

The Developmental Origins of Adult Human Disease

Teratogenesis is usually associated with congenital disease (i.e., a condition appearing at birth) and is also associated with disruptions of organogenesis during the embryonic period. However, David Barker and colleagues (1994a,b) have offered evidence that certain adult-onset diseases may also result from conditions in the uterus prior to birth. Based on epidemiological evidence, they hypothesize that there are critical periods of development during which certain physiological insults or stimuli can cause specific changes in the body. The “Barker hypothesis” postulates that certain adult anatomical and physiological parameters become established during embryonic and fetal development, and that deficits in nutrition during this time can produce permanent changes in the pattern of metabolic activity—changes that can predispose the adult to particular diseases.

Undernutrition and the adult phenotype

Specifically, Barker and colleagues showed that infants whose mothers experienced protein deprivation (because of wars, famines, or migrations) during certain months of pregnancy were at high risk for having certain diseases as adults. Undernutrition during a fetus’s first trimester could lead to hypertension and strokes in adult life, whereas those fetuses experiencing undernutrition during the second trimester had a high risk of developing heart disease and diabetes as adults. Those fetuses experiencing undernutrition during the third trimester were prone to blood clotting defects as adults.

Recent studies have tried to determine whether there are physiological or anatomical reasons for these correlations (Gluckman and Hanson 2004, 2005; Lau and Rogers 2005). Anatomically, undernutrition can change the number of cells produced during a critical time of organ formation. When pregnant rats are fed low-protein diets at certain times during their pregnancy, the resulting offspring are at high risk for hypertension as adults. The poor diet appears to cause low nephron numbers in the adult kidney (see Moritz et al. 2003). In humans, the number of nephrons present in the kidneys of men with hypertension was only about half the number found in men without hypertension (Keller et al. 2003). In addition, the glomeruli (the blood-filtering unit of the nephron) of hypertensive men were larger than those in control subjects.

Similar trends have been reported for non-insulin dependent (Type II) diabetes and glucose intolerance (Hales et al. 1991; Hales and Barker 1992). Here, poor nutrition reduces the number of β cells in the pancreas and hence the ability to synthesize insulin. Undernutrition in rats changes the histological architecture in the liver as well. A low-protein diet during gestation appeared to increase the amount of periportal cells that produce the glucose-synthesizing enzyme phosphoenolpyruvate carboxykinase while decreasing the number of perivenous cells that synthesize the glucose-degrading enzyme glucokinase in the offspring (Burns et al. 1997). These changes may be coordinated by glucocorticoid hormones that are stimulated by malnutrition and which act to conserve resources, even though such actions might make the person prone to hypertension later in life (see Fowden and Forhead 2004). Since, historically, most humans died before age 50 (see Chapter 23), this would not be a detrimental evolutionary trade-off.ⁱ

The “thrifty phenotype”

Hales and Barker (2001) proposed the existence of a “thrifty phenotype” wherein a malnourished fetus is “programmed” to expect an energy-deficient environment. The developing fetus sets its biochemical parameters to conserve energy and store fat.* Those who as adults do indeed meet with the expected poor environment are ready for it and can survive better than individuals whose metabolisms were set to use energy rather than store it as fat. However, if such a “deprivationally developed” person lives in an energy- and protein-rich environment, their cells store more fats and their heart and kidneys have developed to survive more stringent conditions—both developments that put the person at risk for several adult-onset diseases. It appears the fetus is making developmental decisions in response to low nutrient intake that anticipate its living after birth in a nutritionally deprived environment. Accordingly, it “expects” to stay small and thin and programs its development accordingly. However, if it is born into a nutritionally abundant environment, the thrifty phenotype that the fetus selected stores the extra calories and causes the person to become obese and at risk for cardiovascular problems. This has been called the “environmental mismatch hypothesis” (Figure 1; Gluckman and Hanson 2005).

