Pediatr Nephrol (1991) 5: 412–421

Pediatric Nephrology

Nephrology review

Recurrent primary disease and de novo nephritis following renal transplantation

J. Stewart Cameron

Clinical Science Laboratories, 17th Floor Guy's Tower, Guy's Hospital, London SE1 9RT, UK

Received and accepted March 27, 1991

Abstract. Recurrent or de novo diseases account for only 5% of graft failure in children, but have much to teach us about mechanisms. In children, almost the only metabolic disease with recurrence is type I hyperoxaluria, in which the poor long-term results of isolated renal transplantation make combined liver and renal transplantation, or even prophylactic liver transplantation before renal failure the preferable alternatives. While many forms of nephritis may show histological recurrence in allografts, it is notable that in many patients this is accompanied by no clinical manifestations or only mild disease: this is particularly so in mesangiocapillary glomerulonephritis (MCGN) type II, IgA-associated nephropathy and Henoch-Schönlein purpura. However focal segmental glomerulosclerosis and MCGN type I recur with sufficient frequency and severity to deter the use of living donors unless there is no alternative. The same is true of haemolytic-uraemic syndromes. As many as 10% of paediatric grafts may show de novo membranous nephropathy, but in the majority this is mild or not clinically evident. In contrast, the rare anti-glomerular basement membrane nephritis affecting some patients with Alport's syndrome usually results in graft failure, but occurs in only a minority of recipients with the syndrome. For all types of disease in allografts, risk factors for recurrence are poorly worked out, and attempts at treatment generally ineffective.

Key words: Renal transplantation – De novo nephritis – Recurrent primary disease

Introduction

The principal, indeed the overwhelming, cause of graft loss remains either an acute immunological attack on the allograft during the first few months, or the slower process usually called "chronic rejection", although the nature of this slow graft failure is far from clear. However, there is a small proportion of patients in whom graft failure is the direct result of recrudescence of the original disease in the allograft, or the appearance of de novo disease. This is likely to be commoner in children because of the higher proportion of inherited metabolic diseases as a cause of renal failure, and the greater proportion of types of nephritis known to recur in allografts which are causes of childhood renal failure. Also, as the results of allografting improve and the incidence of irreversible rejection declines, the recurrence of disease in the allograft becomes of greater importance.

Even so, in a recent report from the American paediatric transplant registry, only 7 of 152 (4.6%) grafts which had failed were lost because of recurrent disease [1] out of a total of 750 transplants. The topic has, however, an importance above its frequency as a cause of graft loss, because of what these observations on experiments of man and nature combined have to tell us about the mechanisms of the diseases concerned.

I have reviewed recurrent glomerulonephritis in the past [2, 3], and this brief account will concentrate on more recent data published since 1982; these references [2, 3] can be consulted for earlier papers. In addition several general reviews of recurrent glomerulonephritis or other forms of recurrent primary disease have been published in the past few years, particularly by Mathew [4–6], and also in children by Habib et al. [7, 8], and Leumann and Briner [9], whilst further series of adult cases from individual units have been published by Honkanen et al. [10], O'Meara et al. [11] and Vangelista et al. [12].

In paediatrics the recurrence of a number of diseases which are of concern to the internist, such as plasma cell dyscrasias and monoclonal gammopathies, diabetes mellitus, systemic sclerosis, "essential" cryoglobulinaemia, and sarcoidosis are of no concern; paediatricians curious to learn about these phenomena can consult the texts cited above, particularly that of Mathew [6].

For a disease to recur in the allograft following renal failure implies that a milieu persists in that individual which leads to renal involvement. Table 1 lists most of the circumstances in which recurrence might be expected.

Table 1. Reappearance of disease in transplanted kidney depends upon persistence of a milieu damaging to the kidney

Metabolic product toxic to kidney	Oxalosis etc.
Organ-specific antibody	Anti-GBM disease ? membranous nephropathy
Amyloidogenic proteins	Amyloid
Immune aggregates	Other forms of glomerulonephritis
Sickling red cells	Sickle cell disease
Unknown	FSGS type II MCGN diabetes HUS

GBM, Glomerular basement membrane; FSGS, focal segmental glomerulosclerosis; MCGN, mesangiocapillary glomerulonephritis; HUS, haemolytic-uraemic syndrome

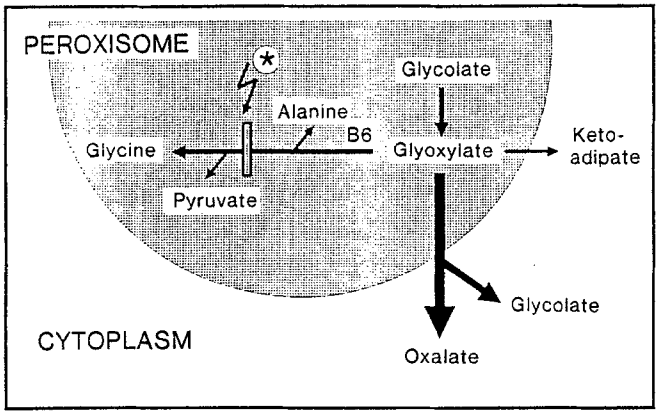

Fig. 1. The metabolic defect in primary hyperoxaluria type I. Deficiency of * alanine glyoxylate aminotransferase (cofactor, pyroxidal phosphate) leads to elevated production of oxalate and glycolate (from reference [20] with permission)

Oxalosis is the only common metabolic disorder in which recurrence of the disease is the result of accumulation of an abnormal metabolite, although theoretically this should be seen also in renal failure resulting from tyrosinaemia, galactosaemia, Fabry's disease [13], or any other inherited metabolic defect which is not cured by transplantation of a normal kidney bearing the deficient enzyme. In cystinosis, of course, the kidney is *not* affected in the strict sense with recurrent disease, since the transplanted renal cells have normal transport of cystine out of lysosomes; the problem here is one of progressive failure in other recipient organs. However, it has been known for 30 years that cystine crystals may be seen throughout the graft, in host cells invading the organ [14].

Other diseases in which the milieu is not changed by renal transplantation per se are homozygous sickle cell disease, and amyloidosis. In glomerulonephritis, a putative mechanism of damage in the form of organ-specific antibodies exists in anti-glomerular basement membrane (GBM) disease, and possibly some forms of recurrent membranous nephropathy, although in the latter condition the autoantigen in man has not yet been identified. In focal segmental glomerulosclerosis (FSGS), in dense "deposit" disease and in the haemolytic-uraemic syndrome (HUS) and in diabetes mellitus, the route by which the transplanted kidney is affected is not clear yet.

