Paper

Human Development 2003;46:337–355
DOI: 10.1159/000073306

Human Development

On Making Behavioral Genetics Truly Developmental

Gilbert Gottlieb

Center for Developmental Science, University of North Carolina, Chapel Hill, N.C., USA

Key Words
Behavioral genetics · Developmental behavioral genetics · Statistical interactions

Abstract
What will it take to make behavioral genetics truly developmental? In my opinion, the purely statistical population view will have to be abandoned in favor of the study of individuals: An analysis of the bi-directional relations from gene action to the external environment over the life course, including the prenatal period. I critically examine the somewhat vexed concept of 'gene-environment interaction', a crucial first step in correctly understanding the relational view of causality at the organism-environment level of analysis. I conclude by presenting a highly detailed psychobiological model for analyzing behavioral development, with special attention to the genetic level of analysis.

The present essay is an extension of an earlier critique of the population view of behavioral genetics that appeared in this journal [Gottlieb, 1995]. In that critique I described why the traditional population approach of behavioral genetics is not applicable to an understanding of individual development and offered a preliminary statement of a multilevel, bi-directional, developmental systems model by way of attempting to make behavioral genetics truly developmental. In the current essay, after briefly recounting the earlier criticisms, I present a further critique of the statistical view of gene-environment (G-E) interaction, new data on the long-term effects of selective breeding and their significance for understanding development and G-E interaction, and a new model elaborating the bi-directional pathway from genetic activity to behavior.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Accessible online at:
www.karger.com/hde

Gilbert Gottlieb, Center for Developmental Science
CB# 8115, University of North Carolina
Chapel Hill, NC 27599-8115 (USA)
Tel. +1 919 962 6580, Fax +1 919 966 4520
E-Mail gottlieb@email.unc.edu

Population (Quantitative) Genetics

Currently, the practice of behavioral genetics is mainly a purely statistical enterprise derived from population genetics. The population view of behavioral genetics is not developmental. It is based on the erroneous assumption that a quantitative analysis of the genetic and environmental contributions to individual differences sheds light on the developmental process of individuals. Any light shed on individual development from a population view of behavioral genetics would be of a very general, nonspecific nature, such as the finding that the heritability of personality traits increases over the lifespan [Loehlin, 1996]. While such a finding cannot validly be applied to individual development, most people take this conclusion to mean that, over the course of individual development, the genetic influence on behavioral and psychological outcomes increases with age, in comparison to environmental influences. Let's look at this conclusion analytically.

First, in reaching the conclusion that genetic influences on individual development increase over the lifespan, we have departed significantly from the actual finding based on a purely statistically defined heritability estimate which says that, among older individuals, more of the variance (differences between individuals) is accounted for by hereditary factors. Is it valid or legitimate to generalize this finding to an understanding of the causes of changes in individual development? I would say, No. Why? Two reasons: (1) The finding of variance between individuals cannot be validly applied to an explanation of variation within individuals: Inter-individual variation does not explain intra-individual variation [Gottlieb, 1995, 1996; Molenaar, Huizenga, & Nesselroade, 2003]. (2) Because an understanding of the changes in individual development over the lifespan cannot be ascribed to singular causes (e.g., hereditary factors) operating in isolation: Understanding the development of individuals requires a relational concept of causality [Gottlieb & Halpern, 2002; Overton, 1998, pp. 114–115; more on this point below]. Thus, the negative answer would be the same if it had been found that the contribution of environmental influences increased over the lifespan. Individual development is always a consequence of organism-environment interrelationships in which the *quantitative* contribution of either cannot be specified. Organismic factors (genes, nervous system, etc.) and environmental factors (parenting, schooling, diet, culture, etc.) are of course analyzed in developmental research, but their contribution to individual development cannot be specified in additive quantitative terms (e.g., 65% of this outcome is due to genes or to neural influences). This is not a statistical limitation but, rather, logically indefensible.

Second, a further difference in the population vs. individual points of view is that in the former the actual hereditary or environmental factors cannot be specified, whereas in the latter that specification is what developmental analysis is all about. To be fair, some behavioral geneticists have recently begun to recognize that the nonspecificity of environmental and hereditary components of variation is a significant deficiency that needs to be addressed. For example, here is what Rutter, Pickles, Murray, & Eaves have to say [2001, p. 294]:

> On the whole, genetic studies so far have been singularly uninformative about which aspects of the environment carry risks for particular outcomes … [T]he evidence that some unspecified environmental factor accounts for this proportion of the variance rather than

some other proportion is of no theoretical or practical value … Quantification of the environmental index is of no greater utility than the same finding with respect to heritability … The need, as always, is to move from this very general, and therefore unhelpful, conclusion that environmental influences matter to specific conclusions on which environmental influences have which effects, of what degree, in which circumstances, on which individuals.

Although the Rutter et al. recognition represents an improvement in the scope of traditional behavior-genetic analysis, it will not make the population view of behavioral genetics developmental. In order to study and understand the development of the individual it is necessary to study the individual as such; as stated earlier, generalizations from individual differences do not illuminate individual development.

What will it take to make behavioral genetics truly developmental? In my opinion, the purely statistical population view will have to be abandoned in favor of the study of individuals: An analysis of the bidirectional relations from gene action to the external environment over the life course, including the prenatal period. Quantitative genetics is used when one has no idea of how many or which genes may be involved in an outcome, hence it can never become truly or fully developmental. Behavioral genetics only moves toward becoming potentially developmental when the actual genes that are involved in the developmental process are identified [Wahlsten, 2003]. Before presenting a model on how to proceed in a truly developmental behavioral genetics, I will critically examine the somewhat vexed concept of 'gene-environment interaction', a crucial first step in correctly understanding the relational view of causality at the organism-environment level of analysis.

Gene-Environment Interaction

The organism-environment interrelationship is at the heart of developmental psychology. Much of what passes for gene-environment interaction is actually organism-environment interaction. As an aside, it is telling that what represents the heart of developmental analysis is rarely found in the population form of behavioral genetics. For sheerly statistical constraints [Wahlsten, 1990], heritability analysis rarely finds gene-environment interaction. However, the venerable biological concept of norm of reaction indicates that gene-environment interaction is the rule, not the exception. To understand the ensuing discussion, it will be helpful to contrast the concept of the *norm* of reaction with that of the *range* of reaction.

