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Epigenetic Inheritance and the Intergenerational Transfer of Experience

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Currently, behavioral development is thought to result from the interplay among genetic inheritance, congenital characteristics, cultural contexts, and parental practices as they directly impact the individual. Evolutionary ecology points to another contributor, *epigenetic inheritance*, the transmission to offspring of parental phenotypic responses to environmental challenges—even when the young do not experience the challenges themselves. Genetic inheritance is not altered, gene expression is. Organismic pathways for such transmission exist. Maternal stress during the latter half of a daughter's gestation may affect not only the daughter's but also grand-offspring's physical growth. The author argues that temperamental variation may be influenced in the same way. Implications for theory and research design are presented along with testable predictions.

Keywords: epigenetic inheritance, temperament, socialization, maternal inheritance

Traditionally, similarities in behavior between members of one generation and the next have been explained in terms of the influences of shared heredity, shared environment in the form of common experiences, or combinations of these two classes of influence. Likewise, differences across individuals or generations have been attributed to differences in heredity (different combinations of alleles) and/or nonshared environment in the form of unique experiences, or differential parental treatment (e.g., Rutter, 2002a).[1] This dichotomous conception has been criticized over the years for treating genes and environments as essentially separate contributors to ontogeny, thereby failing to consider the complex ways in which they coact to lead to development of the individual (e.g., Gottlieb, 1970). In addition, it has been faulted because it fails to fully credit the role of the developing individual as an active participant in exchanges (i.e., transactions) with its environments (Bell, 1968; Gottlieb, 1970; Sameroff & Chandler, 1975).[2]

The limitations of existing theories have been further highlighted on a number of occasions by work with animals that seemed to demonstrate the existence of pathways of intergenerational transmission that did not fit these models. For example, Denenberg and Rosenberg (1967) showed that, depending on the postweaning environment in which rats were reared, early handling influenced rats' "emotionality" in an open field relative to nonhandled controls. Moreover, this difference in emotionality also was observed in the (nonhandled) offspring of the handled females.[3] Similar findings were reported for primates by Sackett (1991) and led him to reiterate the call for a new conception of behavioral development that could explain how the experiences of one generation could influence subsequent generations not exposed to those same events. However, perhaps because the effects of early handling in rats later proved to be related to across-generation continuities in parental behavior (e.g., Francis, Diorio, Liu, & Meaney, 1999), relatively little attention has been devoted

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[1] There also is stochastic "noise" in the developmental process itself (Gottlieb et al., 1998; Molenaar, Boomsma, & Dolan, 1993; Waddington, 1957) that typically is included in "nonshared" environmental variation—along with measurement error (e.g., Cherny et al., 2001).

[2] Perhaps one of the most striking example of the latter phenomenon is Bertenthal, Campos, and Barrett's (1984) experimental demonstration that self-produced locomotion affected infants' responses to depth cues and to unfamiliar persons.

[3] Other research, not specifically related to behavioral development yielded similar results. For example, Skolnick, Ackerman, Hofer, and Weiner (1980) showed that in rats, early weaning led to increased susceptibility to stress-induced ulcers in both the early-weaned animals themselves and also in the females' normally reared offspring. Similarly, in female hamsters, early food restriction led to altered sex ratios of their first litters as compared with typically fed controls. Altered sex ratios—and an absence of (typically) greater weight of male pups relative to their female littermates at birth—were observed in these females' normally fed offspring's litters (Huck, Labov, & Lisk, 1986), and in the grand-offspring of the diet-restricted animals (Huck, Labov, & Lisk, 1987). In another experiment, sex ratios of litters in hamsters were related to vaginal pH at mating (Pratt, Husk, & Lisk, 1987). I could find no report linking vaginal pH to early dietary restriction, however.

Another series of experiments with mice indicated that males' physiological adjustments to environmental conditions might be transmitted across generations. Kahn (1970) showed that alterations of male mice's blood hemoglobin concentration as a result of extended periods of early restricted air circulation during adulthood influenced the hemoglobin concentration of their female—but not their male—offspring who were conceived with control females. He also showed (Kahn, 1982) that when male mice were subjected to restricted air circulation during gestation and the perinatal period (but not when instituted some 6 weeks post-weaning), their male offspring likewise showed altered—but lower—blood hemoglobin concentrations. This effect was less marked in the third generation. Likewise, males whose mothers were given water with dilute yeast RNA from conception until the pups were 12 weeks of age showed increased hemoglobin levels; when mated with control females, they sired male offspring who showed a comparable alteration in hemoglobin levels. These studies demonstrated intergenerational effects that apparently were transmitted via the male gametes.

to examining possible alternative pathways by which early experiences of parents might influence the phenotypes of offspring (but see Stamps, 2003, for a recent examination of this issue).

In the past quarter century, a number of attempts have been made to address several of these concerns by integrating concepts from developmental and evolutionary biology into models of behavioral development. In particular, attempts have been made to break down the rigid separation between genetic and environmental influences and to acknowledge the active role of the developing individual in shaping its own growth (e.g., Bjorklund & Pellegrini, 2002; Gottlieb, 1970, 1976; Gottlieb, Wahlsten, & Lickliter, 1998; Harper, 1989; Ho, 1998; Sameroff, 1983) and how these influences are embedded in and shaped by culture (e.g., S.-C. Li, 2003; Tomasello, Kruger, & Ratner, 1999) throughout the life span (e.g., Baltes, Staudinger, & Lindenberger, 1999). Likewise, in evolutionary theory, with the realization that the entire life history is subject to selection (e.g., Williams, 1966), there has been a resurgence of interest in the relationships between ontogeny and phylogeny (e.g., Gottlieb, 1992; Gould, 1977; Oyama, 1985; West-Eberhard, 2003).

Although psychologists have long held the belief that experiential modifications of behavior might influence evolution (the "Baldwin effect"; see, e.g., Gottlieb, 1992; Weber & Depew, 2003), until recently (e.g., Tomasello, 1999), plausible pathways for such transmission have not been presented. Even then, with the exception of Storfer's (1999) article on the possible links between myopia induced by visual complexity and intergenerational alterations in brain structure and intelligence, the emphasis has remained on examining and conceptualizing proximal influences on the individual. However, evolutionary ecologists have begun to identify several pathways, other than learning, by which the effects of experience can be transmitted across generations.

In this article, I argue that these new insights in developmental and evolutionary biology not only help one to understand how genes and environments coact to shape behavior but also indicate the necessity for an expansion of the time frame in which to consider the effects of experience in order to fully appreciate the intergenerational impact of environmental events. In particular, work in the area of evolutionary ecology documents the existence of a pathway for at least one additional source of across-generation continuities. This is a phenomenon called *epigenetic inheritance*. It refers to the fact that some phenotypic responses made by the parent to environmental challenges may be displayed by offspring even though the offspring themselves do not encounter the challenge. It might be likened to a kind of phenotypic inertia: There is no change in genetic inheritance, but gene expression (the phenotype) is altered in subsequent generations, thereby resulting in intergenerational continuity—even when the young never experience the conditions that led to the parental trait. For psychology, this phenomenon represents an all but ignored pathway, one that supplements such traditional concepts as socialization and other models of cultural transmission.

In this article, I review evidence indicating that some classes of parental—or ancestral—experience may not only affect the parental phenotype but also constrain the possible range of variation in offspring reaction to environmental influences. This work shows that developmental modifications can be transmitted across generations in the absence of the original, precipitating conditions. These intergenerational modifications are not necessarily permanent; when the precipitating conditions occur cyclically and remain absent for several generations, the phenotypic alterations "decay" gradually.

To place this proposal in perspective, and to focus on a domain in which epigenetic inheritance seems likely, I first present a limited overview of traditional and more recent approaches to understanding intergenerational transmission of traits such as attachment styles, psychopathology, and domestic violence. To further set the stage for a consideration of possible biological pathways of transmission, I also examine examples of recent research relating to interactions between child characteristics and parenting, including work showing that reactions to parenting and other experiences differ according to inherited variations in neurotransmitter dynamics. These findings are compatible with current "dynamic systems" models of development and evolution that include recognition of the (developing) individual's role in shaping its own experiences (see, e.g., Oyama, Griffiths, & Gray, 2001). However, the dynamic systems approach provides only a general framework for conceptualizing ontogenetic processes. Therefore, as background for the hypotheses to be developed in subsequent sections, I present an overview of current conceptions of developmental genetics, including selective X chromosome inactivation and genetic imprinting, to demonstrate the existence of biological pathways by which intergenerational transmission of phenotypic modifications could be accomplished.

With that as background, to identify behavioral phenomena that might be so influenced, I later touch on current work in evolutionary ecology that focuses on the phenomena of "maternal effects" and epigenetic inheritance, and I selectively review comparative work spanning almost 50 years that indicates that the phenotypic adjustments to stress made by one generation may alter the phenotype of at least the following generation. The likely pathways for this kind of transmission are examined along with the conditions under which one should expect to find such effects. Finally, I present the hypothesis that temperament in humans is one behavioral domain in which individual differences are influenced by epigenetic inheritance. The theoretical and methodological implications of this hypothesis are considered, and some testable predictions are presented.

Background

Current Status

The earlier presumption that variations in parenting would prove to be a major, if not the primary, source of the variance in child outcomes (e.g., Maccoby & Martin, 1983) has been challenged (e.g., Harris, 1995). On the one hand, the evidence clearly shows that parenting influences do matter. For example, Sroufe (2002) reported striking results from a long-term longitudinal study of low-socioeconomic status families. He found that early quality of care predicted a range of later outcomes including competence in peer relations, adolescent risk taking, emotional problems, and school success. In the latter case, a composite of six measures of quality of parenting, the home environment, and the quality of stimulation afforded the child could predict high school dropout with 77% accuracy.

On the other hand, simple "main effect" models have been disappointing. For example, Gallagher (2002) wrote that "[gross] maltreatment aside . . . predictions of child adjustment outcomes from parenting behaviors have been modest" and that "links be-

tween parenting styles and child adjustment outcomes have sometimes been equivocal" (p. 626). Similarly, from a review and meta-analysis of the effects of punishment on children's adjustment, Gershoff (2002) observed that "crucial questions remain unanswered, such as what range of child behaviors and experiences are empirically associated with parental corporal punishment, as well as why, how, and for whom corporal punishment might have such effects" (p. 539). She indicated that to fully understand the issue, research would have to include evaluations of individual constitutional differences across children as well as the sociocultural contexts in which punishment is administered. Likewise, Bugenthal and Goodnow (1998) suggested that to better account for variations in child socialization, one may have to examine the interactions among the kinds of variables emphasized by a cultural context perspective (e.g., Gauvain, 2001; Rogoff, 1998) in conjunction with the child's biological make up.

Models of Developmental Influences

Indeed, analyses using main effect designs to explain intergenerational continuity in behavior often indicate that more complex models are required even when examining explicit theoretical predictions. For example, van IJzendoorn's (1995) meta-analyses of the relationship between parental and offspring attachment styles led to the conclusion that, although there was a significant link, there remained a "transmission gap" in security of attachment between generations. That is, a substantial proportion of the variance remained unexplained. Moreover, an examination of the changes brought about by programs to increase maternal responsiveness indicated that variation in maternal sensitivity by itself was insufficient to predict the style of offspring attachment (van IJzendoorn, Juffer, & Duyvesteyn, 1995).

