

## Letter to the Editor

The origins of the developmental origins hypothesis and the role of postnatal environments: response to Koletzko

Professor Koletzko's recent letter to the editor [*AJHB* 17(3): 381–382] was in reference to the journal volume devoted to the 2004 Human Biology Association plenary session, "The fetal origins of developmental plasticity: life history, adaptation, and disease" [*AJHB* 17(1)]. Koletzko raises questions about the intellectual lineage of the hypothesis that early environments have lasting effects on health. He further suggests that the volume's contributions "only focus on fetal programming" (p. 381) and thereby ignore the importance of the postnatal environment to the development of cardiovascular risk. As one of the organizers of the session and a co-editor of that volume, I would point out that our aim was to promote evolutionary approaches to this literature, which until recently has been dominated by biomedical models of the proximate determinants of disease (Kuzawa and Pike, 2005). I would further point out that many of the volume's contributions did in fact discuss the importance of both pre- and postnatal environments as long-term influences on life history, function, and health. That said, the letter does raise several general issues that deserve a thoughtful response.

Koletzko suggests that the developmental origins hypothesis should be attributed to Günter Dörner, whose important work on the organizational effects of prenatal hormones on the developing brain included speculations on the possible long-term health effects of these processes, including a connection between early overnutrition and later obesity (Dörner, 1975). In fact, the hypothesis that early environmental deprivation might condition future health and mortality was first proposed much earlier by Kermack, McKendrick, and McKinlay, who documented birth cohort effects on mortality in Sweden, England, and Wales. In a 1934 article published in the *Lancet*, they noted that secular trends in mortality were predicted by year of birth and concluded that "the expectation of life was determined by the conditions which existed during the child's earlier years," an

observation that confirmed and extended work by several actuaries published in 1927 (Smith and Kuh, 2001). Forsdahl (1977, 1978) later provided additional support for this hypothesis from analysis of Norwegian demographic data and expanded the focus specifically to cardiovascular risk factors.

Ounsted and colleagues (1985) may have been the first to report an inverse relationship between birth weight and later blood pressure, while a decade prior, Ravelli and colleagues (1976) found an increased risk of adult obesity among individuals exposed to the Dutch Famine during the first trimester of pregnancy. In a lesser-known, earlier study published in the *American Journal of Physical Anthropology*, Rashad and Mi (1975) reported a relationship between fingerprint ridge counts and myocardial infarction, leading them to propose an influence of prenatal factors on cardiovascular disease risk. Clearly, many researchers have independently discovered similar relationships, and in some cases have converged upon similar hypotheses. Barker and collaborators (1989) have done much to develop and promote the currently favored hypothesis, which draws heavily upon prior research into such factors as critical period effects of nutrition on early growth (Winick and Noble, 1966), maternal constraint on offspring birth size (Walton and Hammond, 1938), organizational effects of prenatal hormonal exposures (Dörner, 1975), the hormonal and nutritional regulation of placental and fetal growth (Gluckman, 1986), and catch-up growth (Prader et al., 1963). The field has recently settled on the label "developmental origins of health and disease" (DOHaD), which seems an appropriate descriptor that acknowledges not only the prenatal but also the postnatal contributions to long-term health.

On this note, it would be difficult not to agree with Koletzko's suggestion that developmental processes after birth continue to have implications for adult health, a point made by multiple contributors to the *AJHB* volume. The relative importance of exposures at different ages has been a subject of debate for some time. Lucas and colleagues (1999) noted that when the relationship between small birth size and later CVD risk is significant only after holding adult size constant, this may be capturing an effect of the change in size between the two measurements, or postnatal centile crossing. Singhal

and Lucas (2004) have since extended this idea to hypothesize that postnatal catch-up growth may be a “unifying hypothesis,” or a final common pathway, linking early developmental processes to adult health. In this spirit, Koletzko suggests in his letter that the “interpretation [that prenatal growth restriction increases adult CVD risk] has recently been challenged based on the observation that low-birth weight is associated with catch-up growth after birth, and accelerated weight gain by itself seems to be a risk factor for later disease” (p. 381).