The major defining difference between the reaction range and norm of reaction is as follows. The reaction range sets strict and predictable upper and lower limits for a genotype, once the phenotype has been measured in the usual habitat ('median' in the left side of figure 1 and 'natural habitat' in figure 3). Because genotype strictly circumscribes phenotypic expression according to the reaction-range view, given knowledge of phenotypic expression in the usual environment, any phenotypic difference between genotypes would be preserved in the restricted and favorable environments (fig. 3). The sort of theorizing underlying the reaction range yields more or less parallel phenotypic lines for the four genotypes in figure 3, reflecting the essence of the reaction-range concept. The key question is whether this understanding of the influence of genotype is correct or valid. The difference between the norm of reaction and range of reaction concepts is that the

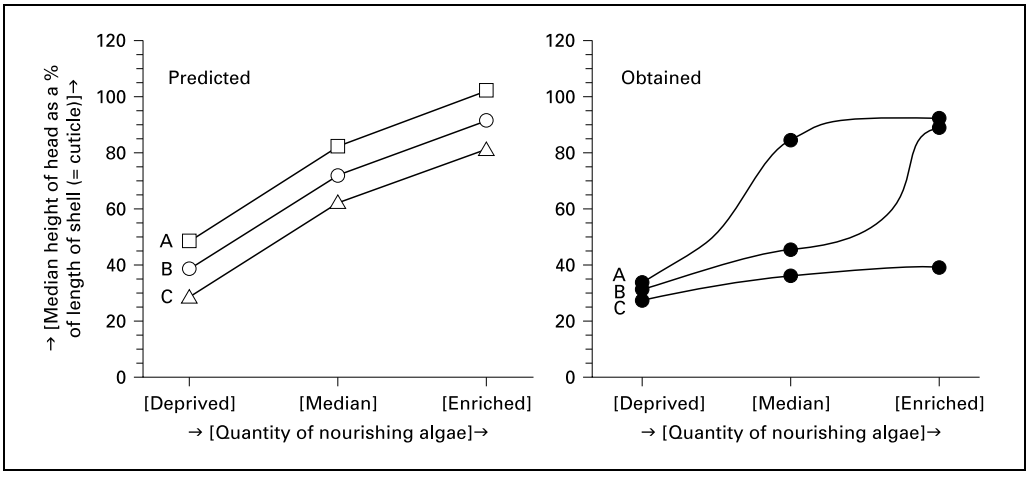

Fig. 1. Woltereck's interpretation of Johannsen's notion of the genotype's influence on phenotypic expression (predicted) and the actual results (obtained) of rearing three geographic varieties of *Hyalodaphnia cucullata* (females) on different levels of nourishment. [Translated and redrawn from Woltereck, 1909, fig. 11 and 12, pp. 138–139.]

former allows no prediction of the preservation of relative differences in phenotype when rearing conditions are changed: that is the essence of the conceptual difference between a *norm* of reaction and a *range* of reaction. With knowledge of the outcome of rearing different genotypes in a single environment, the range of reaction predicts the occurrence of more or less parallel phenotypic lines when the different genotypes are subsequently reared in different environments: that is, the relative differences in phenotype are predicted to be maintained across a variety of novel rearing environments. The norm of reaction, in contrast, holds that a knowledge of phenotypic outcome under one or many rearing conditions does not allow one to predict the outcome when novel rearing conditions are encountered.

The norm of reaction (NOR) was originated by Woltereck in 1909 to help to operationally and experimentally define Johannsen's [1909] newly coined concepts of gene, genotype, and phenotype. (See the review by Sarkar [1999], for the great deal of research done in the NOR context in the 1900s.) As pointed out by Dunn [1965], Johannsen's synthesis was magnificent and stimulated great progress in experimental genetics because of the analytic clarity of his concepts. However, Woltereck, while acknowledging the general utility of Johannsen's constructs, argued that Johannsen's concept of genotypic influences on phenotypic outcomes under different rearing circumstances was incorrect. Woltereck portrayed Johannsen's understanding of phenotypic development as what Gottesman [1963] introduced into psychology as a reaction range – the preservation of relative phenotypic differences between different genotypes across a number of rearing environments (the more or less parallel lines on the left side of figure 1 – Gottesman's depiction is shown in figure 3). The insufficiency (i.e., the lack of generality) of the reaction range concept, in contrast to the norm of reaction, will be discussed below. The

wide utility of the NOR in biology has been reviewed by Schlichting & Pigliucci [1998], and its crucial relevance to the appropriate understanding of the role of genes in development is documented by Falk [2000] and by Gottlieb [1995].

When Woltereck experimentally examined the influence of three different quantities of nourishment on the development of head size (helmet height) in three geographic varieties of the freshwater crustacean daphnia *(Hyalodaphnia cucullata)*, he obtained three very different curves in moving from the deprived through the normal to the enriched conditions of nutrition, as shown on the right side of figure 1. Woltereck regarded the outcomes of these kinds of developmental experiments – ones designed to empirically determine the phenotypic curves for a range of rearing conditions in closely related but genetically distinct groups – as defining what Johannsen called the genotype. The generality of Woltereck's concept of the unpredictability of the phenotype of different genotypes when confronted with novel rearing circumstances has been validated repeatedly in psychology [Erlenmeyer-Kimling, 1972], as well as in biology, down to the present day, and these results conform to the notion that epigenetic outcomes are probabilistic rather than predetermined [Gottlieb, 1970, 1991]. For example, in one of the most ambitious studies of reaction norms, Gupta and Lewontin [1982] examined the number of bristles, viability, and development time in 32 strains from three different natural populations of fruit flies *(Drosophila pseudoobscura)* at two egg densities and three temperatures. They found a considerable number of reversals in relative position in pairwise comparisons between genotypes (e.g., 30–45% reversals when temperature was changed). They conclude, 'Thus, it is not possible to characterize one genotype as having a higher bristle number or faster development than another, since this can only be relative to a given environment' [p. 947]. Their results contradict rather strongly the reaction-range concept, as well as the utility of the breakdown of phenotypic variance into independent hereditary and environmental components as gleaned from heritability estimates.

