*Social Science & Medicine* (2004) 58 (4): 767–785. doi:10.1016/S0277-9536(03)00243-0

# Exploring the Pathways Leading from Disadvantage to End-Stage Renal Disease for Indigenous Australians

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## Abstract

Indigenous Australians are disadvantaged, relative to other Australians, over a range of socio-economic and health measures. The age- and sex-adjusted incidence of end-stage renal disease (ESRD) – the irreversible preterminal phase of chronic renal failure – is almost nine times higher amongst Indigenous than it is amongst non-indigenous Australians. A striking gradient exists from urban to remote regions, where the standardised ESRD incidence is from 20 to more than 30 times the national incidence. We discuss the profound impact of renal disease on Indigenous Australians and their communities. We explore the linkages between disadvantage, often accompanied by geographic isolation, and both the initiation of renal disease, and its progression to ESRD. Purported explanations for the excess burden of renal disease in indigenous populations can be categorised as:

(1) primary renal disease explanations;
(2) genetic explanations;
(3) early development explanations; and
(4) socio-economic explanations.

We discuss the strengths and weaknesses of these explanations and suggest a new hypothesis which integrates the existing evidence. We use this hypothesis to illuminate the pathways between disadvantage and the human biological processes which culminate in ESRD, and to propose prevention strategies across the life-course of Indigenous Australians to reduce their ESRD risk.

Our hypothesis is likely to be relevant to an understanding of patterns of renal disease in other high-risk populations, particularly indigenous people in the developed world and people in developing countries. Furthermore, analogous pathways might be relevant to other chronic diseases, such as diabetes and cardiovascular disease. If we are able to confirm the various pathways from disadvantage to human biology, we will be better placed to advocate evidence-based interventions, both within and beyond the scope of the health-care system, to address the excess burden of renal and other chronic diseases among affected populations.

**Keywords:** Aboriginal health; renal disease; social determinants; biological pathways; prevention; Australia

## Introduction

On November 11, 2000, Sotheby's held an auction of Australian Aboriginal artworks at the Art Gallery of New South Wales, in Sydney. Thirty-five pieces were auctioned, including canvases painted by residents of Kintore and Kiwirrkura, remote Aboriginal communities hundreds of kilometres west of Alice Springs in central Australia. The auction was part of the Western Desert Dialysis Art Appeal, which raised over one million Australian dollars. Why would two remote Aboriginal communities, each with only a few hundred residents, need haemodialysis units?

Haemodialysis is used to treat end-stage renal disease (ESRD), the irreversible pre-terminal phase of chronic renal failure. Someone suffering ESRD will die without treatment. In the developed world, treatment for ESRD is generally available, either maintenance dialysis (the majority of which is haemodialysis) or renal transplantation. Haemodialysis is an expensive

tertiary care service, usually provided in urban centres only. Almost one in five Indigenous Australians (Aborigines and Torres Strait Islanders) live in remote communities like Kintore and Kiwirrkura, compared with less than one in 100 of the total Australian population (Australian Bureau of Statistics and Australian Institute of Health and Welfare, 2001). Indigenous Australians with ESRD in remote communities must leave their community to commence dialysis. Very few receive transplants; most remain on haemodialysis, hundreds of kilometres from home, in a satellite unit of an urban hospital. The people of Kintore and Kiwirrkura have taken drastic action to keep sick members in the community. But why are these communities so affected by ESRD in the first place, when fewer than 1 in 10,000 Australians start ESRD treatment each year (Russ, 2002)?

As a group, Indigenous Australians are disadvantaged, relative to other Australians, over a range of socio-economic and health measures. In 1996, indigenous adults were less likely to have a post-school educational qualification (11% versus 31%), more likely to be unemployed (23% versus 9%), and much less likely to own or to be purchasing their home (31% versus 71%) (Australian Bureau of Statistics and Australian Institute of Health and Welfare, 1999). The median weekly income for indigenous males was $189, compared with $415 for non-indigenous males. The disparity between females was not as marked, with median weekly incomes of $190 and $224, respectively (Australian Bureau of Statistics and Australian Institute of Health and Welfare, 1999).

In 1997–1999, estimated Indigenous Australian life expectancy at birth was 56 years for males, compared with 76 for all males, and 63 years for females, compared with 82 for all females (Australian Institute of Health and Welfare, 2002). Most of the difference is due to premature adult mortality from chronic diseases (Cunningham & Paradies, 2000). There were seven–eight times more deaths from genitourinary diseases than expected; most were due to renal failure (Cunningham & Paradies, 2000).

The incidence of ESRD throughout the developed world is markedly higher amongst indigenous people (Dyck, 2001; Russ, 2002; US Renal Data System, 2001). In 2000, Indigenous Australians constituted less than 2% of the national population, but comprised over 8% of new patients commencing treatment for ESRD (Russ, 2002). ESRD is generally a disease of older people. However, the Indigenous Australian population, as a whole, is much younger, with a median age in 1996 of20 years, compared to 34 years for the total Australian population (Australian Institute of Health and Welfare, 2002). After adjusting for age and sex, the ESRD incidence rate in 1997 was almost nine times higher for Indigenous Australians (Cass, McDonald, & Wang, 1999).

The burden of ESRD is greater everywhere for Indigenous Australians, but there are striking geographical differences in incidence within this population (Fig. 1). A large gradient exists from urban to remote regions (Cass, Cunningham, Snelling, Wang, & Hoy, 2002b). In remote communities, including places like Kintore and Kiwirrkura, the standardised ESRD incidence is from 20 to more than 30 times the national incidence (Cass, Cunningham, Wang, & Hoy, 2001b). Can we explain the link between, on the one hand, disadvantage and geographical isolation and on the other, the initiation of renal disease and its progression to ESRD?

The explanations offered for the excess burden of renal disease in Indigenous populations and in other minorities, for example, African Americans, can be categorised as:

1. primary renal disease explanations – population differences result from a higher incidence, and greater severity, of various primary diseases which cause ESRD;
2. genetic explanations – genetic differences determine various patterns of ESRD;
3. early development explanations – some form of adverse intrauterine environment affects kidney development, leading to a vulnerability to ESRD and;
4. socio-economic disadvantage explanation – greater socio-economic disadvantage in minority and Indigenous populations results in a higher incidence of ESRD.

In this paper, we review the strengths and weaknesses of each of these explanations and put forward a new hypothesis which integrates all the existing evidences. Using this hypothesis, we illuminate the pathways between disadvantage and the human biological processes which culminate in ESRD, and propose prevention strategies across the life-course of Indigenous Australians to reduce their risk of ESRD.

