 3 cases in whom VUR (to the graft) had been surgically corrected. VUR into the transplanted kidney is a threat to renal function with a risk of scarring even if the kidney is obtained from an adult donor (Hanevold et al. 1987; Ramirez et al. 2001; Howie et al. 2002). Reflux into the graft ureter poses a risk of reflux nephropathy after transplantation (Howie et al. 2002). Vesical calculus was found in 2 children, a complication that is described as rare (Klein and Goldman 1997). The calculus' were in the sutures at the site of the neocystostomy in the cases we report, as in 7 cases reported by Klein et al. (Klein and Goldman 1997). Graft survival and GFR at 5 years were similar in children with PUV and the prune belly syndrome and in children with nonobstructive end stage renal disease. Persistent bladder dysfunction caused by the initial obstruction in children with PUV can increase intra-vesical pressure and lead to secondary reflux into the ureter of the graft and the valve bladder may have a role in the deterioration of renal transplants (Salomon et al. 2000). Some authors have reported higher rates of graft loss and lower renal function after transplantation (Reinberg et al. 1988) but others have found that children with PUV have the same outcome as controls (Salomon et al. 1997). Children with the prune belly syndrome may develop urological complications and graft impairment because of bladder dysfunction and refluxes in the native kidneys (Ramirez et al. 2001), but some report that renal transplantation is not associated with a higher rate of failure in children with the prune-belly syndrome (Fontaine et al. 1997). Urodynamic studies should be included in the pretransplant evaluation, especially of children with PUV and the Prune Belly syndrome (Lopez Pereira et al. 2000), followed by a regular posttransplant urological evaluation (Fontaine et al. 1997).

Nephrectomy of the native kidneys was performed in 19% before and in 13% after transplantation, in the latter because of urinary tract infections. Seven children developed cysts in the native kidneys, and 1 was nephectomized because a malignancy could not be excluded. End-stage kidneys are known to undergo cystic transformation, especially in patients on long-term hemodialysis. Dunnhill first described the occurrence of acquired cystic kidney disease (ACKD) - i.e., replacement of the parenchyma by several small cysts, and the main complications of this condition, hemorrhage and tumor formation (Dunnill et al. 1977; Kliem et al. 1997). Regular imaging of the native kidneys is therefore advisable after transplantation, particularly when the cysts are present before transplantation (Levine and Gburek 1994; Gulanikar et al. 1998).

Infections

Infections represent a great risk for the child and are the single commonest cause of death in children after transplantation (Benfield et al. 1999; Elshihabi et al. 2000; McDonald et al. 2000). Younger recipients are more likely to develop an infection after a transplant than older ones and the incidence of bacterial infections is higher in the youngest (Chavers et al. 1997).
The bacterial - i.e., septicemia and pneumonia being the commonest- and fungal infections we found the first 6 months, are similar to those reported by others (Chavers et al. 1997). We had 3 children, transplanted under the age of 2 years, with *Clostridium difficile* diarrhea which appears to be the commonest type of infection after transplantation in children less than 5 years of age at transplantation, with urinary tract infection as the second commonest overall and the commonest in children older than 5 years of age at transplantation, according to Chavers et al. (Chavers et al. 1997). In our children, urinary tract infections (pyelonephritis and/or urosepsis) were the commonest bacterial infection after the first 6 months, in line with the above-mentioned report by Chavers et al.
Pneumocystis carinii pneumonia, a parasitic infection that caused one death, is much less frequent since the start of prophylaxis with trimethoprim/sulfamethoxazole, which are routinely given the first 6 months to all patients receiving a renal transplant since 1988 at our unit (2002).
CMV infections are common among the viral infections. Before the introduction of antiviral acyclovir / ganciclovir prophylaxis, severe invasive primary CMV infections were not uncommon and, as in our 2 cases had a fatal outcome. Prophylactic treatment with has reduced the incidence of CMV disease and lowered the rate of CMV infection (Couchoud 2000);(Lowance et al. 1999).
EBV infection was detected in 6% in our study, but not all children had been antibody-tested at that time (during the 1980s). No life-threatening complications occurred. EBV virus can induce B-cell lymphoma and primary EBV infection is a risk factor for PTLD (Ellis et al. 1999).
We had only one patient with a BK virus infection, and it was associated with graft dysfunction and ureteric stenosis. The manifestations of BK virus infections range from asymptomatic replication to ureteric stenosis, transient impairment of renal function to severe viral nephropathy and graft loss (Hirsch 2002). Treatment is the reduction of immunosuppression, which entails the risk of rejection. Antiviral treatment is not yet

established but recently, there have been reports on the use of cidofovir (Hirsch 2002; Kwak et al. 2002).

