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# Role of the kidney in the fetal programming of adult cardiovascular disease: an update

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It is well established that an adverse *in utero* environment can impinge upon fetal development and place the offspring on a track leading to future cardiovascular disease. Significantly, this may occur in the absence of any outward manifestations at birth. In this brief review, we focus on potential renal mechanisms that lead to adaptations in glomerular and tubular function that initiate hypertension of developmental origin and examine potential therapeutic interventions. This report updates recent data in this field.

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## Introduction

Once it was thought a fetus was conceived with a 'template' for development based on their parents' genes. As long as the growing fetus received the right nutrients and avoided harmful substances, this template would develop into a healthy baby. This view has been completely overturned. At each stage of development, the organism uses cues from its environment to decide how best to construct itself within the framework of its genes.

Indeed, in the last two decades it has become widely acknowledged that exposure to a poor intra-uterine environment increases the risk of cardiovascular, metabolic and renal disease in adulthood [1–3]. This has evolved into the '*developmental programming*' hypothesis that states if a fetus is exposed to a suboptimal environment it makes adaptive responses to ensure short-term survival, which alters fetal growth or development of particular organs leading in later life to increased risk of adult disease [4••]. More recently this hypothesis has evolved to also encompass perturbations that occur during the early postnatal period [5,6].

Epidemiological [7,8,9••], clinical [10•] and animal studies [1–3,11•] have demonstrated convincingly that, hypertension can be programmed by an adverse maternal or postnatal environment. These animal models offer the opportunity to explore the mechanisms involved in the initiation of hypertension of developmental origin and to investigate potential therapeutic interventions.

## Nephron complement

Suboptimal renal development, leading to reduced renal mass and a low nephron number is a common pattern observed in the fetal programming of hypertension and cardiovascular disease in animal models (i.e. maternal glucocorticoids, protein restriction or hypoxia); though this is not a universal finding [1,3,12–14]. Similarly, in humans, low birth weight (a surrogate marker of a poor *in utero* environment), has been shown to correlate strongly with a reduced nephron endowment [15]. In addition, studies in humans provide evidence that a low nephron number correlates with elevated blood pressure. Keller *et al*. [16•] showed that nephron number was significantly lower in people with demonstrated hypertension and similar findings have been reported in indigenous populations [9••]. Conversely, in transforming growth factor-beta2 heterozygous mice, a growth factor important in nephrogenesis, a high nephron number, has been suggested to protect against hypertension [17•]. Thus, nephron complement at birth appears to be a predictor of future cardiovascular risk.

## A reduction in glomerular podocyte number

A theory, that has gained increasing acceptance, is that reduced nephron endowment contributes to the development of hypertension. In 1988, Brenner and colleagues first postulated that reduced filtration surface area associated with a low nephron number would lead to sodium retention and ultimately the development of systemic hypertension as a compensatory response to maintain sodium homeostasis [18,19]. They further suggested that the elevation in systemic pressure would lead to glomerular hypertension, hypertrophy, hyperfiltration and ultimately glomerulosclerosis [18,19]. Such changes would lead to further reductions in filtration surface area, so initiating a vicious cycle leading to the exacerbation of systemic hypertension.

