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Enamel Hypoplasia and Early Mortality: Bioarcheological Support for the Barker Hypothesis

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The Barker hypothesis asserts that stressful events early in the life history of an individual have negative health consequences later in adulthood. The hypothesis initially focused on prenatal stressors as indicated by birth weight and related outcomes. This initial concern with the fetal phase of development led to its description as the "fetal programming" or "fetal origins" hypothesis. The realization that stressors in the postnatal phase had similar impacts on adult health has led to its latest characterization as the Developmental Origins of Health and Disease Hypothesis (DOHaD). In this paper, we review the history and evidence in support of the DOHaD hypothesis. We then introduce an untapped source of information on early life stress: enamel hypoplasias and other developmental defects of enamel. Enamel defects are nearly indelible records of physiological perturbations, or stress, to developing ameloblasts (enamel-forming cells). Furthermore, the location of the defects translates to specific periods of growth, providing a permanent temporal record of early life stressors from *in utero* to approximately twelve years of age. As we discuss, a handful of studies of different populations reveals that individuals with enamel defects that developed *in utero* and early in infant-childhood development tend to be subject to earlier adolescent or adult mortality.

The Barker hypothesis was coined in an editorial in the *British Medical Journal*[1] to describe the innovative and controversial idea that many adult diseases have their origins in fetal development. Named after David J. P. Barker, an epidemiologist at the University of Southampton, this hypothesis was initially met with skepticism. However, after a great deal of replication and testing, the Barker hypothesis has expanded into a widely accepted phenomenon. In this review, we add evidence from bioarcheology that supports the Barker hypothesis. The story of how it gained acceptance is revealed in a quarter-of-a-century journey in which many intellectual skirmishes were fought. We offer additional support for the Barker hypothesis from

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Figure 1. Ethel Margaret Burnside, the midwife whose records were the basis for testing the Barker hypothesis. Source: Hertofordshire Cohort Study. Southampton School of Medicine.

bioarcheological evidence that dental enamel defects occuring *in utero*, infancy, and childhood have a significant impact and, indeed, are associated with decreases in longevity.

The story begins when David Barker and Clive Osmond were examining the newly published *Atlas of Mortality from Selected Diseases in England and Wales, 1968–1978*[2] and were struck by maps of the distribution of cardiovascular diseases, which revealed a remarkable geographic pattern. Barker and Osmond expected to find the highest level of cardiovascular disease in the most affluent areas in Great Britain, since that would mirror the epidemiological trends for heart disease in the United States and other high-income nations. Instead, the maps presented them with a conundrum. The *Atlas* showed that in Wales and England, the highest ischemic heart disease mortality rates in 1968–1978 were in areas that had experienced high infant mortality rates six decades earlier (1921–1925).[3] To test this observation, they used the 212 geographic areas in Wales and England to evaluate the association between early infant mortality and later adult health.[3] They found respective correlations of 0.69 and 0.68 between rates of ischemic heart disease and rates of neonatal and postnatal deaths.

Barker, Osmond, and Law[4] then tested the earlier findings with additional data from the 212 localities in England and Wales, this time separately studying ischemic heart disease and stroke. The completeness and detail of infant mortality records from 1911 to 1968–1978 allowed them to examine rates of infant mortality at different ages and from different causes. For example, they could distinguish neonatal mortality (before 1 month of age) from postneonatal mortality (from 1 month to 1 year). Using these data, they were able to show two factors that were associated with cardiovascular disease (CVD). In the first group, CVD was associated with lower standards of living in which the fetus and infant were subjected to negative stressors; in the second group, CVD arose later in life and was linked to an affluent lifestyle.

While these associations were intriguing, Baker and his team needed a cohort to more rigorously test these earlier findings. Baker and coworkers[5] decided to use a national cohort sample of 9,921 ten-year-olds and 3,259 adults from Wales and England to show that systolic blood pressure was inversely related to birth weight, controlling for gestational age. The critical evidence that the findings were independent of gestational age confirmed that the observed relationships were related to compromised fetal growth.

Barker's group then began a relentless search for archival data that could provide an even more refined analysis. After reporting many false starts, in which he uncovered incomplete archives in hospitals, county halls, and other places, Barker uncovered the records of Ethel Margaret Burnside (Fig. 1), a midwife from Hertfordshire County, England, located 40 miles north of London.[6] Beginning in early 1911, Burnside had recorded birth information, weight at birth, weight at age one, method of feeding, and illnesses of those born in the county[6] (Fig. 2).