During the 1980s, our children were not routinely immunized against varicella and several infections occurred during follow-up. No child died, probably because all of them had been given antiviral treatment within 2 days of developing symptoms. One can not evaluate the efficacy of vaccination since only 1 child in this cohort had received all 3 injections. Broyer reports, that even after vaccination, some become seronegative and develop varicella but vaccination seem to protect from the most serious diseases even when the antibodies have disappeared (Broyer et al. 1997). Mortality rates up to 25% have been reported after varicella, although more recent data suggest that it is less than previously reported (Lynfield et al. 1992; Furth et al. 1997; Kashtan et al. 1997). Pretransplant varicella vaccination is now recommended (Olson et al. 2001; Furth and Fivush 2002).

We had a low frequency of hepatitis B- and C-infected children who had a fairly mild involvement of the liver. Others have reported a prevalence of about 20% HCV infections in children on dialysis and after transplantation and abnormal alanine aminotransferase (ALT) levels in about 80% of the infected children (Jonas et al. 1992; Greco et al. 1993; Molle et al. 2002). Our low prevalence is probably due to a low frequency of pretransplant dialysis and especially of HD, and a lower frequency of HBV and HCV in the community. The number of blood transfusions, length of time on HD and age are reported risk factors for HCV (Jonas et al. 1992; Greco et al. 1993). Our study was conducted before the screening of blood products for HCV was instituted and before the widespread use of erythropoietin.

Malignancies

In this 10-20-year follow-up, the only malignancies that were found were 2 cases of renal cell carcinoma (Tyden et al. 2000). Cysts were seen on ultrasound years before the diagnosis, which would suggest slow growth. The outcome was good, and both were successfully retransplanted and the two donors (parents) had no signs of tumor when examined by ultrasound. Renal cell carcinoma associated with acquired renal cystic disease is less frequent in the allograft kidney than in the native kidneys (Williams et al. 1995). Several authors have reported occasional de novo renal cell carcinomas in renal grafts, however, mostly CD grafts (Claudon et al. 1998; Tyden et al. 2000; Gunji et al. 2001; Wunderlich et al. 2001). In 4 cases, the carcinomas developed in the grafts during rhGH-therapy (Mehls et al. 2002). No data from other studies support that rhGH is the cause in such tumors (Mehls et al. 2002). Immunosuppression increases the risk of tumors 3 to 4 times after organ transplantation (Penn 2000). The types of malignancies that occur in pediatric recipients differ from those in the general pediatric population and from adult transplant recipients (Penn 1998; Shapiro et al. 1999). An explanation of the absence of PTLD in our patients may be that they did not receive monoclonal antibodies as induction therapy, which is common in several other centers and is a risk factor (Swinnen et al. 1990).

A dermatologist made careful skin examinations without finding any malignancies. In children with renal allografts, melanocytic nevi (usually on the back and at acral sites) are described as common (Smith et al. 1993). This would suggest that malignant transformation into melanoma might occur, which merits regular dermatological examinations.

Cardiovascular

Hypertension was common before transplantation and most children needed treatment after transplantation as well. The primary causes were probably high doses of steroids and cyclosporine but the primary renal disease is another factor. The slight increase in antihypertensive treatment from 5 to 10 years could be due to a reduction in graft function. Before cyclosporine, 62% and 48% of CD and LD graft recipients, respectively, were hypertensive for more than 6 months after transplantation (Broyer et al. 1987). Offner et al. reported a rate of hypertension of 73-83% 10 years after transplantation in patients with functioning first grafts in another long-term follow-up with or without cyclosporine (Offner et al. 1999). In a recent study, hypertension was found in 33% of patients on casual determinations of blood pressure and in 40% when monitoring ambulatory blood pressure (Morgan et al. 2001). Abnormal nighttime dipping was seen in 58% of patients (Morgan et al. 2001). In a NAPRTCS report, anti-hypertensive medication was given to 79% of patients on day 30 and to 58% at 5 years after transplantation (Sorof et al. 1999).

Hypertension may cause end organ damage, and we therefore examined all children regularly by echocardiography. Of the 31 children with hypertension at 10 years, we detected mild left ventricular hypertrophy in 6%, to compare with a significant increase in left ventricular mass in 14% of children with essential hypertension (Daniels et al. 1998).