An important question is whether immunosuppression with cyclosporine prevents or leads to a reduction in the incidence of recurrent glomerulonephritis compared with recipients treated with azathioprine. Certainly cyclosporine does not prevent recurrence, since recurrence of all types of glomerulonephritis has been recorded in patients treated with cyclosporine, with the possible exception of the rare dense "deposit" type of mesangiocapillary glomerulonephritis (MCGN), probably from lack of numbers. Whether there is a reduction in the number of cases of recurrence under cyclosporine immunosuppression is more difficult to judge, again because of the small numbers involved; as will be reviewed below, in the case of individual diseases, there seems to be no good evidence that this is so. I will now consider individual conditions which may recur in the allograft and impair graft function.

Oxalosis

Type I primary hyperoxaluria results from a deficiency of the hepatic peroxisomal enzyme alanine-glyoxalate aminotransferase [15] (Fig. 1). Thus overproduction of oxalate persists in patients given renal transplants alone, and although the plasma oxalate levels are lower than the extreme levels found in patients on dialysis, the concentration is still elevated to the point where accumulation of oxalate in the vascular tree and elsewhere in tissues (including the grafted kidney itself) persists.

Initially oxalosis was considered an absolute contra-indication for renal transplantation, because of early graft failure from oxalosis, or later death of the recipient with a functioning graft. Today results with renal transplantation alone appear somewhat better that at first supposed [16], but whether it is useful to do the operation, with the option of later liver transplantation as a separate procedure, remains unclear [17, 18]. Even with good transplant function plasma oxalate levels may be 10 times normal, and the long-term survival of these patients must remain in doubt. Broyer et al. [16] present a large pan-European series of 98 patients transplanted with first renal allografts from 1965 to 1986: 79 received a cadaver and 15 living donor grafts (in 4 the source was unknown) at age 6–55 years (mode 24 years). After 3 years, only 23% of living donor and 17% of cadaver donor grafts survived, and 39 recipients (40%) had died. Neither time on dialysis nor age at end-stage renal failure influenced results.

Obviously if renal transplantation alone is performed despite these gloomy figures, then attempts should be made to minimise subsequent damage by oxalate to the allograft. These include administration of large doses of pyridoxine (which is a co-factor for the missing enzyme) and phosphate [19], together with magnesium chloride and the maintenance of a high urinary output. With these meas-

Table 2. Risk of recurrent glomerulonephritis after renal transplantation

	Histological	Clinical
Anti-GBM disease (with antibody)	High	High
FSGS	High	High
MCGN type I	Moderate	Moderate
MCGN type II	High	Low
IgA nephropathy	High	Low
HSP nephritis	High	Low
Membranous (de novo)	Low	Low
Crescentic	Low	Low
Vasculitis	Low	Low
Lupus glomerulonephritis	Almost never	

HSP, Henoch-Schönlein purpura; MCGN, mesangiocapillary glomerulonephritis

ures graft survival of up to 10 years can be achieved [16], but the really long-term outcome for these patients remains in doubt. It goes almost without saying that living donor transplantation should be avoided if at all possible in oxalosis.

In contrast to the miserable story of kidney allografting, combined liver and kidney transplantation is apparently curative, judged from the 4-year survival to date of the first successful combined operation [15, 18]; by 1990 some 20 patients had been so treated worldwide [20]. Today this seems to be the preferable approach in almost all children with this fatal disease, given the increased survival of such combined operations using cyclosporine as part of the immunosuppressive regime. A case can be made also for performing a hepatic allograft *before* renal failure appears [15].

Glomerulonephritis

Although recurrence of virtually all types of nephritis has been reported on occasion, the risk of recurrence varies greatly according to the type of glomerular disease, as summarised in Table 2. This table also emphasises that in several forms of glomerulonephritis there may be histological recurrence with few or no clinical consequences.

Anti-GBM disease

In some types of nephritis we have little more information than was available 10 years ago [2]. This is true of *anti-GBM* disease, which is in any case very rare in childhood (3 of 410 recipients in the series of Habib et al. [8] and none of the American series of 750 grafts [1]). Although antibody can deposit without damage, recurrence of active disease is usual in those still showing elevated anti-GBM antibody titres in their plasma. Conversely, in those with normal anti-GBM antibody titres, either the result of spontaneous disappearance [21] or (more usually) accelerated by treatment, recrudescence of antibody and recurrent disease have not been recorded. Thus, management centres on dialysis, until antibody levels become or are reduced to normal. How long one should then wait is not clear – most clinicians wait 6–12 months and recurrent disease has not been recorded in the literature for some time.

Focal segmental glomerulosclerosis

The main concern today, especially in paediatric transplantation, centres on recurrent *FSGS*; this condition is a common cause of renal failure in children, waiting does not apparently reduce the possibility of recurrence, and the nature of the transmitting agent remains obstinately obscure. We have reviewed our own and others' experience recently [22, 23] which provides a good data base on 250 patients (Table 3); these papers may be consulted for a detailed review of the rather extensive literature on the subject. Overall, recurrence is about 25% and the graft loss rate is about half this. However, the risk varies greatly from patient to patient, the main risk factors for recurrence being age, especially under 15 years, and above all below 6 years of age, a rapid evolution into renal failure (<3 years), and mesangial expansion in the renal biopsy. Thus in those

Table 3. Summary of the literature on recurrence of FSGS in allografts[a]

Author[b]	Year	No. of cases		No. of grafts with recurrence	% Recurrence	Graft/nephrx	Failure %
		Grafts	recipients				
Maizel	1981	33	25	5	15	2	6
Currier	1979	12	12	2	17	1	8
Malekzadeh	1979	18	18	3	17	2	11
Hamburger	1978	14	14	4	29	2	14
Morzycka	1982	21	20	4	19	2	9
Striegel	1986	37	24	16	43	14[c]	38
Habib	1987	?47	47	14	30	2	8
Senguttuvan	1990	59	43	13	22	4	7
		241	203	61	25.3	29	12.0

[a] Only series in which the total number of grafts performed in patients with FSGS was available have been included

[b] For detailed references see [22]

[c] Six lost exclusively from recurrent FSGS

aged less than 5 years the recurrence rate is about 50% [22], and in those aged less than 15 years at onset who go into renal failure within 3 years and also have mesangial expansion, the recurrence rate is 80%–100%. It has been suggested that haplo-identity or living donor transplantation makes recurrence more likely, but our data do not support this [22].