> … [A]s our experiments show, norms of reaction are not parallel, so effects of changing environment and genotype on variance are general. … A second consequence of the complex norms of reaction displayed by genotypes in natural populations is that the ordering of different populations in terms of the amounts of the genetic variation they contain may change with environment. … A third, and probably most important, consequence of the observed reaction norms is the 'myopia' of selection. This is most clearly seen in the viability results … genotypes favored by natural selection at 14°C may be quite poor at other temperatures. In fact, there is almost a complete reversal of viabilities in Strawberry Canyon heterozygotes between 14 and 21°C [Gupta & Lewontin, 1982, p. 945].

Thus, the limitations implied by the norm of reaction are best viewed as developmental, rather than strictly or solely genetic. The absence of strict predictability is now recognized in many quarters as a defining feature of development. It is specifically taken into account in such diverse formulations as wholistic views of personality [Magnusson and Törestad, 1993], dynamic systems theory [Thelen, 1990], individual-socioecological approaches [Valsiner, 2001, pp. 49ff.], and developmental contextualism [Lerner, 2002]. The point is that individual developmental trajectories are now recognized as not being strictly predictable from foregoing circumstances – this is now accepted as a datum in developmental psychology, not just as unwelcome 'noise'.

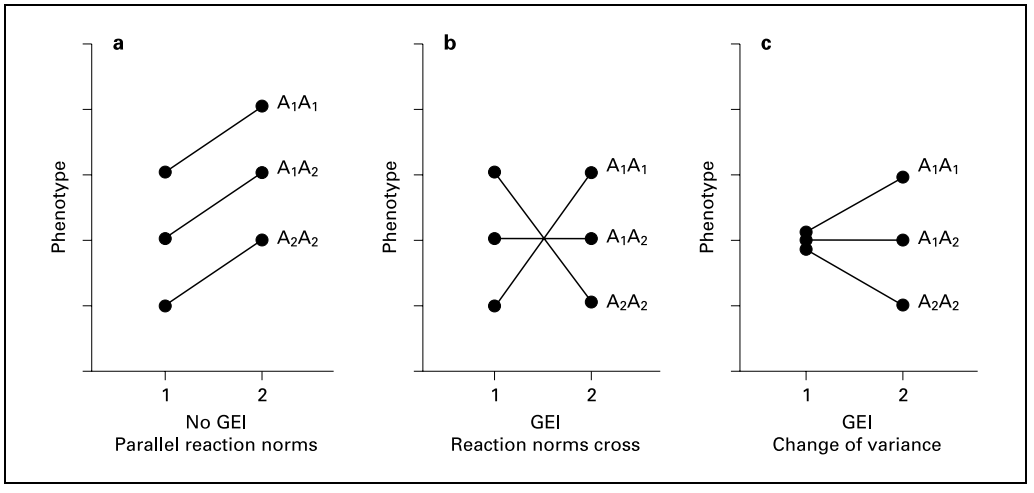

Fig. 2. Phenotypes are typically sensitive to changes in the environment. Here, the phenotypic value of each of three genotypes is plotted in two different environments (1 and 2). The environments can be the two sexes, social and physical environments (for example, diet, temperature), or alternative genotypes at a second genetic locus that affect the trait. (To avoid confusion, the latter type of interaction is best viewed as gene-gene interaction, conventionally termed epistasis, rather than gene-environment interaction as suggested by Mackay.) The line joining the phenotypes of the same genotype in different environments is the norm of reaction of the genotype. **a** Here, there are differences in the mean value of the quantitative trait between the two environments, but alternative genotypes react in the same manner to the change in mean. The rank order and absolute magnitude of the difference between the genotypes remains constant, and the norms of reaction are parallel. In this case, there is no statistical genotype-by-environment (GEI) interaction. **b** Genotype-by-environment interactions occur when there is a change of rank order in the two environments. **c** Interactions also occur when there is a change of variance with sex, environment, or genetic background. [Modified from Mackay, 2001; reproduced with the permission of the author and Nature Reviews-Genetics, copyright Macmillan Magazines, Ltd.]

To elaborate further on the statistical aspects of G-E interaction, as documented by Wahlsten [1990], the calculation of heritability using the analysis of variance (ANOVA) is often insensitive to the statistical interaction of G and E because the detection of such interactions by that statistical procedure requires larger *N*s than are usually available in studies using humans.[1] The other weakness (not to say distortion) of relying on ANOVA-like statistics to determine the presence of a G-E interaction is the peculiar conclusion (for the statistically uninitiated) that obvious empirical interactions do not qualify as statistical interactions, such as the

[1] As the next paragraph makes clear, the statistical concept of an interaction does not have the same meaning as the omnipresent notion of an interaction denoting a primary inseparability or interconnectedness of genes and environment, in the sense that all outcomes are the result of genes operating in a particular developmental milieu and that outcomes are likely to change when the developmental milieu changes. The statistical concept of interaction only recognizes certain changes as qualifying for the term interaction, as described in the next paragraph.

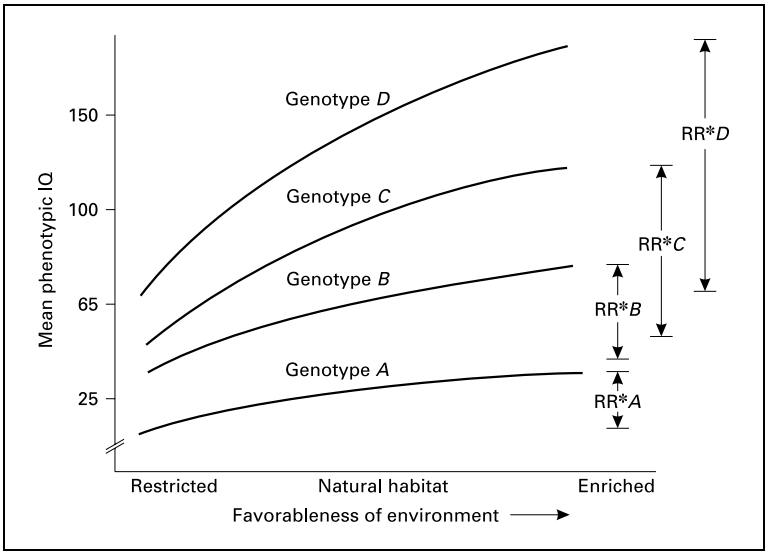

Fig. 3. Gottesman's schematic illustration of the reaction range concept for four hypothesized genotypes. RR = Reaction range in phenotypic IQ [From Gottesman, 1963, p. 255].

example in the left side of figure 1. To clarify this point further, figure 2 portrays three different forms of norms of reaction for phenotypes that vary quantitatively, such as height, weight, IQ, amount of extraversion, etc.