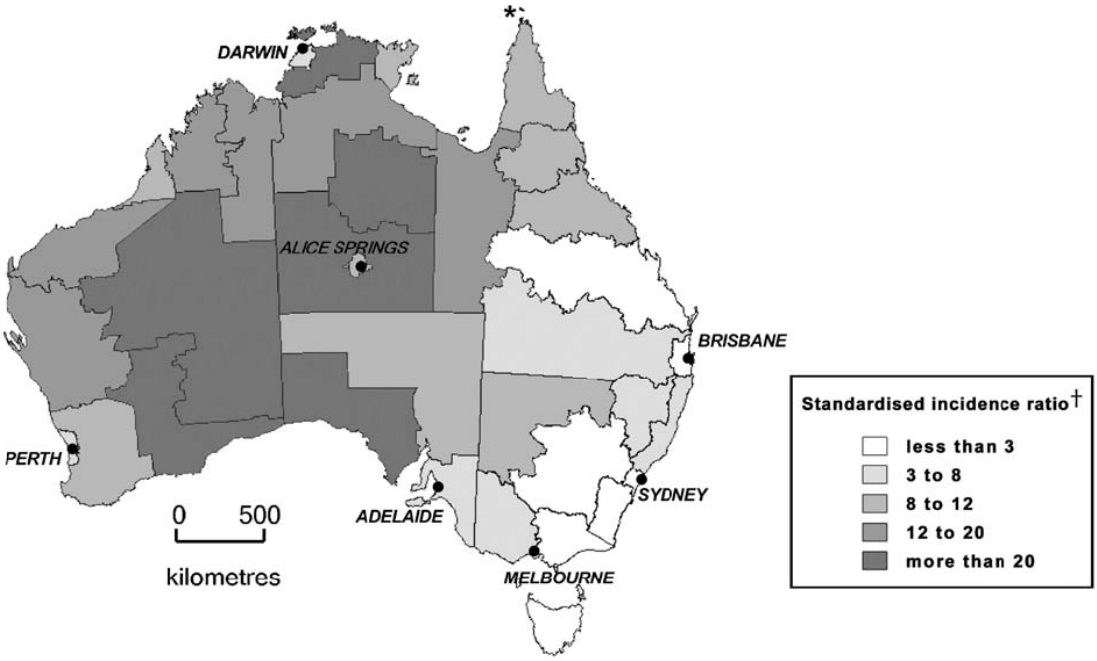


***Fig. 1.*** Standardised incidence of ESRD in the Indigenous Australian population by ATSIC region: (*) The standardised incidence ratio for the Torres Strait ATSIC region was 15.0. The region is too small to represent at this level of map resolution. (†)The index population for standardisation was the total Australian resident population. (Cass, A., et al. (2001). Regional variation in the incidence of ESRD in Indigenous Australians. *Medical Journal of Australia*, 175, 24–27. Copyright 2001, reproduced with permission.)

## Primary renal disease explanations

Nephrologists conceive of the causes of ESRD in terms of primary renal diseases which cause kidney tissue damage, resulting eventually in ESRD. In the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), which covers all Australian renal units, cases are assigned to one of69 primary renal diseases (Russ 2002). Examples include membranous glomerulonephritis, analgesic nephropathy, renal vascular disease due to hypertension, polycystic kidney disease and type 2 diabetes. The diagnostic criteria are not mutually exclusive and the boundaries between the various disease entities are not clearly defined (Perneger, Brancati, Whelton, & Klag, 1995a). However, in order to facilitate discussion of the distribution of causes of ESRD, the 69 primary renal diseases may be classified according to eight major diagnostic categories (see Table 1) (Russ, 2002).

Among new ESRD cases in Australia during 1993– 1998, there were different patterns of primary renal disease, according to whether or not the patient was indigenous (Table 1). Almost half of ESRD cases in Indigenous Australians were attributed to diabetes, compared to approximately one in six non-indigenous cases. Glomerulonephritis was attributed as the cause of approximately one in four indigenous and one in three non-indigenous patients. An uncertain diagnosis was significantly more likely to be recorded in respect of Indigenous Australian patients. Other disease categories were less common among the indigenous patients (Table 1).

High ESRD rates in indigenous populations have been related to the growing epidemic of type 2 diabetes (Dyck, 2001; Nelson, 2001). Surveys in Australian Aboriginal communities have confirmed a very high prevalence of impaired glucose tolerance (IGT) and type 2 diabetes (Daniel, Rowley, McDermott, & O'Dea, 2002). Almost 2/3 of indigenous ESRD patients have diabetes at the time of commencement of RRT ( Russ, 2002). Attributing the excess burden of ESRD to a higher incidence, prevalence and greater severity of diabetes is consistent with both genetic and early development explanations. However, the validity of the attribution of ESRD to primary causes, such as diabetes, has been questioned (Perneger et al., 1995a).

**TABLE 1**: Attributed primary cause of ESRD for new Australian ESRD patients, 1993–98[a]

| Cause | Indigenous ($n$ = 719) | | Non-indigenous ($n$ = 7409) | | $P$ value[b] |
|---|---|---|---|---|---|
| Diabetes | 322 | (44.8%) | 1281 | (17.3%) | < 0.001 |
| Glomerulonephritis | 204 | (28.4%) | 2535 | (34.2%) | 0.001 |
| Uncertain | 100 | (13.9%) | 436 | (5.9%) | < 0.001 |
| Hypertension | 35 | (4.9%) | 837 | (11.3%) | < 0.001 |
| Miscellaneous | 31 | (4.3%) | 813 | (11.0%) | < 0.001 |
| Reflux | 13 | (1.8%) | 396 | (5.3%) | < 0.001 |
| Analgesic use | 8 | (1.1%) | 552 | (7.5%) | < 0.001 |
| Polycystic kidney disease | 6 | (0.8%) | 559 | (7.5%) | < 0.001 |

[a]Data sourced from ANZDATA Registry, 2001.
[b]Pearson's chi-square test was used for comparison of indigenous and non-indigenous patients.

Disparate systems of classification of primary renal diseases in different countries hinder cross-national comparisons of the frequency of primary renal diseases leading to ESRD (Maisonneuve et al., 2000). Because histopathological examination of renal tissue obtained at percutaneous biopsy has been considered the diagnostic gold standard, it could be argued that increased use of renal biopsy might improve the accuracy of diagnosis of the causes of ESRD. However, few biopsies are performed in indigenous ESRD patients and there is evidence that even the interpretation of histological findings is affected by the nephrologist's knowledge of the patient's 'race' (Perneger et al., 1995a).

Since 1998, ANZDATA has collected data recording whether or not new ESRD patients have a diagnostic renal biopsy. During 1998–2000, 37% of 5115 new ESRD patients had a diagnosis based on renal biopsy (ANZDATA, special data request, 2002). Fewer indigenous patients underwent biopsy (27% versus 38%, $p < 0:001$). This can be explained, at least in part, by a greater proportion of indigenous ESRD patients presenting late in the course of their disease and by their much greater prevalence of diabetes.

A study of the consequences of late referral for specialist care showed that almost 40% of Indigenous ESRD patients needed to commence dialysis within three months of referral to a nephrologist (i.e. they were referred late) (Cass et al., 2002a). For patients near to needing dialysis, not only is the risk of significant complications with renal biopsy much greater (Stiles et al., 2000), but biopsy specimens are often uninformative, showing only non-specific evidence of scarring and atrophy (Perneger et al., 1995a). Thus, in almost 40% of indigenous ESRD patients, the performance of a renal biopsy to help establish a diagnosis is associated with enhanced risk of complications and poor diagnostic yield. Indigenous patients referred late were three times more likely to have an uncertain diagnosis than those not referred late (Further analysis of data from Cass et al., 2002a). Patients whose ESRD was attributed to diabetes were less likely to have undergone biopsy (ANZDATA, special data request, 2002). Among the 45% of indigenous cases attributed to diabetes, only 17% had a confirmatory biopsy.