The severity of recurrence varies greatly from patient to patient, from immediate life-threatening massive proteinuria to milder forms of later onset. In the precocious onset with massive proteinuria, immediate transplant nephrectomy is necessary or the recipient's life may be put at risk, and attempts to treat the condition with plasma exchange or other means usually fail. Even in these patients, it has proved impossible in many attempts to induce proteinuria by injecting serum into experimental animals, with the possible exception of the report by Zimmerman and Mann [24].

Plasma exchange, although logical and attractive, does not appear to be of much benefit [23], although the report of Laufer et al. [25] is at variance with this conclusion. Likewise treatment with non-steriodal anti-inflammatory drugs has been recommended [26] but many other observers (including ourselves) have not noted any benefit from their use. The recurrence rate appears to be identical in recipients treated with cyclosporine when compared with those receiving azathioprine, despite some limited success with cyclosporine in the primary disease. Ingulli et al. [27] and Morales et al. [28] suggest that high-dose cyclosporine may reduce proteinuria and may induce remission in recurrent disease, but others have not observed this.

Second grafts in those who have had recurrence in their first graft are accompanied in 85% by a further recurrence [23], but we [22] and others [29] have recorded patients in whom a successful second graft was achieved after loss of the first from recurrent disease.

In three large series of grafts [8, 22, 30] the authors have examined the frequency of recurrence in recipients treated with azathioprine or with cyclosporine; in none of the three series nor in the pooled data was there any difference in incidence.

It is our feeling, shared by many, that where possible living donor grafts should be avoided in those patients with FSGS judged to be at high risk, unless a first cadaver graft is lost from rejection without evidence of recurrence.

Mesangiocapillary glomerulonephritis

The data are less complete for *MCGN*, type I or II (dense "deposit" disease), because fewer recurrence have been reported and there is no comparable extensive data base on complete series to judge the frequency of recurrence accurately. Since 1982 [2] only anecdotes have been reported (including descriptions of recurrence in two successive grafts [5, 8, 31] which we have observed also in an adult patient). In the American series [1] the graft loss rate was only 1 in 13 grafts, but in the French experience 7 of 11 recipients grafts, including 2 graft losses. Thus, 3 of 24 grafts with type I MCGN were lost in large paediatric series. The reported data from the French and our own adult series [2] suggest a lower overall recurrence rate in type I MCGN of about 20%–25%, but with a similar graft loss rate. Again it seems prudent to avoid living donor grafts in these patients where possible. No extensive data on recurrence in recipients treated with cyclosporine have been published, but we have seen this in the patient who lost two successive grafts, and others [32, 33] have published cases of recurrence under cyclosporine treatment.

In *type II MCGN* (dense "deposit" disease) it seems clear that histological recurrence of electron-dense material in the basement membranes of the transplant is seen in at least 85% of recipients (and in all 7 children reported by Habib et al. [8]), whilst clinical recurrence is much less common [2], and graft failure even more rare (2/7 recipients in the series of Habib et al. [8]). The exception seems to be patients showing extensive crescent formation, in whom more frequent clinical recurrence with graft loss has been observed [34, 35]. Mathew [6] reports the collected ANZDATA as 7 graft losses in 52 patients during 18 years. There are no records of histological or clinical recurrence in recipients treated with cyclosporine as yet, but the disease is rare. In neither type of MCGN does the concentration of C3 or C4 in the serum correlate with recurrence, suggesting that the complement concentrations are epiphenomena. Mathew [5] reports successful regrafting in 1 patient after loss from recurrence, albeit with histological reappearance of "deposits" in the second graft. Oberkircher et al. [36] suggest that aggressive treatment with plasma exchange in crescentic recurrent disease may be effective, but the general experience in the few severe cases is that no treatment is effective.

IgA nephropathy and Henoch-Schönlein purpura

In *IgA nephropathy* and in *Henoch-Schönlein purpura nephritis* recurrence of the mesangial IgA "deposits" is seen in at least 25%–45% of recipients [2–8]; these figures are almost certainly underestimates, since not all recipients are biopsied and in others IgA is not sought in the biopsy. Clinical recurrence is very rare [37–39]. In the original series of Berger et al. [40] in which all 32 patients were biopsied, the recurrence rate of IgA "deposits" was as high as 53%. Mathew [5] noted only 1% (2/200) recipients were affected clinically in the the ANZDATA, and only 4 grafts have been recorded as lost as a result of recurrent IgA nephropathy [6], although we have seen a further unpublished case in an adult. The rather rare subjects with extensive crescent formation may be an exception [38, 39] as in our patient, with a higher risk of recurrence. Brensilver et al. [38] discuss a possible extra risk of living donor grafts from siblings, but the significance of their observation is not clear. Certainly the risk of clinical recurrence is so low (about 1%) that in general living donors can be used without much fear in children with IgA nephropathy and renal failure, which is in any case itself a rare event (7/410 children in the series of Habib et al. [8]).

In Henoch-Schönlein purpura nephritis also, reappearance of IgA in the allograft affects one-third to three-quarters of cases, although clinical recurrence is rare: we have

Table 4. Recurrence of clinically evident nephritis in HSP (biopsy confirmed in all cases)

Author	Year	Age (years)	Sex	Donor	Recurrent purpura?	Time	mani-festation	Outcome	Rx
Bar-on and Rosenmann	1971	26	m	LD (twin)	yes	?	"deteriorated renal function"	?	
Baliah	1974	8	m	LD	yes	3 days	proteinuria/haematuria	failed	HD
Sakai	1975	5	f	?	–	5 months	proteinuria/haematuria	failed	HD
Nast	1987	20	f	LD	yes	3 months	proteinuria/haematuria	failed	regraft
Pirson	1988	?	?	?	–	20 months	nephrotic	failed	?
Hasegawa	1989	14	m	LD	–	immediately	proteinuria/haematuria	failed	
		5	f	LD	–	3 months	proteinuria/haematuria	failed	regraft
		10	m	LD	–	2 months	proteinuria/haematuria	died with functioning graft-pneumonia	
		14	m	LD	–	11 months	proteinuria	proteinuria disappeared	

LD, Living donor graft; HD, Haemodialysis; m, male; f, female
(see Hasegawa [42] and Nast [41] for references)

never seen it in 30 patients transplanted over 25 years. Data on patients reported with clinical recurrence are shown in Table 4. Transplantation into those still having recurrent attacks of purpura may be relatively hazardous [41, 42], but not all observers concur. Recurrence seems to occur as readily under cyclosporine treatment as with azathioprine.