Barker and colleagues were able to link the birth records in the Burnside database with the subsequent death records of these individuals. Their cohort study[7] of linked individual-level birth and death data was completed by the Medical Research Centre Environmental Epidemiology Unit, which computerized Burnside's Hertfordshire County records. The resulting dataset contained information on mortality outcomes as of 1992 for more than 15,000 men and women born between 1911 and 1930. In the first study based on individuals rather than ecological data, they found that death rates from cardiovascular disease among women and men fell pro-

Figure 2. Ledger showing the format for Ethel Margaret Burnside's records that were used in testing the Barker hypothesis. Source: Hertofordshire Cohort Study. Southampton School of Medicine.

gressively between the low and high birth weights groups ($\chi^2 = 4.3$, p = 0.04 for women; $\chi^2 = 8.5$, p < 0.005 for men). In addition, they demonstrated that high levels of weight gain during infancy decreased men's risk of CVD while rapid weight gain after age two increased CVD risk.[8]

This led to the next step, in which Barker and colleagues examined a cohort of individuals from Hertfordshire born between 1920 and 1930 who were still alive.[7] This cohort provided an adequate sample of a group that was still living. Studies on this group demonstrated a link between low birth weight and a variety of health issues. The investigators found a relationship between stress during fetal development and a variety of adult diseases,[4,9] including hypertension,[10] respiratory disease,[11] type 2 diabetes,[12] insulin resistance and metabolic syndrome,[13] osteoporosis,[14] and sacropenia[15] (loss of muscle mass) later in life.[7]

In a subsequent extension of this study, known as the Hertfordshire Cohort Study (HCS), 3,000 men and women born between 1931 and 1939 from Burnside's data were included, allowing greater power to detect and characterize statistical associations. This cohort, which was a subsample of Burnside's database, has been subjected to an array of medical testing, including dual energy X-ray absorptiometry, which measures bone density. Subjects' proximal femora, lumbar spines, and knees were scanned.[7] The HCS again found that higher birth weight reduced the risk of circulatory disease mortality, decreased risk of mortality from falls,[16] and decreased risk of mortality from pneumonia, diabetes, and musculoskeletal disease in women.[17]

DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE HYPOTHESIS

The Barker hypothesis[18,19] has been called the fetal programming hypothesis,[20–23] the intrauterine growth restriction hypothesis,[24,25] and the prenatal programming hypothesis.[26] However, since many of the physiological features of adaptation occur in the postnatal phase of development,[27] the model has been reformulated as the DOHaD hypothesis.[28,29]

A growing body of animal research is beginning to elucidate the mechanism by which developmental changes in the fetus and during early life have an impact on adult morbidity and mortality. Animal studies[30,31] provide a model in which maternal physiology can be manipulated,[32] in ways that are not possible with humans. Such studies have revealed that feeding pregnant mice a protein-restricted diet played a decisive role in fetal programming, mediated by

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As the concern of the DOHaD moves beyond circulatory diseases, explanations other than the thrifty phenotype will have to be considered. Associations between prenatal or early childhood insults and many conditions may reflect disruption of normal developmental processes rather than any sort of adaptation.

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serum-and glucocorticoid-inducible kinase SGK-1, of hypertension in offspring.[33] There is also evidence that excessive exposure to glucocorticoids links fetal maturation and adult pathology, with transgenerational effects.[34] In sum, animal studies of fetal programming have supported the proposed pathways in humans for such conditions as hypertension,[35] vascular function,[36] metabolic syndrome,[37] and hyperphagia.[38]

EFFECTS: BEYOND CIRCULATORY DISEASE

While the effects of early stresses on diseases such as hypertension, coronary heart disease, and diabetes are best characterized and reinforce the relationship found in the original Barker hypothesis, increasing evidence suggests that other adult health outcomes are also profoundly influenced by experiences during early development. For example, multiple independent studies of infants whose mothers were exposed to famine early in pregnancy have shown an increased risk of developing schizophrenia.[39–41] Similarly, mothers subjected to extreme psychological stress early in pregnancy bear children with an increased risk of developing schizophrenia.[42,43]

Animal studies have demonstrated that early dysregulation in fetal programming of the hypothalamic-pituitary-adrenal (HPA) axis during especially sensitive periods of fetal development results in permanent neurological changes in offspring that affect behavior in complex ways.[44] The importance of HPA programming in response to insults is currently being investigated in humans.

There is also evidence that development of the immune system is affected by early life stressors, with lasting effects. For example, an association has been found between maternal respiratory infections during pregnancy and the risk of asthma in offspring.[45] In another sample, this relationship was also found for prenatal vaginal infections, as well as other types of febrile infection.[46] Various other disorders may also be related to the DOHaD hypothesis, including earlier onset of puberty,[47] osteoporosis,[48] small kidney size,[49,50] and kidney disease.[51]

WHY THE RELATIONSHIP EXISTS: A THRIFTY PHENOTYPE

The concept of the thrifty phenotype[52,53] has been developed to explain the impact of early life stressors on adult health. Supporters of this hypothesis propose that metabolic syndromes result from the impact of poor nutrition during the fetal, infant, and childhood periods, producing permanent changes in metabolism that affect adult health.[52] The thrifty phenotype hypothesis seems to correct unnecessary assumptions of the thrifty genotype hy-

pothesis,[54,55] that during the Paleolithic period there was selection for a suite of alleles well-adapted to the feast-or-famine environment. Such genetic adaptation would minimize metabolism in times of plenty to enhance the storage of fat that could be used in time of famine. However, the benefits of this once-favored genotype were rendered obsolete if its host lived in a modern, high-income environment characterized by an overabundance of nutrients. The thrifty phenotype hypothesis asserts that selection for genetic changes is not necessary to explain the metabolic syndromes proposed by James Neel's thrifty genotype hypothesis. Instead, it posits that early-life metabolic changes in uterine and childhood development aid survival of the fetus and child while having a negative impact on adult health.[56,57,62]