We found elevated cholesterol levels in a slightly lower frequency than reported by others (Sharma et al. 1994; Silverstein et al. 2000) but no signs of plaque or stenosis on carotid examination. Cardiovascular disease accounts for 11-40% of deaths in children and young adults with ESRD, even in the transplantation era (Chavers et al. 1994; Foley et al. 1998; Offner et al. 1999). The risk factors of cardiovascular disease have to be addressed in children after renal transplantation.

Other

Dermatological examinations revealed some minor disturbances, the commonest finding being warts. Skin infections were reported by Hogewoning to be frequent complications in transplanted patients - i.e. candida, herpes simplex and impetigo were the commonest during the first year after transplantation, followed by dermatomycoses, herpes zoster and follikulitis after the first year (Hogewoning et al. 2001).

Mild, subcapsular cataract was found in 45%, with none of the cataracts being visually significant. A posterior subcapsular cataract is a known complication of systemic corticosteroid therapy. The incidence of cataract in children and adults has varied from about 20 to more than 70% as reported by various transplant centers (Nishimoto et al. 1992; Kaye et al. 1993; Jayamanne and Porter 1998). Studies in children are scarce (Fryer et al. 1994). An association with cataract formation and the methyl-prednisolone dose was found, as also reported by others (Fournier et al. 1990). We described two patients who developed pseudotumor cerebri in the course of their follow-up. Others have reported this syndrome in children after renal transplantation but the incidence in renal transplant recipients is unknown (Sheth et al. 1994). Growth hormone treatment is reported as a precipitating factor for the development of pseudotumor cerebri (Koller et al. 1997) but was not given in these cases.

Pregnancies

Various complications with premature deliveries are not uncommon in transplanted mothers. However, we have been unable to evaluate the health and development of the 3 children in this study. Premature deliveries and children small for gestational age (birth weight < 2.500g) are reported (Willis et al. 2000). In a recent study (Sgro et al. 2002) of the outcome of 44 pregnancies, stillbirths, premature deliveries and lower birth-weights were commoner than in a control group.

Renal function in the transplanted kidney

GFR after transplantation is often evaluated by serum creatinine, clearance of creatinine or formula clearance (Counahan et al. 1976; Schwartz et al. 1976). Several other studies from our department have assessed various aspects of renal function after transplantation using inulin clearance.
Formula clearance is easily done and was used to evaluate graft function the first year after surgery. The day of the lowest creatinine was reached earlier in LD recipients and, as expected, GFR was higher in children who had received a kidney from a living donor, which may indicate less damage to the graft during the surgical procedure. GFR at 5 years was similar to that in other reports (Williams et al. 1994; Gellert et al. 1996; Dubourg et al. 1998). GFR at 10-years, was almost the same as that reported by Offner et al. (41 mL/min/1.73m^2 BSA) (Offner et al. 1999), although they determined GFR by the formula clearance, which tend to overestimate GFR.

5.2 PAPERS II AND III, RENAL FUNCTIONAL RESERVE

Children with a renal transplant and their (living) kidney donors have a reduced renal mass. We wished to study whether the transplanted kidneys were maximally hyperfiltrating or if they still had some renal reserve - i.e., an ability to increase GFR after a protein load (ΔGFR). We also wished to know whether there was a difference in the renal reserve between the donor and recipient kidneys, the latter being subjected to nephrotoxic substances, renal surgery and, in some cases, acute rejections. We therefore investigated renal function (GFR and ERPF) before and after a protein rich meal following renal transplantation in children and, in controls (their kidney donors and children with a single kidney due to nephrectomy or agenesis).

5.2.1 Results

The investigations were performed 0.2-8.0 years after renal transplantation in children and adolescents transplanted at the age of 1.4-19.4 years. GFR was lower during baseline conditions in transplanted children than in controls. GFR increased in all groups following the protein load, with a higher fractional (%) increase in the transplanted children. ERPF increased more than GFR after the protein meal in transplanted children, which reduced the filtration fraction.
When we compared the recipient – donor pairs, no difference was seen between the recipients and donors in baseline and stimulated GFR.

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Even transplanted children with a GFR below 40 mL/min/1.73 m^2 BSA were able to increase GFR after stimulation. A higher fractional increase after the protein load was found in transplanted children with a lower baseline GFR.

When the test was repeated after 1-8 years to find out whether a decline in baseline GFR was associated with, or preceded by, a reduced ΔGFR, we found that the capacity to increase GFR after a protein-rich meal was preserved in the transplanted children. In the transplanted children, the length of the kidney correlated with the baseline and peak values of the GFR after the protein load.