Membranous nephropathy

Renal failure from *membranous nephropathy* is almost unknown during childhood [8, 43] with only 1 case in the series of Habib et al. [8] and 3 in the American [1], but it is worth noting, especially in relation to the de novo membranous nephropathy discussed below, that recurrence has been reported in about 25 cases [2, 44–46] all adults, although even in them membranous nephropathy is not a common cause of renal failure. The proportion of recurrence is difficult to determine, especially as de novo membranous nephritis is much more common (see below); we have seen 3 cases in only 14 transplanted adult recipients (22%). Again recurrence is not apparently inhibited by cyclosporine [47]. The timing of the clinical appearance of the lesion is earlier in those with recurrent (mean 10 months, range 1 week to 2 years) than in those with de novo disease (mean 22 months, range 4 months to 6 years). About half the grafts affected by recurrent membranous nephropathy have failed, but as usual it is difficult to assess what role the glomerulonephritis may have played in these failures. Renal venous thrombosis may be seen in allografted kidneys in both recurrent and de novo membranous nephropathy [46]. Although it has been suggested that more aggressive disease is more likely to recur [44], we have not seen any relationship, including no recurrence in one patient who went from normal renal function (glomerular filtration rate 110 ml/min) to end-stage disease in only 15 months and was transplanted only a few months later.

Crescentic glomerulonephritis (other than anti-GBM)

No further data on the recurrence of *crescentic glomerulonephritis*, other than that depending upon anti-GBM antibody, have appeared in recent years [2]. In childhood this is a rather rare cause of renal failure (6 cases /410 in the Paris series [8] and 13/750 in the American [1]), and the risks of recurrence, surprisingly in view of the rapid evolution of this type of nephritis, appear to be small in this group: 1 paediatric case has been recorded [1] and recurrence is not avoided by cyclosporine [48]. Although rare, Wegener's granuloma can lead to renal failure in childhood [49, 50] and in a few adult patients recurrence of crescentic vasculitis in the allograft have appeared, together with one child [50]. One unresolved problem is what immunosuppressive regime to give such patients: improvement following transfer to cyclophosphamide has been recorded [51] and the possibility that relapse may occur under treatment with cyclosporine has been raised [50].

Systemic lupus erythematosus

Three further (see [2] for review of the previous literature) cases of probable recurrence of lupus nephritis have been published recently [52–54] to bring the total recorded cases only to seven, with two other doubtful cases; but the striking feature of lupus is the almost complete *absence* of recurrence. The incidence must be 1 in 100 cases or less, and even in those in whom recurrence has been clearly identified, it has been of little clinical significance and not a cause of graft loss. This surely tells us that the kidney itself must have some determinant which allows the appearance of nephritis, and which is missing from the allografted kidney, since a number of patients [55] (including in our own unit) have been transplanted at times of activity, with circulating immune complexes, raised plasma anti-DNA antibody and requirement for steroid treatment. Lupus is a rare cause of renal failure in childhood, but we have had to transplant two children with this disease, in neither of whom was recurrence observed, despite disease activity.

Amyloidosis

Amyloidosis as a cause of renal failure is very rare in childhood in the developed world, but chronic sepsis is still a problem in many countries including children. Recently a large single centre experience [56] has been published in which 4 of 45 patients (8%) showed recurrence in their allografts, 3 of whom had rheumatic disorders and one AL amyloidosis, other cases have also been published [57]. Recurrence has been recorded also in patients with familial Mediterranean fever [58, 59] but does not seem to be a major deterrent to transplantation, although no systematic survey of the frequency has been done; unfortunately the recent large survey of renal failure as a result of amyloidosis conducted by the European Dialysis Transplant Association – European Renal Association did not contain an estimate of the frequency of amyloid in the allografts.

Haemolytic-uraemic syndromes

This is an important topic for the paediatric nephrologist since HUS is an important cause of chronic renal failure in both infants and older children (about 5% of all cases [1, 8], as well as occurring in adults at all ages, although in much smaller numbers. It is somewhat difficult to assess the true significance of recurrent disease in patients bearing renal allografts, since both the histological and haemotological features of the syndrome may appear in severe allograft rejection, and cyclosporine itself may give rise to a similar picture even in individuals with normal kidneys, such as after bone marrow transplantation [60]. At one extreme, 5 of 11 children whose renal failure arose from HUS lost their grafts with a similar syndrome [61], 1 losing three consecutive grafts to the disease; at the other, 0 of 12 adults and 4 children experienced recurrence [62]. Eijenraam et al. [63], in probably the largest single centre experience reported, found probable recurrence of HUS in only 2 first grafts out of 24 placed into 20 children. In adults, recurrence seems to be rare [64], and the Australian-New Zealand data showed only 5 graft losses in 36 cases [6]. Thus overall about 10% of recipients may be expected to show recurrence, in the majority of whom the graft will be lost. The heterogeneity of outcome is not surprising, given the heterogeneity of the syndrome itself.

Possible factors favouring recurrence are early placement of grafts in acute disease, since it was rare in patients who remained on dialysis for several months before grafting [64], whereas we lost four cadaver grafts in two adult patients transplanted within 3 months of onset, with a pattern consistent with recurrent disease. However Hebert et al. [61] report immediate recurrence after 3–5 years on dialysis in two children. Perhaps the use of living donors rather than cadaver donors may increase recurrence rates, as suggested by the same authors [61]. Whether cyclosporine should be used in these patients has been debated [65, 66] in view of the HUS-like syndrome which may develop de novo in cyclosporine-treated patients with other causes of renal failure. One patient who developed HUS after transplantation under cyclosporine treatment was transferred to FK 506 [67]. Certainly cyclosporine has been used without problems on a number of occasions (including in our own unit) without recurrent HUS, but whether the incidence of recurrence is higher in those so treated has not been established.

All the treatments which have been used for the primary disease have been used for its recurrence: corticosteroids, anti-platelet agents, vasodilatory prostaglandins, plasma exchange and plasma infusions. There is no clear evidence, as with the original disease, that any intervention affects the course of the recurrence in allografts; this has not affected their use, perhaps as a gesture of desperation when faced with a failing graft.