The thrifty phenotype hypothesis has been used to understand the development of type 2 diabetes, which originates in intrauterine life and is exacerbated by rapid childhood growth, resulting in a biphasic nutritional insult.[58] These fetal insults, followed by subsequent catch-up, are implicated in obesity[56,59] and higher body mass indexes (BMI). In an eight-year follow-up study, Meas and coworkers[60] showed that adults born small for gestational age exhibited a larger gain in BMI than did those who had an appropriate size for gestational age. As adults, they had greater fat mass with more abdominal fat, indicating that the effects of fetal growth restriction on body composition continue long beyond the early postnatal catch-up growth.

As the concern of the DOHaD moves beyond circulatory diseases, explanations other than the thrifty phenotype will have to be considered. Associations between prenatal or early childhood insults and many conditions may reflect disruption of normal developmental processes[61] rather than any sort of adaptation.

CRITICISMS OF THE BARKER HYPOTHESIS

While the studies that stemmed from Barker's hypothesis captured the interest of the medical commu-

nity, they were also met with skepticism.[61–63] Joseph and Kramer,[61] for example, questioned whether possible selection bias might be at work, since Barker and colleagues were only able to link birth and early weights with adult outcomes for 5,700 of the 15,664 individuals in the Burnside database. In support of this critique, they observed that individuals traced later, because of difficulty in linking data, differed in important respects from those traced earlier in the study.

In addition, they described the much-repeated argument that there is the possibility of confounding factors in linking coronary heart disease with childhood lifestyle and subsequent

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poverty,[62,63] as well as outlining inconsistencies within and between studies, conflicting evidence, and inability to replicate findings in animal studies. Subsequent meta-analyses have echoed some of these concerns. One, for example, concluded that claims of strong inverse associations between weight at birth and subsequent blood pressure may be attributable, in large part, to random error, the selective presentation of results, and inappropriate adjustments for current weight and confounders.[64] In fact, while the Barker hypothesis is intriguing, it is difficult not to view continued poverty as an overarching cause of both fetal growth retardation and adult health deprivations.

Studies of select cohorts exposed to famine during gestation have yielded mixed results. These results are of special interest because, typically, the whole population was exposed to the stress, eliminating some of the problems in controlling for SES and genotype. Studies of babies born during the Dutch Hunger Winter revealed that exposure during early gestation increased the odds of developing coronary heart diseases[65] and, in females only, increased BMI and waist circumference at the age 50 years.[65] In addition, babies exposed during late gestation experienced decreased glucose tolerance as adults.[66]

However, the results found in the Dutch cohort have not been replicated in other cohorts exposed to famine. A study of babies born during the nineteenth-century Finnish famine found no effect on mortality rates.[67] Similarly, those who were born during the siege of Leningrad displayed no increased glucose intolerance, hypertension, or cardiovascular disease as adults, though they did exhibit increased levels of markers of endothelial damage, as well as a stronger association between obesity and blood pressure.[68]

In twin studies, the effects of restricted *in utero* growth for babies in multiple births can be compared to singleton siblings, thus controlling for mother's socioeconomic status (SES) and genotype. One study analyzed within-pair differences in birth weight and adult blood pressure, finding a significant inverse association between the two.[69] However, a study using similar methods found no such association,[70] and another examining twins that were discordant for acute myocardial infection found no difference in birth measurements (weight, length, or head circumference) between affected individuals and their unaffected siblings or control twinpairs.[71] It was noted that the number of twins available for the latter study significantly limited the power of this analysis to detect differences.[72] This limitation is true of most twin studies, in which statistical power is rarely discussed. Studies of twins versus singleton births have also been performed, as twins tend to experience

growth retardation *in utero*. One such study on a large Danish sample found no relationship between being a twin and higher mortality rate after the age of six years.[73]

Because of the conflicting results arising from more rigorous tests of the Barker hypothesis, many skeptics[74] argue that much more research is needed in both humans and animals. At a minimum, it seems clear that while there is a strong general association between early life stresses and adult diseases, the results are variable. Certainly, on an individual level, early deprivation may be overcome and, at times, appears to leave no evidence. To the ample data on the impact of DOHaD on mortality, we add evidence from prehistory and ancient populations that supports the observation that early lifetime stressors have an influence on earlier mortality in these groups.

Figure 3. Enamel hypoplasia from the Chokepukio site, Cuzco region of Peru. Source: Valerie Andrushko.