In part, van IJzendoorn's (1995) transmission gap might have been explained by the fact that a retrospective measure was used to assess parental security. However, Sroufe (2002) reported a longitudinal study across two generations in which attachment security in infancy was measured in both generations at comparable times in ontogeny and by the same procedures. Although early attachment patterns predicted later parenting behavior, he found that it was the violation of parent–child boundaries, that is, atypical relationships, that predicted similar violations—but not necessarily the same behavior—when these children became parents themselves some 20 years later. He argued that different patterns of attachment led to developmental trajectories that were "only probabilistically related to particular outcomes," that "strong predictions" specifying particular outcomes would be possible only when "multiple factors supporting or deflecting individuals from the initial pathway [were] . . . also considered" (Sroufe, 2002, p. 191). Indeed, Braungart-Rieker, Garwood, Powers, and Wang (2001) examined both parental sensitivity to infants' signals at 4 months of age and the 4-month-old infant's responses in the still-face situation as predictors of the quality of attachment displayed at 12–13 months. They found that the effects of early parental sensitivity were mediated by a composite measure of infant affect-regulation behaviors in the still-face situation at 4 months.

Similarly, in the realm of psychopathology, Merikangas (2000) noted that, although the Yale family study of comorbidity indicated a "strong degree of specificity of transmission of anxiety disorders and dose–response relationship between parental and child anxiety disorders" (p. 302), relatively little variance could be directly attributed to parenting. As in the case of attachment, the effects of parenting may not be direct; they may be mediated by the child's reactions to them. For example, in a later report of their longitudinal study of low-socioeconomic status families, Carlson, Sroufe, and Egeland (2004) reported that early attachment quality at 12 months and the quality of the child's relationship with the mother at 24 months were indirectly related to social functioning at the age of 19 years. Both early variables were mediated by interactions with measures of the child's representations of relationships and teacher assessments of peer competence and emotional health at 4–5, 8, and 12 years of age.

In sum, the evidence to date suggests that early parenting does influence later offspring socioemotional behavior, but to more fully account for these effects, it is necessary to examine at least the interactions among parenting and contextual variables (cf. Bugenthal & Goodnow, 1998; Gershoff, 2002), as well as interactions among the foregoing and differences in children's responses to them (see also Collins, Maccoby, Steinberg, Hetherington, & Bornstein, 2000). In the latter connection, there has been a good deal of interest in the ways in which child characteristics, particularly temperament, interact with parental practices to affect offspring outcomes.

Interactions Between Child Characteristics and Parenting

Recent studies indicate that an assessment of the characteristics of the child is an important factor in gaining an understanding of the processes by which parenting influences offspring in a number of behavioral domains. For example, Simons and Johnson (1998) tested three theoretical explanations for the intergenerational transmission of violence using a sample of 324 families drawn from the Iowa Youth and Families Project. Four waves of annual visits and questionnaire responses were examined. The data showed that family violence persisted across generations, with correlation coefficients around .50–.60. Questionnaire data regarding grandparental violence predicted fathers' and mothers' violence toward their own offspring. Structural equation models indicated that antisocial behavior (substance abuse, fighting, arrests, etc.) also showed continuity across generations that was related to harsh parenting. Overall, the results most closely fit a model that explained domestic violence as the transmission of a general pattern of antisocial behavior, as opposed to a specific trait.

This interpretation received support from an investigation by Capaldi and Clark (1998), who examined patterns of male aggressiveness toward female partners. They looked at young men from high-risk areas who had been enrolled in the Oregon Youth Study since fourth grade until they were 17 to 20 years of age and who had a romantic relationship of at least 2 months' duration. Their results showed a relationship between the subjects' earlier exposure to unskilled parenting and later aggression toward their partners that was mediated via the boys' prior antisocial behavior.

These results are tantalizing and are consistent with the position that some across-generation continuity interpersonal behavior may be attributed to dynamic interactions across time between child characteristics and parenting style. However, more recent research has further demonstrated that, as argued by Collins et al. (2000), one should not expect variations in parenting to affect all children in the same way or to the same extent.

For example, Rubin, Burgess, and Hastings (2002) examined the temperamental dimension of inhibition at age 2 as a predictor of later behavior at age 4. They found that at age 2, child inhibition, as measured by observed onlooker behavior, or long latencies to social exchanges with peers, predicted reticence (longer latencies) to engage with others or in tasks in unfamiliar situations at age 4. However, most of the predictive variance resulted from the mothers' behavior toward the more inhibited children. It held ($r = .67$) only for the children whose mothers were rated as highly intrusive/overprotective or derisive. This provided a clear example of a relationship between parenting variables and specific child characteristics.

These findings indicate that detailed examinations of interactions between child characteristics and parenting styles are likely to yield important information. Indeed, Bates and McFadyen-Ketchum (2001) summarized 15 studies relevant to the question of interaction, 10 of which were longitudinal. They concluded that the influence of parenting as a determinant of child adjustment became more apparent in the longitudinal studies that controlled for the effects of child characteristics before assessing outcomes.

Moreover, as one might expect from Carlson et al.'s (2004) findings, the quality and outcomes of the interactions between parenting and child characteristics may vary according to child age. For example, Fox and Henderson (2000) reported that a longitudinal study of the temperamental trait of "social withdrawal" revealed as much discontinuity as continuity. Whereas a group of infants rated as highly "positively reactive" seemed to show continuity (albeit across developmentally different situations), "highly withdrawn" infants showed more change in reaction to events as they grew older. Thus, they cautioned that stability of a behavioral trait across time may be influenced by culture or other environmental factors. This finding is also consistent with the view that child–environment interactions could lead to self-sustaining or self-amplifying exchanges (cf. Oyama et al., 2001).

Until very recently, there was relatively little direct evidence relating to the origins of such individual differences in children. Results of a longitudinal study conducted in Dunedin, New Zealand, have now shown how more exacting measurement at different "levels" (cf. Zahn-Waxler, 1996), including biology, can lead to clear and compelling findings.

In the first of these reports, Caspi et al. (2002) compared groups of individuals according to differences in the structure of a regulatory region (the *promoter*) of a gene for an enzyme that affects neurotransmitter dynamics in the brain, monoamine oxidase A (MAOA). They compared groups in terms of violent/antisocial behavior in adulthood as a function of being maltreated as a child. MAOA status itself did not predict maltreatment. However, of those men who carried an allele leading to low MAOA levels, 85% who were maltreated severely in childhood showed some form of antisocial behavior. They had over twice as many convictions for criminal offenses as the normal MAOA boys who had been mistreated. Although the same trends were seen in both groups, the low MAOA individuals were much more likely to be adversely affected by early mistreatment.

A second report by Caspi et al. (2003) provides evidence that the effects of other forms of life stresses vary according to inherited variation in genes controlling the dynamics of the neurotransmitter serotonin. Young adults who carried a "short" allele that coded for relatively less efficient reuptake of the neurotransmitter (via an intracellular *transporter*) were compared with their peers who were homozygous for an allele coding a more efficient pathway. As compared with the respondents who carried the "long" allele, those who had inherited the short allele were more likely to report depressive symptoms, including suicidal ideation, after experiencing stressful life events in early adulthood such as unemployment or difficulties with personal relationships. (Depressive responses were not related to MAOA status.) These results provide clear examples of gene–environment interactions, and they demonstrate the promise of precise specification and measurement of biological variables such as (inherited) individual differences in neurotransmitter function.

As the Dunedin findings indicate, a strong case can be made for an interdisciplinary approach in the study of behavioral development. In his 2001 presidential address to the Society for Research in Child Development, Rutter (2002b) was quite explicit on that point. He argued that although there is no question that genetic factors account for substantial amounts of the variance in "all psychological traits" (p. 2), much more must be learned about both the genes involved and the interplay of identifiable genes and specific environmental influences. Among the areas of biological inquiry identified as holding significant potential for understanding these questions, Rutter (2002b) singled out the study of the epigenetic regulation of genes, genomic imprinting, and the phenomenon of X-inactivation. He argued, "If psychosocial research is to deliver effectively on its very considerable potential, it is essential that psychosocial research be a part of biology, and not separate from it" (Rutter, 2002b, p. 11).

A current framework for such a rapprochement is "dynamic systems theory." However, "it is not a theory in the sense of a specific model that produces predictions to be tested against rival models. Instead, it is a general theoretical perspective on development, heredity and evolution" (Oyama et al., 2001, pp. 1–2). Given this generality, its relevance in any particular case requires specification of the variables in question and the relevant pathways (e.g., Keller, 2001; Neumann-Held, 2001). As Bateson (2001) has pointed out, "The only way to unravel the [underlying relations between genes and experience] . . . is to understand the developmental processes" (p. 163).

Fortunately, recent advances in developmental biology suggest that Anastasi's (1958) question of "how" genes and environmental conditions coact to produce the phenotype soon may be more amenable to answer. Therefore, insofar as an understanding of epigenetic gene regulation, genetic imprinting, and X chromosome inactivation (cf. Rutter, 2002b, as discussed) provides a basis for conceptualizing pathways for the intergenerational transfer of phenotypic modifications, I turn to a consideration of current concepts in developmental genetics, including X-inactivation and genetic imprinting.

Developmental Genetics: Implications for Understanding Intergenerational Transfer

Epigenesis: The Regulation of Gene Expression During Development

Cellular differentiation. The successful cloning of several different mammalian species by transplanting the nucleus of a differentiated cell into the cytoplasm of an egg (e.g., Shin et al., 2002; Wilmut, Schnieke, McWhir, Kind, & Campbell, 1997) has made it clear that essentially every cell inherits a full nuclear complement

of DNA. That is, all cells in the organism have the same genetic potential. In the presence of appropriate external conditions, what underlies the development of multicellular organisms is a progressive, differential production (*expression*) of certain subsets of this genetic potential in different tissues (Slack, 1991). As a result, the cells in each tissue type display a distinctive pattern of enzymatic (gene) expression and metabolism (see, e.g., White, Rifkin, Hurban, & Hogness, 1999). That is, the fertilized egg is totipotent, and interactions among the cells and their environment lead to differential patterns of gene expression that result in specialized, differentiated cell types and, ultimately, organs (Anderson & Ingham, 2003; Slack, 1991; Surani, 2001).

The features of each tissue type thus are determined by the pattern of gene expression, the genes in the cells that are "turned on" or "off" or show distinctive rates of production of gene products (Hawley & Mori, 1999; White et al., 1999). For the thesis presented here, the important point is that, as this process unfolds and cells begin to differentiate, cellular identity remains stable within a tissue. That is, in the intact organism, the tissue-specific pattern of gene expression is transmitted from differentiated cells to their offspring; daughter cells inherit the same pattern of gene expression as shown by the parental cells, a cellular (Felsenfeld & Groudine, 2003) or molecular (Surani, 2001) "memory" of the modifications of DNA expression.