In a US study, nephrologists were sent written case histories based on the presentation of seven ESRD patients. Race was randomly allocated as 'black' or 'white'. When the race was specified as 'black' rather than 'white', the same case history of renal failure was almost twice as likely to be diagnosed as ESRD due to hypertension (Perneger, Whelton, Klag, & Rossiter, 1995c). Similarly, Indigenous Australian ESRD patients, who are more likely than non-indigenous patients to have diabetes at the time of commencement of treatment (66% versus 24%, p o 0 :001), may be more likely to have their ESRD attributed to diabetes, whether it is the fundamental cause of renal damage or, is instead, a concurrent and contributory illness. Although intuitively appealing, the primary renal disease explanations add little to our understanding of Indigenous Australians' higher burden of ESRD. In practice, they offer an imperfect taxonomy rather than an explanation.

## Genetic explanations

Many researchers propose that both the initiation of renal disease and its progression to ESRD are genetically determined (Iyengar, Schelling, & Sedor, 2002). Research examining the high ESRD incidence in ethnic minorities, including indigenous minorities, has focused on 'racial' differences in physiological processes and pathological responses (Freedman, 2002). These re-sponses have been attributed to genetic factors (Freed-man, 2002; Iyengar et al., 2002; Parmer,

Stone, & Cervenka, 1994).

There is substantial evidence that ESRD clusters in families (Fogarty, Rich, Hanna, Warram, & Krolewski, 2000; Freedman, Bowden, Rich, & Appel, 1998; Schelling, Zarif, Sehgal, Iyengar, & Sedor, 1999). This familial aggregation occurs in excess of that predicted by the clustering of risk factors, including the presence and severity of diabetes and hypertension (Lei, Perneger, Klag, Whelton, & Coresh, 1998). Familial clustering of diabetic and non-diabetic renal disease has been reported among Pima (Pettitt, Saad, Bennett, Nelson, & Knowler, 1990) and Zuni American Indians (Hoy, Megill, & Hughson, 1987). Familial clustering of proteinuria, a marker of renal disease, has also been demonstrated in a number of Indigenous Australian communities (Hoy et al., 1998; Van Buynder, Gaggin, & Mathews, 1993). However, familial clustering might reflect shared exposure to adverse socio-economic or environmental factors, rather than a genetic predisposition.

We have already discussed the attribution of high ESRD rates among indigenous populations to the growing epidemic of type 2 diabetes (Dyck, 2001; Nelson, 2001). The 'thrifty genotype' hypothesis suggests a possible explanation for the epidemic of type 2 diabetes in indigenous populations, as they make the rapid transition from traditional lifestyles to western diets and lifestyles (Neel, 1962). Neel postulated that the 'feast and famine' conditions which prevailed through-out most of human history might have selected for a 'thrifty' metabolism, facilitating efficient fat storage in times of food abundance and providing an energy buffer in times of scarcity (Neel, 1962). Using this hypothesis, the steep gradient in incidence of ESRD from urban to remote regions among Indigenous Australians (Cass et al., 2002b) could be explained by 'genetic admixture': urban Indigenous Australians might be protected to some degree from type 2 diabetes, and therefore from ESRD, through several generations of non-indigenous admixture (Williams, Moffitt, Fisher, & Bashir, 1987).

The 'thrifty genotype' hypothesis has subsequently been questioned, not least by its original proponent. Neel recently suggested that his early hypothesis had presented an overly simplistic view of the physiological adjustments involved in the transition from a hunter-gatherer lifestyle to a western lifestyle (Neel, 1999). He reviewed evidence relating to the high incidence of type 2 diabetes among American Indians and concluded that it must predominantly reflect environmental changes rather than a 'racial' or genetic predisposition (Neel, 1999). Similarly, the rapidity of the increase in ESRD incidence among Indigenous Australians over the last 25 years (Spencer, Silva, Snelling, & Hoy, 1998) is not compatible with a genetic explanation.

Nevertheless, as with other chronic diseases, genes are not irrelevant, and differences in susceptibility, possibly attributable to genetic differences, are of interest. Genetic studies have reported possible locations of 'renal failure susceptibility genes' in indigenous populations (Nelson, 2001). Two strategies have been widely used in searches for genetic linkage (Freedman et al., 1998). The first, a 'candidate gene' approach, analyses the relationship between the disease of interest and the presence of a polymorphic DNA marker within or near a possible causative gene. One limitation with this approach is that it is constrained to testing for known genes.

In nephrology, this line of research has focused predominantly on genes coding for the renin–angiotensin system, which plays a central role in blood pressure regulation (Nelson, 2001). It has been postulated that, in Caucasians, the DD genotype of the angiotensin-I-converting enzyme (ACE) gene is an independent risk factor for renal disease (Dudley, Keavney, Stratton, Turner, & Ratcliffe, 1995), associated with an increased rate of progression of kidney damage in diabetes (Parving et al., 1996; Yoshida et al., 1996) and IgA glomerulonephritis (Harden et al., 1995). However, others have failed to replicate these associations (Schena, D'Altri, Cerullo, Manno, & Gesualdo, 2001; Schmidt, Schone, & Ritz, 1995). The DD genotype of the ACE gene occurs infrequently in Indigenous Australians (Lester et al., 1999), in whom no significant influence on renal disease has been demonstrated. A recent study in a remote Indigenous Australian community has, however, found an association between a common polymorphism of the p53 gene and proteinuria (McDonald et al., 2002).

The second approach to genetic linkage studies, involving a genome-wide search, has the potential to locate previously unknown genes which might contribute to disease. In this strategy, hundreds of highly polymorphic microsatellite markers, which provide complete coverage of the human genome, are tested for coinheritance with a disease (Freedman et al., 1998). For diseases demonstrating late age-at-onset, such as ESRD, affected sibling pairs are commonly used to evaluate evidence of genetic linkage (Freedman et al., 1998). This is because few ESRD patients will have living parents, and the children of the affected individuals might be too young to

demonstrate even early markers of renal disease.

Imperatore et al. (1998) undertook a genome-wide scan for loci linked to diabetic nephropathy among 98 diabetic Pima Indian sib-pairs. They found four chromosomal areas with possible linkage to diabetic nephropathy. The strongest evidence for linkage was on chromosome 7. The peak LOD score (an indicator of the strength of linkage between the genetic locus and disease phenotype under investigation) for the area on chromosome 7 did not reach the threshold for statistical significance in a genome-wide scan (Imperatore et al., 1998). The evidence for linkage for three other regions on chromosomes 3, 9 and 20 was suggestive, but again not statistically significant (Imperatore et al., 1998). Among Indigenous Australians, a genome-wide scan for susceptibility to type 2 diabetes reported linkage to an area on chromosome 2 (Busfield et al., 2002), but this methodology has not been used to examine renal disease susceptibility in Indigenous Australians.

Explanatory models for disease which give primacy to genetic determinants focus almost exclusively on individual biological and behavioural correlates of illness (Baird, 2000). However, in disorders of multi-factorial origin, including ESRD, where environmental and socio-economic factors influence health status, gene/gene and gene/environment interactions are complex (Baird, 1994). Much of the genetic research has been based on 'racial difference', a concept which lacks a firm scientific foundation (Williams, 1997). The American Association of Physical Anthropology has concluded, 'pure races in the sense of genetically homogeneous populations do not exist in the human species today' (American Association of Physical Anthropology, 1996). By contrast with the considerable biological variation *within* human populations, the biological differences *between* population groups are small. These differences reflect both inheritance and the influence of the natural and social environment, with most differences being attributed to their interaction (Williams, 1997). Genetic approaches to understanding Indigenous ESRD tend to ignore a large and growing body of literature emphasising the primacy of social, cultural and environmental factors in determining patterns of disease in particular populations (Baird, 2000).