EVIDENCE FROM BIOARCHEOLOGY

To expand the range of studies of the relationship between early life stresses and adult health, as well as to introduce new methods of tracking early life stress, we next consider bioarcheological evidence. We summarize the bioarcheological evidence for the Barker hypothesis. Current studies focus on the relationship between early development and chronic diseases such as coronary heart disease and diabetes. However, in most of human history and in many areas of the world today, these chronic adult conditions are not the most important threats to health. Rather, combinations of infection and endemic undernutrition have been and are the challenges that end the majority of human lives.

A wide variety of studies have demonstrated that earlier stressors have an impact on infection-related adult immunity, which affects life spans.[75] These studies have been able to link immunity and lifespan to months of birth.[76,77] Other factors that affect immunity,[78] including thymic function[79] and the impact of non-nutritional maternal illness on fetal growth[80] play a role in adult health, immunity, and

life span. We ask, then, whether in ancient populations a relationship between early life challenges and mortality can be found and, if so, what it means.

Dental enamel permanently records an organism's response to physiological and chemical conditions from the second trimester though early childhood. Furthermore, because teeth are abundant in the bioarcheological record and skeletons can be aged at the time of death, it is possible to link early conditions to longevity.

DEVELOPMENTAL DEFECTS OF ENAMEL

Dental enamel hypoplasia (Fig. 3), a well-studied class of developmental defects of enamel, provides a nearly indelible record of evidence of physiological disruption. In order for this type of defect to affect the permanent teeth, an insult must occur between birth, when enamel apposition begins in some permanent teeth, and around the beginning of adolescence, when third-molar apposition ends.[81] The deciduous teeth are affected earlier, from around the fifth fetal month to the tenth to twelfth postnatal month.[81] Since teeth are

not subject to remodeling, they remain a permanent record of these early events.[82] Only the loss of teeth due to dental disease or some other unfortunate incident, dental attrition, loss in height of enamel crowns and, in some cases, dental abrasion, a light wearing away of labial and lingual surfaces, would result in loss of this information.

In their discussion of linear enamel hypoplasia, Goodman and Rose[83] have described the wide variety of stressors that can initiate the physiological mechanisms that lead to changes in ameloblastic behavior and cause these enamel defects.[84] Nutritional deficiencies,[85] disease,[86] congenital abnormalities,[86] and trauma[87] are all reported to cause disruptions in matrix formation. For this reason, linear enamel hypoplasias (LEH) must be considered nonspecific indicators of stress.[88] In modern populations, for example, LEHs have been found in 18%–62% of the deciduous dentition of rural Guatemalan children,[89] but had a prevalence of 6% in the population of Iowa.[90] The nonspecific etiology of LEHs is the precise reason why they are often used as part of a toolkit of multiple stress indicators to assess physiological disruption in past populations.
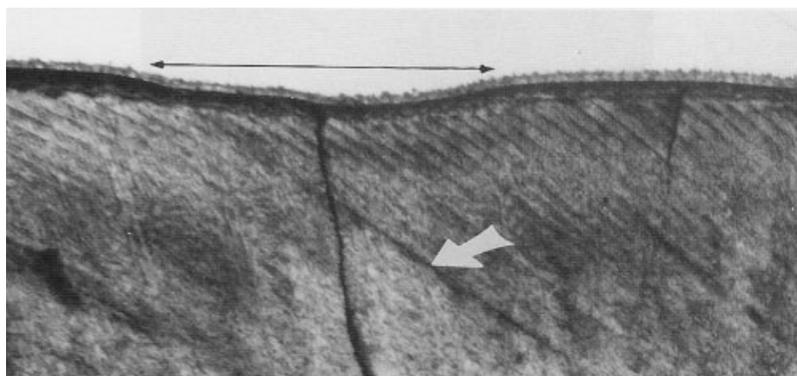
Figure 4. Hypoplasia beneath the double arrow and a Wilson band leading the formation of the hypoplasia labeled with an arrow (× 20). A second Wilson band located at the base of the arrow follows and is associated with an undulation in the floor of the hypoplasia. From Goodman and Rose.[83]

A description of how enamel hypoplasias occur may be helpful in understanding why they are indelible markers of stress that can be dated to precise periods of development. Because enamel is secreted in a regular ring-like fashion, the tooth's crown provides a permanent chronological record of any disruption in enamel development. Hypoplasias are caused by disruptions of ameloblast function during the secretary phase in which successive layers of enamel matrix are layed down.[91] In a sense, enamel hypoplasia provides a kymographic record that is a "window into the past." Since the chronology of enamel development in humans is well known,[92] it is possible to determine the age at which a physiological disruption caused the enamel hypoplasia.