In short, the pattern of gene expression within cell lineages is stably altered as a result of the interactions that lead to differentiation.[4] This means that pathways exist by which alterations in (cellular) phenotype—that is, gene regulation—can be transmitted across (cellular) generations without any fundamental change in the DNA itself, an essential element in the argument for epigenetic inheritance. Moreover, some of the underlying processes by which such transmission is accomplished are becoming clear; several mechanisms have been identified that operate, singly or in conjunction, to control the expression of gene subsets that lead to differentiated cell types.

Gene regulation. Gene expression is controlled by regulating the process by which nuclear DNA is transcribed into messenger RNA (mRNA)—which is ultimately translated into protein elsewhere in the cell. The molecular machinery underlying the nuclear transcription process is complex. Before the enzymes responsible for the transcription of the DNA code into mRNA can gain access to a gene, a number of other events must be orchestrated. They include the production of general transcription factors, which must be assembled at the core promoter site of the DNA sequence at the starting point of the gene. This assembly process is controlled by one or more other DNA sequences, called *enhancers*, which are usually upstream on the DNA strand from the promoter. The enhancer's products form chemical linkages with sequence-specific DNA-binding proteins (*activators*). These, in conjunction with *coactivators*, override or neutralize any inhibitory effects of proteins just downstream of the promoter (the *operator*), and actually control enzymatic access to the DNA at the promoter site (Mizzen & Allis, 2000; Verrijzer, 2001). These interacting elements may involve "cross-talk" among the products of different chromosomes (Persec, Plenge, Nadeau, Bartolomei, & Willard, 2002) and between cells (Slack, 1991).

The process of transcribing DNA into mRNA thus involves the activity of many—sometimes more than 100—proteins (Freiman & Tjian, 2002), often with a number of nonmessenger RNAs as intermediaries (Jenuwein, 2002; Lim, Glasner, Yetka, Burge, & Bartel, 2003). The complexity of the linkages underlying the transcription of a cell's genes allows for precise regulation, not just of whether a gene product is expressed, but also of the amount of the product that is expressed (e.g., Hawley & Mori, 1999; Turner, 2001).

The activation and/or repression of these controlling elements often involve the physical structure of the chromosomes. Indeed, it is likely that (developmental) alterations in these structures are major factors in determining what gets transmitted across cellular generations.

The DNA in chromosomes is wound around proteins called *core histones*, themselves products of the cell's DNA. The configurations of the histone proteins affect the accessibility of the promoter regions of DNA to transcription factors (Turner, 2001). The histone configurations that control DNA accessibility are influenced by the activities of still other gene products. Among them are enzymes that, in conjunction with other proteins, lead to alterations of the DNA arrangement around the histones (e.g., de la Serna & Imbalzano, 2002; Henikoff, 2003; Turner, 2001).

Of particular importance are enzymes that lead to the attachment of at least two classes of relatively simple hydrocarbon molecules to the histones (Bird, 2002; Turner, 2001). These hydrocarbon molecules appear to be crucial in determining whether a gene's promoter region will be accessible. Accessibility for transcription is enhanced when acetyl groups are attached to specific sites on the "tails" of the histone proteins; inhibition of transcription occurs when methyl groups are attached at the same sites (see also Cheutin et al., 2003; Dillon & Festenstein, 2002). In vertebrates, methyl groups also can become attached to the DNA itself. This attachment process is particularly likely to occur when acetyl groups are removed from the neighboring areas of the histone as a result of the action of enzymes (Bird, 2002; de la Serna & Imbalzano, 2002; Turner, 2001). The methyl groups attach to the DNA bases in the promoter region of a chromosome and alter the physical configuration of the DNA chain so that it is inaccessible to proteins involved in regulating the expression of the associated gene (Hawley & Mori, 1999). This means that, in principle, the biochemical code for (tissue-specific) gene regulation can be deciphered and the patterns of regulation can be measured at the cellular level (White et al., 1999).

To make matters even more complex—albeit helping to elucidate pathways for epigenetic modifications—recent work has indicated that what used to be regarded as "junk" DNA contributes to the process. This involves the non(protein)coding *introns* on the DNA strand between the *exon* sequences (which are translated into proteins). It now appears that these introns may also play a role in helping to maintain the intracellular regulatory network (cf. Davidson et al., 2002) that is responsible for the differentiated state of cell types. They do so in (at least) two ways.

On the one hand, repetitive noncoding DNA sequences seem to provide especially sensitive sites for the attachment of silencing

[4] Some tissues in long-lived animals may accomplish replacement by means of the differentiation of (relatively) "uncommitted" stem cells (Stocum, 2002). In addition, certain forms, such as flatworms, can regenerate whole animals from a part as a result of alterations in the intercellular environment (Echeverri & Tanaka, 2002). However, in general, in the intact organism, cellular identity remains stable within a tissue and is transmitted from differentiated cells to their offspring.

methyl groups (e.g., Grewal & Moazed, 2003). On the other hand, different noncoding DNA sequences are the sites for the transcription of a class of RNA that does not get translated into protein. These regulatory RNAs also help to determine the ways in which the histone–DNA complexes are configured to control the accessibility of the exon promoters for transcription (Grewal & Moazed, 2003; Kwek et al., 2002; Volpe et al., 2002). These RNAs also can act either to block or facilitate the formation of activators and coactivators (Gottesman, 2002; Matzke, Matzke, & Kooter, 2001; Volpe et al., 2002).[5] In short, it is now thought that many of the RNAs produced from introns are key elements in establishing or maintaining the differentiated states of tissues (see also Cheutin et al., 2003; Jenuwein, 2002). RNA may also be involved in editing the transcribed gene products as they are spliced together to form proteins (Bray, 2003).

Of particular relevance to the understanding of behavioral ontogeny is the fact that, in the process of development, cellular gene expression can be stably altered in response to conditions outside the organism to permit it to adapt to its environment. That is, not only do cells differentiate (specialize in function) in response to external signals, but once so differentiated, their subsequent functional activity as, for example, nerves or glandular tissue, also can be modified at the molecular level. Probably the most obvious example of such altered activity of specialized cells is the development of immunity to pathogens (e.g., Bernasconi, Traggiai, & Lanzavecchia, 2002; Gilbert, 2003). An example of modifications related to behavior can be drawn from the work cited earlier on the effects of mother rats' responsiveness to their offspring. Francis et al. (1999) related the degree of maternal responsiveness, and subsequent offspring behavior, to differences in expression of mRNAs in brain related to corticotropin release hormone and glucocorticoid receptors. (See also Gottlieb, 1998; Liu et al., 2004, and references cited in the Evolutionary Ecology and Epigenetic Inheritance section, for additional examples of experience-dependent alterations in gene expression.) These alterations are thought to involve similar, if not the same, pathways that control tissue differentiation (Jaenisch & Bird, 2002)—including the regulatory activities of nontranslated RNAs (Gottesman, 2002).

In sum, recent work has revealed a highly complex system of gene products that regulates the expression of the DNA as the totipotent zygote differentiates into a multicellular organism and adjusts to the demands of the environment. Such adjustments to the environment include intertissue signals, for example, responses to hormones (White et al., 1999) and reactions to receptor-mediated signals from "outside the skin" (Francis et al., 1999), including its own activities (see below). These altered regulative processes—including those evoked by experience—persist as tissues differentiate and, once established, are passed on to daughter cells within the developing organism.

Given that differentiated states have proven to be reversible by inserting the nucleus of a differentiated cell in the cytoplasm of an egg (e.g., Beaujean et al., 2002; Shin et al., 2002), cellular memory might seem an unlikely model for intergenerational transfer of responses to the environment. However, there are two related phenomena that indicate that some kind of message involved in determining the expression of tissue-specific patterns of DNA does get transmitted across generations. These are the selective inactivation of one X chromosome and what is called *genetic imprinting*, the (frequently tissue-specific) selective inhibition of expression of genes inherited from one parent or the other. That is, despite the fact that most epigenetic modifications of DNA that occur during tissue differentiation are "erased" in the germline (e.g., Turner, 2001), the phenomena of X-inactivation and genetic imprinting provide clear evidence of a selective "marking" of DNA for expression that crosses generations. In this instance, the DNA transmitted across generations by the gametes carries information regarding its origins—whether it comes from the mother or the father.

The key point for the argument presented here is the fact that some alterations in accessibility of DNA are passed from one generation to the next—that, in principle, pathways exist for the intergenerational transfer of developmental adjustments in response to conditions prevailing for the parental generation. Moreover, as indicated below, these pathways are thought to involve the same kinds of modifications of gene expression that are involved in tissue differentiation.

X Chromosome Inactivation and Genetic Imprinting

X-inactivation. Insofar as a double dose of gene products usually is deleterious (e.g., Hawley & Mori, 1999), only one X chromosome can be expressed in most tissues of female mammals. Whereas the inactivation of one X chromosome is random in many tissues (Hawley & Mori, 1999; Turner, 2001), there do exist phase- and tissue-specific examples of X-inactivation that are determined by the parent of origin. For example, in female mammals, before implantation in the uterine wall, the paternal X chromosome is preferentially silenced in the outer layer of blastocyst cells. Subsequent to implantation, X-inactivation in the cells in the inner layer occurs more randomly (Clerc & Avner, 2000).

Whether selective or random, the X-inactivation process also involves both the differential methylation of the chromosomes and the expression of RNA in the initial silencing of the "extra" X chromosome. The inactivated X shows relatively more methylation in certain DNA regions and, at the same time, has less acetylation on two core histones. The initial silencing is mediated in part as a result of activation of a noncoding region on the X that appears to be pivotal in switching on the silent state via a functional RNA. This RNA "recruits" proteins that alter the histone configuration of the chromosome to effectively silence it. Once X chromosome inhibition has occurred during differentiation, the resulting *heterochromatin* state of the inactivated X remains essentially stable in the absence of the initiating conditions (D. E. Cohen & Lee, 2002; Plath et al., 2003).

One feature of the X chromosomes that apparently makes (one of) them more likely to be silenced across its entire length is a higher frequency of long stretches of DNA that contain repeated sequences of bases. These sites are particularly prevalent in the region of the control center for inactivation and in the region coding for the RNA involved in the initial X silencing (Bailey, Carrel, Chakravarti, & Eichler, 2000). How exactly one chromosome gets chosen for inactivation is uncertain. In rodents (Persec et al., 2002) and humans (Judson, Hayward, Sheridan, & Bonthron, 2002) some of the signals controlling the selective

[5] It should be noted that these states of DNA exon accessibility are dynamic. They are not absolute but relative, although the duration of inaccessibility, in particular, can be orders of magnitude greater than periods of accessibility (Cheutin et al., 2003; Festenstein et al., 2003).

inactivation of the X derive from other, nonsex chromosomes (*autosomes*).

What is important for the argument presented here is the fact that, although not fully understood, the processes underlying the parent-of-origin marking phenomenon appear to involve general mechanisms. That is, the molecular signaling pathways that selectively block the expression of the silenced X chromosome overlap with those involved in tissue differentiation and function. For example, in addition to a prominent role for methylation, there is evidence that one of the proteins involved in the process of transcribing a silencing RNA is also involved in genetic imprinting (Futscher et al., 2002)—discussed below.