This hypothetical figure portrays the phenotypic outcomes of three genotypes studied over two environments. In the left panel, there is said to be no gene-environment interaction because the genotypes have maintained their ranking and the magnitude of the differences among them, resulting in parallel reaction norms. Obviously, this is a very specialized (sheerly statistical) use of the term interaction because the phenotype associated with each of the genotypes has changed from environment 1 to environment 2. The middle and right panels are said to be examples of gene-environment interaction because in the middle panel the reaction norms cross and in the right panel a phenotypic difference among them is brought out only in environment 2. The term environment is used here in its broadest connotation: 'The environments can be the two sexes, physical environments … or alternative genotypes at a second [locus] that affect the trait' [Mackay, 2001, p. 12]. (To avoid confusion, the latter type of interaction is best viewed as gene-gene interaction, conventionally termed epistasis, rather than gene-environment interaction.) While earlier we asserted that gene-environment interaction is the rule, in light of the above we will adopt the term gene-environment *coaction* to implicate the interconnectedness, if not the statistical interaction, of gene-environment interrelations as far as individual development is concerned. The statistical problem concerning interaction, particularly the need for non-ANOVA, nonlinear statistics to document interaction, is discussed at length by Vreeke [2000], and is beyond the methodological reach of the present author. The stultifying effect of utilizing linear statistics for developmental analysis has been recognized for quite some time [e.g., Overton

& Reese, 1973], but it is a very difficult problem to overcome and solutions have been difficult and slow in coming (for a rare attempt in that direction, see Molenaar & Boomsma [1987]).

Norm of Reaction vs. Reaction Range

The NOR holds that, if we know the phenotypic outcome of two genotypes under one rearing (environmental) condition, we cannot predict their relative standing when these genotypes (actually, organisms) are reared in a different environment. Gottesman's [1963] reaction range concept, on the other hand, '… presumes that the genotype imposes a priori limits (a range) on the expression of a phenotype' [Platt & Sanislow, 1988], such that the phenotype has upper and lower bounds that cannot be transcended. In Waddington's terms, the developing phenotype is genetically buffered or genetically canalized [Waddington, 1957, p. 36, fig. 5]. This state of affairs is diagrammed in figure 3. On the right side of the figure, the reaction ranges of the four genotypes are bracketed, as depicted by Gottesman.

It happens that there is an empirical study in the psychological literature that explicitly addresses the reaction-norm concept, a study by Cooper and Zubek [1958]. The results very clearly support the reaction-norm concept. It is interesting to note that the study was carried out with the idea of a reaction range in mind, and that it is cited by Gottesman [1963, p. 273] as supporting the reaction-range concept. Cooper and Zubek reared maze-bright and maze-dull rats in either an enriched or a restricted environment and then tested them in a Hebb-Williams maze. Since they had the reaction-range concept in mind in performing the experiments, they thought that the learning of both the bright and dull rats would improve relative to each other under the enriched rearing circumstances and would be poorer relative to each other when reared under the restricted (deprived) condition. (This prediction is illustrated on the left side of figure 4.) Instead, as shown on the right side of figure 4, they found equality of performance under both rearing conditions. The dull rats made as few errors as the bright rats after enriched rearing and the bright rats made as many errors as the dull rats after restricted rearing. (In line with the earlier critical remarks about the ANOVA, while the results in the right side of figure 4 look like a strain by environment interaction, an actual ANOVA fails to detect the interaction, i.e., $p > 0.05$.)[2]

When the so-called bright and dull rats were tested in the Hebb-Williams maze after being reared in their usual way (neither enriched nor deprived), a significant difference between the strains appeared (middle points, right side of figure 4). The reason is that this developmental situation repeats the rearing condition under which the original selective breeding for superior and inferior performance was carried out [Hughes & Zubek, 1956]. If the reaction-range idea were correct and the genes coded for a range of learning ability (brackets on the right side of Gottesman's figure 3), when these rat strains were reared under enriched or restricted con-

[2] In a response to my earlier critique [Gottlieb, 1995], Gottesman and colleagues [Turkheimer, Goldsmith, & Gottesman, 1995] acknowledged to some extent the shortcomings of the reaction-range concept and began work on a new version to bring it more in line with empirical findings.

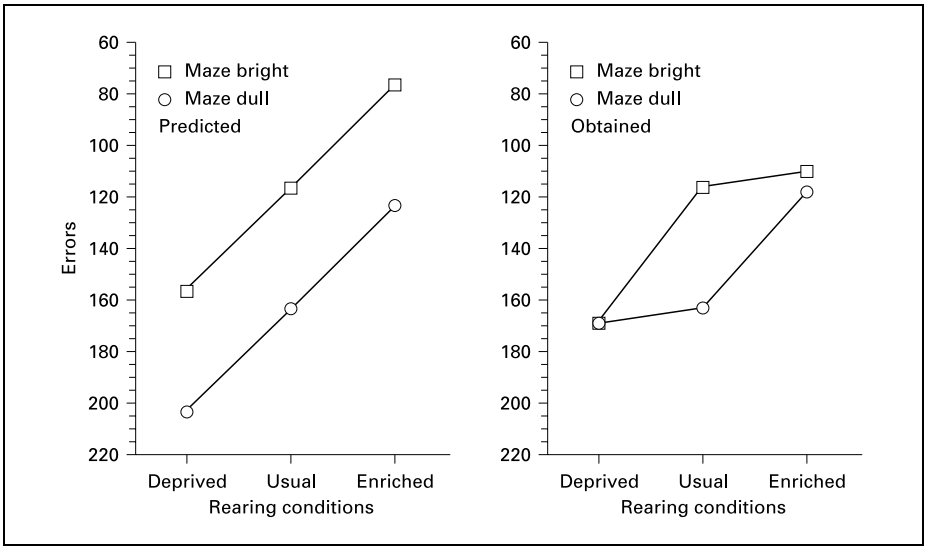

Fig. 4. Behavioral reaction range (predicted) and norm of reaction (obtained) for maze-bright and maze-dull rats' performance in a Hebb-Williams maze after rearing in three different environments. Obtained deprived and enriched data points are from Cooper and Zubek [1958]; obtained usual data points are from Hughes and Zubek [1956]. Only the obtained usual data points are significantly different from each other.

ditions, the relative difference between them would be preserved. Instead, the experiment shows the genes are part of a developmental system or manifold. The highly specific consequences of rearing under a certain developmental condition were realized by selective breeding under that condition: The animals were selectively bred on the basis of their developmental reaction of that rearing condition. And, as called for by the norm-of-reaction concept, selective breeding under one developmental regimen does not predict outcomes under different rearing conditions. (In the face of my earlier empirically-based criticism [Gottlieb, 1995], Gottesman and colleagues have retained the predictability of the reaction range concept: Turkheimer, Goldsmith, & Gottesman [1995].) The results of selection depend on the entire developmental manifold, not only on the genes that are involved: To get stable outcomes, the developmental conditions have to remain the same from generation to generation [Gottlieb, 2002].

