Trends in birthweight and infant weights: Relationships between early undernutrition, skin lesions, streptococcal infections and renal disease in an Aboriginal community.

*Thesis submitted for the degree of Bachelor of Medical Science*

Kate Walker
University of Melbourne

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ABSTRACT.

Undernutrition is prevalent in Aboriginal communities, in utero, infancy and childhood. It influences childhood morbidity and mortality and growth patterns. Undernutrition and poor socio-economic status also contribute to endemic and epidemic infectious disease, including scabies and streptococcal infection. It has been suggested that early undernutrition, and streptococcal and scabies infection are risk factors for renal disease, which is at epidemic levels and increasing.

This thesis examines the prevalence of undernutrition in newborns and infants in an Aboriginal community over time, and its impact on childhood growth and child and adult renal markers. The association between skin lesions, streptococcal serology, post-streptococcal glomerulonephritis (PSGN) and renal markers as evaluated through a community wide screening program in 1992-1995 is also examined.

Birthweights have increased since the 1960s, but they are still much lower than the non-Aboriginal values. Weights in infancy have decreased since the 1960s. At screening in childhood stunting was common, reflecting the presence of long-term poor nutrition in infancy. In both adults and children, birthweight and infant weights were negatively associated with albuminuria measured by the albumin to creatinine ratio (ACR).

Rates of scabies, sores, PSGN and streptococcal serological markers were all high. PSGN was powerfully predictive of ongoing urinary abnormalities in children and adults, with an odds ratio of 4 for ongoing elevated ACR four years after the initial episode (p<0.05). Scabies and sores at the time of screening were also significantly associated with ACR, however ASOT and anti DNase titres were not.
This study confirms the multifactorial nature of renal disease in Aboriginal Australians. The findings reaffirm the need for improved maternal and child primary care health education programs and access to affordable, nutritious food. Improved housing and hygiene are essential for prevention of scabies, skin sores and renal disease. Early and effective scabies and skin sore management is paramount. Education and employment are inextricably linked to the overall disease burden and their improvement must be a fundamental goal.
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The Study Community

The study community was on Bathurst island, 80km North of Darwin. The Tiwi people who live here have retained much of their language, kinship system, ceremonies and art since the establishment of the mission in 1911. This is obvious in the bilingual schools, the Tiwi designed church where the service is in local language and the successful local craft and tourist industries.

Unemployment benefits started in the 1960s and the local club soon after, where a large proportion of the money is spent. Alcohol is often the trigger for community violence. At the local store, cigarettes are the source of the biggest expenditure. There is little fresh fruit and vegetables which are much more expensive than the many canned, frozen and takeaway foods. Thankfully, many Tiwi people supplement their diet with bush tucker, but the combination is often inadequate.

I lived on Bathurst Island during the wet season before this project and made five visits during the year, helping with the children’s screening and searching through clinic records. I found the Tiwi people to be very family orientated, commonly explaining their family relationships in depth upon a first meeting. They were very welcoming, the smallest children confidently asking me who I was. I was taken hunting, to funeral ceremonies, the popular local football competition, the club and the disco. Many people were entertaining story-tellers, relating local culture and life with enthusiasm. I was also taught a little local language. The welcoming, open nature of the Tiwi people gave me a greater understanding of their lives and made my stay very enjoyable. (photo: Ngulu 1996. courtesy of Susan Jacups)
Declaration.

I declare this thesis is all my own work, which is submitted for the degree of Bachelor of Medical Science.

Much of the data was gathered as part of ongoing renal research being conducted at the Menzies school of Health Sciences. I participated in the 1996 children's examinations, reviewed some of the medical records and performed the statistical analysis under supervision.

The findings were presented at a clinic feedback session and a local health board meeting. They have also been submitted to the International Nephrology Conference and the Australian Dieticians Conference, both in 1997.
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*Figures 10, 11 and 12 are courtesy of W Hoy.
Abbreviations.

The following is a list of abbreviations used in this thesis.

ACR. Albumin to creatinine ratio
Anti-DNAse. Anti-Deoxyribonuclease
ASOT. Anti streptolysin O
ESRD. End stage renal disease
GFR. Glomerular filtration rate
HAZ Height for age z score
LBW. Low birthweight (<2.5kg)
LDL. Low density lipoproteins
NCHS. National Centre for Health Statistics
NIDDM. Non insulin dependant diabetes
PSGN. Post streptococcal glomerulonephritis
USA. United States of America
WAZ$_{12}$ Weight for age z score at 12 months or the closest age from 24 months.
WAZ$_{6}$ Weight for age z score at 6 months or closest age from 1 month
WAZ$_{1}$ Weight for age z score at screening
WHZ Weight for height z score
WHO. World Health Organisation
WWII. World War Two
INTRODUCTION

Undernutrition, skin lesions and streptococcal infections are all common in Australian Aboriginal Communities. In addition, rates of renal disease are increasing dramatically. The possible contribution of early nutrition and infections towards chronic renal disease is currently being defined.

OBJECTIVES

With this in mind the following questions were formed.

1) Undernutrition
   i) What are the growth patterns in the children of the study community?
      How have they changed with time?
   ii) How do birthweight and infant weights correlate with subsequent growth in childhood?

2) Infections and Renal Disease.
   i) What is the prevalence of the following parameters in Aboriginal children?
      a) skin lesions
      b) antibody profiles to group A streptococci
      c) post-streptococcal glomerulonephritis

3) Renal Disease.
   i) What is the prevalence of albuminuria and haematuria in Aboriginal children?
   ii) Does early growth correlate with these abnormalities in later life?
      a) in children
      b) in adults
   iii) Are the infectious markers, described above, associated with renal disease?
BACKGROUND.

Undernutrition.

Undernutrition is common in Aboriginal children both before and after birth and has a large impact on short and long term health.

*How Is Undernutrition Measured?*
Measurements of height and weight relative to age are the most important indicators of a child's nutritional state and growth rate (WHO 1986).

Weight for age is an easily obtained parameter for the study of nutritional state. Low weight for age can reflect weight loss or failure to gain weight. Low weight for age can reflect a short term nutritional inadequacy or repeated episodes of undernutrition but cannot identify previous states of undernourishment from which children have recovered. Weight loss is frequently exacerbated in undernourished children by recent infections, particularly of the gastrointestinal tract. While weight for age is a useful indicator of the current health of the child it is unsatisfactory for the study of long-term undernutrition as it is too subject to rapid change (WHO 1986).