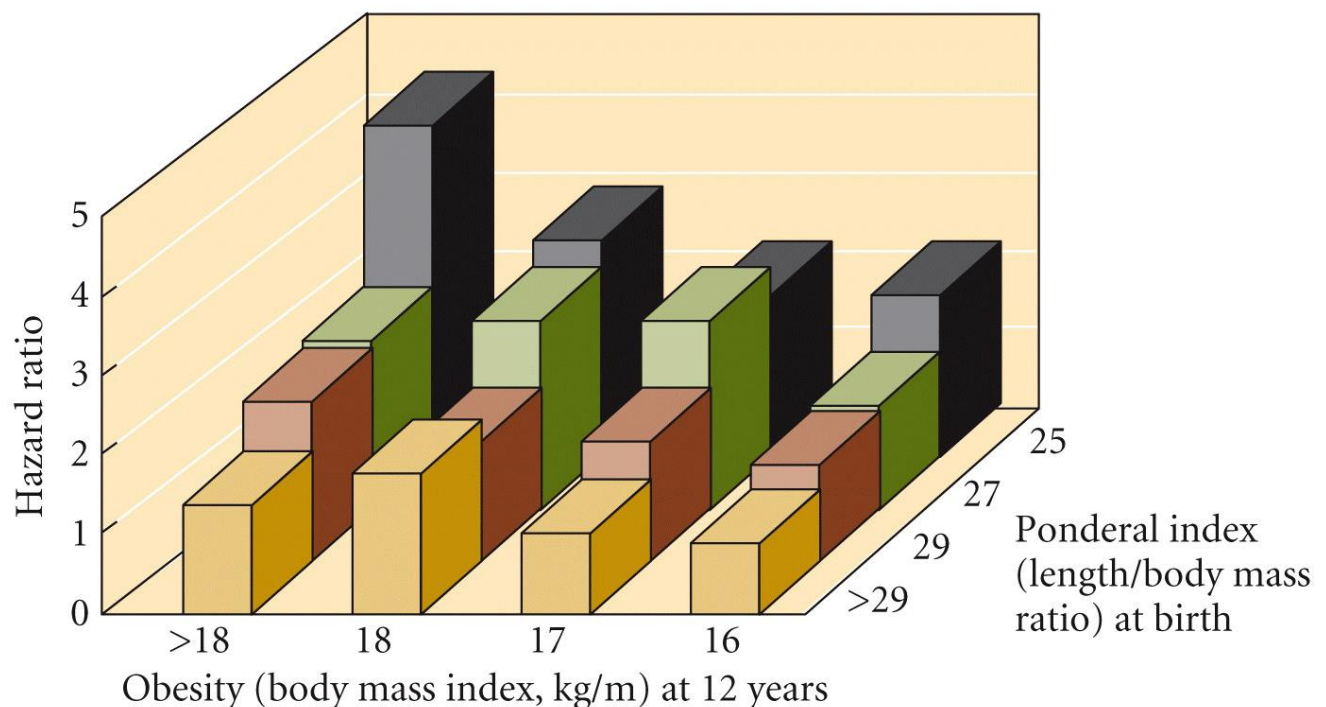


Figure 1 Environmental mismatch. The risk of coronary disease is increased by small birth size (poor prenatal nutrition) followed by greater eating in childhood. The prenatal conditions cause the expectation of a low caloric environment and set gene expression for a “thrifty phenotype” that conserves fat. This mismatch between the expected and the actual environment can make the person susceptible to conditions such as artery blockage. (After Eriksson et al. 2001.)

How can conditions experienced in the uterus create anatomical and biochemical conditions that will be maintained throughout adulthood? One place to look is DNA methylation. Lillycrop and colleagues (2005) have shown that rats born to mothers having a low-protein diet had a different pattern of liver gene methylation than did the offspring of mothers fed a normal diet. These differences in methylation changed the metabolic profile of the rats’ livers. For instance, the methylation of the promoter region of the *PPARα* gene (which is critical in the regulation of carbohydrate and lipid metabolism) is 20% lower in the offspring of protein-restricted rats, and the

gene's transcriptional activity is tenfold greater (Figure 2). Moreover, the difference between these methylation patterns can be abolished by including folate in the protein-restricted diet.ⁱⁱ Thus, the difference in methylation probably results from changes in folate metabolism caused by the limited amount of protein available to the fetus.

