Invited Comment

Renal disease in Australian Aborigines

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Introduction

In this era of increasing accountability in population-based research, and demands for strong evidence base of clinical practice, we need to examine justifications for the study of catastrophic problems in indigenous or transitional people. One justification might be the illumination of risk factors for, and mechanisms of, disease that can be generalized to the broader population, where they might be obscured by lower disease rates and density of risk factors. A more important justification is to arrive at, and model, solutions. We report a programme which has happily done both.

Australian Aborigines are a disenfranchised and marginalized people in a crisis of epidemiologic transition. Most Aborigines in the Northern Territory of Australia live in remote areas, in serious poverty and disadvantage, with inadequate services of all types. Standardized adult mortality rates are more than four times that of non-Aboriginal Australians, with all major conditions, including cardiovascular disease, represented in excess [1]. Premature death in young and middle age adults is contributing to family, community and cultural breakdown.

Renal disease and renal failure marks this ‘force of mortality’. Renal deaths are increased 18- to 30-fold, while the incidence of treated end-stage renal disease (ESRD) is approaching 1000 per million, and doubling every 3–4 years, as shown in Figure 1 [2]. Increased ascertainment and referral probably contributed to this increase over the 1980s, but later increases have been real. Renal disease has attracted especial concern because of the cost of treating people with ESRD, with an annualized cost per patient on haemodialysis (the main form of treatment) recently estimated at $100 000 [3]. In 1998, 96% of people on dialysis in the Northern Territory were Aboriginal, although they constitute only 28% of the population. The costs are enormous, quality of life is poor, and survival, reflecting the generally poor health of Aboriginal people, is short [2].

Rates and associations of renal disease

On cross-sectional examination of the community profile [6], there was a relentless increase in ACR with increasing age (Figure 2). Pathologic albuminuria was pervasive in adults (20+ years); 23% had microalbuminuria, (ACR 3.4–33) and 30% had overt albuminuria (ACR 34+). There was a progressive decrease in GFR with increasing ACR starting in the early-mid microalbuminuria range (Figure 3). Factors that correlated significantly with ACR included increasing age, birth weight and infant weight at one year (inversely), adult weight gain with central fat deposition and the accompanying features of Syndrome X (increasing blood pressure, levels of insulin, blood glucose, lipids, and diabetes). They also included skin sores, scabies and a history of poststreptococcal glomerulonephritis (PSGN), heavy drinking, multiparity in women (3 or more children), and a family history of renal disease. The estimated risk enhancement for overt albuminuria associated with these ‘diagnoses’ was substantial [5,6].

We thus proposed a multideterminant model of renal disease in which the simultaneous operation of several risk factors progressively enhances the increase in albuminuria that accompanies increasing age. Multivariate models predict a fairly low prevalence of renal disease in people with no risk factors, but almost inevitable presence of overt albuminuria by middle life in people with a full menu of risk factors [5]. In such a model, nephropathic factors would potentiate renal
disease expression and progression rather than act as 'single cause' agents.

**Natural history of renal disease**

ACR increased and GFR fell in individuals with time, at rates that were strongly correlated with the severity of baseline disease [7]. In people with ACR 34+ at baseline, the average fall in GFR was 4.1 ml/min/year. All renal failure arose in people who had heavy albuminuria at baseline, as shown in Figure 4 [7,8]. There was also a strong correlation between baseline ACR and subsequent natural death (Figure 4), which included, but were not restricted to, cardiovascular deaths [8,9]. After accounting for age and sex, the hazard ratio of persons with microalbuminuria for natural death compared with those of lower ACRs was 2.3 (95% CI 1.0–5.3), for those with ACR 34–99
was 3.2 (1.3–7.9), and for those with overt albuminuria was 5.1 (2.1–12.8). The estimated 5 year mortality (nonrenal and renal) in people with ACR 34+ at baseline was 35%. Thus ACR in this population marks not only renal disease and risk of ESRD, but also cardiovascular risk and the general force of mortality.

**Renal size and renal morphology**

Our studies suggest that reduced nephron endowment or impaired nephron maturation might predispose to renal disease. This might be a consequence, in part, of intrauterine growth retardation and infant malnutrition, as we have shown a clear relationship of body-surface-area adjusted kidney volume to birth weight by ultrasound study of children in this community [9]. In view of the 4-fold difference in nephron number described in the general population [10], lower renal volume might also have a genetic component. This is likely to be adaptive; a smaller number of nephrons might have been entirely adequate in the previous subsistence state, or even a survival advantage in conditions of salt and water deprivation.