Weight for height is also a useful measure of current nutritional status and is not age dependant. "Wasting" is defined as deficiency in weight for height which is outside the range for a healthy child (Waterlow 1972). The cut-off point often used is 2 standard deviation scores below the National Centre for Health Statistics (NCHS) reference median. Wasting reflects similar aetiologies to low weight for age.
Height for age is a better parameter of long-term health and nutritional status. Height is a stable measurement that takes into account the child's overall history. However, it cannot differentiate between an ongoing chronic process and a past event. Waterlow defined the term “stunted” as height deficient for age. The cut-off point is now accepted as 2 standard deviation scores below the NCHS reference median. Many conditions may result in stunting. These include almost any nutritional deficiency, particularly protein or carbohydrate, chronic or repeated mild to moderate infections, endocrine disturbances such as growth or thyroid hormone deficiencies, many chronic childhood diseases such as congenital heart disease, cystic fibrosis, and chronic nephritis, inadequate psychosocial stimulation, poverty and deprivation (WHO Working Party 1986, Waterlow 1992). However in populations with a high prevalence of low height for age, a reduction in linear growth is more likely to be due to nutritional deficits.

Wasting and stunting reflect different biological processes and are suggested to be not statistically associated (Keller and Fillmore 1983 cited Waterlow 1992). There is evidence that catch-up in weight occurs in preference to height gain. Height gain is not restarted until 85% of the expected weight for height has been achieved.

_Which Reference Should be Used for Comparison?_

The reference used for comparison of childhood weights and heights is taken from the NCHS. These have been developed from heights and weights from middle class American children from a variety of ethnic backgrounds.
The utility of these charts in populations with different cultural, ethnic and socioeconomic backgrounds has been questioned, particularly in developing countries. However, ethnic influences on growth are much smaller than those caused by disease and malnutrition (WHO 1986, Martorell et. al.1974). It is debatable whether the growth of North American children is ideal as many may be overweight (Waterlow 1992). The NCHS reference population is also limited by some of the figures which were collected as long as 60 years ago, when rates of bottle feeding were much higher. Recent research has highlighted lower weight for age in breastfed infants under one year relative to the NCHS figures based on bottle fed infants, although for the first three months the breast fed infants grew more rapidly (Dewey et. al. 1995, Hitchcock and Coy 1989). The result in Aboriginal children would be artificially lowered anthropometric outcomes as breast feeding is common. Data for new standards are currently being gathered to include breastfed babies.

When compared with the same reference, the relative risk of poor outcomes such as mortality or future functional impairment varies enormously between populations. This is due to differing environmental conditions, particularly rates of infective illness. It has been suggested local references would be an ideal alternative (Van Loon et.al.1986). There would be many practical problems with a separate reference for each local area, all of which would need periodic upgrading due to changes in growth patterns with time.
Although there are limitations to comparisons of childhood growth between populations, the NCHS reference is the best available alternative at present. If the goal is to contrast growth patterns between populations, then using the NCHS charts gives relative placing even if the comparison is not with the ideal.

*Degrees of undernutrition*

The risk of poorer outcomes based on reference curves is continuous, but practitioners prefer cut-off points as a guide to action. Standard deviations or z scores are recommended for comparison of rates of undernutrition among populations. One commonly used cut off point is two standard deviations or z scores below the median. Malnutrition is defined as 2 standard deviations below the median NCHS weight for age. Two standard deviations below the median weight for height is termed “wasted” and for height for age is termed “stunted”. Another common description measure of degrees of undernutrition in the past was percentages below the median weight for age. 71- 80% below the NCHS median was mild malnutrition, 61-70% moderate and below 60% severe malnutrition. This has limited accuracy at the extreme ends of the risk group and does not correspond across age or height for a fixed point.

The disadvantage of any cut-off points is that they are a purely statistical measure and the risk is continuous. It must be remembered children just above the cut-off point are not necessarily optimum.
Growth Outcomes.

Children’s rates of growth change considerably over time. For the reference population the constant rates of stunting and wasting are 4.6%. In any population rates of wasting and stunting vary with age from the reference. Keller (1988FEM) suggests the abnormal growth processes of stunting and wasting starts as early as 3 months. Height gain over time followed a similar pattern when compared among 3 different developing populations. The rate of height gain decreased over the first year to a minimum at one year in comparison to the reference. It stayed at this poor level until rising again at three years of age.

Low birthweight (LBW) influences subsequent infant growth strongly and catch-up growth is often limited. A study in the USA found the contribution of LBW to undernutrition estimates was between 21% and 29% for three different ethnic groups (Gracey 1991). A study in Guatemalen children found stunting in the first five years is likely to lead to permanent stunting later in life (Gracey cited Martorelli 1991). Given the poor continuing environment of low birthweight babies and undernourished children it is difficult to separate this as an independent risk factor from childhood undernutrition.

Undernutrition In Aboriginal Children.

What is the Prevalence of Undernutrition in Aboriginal Children?

Undernutrition is still endemic in Aboriginal children, particularly in rural areas (figure 1, TIME 1994). A recent report in the Top End of the Northern Territory estimated rates of malnutrition at 20% (using the WHO definition of 2 standard
deviations below the NCHS mean). This was an underestimate as it was calculated from hospital admissions for diarrhoeal illness and used the census population as a denominator. The figure is higher than many underdeveloped countries (Ruben and Walker 1995). Of those admitted to hospital for diarrhoeal illness, 59% were malnourished, 36% wasted, 10% stunted and 13% both wasted and stunted, demonstrating the vicious cycle of malnutrition and infection. Although at the Royal Darwin Hospital, the mortality rates have fallen from the late 1960s from approximately 9% to 0.3-0.4% (Walker 1994) the estimates of malnutrition have not changed.

Rates of malnutrition among Aborigines in the N.T. were similar to those in Aboriginal communities in other states. A community based study in 1986 in the Murray Valley, bordering Western Victoria and N.S.W., described rates of moderate malnutrition (less than 70% of the WHO median weight for age) that varied from 11% to 26% (Cameron et.al. 1986). In Northern W.A. 34% of children examined had evidence of growth retardation, the result of long-term undernutrition (Gracey 1990).

Other areas of Australia report better statistics of Aboriginal children's growth. A study in rural Queensland (Dugdale et. al. 1990) described near normal growth rates using weight and length for age. However, there was a continuing pattern of poor growth between the ages of 3 to 12 months which was compensated for at later ages. This was perhaps due to the reference NCHS population not including breast fed babies who have slower growth up to one year as discussed earlier (Dewey et. al. 1995, Hitchcock and Coy 1989). This estimate was an improvement on the
For Charlotte and too many other indigenous Australians, health is only a dream.
rate of growth retardation in children between 0.5-3 years in Queensland estimated at 50% in the 1960s (Jose and Welch cited by Gracey 1992).