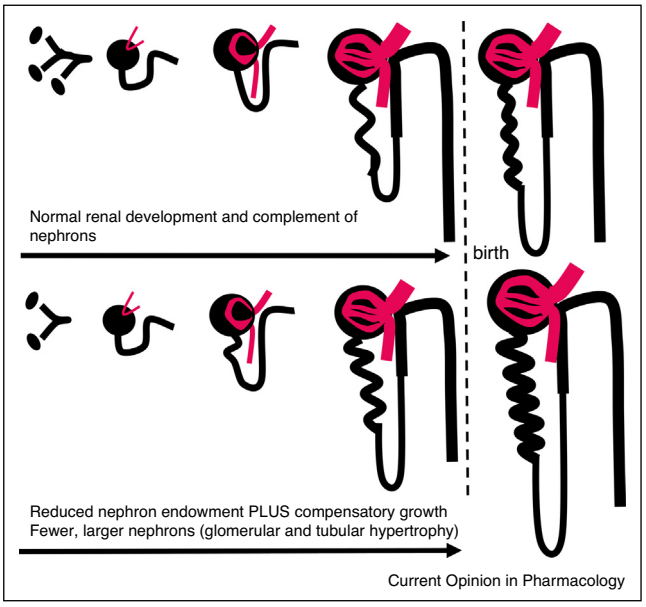
Podocytes as part of the glomerular filtration barrier help to oppose the normally high glomerular capillary pressure, act as a mechanical barrier to the filtration of large molecules and secrete a number of substances including the glomerular basement matrix. Loss of these cells is a hallmark of progressive renal disease. Thus, podocyte depletion may represent a unifying pathway via which this cycle of nephron loss ensues [20••]. In the situation of a low nephron number the podocytes, which have little capacity for proliferation and replacement, are required to cover an expanded glomerular filtration surface area as a result of glomerular hypertrophy [21•,22]. This may lead to podocyte detachment from the basement membrane and subsequent cell death. The expose of the underlying basement membrane results in glomerular sclerosis and a further reduction in the surface area available for filtration. Podocyte effacement has been observed in hypertensive offspring with low nephron number as a result of maternal protein restriction [23] and maternal exposure to di-(2-ethylhexyl)phthalate [24].

Thus, a considerable weight of evidence demonstrates a strong association between a reduced filtration surface area and hypertension [19,22]. However, an increasing number of studies, our own included, demonstrate that a reduced nephron number alone is not sufficient to cause adult hypertension [25•,26,27]. Although in some instances secondary factors such as a high-salt diet, have unmasked the negative effects of a nephron deficit [28•]. However, a kidney with a low nephron number maybe close to its functional capacity and therefore more susceptible to an additional insult such as an increase in excretory load associated with rapid postnatal growth. This may compound the effect of the reduction in filtration surface area leading to adaptations in tubular growth affecting the other major determinant of urinary sodium excretion, tubular sodium reabsorption.

## Renal adaptations to life *ex utero*

In the newborn, the kidney avidly retains sodium such that a state of positive sodium balance exists. This is essential for normal growth to occur. Thus, the developing kidney can conserve sodium efficiently. However, the young compared to the adult kidney has a reduced ability to excrete a sodium load (see [11•]). At birth, each nephron must rapidly adapt to takeover the role of maintaining extracellular fluid homeostasis from the placenta. In a kidney with fewer nephrons, the glomerulus and tubule will grow to a greater extent to handle its share of extracellular fluid, which will of necessity be larger (Figure 1). These changes will lead to alterations in the glomerular filtration barrier and in the mechanisms that normally regulate sodium reabsorption. In the short-term these adaptations will normalize renal function, but in the long-term will increase the risk of renal and cardiovascular disease.

**Figure 1**




Pictorial representation of the compensatory glomerular and tubular hypertrophy growth that occurs in a kidney with a reduced nephron endowment.

Nephrogenesis is complete prior to birth in humans and sheep, whereas it is complete at seven days after birth in the rat [29•]. Sheep and rats have been the most utilized species in studies of fetal programming. In the normal developing kidney, glomerular filtration rate (GFR), in absolute terms or relative to body weight, is low in newborn rat as compared to the adult. Adult levels are reached (when expressed per body size) in the human at about 1–2 years of age [30], the sheep at about three months of age [31] and 4–6 weeks of age in the rat; in total GFR increases ~25 fold over this period [11•]. The increase in GFR is in part caused by an increase in glomerular capillary hydrostatic pressure ~10% [32], in part by an increase in permeability of the glomerular capillaries ~5% [33], but the main factor in the postnatal rise in GFR is an increase in glomerular surface area [34]. The tubule also undergoes significant maturation (see [11•]).

## Impaired renal sodium handling

Sodium excretion by the kidney is tightly regulated, with urinary sodium output precisely matched to dietary intake. Powerful renal mechanisms ensure that changes in sodium intake are matched by equivalent increases or decreases in renal sodium excretion [35]. Thus the kidney plays a major role in the maintenance of an optimal internal fluid environment and the regulation of arterial pressure. It is widely accepted that sustained hypertension is not possible without an alteration in kidney function. It is proposed that renal compensatory adaptations