Findings in ‘diseased’ renal biopsies in this community and other NT Aboriginal people are compatible with these hypotheses. All the usual morphologic diagnoses are represented to some degree, which supports the multideterminant hypothesis, and many biopsies show nonspecific change [11]. The striking consistent findings are glomerulomegaly and various degrees of glomerular sclerosis, with which glomerular size is strongly correlated [12,13]. This glomerulomegaly probably represents excessive nephron hypertrophy. Nephron hypertrophy is the mechanism by which all kidneys enlarge until adulthood, and might be exacerbated by the trophic effects of the Syndrome X state in adolescence and adult life. This trophic stimulus would be further magnified if the number of existing nephrons were already reduced, due to compromised nephron endowment in utero [14], or destruction of nephrons by nephropathic factors during postnatal life. Hyperperfusion associated with nephropathy provides a theoretical mechanism for increasing albuminuria and accelerated nephron loss in this state.

**Health services and disease expression**

Health services and other services also influence renal disease expression. Some initiatives should reduce disease rates (environmental hygiene, vaccines, improved nutrition etc), and medicines may reduce disease progression, as described later. However, improved services are also, ironically, enhancing disease expression. Dramatic recent reductions in infant mortality between the 1960s and 1980s have allowed large cohorts of low birth weight persons to survive to adult life at high risk for chronic disease [6]. In addition, prolongation of life due to better management of infections and diabetes, and postponement of cardiovascular deaths by patchy antihypertensive treatment, coronary angioplasties, bypass grafting etc, are now allowing the more leisurely development of nephropathy to run its full course in a larger proportion of people.

**Pharmacologic renal and cardiovascular protection**

In November 1995 we introduced a systematic treatment programme for people in this community with pathologic albuminuria or hypertension. The primary treatment agent was the long acting angiotensin converting enzyme, perindopril (Coversyl, Servier). Target blood pressure was <130/80 mmHg at first, and more recently <120/75 mmHg [17,18]. By December 1998, 240 people had enrolled, 46% were diabetic, 64% in adolescence and adult life. This trophic stimulus would be further magnified if the number of existing nephrons were already reduced, due to compromised nephron endowment in utero [14], or destruction of nephrons by nephropathic factors during postnatal life. Hyperperfusion associated with nephropathy provides a theoretical mechanism for increasing albuminuria and accelerated nephron loss in this state.

**Family clustering of renal disease**

A recent study from our group has shown a correlation between socioeconomic disadvantage and ESRD rates among Aboriginal people that was so powerful, given the serious poverty of people in most high risk areas, there might be little need to propose an additional major intrinsic predisposition [15]. However, it is clear that renal disease is more frequent and more severe in some families than others. We are attempting to ascertain the relative contributions of environment and genotype to this phenomenon, with studies of family clustering of phenotypic and clinical features, as well as potential susceptibility genes. We already know that the D allele of the angiotensin converting enzyme gene is underrepresented in this and other Aboriginal groups, so while it may enhance disease progression in the few people so endowed, this allele is not the major driving element in renal disease expression [16].

Participation has been enthusiastic, and compliance has been good in 67%. Blood pressure responses have been dramatic, and albuminuria and GFR have stabilized on a group basis. By December 1998, with a mean time on treatment of 2.1 years, there had been a estimated 55% reduction in new cases of ESRD and a 45% reduction in natural deaths in the ‘intention to treat’ group compared with historical controls matched for disease severity. Maximum benefit (62% reduction) accrued in people with overt albuminuria, in whom most of these events were segregated, as shown in Figure 5. Reductions in community-based rates of ESRD and natural deaths support these estimates (Figure 6). We estimate savings on dialysis costs alone in this small community (est 1800 people) between $700 000 Aust and $3.1 million, in the first 3 years, depending on whether ESRD and death rates would have continued to escalate or would have achieved a plateau in the absence of the programme [2,3,18]. The reduction in sickness and death is, however, a more important gain.
Renal disease is pervasive in this population and progresses over time. It is multideterminant, educated by a number of factors operating in a high risk environment, and intimately related to the general health profile [22]. Risk factors derive from, or are exacerbated by, rapid epidemiologic transition, serious poverty and disadvantage, and the deficiencies and successes of health services. Environmental factors have probably also influenced genotypes over time.

Prevention depends on sustained improvements in socioeconomic circumstances, infrastructure and health services. For persons already afflicted, disease is easily diagnosed and progression is dramatically altered by standard interventions within our reach [20]. Control of blood pressure, adult weight and infections are especially important. Pharmacologic treatment reduces premature death in early and mid adult life and might postpone renal failure beyond reasonable life expectancies in many people. The expansion of ESRD treatment services is enormously expensive and achieves no net gain in population-based health.

Many of these findings might be generalized to other high risk populations. The medical community should advocate for intersectoral initiatives to improve general living standards, where needed, and foster inter-specialty collaborations for a unified approach to health services, based on community-based prevention, screening and treatment programs. We must direct substantial intellectual and material resources to these issues and reposition medical and specialist training curricula to reflect those views. Constant evaluation of the outcomes of such community-based programmes is essential to modify strategies appropriately. With these approaches, better health, reduced deaths and lower health care costs can probably be achieved over a shorter term than ever imagined.

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