**How Does Undernutrition Affect Growth Patterns in Aboriginal Children?**

The deficiency in Aboriginal children's growth starts before birth. Low birth weights are common, reaching twice the incidence of the non-Aboriginal population in Western Australia (Gracey 1990). In the N.T. 14.3% of Aboriginal newborns are less than 2.5kg compared with 6.7% of non-Aboriginal babies (NT Midwives collection 1994).

A review article by Gracey (1991) looked at nutrition in Aboriginal children over time in a W.A. community. After a lower birth weight and a satisfactory weight gain in early infancy, Aboriginal children's weight for age dropped off soon after weaning around six months (although height velocity fell as early as three months). This period was usually associated with repeated gastrointestinal and respiratory infections which lead to further weight loss and growth retardation not improving until two years of age.

The "catch-up" growth in Aboriginal children is ineffective and growth deficits persist up to the age of fifteen, when Aboriginal children's height is still substantially below the NCHS median. Both low birthweight and normal birthweight children in the Kimberly region were shorter and lighter than non-Aboriginal children by five years of age. This suggests an ongoing poor nutritional environment (Roberts,
Gracey, Spargo 1988, Gracey and Anderson 1989). In the LBW group the figures were more marked with the boys being 4.2kg and 5.9cm behind the reference values and the girls 3.15kg and 5.3cm behind. The normal birth weight Aboriginal children were still lagging below the reference growth values at five years by 2.13kg and 3.6cm in boys and 1.29kg and 2.9cm in girls.

What Are the Antecedents to the Undernutrition?

Poor nutrition in children is related to their local community's conditions. A study in several countries revealed differences of up to 12% in height and 30% in weight by social class (Habicht J-P cited by the WHO). In an Aboriginal community in the Murray valley the rates of moderate malnutrition (defined as 80% of the NCHS weight for age) varied from 11% to 26% depending on the housing conditions, the degree of community organisation and social pressures experienced locally (Cameron and Debelle 1986). Childhood hospitalisation patterns from NT communities varied up to sevenfold according to local socio-economic factors (Munoz, Powers Matthews 1992). The housing conditions and availability of fresh food were particularly important associations. A community in Bourke achieved improved childhood nutrition through a series of community development schemes focusing on housing and health. (Harris and Kamien 1990).
Outcomes Of Undernutrition.

Short-term Outcomes.

Infectious Disease.

The synergistic pattern of infection and malnutrition is important in the perpetuation of growth retardation in undernourished Aboriginal children (Gracey 1991). Nutritionally vulnerable infants and children are susceptible to repeated infections which in turn worsens their nutritional status. There is a well-recognised phenomenon of repeated bowel infestation, diarrhoea, malabsorption, failure to thrive, reduced resistance and malnutrition. Malnutrition is now recognised to have a substantial impact on humoral, mucosal and cellular immunity which provides more detail to the cycle of malnutrition and infection.

Diarrhoea is a particular problem in undernourished children. Diarrhoea exacerbates poor nutritional status through loss of fluid, nutrients and electrolytes, loss of body weight and the negative energy balance brought about by anorexia and fever (Gracey 1991). Diarrhoea is more frequent and prolonged in undernourished children, although it is often difficult to establish whether the undernutrition or the diarrhoea is the antecedent (Bhandari et. al. 1989, Tomkins 1981). Small bowel mucosal abnormalities and post-infective food intolerance are suggested mechanisms for persistence (Walker-Smith 1993, Gracey 1991). In addition intestinal parasites often complicate the picture (Saway et. al. 1990, Hlaing 1993, Gupta 1990) with an estimated prevalence of 32% in rural Aboriginal children from the Kimberley region (Meloni et. al. 1993). Other factors leading to prolonged diarrhoea, such as concomitant chest infections, lack of breast feeding and vitamin
A deficiency signs, are common in undernourished children (Mahalanabis et.al. 1991).

Respiratory tract infections in Aboriginal children cause 8-16 times the bed usage of the non-Aboriginal population and have a hospital admission rate three to four times that of gastrointestinal infection in Aboriginal children(Gracey and Anderson 1989). Respiratory tract infections are more likely in children with low weight for age and in children who live in overcrowded houses, containing smokers (Leader 1976 cited by Barker, Stephen 1995), both of which are common in Aboriginal communities.

Ongoing chronic respiratory infections can lead to bronchiectasis and chronic bronchitis in later life (Walker 1994, Barker 1994). An inverse relationship has been found between birth weight and weight at one year, and chronic bronchitis in adult life (Barker 1994). Barker suggested that while recurrent respiratory tract infections in infants may deleteriously affect the respiratory system directly, these may also be marking children whose airway function is already constrained by poor nutrition in utero.

*Undernutrition and the immune response.*

Low birth weight infants have impaired immune responses with lower numbers of helper /inducer T lymphocytes. This further predisposes them to infective illness.
However, the effects of undernutrition are not limited to those on growth and susceptibility to infection.

Anaemia

Iron deficiency anaemia is very common in Aboriginal children reaching 25% in a hospital based study (Walker 1994). The causes are suggested to be multifactorial, with reduced stores of iron at birth, followed by dietary deficiency and parasitic infections in infancy, which further diminish the supply. While lethargy is a troublesome short-term effect of anaemia, long-term anaemia can impair intellectual and motor development imparting a long-lasting disadvantage (Summary 1989, Lozoff et al 1988). The positive news is behavioural changes caused by iron deficiency have been found to be managed by supplemental iron.

Urinary Tract Infections.

Urinary tract infections are frequently asymptomatic in children but are undoubtedly very common. 10% of Aboriginal children admitted to hospital with diarrhoeal disease were found to have urinary tract infections proven by suprapubic aspiration and culture (Jones & Henderson 1988, Walker 1994). Urinary tract infection is especially common in undernourished children.

Renal Function.

Several studies in India have looked at renal pathology in protein energy malnutrition. Of 60 renal biopsies studied from cases of protein energy malnutrition the most common pathologies were cloudy swelling and hydropic degeneration of
the proximal and distal tubules (Dayal 1968). No correlation could be found between any histopathological and urinary biochemical abnormalities but a variety of hypothesis were formed. The cloudy swelling and hydropic changes, found in dehydrated patients could result from shock causing renal ischaemia. Anaemia, which was found in all cases, could also contribute to the histopathological changes by leading to cellular hypoxia and tissue damage. It was also suggested that prolonged protein deprivation leading to hypokalaemia would increase the likelihood of chronic pyelonephritis and consequent renal pathology.