In addition to being an example of the intergenerational transmission of marks on the DNA, an important point for the argument developed here is evidence that differential X chromosome inactivation—the result of such marking—regulates genes that influence the development of behavior in humans. Skuse et al. (1997) examined the differences in behavior of girls and adult women who had Turner's syndrome, the inheritance of a single X chromosome (X, 0 genotype). Girls who had inherited their X chromosome from their mother ($n = 55$) were compared with girls who had inherited their X chromosome from their father ($n = 25$). Of the school-aged girls who had a maternal X, 40% had difficulties requiring special educational assistance, in contrast to 16% of those who had a paternal X. Moreover, 72% of the maternal X group who were over 11 years of age had "clinically significant" social difficulties, whereas only 29% of the same-aged, paternal X group had comparable problems. A social questionnaire was administered to the parents of the Turner's syndrome sample and to the parents of age-matched groups of girls and boys (XY genotype). For children between 6 and 18 years of age, non-Turner's girls and the Turner's paternal X group were judged to be more adept socially than were the maternal X group. The boys were judged to have significantly more social difficulties than were non-Turner's girls. On tests of behavioral inhibition, non-Turner's girls outperformed boys, and the paternal X Turner's group performed significantly better than the maternal X Turner's group.

The fact that the paternal X group resembled non-Turner's girls more closely whereas the maternal X group seemed to behave more like the group of male controls indicates that there was a gender-specific link between the X chromosome and behavior. In this case, genes on the X derived from the opposite-sex parent are normally selectively expressed in boys and girls. This illustrates two points central to the thesis presented here: First is that pathways exist for intergenerational transfer of gene regulation insofar as the X that gets expressed is selected on the basis of being inherited from the opposite-sexed parent. That means that there must be some identifying mark that is passed from one generation to another indicating which X will be inactivated, depending on its origin. The second point is that such marked genes can affect behavioral development.[6]

The phenomenon of genetic imprinting also involves parent-of-origin intergenerational marks that can influence behavioral development.

Genetic imprinting. Genetic marking is not limited to selective X-inactivation; some autosomal genes also are expressed selectively according to the parent from which they were inherited. This too seems to be the result of certain alleles inherited from one or the other parent being marked for silencing via methylation (Reik & Walter, 2001; Rideout, Eggan, & Jaenisch, 2001). Maternal and paternal imprints are reciprocal, and typically, the active male gene contribution is required to balance the silenced female complement and vice versa (Rideout et al., 2001; Surani, 2001). As in X-inactivation, there is evidence for the involvement of noncoding regions on the (autosomal) chromosome that lead to the transcription of an RNA that plays a role in repression (Sleutels, Zwart, & Barlow, 2002). As indicated above in connection with tissue differentiation, whether and to what degree any gene is expressed is a function of the overall pattern of gene activation and repression in a cell line. Thus, selective repression of imprinted genes may vary according to tissue type as well as parent of origin. As with the inactivation of the X chromosome, selective allelic expression according to parent of origin also may vary with developmental stage (Aldred, 2002; Surani, 2001).

Imprinted genes play important roles in a wide range of phenomena in mammals. For example, in mice, an identifiable paternally inherited gene is implicated in the control of nutrients supplied to the fetus via the placenta as well as the fetal demand for nutrients (Constanica et al., 2002). Imprinted genes are not only involved in fetal growth and viability; they also affect postnatal growth and behavior. For example, again in mice, a paternally derived imprinted gene, *Mest,* is expressed in the hypothalamus and affects both pup growth and maternal behavior, the latter effect apparently due to regulating the numbers of oxytocin-positive neurons in the female hypothalamus (L.-L. Li et al., 1999). In general, neurons selectively expressing genes inherited maternally tend to be more common in the mammalian neocortex, whereas those expressing paternally derived alleles are more frequently found in the hypothalamus and other areas involved with affect (see Reik, 1996, for a review). Here, too, genes are marked for expression according to parent of origin and influence the behavior of subsequent generations.

In sum, not only can entire chromosomes be selectively silenced according to parent of origin, but individual alleles also are subject to differential expression depending on the identity of the parent from which they were inherited. Moreover, the biochemical mechanisms underlying this selective, across-generation inactivation of gene expression involve many of the same pathways that are involved in tissue differentiation.

To recapitulate, in development of multicellular organisms, there is a progression from one differentiated state to another that reflects selective, tissue-specific expression of subsets of a cell's nuclear genes. This differentiation does not involve a change in the nuclear DNA itself; rather, it represents alterations in gene regulation via additions of molecules "coating" particular points on the DNA chain or alterations in the configurations of the histone–DNA chain. These modifications result in changing patterns or degrees of expression of gene products. Once committed to a particular pathway in development—to expressing a specific pattern of genetic activation—cells in a given tissue pass this commitment on to their daughters. That is, daughter cells inherit the commitment made by the parent cell. Similar pathways underlie the process of developmental adjustments to environmental conditions. Moreover, the phenomena of selective X-inactivation and imprinting indicate that across generations, the sex chromosomes

[6] In addition, this phenomenon has implications for understanding findings of differential offspring–parent patterns of similarities (see *Implications for Research*).

and certain autosomal alleles are marked and repressed selectively according to the parent of origin. This selective, intergenerational repression is accomplished by means that are similar to, if not the same as, the mechanisms identified underlying the process of tissue differentiation. At least in certain tissues, including brain, some X-linked and imprinted genes influence behavior in mammals, including humans.

The fact that not only entire (sex) chromosomes but also autosomal alleles can be marked for repression across generations according to parent of origin indicates that a mechanism exists for the intergenerational transmission of modifications of DNA expression via the gametes.[7] Given that pathways exist for such intergenerational transmission, the obvious question is whether there is any evidence for such transmission of adjustments to environmental conditions. This issue has been the subject of inquiry in the area of evolutionary ecology, to which I now turn for theoretical and empirical support for the view that alterations in gene regulation may be transmitted from one generation to another.

Evolutionary Ecology and Epigenetic Inheritance

It has long been recognized that organisms inherit the genetic potential to adjust to environmental conditions, called a *norm* (or range) *of reaction*: "the total range of phenotypes which a given genotype can engender in all possible environments" (Dobzhansky, 1951, p. 20). That is, essentially every species has the capacity to alter its phenotype to adjust to variations in environmental demands. The most obvious example is differential growth in size and mass as a function of the availability of nutrients (e.g., Tanner, 1990). The possibility that such plasticity—including behavioral plasticity (e.g., the "Baldwin effect"; see, e.g., Weber & Depew, 2003)—could be a factor in evolution has been raised on and off for over a century (e.g., Waddington, 1942; see Gottlieb, 1992, for a review). In recent years, the plasticity of the phenotype has again become recognized as a neglected—and probably key—element in the evolution of species (e.g., West-Eberhard, 2003). As Jablonca and Lamb (1995) pointed out, if selection—differential reproductive success—could occur only after the appearance of a novel mutation, as the process is traditionally envisioned, there is a high probability that the "hopeful monster" would be an isolate and therefore unlikely to reproduce. However, if there were existing genetic variation within a population that conferred different potentials to react to novel environmental conditions, there would be a pool of individuals varying in responsiveness—a condition favorable for selection to act on those best prepared to meet the exigencies of the situation.

That selection could operate in this way was established more than half a century ago. In 1942, Waddington showed that alterations in the phenotype of fruit flies induced by (unusual) environmental conditions (high temperatures) could be fixed in a population by selective breeding and then would endure in the absence of the precipitating conditions (see Waddington, 1957). This phenomenon, *genetic assimilation*, has been replicated (e.g., Gibson & Hogness, 1996). Moreover, recently, it also has been argued that the *genetic buffering* of species-typical developmental pathways by the production of proteins, *chaperones,* that help to maintain the appropriate configurations of mRNA and other important molecules underlying cellular function, may be a means whereby a species may accumulate a significant amount of unexpressed genetic potential for reacting to changes in environmental conditions (Rutherford & Lindquist, 1998; see also Sollars et al., 2003). Such potential for phenotypic adjustment would be essential for the adaptive radiation of a species insofar as it would increase the likelihood that members of the clade could exploit new habitat(s) and resources (e.g., Gottlieb, 2002), "constructing" a new niche, thereby potentially establishing another cycle of selection (cf. Laland, Odling-Smee, & Feldman, 2001), which then could lead to the evolution of a new species via "tinkering" (cf. Jacob, 1977) with the regulation of existing developmental pathways.

In short, the pathways from genotype to phenotype are becoming more clear, and their implications for understanding development and evolution are gaining recognition in both biology and psychology (e.g., Ho, 1998; Oyama et al., 2001; Weber & Depew, 2003; West-Eberhard, 2003). The phenomenon of primary interest here, epigenetic inheritance, might be seen as something like an intermediate step between individual ontogeny and speciation in that it involves a (potentially) reversible, intergenerational transfer of an experience-dependent modification of the phenotype resulting from alterations in gene regulation.

The question then arises as to when such modifications would be evolutionarily advantageous. Theoretically, any adaptive, phenotypic adjustment to environmental demands made by the parent which, if transmitted to the offspring, would improve the young's chances of survival and successful reproduction should be favored by evolution (see *The Biology of Maternal Effects*). That is, insofar as organismic adjustments to the environment involve alterations in gene regulation (e.g., Jaenisch & Bird, 2002), under certain conditions, such intergenerational transmission would be expected. Jablonca and Lamb (1995) have reviewed a large body of evidence showing that, from protozoa to mammals, selection has indeed favored the intergenerational transmission of modifications in gene expression. The genome itself is not altered; the degree of expression of inherited potentials for tracking an environment is influenced by events impinging on the parent. The evidence indicates that when certain aspects of an individual's inherited range of reaction are expressed in response to events in the environment, the resulting epigenetic states may be transmitted, not just to daughter cells in that individual, but across generations (see also Rossiter, 1996). These phenomena typically are subsumed under the broader rubric of *parental* or *maternal effects* in evolutionary ecology.

The Biology of Maternal Effects

In evolutionary ecology, maternal effects have been defined as parental influences "on offspring phenotype that cannot be attributed solely to offspring genotype [shared heredity], to the direct action of the nonparental components of the offspring's environment [e.g., climate], or to their combination" (Lacey, 1998, p. 56). According to Lacey (1998), such environmentally induced parental effects on offspring have been demonstrated in almost all living organisms, affecting traits ranging from egg size, growth rate, and resistance to pathogens to behavior. These parental effects can

[7] A recent study with fruit flies has identified a pathway by which conditions affecting the mother could lead to alterations in chromatin state and development of subsequent generations (Sollars et al., 2003).

impact offspring development at a number of points in time: while the (maternal) gametes are developing prior to fertilization and in the postfertilization and prenatal phases, as well as postnatally (Wade, 1998).

