

The Dutch Hunger Winter and the developmental origins of health and disease

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In the early 1980s, David Barker and others noted a paradox: although overall rates of cardiovascular disease increase with rising national prosperity, the least prosperous residents of a wealthy nation suffer the highest rates. He and others proposed over a series of studies that an adverse fetal environment followed by plentiful food in adulthood may be a recipe for adult chronic disease, a claim referred to as the Barker Hypothesis. These studies generally correlated birth weight and other infant parameters to the incidence of adult disease. Detractors, including an editorial in *BMJ* in 1995, complained that “[e]arly nutrition is inferred indirectly from fetal and infant growth, and fetal growth especially is a doubtful surrogate measure” (1). Most of the epidemiological studies were also vulnerable to confounding factors, particularly social class, that influence both intrauterine and adult environment, which delayed acceptance of the hypothesis. In *PNAS*, Rooij et al. (2) present another chapter in the ongoing study of the children of the Dutch Hunger Winter, a key test of the hypothesis (2). They show that, in addition to the previously shown effects of food restriction in utero on metabolism and cardiovascular health, there are effects on age-associated decline of cognitive functions. In the winter and spring of 1944 after a railway strike, the German occupation limited rations such that people, including pregnant women, in the western region of The Netherlands, including Amsterdam, received as little as 400–800 calories/d. The famine affected people of all social classes and was followed by growing prosperity in the postwar period. Thus, the Dutch Hunger Winter study, from which results were first published in 1976, provides an almost perfectly designed, although tragic, human experiment in the effects of intrauterine deprivation on subsequent adult health. This study has provided crucial support and fundamental insights for the growing field of the developmental origins of health and disease (DOHaD).

Birth Weight

One of the important observations from the Dutch Hunger Winter Study was that intrauterine exposures that have long-lasting consequences for adult health do not necessarily result in altered birth weight. Women exposed to the famine

during mid- to late gestation had babies with significantly reduced birth weights. Babies whose mothers were exposed only during early gestation had normal birth weights; however, they grew up to have higher rates of obesity than those born before and after the war and higher rates than those exposed during mid- to late gestation (3). Thus, although reduced birth weight is the most easily measured proxy for intrauterine deprivation, it is not

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the cause of later adult disease, and it does not always accompany the types of exposure that lead to adult disease. The programming of adult obesity by intrauterine food restriction without accompanying changes in birth weight has been replicated in rodent and sheep animal models (4, 5).

Critical Periods of Development

A related observation from the Dutch Hunger Winter Study has been the importance of timing in the programming of adult disease. Those who were exposed to the famine only during late gestation were born small and continued to be small throughout their lives, with lower rates of obesity as adults than in those born before and after the famine. However, as indicated above, those exposed during early gestation experienced elevated rates of obesity, altered lipid profiles, and cardiovascular disease. In contrast, markers of reduced renal function were specific to those exposed in mid-pregnancy (3). This idea is extended in the paper by Rooij et al. (2), which shows that only in those exposed to famine during early gestation is there a significant impairment in a test of selective attention at ages 56–59 y. The concept that there are critical windows during development existed before the DOHaD hypothesis, and it is relatively easily tested in laboratory animal experiments (4, 5). However, there is no ethical way to test prospectively for critical periods in human development, and such in-

formation is almost impossible to glean from most epidemiological studies. Hence, the Dutch Hunger Winter study is important because of its ability to provide insight into how a starvation diet during limited periods of gestation influences subsequent health of the offspring.

Interestingly, although the importance of exposure during early gestation was identified nearly 35 y ago, the reason that this period is important is still not fully understood. As discussed by Rooij et al. (2), CNS structures are formed in the first trimester of pregnancy, and changes underlying mental illness, altered appetite regulation centers, or even later declines in cognitive function likely occur during this period. Others have shown that alterations in placental growth, which outstrip that of the fetus in early gestation, are programmed by food restriction (6, 7). Because the placenta is responsible for providing the fetus with nutrients and oxygen and because it releases hormones that adapt the mother to fetal needs, any transient exposure to deprivation or excess affecting placental development can affect the fetus at later stages. Finally, animal experiments have shown that even nutritional changes occurring only during oocyte development and very early in gestation may permanently alter the methylation status of many genes and probably their subsequent expression (8).

Inappropriate Adaptation

One of the predictions made by the DOHaD is that fetal adaptations to scarcity become maladaptive only when affected individuals are later exposed to an environment of plenty. This is dramatically shown by comparing those exposed to the Dutch Hunger Winter with babies born after the siege of Leningrad. In both cases, pregnant women were exposed to severe famine. However, whereas The Netherlands returned to a complete diet quite quickly after the time of severe restriction, there were continuing shortages in the U.S.S.R., where those exposed to famine in utero did not exhibit higher rates of either obesity or cardio-

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vascular disease as adults (9). It should be emphasized that those exposed to the Dutch Hunger Winter during late gestation (i.e., were born a few months into the famine) were also exposed during early infancy, whereas those exposed during early gestation (i.e., near the end of the famine) were born several months after the war when diets had improved. The importance of catch-up growth after adverse intrauterine conditions to the programming phenomenon has since been shown in numerous animal studies (10, 11).

New Directions

DOHaD has expanded considerably beyond examining the effects of nutrient restriction on subsequent rates of adult obesity and cardiovascular risks. The effects of other intrauterine exposures such as environmental toxicants (12), maternal disease states (13), and overnutrition on adult health have now been shown. Additional endpoints are also being examined, as in the PNAS report of accelerated cognitive aging in those exposed to the Dutch Hunger Winter during early

gestation (2). Although the DOHaD field began largely within epidemiology and reproductive biology, studies like this one necessarily involve expertise in other areas, including psychology, developmental biology, and physiology of numerous systems. Much of the 20th century was dominated by debates about nature versus nurture. The DOHaD field has helped us come to a more nuanced understanding of the inseparable actions of nature and nurture that will inform biological investigations in multiple fields moving forward.

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