Bischet al. (1969) observed that 12/23 adult patients with malnutrition had mild intermittent proteinuria. Renal biopsies showed thickening of the glomerular basement membrane, hypercellularity and hyalinisation of the glomeruli with dilation and degeneration of the tubules. (There was no correlation between the histopathology and the renal functional changes. Urinary tract infection was ruled out as a cause of persisting albuminuria after urine cultures were clear of infection.)

Undernutrition restricts the concentrating ability of the kidney. A study in protein-deprived rats found an impairment in NaCl transport in the thick ascending loop of Henle (Kudo et.al.1991). Previous studies cited by Kudo found a fall in the GFR of chronically undernourished rats was due to a decrease in both the glomerular plasma flow and in the ultrafiltration coefficient due to reduced filtration area. The decreases in osmotic concentration in the medullary interstitial fluid were due mainly to a deficiency in sodium and urea.
One study found sodium balance to be poor in malnourished children (Zin-Thet-Khine et al. 1992), with poor conservation of sodium by the colon and greater sodium losses in their urine. This suggests poor renal concentrating mechanisms perhaps due to reduced glomerular filtration rates, renal plasma flow and maximal concentrating ability as found in malnourished children in previous studies. The lower sodium to potassium ratios in malnourished children's urine indicated their kidneys were trying to conserve sodium.

*Long-Term Outcomes.*

*Mortality.*

Children with lower anthropometric indices have a marked rise in mortality risk. Some suggest this is evident even in mild to moderate undernutrition (WHO 1995). Keilmann and McCord (1978) reported that mortality doubled with each 10% decrease of weight for age below 80% of the median. Others maintain that only severely malnourished infants (<60% of the mean) are at an increased risk of death (Chen 1980).

*Adult Size*

Childhood stunting contributes substantially to decreased adult size (Martorell cited by WHO 1995). This limits adult productivity, especially in occupations which rely on manual labour as shorter people have a reduced absolute capacity for manual work (Spurr 1984 cited by Waterlow 1992).
Maternal size has reproductive consequences. Smaller women are more likely to have obstetric complications. There is also an intergenerational link in less developed countries, as smaller mothers are more likely to have lower birth weight infants. Lower birthweight infants in turn may be predisposed to adult disease by their low birth weight (WHO cited Kramer, Klebanoff and Brinkin 1995).

*Mental Development.*

A wealth of studies have examined the influence of chronic mild-moderate undernutrition on the developing brain. A recent review by Connolly and Kvalsvig (1993) cited many studies which have found an association between growth retardation in children and their intellectual development. School performance has also been found to be associated with growth status (WHO cited McGuire and Austin). (There has been no relationship between height attainment and intellectual development in more well off populations (Waterlow 1992)). There are, however, many difficulties in separating the many compounding social and biological factors associated with poverty which would also restrict their intellectual development and render it difficult to be assessed by conventional methods.

Low birthweight and poor infant weights have also been hypothesised as risk factors for chronic disease in adulthood.
Chronic Disease in Transitional Populations.

In transitional populations there has been an exponential rise in the rates of chronic adult diseases, such as NIDDM, cardiovascular and renal disease. There are several theories regarding the likely mechanisms.

*Early Undernutrition and Chronic Adult Disease.*

Barker et. al. were the first to postulate the relationship between chronic adult disease and early undernutrition, particularly undernutrition in utero. This was termed the low birthweight or “Barker” hypothesis (figure 2). Hypertension, cardiovascular disease and stroke were all found to be associated with birthweight in a large retrospective cohort study (Barker et. al 1988).

Birthweight was inversely related to systolic and diastolic blood pressures (Barker et. al.1993). This risk rose with decreasing birth weights, adult age and weight. Cardiovascular disease rose with decreasing birth weights which may have been explained in part by the effect of early undernutrition on blood pressure. In addition, low birth weight has been associated with increasing levels of LDL cholesterol, hyperlipidaemia and blood clotting factors fibrinogen and factor 7, all of which have been found to increase cardiovascular risk. It is thought that intra-uterine malnutrition impairs liver development which programs higher plasma concentrations of these cardiovascular risk factors.
Figure 2. A low birthweight Aboriginal newborn (Royal Darwin Hospital, courtesy Sue Sayers).
There has been limited study on the correlation of infant weights and chronic adult disease. In men the cardiovascular death rate rose with decreasing weights at one year of age (Barker et.al. 1994).

Further studies (Valdez et.al.1994) have compared adult outcomes in different ethnic populations of low birth weight infants. Significantly higher levels of fasting insulin were found in the lower birth weight groups, independent of ethnicity, sex, and current socioeconomic circumstances. The worst metabolic outcome was associated with the progression from low birth weight baby to obese adult.

NIDDM and glucose tolerance were associated with birthweight (Barker 1994). Glucose tolerance was found to fall progressively with lower birth weights. These associations remained after controlling for the possible confounding factors of cigarette and alcohol consumption and social class. Undernutrition in utero is thought to impair the development of the endocrine pancreas, reducing numbers of cells and insulin responses. In addition, it is also suggested to lead to insulin resistance in adult life.

The relationship between low birth weight and hypertension has been suggested to involve renal mechanisms (Brenner et. al. 1993). Brenner cited animal studies in which it was shown low birth weight retards renal development sufficiently to reduce the overall size of the kidneys and the number of glomeruli at birth. Human
infants of low birth weight have lower kidney weights and fewer glomeruli per renal sectional area. Long-term follow-up studies of rats born of either protein restricted or gentamycin exposed mothers found that in addition to congenital oligonephropathy, they developed premature nephrosclerosis. This suggests that a congenital deficiency of nephrons initiates a process of progressive glomerular damage after birth. The proposed mechanism is that the resulting reduced total glomerular filtration surface area leads to hypertension. This would then contribute to the glomerular capillary hypertension and eventually to nephrosclerosis, thus reducing the filtration surface area further and exacerbating the original pathology. This theory suggests given the same environmental conditions the total nephron supply at birth determines the susceptibility to hypertension.