## Early development explanations

Early development provides good examples of the nexus between genes and the environment, and of the difficulty in separating them. There has been much interest recently in the relationship between fetal and/or infant growth and nutrition and adult chronic disease (Barker & Osmond, 1986; Barker & Osmond, 1987a; Barker & Osmond, 1987b). Fetal malnutrition, marked by low birth weight (LBW), has been linked with a predisposition to hypertension, type 2 diabetes, dyslipidaemia and cardiovascular disease (Barker et al., 1993; Barker & Martyn, 1992; Hales & Barker, 1992). Among Pima Indians, evidence suggests an intergenerational effect of maternal diabetes consistent with the 'fuel-mediated teratogenesis' hypothesis (Freinkel, 1980). High rates of obesity (Pettitt, Baird, Aleck, Bennett, & Knowler, 1983) and early onset of type 2 2 diabetes (Pettitt et al., 1988) have been demonstrated among the offspring of Pima mothers who had diabetes during pregnancy. In this review however, we focus on the proposed linkage of intrauterine malnutrition with the progression of renal injury (Brenner & Chertow, 1994) and a predisposition to ESRD among Indigenous Australians (Hoy, Rees, Kile, Mathews, & Wang, 1999). The uterine environment might be directly relevant to ESRD through its influence on kidney development during intrauterine life.

Nephrons, the functional units of the kidney, begin to form around week 8 of gestation (Merlet-Benichou, Vilar, Lelievre-Pegorier, Moreau, & Gilbert, 1997), but the majority form in the third trimester (Hinchliffe, Sargent, Howard, Chan, & van Velzen, 1991). None develop after birth (Hinchliffe, Lynch, Sargent, Howard, & Van Velzen, 1992; Merlet-Benichou et al., 1997). The number in a whole kidney can be reliably estimated using direct stereological counting (Bertram, 2001). Evidence from autopsy studies suggests a wide range in the number of nephrons in the 'normal' kidney (Hoy et al., 2003; Nyengaard & Bendtsen, 1992). Nephrons are lost both with ageing (Moore, 1931; Nyengaard & Bendtsen, 1992; Tauchi, Tsuboi, & Okutomi, 1971) and due to a variety of nephropathic insults. Damage to the glomerulus, the filtration segment of the nephron, is marked by protein leakage into the urine, making the appearance of urinary protein or albumin a marker of early renal disease.

Although the number of nephrons is fixed at birth, glomerular size can increase in response to a deficit in numbers (Merlet-Benichou et al., 1997), with a resulting restoration of total filtration

surface and excretory homeostasis. However, this adaptation might come at a high price. The excessive glomerular enlargement might accelerate the loss of nephrons through glomerular hypertension and hyperfiltration injury (Brenner, Lawler, & Mackenzie, 1996). Increased glomerular capillary pressure has been postulated as a key mediator of progressive scarring (sclerosis) (Fogo, 2000). This scarring induces a self-perpetuating cycle of nephron loss, leading to further enlargement, increased flow and pressure in the remaining glomeruli, leading to further sclerosis and nephron loss. This process might culminate in ESRD when there are insufficient nephrons to sustain life. It seems plausible that people born with fewer nephrons might be predisposed to develop hypertension, progressive renal insufficiency and ESRD (Brenner & Chertow, 1994; Brenner, Garcia, & Anderson, 1988). They might, in effect, have less renal reserve to lose.

Intrauterine (Hinchliffe et al., 1992; Merlet-Benichou et al., 1997) and/or genetic influences (Lipschutz, 1998; Rauchman, 2000) might determine nephron number. Intrauterine growth retardation (IUGR), usually defined as being within the lightest 10% of birth weights in a standard population in each gestational age stratum, is not a specific disease entity per se, but rather a manifestation of various fetal and maternal disorders (Resnik, 2002). Among Indigenous Australians, maternal malnutrition, smoking and teenage pregnancy have been established as important causes of IUGR ((Sayers & Powers, 1997). In a 1987–1991 study in a large hospital, 114 (22.7%) of 502 Indigenous Australian babies were recorded as having IUGR (Sayers & Powers, 1993). In 1994–1996, LBW (also a marker of fetal malnutrition) occurred in 12.4% of indigenous births compared with 6.2% of non-indigenous births (Day, Sullivan, & Lancaster, 1999).

Merlet-Benichou and colleagues, using rat models of kidney development, have suggested that the fetal environment plays a determining role in kidney development (Lelievre-Pegorier & Merlet-Benichou, 2000). Research has suggested that maternal malnutrition (Zeman, 1968), maternal hyperglycemia (Amri, Freund, Vilar, Merlet-Benichou, & Lelievre-Pegorier, 1999), drug exposure (Nathanson, Moreau, Merlet-Benichou, & Gilbert, 2000) and vitamin A deficiency (Lelievre-Pegorier et al., 1998) impair kidney development and result in reduced nephron number in the offspring. In animal models, IUGR produced by partial uterine artery ligation leads to a permanent nephron deficit (Merlet-Benichou, Gilbert, Muffat-Joly, Lelievre-Pegorier, & Leroy, 1994). However, the relevance of such animal models to human renal development has been questioned (Jones, Nyengaard, Flyvbjerg, Bilous, & Marshall, 2001).

A small number of histological studies in humans have explored the association between nephron number and IUGR or birth weight. A retrospective study of 35 neonatal deaths (Manalich, Reyes, Herrera, Melendi, & Fundora, 2000) showed a strong correlation between glomerular number and birth weight ($r = 0{:}87$; $p < 0.0001$). IUGR was associated with a significant reduction in nephron number in a prospective study of 32 stillbirths and infant deaths (Hinchliffe et al., 1992). In a study of 24 full-term infants who died in utero or within 6 months of birth, nephron number was reduced by 30% in those with IUGR (Merlet-Benichou, Leroy, & Gilbert, 1993). A current autopsy study is examining the relationship between nephron number, size and birth weight in Australian Aborigines, African Americans and Caucasians (Bertram, Johnson, Hughson, & Hoy, 2001). A preliminary report indicates that children and adults with LBW have, on average, 37% fewer nephrons than those with higher birth weights (Hughson et al., 2003).

There is also evidence of a relationship between birth weight and clinical or pathological evidence of progressive renal disease in indigenous populations. IUGR or LBW has been associated with albuminuria (albumin excretion in the urine) in Pima Indians with type 2 diabetes (Nelson, Morgenstern, & Bennett, 1998). (In this paper, we use the term albuminuria to indicate albumin excretion of more than 300 mg per 24 h.) High rates of albuminuria have been found in rural and remote indigenous communities in Australia (Guest, Ratnaike, & Larkins, 1993; Hoy et al., 1998; Rowley et al., 2000b). In one prospective cohort study, the level ofalbuminuria at screening predicted risk of death and risk of progression to ESRD (Hoy et al., 2001). Birth weights were available from clinic records for the majority of the adults screened. After adjustment for age, gender, BMI and blood pressure, the odds ratio for albuminuria in LBW persons, compared to those with higher birth weights, was 2.82 (95% CI 1.26–6.31) (Hoy et al., 1999). There is evidence, therefore, among Indigenous Australians, that birth weight is linked to albuminuria, which predicts progression to ESRD.