Maternal effects do not result from the differential inheritance of the genetic material itself; rather, they represent alterations in the regulation of nuclear gene activity and include genetic imprinting and (other) asymmetrical (maternal/paternal) contributions that might arise via "extranuclear inheritance" (Lacey, 1998, p. 57). The foregoing overview of developmental genetics indicated that alterations in gene regulation might be transmitted, not only from one cellular generation to the next, but from parent to offspring. New work in evolutionary theory suggests that such transmission would convey selective advantage under certain conditions. Evidence from work with plants and animals indicates that some of these environmentally induced variations may persist across generations in the absence of either the original inducing conditions or changes in the structure of the genome. Reports indicating that such phenomena—involving alterations in behavior—occurred in animals were published in the comparative literature almost 50 years ago.

Ancients Revisited

Most current models of behavioral development still assume that in conjunction with one's heredity, variations in outcome are primarily the result of environmental events directly impacting the individual. However, some time ago, there were reports indicating that this assumption may have been too limiting. Several studies indicated that events not directly impacting the individual could affect behavioral development and that modifications of neural function might endure across "generations."

McConnell, Jacobson, and Kimble (1959) showed that a classical conditioned response (a motor reaction to shock signaled by an increase in illumination) could be established in marine flatworms (planarians). These animals are capable of regenerating a whole worm from a part. McConnell and his coworkers reported that when trained flatworms were sectioned transversely and both halves were allowed to regenerate, both halves displayed the conditioned response as reliably as flatworms that had been trained to the same criterion and tested, uncut, after the same interval of time. Despite the fact that the flatworms' major photoreceptors and sensory ganglia are located in the anterior half, both the anterior and posterior halves displayed comparable retention of the conditioned response.

Corning and John (1961) examined this phenomenon further. When planaria were conditioned as in the McConnell et al. (1959) experiment and allowed to regenerate, both halves showed comparable retention of the conditioned response. However, if the animals were allowed to regenerate in a medium ("pond water") containing ribonuclease (RNAse) at a concentration below that which led to "visible structural anomalies" (Corning & John, 1961, p. 1364), the regenerated heads of trained worms retained the response, but the regenerated tails of the same animals did not. A control condition indicated that RNAse did not interfere with acquisition of the response.

To ensure that these effects were not limited to the particular stimulus conditions (shock paired with light) Corning (1966) conditioned planarians to select one arm of a T maze in order to avoid an aversive stimulus (being poked "gently . . . on the anterior end with a camel's hair brush"; Corning, 1966, p. 17). When the conditioned animals were sectioned transversely just forward of the pharynx and allowed to regenerate, both halves showed retention. Thus the retention of conditioned responses in regenerating animals of this species seemed to be a general phenomenon. Moreover, these effects were not limited to just one species. Cherkashin and Sheimann (1967) conditioned another species of planarians' motor responses to shock paired with vibratory stimuli. When animals were transected, retention could be observed in both halves some 14 days after sectioning.

These experiments pointed to the retention of experientially induced modifications in regenerating tissues. The posterior segments of the worms regenerated heads that retained the conditioned responses. These data are compatible, at least in principle, with the possibility that functional alterations also could be transmitted across generations, that conditions altering the parental behavioral phenotype could also influence offspring phenotype directly. Corning and John's (1961) results with RNAse suggested that these phenomena in some way involved an alteration of the expression of genetic material.

At about the same time, even more suggestive results also were reported from work with mammals. Cowley and Griesel (1966) found that the male grand-offspring of female rats that were prenatally malnourished performed more poorly than controls on the Hebb-Williams maze, despite the fact that their mothers had been on a standard diet from conception through weaning. That is, the effects of a low protein diet lingered across subsequent, well-fed, generations (findings to which I return in the next section).

Additional Findings

Since these studies were published, evidence has continued to accumulate attesting to the widespread prevalence of intergenerational transfer of adaptive modifications. Jablonca and Lamb's (1995) review indicates that intergenerational epigenetically inherited alterations in phenotype are not always permanent. However, in the absence of the original precipitating conditions, they may endure for anywhere from one or two to many generations before reverting to their original state.

Recent experimental work has shown that, not only can both plants and animals adjust to environmental threats, but these epigenetic adjustments do enhance survival. Wild radishes produce physical spines and insect-repellant chemicals in response to attack by caterpillars. Agrawal, Laforsch, and Tollrian (1999) showed that these alterations provided the plants with protection against subsequent attacks. Seedlings from the parent plants that had been damaged by caterpillars but not under attack when producing seeds developed phenotypic features more like their parents than seedlings from unexposed control plants. Moreover, as compared with the seedlings of controls, these daughter plants were less severely damaged by attack from caterpillars. Here, the mother plants' seeds continued to develop the defensive characteristics even though they were grown in the absence of caterpillars. That is, the composition of the seeds produced by the mother was altered as a reaction to a prior exposure to predation.

Agrawal et al. (1999) also examined the defensive responses of the water flea, *Daphnia*, which is subject to predation by other insects. When females were exposed to chemical signals associated with the presence of predators, they developed a protective increase in cuticle depth that rendered them less vulnerable when

attacked. Females exposed to these signals when pregnant later laid eggs that, as hatchlings, developed the same defense as their mothers—even in the absence of the predator-related signals. Subsequent maternal broods initiated after the mothers were transferred into signal-free environments also showed enhanced defenses as hatchlings. Although control juveniles exposed to the predation signal did develop a defensive shield, the extent of the modification was less than that induced by the maternal effect. After two generations in a signal-free environment, the effect had diminished.

Subsequently, Alekseev and Lampert (2001) reported that they could influence the production of potentially long-lasting dormant eggs in *Daphnia* by manipulating photoperiod. These insects can lay eggs that develop upon being laid or, in times of seasonally reduced food supplies, remain dormant for a period of time before developing. When the changes in photoperiod were typical of conditions that would predict poor food supply (a seasonal phenomenon)—even though the mother had ample food—the daughters were more likely to produce the "resting eggs." That is, information relevant to the likely availability of food, as indicated by the changing photoperiod, was transmitted to the offspring through the mother's eggs thereby influencing the offspring's egg-laying phenotype.

What makes these studies noteworthy is the fact that all demonstrated clear adaptive advantages for the transmission of an altered phenotype from one generation to the next. This occurred even in the absence of the immediate condition to be dealt with and without maternal alteration in the hatching environment or action on the offspring. Given that these examples of alterations in phenotype eventually were reversible in the sustained, across-generation absence of the relevant signals (e.g., Agrawal et al., 1999), they cannot reflect a change in the genome per se. Rather, they must represent an intergenerational transmission of alterations in the regulation of gene expression. Although these examples were derived from simpler organisms, there is evidence for comparable phenomena in mammals—including human beings.

As mentioned above, Cowley and Griesel (1966) reared rats on low protein diets from weaning until they had delivered and weaned a litter of young. Then, the females from these litters were placed on a standard laboratory diet. As adults, the second-generation females were smaller than control rats from the same strain. When the second-generation rats that had been gestated and nursed under dietary restrictions but reared from weaning on a typical diet themselves bore offspring, their pups tended to be lighter, mature later, and perform more poorly in the Hebb-Williams maze than control pups.

Similar results were reported by Zamenhof, van Marthens, and Grauel (1971), who reared female rats on a low protein diet from 1 month before mating until they had given birth to a litter. Pups delivered by mothers that were on the restricted diet had lower body weights, and a subset that were sacrificed also had lower cerebral weights and less cerebral DNA and cerebral protein than did controls. The remaining pups were divided into three groups. Group A pups were nursed by their mothers, which were still on the reduced diet; Group B pups were nursed by mothers that had been reared on a reduced diet but were nursing while on a normal diet; and Group C pups were fostered on control mothers that were on a normal diet. All groups were fed normal diets postweaning. When reproductively mature, the females were mated with normally reared males. When they littered, the offspring of mothers from Groups B and C had body and brain weights that were significantly lower than the controls' body and brain weights; for all three experimental groups, the offspring's brain DNA content was reduced relative to that of controls.[8] No effect on offspring weight or cerebral content was apparent when males born to restricted-diet animals were mated with control females.

These findings in rats are clear examples of the intergenerational transfer from mother to offspring of adjustments to conditions obtaining during the mother's early development. That is, the offspring resembled their mothers even though they did not endure reduced nutrition either pre- or postnatally. The data also suggest that alterations so transmitted can affect behavior.

Comparable phenomena have been reported for human physical growth. Susser and Stein (1994) reviewed follow-up studies of the effects of a Nazi embargo of food supplies to western Holland during the waning days of World War II. Fertility declined under these conditions. For those women subjected to severe dietary restriction during the last trimester of pregnancy, but who still delivered viable offspring, there was a correlation between the neonate's birth weight and maternal weight at parturition. A follow-up of the sample to the second generation, which was conceived and reared under no food restrictions, indicated that there was a lingering relation between the mothers' birth weight and the birth weights of their offspring.

To recapitulate: The differentiation of cells and organs and their functions have been shown to result from environmentally induced alterations in the regulation of (cellular) gene expression. The biochemical processes underlying this altered regulation are becoming better understood. Mechanisms exist for the marking of certain genes for altered expression across generations that involve (some of) the same biochemical pathways underlying tissue differentiation, and there is evidence that some of the genes thusly marked influence behavior. Intergenerational transmission of adaptive alterations of phenotypes has been demonstrated experimentally in insects and plants. Moreover, there are documented phenomena, largely relating to physical growth (Cowley & Griesel, 1966; Susser & Stein, 1994; Zamenhof et al., 1971), that indicate intergenerational transmission of phenotypic traits in mammals. These alterations may endure for several generations despite the subsequent removal of the conditions that precipitated them in the founding generation. Zamenhof et al.'s (1971) and Cowley and Griesel's (1966) reports also indicate effects on brain development and maze performance, respectively, in rats. Thus, epigenetic inheritance of behavioral traits in humans is plausible. That said, the challenge is to identify what aspects of human behavior would be most likely to show such effects and the conditions that might lead to them. The work on maternal effects in evolutionary ecology provides clues as to where epigenetic inheritance might be expected.

Conditions Favoring Epigenetic Transmission

Jablonca and Lamb (1995) summarized a body of work suggesting that "heritable epigenetic variations" are advantageous when organisms live in environments in which certain traumatic

[8] Insofar as the brain consumes disproportionately more energy than other tissues, in times of severely limited resources, there would be an arguable trade-off between starvation and neural reserve capacity.

events occur regularly but unpredictably. Epigenetic inheritance is favored when the traumatic event often does not occur within the lifetime of a given generation, but does reoccur more often than the time necessary for the spread of mutant alleles or a major shift in population allele frequencies. (Note here that epigenetic inheritance can still evolve even against a background of allelic variation that also leads to heritable, quantitative, individual differences in the same trait.) Likewise, Lacey (1998) argued that an environmentally induced parent effect that persisted across generations—even in the face of more favorable conditions—should be expected when stressful environmental cycles often lasted for two generations or more, on average. As Rossiter (1998) noted, natural selection favors the preparation of offspring for environmental exigencies, especially when there were large potential discrepancies in conditions between generations.