Criticisms of the low birthweight hypothesis have been based on conflicting results from other studies rarely cited in papers by the Southampton group. A study in England (Phillips et. al. 1994) refuted the role of low birth weight in the pathogenesis of insulin resistance which was evaluated through a intravenous glucose tolerance test. In addition, although weak evidence for causality, ecological associations are inconsistent with the hypothesis, with a rise in the incidence of cardiovascular disease in many developed counties since WWII despite constantly high mean birthweights (Kramer, Joseph 1996).

The design of Barker’s low birthweight studies has been criticised as the study sample contains only a fraction of the original cohort. This would only be problematic if the rates of chronic disease were higher in those lost to follow-up. Furthermore, the degree of nutrition is not measured directly, only by the growth
in utero or infancy (Paneth 1995). Barker used birthweight as a proxy for in utero undernutrition whether the babies’ dimensions were proportionate (a sign of undernutrition) or not (a different cause of low birthweight). In Aboriginal populations and other developing countries it is agreed that most low birthweight babies are small for dates (figure 2), a result of undernutrition in utero (Villar et al 1982, Sayers 1993, 1996, Blair 1994).

"Syndrome X"

It has been suggested this “Barker hypothesis” be renamed “syndrome X” as both mark cardiovascular disease and NIDDM. “Syndrome X” includes hyperinsulinemia, insulin resistance, obesity, hyperlipidaemia, and hypertension, many of which have been associated with undernutrition.

Albuminuria has also been suggested to be included in “syndrome X” (Hoy et.al 1996). Hypertension increases the rates of albuminuria in at risk populations. In Navajo Indians who have rates of albuminuria at 15% (Hoy et.al. 1994), hypertension in diabetics increased nephropathy sixfold and hypertension in non-diabetics increased albuminuria threefold. Hypertension has been associated with a higher albuminuria risk in an Aboriginal community (Van Buynder 1993).

Insulin resistance has been found to be associated with albuminuria in NIDDM patients (Niskanen, Laakso 1993). (More NIDDM patients with albuminuria were
found to have impaired insulin action than those without albuminuria after controlling for hypertension and diabetes.) It has been hypothesised that albuminuria reflects not just increased glomerular permeability, but generalised vascular permeability in NIDDM patients. Hyperinsulinemia has also been found to increase transcapillary escape of albumin in non-diabetic subjects, providing a possible link between hyperinsulinemia (a result of insulin resistance) and albuminuria.

The “thrifty gene” hypothesis.

The “thrifty gene” hypothesis developed to explain the high rates of NIDDM in populations at high risk of developing diabetes. This was applied to Aboriginal Australians who have rates of NIDDM at two to six times that of non-Aboriginal Australians, which is higher in the more Westernised communities (Guest, O’Dea 1992). Previously diabetes was uncommon. The high prevalence at present has been suggested to be due to an interaction between an underlying metabolic predisposition termed the “thrifty gene” and a Westernised lifestyle. The “thrifty gene” is marked by insulin resistance and hyperinsulinemia and both of which are common in indigenous people such as Aboriginal Australians and Pima Indians. This would have conveyed a survival advantage in an environment of changeable food intake patterns. The survival advantage was lost with a constant diet of a large quantity of sugar and fatty foods and little physical activity (O’Dea 1991). This results in high levels of obesity, NIDDM and cardiovascular disease (O’Dea 1992).
Either or both the Barker and the “thrifty gene” hypothesis could be correct. While
the “thrifty gene” would be difficult to prove, requiring the identification of a gene,
a randomised controlled trial of early undernutrition would be unethical and many
years in the follow-up. A closer test of the Barker hypothesis would involve a
population in which the vast majority of the early growth deficiencies is due to
undernutrition such as in Aboriginal communities. In addition the association of
early infant weight with chronic adult disease requires further investigation.

Renal Disease In Aboriginal Australians.

Renal disease is widespread in Aboriginal populations. The incidence of end stage
renal disease (ESRD) in Top End Northern Territory Aborigines is eighteen times that
of non-Aboriginal Australians and is doubling every four years. (These figures are
based on those entering the ESRD treatment program only) (Hoy 1995, Hoy
unpublished 1996). In addition ESRD develops twenty to thirty years earlier in
Aborigines. Aboriginal patients receive significantly lower proportions of kidney
transplants and once grafted also have a worse prognosis (Kirubakara 1992). A
clear understanding of the prevalence and aetiologies is essential for improvement
to take place through effective public health program development.

High rates of albuminuria measured by the ACR have been shown to reflect the high
levels of progressive renal disease in the study population (Hoy et. al. 1996). Most of
the hypertension in the community was associated with renal disease and all renal
insufficiency, demonstrated by elevated serum creatinine, was in those with progressive albuminuria in the highest category.

*What does albuminuria signify?*

Albuminuria has also been found to mark cardiovascular morbidity and mortality on a population basis, suggesting that it marks a widespread vasculopathy not restricted to glomeruli. In addition, microalbuminuria has been identified as a risk factor for future mortality rates in NIDDM, mainly due to increased cardiovascular mortality (Morgensen 1984, Mattoo et al 1992).

*What is the Prevalence of Renal Disease in Aboriginal Populations?*

A comparison study between rates of albuminuria in Europids and Aborigines in Victoria and Southern NSW (Guest et al. 1993) defined an ACR exceeding 1.30mg/mmol as a pathological level. Rates were significantly higher in the Aboriginal population with 61% of Aboriginal men and 56% of Aboriginal women having pathological albuminuria compared with 18% of Europid men and 23% of Europid women. In a community based study in Central Australia (Iser 1995) 36% of Aboriginal adults screened were found to have albuminuria (ACR>3.4 mg/mmol).

*What Are The Possible Causes Of The Renal Disease?*

Some of the renal disease in Aborigines is attributed to the diseases associated with a Western lifestyle, which are becoming increasingly prevalent in Aboriginal people.
NIDDM, hypertension, obesity and ischaemic heart disease, while previously rare as assessed from the limited medical records at the time, are all now common. NIDDM, hypertension and insulin resistance interact closely with the renal disease.

**NIDDM and Renal Disease.**

Although the association between NIDDM and renal disease is well recognised, the mechanism for progression is still poorly understood. In the older age group, when NIDDM is more common, there are often other disease processes. Microalbuminuria is present in up to 20% of NIDDM patients at diagnosis, which suggests renal damage occurs during the asymptomatic period. This progresses at a rate of approximately 17% per year which may be reversible with control of the hyperglycaemia. It has been estimated 25% of NIDDM patients with albuminuria progress to ESRD (Mogensen 1984). While direct comparison of the figures between populations is problematic, the link between albuminuria in NIDDM and future renal disease is consistently evident.