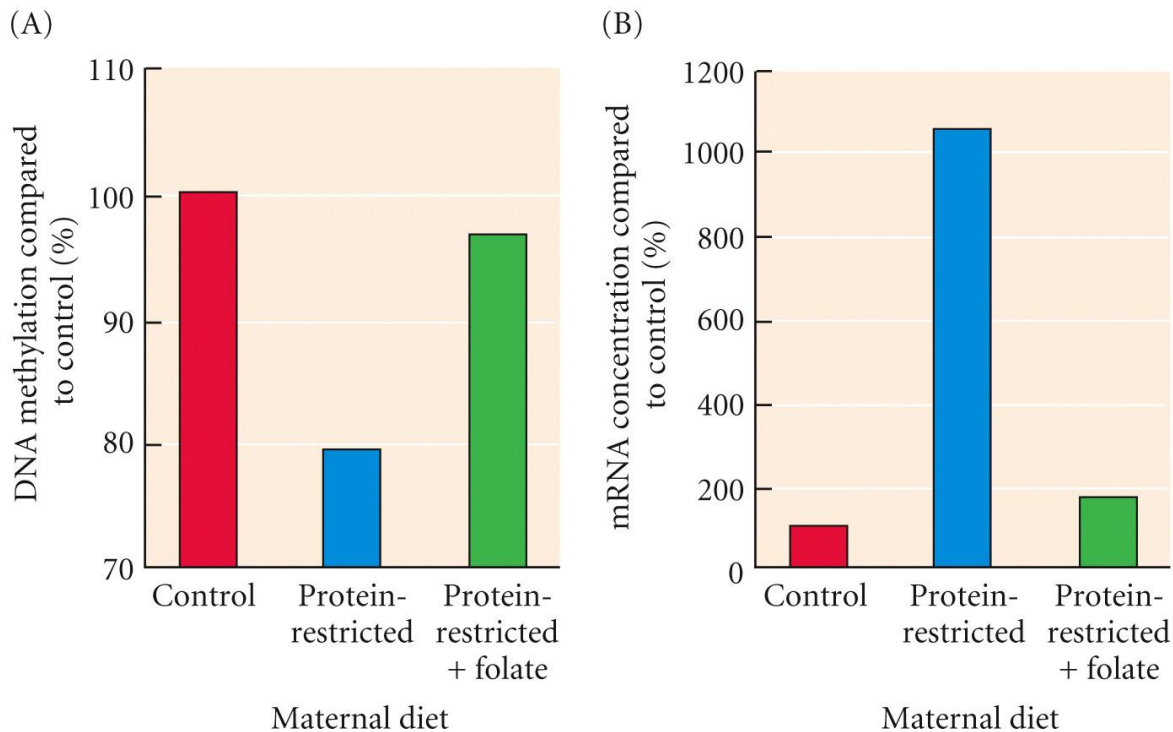


Figure 2 Activity of the liver gene for peroxisomal proliferator-activated receptor (PPAR α) is susceptible to dietary differences. (A) DNA methylation pattern of the PPAR α promoter region, showing highly methylated control promoters compared with poorly methylated promoters from the livers of mice whose mothers had protein-restricted diets ($p < 0.001$). Adding folate to the protein-restricted diet abolished this difference. (B) Levels of mRNA for the PPAR α gene were much higher in the mice fed the protein-restricted diet ($p < 0.0001$). (After Lillycrop et al. 2005.)

Prenatal nutrition appears to possess the ability to induce long-lasting, gene-specific alterations in transcriptional activity and metabolism. The prevention of adult disease through prenatal diet could thus become a public health issue in the coming decades.

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ⁱ In other words, the fetus is displaying phenotypic plasticity—the ability to modulate its phenotype depending on the environment. Environmental factors, not the genes, are determining the phenotype.

ⁱⁱ Although the folate supplementation of foods has probably caused a major decrease in the number of babies born with neural tube defects (see Chapter 13), aggressive folate supplementation during pregnancy may actually be teratogenic (Marean et al. 2011; Mikael et al. 2013; Vasquez et al. 2013).