Use of living donors

Obviously the data reviewed above on recurrent glomerulonephritis have relevance for the use of living, usually parental, donors in paediatric transplantation. However, it is only in a few situations that there is a major clinical impact. First, to my mind the evidence that using related donors increases the rate of any recurrent disease dissolves on close examination. Second, only in oxalosis and FSGS with features strongly predicting recurrence (see above), does it seem completely inadvisable to use living donor grafts unless there are no alternatives. In more indolent FSGS the risk may be worth taking. In MCGN type I also and HUS, the risks seem high enough to avoid living donors where possible. In other forms of glomerulopathy, the recurrent and failure rates are low enough to permit free use of parental or other familial grafts.

De novo glomerulopathy

De novo disease is much less well worked out than recurrent disease: in theory, the transplanted kidney could be affected by *any* form of acquired renal disease just as native kidneys are, and occasional patients with what appear to be coincidental nephritis have been described – for example post-infectious glomerulonephritis. We observed one patient who appeared to develop serum sickness nephritis in relation to a reaction against horse anti-lymphocyte globulin. The chronic condition usually known as allograft glomerulopathy or transplant glomerulopathy, which appears to be a glomerular manifestation of chronic rejection will not be discussed here (see [2, 8] for treatment of this topic).

Several patients with the appearance of what may have been reversible minimal-change nephrotic syndromes have been described [8]. Focal segmental sclerosing glomerular lesions are common in long-surviving allografts, may have little significance, and probably do not merit the term "de novo FSGS". Habib et al. [8] report two patients who developed both the appearances and immunohistological characteristics of MCGN type I in their allografts; the original cause of their renal failure is not given.

However, the most important de novo diseases are de novo membranous nephropathy, and de novo crescentic anti-GBM antibody glomerulopathy in patients with Alport's syndrome.

Table 5. De novo anti-GBM nephritis in Alport's syndrome[a]

Author	Year	Ref.	Age (years)	Sex	Time after Tx	anti-GBM antibodies	pph	Outcome
McCoy et al.	1982	73	15	m	5	+		Graft loss HD
Milliner et al.	1982	74	34	m	LD 9 ?source	+		Graft loss new LDTx IF + ve OK despite antiGBM antibody
			27	m	43	– IIF only		Graft loss new Tx OK
Teruel et al.	1987	75	24	m	6	+		Graft loss HD
Fleming et al.[c]	1988	76	27	m	9	+		Graft loss HD
Shah et al.[b, c]	1988	77	19	m	LD 5 mo	+		Graft loss HD
			20	m	LD 18 sib	+	pph	Graft loss new CDTx rejHD
van der Heuvel	1989	78	10	f	6	+	pph	Graft loss HD
			17	m	7	+		Graft loss HD
Rassoul et al.	1990	79	18	m	4	+		Graft loss new Tx pph OK
Kashtan et al.[c]	1990	80	19	m	8	+		Graft loss
Goldman et al.[c]	1990	81	25	m	LD 7 mo	+		Graft loss HD
					1	+		Graft loss HD

sib, sibling; mo, mother; Tx, allograft; pph, plasma exchange; OK, functioning graft; IIF, indirect immunofluorescence;

[a] All unspecified donors are cadavers

[b] These 2 patients were further studied by Kashtan et al. [82] and were members of the same kindred, which was not mentioned in the original report

[c] Patients treated with cyclosporine and prednisolone, other patients azathioprine and prednisolone

De novo membranous nephropathy

In about 1%–2% of most series of renal transplants in adults, after about 1–2 years profuse proteinuria or a frank nephrotic syndrome heralds the appearance of a classical membranous nephropathy in patients whose original disease was different; in a recent analysis of 95 cases from the literature [68] there was no predilection for any particular type of original cause for the chronic renal failure. About three-quarters (62/85) were nephrotic, and both living and cadaver donors appear equally affected (79/13). Mean time to appearance of proteinuria was 16 months, to diagnosis 23 months. Evolution into graft failure was slow, with half the grafts surviving a further 3 years. These data are derived from patients selected for biopsy because either they had graft dysfunction, or more commonly developed a nephrotic syndrome.

In the single series in which routine histology and immunohistology was done on biopsies performed routinely in all allografts [69], a much higher prevalence of over 9% was noted, symptomless in about one-quarter and with only minor proteinuria in another quarter of patients. In many cases the histological changes were slight, and evolution was correspondingly favourable. It is known if a similar investigation in adults or in another paediatric unit would reveal a similar high incidence.

The pathogenesis of the condition is obscure: suggestions that it might arise from alloantibody immune complex formation are made less likely by its appearance in an isograft performed later between conjoined twins separated after birth [70]. No autoantibodies analagous to those present in Heymann nephritis have been identified in patients with de novo membranous nephropathy, with the exception of a single report [71]. No association with HLA antigens has been reported, nor has HLA-A or -B matching been particulary close or divergent in affected cases. In one autopsy report, the native kidneys showed no nephritis even though the graft did [69]. In general, biopsies showing de novo membranous nephropathy also show features of chronic cellular rejection, but whether more commonly than in a random series is not clear.

Anti-GBM antibody nephritis in Alport's syndrome

Alport's syndrome arises from mutations recently located in a gene at Xq 22 coding for an $\alpha 5$ non-collagenous portion of type IV collagen, found in the glomerular and other basement membranes [72]. Thus male Alport hemizygotes lack or have substituted a portion of the normal collagen structure, whilst allografts placed into such patients possess the normal epitope. In some patients this seems to be sufficient to evoke an immune response with production of antibody directed against the "new" antigen, which is capable of fixing to the allograft, but in only some patients actually showing fixation to induce a severe crescentic glomerulonephritis: the 13 cases reported since its first description in 1982 [73–81] are summarized in Table 5. Querin et al. [83] noted linear deposition of IgG along the GBM in five cases of Alport's syndrome *without* nephritis, but no anti-GBM antibody was detectable in the serum. Both they and Habib et al. [8], however, noted such appearances in patients with a random selection of other underlying renal diseases.