Published biopsy series from Indigenous Australians with overt renal disease show a wide range of morphological diagnoses (Moore, Lloyd, Pugsley, & Seymour, 1996). Pathological changes in the glomerulus can usually be characterized by one or more of the following basic tissue reactions

(Cotran, Kumar, & Collins, 1999): hypercellularity, basement membrane thickening, hyalinisation or sclerosis. However glomerulomegaly, or glomerular enlargement in the absence of hypercellularity, is a striking finding in kidney biopsies from Indigenous, but not from non-indigenous Australians (Bertram, Young, Seymour, Kincaid-Smith, & Hoy, 1998; Moore et al., 1996; Young, Hoy, Kincaid-Smith, Seymour, & Bertram, 2000). Glomerulomegaly has also been demonstrated in African Americans (Abdi, Slakey, Kittur, & Racusen, 1998; Pesce et al., 1994). A current autopsy study, which includes Indigenous Australian, African American and Caucasian subjects, has demonstrated a significant inverse relationship between glomerular number and glomerular size (Bertram et al., 2001; Hoy et al., 2003). These findings are consistent with the hypothesis that reduced nephron number at birth might confer an increased susceptibility to renal disease and that compensatory enlargement of remaining glomeruli might lead to progressive damage through glomerular hyperfiltration and scarring.

This substantial body of research suggests that nephron endowment at birth, crucially influenced by the intrauterine environment, might be causally related to the development of ESRD in adult life. However, fetal growth might not be linked causally to chronic disease. There might be shared genetic mechanisms for fetal growth and later chronic disease (Wilcox, 2001). The validity of the suggested association between fetal development and chronic disease has also been questioned on the basis of a perceived failure to define, measure and adequately control for confounding due to socio-economic disadvantage (Joseph & Kramer, 1996).

## Socio-economic disadvantage explanations

There is strong evidence of a relationship between socio-economic position and overall morbidity and mortality (Krieger, Williams, & Moss, 1997). The gradient in the occurrence of disease progressively favours those of higher socio-economic status (Marmot, 2000). This has been confirmed amongst Australians (Glover, Harris, & Tennant, 1999; National Health Strategy, 1992; Turrell, Oldenburg, McGuffog, & Dent, 1999). In general, research into Australian health inequalities has inadequately controlled for confounding by indigenous status and has failed to investigate health gradients within the indigenous population.

Inconsistent results have been obtained from the few previous studies of the association between socio-economic status and the incidence of ESRD (Byrne, Nedelman, & Luke, 1994; Cass, Cunningham, Wang, &Hoy, 2001c; Khan, Cheng, Catto, Edward, & MacLeod, 1993; Perneger, Whelton, & Klag, 1995b; Young, Mauger, Jiang, Port, & Wolfe, 1994). A study in the Grampian region of Scotland (Khan et al., 1993) found no association between socio-economic status and the incidence of ESRD. In New York (Byrne et al., 1994), an association was found in White Americans, but not in African Americans. In a nationwide US study (Young et al., 1994), a 60% higher incidence of ESRD was found in the lowest compared to highest income categories for both White and African Americans. In a study of ESRD incidence in Australian capital cities, we found a significant association between the incidence of ESRD and a regional-level index of disadvantage (Cass et al., 2001c), with up to three-fold variation in incidence. An individual level, population-based, case-control study of patients starting ESRD treatment in four East Coast states in the US (Perneger et al., 1995b) found that the adjusted risk for development of ESRD was 4.5 times higher in the lowest compared to the highest income category, with White and African Americans demonstrating a similar gradient.

Only one study of social disadvantage and ESRD in Indigenous Australians has been reported to date (Cass et al., 2002b). In this ecological study, strong associations were evident between age- and sex-standardised, area-level, ESRD incidence (based on ANZDATA Registry information) and area-level markers of social disadvantage (Table 2). The correlation with the overall rank of socio-economic disadvantage was particularly strong (Table 2 and Fig. 2). Although it has been argued that area-level measures of social disadvantage are poor surrogates for individual-level characteristics (Robinson, 1950), it is becoming increasingly accepted that community-level exposures to features of the social and physical environment in which people live might directly affect health outcomes (Macintyre & Ellaway, 2000). For example, in many disadvantaged indigenous communities there is poor access to preventive health services and to stores selling healthy foods at reasonable prices, as well as a lack of community infrastructure for basic water, sewerage and housing needs (Bailie et al., 2002).

**TABLE 2.** Correlation between indicators of socioeconomic disadvantage and age and sex-standardised incidence of ESRD for Indigenous Australians for the 36 ATSIC regions[a]

| Socioeconomic indicator (units) | Range | Correlation coefficient | *P* |
|---|---|---|---|
| Early school leavers[b] (%) | 12.5–52.4 | 0.68 | <0.001 |
| Unemployment rate[c] (%) | 20.2–74.8 | 0.72 | <0.001 |
| Household income[d] ($AUS) | 80–194 | –0.71 | <0.001 |
| House crowding[e] | 1.1–3.2 | 0.84 | <0.001 |
| Low birth weight[f] (%) | 7.6–21.6 | 0.49 | 0.003 |
| Summary rank of disadvantage g | 1–36 | 0.88 | <0.001 |

Cass, A., et al. (2002). ESRD in Indigenous Australians: a disease of disadvantage. Ethnicity and Disease, 12(3), 373–378. Copyright 2002, reproduced with permission.

[a]Aboriginal and Torres Strait Islander Commission regions are legally prescribed administrative areas and are the smallest geographical areas for which accurate Indigenous Australian population estimates are available (Australian Bureau of Statistics, 1999 ).
[b]The proportion of adults who left school aged 15 or less, or who did not attend school (Australian Bureau of Statistics, 2002 ).
[c]People employed through the Community Development Employment Projects scheme, a 'work for the dole' scheme targeted at indigenous communities, were classified as unemployed (Australian Bureau of Statistics, 2002 ).
[d]Median household income divided by the average number of persons per household – units are $AUS per household member per week (Australian Bureau of Statistics, 1998 ).
[e]The average number ofpersons per bedroom ( Australian Bureau of Statistics, 2002 ).
[f]The proportion ofbirths less than 2500 0g g ( (Day, Sullivan, & Lancaster, 1999).
[g]We combined the regional rankings on each indicator, with each indicator given equal weight, to derive a summary rank of disadvantage.