Enamel hypocalcification is another type of defect. It occurs during the second stage of enamel development, when mineralization occurs. It produces a chalky band as extrinsic pigments are incorporated into the enamel. Hypocalcified enamel segments involve the deeper enamel, leaving the outer enamel "skin" intact, without the characteristic indentation of hypoplasias caused by matrix apposition.[91]

It is not necessary to analyze all teeth in order to gain information about an individual's health. Goodman, Rose, and Armelagos[93:526] suggested a "best tooth" analysis that includes two maxillary incisors and two mandibular canines; this approach reveals about 95% of the information that could be obtained if all teeth were examined. Researchers are explicit in reporting whether they used the total sample of dentition, performed "best tooth" analysis, or just examined a specific segment of the teeth that developed during a particular phase. For example, Goodman and Armelagos[82] used the segments of the teeth that mineralized from 3.5 to 7 years to assess the impact of enamel hypoplasia on adult mortality.

BIOARCHEOLOGICAL TESTS OF THE BARKER HYPOTHESIS

White[94] provided the first archeological evidence suggesting that childhood linear enamel hypoplasia is associated with lower age at mortality. White examined enamel hypoplasias on permanent maxillary first molars of Australopithecines from the South African Pleistocene (ca. 2.0–1.0 myr). He determined that individuals from the Swartkrans site with enamel hypoplasia on the first maxillary molar (N = 6) died earlier (between the ages of four and ten years) than did those without enamel defects. The individuals without enamel defects on their first molars (N = 100) died between 8 and 31 years of age. Subsequently, Goodman[95] used White's data and computed the mean age at death for those with LEHs as 7.8 years and those without LEHs as 19.6 years. Unlike subsequent studies, the difference in mean ages at death could be explained in part by the fact that older individuals had less enamel available for study due to enamel attrition and abrasion. However, even with this methodological possibility, small sample size, and problems inherent in analyzing age at death in fragmentary material, the nearly 12-year decrease in mean life expectancy associated with LEHs is remarkable.

Rose, Lallo, and Armelagos,[96] used histological techniques to study areas of disturbed enamel formation (Wilson bands) (Fig. 4) in Middle Woodland, Mississippian Acculturated Late Woodland, and Middle Mississippian samples from Dickson Mounds, Illinois. Remarkably, Wilson bands are not affected by surface abrasion. In this group who underwent a transition from horticulture to intensive agriculture, they found that individuals with Wilson bands, histological measures of stress, had an earlier mean age at death (26.7 years, N = 210) than did those without Wilson bands (42.1 years, N = 66). That is, individuals with a record of early life stress lived 15.4 years less than did those without the defect.

Cook and Buikstra[97] were the first to use a large sample to demonstrate that early mortality was greater in individuals who experienced stress events as measured by defects in enamel development during uterine development. In their benchmark study,[97] they analyzed LEHs in the deciduous teeth in pooled Middle (ca. 100 BCE to 500 CE) and Late Woodland populations from the Lower Illinois Valley. The Middle Woodland sample included individuals from the Gibson, Pete Klunk, Lawrence Gay, and the Joe Gay mound groups; the Late Woodland sample incorporated materials from the Gibson, Pete Klunk, Joe Gay, and Ledders mounds. The 170 children represented died during the interval from birth to seven years of age. The age at which these individuals suffered the stressors that produced the hypoplasias was determined to be from the fourth fetal month to a year after birth. We have pooled the data and constructed a survivorship curve comparing those with and without hypoplastic events (Fig. 5). It is evident that the survivorship of those without hypoplasias is greater.
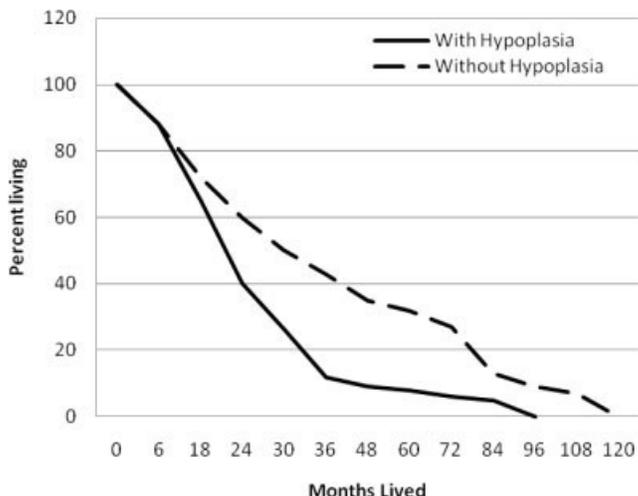
Figure 5. Survivorship (data from Cook and Buikstra,[97] Tables 3 and 4).

Following the work of Cook and Buikstra, Goodman and co-workers[92,93] analyzed the relationship between enamel defects and longevity at Dickson Mounds, another Mississippian sample. Using all permanent teeth except the third molar, 14 half-year periods from birth to 7.0 years were examined for enamel hypoplasias. The distribution of enamel hypoplasias by half-year intervals showed a peak between 2.5 to 3.5 years (Fig. 6).