Following these lines of reasoning, Harvell and Tollrian (1999) proposed four specific prerequisites for the evolution of "inducible defenses" (p. 3). They are that (a) the severity of the environmental threat is variable, unpredictable, and sometimes strong; (b) the imminence of a threat is signaled reliably by some detectable cue that can activate the individual's defense(s); (c) the defense(s) so activated are available (i.e., the individual is able to adjust or mount a defense) and effective in reducing the injury to the individual; and (d) such a defense mounted in anticipation of a threat is less costly than if it were evoked only after the threat actually materialized.[9]

If these criteria specify the conditions necessary for the evolution of induced, reversible defenses, then one needs to consider the kinds of vicissitudes that have faced the human species. Of particular importance is the degree to which they occur cyclically but relatively unpredictably, sometimes endure for several generations, are beyond the individual's control, whether the individual is already equipped to deal with them, and the relative costs and benefits of adjusting to a challenge after encountering it as opposed to being prepared in advance.

Where to Look

An even cursory perusal of human history indicates that famine and conquest are recurring events that can alter environmental conditions drastically and for substantial periods of time but that are not easily predictable.

Physical growth. Insofar as famine reduces energetic resources, an induced defense that would prepare the next generation for such conditions would be restriction of physical growth. Environmentally induced variations in physical size in response to food availability are documented in humans (e.g., Tanner, 1990), and anticipating limited food availability would be less risky than attempting to cope with markedly reduced resources after attaining greater body mass (and thereby greater energetic requirements).[10] Thus, the phenomenon reported by Susser and Stein (1994) represents a likely example of epigenetic inheritance.

Temperament. Conquest, or a sudden change in relative status or access to resources, that is, oppression, is another recurrent, if unpredictable, and often long-term event that also meets the criteria for a selective advantage for epigenetic transmission. In this case, the nature of an adaptive response is not so obvious, but some aspects of temperament would be likely candidates for consideration. Given that members of the conquered population would be at increased risk of attack or enslavement, or at least subservient status, caution would be adaptive in conditions of uncertainty. There is no question that humans and other animals can learn to react appropriately to danger and that they can show caution or deference in the presence of more dominant competitors (e.g., Fairbanks, 1996). To the extent that undue bravery in the face of a potential enemy could lead to anything from reduced access to resources to death, caution would be an adaptive trait. Insofar as human history chronicles cycles of domination and subjugation, a reversible response would be advantageous.

As indicated above, Fox and Henderson (2000) showed that children who displayed early tendencies for social withdrawal were particularly responsive to later rearing conditions. Thus, temperamental variations from "uninhibited" or "low reactive" to "inhibited" or "high reactive" to novelty—or possible danger—would be fruitful areas in which to look for epigenetic intergenerational continuity.[11] An initial question would be whether there is any evidence for either hereditary transmission or shared environment (which would include epigenetically inherited maternal effects) on temperament. There is. DiLalla and Jones (2001) reviewed the literature on temperament and concluded that the findings were consistent with the position that certain aspects of temperament are heritable, in particular, traits like inhibition. Moreover, they concluded that there was also evidence for the influence of shared environment in the expression of the trait of inhibition (what one might expect if transmission were via the matriline; see *Maternal transmission*).[12]

The next relevant issue would be to examine what is known about the mechanisms underlying inhibited behavior and the gene products that are related to such behavior. With respect to the underlying structures, recent work has identified at least one organismic pathway for adaptation to a threatening environment—heightened alertness to cues indicating potential danger. It is commonly held that the amygdala is involved in alerting individuals to even dimly perceived indications of (potential) threat (e.g., Adams, Gordon, Baird, Ambady, & Kleck, 2003), and there is evidence for stable individual differences in human amygdalar responsiveness. Adults who were identified as inhibited as toddlers showed greater amygdalar arousal in response to novelty than did their peers who were classified as uninhibited at age 2 (Schwartz, Wright, Shin, Kagan, & Rauch, 2003).

With respect to the question of gene–temperament relations, differences in response to potential threat also have been related to

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[9] The latter two conditions would favor genetic assimilation (cf. Waddington, 1957) of the transmitted response. However, to the extent that the response is costly in some way and the conditions evoking it are not constant—although enduring—selection would not favor a permanent alteration in phenotype and possibly the evolution of a new species.

[10] To the extent that greater size and strength confers advantages in intraspecific competition, a permanent reduction in size would not be adaptive so long as periods of plenty are encountered nearly as often as periods of famine.

[11] Insofar as both uninhibited behavior and timidity can be advantageous given the complexity of most environments, one might expect that there would be allelic variation predisposing individuals to displaying either extreme as well as the potential to modify such traits.

[12] Although many of the phenomena reviewed above and the postulated existence of epigenetic inheritance render questionable the assumptions underlying the partitioning of variance as "genetic" or "environmental," these findings do suggest that the hypotheses presented here are plausible.

identifiable genetic polymorphisms. Adults' amygdalar responses to affectively charged stimuli differ according to inherited variations in the reuptake of free serotonin via a neuronal transporter protein (Hariri et al., 2002—the same gene examined in the Caspi et al., 2003, study). Moreover, genetic polymorphisms related to neurotransmitter function—including interactions involving this serotonin transporter—correlate with the degree of affective response to unfamiliarity and novelty seeking in infants and young children (Ebstein & Auerbach, 2002).

There also is evidence for individual differences in novelty seeking, or "exuberance" related to dopamine production (Schmidt & Fox, 2002). I have already reviewed evidence for behavioral correlates of genetic variation in the promoter of the MAOA gene (Caspi et al., 2002), which produces an enzyme involved in the dynamics of dopamine, as well as norepinephrine and serotonin.

Critical to the argument presented here is the question of whether the dynamics of these neurotransmitters can be modified as a result of experience. Comparative studies do show that early stressful experiences are capable of altering serotonin dynamics in rat brains (Miura, Qiao, & Ohta, 2002; Vasquez, Lopez, Van Hoers, Watson, & Levine, 2000; Whitaker-Azmitia, Zhou, Hobin, & Borella, 2000). Furthermore, experimentally induced alterations in the serotonin pathways in mice lead to behavioral changes that mimic the differences seen when humans are compared according to polymorphisms in the serotonin transporter gene (Murphy et al., 2001). In mice, there also is evidence for Strain × Early Experience interactions in alterations of dopamine dynamics as well as evidence that these alterations are related to both open field and attack behavior (Gariépy, Rodriguiz, & Jones, 2002).

In sum, then, some of the conditions for expecting epigenetic inheritance of individual differences in human temperament have been met. Conquest is a recurring, if unpredictable, event in human history that would place a premium on caution. Humans can show caution appropriately in response to threat, and it is arguable that it would be less costly to anticipate danger rather than to react with caution after the fact. There exist known heritable variations in neurotransmitter dynamics that are related to the relevant human temperamental traits. Moreover, in other mammals, including primates, variation in these neurotransmitters can be altered by prenatal and postnatal experience (see Suomi, 2000; Suomi & Levine, 1998, for reviews). Thus, identifiable pathways are available for experience-induced alterations in the regulatory patterns of temperament-related neurotransmitter dynamics—a final condition considered necessary for epigenetic intergenerational transmission. This leads to the questions of how and when such an effect might be induced.

Maternal transmission. As indicated above, there is evidence that selection has favored the ability of parents to prepare offspring phenotypes to anticipate the exigencies of a cyclically variable environment by appropriately altering their development prior to birth (e.g., Jablonca & Lamb, 1995; Lacey, 1998). Although there is some evidence for paternal transmission of physiological responses to environmental conditions in mice (Kahn, 1970, 1982), anticipatory adjustments seem most likely to be transmitted maternally. Many examples of epigenetic inheritance have been documented in forms that reproduce asexually (Jablonca & Lamb, 1995). In sexually reproducing forms such as *Daphnia* and the radish (Agrawal et al., 1999), for which an adaptive advantage could be demonstrated, the effect was mediated via maternal experience. In mammals, although intergenerational growth restriction and alterations in timidity might be mediated by some modification of the (uterine) environment—begging the question of how that modification would be transmitted across generations only to reverse itself—the maternal egg would seem to be the most likely vehicle.

Moore (1995) has summarized evidence in mammals showing that, typically, correlations between maternal and offspring traits are higher than those between the same paternal and offspring traits. In this connection, it is significant that in Zamenhof et al.'s (1971) study on the effects of early protein deprivation on development in rats, no effect of parental diet on offspring weight or cerebral content was apparent when male restricted-diet rats were mated with female rats that were reared on a normal diet.

Maternal stress in animals, particularly during gestation, leads to changes in offspring responses to their own young, aggression, and exploration, among other behaviors (see Moore, 1995, for review). Work with both rodents and primates has demonstrated the effects of prenatal maternal stress on a variety of offspring behavioral patterns, including exploration as well as correlated alterations of the excitability of the hypothalamo–pituitary axis and levels/turnover of neurotransmitters (Kofman, 2002; Suomi, 2000; Suomi & Levine, 1998). There also is evidence that maternal stress during gestation may affect later behavior in humans (Kofman, 2002). Thus, the bulk of the evidence suggests that maternal transmission is the most likely route. Indeed, Jablonca and Lamb (1995) pointed out that because the egg provides the larger contribution to the developing zygote, any epigenetic modifications are most likely to be transmitted via the mother (see also Turner, 2001).

Insofar as imprinted genes often remain marked for repression—even through the process of gametogenesis—a mechanism exists for transmission across generations, and there is substantial evidence that the egg contains enzymes involved in "genomic remodeling" (Pirrotta, 2003). Thus, the most likely pathway for intergenerational epigenetic transmission is via the matriline.

Timing. The effects of dietary restriction in the rat studies (Cowley & Griesel, 1966; Zamenhof et al., 1971) spanned the period of oogenesis. Susser and Stein (1994) reported that the long-term intergenerational effects of dietary restriction on human birth weight and adult size were most apparent in those Dutch women who were in the last trimester of pregnancy. This is the period when the primary oocytes and primary follicles are developing in human female ovaries (Sherwood, 2001).[13] Thus, the most likely developmental epoch for modification is during the period of primary follicular development: when oocytes accumulate the maternal effect factors that are required to support the early embryonic development that occurs before the onset of new transcription of either maternally or paternally inherited genes. These products include an oocyte-specific enzyme that maintains genomic imprinting crucial for viability of the developing fetus (Matuzuk, Burns, Viveiros, & Eppig, 2002).

[13] Recently, Johnson, Canning, Kaneko, Pru, and Tilly (2004) reported that, contrary to current belief, at least in the mouse, new oocytes are formed postnatally. They found germline stem cells on the epithelial cell layer on the surface of the ovary. These apparently were capable of self-renewing after division, and the new oocytes were incorporated into the follicular tissue. However, given that these germline stem cells were found in the early postnatal period (Day 4), and to the extent that they had already differentiated prior to or concurrent with the primary oocytes, they would be expected to carry the effects of prenatal experiences.