A recent study by Kathryn Hood [in press] provides striking support for the developmental manifold idea in the continued dependence of the phenotypic outcome on the specifics of the rearing environment utilized as the basis for selective breeding. Hood and her colleague, Robert B. Cairns, were interested in selectively breeding mice for the expression of high and low levels of aggression. To this end, they placed animals in social isolation after weaning (such rearing enhances aggressive tendencies in some mice) and observed them in aggressive encounters around four weeks later. After only several generations of selective breeding based on the animals' response to isolation rearing in each generation, the high and low lines were clearly differentiated. Hood was interested in the question of gene-environ-

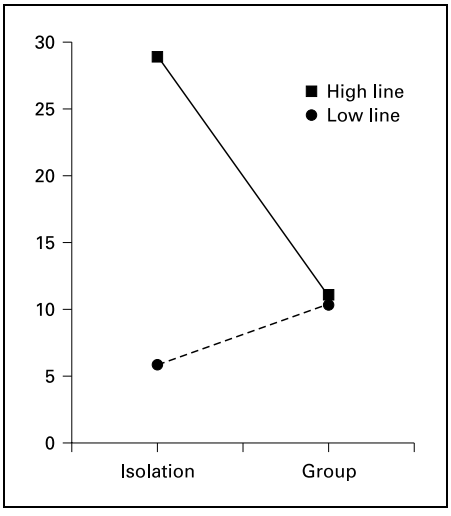

Fig. 5. After five generations of selective breeding for high and low aggression as a consequence of isolation rearing, Hood (in press) reared the two lines under social conditions ('group') and found no differences in aggressive behavior (i.e., the high line dropping to the level of the low line when socially reared). [Figure kindly supplied by K.E. Hood.]

ment coaction, so after five generations of selective breeding, she raised one-half of each line in social conditions after weaning and examined their attack frequency in comparison to the other half of the lines reared in social isolation.

As can be seen in figure 5, high line mice reared under social conditions ('group') were as non-aggressive as the low line, whereas the high line mice reared in isolation continued to show a high level of aggressive attack behavior. A nice demonstration of gene-environment coaction: The continued dependence of the selectively bred attack response on the rearing environment in which it was selectively bred. What may come as a surprise to some readers is that, under the same testing conditions as before, after a further 34 generations of selection, the aggressive behavior of the high line is no less dependent on isolation rearing for its manifestation. As shown in figure 6, the attack frequency of the high line drops to slightly below that of the low line when the mice are socially reared in the 39th generation. In figure 6, the control line is an unselected line and their attack frequency is midway between the high and low lines when they are reared in isolation and drops to zero when they are reared socially, yet another example of gene-environment coaction, if we assume a genetic difference between the selected and unselected (control) lines.

Behavioral development is not unique in its continued dependence on gene-environment coaction. Even under strong evolutionary selection pressure, morphological variation is similarly dependent [Griffiths, Owen, & Burke, 1999]. Both the behavioral and morphological findings support the idea that understanding development requires a *relational* concept of causality: development outcomes are a consequence of at least two specific components of coaction from the same or different

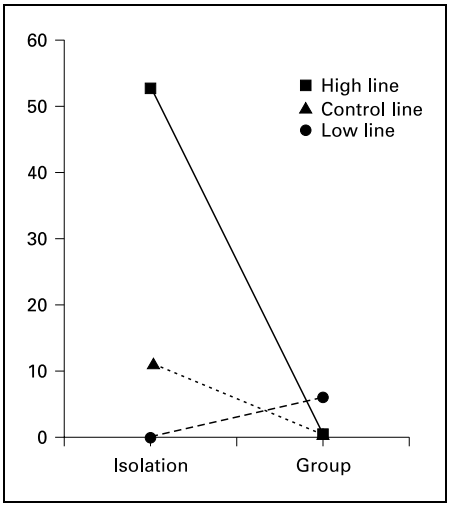

Fig. 6. After 39 generations of selective breeding for high and low aggression as a consequence of isolation rearing, Hood (in press) reared the two lines under social conditions ('group') and found no differences in aggressive behavior (i.e., the high line dropping to slightly below the level of the low line when socially reared). The control line is an unselected line. [Figure kindly supplied by K.E. Hood].

levels of analysis [Gottlieb & Halpern, 2002]. The basic notion here is that the emergent products of development are epigenetic, not just genetic, and this continues to be the case even when we are considering the evolutionary process. A small number of evolutionary biologists are now actively espousing the continued epigenetic basis of morphological evolutionary outcomes, in the sense that the genes correlated to these morphological outcomes may change during the process of evolution while the outcomes are kept stable by epigenetic mechanisms [Newman & Müller, 2000; Weiss & Fullerton, 2000].