Enamel hypoplasias are not benign markers of growth disruption. We can measure the impact of enamel hypoplasias by looking at the relationship between these growth disruptions and mean age at death (Fig. 7). Goodman and Armelagos[82] examined enamel defects between 3.5 and seven years of age and selected individuals without a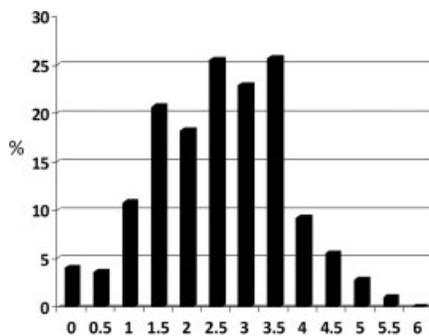ttrition that obliterated this time period. Studying earlier development would have been more difficult as older individuals displayed dental attrition that led to the loss of earlier developing enamel. They found that adults and adolescents with no evidence of enamel hypoplasias had a mean age at death of 35.8 years compared to 31.6 years for with those with a single hypoplasia and 25.6 years for those with two or more hypoplasias (t = 3.52 and P <0.001).

Another set of data is relevant to weaning and mortality. Blakey and Armelagos[91] analyzed the month of onset, duration, and incidence of dental enamel hypoplasia and hypocalcification on the deciduous dentition of 50 subadults from Dickson Mounds. The inclusion criteria for individuals in this sample were complete crown enamel development and the presence of at least four teeth. The information obtained for each member of the sample covered the entire 16 months of deciduous tooth development.

Nearly two-thirds (64%) of the 50 individuals showed evidence of at least one enamel defect. Among these individuals, 93.8% showed evidence of hypocalcified enamel and 56.3% had a hypoplasia. The incidence of enamel defects, including both enamel hypoplasias and hypocalcifications, steadily increased from the fifth prenatal month until the first postnatal month; this was followed by a steady decline until the eleventh postnatal month (Fig. 8). This pattern shows that as the fetus grows, it is more prone to growth disruption. Heinke and Kuzawa[80] have shown that symptoms of illness during pregnancy had a larger effect when they occurred later in gestation.

If we distinguish between enamel hypoplasia and hypocalcification (Fig. 9), an interesting pattern emerges. Hypocalcification peaks at the eighth prenatal month, while hypoplasia peaks during the first postnatal month. The impact of these enamel defects is evident from a survivorship curve (Fig. 10). All individuals with enamel defects have a greater rate of mortality, which peaks during the first year. However, individuals with hypocalcification show the greatest mortality. This may be related to the timing of the stress that causes them, as it occurs during critical phases of fetal development and may have a greater impact on subsequent mortality.
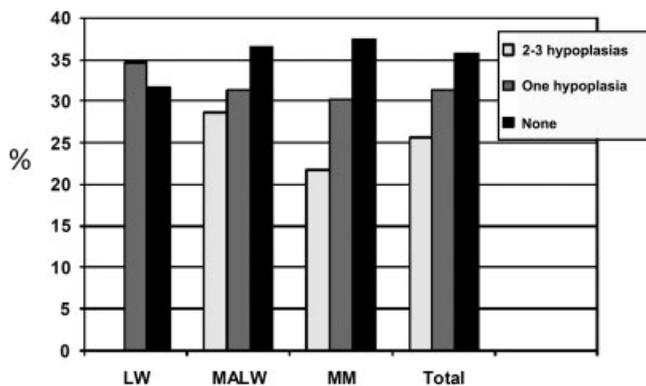

Figure 6. Frequency distribution of enamel hypoplasias by half-year intervals in Dickson Mounds. Modified from Goodman et al.[92,93]

Figure 7. Mean age at death of Dickson Mounds adolescents and adults by number of hypoplasia-stress periods between 3.5–7.0 years. LW, Late Woodland; MALW, Mississippian Acculturated Late Woodland; MM, Middle Mississippian. Modified from Goodman and Armelagos.[82]
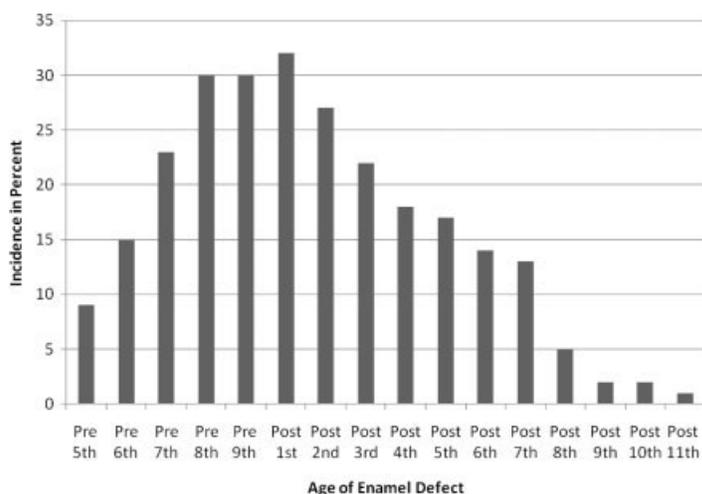
Figure 8. The incidence of enamel defects (combined hypoplasia and hypocalcification) in the deciduous dentition of the combined Dickson Mound population from prenatal month five to postnatal month eleven.