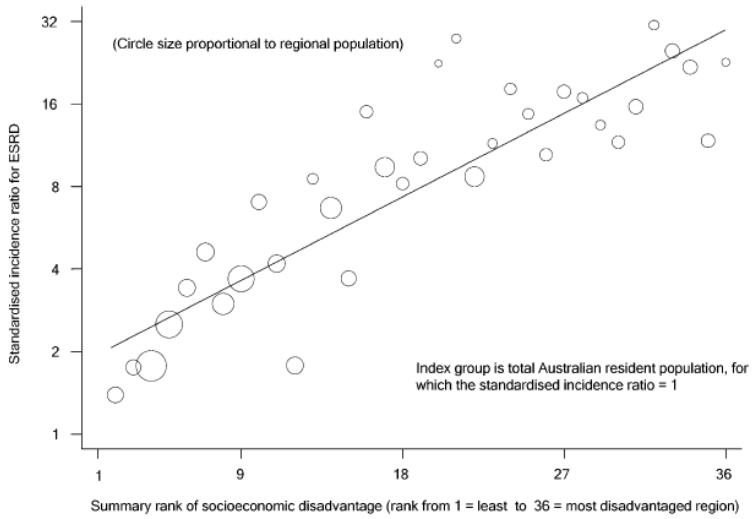


*Fig. 2.* Socio-economic disadvantage and indigenous ESRD incidence by ATSIC region, Australia 1993–98. (Cass, A., et al. (2002). The relationship between the incidence of ESRD and markers of socio-economic disadvantage. *New South Wales Public Health Bulletin*, 13(7), 147–151. Copyright 2002, reproduced with permission.)

## A novel explanation of Indigenous ESRD

How might disadvantage lead to ESRD? What pathways or mechanisms lead to the biological expression of Indigenous Australians' experiences of economic and social disadvantage, thereby producing the steep social gradient in the incidence of ESRD? How can we integrate our understanding of the suggested pathophysiological pathways to ESRD with what we know about the social determinants of health?

Chronic disease epidemiology has generally conceived risk of disease as residing within individuals and in their personal behaviour (Schwartz, Susser, & Susser, 1999) and has therefore focused on proximate, individual-level risk factors (McMichael, 1999). The interactions among individuals, and between individuals and their social and physical environment, are either considered as potential confounders or fall completely outside the scope of most research (Schwartz et al., 1999). However, individual-level risk factors do not completely explain social gradients in health. For example, in the original White-hall study, a prospective cohort study of 17,530 male public servants in London, conventional individual-level risk factors for coronary artery disease – blood pressure, smoking, cholesterol, BMI and level of physical activity – explained only one quarter of the observed social gradient in coronary disease mortality (Marmot, Rose, Shipley, & Hamilton, 1978). In recognition of the shortcomings of the traditional approach, interest in what has come to be known as 'social epidemiology' has grown markedly in recent years.

Social epidemiology is concerned with the social distribution and social determinants of Health and illness (Berkman & Kawachi, 2000). According to Krieger (2001), the three main theories invoked to explain social inequalities in health are: (1) psychosocial; (2) the social production of disease or the 'political economy' of Health; and (3) ecosocial theory and related multilevel frameworks.

*Psychosocial theories* concentrate on endogenous biological responses to human interactions (Krieger, 2001). Chronic anxiety, insecurity, low self-esteem, social isolation and lack of control over work affect mental and physical health (Brunner & Marmot, 1999). Psychosocial stressors might be directly pathogenic (Krieger, 2001), affecting a range of physiological pathways, or they might affect health indirectly through stress-induced behaviours such as smoking. The physiological systems mediating biological responses include the autonomic nervous system, the hypothalamic– pituitary–adrenal (HPA) axis, and the cardiovascular, metabolic and immune systems (McEwen, 1998). Acute stress initiates adaptive, physiological responses involving the autonomic nervous system and the HPA axis, the 'fight or flight' response, but chronic and/or repeated stress might lead to maladaptive, pathological responses (McEwen, 1998).

*The social production of disease theories* propose, by contrast, that the fundamental causes of social inequalities in health are the actions of the economic and political institutions which create and perpetuate economic and social privilege and disadvantage (Krieger, 2001). Health inequalities result from the differential accumulation of exposures and experiences which originate in material disadvantage (Lynch, Smith, Kaplan, & House, 2000). Health inequalities are rooted in the social structure, rather than in individuals' behaviour or in their inability to manage stress (Krieger, 2001).

*An ecosocial theoretical framework* integrates biological and social explanations for health inequalities by examining how we embody, or incorporate biologically, the material and social world in which we live (Krieger, 2001). The pathways linking disadvantage and disease are formed both by societal arrangements of power and property, and by the constraints and possibilities of our biology (Krieger, 2001). There is a cumulative interplay between exposure, susceptibility and resistance, with each factor and its contribution conceptualised at multiple levels – individual, community, regional, national and global (Krieger, 2001). Can we use an ecosocial framework to understand the ESRD burden in Indigenous populations? What evidence would enable us to outline discrete pathways linking disadvantage and biological processes, culminating in ESRD in Indigenous Australians?

## Pathways, operating at different levels, linking experiences of disadvantage with their biological embodiment in ESRD in Indigenous Australians

In the following section, we will outline a number of direct and indirect pathways linking disadvantage with kidney disease and present the evidence, largely from research amongst Indigenous Australians, to support six such pathways:

1. direct linkage from disadvantage to renal damage;
2. indirect linkage via psychosocial factors;
3. indirect and intergenerational linkage via damaging health behaviours;
4. indirect linkage via factors in the health-care system;
5. linkage of cultural factors and renal disease; and
6. linkage of government/corporate policies to renal disease.

## *Direct linkage from disadvantage to renal damage*

There is strong evidence linking house crowding, via endemic and epidemic streptococcal skin infection, to the incidence of ESRD (Cass et al., 2002b). Living conditions, notably overcrowded sleeping arrangements, have been associated with the presence of scabies (Currie & Carapetis, 2000; Gulati, Singh, & Braganza, 1977; Landwehr, Keita, Ponnighaus, & Tounkara, 1998). Scabies and streptococcal skin sores are the most important skin infections in central and northern Australia (Currie & Carapetis, 2000). Scabies is endemic in many remote communities, being found in up to 50% of children. The cycles of scabies transmission underlie the high prevalence of skin sores. Up to 70% of children have skin sores, with group A streptococcus (GAS) being the major pathogen (Currie & Carapetis, 2000; Streeton, Hanna, Messer, & Merianos, 1995).

In a cross-sectional study in a high-risk remote community, the presence of skin sores and scabies in both children and adults was associated with albuminuria (Hoy et al., 1998). Adults with persistent antibodies to streptococcal M protein, markers of past GAS infection, were far more likely than those lacking such antibodies to have albuminuria (Goodfellow et al., 1999). GAS is responsible for the continuing outbreaks of acute post-streptococcal glomerulonephritis (APSGN) (Atkins, 2001; Currie & Carapetis, 2000; Streeton et al., 1995). A retrospective cohort study showed that adults with a documented history (14.6 years earlier on average) of APSGN had an adjusted odds ratio of6.1 (95% CI, 2.2–16.9) for albuminuria, compared with adults lacking a history of APSGN (White, Hoy, & McCredie, 2001).

## *Indirect linkage via psychosocial factors*

It has been proposed that biological responses to environmental stress could mediate the predisposition to poor health outcomes of indigenous populations in industrialised countries (Daniel, O'Dea, Rowley, McDermott, & Kelly, 1999). In one study, glycosylated haemoglobin concentration, which is elevated by stress-associated catecholamine release, was measured as a biomarker of 'psychogenic stress'. An analysis of the data, controlled for diabetic status, found that glycosylated haemoglobin concentration was higher in Indigenous Australians (Daniel et al., 1999). We have demonstrated a strong association between high unemployment, low educational attainment, low income and the incidence of ESRD (Cass et al., 2002b). Unemployment, poor education and low income result in a lack of control over one's life, social isolation and alienation, all of which are potent stressors (Berkman & Kawachi, 2000).

