Introduction

Hypertension causes more deaths in developed countries than any other single condition (1). In the United States, the most recent American Heart Association statistics indicate that one in four adults has hypertension and 10 percent of all deaths can be directly attributed to this disorder (2). Despite this tremendous morbidity and mortality, the scientific community has still discovered relatively little about the etiology of chronically elevated blood pressure. Approximately 90-95% of cases are termed "essential hypertension" and have unknown cause, while the remaining cases are secondary to other disease processes and resolve along with disease treatment (1). A number of hypotheses have been suggested regarding the origin of essential hypertension, but none have proven definitive. It is probable that the etiology is multifactorial, given the number of systems involved in regulation of blood pressure, and different causes could be at work in different individuals (1).

In the late 1980s, a new hypothesis to account for some cases of hypertension was proposed based on observations of birth and death records in Britain from the early 20 th century. Researchers observed that regions of Britain where babies had the lowest birth weights (adjusted for gestational age) also had higher rates of death from coronary heart disease (CHD) (3). Furthermore, longitudinal studies of two large mixed-gender cohorts in Britain found that rates of death from CHD and stroke increased with lower birth weights as reported on birth records (3). Since both CHD and stroke are consequences of hypertension-induced end-organ damage, these findings led researchers to investigate whether low birth weight might increase incidence of hypertension later in life. Although the studies have obtained somewhat mixed results, experiments on animal models and epidemiological studies of human cohorts have generated intriguing evidence suggesting that low birth weight may indeed precipitate chronically elevated blood pressure.

II. THE HYPOTHESIS

Researchers first began to consider what differentiates low birth weight infants from those born in a normal weight range, and especially the relative roles of genetics and environment. yes"> From conception, nature and nurture begin to interact in determining the structure and function of a human being. It is known that the fetal genome determines an organism's growth potential, but the maternal intrauterine environment is a stronger determinant of actual growth achieved by the fetus (3). For example, in embryo transfer using donated ova, it is the recipient mother's weight that correlates best with the infant's birth weight, while there is no correlation between the infant's birth weight and the weight or birth weight of the donator or birth weights of the donating mother's other children (4). yes"> This situation illustrates the fact that maternal physiology (and possibly anatomy) exerts powerful effects on fetal growth.

Because intrauterine physiology influences fetal growth, and maternal nutrition affects intrauterine physiology, it was concluded that poor maternal nutrition may stunt fetal growth. In fact, epidemiological studies have confirmed this link in many cases (5). It is probable, however, that low birth weight is not the only consequence of maternal undernutrition and altered intrauterine physiology, but that other subtle developmental processes are also affected. While not grossly obvious, these effects may have long-term consequences (5).

This concept of "fetal programming" addresses the effects of the intrauterine physiological milieu on expression of the fetal genome, with long-term effects on cell number and type, organ structure, homeostatic set points, and metabolic activity in the body (3,6). yes"> An important mediator of these effects is timing, as certain organs and systems undergo rapid cell growth and maturation at critical periods of fetal development (3,6). Furthermore, developing mammals must be able to establish a degree of physiological autonomy from the mother in order to survive after birth, so mechanisms for regulation of essential processes must be set prenatally (5).

Based on these observations a number of studies have been conducted to examine the hypothesis that maternal undernutrition with consequent decreased levels of essential nutrients at a critical period prenatally might adversely affect establishment of blood pressure homeostasis.

III. THE EVIDENCE

Human Studies:

Before investigating the fetal programming hypothesis further, researchers had to prove that maternal undernutrition really does lead to blood pressure elevations later in life, as earlier studies had suggested. A large number of follow-up studies were performed, with various methodologies (see Discussion for comments on methodology).

One study in Aberdeen, Scotland retrieved birth weight records of 253 babies born from 1948-1954 and examined these individuals at 40 years of age for height, weight, and blood pressure. yes"> When blood pressure readings were adjusted for sex, age, body mass index and cuff size, adults with birth weights under 2.95 kg were found to have a mean blood pressure of 140/87, while those weighing more than 3.86 kg had a mean blood pressure of 132/77 (7). A Japanese study of 3-year-old subjects found similar results: those whose weight was over 3.52 kg at birth had 3 mm Hg lower mean systolic pressures than children whose birth weight was 2.99 kg or less (8). It is possible, therefore, that the discrepancy in blood pressures between high and low birth weight individuals increases over the lifespan.

A recent review of 34 studies investigating the relationship between birth weight and blood pressure in children and adults found in the majority of studies an inverse correlation that held at all ages except during adolescence (the authors hypothesized that this may be due to growth and hormonal changes) (9). These studies were performed in, among other countries, Great Britain, Sweden, Croatia, Jamaica, India, and the United States. The authors concluded, therefore, that the relationship between birth weight and increased blood pressure holds true, and researchers should begin investigating the mechanisms underlying this link (9).

Animal Models:

In order to study the mechanisms for birth weight effects on blood pressure, it became necessary to develop animal models. A number of experiments have been performed in the past five years, the majority using rats, guinea pigs, and lambs. The results have been interesting, and have added strength to the prenatal nutrition/hypertension hypothesis.