Duray[98] also found support for the hypothesis that developmental enamel defects represent stress-induced growth disruptions with long-term health effects. In a sample from the extensively studied Libben population from Ottawa County, Ohio, he demonstrated a relationship between enamel defects and age at death. He examined defects in the permanent dentitions of 143 individuals using the Developmental Defects of Enamel Index.[99] The population age at death was determined using multifactorial methods. Duray found a significantly lower mean age at death for individuals with enamel defects than among those without defects (Table 1).

The age-at-death distribution for individuals with enamel defects showed two peaks: one in the 15–20-year age class and one in the 30–35-year age class. Duray suggested that the earlier mortality of individuals with enamel defects may be due to biological damage to the immune system during prenatal or postnatal development. Among individuals with enamel defects, the mean age at death was 5.37 years lower (26.92 years compared to 32.29 years) than that among individuals with no enamel defects.[98] This result was significant at the 0.01 level (pooled t-test).

Duray also found a "dose response" effect between the severity of the hypoplastic events and age at death. Individuals with grade A or B linear enamel hypoplasias died, on average, 5.88 years younger (26.41 years) than did individuals without enamel defects (32.29 years) $(P < 0.004)$. The mean age at death for individuals with pitting hypoplasias (19.14 years) was 13.15 years lower than that for individuals without enamel defects $(P < 0.004)$. Individuals with demarcated hypocalcifications (24.65 years) died 7.64 years younger $(P < 0.003)$ and those with diffuse hypocalcifications (14.80 years) died 17.49 years younger $(P < 0.001)$ than did individuals without enamel defects.[98]

DISCUSSION

The relationship between physiological disruption and increased mortality rates in adulthood suggest at least three possible mechanisms.[82] The first is that there is a differential lifelong pattern of frailty to physiological disruption. That is, the frailty of these individuals may make them more susceptible to hypoplasia and also cause them to die earlier. In this scenario, the hypoplasias reflect a pre-existing condition rather than harsh early conditions that programmed the individual for later health problems. The second possibility is that the data could be interpreted as indicating a differential pattern of social, cultural, and behavioral exposure to stressors. In this scenario, individuals exhibiting enamel defects experienced high levels of stress as infants and children and continued to be differentially stressed as adults. Hypoplasias represent adverse environmental conditions that are characteristic of an individual's life. Here, a major criticism of the Barker hypothesis is that the impact of later environments is not adequately controlled. The last possibility is that the physiological stress that results in enamel defects may decrease individuals' ability to respond to further stressors. In a sense, these individuals are "biologically damaged" by these earlier stressors, in accordance with Barker's hypothesis. For example, it is possible that the immunological system may be compromised by the physiological disruption that has left its mark on the teeth.

Currently, there is no way to differentiate among these hypotheses. However, future studies may be able to tease apart the processes yielding
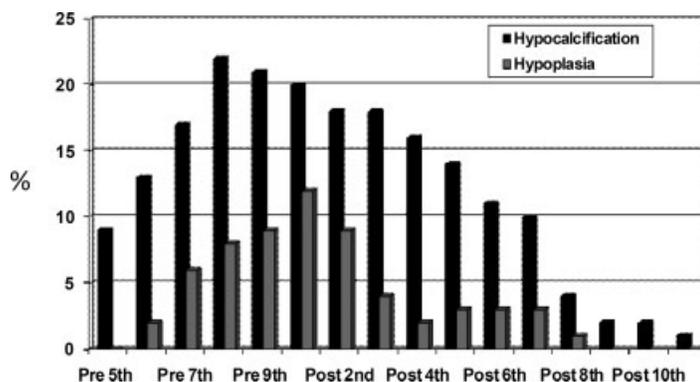

Figure 9. The incidence of enamel defects (hypoplasia and hypocalcification) in the deciduous dentition of the combined Dickson Mound population from prenatal month nine to postnatal month eleven. N=231. Modified from Blakey and Armelagos.[91]
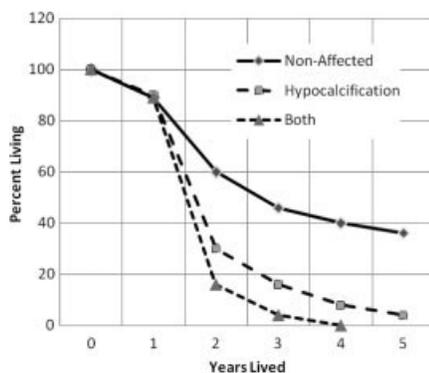
Figure 10. Survivorship of those with and without linear enamel hypoplasia and enamel hypocalcification. Modified from Blakey and Armelagos.[91]