In sum, then, there are indications that certain adaptive phenotypic adjustments in the parental generation may influence the phenotype of subsequent generations. In mammals, these traits include physical growth and probably behavioral inhibition. The pathways for such transmission can be understood in terms of general developmental principles—the processes underlying tissue differentiation and across-generation persistence of marks characteristic of genetic imprinting. Moreover, they represent alterations in gene regulation that are transmitted via the egg. Given maternal transmission via the egg, the most likely period for an experience to influence subsequent generations is during the period in which the maternal oocytes are developing and accumulating the factors that influence zygotic development, which, in the case of humans, is the latter part of prenatal development.

Implications

For Theory

The phenomena I describe in this article and the proposed mode of intergenerational transmission of behavioral variations require a theoretical framework more akin to current dynamic systems models than to traditional conceptions of either behavioral development or evolution. They are consistent with and supportive of the emerging view of evolution as operating largely, if not primarily, via the differential reproductive success of individuals differing in developmental responses to environmental conditions (e.g., West-Eberhard, 2003). That is, they are consistent with a position that explains speciation in terms of selection acting on existing genetic variation in potentials for phenotypic response as opposed to one that emphasizes the emergence of genetic novelties via mutation. However, insofar as the purpose of this article is to suggest a new pathway for transmission of behavioral traits across generations, I focus on the more immediate implications of the ideas and empirical findings presented here as they relate to the understanding of behavioral development.

It is widely accepted that events affecting parents may have impacts on offspring. However, even when such influences represent the transmission of cultural (ancestral) knowledge (e.g., Gauvain, 2001; Tomasello et al., 1999), these are typically considered to be restricted to influences that the parents experienced postnatally and are thought to exert their influence primarily via alterations in parental behavior (e.g., Serbin & Stack, 1998)—or via alterations of the environment as a result of that behavior (cf. Laland et al., 2001). These altered behaviors or settings are thought to exert their influences directly on the developing young.

In contrast to these traditional pathways of transmission, the evidence presented above suggests that the parental phenotype may be influenced by events that impacted the grandmother during gestation of the parent. Moreover, the same alteration in phenotype may be passed on to the grand-offspring in the absence of the conditions leading to that same response in the parental generation. Therefore, to fully understand the role of experience in intergenerational transfer, environmental influences that may have modified the parental phenotypes must be assessed as well as those experiences directly impacting the offspring. That is, in addition to shared (Mendelian) inheritance, including genetic imprinting and selective, X-linked gene expression (see also below), the influence of grandmaternal experience may represent an additional source of systematic variation, one that may interact with Mendelian heredity and postnatal experience to influence the development of behavior.

This raises issues regarding the definition of *experience* and the *individual*: Typically, perhaps with allowances for effects of nutrition (e.g., Wachs, 2001), psychologists most often investigate experiences that involve activation of receptors and nerve pathways. However, in this case, one is dealing with a wider range of (bio)chemical signals than would be the case with receptor transducers or neurotransmitters. In the domain of physiological psychology, the effects of hormones might seem to present an analogous phenomenon except for the fact that such effects usually are on differentiated tissues in an already complex phenotype. Thus, the definition of *experience* needs to be expanded. Following Gottlieb's (1976; Gottlieb et al., 1998) lead, the definition of *experience* would be extended to read: "any influence that alters patterns of gene activation or regulation." This definition of *experience* would be consistent with evidence for neuronal changes in response to either receptor-evoked or spontaneously released signaling molecules in the nervous system (e.g., Armstrong & Montminy, 1993; Liu et al., 2004; Nedivi, Wu, & Cline, 1998), hormonally induced alterations in cellular differentiation or metabolism (e.g., White et al., 1999), changes in muscle-fiber type in response to different patterns of nerve impulses (e.g., Caplan, Fiszman, & Eppenberger, 1983; Salmons & Srèter, 1976), and the effects of work or gravity on bone growth (Caplan et al., 1983; Goode & Rambaut, 1985).

That said, it also would seem imperative to focus more attention to the details of the effective stimulus, as exemplified by classical ethology (e.g., Tinbergen, 1951) and recent work on the effects of maternal stimulation in rats (Gonzalez, Lovic, Ward, Wainwright, & Fleming, 2001). Moreover, for phenomena such as epigenetic inheritance, conceptions of the stimulus may benefit from attention to those general environmental conditions, "environmental signs" (cf. Harper, 1989) such as photoperiod (Alekseev & Lampert, 2001), that provide reliable, if indirect, cues relating to the probability of occurrence of more specific events. Indeed, it is arguable that more attention to the implications of evolutionary theory (e.g., Bjorklund & Pellegrini, 2002; Hrdy, 1999) might help to develop models that would permit better prediction of the kinds of conditions that are most likely to affect development.

Likewise, the definition of the individual organism has to be reexamined. Examples of prenatal experiential modifications of behavior are well known (e.g., Gottlieb et al., 1998). However, the possibility that the oocyte could store "experiential" information that would influence subsequent postfertilization development and the behavior of the developing organism has not been considered. The data reviewed here indicate that to fully appreciate parental influence and the dynamic interplay between the individual and environment, the time frame for affecting the individual may be as early as gametogenesis.

Finally, the possibility that (grand)maternal experiences could affect the (temperamental) responses of (grand)offspring to parenting and other pre- and postnatal experiences will require an expanded time window to fully account for the quality and outcomes of interactions between the congenital predispositions of the individual and its environment. The evidence provided by the research reviewed above has implications that go beyond the thesis proposed here.

For Interpreting Current Findings

Genetic imprinting. The phenomena of selective X-inactivation and genetic imprinting indicate that a number of phenotypic traits are differentially affected according to the parent of origin. These traits include behavior, and they may involve cross-gender transmission as indicated by the Skuse et al. (1997) findings. Therefore, apparently anomalous or heretofore uninterpreted results may be seen in a new light.

For example, Simpkins and Parke (2001) examined the relationships between mothers' and fathers' self-reports of their friendships and their children's observed and self-reported behaviors with friends. They found relatively few significant correlations between parental reports and child reports. However, over half of all the correlations that reached the .05 level of statistical significance were between fathers' and their daughters' reports of friendship qualities. Similarly, in van IJzendoorn's (1995) meta-analysis of intergenerational continuity in attachment, paternal responsiveness and child attachment security were more closely related than maternal responsiveness and child security. Comparable patterns of attachment relations were reported in a study with an Australian sample by Feeney (2002).

Complementing the cross-gender associations between fathers and daughters are findings from Cairns, Cairns, Xie, Leung, and Hearne (1998). These authors examined similarities between mothers who were first assessed beginning either at fourth grade or at seventh grade and their offspring who were assessed at birth and then annually after age 4 into school age. The mother–son and mother–daughter linkages often differed and, although there were apparently nonsignificant difference between sons and daughters on an Aggressiveness factor, the similarities in aggressiveness between mother at school age and child at school age showed a mother–son correspondence of .614 as compared with a –.100 mother–daughter relationship (see their Table 4), as might be expected from the findings of Skuse et al. (1997). These otherwise counterintuitive findings need to be taken seriously as possible indices of selective X-inactivation or imprinted autosomal alleles.

Epigenetic inheritance. Among children born to the same mother, phenotypic variation that is now typically attributed to shared (postnatal) environment could include a component resulting from epigenetic inheritance. For example, in twin studies,[14] in which comparisons among same-sex monozygotic and dizygotic twins have shown greater than expected similarities, additional analyses are indicated. When measures are available of across-pair consistency in parenting and other experiential opportunities, and multivariate analyses indicate the existence of unexplained variance in similarities, a plausible interpretation would be epigenetic inheritance. Thus, when examining the results of twin or adoption studies (e.g., Riess, 2003), once environmental conditions were equated as closely as possible,[15] an attempt to consider maternal and grandmaternal experiences and attributes would be called for. Similarly, given that epigenetically transmitted influences would be expected to decline across generations, if the precipitating conditions no longer obtained, even in otherwise comparable environmental conditions, one might also expect cohort or subsample differences in the degree of monozygotic–dizygotic similarities. Thus, to reduce overestimation of the effects of shared pre- and postnatal experience, and to better assess the influence of genomic imprinting, assessments of the attributes of both grandparents and the histories of the mothers and grandmothers would be required.

For Future Research

Design. An experimental test of the model of transmission presented here is only feasible with animals. To unambiguously demonstrate matrilineal epigenetic inheritance via the egg, one would have to harvest eggs from females (F1) whose mothers (Fo) were subjected to a relevant treatment such as undernutrition or disturbances of the nest area beginning before and lasting through the F1 females' period of primary oogenesis, fertilize these eggs in vitro, and implant the resulting zygotes in untreated same-strain females whose mothers also were not subjected to the treatment. Controls would be eggs harvested from females never subjected to the treatment, fertilized in vitro, and the zygotes implanted into both treated (F1) females and nontreated females. If transmission is via the egg and not mediated in some way by lingering effects on the maternal environment, the treatment background of the donor grandmother should account for more variance than the history of the birth mother or the latter's mother. Likewise, if transmission is via the egg and not sperm (contra Storfer, 1999), the grand-offspring of F1 females should differ from their male littermates' grand-offspring if the latter are mated with control females.

If animal models provide positive results in terms of physical growth and/or measures of timidity, an appropriate, quasi-experimental approach in humans would be to examine the growth and/or temperamental resemblance between offspring of egg donors to the donor and the recipient who gestates the fetus to determine whether the (prenatal) history of the egg donor can explain variance over and above that which is attributable to the identity of the father, the birth mother, and/or those responsible for child rearing. If transmission is via the egg, then the appropriately timed experiences of the donor's mother should explain more variance than the comparable experiences of the birth mother's mother.

To adequately assess the relevant sources of variance, especially in the case of humans, relatively complex designs would be needed. Recent work on the determinants of human behavioral development indicates that, in addition to the effects of Mendelian heredity and the likely existence of imprinted cross-gender inheritance (see also *Predictions* below), a number of combinations of influences must be considered. These include interactions between parenting and the parent–child environment in general, as well as the interaction among parental practices, offspring characteristics,

[14] In the absence of direct measures of genetic (DNA) variation, twin studies have made a solid case for the substantial influence of inherited allelic variation in behavioral differences. However, these analyses have relied on an often questionable assumption of additivity and have had difficulties in accurately assessing such phenomena as epistasis, dominance, and imprinting (see, e.g., Meffert, Hicks, & Regan, 2002, for a discussion of these complexities and Nijhout, 2001, for examples of the difficulties in interpreting apparent relations between quantitative trait variation and allelic influences in development). As the Caspi et al. (2002, 2003) studies have demonstrated, current technology will soon permit researchers to go beyond what was essentially a "black box" model of sources of variance to address how specific allelic variants influence development under specified conditions.

[15] See S.-C. Li (2003) for a discussion of how heritability estimates can vary across different cultural contexts and Stamps (2003) for examples of variation in different ecological settings.

and the offspring's unique environment (e.g., Collins et al., 2000), particularly as it shapes the spontaneous activities of the young (cf. Bertenthal et al., 1984). This argues for direct assessments of the characteristics of the physical and social surroundings.