Understanding Development from Genes to Behavior

To provide some preliminary insight into what would today constitute a truly developmental behavior-genetic analysis, we reproduce a diagram of the four major levels that are involved in moving from genetic activity to behavior and back again (fig. 7). This is a fully bidirectional coactional system, with traditionally trained developmental psychologists working at the Behavior ↔ Environment level, developmental neuropsychologists and neuroscientists at the Neural Activity ↔ Behavior ↔ Environment levels, and biologically trained persons beginning now to work on the Genetic Activity ↔ Neural Activity levels. (For an outstanding example of the latter, see Rampon et al. [2000].) Viewed in this way, developmental understanding or explanation is a multilevel affair involving at least culture, society, immediate social and physical environments, anatomy, physiology, hormones, cytoplasm, and genes. Hierarchical, multilevel, or developmental systems analysis is

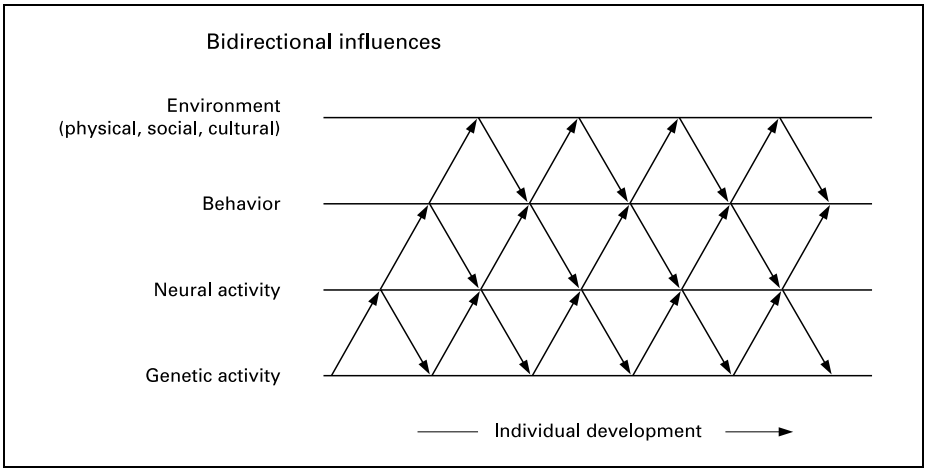

Fig. 7. Depiction of the completely bidirectional nature of genetic, neural, behavioral, and environmental influences over the course of individual development. [From Gottlieb, 1992, p. 186.]

methodologically reductionistic in the sense that biological factors are included to make investigations more complete. However, it is not theoretically reductionistic in the sense that psychological understanding or explanation does not come from lower levels (or reside in the lower levels), but that both higher and lower levels of analysis are necessary to explain developmental outcomes. The term coaction is used to emphasize the multilevel systems nature of developmental analysis.

The present specific form of the levels concept derives from the more general writings of earlier psychologists such as Schneirla [1949], Lehrman [1970], Kuo [1970], and Tobach [1972], as well as biologists such as von Bertalanffy [1933/1962], P. Weiss [1959], Wright [1968], Edelman [1988], and Alberch [1991]. Other versions are being actively pursued by Cairns, Gariépy, and Hood [1990], Curtis & Nelson [in press], Greenough and Black [1992], Hinde [1990], Lerner [1991], and Magnusson and Törestad [1993], to mention just a few developmentalists who advocate this methodological (but not theoretical) kind of reductionism. More recent summaries can be found in the volume edited by Bergman, Cairns, Nillson, & Nystedt [1999], *Developmental Science and the Wholistic Approach*, and the review by Cacioppo, Berntson, Sheridan, & McClintock [2000].

Since the notion of genetic activity or expression being influenced by supragenetic factors may be unfamiliar to some readers, we make preliminary mention here of certain means whereby this can occur. Gene expression is influenced by cytoplasmic factors, which provide the immediate environment of the nucleus of the cell. (Structural DNA is found in the nucleus of each cell.) Cytoplasm can be influenced by the external environment of the organism [reviewed by Ho, 1984] via the behavior of the organism, which gets the organism into and out of exposure to different environmental influences (physical, social, cultural). Likewise, hormones make their way into the nucleus of the cell and trigger gene expression, and hormones themselves are responsive to the organism's experiences in the external

world. In fact, the action of some genes ('immediate-early gene expression') is dependent on sensory stimulation early in development (described in the next section). Finally, different proteins are formed depending on the particular factors influencing gene expression (next section). Hence, genes do not stand outside the developmental system acting as independent causes. They are part of the developmental system. Thus, their expression – whether they are active or inactive – is determined by influences from other levels of the system. (Recall that DNA is an inert molecule, thus it requires a signal to be activated.) Moreover, as documented below, genetic activity does not by itself produce a finished neural or behavioral product, even if behavior geneticists seem to sometimes imply a direct link between genetic activity and the behavioral phenotype (or differences in behavioral phenotypes).

I now present a model that, in my opinion, would make behavioral genetics truly developmental.

A Psychobiological Model for Analyzing Behavioral Development

The following sketch is based on a recent article by Johnston & Edwards [2002], in which they have substantially 'unpacked' the model presented in figure 7 here.

Figure 8 makes clear the large number of analytic steps that intervene between genetic activity and behavior. Johnston & Edwards document each of the steps, so I will only briefly recapitulate them here. Johnston & Edwards also deal with the issue of time in their section on Successiveness and Simultaneity [pp. 29, 30] that is crucial to a developmental analysis. The significance of figure 8 is that it raises the kinds of developmental questions raised by findings that might otherwise be misinterpreted as evidence of a direct link between genes and behavior. Even within the same species there is not just one way to get from genes to behavior [Schaffner, 1998].

Figure 8 extends and explicates the important features of figure 7 in four ways, as follows from the discussion of Johnston and Edwards [pp. 27–29]. First, it includes both neural and nonneural components. Certainly, the most thoroughly studied examples of nonneural contributions to structural, physiological, and behavioral development involve hormones; however, development also involves bones, muscles, horns, feathers, and other bodily structures, and all of these need to be taken into account. For example, in Thelen's [1995] analysis of infant locomotion, gross morphological changes play a critical role.

Second, the immediate consequences of genetic activity are confined to the cell. Genetic effects on behavioral development must take into account the various coactions that follow from protein synthesis and its consequences for events at the cell membrane, coactions among cells, and so on. The model treats genes as an integral part of the developing system, rather than placing them outside the system, and sees genes as influencing behavior indirectly, not directly. When a particular gene has been implicated in the development of some behavior, the model would accommodate the identification of various roles that the gene's activity might play in development. For example, in a review of the effects of single-gene mutations on the development of touch receptors in nematodes, Chalfie [1993] proposed four developmen-