Studies are in agreement that while diabetes is an important contributing factor, it is insufficient to explain in total the magnitude of renal disease in Aboriginal populations. Guest (1993) also noted the difference in rates of heavy albuminuria in Aborigines in Victoria and Southern NSW was not accounted for by glucose tolerance or hypertension. Another important risk factor is streptococcal disease.
Streptococcal Disease in Aboriginal Communities.

Infective illness is endemic in Aboriginal communities in all age groups. Undernutrition, overcrowding and poor housing and sanitation have all contributed to the high rates of infectious disease.

Western Australian Aboriginals aged from 50 to 65 years had a 6 to 12 fold increase in infectious and parasitic illness (Gracey and Veroni 1995). Aboriginal children also have a particularly heavy load of infectious disease commonly involving the skin, gastrointestinal and respiratory tracts and endemic chronic supplicative otitis media (Walker 1994).

Streptococcal Infection and Renal Disease.

The best described and longest recognised form of Post-streptococcal glomerulonephritis follows beta haemolytic streptococcal infection, most commonly group A. Antecedent infections are mostly streptococcal impetigo in the Northern Territory (Van Buyneder et.al.1993) but pharyngitic infections are also recognised. While the short-term history of acute nephritic illness is well understood, there is still argument about the long-term outcomes of post-infective glomerulonephritis. High incidence of streptococcal carriage is closely linked to poor housing and
crowded conditions. The levels in the total Australian population have dropped dramatically this century, leaving Aboriginal rates unacceptably high.

*Use of streptococcal markers.*

Evidence of beta-haemolytic streptococcal infection can be demonstrated by topical swabs and serological markers. Recovery from throat and swabs is generally low. Antibody markers induced by the streptococcal infection are more useful. Common markers used are the Antistreptolysin O (ASO) and anti-DNAase antibodies measured in titres. The ASO titre rises 1 to 3 weeks after streptococcal infection reaching a maximum at 3 to 5 weeks. An ASO titre of 250 Todd units is generally accepted as significant evidence of recent or repeated infections but this should take into account a community’s background levels of streptococcal carriage (Jawetz et al 1989 and Boineau and Lewy 1989). The ASO titre levels are elevated in 60 to 80% of people following a throat infection but much fewer following a skin infection. Levels of anti-DNAase are more commonly elevated following a streptococcal skin infection with 85% of patients having elevated titres.

*Incidence of Streptococcal Infection in Aboriginal Communities*

The continued high incidence of post-streptococcal diseases, acute post-streptococcal glomerulonephritis (PSGN) and rheumatic fever throughout Northern Australian Aboriginal people suggests a wide carriage rate of group A streptococci in much of this region.
Streptococcal infection has been reported at very high levels in Aboriginal communities. A study by Nimmo et. al. (1992) in Northern Queensland showed 36% of children were positive for group A streptococci from infected skin lesions and asymptomatic throat swabs. Both the ASO and Anti-DNAase titres were remarkably high in this community, particularly in school age children. 55% had ASO titres above the accepted upper limit of normal (200 I/U) and 93% had higher than the normal upper limits for anti DNAse (160 I/U). A study in the Top End found even higher carriage rates (Van Buynder 1992). 65% of skin lesions tested had streptococcal isolates. The ASO titre was above the reference range in 43.7% of all subjects and the ADB titre was raised above the reference range of 256 IU in all subjects, demonstrating that the infection is endemic.

Among children with glomerular haematuria in three Aboriginal communities 7/16 (44%) had at least one marker of recent streptococcal infection compared with 45/164 (27.4%) of those without haematuria which was not statistically significant (Van Buynder et. al.1992). Although these results were inconclusive, a role for childhood origins in chronic nephritis in later life was suggested by higher rates of proteinuria in the children from the community with highest prevalence in the adults. The relationship between streptococcal infection and chronic nephritis was suggested by an association between the long lasting antibody to Streptococcal M protein and proteinuria in adults (Goodfellow et.al 1996).

*Epidemics of Post-streptococcal glomerulonephritis in Aboriginal communities.*
children and in the epidemic form of the disease, which is more prevalent in children. The difference in prognosis may be due to the fact that the endemic form is more common in older patients who are more likely to have an undiagnosed pre-existing chronic glomerulonephritis so consequently a poorer outcome (Kurtzman 1978). Ideal studies would have baseline urinalysis before PSGN infection. Comparisons between studies are difficult due to differing parameters of ongoing disease and quite different populations.

In developing countries the prognosis varies in the long-term. 3.5% of the 534 patients with PSGN had persistent urine abnormalities after 12 to 17 years in Trinidad (Potter et. al. 1982). Studies in Thailand and the West Indies with short follow-ups found a similarly good prognosis with 1/61 patients with mild proteinuria after 4 years and 11% with persistent proteinuria after less than 2 years follow up period (Williams 1987, Tapaneya-Olarn et.al. 1989). A follow-up of 193 patients in India (142 children) for 10 years found 31% with either hypertension, renal insufficiency or proteinuria (Chugh et. al. 1987). A study in Macaibo 11-12 years after PSGN found a persistent abnormality including proteinuria, reduced creatinine clearance and microhaematuria in 21.1% of the 71 patients (Garcia et al. 1981), all of which had increased since the 5 year follow-up.

Studies in developed countries also have a varied prognosis. In New York 90 cases in adults and children were followed for 2-15 years. Fifty percent had proteinuria, hypertension or a reduced glomerular filtration fraction. Of the 18 biopsies taken from 1 to 15 years after the initial episode 33% showed evidence of sclerosis (Baldwin et. al. 1974). A similarly poor outcome was found in a New Zealand study.
with only 36.6% of the 42 adult cases followed for a mean of 13 years having
normal renal function. Two of 26 cases followed for an average of 131 months in
Italy had renal insufficiency (Buzio et.al. 1994). All three biopsies taken from cases
with normal urine albumin were normal suggesting that normal urine albumin is a
good prognostic sign while biopsies from patients with albuminuria consistently
showed a pattern of mesangial proliferative glomerulonephritis. Other reports
varied substantially; Whitworth and Lawrence (1994) cited rates of 1-2% for
children and approximately 5% of adults developing chronic renal failure after
post-infective glomerulonephritis.

Given the inconclusive nature of these figures, the influence of endemic and
epidemic PSGN in the chronic renal disease of Aboriginal people needs further
examination. Although the epidemics occur mostly in children, who are generally
thought to have a good prognosis, the epidemics only reflect a fraction of the total
burden of streptococcal infection in Aboriginal communities and probably its renal
effects. The influence of ongoing streptococcal infection on renal disease markers
needs to be examined in addition to the epidemic form. It is also essential that the
results of the combination of PSGN with the many other renal risk factors in this
population is examined.