To properly evaluate the relative effects of such variables in accounting for intergenerational continuity, longitudinal designs are required. Furthermore, to fully assess the spectrum of epigenetic effects, because they cross generations, multigenerational designs are indicated in which individual differences are tracked longitudinally.

Moreover, it is not certain whether all epigenetically transmitted alterations of phenotype would affect sons and daughters similarly. For example, Coss and Moore (2002) have presented evidence indicating possible gender differences in preschool-aged boys' and girls' choices of refuge from a predator. The hypothesis developed here is that threat or oppression (potential danger) would affect offspring's reactions to such types of danger as might be presented by predators. Therefore, comparisons of temperamental similarities should initially be conducted separately by gender.

Participants. As indicated above, the pathway for intergenerational epigenetic inheritance is most likely via the maternal egg. Therefore, grandmaternal experiences during the latter half of the period when the mother was in utero would be expected to correlate with later grand-offspring traits as well as maternal characteristics. At a minimum, then, to assess the relative contributions of Mendelian and epigenetic inheritance, not only must both parents be assessed (cf. Rutter, 1998; Serbin & Stack, 1998), but wherever possible, the experiences of their mothers also should be examined. Given maternal transmission, to assess epigenetic inheritance, participants should also include the parents' siblings and their offspring (see *Predictions*).

Insofar as epigenetic modifications are transient across generations (Agrawal et al., 1999; Jablonca & Lamb, 1995), comparisons of phenotypic similarities in the traits of interest should be made across at least three generations to assess stability and rates of decay. In contrast to Mendelian inheritance, epigenetically transmitted variation should begin to diminish after two or more generations. To identify possible precipitating factors, families should be chosen to differ in terms of stressful conditions undergone by maternal grandmothers with onsets before, and enduring throughout, the latter half of the mother's gestation.

Measurement. Ideally, in addition to direct observations of behaviors of interest, direct assessments of environmental conditions impacting each generation are indicated. However, retrospective (grand)maternal reports can be augmented to the extent that the mother's birth date and the location in which the mother was conceived and gestated can be determined. Historical records of the existence of such relatively enduring conditions as war, famine, or other stressors that would be expected to affect the grandmother's emotional state, access to resources, or personal status may provide appropriate information.

With respect to personality and, in particular, parenting practices, as Collins et al. (2000) and Serbin and Stack (1998) among others, have pointed out, independent assessments (especially as opposed to reliance on retrospective reports of others' behavior) increase the strength of a case for causality across generations. Moreover, as P. Cohen, Kasen, Brook, and Hartmark (1998) have argued, to adequately evaluate similarities in parent–offspring behavioral patterns, assessments of both generations should be made during comparable developmental periods and, wherever possible, using comparable measures.

Furthermore, to permit "strong predictions" (cf. Sroufe, 2002), particular attention should be paid to stage-related or normative shifts. For example, assessments should be made at the onset of stranger anxiety and the development of locomotion (e.g., Bertenthal et al., 1984). The interrelationships of such normative shifts also should be assessed in conjunction with simultaneous assessments of the specifics of caregiver behavior and the nature of the physical and noncaregiver social surroundings (cf. Collins et al., 2000).

The debate concerning the validity and reliability of parent ratings of offspring temperament is not resolved (e.g., DiLalla & Jones, 2001; Kagan, 1998; Rothbart, Derryberry, & Hershey, 2001; see also Rothbart & Bates, 1998; Saudino, 2003). However, the predictive power of direct observational measures often is impressive (e.g., Fox, Henderson, Rubin, Calkins, & Schmidt, 2001; Rothbart et al., 2001; Schwartz et al., 2003; Woodward et al., 2001). Therefore, whenever possible, investigations would benefit by using direct assessments of both child and parental temperament.

Moreover, Fox and Henderson (2000) have cautioned that, although traits like temperament refer to "predictable modes of response," there are various ways in which there might be "predictability" across developmental time. There are likely to be age-related changes in the kinds of events that would provoke a particular type of response as well as developmental changes in the form of the "same" (temperamental) trait. Furthermore, transactions between developing individuals and their environments can affect the apparent degree and kind of continuity of expression of temperamental attributes (cf. Sroufe, 2002). Therefore, ideally, not only should individual differences in reactions to the environment be assessed at different points in ontogeny, but also aspects of the individual's appearance and behavior that cause others to respond in particular ways (which might thereby establish a self-perpetuating or even self-amplifying cycle). In addition, the degree to which individuals have the opportunity to self-select their environments (cf. Scarr & McCartney, 1983) should be assessed across time.

Predictions

At this point, it may appear that a test of the hypotheses presented here would require an almost impossibly elaborate longitudinal design. However, the proposed pathway of maternal transmission and the period of vulnerability for transmitting epigenetic alteration do lead to several testable, but heretofore unexpected, predictions.

The most readily testable of these predictions is based on the postulated pathway of maternal transmission. Thus (with allowances made for decay and for the timing of grandmaternal stresses; see below), in a population with varied backgrounds, cousins of the same sex born to mother's sisters would be temperamentally more similar to the focal child than cousins sired by the mother's brothers or born to the father's siblings. Likewise, matrilineal aunts or uncles would be more similar to a focal child of the same sex than patrilineal aunts or uncles. Thus, initial tests of the existence of epigenetic inheritance could be accomplished by assessments of extended families.

If epigenetic inheritance is determined by the experiences of (grand)mothers during the period of primary oogenesis or follicle development, an additional prediction can be made: In families with several daughters who started their families while living in comfortable or benign surroundings, the children of women born prior to an enduring stressful event should be less inhibited than the children of their sisters who were gestated during or after the onset of that event. Similarly, where two subpopulations of women differ in terms of experiencing an enduring stress, and where that condition ended after the birth of their daughters, leaving both groups in comparable surroundings, the grand-offspring of the stressed subpopulation should include more inhibited individuals than the (grand)offspring of the unaffected subpopulation.

Thus, in contrast to classical Mendelian inheritance, selective X-inactivation, or genetic imprinting, epigenetic inheritance would be indicated where a pattern of intergenerational similarity was demonstrable relative to grandmaternal experience occurring during the gestation period of the mother. As opposed to the effects of shared experience, the phenotype of offspring would be affected even when the precipitating conditions did not exist during the offspring's postnatal development or during the mother's pregnancy. Epigenetic continuity thus should be predictable independently of intergenerational continuity in caregiving and other (concurrent) environmental conditions.

In addition, in contrast to Mendelian inheritance, in the continuing absence of putative precipitating factors, intergenerational similarities should decrease after more than two or three generations. Likewise, because epigenetic modifications decay over time, in a heterogeneous population with random mating, sustained multigenerational continuity would contraindicate epigenetic inheritance and implicate Mendelian transmission; nondecaying linkages to the patriline would suggest imprinted effects or X-linkages. These effects would be most readily testable in studies of adopted children in which comparable assessments were available of the attributes of both the birth and adoptive parents. That is, where epigenetic transmission is expected, assessments of the prenatal context in which the birth mother developed should account for variance over and above that attributable to either Mendelian inheritance from the birth parents or to adoptive parental behavior and other environmental conditions impacting the focal child. In contrast, transmission of genetically imprinted traits would be expected to show stable, cross-generation linkages with the birth father or cross-gender linkages with the birth parents over and above variance attributable to matrilineal experiences or the environmental conditions encountered in the adoptive family.

Summary and Conclusion

The purpose of this article is to propose an additional contributor to the intergenerational transmission of behavior: epigenetic inheritance. In recent years, increased predictive power has been achieved by considering possible interactions among heredity, individual child characteristics and parenting practices, the bidirectionality of influences between parent and child, and the larger context in which specific experiences are gained. Nevertheless, traditional conceptions of intergenerational behavioral and environmental influences on offspring development may be too limited. The comparative literature has documented a number of phenomena that call for new lines of thought more compatible with a dynamic systems approach.

Insofar as the differentiation of tissues and organs of multicellular forms involves the selective and relatively stable regulation of the expression of different genes, and given that gene expression and regulation ultimately are controlled by environmental influences, many differences in phenotype can be explained as the result of different experiences differentially activating or altering levels of gene expression. Developmental genetics provides evidence in humans, as well as in animals, for the selective marking of genes or entire chromosomes for expression according to the identity of the parent of origin, indicating the existence of inherited parent-of-origin influences on gene expression. Moreover, in animals, evolutionary ecologists have documented the cross-generation transmission of alterations in the phenotypes (gene expression) that are induced by environmental conditions impacting the (grand)parental generation. Such alterations tend to endure across at least two generations and have been demonstrated experimentally in the physical growth and behavior of nonhuman mammals. Similar intergenerational continuities in human physical growth support the likelihood of comparable pathways. Thus, the determinants of individual differences may include environmental events that impact prior generations.

Evolutionary ecologists have identified several conditions under which one should expect these effects. They include cyclically appearing stressors that (a) are severe; (b) often endure for more than one generation; and (c) although recurring, are not predictable. These are events to which the individual could adapt in some way by an alteration of phenotype and to which an anticipatory adaptation would be less costly than the same adjustment after the fact.

In human history, at a minimum, famine and conquest are such events. In the former case, restricted physical growth—a documented response in humans to famine—seems to represent a likely example of epigenetic inheritance. With respect to adjustments to conditions resulting from conquest and subjugation, a plausible case can be made for similar anticipatory behavioral responses via alterations in temperament. Inherited individual differences in neurotransmitter dynamics have been related both to adult humans' behavioral responses to environmental threat and to individual differences in children's temperament. Experiments have indicated that experience can modify the function of the same neurotransmitters in animals. Therefore, in response to conquest, or similar enduring social stressors, it is suggested that modifications in temperament, particularly inhibition, would be a likely area for such anticipatory epigenetic alterations in the human behavioral phenotype.

The evidence to date indicates that the most likely pathway for the intergenerational transmission of alterations in phenotypic traits is via the maternal egg. That being so, experiences impacting a mother during the latter half of her daughter's gestation, during the period of primary oocyte and/or follicular development, are predicted to lead to the transmission of altered gene regulation, temperamental variation, in the daughter and the daughter's offspring. This also points to a need to broaden traditional definitions of experience and to expand the developmental time frame for defining the individual.

The implications for research of the phenomena reviewed here and the proposed pathway of transmission of epigenetic modifications are many. They suggest that heretofore unexpected patterns of parent–child similarities could represent examples of selective X chromosome inactivation or genetic imprinting and that assess-

ments of genetic inheritance on the basis of within-family resemblance may have to include allowances for the impacts of events occurring at least during the gestation of the mother, if not during that of the grandmother.

In particular, the phenomenon of epigenetic inheritance calls for longitudinal designs spanning at least three generations and including extended kindred to properly evaluate the different sources of intergenerational (dis)continuity. Although such research agendas might seem daunting, the postulated pathway of transmission does lead to testable predictions that do not require prospective designs. If epigenetic modifications of temperamental phenotype are transmitted via the maternal egg, in a heterogeneous population with relatively low rates of assortative mating, on average, not only will grandmaternal experience predict grand-offspring behavior, but matrilineal kin should be more similar than patrilineal kin.

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