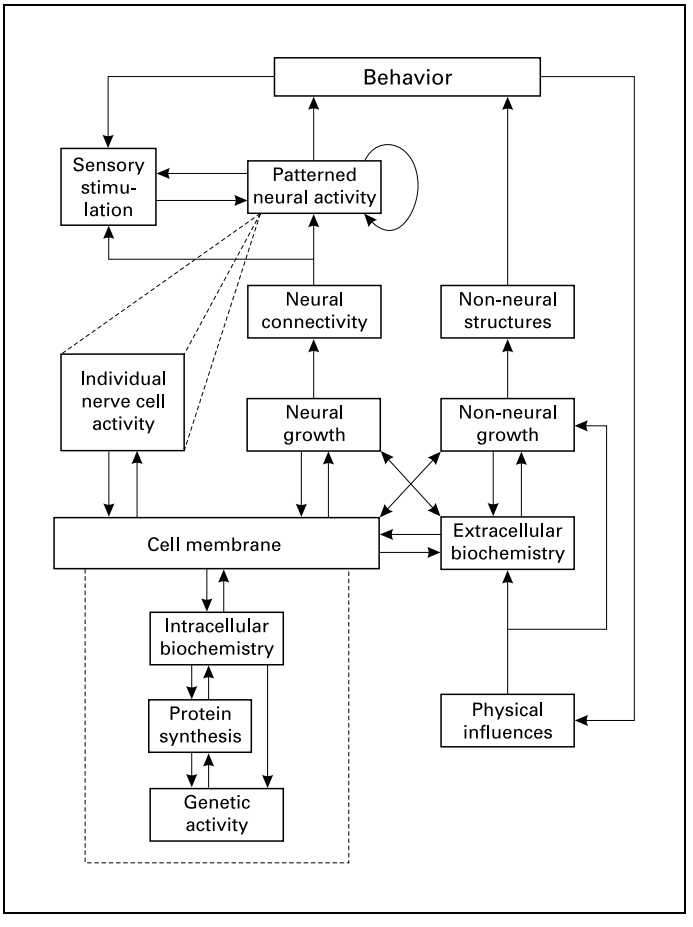

Fig. 8. Completely unpacked model of behavioral development, showing all the coacting factors involved in the developmental construction of behavior and the coactions among them. The model includes both neural and nonneural elements, the latter encompassing such influences as hormones (which constitute part of the extracellular biochemistry), bones, muscles, feathers, and so forth. Sensory stimulation is shown to be influenced not only by behavior (as the animal moves about in its environment, both producing and modifying the stimulation it receives) but also by the connectivity of its nervous system (which partly determines its sensitivity to sources of stimulation) and by the current state of neural activity. The elliptical arrow depicts the effects of spontaneous neural activity. All enduring experiential effects on development that have their immediate impact on patterns of neural activity, act by modifying events at the cellular level, including patterns of genetic activity. Note that there is no direct connection between genetic activity and behavior; all genetic effects on behavior are mediated through the cell membrane and subsequent coactions among cells and neural networks. Solid lines with arrows represent causal relationships between coacting factors. Dotted lines connecting patterned neural activity to individual nerve cell activity indicate that the latter is nested within the former; the relationship between the two is not causal. [From Johnston & Edwards, 2002, with the permission of the authors and the American Psychological Association.]

tal roles (generation, specification, function, and maintenance) for the 18 genes that have been implicated so far in touch receptor development. Although Chalfie's taxonomy deals with anatomy rather than behavior, similar taxonomies might be proposed for behavioral mutations. The Johnston-Edwards model (fig. 8) has the advantage that it provides an explicit representation of the intervening coactions implied by such taxonomies, even though their coactions may not always be specified. Thus, it indicates the kinds of developmental questions raised by findings that might otherwise be taken as evidence of a direct link between genes and behavior.

Third, when experience has more than a transient effect on behavior, the effect is almost certainly mediated through changes in genetic activity. The model implies that all instances in which experience has been shown to affect behavioral development must involve some change in genetic activity. Developmental theory holds that there can be no genetic effects on behavior independent of the environment and there are probably no environmental effects on behavior independent of genetic activity. The model (fig. 8) helps to make this statement more precise by showing the pathway by which experience activates genes through the agency of neural activity, once again supplying a mediating pathway for findings that might otherwise be interpreted as evidence of a direct link between genes and behavior.

Fourth, Johnston and Edwards' model in figure 8 recognizes that nervous system activity needs to be considered at two levels – in terms of neural activity, often involving networks of cells in different anatomical regions, and in terms of the activity of individual nerve cells, within which the genes are located. The dotted lines connecting these two boxes in figure 8 indicate that the activity of individual cells is nested within the patterns of activity of cell networks. Individual cell activity neither causes nor is caused by the patterns of activity in cell networks: rather, there are two levels at which neural activity must be analyzed. Such a dual level of analysis does not mean that an account of genetic activity must be given individual cell by individual cell. Rather, ways of describing the developing nervous system both in terms of populations of cells with similar patterns of genetic activity and in terms of networks of cells that participate in behavior must be found. For example, Brennan, Hancock, and Keverne [1992] have shown that the immediate-early genes c-*fos* and *zif*-268 (but not c-*jun*) show distinct patterns of both transient induction and persistent induction in the accessory olfactory bulb (AOB) of female mice immediately after mating. The induction of c-*fos* is seen only in the granule cells of the AOB, whereas the *zif*-268 induction occurs in both the granule and mitral cells. The AOB is known to be involved in changes in female olfactory responsiveness to male pheromones following mating, and the differential patterns of gene expression in these two cell types indicate the complexity of the relationships that are likely to exist between neural networks and genetic activity in the AOB.

A further caution to those like myself, who wish to establish correlative links between genetic activity and behavior, is posed by the phenomenon of RNA-editing. The role of genetic activity in producing protein is often depicted in a much too simple unilinear formula: DNA → RNA → Protein, in which DNA establishes the nucleotide structure of mRNA which then translates into the structure of the particular protein resulting from the process. Stretches of DNA are composed of exons (coding portion) and introns (noncoding portion). Before the structure of the protein is composed, nearly 40% of human genes are 'alternatively spliced' (i.e., mRNA is edited), not only removing the silent introns but replacing some of the

coding exons! This enormously complicates the identification of which genes are actually involved in the making of particular proteins. As stated on p. 1346 of the report, The Sequence of the Human Genome, '… as was true at the beginning of genome sequencing, ultimately it will be necessary to measure mRNA in specific cell types to demonstrate the presence of a gene' [Venter et al., 2001]. Meanwhile, while we continue to try to correlate genotypes with events at the neural and behavioral levels, we need to remind ourselves of the uncertainty involved. Since much of the genetic analysis in humans involves single nucleotide polymorphisms (SNPs), which are markers for as yet unidentified genes, RNA-editing adds a further complication.