One of the earliest experiments involved ligation of the uterine artery in guinea pigs, which limits supply of maternal nutrients, blood gases, and hormones to the fetus (10). This experiment was shown to reduce fetal growth by up to 40 percent, and these pups showed blood pressure increases of 10 mm Hg (10). This experiment was complicated, however, by the number of factors affected by uterine artery ligation.

A model of fetal undernutrition in the rat found increases in blood pressure in offspring of mothers fed low protein diets during pregnancy. In a recent experiment, mothers fed a control diet containing 18% protein from casein had pups with a mean systolic blood pressure (SBP) of 103 mm Hg at 4 weeks old and 115 mm Hg at 12 weeks. Those fed a low protein diet containing 9% casein instead had pups with mean SBPs of 128 mm Hg at 4 weeks and 148 mm Hg at 12 weeks. Futhermore, protein restricted pups had significantly lower mean birth weights than controls. All pups and nursing mothers were returned to a full 18% casein diet after delivery, so nutritional restriction only occurred in utero (11). The reliability of this rat model had been confirmed in multiple studies, and is now standard for investigating mechanisms of nutritional deprivation in utero (12). Similar results have been found in rats consuming reduced-iron diets and those given overall 70% diet restriction (12).

The low-protein diet rat model has been studied closely, revealing that effects on blood pressure are independent of maternal blood pressure during pregnancy, last throughout the rat life span, and occur even if protein deprivation is not maintained throughout pregnancy. Pups exposed to low-protein in utero from days 0-7, 8-14, or 15-22 all showed increased SBP in postnatal life of between 9-20 mm Hg. Interestingly, the greatest effects were seen for protein deprivation during late gestation (12).

The prevailing hypothesis for the mechanism of lower birth weight effects has actually been in circulation since the early 1990s, but the rat model provided a new way to investigate its accuracy. Researchers suspected that maternal glucocorticoid hormones (cortisol and corticosterone) might be involved in the fetal programming of blood pressure. Glucocorticoids induce the expression of angiotensinogen, angiotensin-converting enzyme (ACE) and angiotensin II receptors, all important in the renin-angiotensin system (RAS) that regulates mammalian blood pressure. Furthermore these hormones are strong regulators of gene expression, growth, and cell maturation, and are known to reduce fetal growth when present in large amounts (10,12). yes"> Interesting evidence was uncovered in favor of an RAS role in programming the blood pressure control system when it was shown that adrenalectomy of female rats before pregnancy ablates the effects of low-protein diet on blood pressure in the pups (12).

In normal mammalian pregnancies, the fetus is protected from exposure to maternal glucocorticoids by the placental enzyme 11b-hydroxysteroid dehydrogenase (11b- OHSD), which inactivates these hormones (13). It was therefore hypothesized that maternal diet restriction might decrease the activity of this enzyme and therefore increase exposure to glucocorticoids in utero.

It was indeed found that the degree of 11b-OHSD activity in rat placenta does correlate positively with birth weight (12, 14) and inhibition of enzyme activity caused elevated blood pressure in adult rats equivalent to that obtained by low-protein diets (12). Furthermore, treatment of the pregnant female rats with dexamethasone (which resists inactivation by 11b-OHSD) decreases birth weight and increases blood pressure in later life (13).

IV. DISCUSSION

These animal experiments provide strong evidence for a link between prenatal nutrition and adult blood pressure, and for the involvement of glucocorticoids in fetal programming. It is unclear, however, whether these two findings are connected. Continuing experiments will undoubtedly investigate this issue.

Whether the same evidence applies to human physiology remains to be seen. In general, the elevations in blood pressure with decreased birth weight are measurable but not dramatic in humans. The correlation remains intriguing, however, especially considering that methodological difficulties in studying prenatal nutrition and development may be masking a more dramatic association. In human subjects it is extremely difficult to clarify fundamental issues such as: How much nutrient deprivation constitutes undernutrition, and which nutrients are the crucial ones? How do we quantify fetal undernourishment? When during pregnancy is the fetus most susceptible to the effects of undernutrition on blood pressure regulation? What mechanisms are responsible for this effect? How severe is the effect attributable solely to nutritional factors?

In fact, criticisms of the human studies were especially concerned with the fact that few studies actually measured nutritional intake of the mothers while pregnant, but instead inferred nutritional status based on the baby's birth weight (15). While birth weight is a rough indicator of maternal nutrition during pregnancy, other maternal and fetal factors complicate this relationship (5). Furthermore, adverse conditions in pregnancy may continue into postnatal life, so it is difficult to assess exactly when these factors act.

Considering the evidence, it is possible that undernutrition during human pregnancy does cause modest increases in adult blood pressures. This link is important however, given the medical consequences of blood pressure elevation. It is unlikely, given the small degree of increase found, that maternal nutrition is the sole factor influencing adult blood pressure. Hypertension is more likely attributable to a number of factors, genetic, behavioral, and environmental. Continuing studies will examine the maternal nutrition/hypertension hypothesis further, but until then, mothers and medical practitioners should keep in mind the importance of good diet during pregnancy and its possible role in the long-term health of offspring. These considerations are especially important among those with limited access to health care or in parts of the world where food restriction is a common occurrence.

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