However, this narrow interpretation of the data is problematic, as it ignores the extensive animal-model literature documenting prenatal influences on a wide range of biological systems. It also assumes that birth weight is the most appropriate basis for evaluating their effect in humans. As many have discussed, it was merely a fortunate accident that such a routinely recorded and crude measure of early growth was found to predict a number of disease outcomes (Gluckman and Hanson, 2004). Countless animal studies have now shown that nutrition and other exposures during the periconceptual (Kwong et al., 2000), prenatal (Seckl and Meaney, 2004), and early postnatal (Weaver et al., 2004) periods may have lasting effects on physiology and metabolism, with or without growth restriction. Experimentalists can isolate and control exposures with precision, thereby uncovering the timing of critical periods. Of course, the observational designs in the human literature generally do not have this luxury and are therefore forced to use rough proxies that are not specific to the timing or type of exposure. Because prenatal and postnatal growth are part of the same developmental trajectory, it is particularly difficult to disentangle their independent associations with later outcomes.

When human studies are forced to use measures like growth as a marker for underlying exposures, their findings are not consistent with Koletzko’s suggestion that “evidence for the fetal origins hypothesis may be a statistical artifact” (p. 381). For one, under the assumption that causes precede effects, it is difficult to see how one could ascribe causal primacy to the catch-up growth triggered in response to prenatal growth restriction, as this interpretation of the data would require. Moreover, when studies find that postnatal centile crossing is a

stronger predictor of later blood pressure than is birth weight, it is not clear how this finding should be interpreted, because the cross-sectional measure of birth weight (an outcome) is not directly comparable to the longitudinal measure of postnatal centile crossing (process). We typically have no way of evaluating centile crossing during *prenatal* life, because in most studies body size is first measured at birth, after fetal growth is already complete. Nor do we know the growth potential of that fetus, which may have ended up small for genetic or perhaps epigenetic reasons rather than as a result of nutritional restriction and growth impairment (Chard et al., 1993; Kuzawa and Adair, 2004). The point is that birth weight does not measure fetal growth in the same way that catch up or catch-down growth measures postnatal growth—they are not comparable. The inconsistencies in the catch-up growth literature, which vary widely in the timing, direction, and strength of documented effects of postnatal growth on later risk factors (Adair and Cole, 2003; Lundgren et al., 2001), suggest that growth per se may not be important. Rather, like birth weight, postnatal growth may merely be a marker for underlying proximate influences that are less routinely measured.

It should be emphasized that dichotomizing the role of exposures before and after birth runs the risk of obscuring the fact that they likely influence health not as independent, additive effects, but in interaction with each other. Any effects of postnatal nutrition or hormonal exposures play out on a biological “matrix” established in utero (Gluckman and Hanson, 2005), itself reflecting the influence of a mix of hereditary (genetic, epigenetic) and experiential factors (Oyama, 2001). Building from the hypothesis that prenatal nutrition provides the fetus with a signal predictive of future nutritional ecology, a number of authors have discussed the health consequences that might result when this cue is unreliable as a result of rapid postnatal ecologic change (Bateson et al., 2004; Gluckman and Hanson, 2005; Hales and Barker, 1992; Kuzawa, 2005), an idea increasingly supported by animal-model work (Kahn et al., 2004). It may be that the relative improvement in nutritional sufficiency reflected in postnatal catch-up growth is one example of such an interaction between exposures at different ages.

As highlighted by the contributions to the *AJHB* volume, the answer to many of the important questions raised by the developmental-origins hypothesis will require input from fields beyond biomedicine and epidemiology. An interdisciplinary approach drawing from comparative biology, ecology, evolutionary theory, developmental genetics, and human population biology will be necessary to reconstruct the origin and function of these early-life responses, which should greatly improve our understanding of the long-term developmental and health trajectories that they set in motion in contemporary human populations.

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