Results from the Study Community.

Rates of Chronic Adult Disease.

On this background of prevalent kidney disease in Aboriginal people, the study
community is a high risk group. The average annual incidence of ESRD over the
four year period 1992-1995 was 2700 per million, more than 60 times the age adjusted non-Aboriginal Australian rate (Hoy et. al. unpublished 1996). Significant proteinuria has been described in 30% of the adult population which increases with age. Albuminuria rates (>34 gm/mole creatinine) reached 40% at middle age with only 15% of people over 55 having normal albumin excretion (Hoy in press). Haematuria was also common and, while rates are increased in people with higher ACRs, much of the haematuria and albuminuria was independent of one another.

There was evidence of lifestyle changes bringing about cardiovascular and metabolic disease in the adult study population. Thirty percent were overweight, 19.6% had NIDDM and 10.7% had impaired glucose tolerance. In addition elevated blood pressure was found in 38% of the men and 18% of the women and 45.6% of the population had elevated triglycerides. Rates of infectious illness were also high with skin sores being common in every age group often in conjunction with chronic scabies infection. Respiratory illness was very common with 95% of over 55 year olds having a loose cough (Hoy in press).

Although the nutrition of infants on Bathurst Island has not been studied in great detail previously, newspaper reports have highlighted the prevalence of low birthweight babies and poor infant nutrition (Figure 2, TIME 1994).

In the study community there is clearly an association between albuminuria and NIDDM and hypertension. In the 19.7% of the study community with NIDDM there was a more than a thirteen fold increase in overt albuminuria (Hoy in press 1996)
and in those with hypertension there was a four-fold increase in overt albuminuria. This confirmed the results of a community based study by Van Buynder (1993) who found other associations with albuminuria to be hypertension, increasing B.M.I., a family history and increasing age.

“Barker” Hypothesis.

In the study community both ACR and insulin resistance are correlated inversely with birth weight, after controlling for current weight, age and sex (W Hoy 1995). The relative risk for a raised ACR (≥34) was 3.78 in adults who have been low birth weight individuals (<2.5kg). The relative risk for an ACR ≥34 was further raised to 8.7 for low birthweight individuals in combination with a raised BMI in adult life. After controlling for sex, age, blood pressure and current BMI, the risk of overt albuminuria was increased by 2.62 for each kilogram of reduction in birth weight (Kile, Hoy 1995). The highest risk for overt albuminuria was in adults who developed a high BMI after a low birth weight. It is also interesting that the most underweight children had the highest ACRs. Undernutrition in infants was not separated from LBW as an independent risk factor. This could be a possible confounding factor, as the nutritional deprivation is commonly ongoing from in utero.

The multifactorial nature of renal disease in this population was highlighted. Given that reduced glomerular endowment, hypertension and a higher fasting insulin level may all be results of low birth weight these factors interact to compound the renal
disease risk. With the added multitude of infection throughout life, there are an abundance of possible interacting factors which lead to renal damage.

*What does the biopsy evidence suggest?*

Renal biopsies from the study community gave a further clue to the aetiology of the renal disease. There was considerable overlap in the biopsy findings reflecting the variety of renal insults. Glomerulomegaly with varying degrees of segmental and glomerulosclerosis was the most frequent finding, present in at least 76% of the biopsies. Mesangial proliferation was seen in 46% of biopsies and with specific diabetic changes often mixed with other pathology in 13%. Glomerulomegaly might be a compensatory response to a reduced number of glomeruli present at birth or represent a response to trophic factors. Possible causes include intrauterine or infant undernutrition and a genetic predisposition or a response to ongoing haemodynamic, metabolic or infectious insults (Howard, Davis et.al.).
SUMMARY.

Undernutrition remains a common problem in Aboriginal infants and children. Undernutrition leads to considerable short-term morbidity. The role of intra-uterine and early infant undernutrition in chronic adult disease is currently being defined.

There are many powerful factors acting on the ever increasing prevalence of renal disease amongst Aboriginal Australians. The "syndrome X" risk factors, hypertension, hyperinsulinaemia and NIDDM all contribute to renal damage. They are hypothesised to be brought about by early malnutrition (Barker), which is also suggested to reduce glomerular numbers in utero. Renal function is put at further risk with infectious insults prevalent in this environment.

In a setting with high levels of streptococcal infection, poor diet and low exercise levels there are many factors to explain the high renal disease rates. Knowledge of the relative importance of each risk factor is vital for the design of effective public health interventions.
METHODS.

Data were collected as part of the ongoing natural history study being conducted at Menzies School of Health Sciences since 1993.

Community Screening.

Mass screening of the children and adults living in the study community took place from 1992 to 1996 to evaluate the rates and associations of the renal disease in this high incidence community. In the children, screened through the school, the following parameters were investigated:

- weight
- height
- skin sore count and examination for scabies
- urinalysis and ACR
- streptococcal serology in children 10-17 years.

Adults were examined for height, weight, waist, hips, blood pressure, scabies, skin sores, weight, urinalysis and ACR, serum creatinine, liver function tests and an evaluation of glucose tolerance.

Examinations were performed by two research assistants and three aboriginal health workers and by myself in 1996. The heights, skin sore and scabies examinations were performed by the same person where possible, minimising inter-observer bias. The weights were measured on a digital scale and blood pressures by an automated system. All examinations were blinded.
Birthweight and Infant Weights.

Weights were recorded at birth, 6, 12, 18 and 24 months or the closest to these dates. Information was recorded from the birth registry, antenatal records and infant health cards kept at the community health clinic since 1955 and was collected by Megan Rees, Emma Kile and Dr. Wendy Hoy from 1994-5. This also included an exhaustive follow-up of missing information from Royal Darwin Hospital. There were insufficient records of length in infants for this to be used in the analysis.

Post Streptococcal Glomerulonephritis.

The clinic records were searched for a history of post-streptococcal glomerulonephritis, with the date noted. This group included patients with clinical symptoms of oedematous face, haematuria, and hypertension and, where noted, the biochemical markers of high ASOT and anti-DNAase titres and low complement levels. Additional names of cases were gained from lists of cases during identified epidemics in 1980, 1987 and 1994. The patients identified from the epidemics had clinical signs, raised asot and antiDNAase titres and most had complement levels measured as low.