The clearance of creatinine overestimated GFR measured by clearance of inulin both at baseline and after the protein load.

5.2.2 Discussion

The glomerular filtration rate is a dynamic parameter that is diet-dependent and can be changed by modifying hemodynamics. Cyclosporine induces reversible vasoconstriction, which causes a transient reduction in renal plasma flow and may even affect the renal response to a protein meal in patients with renal transplants (Nunley et al. 1991; Dello Strologo et al. 1996). Nevertheless, ERPF increased more than GFR after the protein load, and the capacity to increase GFR and ERPF persisted on repeated tests during follow-up. This accords with the findings of others (Ader et al. 1996; Nakamura et al. 1997), but is contrary to the expected vasoconstrictive effect of cyclosporine that is reported (Nunley et al. 1991; Mobb et al. 1992).

Most of the children studied had received grafts from adult living donors with less preservation damage than CD kidneys, which may have affected the ΔGFR. The direct correlation between renal length and GFR (baseline and maximal) is not surprising since the greater number of nephrons could be expected to increase both the baseline and stimulated GFR (Pluvio et al. 1996; Maranes et al. 1998). An inverse correlation between the baseline and the fractional increase in GFR has also been reported by other authors (Ader et al. 1994; Ader et al. 1996).

The clinical significance of the test is unclear and it was found to be less valuable than expected when we started the studies. On one hand, it was encouraging that a capacity to increase GFR and ERPF was found in transplanted children in both studies. This contradicts that a constant hyperfiltration would be present in the single kidney. The response was, on the other hand, seen regardless of baseline GFR and the hypothesis that a reduced ΔGFR would precede a decline in baseline GFR was not confirmed. Therefore, the test was not valuable to predict a decline in graft function and could not be used to discover patients who would benefit from a low protein diet, which we thought when we started. Other authors have also questioned the value of the test (Zuccala and Zucchelli 1990; ter Wee and Donker 1991; Thomas et al. 1994). Ultrasonographic renal parenchymal volume was proposed as a good measure of renal mass, correlating with the GFR (Troell et al. 1988). We showed that, renal size was related to both baseline and stimulated GFR after the protein load. Since our studies, the accuracy of renal ultrasound measurements has been questioned (Ferrer et al. 1997).

6 CONCLUDING REMARKS AND FUTURE PERSPECTIVE

Renal transplantation has become an established treatment modality of renal failure even for the youngest children. The present follow-up shows the outcome of renal transplantation in children who have been followed thoroughly for more than 10 years, which is unusual. Most studies do not have all children included so many years.
Good long-term patient survival was found, even in the youngest age group. Graft survival was superior in LD grafts. Good growth and a promising absence of severe long-term effects of immunosuppression were observed 10-20 years after transplantation.
The long-term care of pediatric kidney transplant recipients involves a balance among sufficient immunosuppression and complications of immunosuppressive medications, optimisation of growth, avoiding graft dysfunction and diagnosis and management of late complications.
Transplantation is a lifelong commitment and this generation of children who were transplanted more than 20 years ago, are "the first generation" who will reach adulthood with a transplant. It is therefore of great importance that we document the progress and outcome of these patients from transplantation in childhood to survival into adulthood.

Certain areas are of special importance.
Renal disease and transplantation are risk factors for premature cardiovascular disease. Information and awareness of other risk factors are important - i.e. hypertension, smoking, family history and disordered lipoprotein metabolism. Treatment of lipid abnormalities is not readily accomplished because of concerns about interactions and side effects. The incidence of fractures have increased dramatically in the western world during the last 50 years and is and increasing health problem. In transplanted patients in general, osteoporosis causes considerable morbidity. Bone mass may be reduced even prior to transplantation because of the underlying disease, nutritional deficits, reduced physical activity and, in some cases, exposure to steroids. Peak bone mass is achieved by early adulthood and is a key determinant of the lifetime risk of osteoporosis and fracture. If the peak bone mass achieved is reduced, the risk of fracture throughout adult life increases. Glucocorticoids affect bone adversely in various manners. Assessment of bone mineralisation and treatment of osteopenia is therefore of benefit for the future health of these patients. Continued surveillance, in order to early diagnose and manage any sign of malignant or pre-malignant changes, is also important. Psychosocial support might be needed, especially during adolescence.

There will probably be a need for a second and third kidney during the lifetime of these patients, which raises the issue of organ donation. The shortage of organs is a problem, and the knowledge of organ donation and transplantation has to increase in the general population.

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