All Alport allograft recipients suffering crescentic nephritis had developed renal failure early in life, and all were

deaf. There was a latent period of some months after grafting before the nephritis appeared, but all grafts but 1 were lost to the severe nephritis, despite plasma exchange in 3. One unexpected feature is that 1 of the patients reported by van der Heuvel et al. [78] was female. Heterozygotes would normally be equal mosaics of normal and abnormal genes resulting from random inactivation of one of each of the pairs of X chromosomes, normal and abnormal, and thus should have tolerance of the antigen in the allograft. It may be that in this individual the great majority of her cells expressed the abnormal chromosome.

The other puzzle is why only a few patients with Alport's syndrome develop the nephritis. For example, we have transplanted 31 children and adults with 46 grafts and have never seen this complication, and in Paris over 50 patients [8, 83] with Alport's syndrome have been transplanted in the adult and paediatric units without any case of de novo nephritis. Numbers are too small to determine risk factors such as haplo-identity, major histocompatibility complex type or closeness of tissue match. The antibodies present in different patients with recurrence seem to be directed against several different specificities [78, 82], making a single gene mutation unlikely. Even so, perhaps particular mutation in the collagen type IV α 5 gene will turn out to be present in those patients susceptile to nephritis, particularly those which lead to large deletions or frame shifts, as suggested by Kashtan et al. [80]; thus it will be worth examining the structure of the Alport locus in patients with the novo crescentic nephritis and their families with particular care using the newly available probes.

References

1. Alexander SR, Arbus GS, Butt KMH, Conley S, Fine RN, Greifer I, Gruskin AB, Harmon WE, McEnery PT, Nevins TE, Nogueira N, Salvatierra O, Tejani A (1990) The 1989 report of the North American pediatric renal transplant cooperative study. Pediatr Nephrol 4: 542–553
2. Cameron JS (1982) Glomerulonephritis in renal transplants. Transplantation 34: 237–245
3. Cameron JS (1983) Effect of the recipient's disease on the results of kidney transplantation (other than diabetes mellitus). Kidney Int 23 [Suppl 14]: S24–S33
4. Mathew TH (1988) Recurrence of disease following renal transplantation. Am J Kidney Dis 12: 85–96
5. Mathew TH (1988) Nephrotic syndrome following transplantation. In: Cameron JS, Glassock RJ (eds) The nephrotic syndrome. Dekker New York, pp 805–847
6. Mathew TH (1991) Recurrent disease after renal transplantation. Transplant Rev 5: 1–15
7. Habib R, Gagnadoux MF, Broyer M (1987) Recurrent glomerulonephritis in transplanted children. Contrib Nephrol 55: 123–135
8. Habib R, Antignac C, Hinglais N, Gagnadoux M-F, Broyer M (1987) Glomerular lesions in the transplanted kidney in children. Am J Kidney Dis 10: 198–207
9. Leumann EP, Briner J (1984) Rezidive der Grundkrankheit im Nierentransplantat. Klin Wochenschr 62: 289–298
10. Honkanen E, Tornroth T, Pettersson E, Kuhlback B (1984) Glomerulonephritis in renal allografts: results of 18 years of transplantation. Clin Nephrol 21: 210–219
11. O'Meara Y, Green A, Carmody M, Donohoe J, Campbell E, Borwne O, Walshe J (1989) Recurrent glomerulonephritis in renal transplants: fourteen years' experience. Nephrol Dial Transplant 4: 730–734
12. Vangelista A, Frasca GM, Martella D, Bonomini V (1990) Glomerulonephritis in renal transplants. Nephrol Dial Transplant [Suppl 1]: 42–46
13. Popli S, Molnar ZV, Leehy DJ (1987) Involvement of renal allograft by Fabry's disease. Am J Nephrol 7: 316–318
14. Spear GS, Gubler MC, Habib R, Broyer M (1989) Renal allografts in cystinosis and mesangial demography. Clin Nephrol 32: 256–261
15. Watts RW, Morgan SH, Danpure CJ, Purkiss P, Calne RY, Rolles K, Baker LRI, Mansell M, Smith LH, Merion RM, Lucey MR (1991) Combined hepatic and renal transplantation in primary hyperoxaluria type I: clinical report of nine cases. Am J Med 90: 179–192
16. Broyer M, Brunner FP, Brynger H, Dykes SR, Ehrich JHH, Fassbinder W, Geerlings W, Rizzoni G, Selwood NH, Tufveson G, Wing AJ (1990) Kidney transplantation in primary oxalosis: data from the EDTA registry. Nephrol Dial Transplant 5: 332–336
17. McDonald JC, Landeranu MD, Rohr MS, Devault GA Jr (1989) Reversal by liver transplantation of the complications of primary hyperoxaluria as well as the metabolic defect. N Engl J Med 321: 1100–1103
18. Watts RWE, Mansell MA (1990) Oxalate livers and kidneys. Combined renal and hepatic transplants transform the outlook in primary hyperoxaluria type I. Br Med J 301: 772–773
19. Scheinman JI, Najarian JS, Mauer SM (1984) Successful strategies for renal transplantation in oxalosis. Kidney Int 25: 804–811
20. Schurmann G, Scharer K, Wingen A-M, Otto G, Herfarth C (1990) Early liver transplantation for primary hyperoxaluria type I in an infant with chronic renal failure. Nephrol Dial Transplant 5: 825–827
21. Flores JC, Taube D, Savage COS, Cameron JS, Lockwood CM, Williams DG, Ogg CS (1986) Clinical and immunological evolution of oligoanuric anti-GBM nephritis treated by haemodialysis. Lancet I: 5–8
22. Senguttuvan P, Cameron JS, Hartley RB, Rigden S, Chantler C, Haycock G, Gwyn Williams D, Ogg CS, Koffman G (1990) Recurrence of focal segmental glomerulosclerosis in transplanted kidneys: analysis of incidence and risk factors in 59 allografts. Pediatr Nephrol 4: 21–28
23. Cameron JS (1990) Ask the expert. Pediatr Nephrol 3: 300
24. Zimmerman SW, Mann S (1984) Increased urinary protein excretion in the rat produced by serum from a patient with recurrent focal glomerulosclerosis after renal transplantation. Clin Nephrol 22: 32–38
25. Laufer J, Ettenger RB, Ho WG, Cohen AH, Marik JL, Fine RN (1988) Plasma exchange for recurrent nephrotic syndrome following renal transplantation. Transplantation 46: 540–542
26. Torres VE, Velosa JA, Holley KE, Frohnert PP (1984) Meclofenamate treatment of recurrent idiopathic nephrotic syndrome with focal segmental glomerulosclerosis after renal transplantation. Mayo Clin Proc 59: 146–152
27. Ingulli E, Tejani A, Butt KMH, Rajpoot D, Gonzalez F, Pomrantz A, Ettenger R (1990) High-dose cyclosporine therapy in recurrent nephrotic syndrome following renal transplantation. Transplantation 49: 219–221
28. Morales JM, Andres A, Prieto C, Parag M, Guterriez Millet V, Rodicio JL (1989) Ciclosporin-induced partial and transient improvement of nephrotic syndrome in recurrent focal segmental glomerulosclerosis. Nephron 53: 283–284
29. Hosenpud J, Piering WF, Grancis JC, Kauffman HM (1985) Successful second kidney transplantation in a patient with focal glomerulosclerosis. Am J Nephrol 5: 299–304
30. Banfi G, Colturi C, Montagnino G, Ponticelli C (1990) The recurrence of focal segmental glomerulosclerosis in kidney transplant patients treated with cyclosporine. Transplantation 50: 594–596
31. Glicklich D, Matas AJ, Sablay LB, Senizer D, Veith FJ (1987) Recurrent membrano-proliferative glomerulonephritis type I in successive renal transplants. Am J Nephrol 7: 143–149
32. Moritz MJ, Burke JF, Carabasi RA (1987) The incidence of membranoproliferative glomerulonephritis in renal allografts. Transplant Proc 19: 2206–2207
33. Yussim A, BenBassat M, Shapira Z, Schmueli D, Shaharabani F, Lustig S, Nakache R (1989) Post transplant glomerulonephritis under