these data. One useful approach could be to match hypoplasia data with markers of immune and neurological development that also are available in the skeletal record. For example, Clark and coworkers[100] used vertebral neural canals (VNC) as markers of childhood stress in an archeological population from Dickson Mounds, Illinois (950–1300 A.D.). They argued that VNC dimensions are stabilized by about four years of age and thus not only reflect early health conditions, but also mirror development of the neural and lymphatic organ systems. They linked reduced VNC diameters to decreased longevity in an archeological population and suggested the use of these diameters by modern xerography as a way to predict adult morbidity and mortality in living populations. They[100] tested the associations between early growth and adult health by measuring 2,060 VNCs, vertebral heights, vertebral wedging, nerve-root tunnel lengths, severity of vertebral osteophytosis, and ages at death in 90 adults (aged 15-55 years). In a subsample (n = 30), they also measured tibial lengths, which can experience catch-up growth. Statisti-

cal analyses showed that small VNCs were significantly associated with greater vertebral wedging and decreased life span (P < 0.05–0.001). VNCs were independent of vertebral body heights and tibial lengths (general body growth). VNCs, but not statural components, were useful in predicting adult health, presumably because they reflect neural and immune development and do not readily experience catch-up growth. If enamel hypoplasias are also correlated with VNC measurements, then it would indicate that important developmental processes are altered early in life, with subsequent effects on later life. This would be consistent with the third possibility, supporting the Barker hypothesis.

Additional studies may also aid in differentiating among these possibilities. Individuals from large samples may be differentiated into "treatment" groups, using different markers of stress: those who experienced stressful events earlier in life, but not later; those who experienced stressful events later but not earlier; those who experienced stress throughout life; and those with no major markers of stress at all. If Barker's hypothesis can be applied to these populations, then those who experience early life stresses should fare worse than those who experience later life stresses. Particularly vulnerable periods could be identified in this way, by observing the timing of enamel defects associated with particularly bad outcomes.

While such studies may be performed in the future, yielding additional information about the relevance of Barker's hypothesis to past populations, some obvious limitations will remain in the analysis of enamel hypoplasias. One is that we can only look at stressful events during fetal development in individuals

who died as children, thus retaining their deciduous dentition. This means that we cannot observe the effects of prenatal stress on adult mortality. In adults, because these markers of fetal development have been lost, we are limited to looking at stressful events in early childhood, a period that some cohort studies indicate is already too late. Another limitation is, of course, that we cannot differentiate between specific causes of stress, such as infections versus malnutrition nor, in most cases, specific causes of death. Instead we must be content with looking at associations between stress generally and mortality from all causes. That said, we advocate further studies of enamel defects and subsequent morbidity and mortality. A wide variety of bioarcheological studies have collected, almost routinely, both hypoplasia data and age at death data. Finally, it would be advantageous to study enamel hypoplasias and subsequent health in contemporary populations.

CONCLUSION

While there are methodological problems that must be addressed, the analysis of skeletal remains provides an essential tool for understanding the adaptation of archeological populations. The use of multiple stress indicators is the key to assessing the impact of morbidity and mortality during the weaning period. This approach has revealed that at Dickson Mounds, the period of fetal development, infancy and early childhood was an extremely stressful phase of growth. At this site, there was compelling evidence that fetuses were exposed to nutritional and/or infectious disease insults that compromised their immediate and future survival. In addition, children exhibited a pattern of nutritional anemia and infectious lesions that also would have compromised their survival during the first ten years of life. Individuals with infectious lesions were severely affected and experienced early death. Individuals with iron-deficiency anemia died between two to six months earlier than those without anemia.

TABLE 1. Mean Age at Death by Class of Enamel Defect[a]

	Age at Death	2-tail prob.
No Defects	32.29	
Class A (Severe) or B (moderate) LEH	26.41	0.004
Pitting Hypoplasias	19.14	0.003
Demarcated Hypocalcifications	24.65	0.003
Diffuse Hypocalcification	14.80	0.001

[a] From Duray.[98]

Children who survived childhood but were stressed, as shown by enamel hypoplasia, experienced earlier death as adults. Those individuals who displayed two or more hypoplastic lesions died, on average, ten years earlier than those who had no enamel hypoplasias. Whether this is due to physiological damage that occurred during a critical phase of development (the damaged-goods hypothesis) or stress that occurred in infancy and childhood and continued throughout life (wear-and-tear hypothesis) cannot be determined at present. However, in the future better evaluation of these two possibilities may be attainable.

The bioarcheological record is a valuable source of data regarding health in past populations, yielding lessons that are still relevant today in the many parts of the world in which infectious diseases and under-nutrition are still bigger killers than are heart disease and diabetes. Because most evaluations of the DOHaD hypothesis have focused on high-income populations, the study of living and nonliving populations in resource-poor environments may provide new insights into the scope of this important theory. Present bioarcheological data is consistent with the DOHaD and future studies may indicate whether or not it is the explanation that best fits the observations.

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