Markers of Renal Disease.

The albumin to creatinine ratio (ACR) on a random urine specimen, was used as the primary renal disease marker, with instructions on techniques to minimise contamination during collection. The ACR adjusts albumin concentration for the variations in urine concentration over time. This assumes the creatinine excretion rate is fairly constant for each person and will give a reliable indication of urine
concentration. Creatinine levels can be affected by muscle mass (Gupta 1986). Women, having a lower muscle mass, have lower creatinine excretion and consequently an higher ACR at every albumin excretion level in comparison to men. It has been suggested that higher cut-offs be made for ACR in women to adjust for muscle size. Concerns that creatinine may vary with glycosuria in diabetic subjects, due to ketones falsely raising the creatinine estimates, have been refuted (Watts 1988).

Random urine specimens were used as this was the only feasible technique in mass screening, especially in aboriginal communities, and it eliminates logistic difficulties and reduces errors associated with poorly timed or fasting or first morning specimens. This technique has been extensively used in a variety of renal and epidemiological studies (Guest 1992, Iser 1995, Wollerton 1987, Nelson 1987, Consensus 1989). Older girls and women were asked to provide a urine sample on another occasion if they were menstruating at the time of screening.

Laboratory Techniques.

_Urine Specimens._

Urinary albumin levels were measured in the clinical laboratory of the Royal Darwin Hospital (RDH) using the portable Beckman Immuno-chemistry System (Brea, California). This nephelometric technique uses a monoclonal antibody that measures albumin concentrations down to less than 1 mg/L. This technique has been employed by the RDH since 1992 and is now widely used as a clinical service. The following categories were used according to accepted standards translated into international units: normal <1.1; suspicious 1.1 to 3.39; micro albuminuria 3.4 to 33.9; overt albuminuria 34 and above (Hoy et. al. 1989, Davis 1984, Woolerton 1987).
Urine specimens that tested positive for nitrates or leucocytes were sent for culture. If cultures were negative, and pyuria persisted, participants were referred to the clinic for testing for sexually transmitted disease. Of 34 urine specimens sent on children, (30 girls and 4 boys), 14 had less than $10^6$ organisms, 13 had an intermediate number and 5 (all girls) had a growth of $>10^8$/L. Only one child had symptoms of a UTI. Urine samples for the purpose of the current analysis were recollected after these problems had resolved.

At the start of the project attempts were made to send urine samples that tested $\geq$ “small” for blood, for examination for dysmorphic red cells, thought to suggest glomerular haematuria. Initially thiomersal, then formalin with dye, was used as the urine preservative, before shipment to and examination at RDH (where 20% or more of dysmorphic cells is considered significant). However, with sporadic indications, changing instructions and sometimes unavailability of preservative, this procedure failed to happen with regularity and was ultimately abandoned. These data are therefore incomplete.

**Streptococcal Serology.**

The serological analyses was undertaken by the Royal Darwin Hospital Laboratories. The laboratory changed tests for the ASOT levels in July 1994. An ASL-Kit by Biomerieux was the second test used for the ASO titre levels which titrates antistreptolysin O levels by a rapid test in strips. The principle is the neutralisation of a serum sample of haemolytic activity of streptolysin O, which is present in strips in a dehydrated form in increasing amounts. The reagent was standardised against a WHO reference. A Streptonase-B tube test by Wampole was used for quantitating the antiDNAse titre levels by enzyme inhibition. DNAse B depolarises the substrate DNA by its enzymic activity, however antibodies to DNAse
An idea about the growth patterns was gained by mapping out 50 children's birthweight and WAZ patterns over the first four years of life. The main exhibition (n=41) was of good weight gains with even partial catch-up over the first 6 months, followed by a fall to a minimum between 9 to 18 months and then a rise again. A much less common pattern (n=5) was rising Z scores through the first 3 years.

Z scores for weights from 1 to 5 months of age (WAZ_{45}) and weight from 13 to 24 months (WAZ_{13-24}) were compared with the values for the precise monthly measurements at 6 and 12 months. The difference in means was not statistically significant. It was concluded weights closest to 6 months from 1 month and the closest to 12 months from 24 months were adequate substitutes for individuals who had no absolute value for weight at 6 or 12 months. The groups used were 6 months or the closest figure from 1 to 6 months termed WAZ_{6} and weight at 12 months, or the closest figure from 13 to 24 months, termed WAZ_{12}.

<table>
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<th>Mean</th>
<th>S.D.</th>
<th>Difference</th>
<th>p value</th>
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<tr>
<td>WAZ at 12, (n=461)</td>
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<tr>
<td>WAZ_{13-24}, (n=71)</td>
<td>-1.52</td>
<td>1.13</td>
<td>-0.065</td>
<td>0.602</td>
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</tbody>
</table>

Early infant growth was analysed both as a continuous variable, and in four categories of weight-for-age Z scores: z less than -2, between -2 and -1, between -1 and 0 and above the WHO mean, 0. Dichotomous variables were also used: birthweight ≤2.5 kg was termed "low birthweight", for infant and childhood weight for age Z scores ≤-2 was termed "malnourished" and for height for age Z scores ≤-2 was termed "stunted".
Streptococcal Serology.

87% of children aged 10-17 consented to have their blood taken for streptococcal serology. ASOT titres were grouped into normal, raised and high categories initially. 59% of children were in the "normal" category, 29.6% in the "raised" and 1% in the "high" category. When the values in the normal range were further dissected out for better discrimination of range at the lower end, 38% were in the high normal group, which was defined as the highest titre for the normal range in both ASO titre tests.

When AntiDNAse titres were also divided into normal, raised and high categories. 80% were found to be in the high category, 18% in the raised and 2% within the normal range. The values for the high range were divided into three for a wider spread at the upper end of the scale. 34% were in the lowest category of high called raised, 26% in the middle, called high and 18% in the highest termed very high.

Statistical Procedures.

The data were checked for the presence of outliers and a normal distribution of the continuous variables. The distribution of early growth parameters was inspected and found to be normal. ACR was skewed so was transformed to a natural log. to bring about a more normal distribution. In addition ACR was divided into dummy variables, suspicious and above (≥1.1), elevated (≥3.4) and overt (≥34), each coded 1 and the lower values as 0. Other categorical variables included the presence of scabies, skin sores and a history of PSGN.

Data from children and adults were often analysed separately. This was not due to any difference in disease aetiology, however as ACR increased with age, different ACR cut-offs were needed for better discrimination.
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Author/s:
WALKER, KATE

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