conventional and cyclosporin A immunosuppression. Transplant Proc 21: 2119–2120
34. Sanz De Castro S, Val F, Francisco ALM de, Canga E, Gonzalez M, Cotorruelo JG, Garijo F, Arias M (1988) Recidiva de glomerulonephritis membranoproliferativa tipo II en riñon trasplantado con evolucion rapidamente progresiva. Nefrologia 8: 70–73
35. Eddy A, Sibley R, Mauer SM, Kim Y (1984) Renal allograft failure due to recurrent dense intramembranous deposit disease. Clin Nephrol 21: 305–313
36. Oberkircher OR, Ewama M, West JC, Campbell P, Moran J (1988) Regression of recurrent membranoproliferative glomerulonephritis type II in a transplanted kidney after plasmapheresis therapy. Transplant Proc 20: 418–423
37. Bachman U, Biava C, Amend W, Feduska N, Melzer J, Salvatierra O, Vincenti F (1986) The clinical course of IgA-nephropathy and Henoch-Schönlein purpura following renal transplantation. Transplantation 42: 511–515
38. Brensilver JM, Mallat S, Scholes J, McCabe R (1988) Recurrent IgA nephropathy in living-related donor transplantation: recurrence or transmission of familial disease? Am J Kidney Dis 12: 147–151
39. Diaz-Tejeiro R, Maduell F, Diez J, Esparza N, Errasti P, Purroy A, Pardo J (1990) Loss of graft due to recurrent IgA nephropathy with rapidly progressive course: an unusual clinical evolution. Nephron 54: 431–433
40. Berger J, Noel LH, Nabarra B (1984) Recurrence of mesangial IgA nephropathy after renal transplantation. Contrib Nephrol 40: 195–197
41. Nast CC, Ward HJ, Koyle MA, Cohen AH (1984) Recurrent Henoch-Schönlein purpura following renal transplantation. Am J Kidney Dis 9: 39–43
42. Hasegawa A, Kawamura T, Ito H, Hasegawa O, Ogawa O, Honda M, Ohara T, Hajikano H (1989) Fate of renal grafts with recurrent Henoch-Schönlein purpura nephritis. Transplant Proc 21: 2130–2133
43. Cameron JS (1990) Membranous nephropathy in childhood. Pediatr Nephrol 4: 193–198
44. Obermiller LE, Hoy WE, Eversole M, Sterling WA (1985) Recurrent membranous glomerulonephritis in two renal transplants. Transplantation 40: 100–103
45. Berger BE, Vicenti F, Biava B, Amend WJ, Feduska N, Salvatierra O (1983) De novo and recurrent membranous glomerulopathy following kidney transplantation. Transplantation 35: 315–319
46. First MR, Mendoza N, Maryniak RK, Weiss MA (1984) Membranous glomerulopathy following kidney transplantation: association with renal vein thrombosis in two of nine cases. Transplantation 38: 603–607
47. Montagnino G, Colturi C, Banfi G, Arnoldi A, Tarantino A, Ponticelli C (1989) Membranous nephropathy in cyclosporine-treated renal transplant recipients. Transplantation 47: 725–727
48. Turney JH, Adu D, Michael J, McMaster F (1986) Recurrent cresentic glomerulonephritis in renal transplant recipient treated with cyclosporine (letter). Lancet I: 1104
49. Hall SL, Miller LC, Duggan E, Mauer SM, Hellerstein S (1985) Wegener granulomatosis in paediatric patients. J Pediatr 106: 7339–7344
50. Clarke AE, Bitton A, Eappen R, Danoff DS, Esdaile JM (1990) Treatment of Wegener's granulomatosis after renal transplantation. Is cyclosporine the preferred treatment? Transplantation 50: 1047–1051
51. Steinman TJ, Jaffe B, Monaco AP, Wolff SM, Fauci AS (1980) Recurrence of Wegener's granulomatosis after kidney transplantation. Successful induction of remission with cyclophosphamide. Am J Med 68: 458–460
52. Kumano K, Sakai T, Mashimo S, Endo T, Koshiba K, Elises JS, Iitaka K (1987) A case of recurrent lupus nephritis after renal transplantation. Clin Nephrol 27: 94–98
53. Nyberg G, Blohme I, Svalander C, Persson H, Brynger H (1987) Rejection and recurrence of SLE nephritis in cyclosporine treated kidney transplant recipients. Transplant Proc 19: 1637–1638
54. Fernandez JA, Milgrom M, Burke GW, Miller J, Roth D (1990) Recurrence of lupus nephritis in a renal allograft with histologic transformation of the lesion. Transplantation 50: 1056–1058
55. Cantarovich F, Hiesse C, Lantz O, Charpentier B, Fries D (1988) Renal transplantation and active lupus erythematosus. Ann Intern Med 109: 254–255
56. Pasternack A, Ahonen J, Kuhlback B (1986) Renal transplantation in 45 patients with amyloidosis. Transplantation 42: 598–601
57. Light P, Hall-Craggs M (1979) Amyloid deposition in a renal allograft in a case of amyloid secondary to rheumatoid arthritis. Am J Med 66: 532–535
58. Benson MD, Skinner M, Cohen AS (1977) Amyloid deposition in a renal transplant in familial Mediterranean fever. Ann Intern Med 87: 31–34
59. Metaxas P (1981) Nephrology forum: familial Mediterranean fever and amyloidosis. Kidney Int 20: 676–685
60. Schulman H, Striker G, Deeg HJ, Kennedy M, Strob R, Thomas ED (1981) Nephrotoxicity of cyclosporin A after allogeneic bone marrow transplantation. Glomerular thromboses and tubular injury. N Engl J Med 305: 1392–1395
61. Hebert D, Kim E-M, Sibley RK, Mauer SM (1991) Post transplantation outcome of patients with hemolytic uremic syndrome: update. Pediatr Nephrol 5: 162–167
62. Pirson Y, Leclerq B, Squifflet JP, Alexandre GPJ, Ypersele C van (1986) Good prognosis of the hemolytic uremic syndrome after renal transplantation (abstract). Abstracts of the 23rd Congress of the EDTA-ERA, Budapest 1986, p 197
63. Eijenraam FJ, Donckerwolcke RA, Monnens LAH, Proesmans W, Wolff ED, Damme B van (1990) Renal transplantation in 20 children with hemolytic uremic syndrome. Clin Nephrol 33: 87–93
64. Arias Rodriguez M, Sraer JD, Kourilsky O, Smith MD, Verroust PJ, Meyrier A, Kinzinger H-E, Kanfer A, Nessim V, Neuilly G, Morel-Maroger L, Richet G (1977) Renal transplantation and immunological abnormalities in thrombotic microangiopathy of adults. Transplantation 23: 360–365
65. Leithner C, Sinzinger H, Pohanka E, Schwartz M, Kretschmer G, Syre G (1982) Recurrence of haemolytic uraemic syndrome triggered by cyclosporin A after renal transplantation (letter). Lancet I: 1470
66. Hamilton D, Calne RY, Evans DB (1982) Haemolytic-uraemic syndrome and cyclosporin A (letter). Lancet II: 151–152
67. McCauley J, Bronster O, Fung J, Todo S, Starzl TE (1989) Treatment of cyclosporin-induced haemolytic-uraemic syndrome with FK 506 (letter). Lancet 300: 1516
68. Truong L, Gelfand J, D'Agati V, Tomaszewski J, Appel G, Hardy M, Pirani CL (1989) De novo membranous glomerulopathy in renal allografts: a report of ten cases and review of the literature. Am J Kidney Dis 14: 131–144
69. Antignac C, Hinglais N, Gubler M-C, Gagnadoux M-F, Broyer M, Habib R (1988) De novo membranous glomerulonephritis in renal allografts in children. Clin Nephrol 30: 1–7
70. Bansal VK, Koseny GA, Fresco R, Vertuno LL, Hano JE (1986) De novo membranous nephropathy following transplantation between conjoint twins. Transplantation 41: 404–405
71. Zanetti M, Mandet C, Duboust A, Bedrossian J, Bariety J (1981) Demonstration of a passive Heymann nephritis-like mechanism in a human renal transplant. Clin Nephrol 15: 272–277
72. Barker DF, Hostikka SL, Zhou J, Chow LT, Oliphant AR, Gerken SC, Gregory MC, Skilnick MH, Atkin CL, Tryggvason K (1990) Identification of mutations in the COL4A5 collagen gene in Alport syndrome. Science 248: 1224–1227
73. McCoy RC, Johnson HK, Stone WJ, Wilson CB (1982) Absence of nephritogenic GBM antigen(s) in some patients with hereditary nephritis. Kidney Int 21: 128–137
74. Milliner DS, Pierides AM, Holley KE (1982) Renal transplantation in Alport's syndrome. Anti-glomerular basement membrane in the allograft. Mayo Clin Proc 57: 35–43
75. Teruel JL, Liano F, Mampaso F, Morteno J, Querada C, Ortuno J (1987) Allograft antiglomerular basement membrane glomerulonephritis in a patients with Alport's syndrome. Nephron 46: 43–44