To some extent, the much steeper social gradient in the incidence of ESRD (Cass et al., 2002b) might be due to the greater relative disadvantage of Indigenous Australians. However, aspects of colonisation and 'westernisation', including dispossession and separation from their land, forced removal of children from family and kin, racial discrimination and social marginalisation, have been recognised as key issues affecting health status (Devitt, Tsey, & Hall, 2001; Wilson, 1997). Loss of control by Indigenous Australians over their own lives, their communities and their environment has been identified as a potent cause of ill-health (Trudgen, 2000).

Although a growing body of evidence associates chronic stress and psychosocial factors with a range of health outcomes relevant to the initiation and progression of renal disease, including hypertension ( Anderson, Myers, Pickering, & Jackson, 1989; Schnall, Schwartz, Landsbergis, Warren, & Pickering, 1992), progression of atherosclerosis (Everson et al., 1997) and susceptibility to infection (Cohen et al., 1997), research along these lines has not yet been undertaken amongst Indigenous Australians.

## *Indirect and intergenerational linkage via damaging health behaviours*

Australians of lower socio-economic status are more likely to smoke, to be overweight and to be inactive (National Health Strategy, 1992). Indigenous adults are even more likely to smoke and to be obese (Australian Bureau of Statistics and Australian Institute of Health and Welfare, 1999). Nationally, approximately 54% of Indigenous Australians smoke, compared with 22% of all Australians (Ivers, 2001). Smoking, obesity and lack of exercise are risk factors for diabetes, hypertension and hyperlipidaemia. These conditions might both initiate renal damage and facilitate

progression of existing renal disease towards ESRD (Muntner, Coresh, Smith, Eckfeldt, & Klag, 2000; Ruggenenti, Schieppati, & Remuzzi, 2001).

Smoking is associated with albuminuria and abnormal renal function (Pinto-Sietsma et al., 2000). It is an established risk factor for ESRD (Klag et al., 1997), and is associated with progression of renal disease (Orth et al., 1998; Ritz, Ogata, & Orth, 2000). Both active (Celermajer et al., 1993) and passive smoking (Celermajer et al., 1996) have been associated with endothelial dysfunction in human studies. Endothelial cell function might be crucial in determining whether healing or scarring will result after renal injury (Fogo, 2000). Normally, glomerular endothelial cells inhibit cellular processes which lead to scarring. However, in response to a variety of stimuli, which might include smoking, glomerular endothelial cells release endothelin (Benigni & Remuzzi, 1998) and plasminogen activator-inhibitor-1 (Oikawa, Freeman, Lo, Vaughan, & Fogo, 1997). These factors have been linked, in vitro, to hypertrophy of the glomeruli, increased cellular matrix and fibrosis – processes which lead to renal scarring (Fogo, 2000).

Smoking might also play a role in the intergenerational transfer of risk for ESRD. Among indigenous births, maternal smoking is a known cause of IUGR (Sayers & Powers, 1997), which might result in lower nephron endowment and a predisposition to ESRD. Maternal malnutrition is another known cause of IUGR (Sayers & Powers, 1997). In many remote indigenous communities, there is poor access to affordable healthy food (Lee, O'Dea, & Mathews, 1994). Low folate intake is prevalent (Lee et al., 1994) and has been associated, in studies in other populations, with LBW (Rao et al., 2001; Scholl, Hediger, Schall, Khoo, & Fischer, 1996).

### *Indirect linkage via factors in the health-care system*

Socioeconomic disadvantage, residence in remote communities and racial discrimination are associated with limited access to the health care which might otherwise prevent ESRD. For example, indigenous women are less likely to attend antenatal care early in their pregnancy and are more likely to have two or fewer attendances (Plunkett et al., 1996). This might relate to both socio-economic disadvantage (Turrell et al., 1999) and to remoteness from antenatal services (Plunkett et al., 1996). Late presentation to antenatal services has been associated with risk of LBW (de Costa & Child, 1996). Almost 200 indigenous communities, mostly in central and northern Australia, are more than 100 km from the nearest primary health-care facility (Bailie et al., 2002). In addition to antenatal services, primary health care provides a range of services which could prevent ESRD, such as scabies eradication programs (Wong et al., 2001).

Remote Indigenous Australians have limited access to secondary prevention programs which might otherwise reduce the risk of renal disease progression. There is evidence from numerous randomised controlled trials and meta-analyses that strict blood pressure control, particularly using ACE inhibitors or angiotensin II receptor blockers, together with rigorous control of diabetes, is effective in preventing progression to ESRD (Ruggenenti et al., 2001). In a remote community in Northern Australia, a community-based cardiovascular and renal protective program was shown to be effective in reducing premature death and progression to ESRD among Indigenous adults with early renal disease (Hoy, Baker, Kelly, & Wang, 2000). The program was based on (1) the use of ACE inhibitors, combined with other antihypertensives, if needed, to achieve blood pressure goals; (2) attempts to improve control of blood glucose and lipid levels; and (3) health education. Screening programs in remote communities have consistently found that at least 25% of adults have albuminuria (Hoy et al., 1998; McDonald et al., 2002; Rowley et al., 2000b). Despite this indisputable evidence, there has been no coordinated national approach to providing secondary prevention services at a community level.

There is also clear evidence of poor access to tertiary ESRD treatment services. Forty-eight per cent of indigenous ESRD patients starting treatment during 1993–1998 lived in regions without ESRD treatment facilities (Cass et al., 2001b). Many needed to travel hundreds of kilometres to obtain renal care. By contrast, virtually all non-indigenous patients (99.8%) lived in regions with ESRD treatment facilities. Indigenous ESRD patients are more likely to be referred to a nephrologist late in the course of their renal disease (Cass, Snelling, Cunningham, Wang, & Hoy, 2002e). Late referral is associated with increased mortality on ESRD treatment (Cass et al., 2002a) and is more common in disadvantaged areas (Cass, Cunningham, Snelling, Wang, & Hoy, 2002c).

Indigenous Australian ESRD patients have significantly reduced access to renal transplantation. This is not explained by differences in age, sex, co-morbidities or cause of renal disease (Cass, Cunningham, Snelling, Wang, & Hoy, 2001a). This finding is consistent with US research focused on African Americans' access to transplantation, which suggests that disparities in access are not accounted for by differences in medical suitability or patient preferences (Ayanian, Cleary, Weissman, & Epstein, 1999; Epstein et al., 2000). It is also consistent with recent research indicating a disparity in the use of diagnostic and therapeutic procedures for indigenous and non-indigenous patients in Australian public hospitals. This suggests that there might be systematic differences in the treatment of indigenous patients (Cunningham, 2002). Further re-search is required to explore the contribution of racial discrimination, whether overt or covert, to reduced access to ESRD treatment.

## *Linkage of cultural factors and renal disease*

Cultural differences affect Indigenous Australians' access to, and utilisation of, health services. It has been suggested that a grossly deficient standard of cross-cultural communication has been accepted as the *norm* in some settings (Devitt & McMasters, 1998). Patients' poor understanding of their own chronic renal disease has been linked to non-compliance and reduced active involvement in their own management (Devitt & McMasters, 1998). In a recent qualitative study investigating the effectiveness of communication in ESRD care for Indigenous Australians, a picture emerged of pervasive miscommunication, often unrecognised by both the patients and their health carers (Cass et al., 2002d). A shared understanding of fundamental issues concerning prevention, diagnosis and treatment was rarely achieved. Other research has suggested that the communication gap might be so wide, and so ingrained in health care, that it is not even perceived by staff (Trudgen, 2000). Effective communication has been shown to correlate with improved outcomes, including physiological criteria such as adequacy of blood pressure and blood sugar control (Stewart, 1995). Therefore, ineffective communication is likely to impede attempts to retard the progression of renal damage to ESRD.

## *Linkage of government/corporate policies to renal disease*

Australian governments have attempted to address the social disadvantage of Indigenous Australians, but with limited success. Large-scale infrastructure development has occurred in some communities, with projects designed to ensure adequate water supply, sanitation, housing and drainage (Bailie & Runcie, 2001). However, a recent survey of houses funded by the Indigenous Housing Authority of the Northern Territory showed that 62% of houses did not meet the required standards for the storage and preparation of food, and that, in 45% of houses, bath and toilet facilities were not functional (Bailie & Runcie, 2001). A recent review of education strategies revealed deteriorating outcomes, with an overall decline in school attendance and very low proportions of students achieving national reading benchmarks in primary school (Collins, 1999). We have discussed above the linkage between both housing conditions and educational outcomes and the development of ESRD.

Corporate policies might also be playing an adverse role. As noted above, the prevalence of tobacco use is much higher among Indigenous Australians. There is evidence of tobacco advertising campaigns specifically targeting this group (Ivers, 2001). The promotion, in some indigenous communities, of particular cigarette brands, with the distribution of 'giveaway' products, such as T-shirts, has been reported, and tobacco companies are prominent in the sponsorship of remote community sporting events. This is consistent with the aggressive marketing tactics used to target indigenous populations of other South Pacific nations (Ivers, 2001). We have discussed above the various pathways linking tobacco use with the initiation and progression of renal disease.

We have outlined six discrete pathways linking disadvantage and kidney disease. Others are likely to exist. It is clear that an ecosocial multilevel framework is both appropriate and useful in understanding ESRD among Indigenous Australians. How might this under-standing lead to an evidence-based approach to the prevention of ESRD?

## A life-course approach to the prevention of ESRD

Nephrologists understand ESRD from a traditional, biomedical perspective, in which ESRD is attributed to one of a range of discrete primary disease processes. This view is inconsistent with the pathophysiological model which we have proposed. A limited biomedical perspective cannot explain the striking social gradient in the incidence of ESRD in Indigenous Australians. The explanation put forward in this paper enables us to bring together an understanding of the social, cultural and environmental determinants of Health with an under-standing of the biology of renal disease. A better understanding of the discrete pathways linking disadvantage and the associated discrimination with their biological embodiment across the life-course (Krieger, 2001), enables us to identify targeted prevention programs to address this excess burden of renal disease.

Individual-level interventions alone, using pharmacological and lifestyle interventions for people at high risk, are necessary but not sufficient to address the many determinants operating at the individual, community, regional and national levels. Despite the relative lack of evidence for efficacy of primary prevention to prevent indigenous ESRD, there is evidence that community-based intervention, in partnership with indigenous communities, can mitigate the early stages in the pathophysiological pathway to ESRD.

Primary preventive initiatives must address the period from before conception to the development of albuminuria. Such initiatives should include:

- improved access to antenatal services to reduce the prevalence of IUGR;
- community initiatives such as the *Strong Women, Strong Babies, Strong Culture Program* which resulted in improvement in birth weights in pilot communities (Mackerras, 1998);
- screening and intensive management of diabetes in pregnancy (Dabelea & Pettitt, 2001) and encouragement of breastfeeding, especially for the children of mothers who had diabetes during pregnancy (Pettitt, Forman, Hanson, Knowler, & Bennett, 1997) to prevent the development of obesity and early onset of type 2 diabetes;
- prevention of obesity in early childhood, particularly due to ‘catch up growth’ in those with LBW, as they are at greatest risk of developing diabetes (Yajnik, 2002) and renal disease (Hoy et al., 1999);
- early childhood development initiatives to improve educational achievement and life-skills;
- increased participation in primary, secondary and tertiary education (Bauert, Brown, Collins, & Martin, 2001);
- training community members to improve housing infrastructure and to maintain improvements (Pholeros, Rainow, & Torzillo, 1994), thus also providing employment opportunities;
- food supply initiatives to improve access to affordable healthy food (Lee, Bonson, Yarmirr, O’Dea, & Mathews, 1995; Rowley et al., 2000a);
- community-based scabies control programs;
- culturally appropriate healthy nutrition, physical activity and quit smoking programs and legislative initiatives to regulate tobacco advertising; and
- intensive nutrition and physical activity programs to delay or prevent the onset of diabetes in people with IGT (Knowler et al., 2002; Tuomilehto et al., 2001).

Secondary prevention, covering the period from the development of albuminuria to ESRD, will require a coordinated, national program to provide community-based screening and intervention for hypertension, diabetes and albuminuria. Strict control of blood pressure with ACE inhibitors as first-line therapy, and of diabetes with oral hypoglycaemics and insulin, has been demonstrated to be effective in preventing progression to ESRD (Hoy et al., 2000). Accumulating evidence, albeit not among Indigenous Australians, suggests that smoking cessation and lipid lowering (Fried, Orchard, & Kasiske, 2001) might also be effective strategies. Improved, early access to nephrological services might prevent progression to ESRD, and should, with appropriate ESRD treatment, improve outcomes (Cass et al., 2002a).

Tertiary prevention initiatives, designed to improve access to renal transplantation and to improve communication between health-care providers and Indigenous ESRD patients, are required to improve ESRD treatment outcomes. However, an emphasis on primary and secondary prevention would result in improvements in health above and beyond the prevention or amelioration of ESRD.

Our hypothesis of the causation of ESRD among Indigenous Australians is likely to be relevant to an understanding of patterns of renal disease in other high-risk populations, particularly indigenous people in the developed world and the people in developing countries. Furthermore, analogous pathways might be relevant to other chronic diseases, such as diabetes and cardiovascular disease. If we are able to confirm the various pathways from disadvantage to human biology, we will be better placed to advocate evidence-based prevention strategies, both within and beyond the scope of the health-care system. Although there might be a compel-ling case *now* for building dialysis units in indigenous communities, we could provide a better long-term answer to the call for help made by the people of Kintore and Kiwirrkura.

## Acknowledgements

There are no conflicts of interest. We thank Dr. Peter Arnold for critically reviewing this manuscript. Alan Cass received PhD scholarship funding from the Colonial Foundation. This research was supported by a Harkness Fellowship to Dr. Cass from the Commonwealth Fund, a New York City-based private independent foundation. The views presented here are those of the authors and not necessarily those of the Commonwealth Fund, its directors, officers, or staff. This study is an approved research project of the Cooperative Research Centre for Aboriginal and Tropical Health. We acknowledge the journals *Ethnicity and Disease*, *Medical Journal of Australia* and *New South Wales Public Health Bulletin* for permission to reproduce figures and tables in this article.

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