76. Fleming SJ, Savage COS, McWilliam LJ, Pickering SJ, Ralston AJ, Johnson RW, Ackrill P (1988) Antiglomerular basement membrane antibody-mediated nephritis complicating transplantation in a patient with Alport's syndrome. Transplantation 46: 857–859
77. Shah B, First MR, Mendoza NC, Clyne DH, Alexander JW, Weiss MA (1988) Alport's syndrome: risk of glomerulonephritis induced by anti-glomerular-basement membrane antibody after renal transplantation. Nephron 50: 34–38
78. Heuvel LPWJ van der, Schroder CH, Savage COS, Menzel D, Assmann KJM, Monnens LAH, Veerkamp JH (1989) The development of anti-glomerular basement membrane nephritis in two children with Alport's syndrome after renal transplantation: characterization of the antibody target. Pediatr Nephrol 3: 406–413
79. Rassoul Z, Al Khader AA, Al-Sulaiman M, Dhar JM, Coode P (1990) Recurrent allograft antiglomerular basement membrane glomerulonephritis in a patient with Alport's syndrome. Am J Nephrol: 73–76
80. Kashtan C, Kelppel MM, Butkowski RJ, Michael AL, Fish AJ (1990) Alport syndrome, basement membranes and collagen. Pediatr Nephrol 4: 523–532
81. Goldman M, Deperrieux M, Pauw L de, Veerstraeten P, Kinnaert P, Noel L-H, Grunfeld J-P, Toussaint C (1990) Failure of two subsequent renal grafts by anti-GBM glomerulonephritis in Alport's syndrome: case report and review of the literature. Transplant Int 3: 82–85
82. Kashtan C, Butkowski RJ, Kleppel MM, First MR, Michael AF (1990) Posttransplant anti-glomerular basement membrane nephritis in related males with Alport syndrome. J Lab Clin Med 116: 508–515
83. Querin S, Noel L-H, Grunfeld J-P, Droz D, Mahieu P, Berger J, Kreis H (1986) Linear glomerular IgG fixation in renal allografts: incidence and significance in Alport's syndrome. Clin Nephrol 25: 134–140