A Currently Acceptable Developmental Behavioral Genetics: Interim Solution

Figure 8 portrays a finished or 'compleat' developmental behavioral genetics. It is an ideal to be sought and will take many years to achieve. In the meantime, we need a model that can be utilized in our day-to-day efforts, so I offer the following, which is based on the notion of the ubiquity of gene-environment coaction documented earlier.

The failure of replications of gene → phenotype associations are legion (extensive review in Wong, Buckle, & Van Tol [2000], the reason being that the environmental (or what I shall call the life experience) component is left out when one merely tries to relate a gene (or genes) to an outcome (e.g., genes for schizophrenia, genes for aggression, genes for novelty-seeking). I am proposing that it is essential to link the gene(s) with a life experience to get a consistent (replicable) result. For example, in a study of the association of a certain genotype (TT genotype) with low concentrations of HDL cholesterol, it was found that only those TT bearers whose fat intake was at least 30% of their total consumed energy manifested low HDL; the other persons in the sample with the TT genotype did not manifest low HDL [Ordovas et al., 2002]. The crucial environmental or life-experience factor here is ingestion of a certain level of particular nutrients. Likewise, in a behavioral example of individuals with a genotype that was associated with low levels of the neurotransmitter monamine oxidase A, it was primarily those who had experienced severe maltreatment in their younger years that were prone to violence in adulthood – those having the same genotype who experienced no maltreatment were unlikely to be violent in adulthood [Caspi et al., 2002]. Eighty-five percent of the males having the low-activity MAOA genotype who were severely maltreated developed some form of antisocial behavior; 15% did not develop antisocial behavior. Obviously, even with the inclusion of the 'crucial' life-experience factor, we are still talking about probabilities (epigenesis continues to be probabilistic).

In sum, the chances of linking genotypes to behavioral (and other) outcomes will be vastly improved when crucial intervening life experiences are routinely included in developmental behavioral-genetic investigations. This follows from the empirical work reviewed earlier indicating that gene-environment coactions are the rule in developmental investigations.

Summary and Conclusions

In order to make behavioral genetics truly developmental, the purely statistical population view will have to be abandoned in favor of the study of individuals. This analysis will involve documenting the bi-directional relations from gene action to the external environment over the life course, including the prenatal period. With some further necessary progress in the nonlinear statistical realm and implementation of the psychobiological models presented herein for the analysis of behavioral development at all levels of inquiry, the analytic apparatus is at hand to begin to pursue a developmental behavioral genetics.

Acknowledgment

The author's research and scholarly activities are supported, in part, by National Institute of Mental Health Grant P50-MH-52429 and National Science Foundation Grant BCS-0126475. Some of the material from my earlier critique of developmental behavioral genetics [Gottlieb, 1995] is repeated here as it is pertinent to the discussion of gene-environment interaction. I am grateful to Carolyn T. Halpern, Michael T. Willoughby, and Jaan Valsiner for their constructive suggestions on an earlier version of the manuscript.

References

Alberch, P. (1991). From genes to phenotypes: dynamical systems and evolvability. *Genetica, 84,* 5–11.

Bergman, L., Cairns, R.B., Nillson, L.G., & Nystedt, L. (Eds.) (1999). *Developmental science and the wholistic approach*. Mahwah, New Jersey: Erlbaum.

Bertalanffy, L. von (1933/1962). *Modern theories of development: An introduction to theoretical biology*. New York: Harper.

Brennan, P.A., Hancock, D., & Keverne, E.B. (1992). The expression of the immediate-early genes c-fos, egr-1, and c-jun in the accessory olfactory bulb during the formation of the olfactory memory in mice. *Neuroscience, 49,* 277–284.

Cacioppo, J.T., Berntson, G.G., Sheridan, J.F., & McClintock, M.K. (2000). Multilevel integrative analyses of human behavior: Social neuroscience and the complementing nature of social and biological approaches. *Psychological Bulletin, 126,* 829–843.

Cairns, R.B., Gariépy, J.L., & Hood, K.E. (1990). Development, microevolution, and social behavior. *Psychological Review, 97*, 49–65.

Caspi, A., McClay, J., Moffitt, T.E., Mill, J., Martin, J., Craig, I.W., Taylor, A., & Poulton, R. (2002). Role of genotype in the cycle of violence in maltreated children. *Science*, *297,* 851–854.

Chalfie, M. (1993). Touch receptor development and function in *Caenorhabditis elegans*. *Journal of Neurobiology, 24,* 1433–1441.

Cooper, R.M., & Zubek, J.P. (1958). Effects of enriched and restricted early environments on the learning ability of bright and dull rats. *Canadian Journal of Psychology, 12,* 159–164.

Curtis, W.J., & Nelson, C.A. (in press). Toward building a better brain: Neurobehavioral outcomes, mechanisms, and processes of environmental enrichment. In S. Luthar (Ed.), *Resilience and vulnerability: Adaptation in the context of childhood adversities*. New York: Cambridge University Press.

Dunn, L.C. (1965). *A short history of genetics*. New York: McGraw-Hill.

Edelman, G. (1988). *Topobiology*. New York: Basic Books.

Erlenmeyer-Kimling, L. (1972). Gene-environment interactions and the variability of behavior. In L. Ehrman, G.S. Omenn & E. Caspari (Eds.), *Genetics, environment, and behavior* (pp. 181–208). New York: Academic Press.

Falk, R. (2000). Can the norm of reaction save the gene concept? In R.S. Singh, C.B. Krimbas, D.B. Paul, & J. Beatty (Eds.), *Thinking about evolution: Historical, philosophical, and political perspectives* (Vol. 2, pp. 119–140). New York: Cambridge University Press.

Gottesman, I.I. (1963). Genetic aspects of intelligent behavior. In N.R. Ellis (Ed.), *Handbook of mental deficiency: Psychological theory and research* (pp. 253–296). New York: McGraw-Hill.

Gottlieb, G. (1970). Conceptions of prenatal behavior. In L.R. Aronson, E. Tobach, D.S. Lehrman & J.S. Rosenblatt (Eds.), *Development and evolution of behavior* (pp. 111–137). San Francisco: Freeman.
Gottlieb, G. (1991). Experiential canalization of behavioral development: Theory. *Developmental Psychology, 27,* 4–13.
Gottlieb, G. (1992). *Individual development and evolution: The genesis of novel behavior*. New York: Oxford University Press. (Reprinted in 2002 by Lawrence Erlbaum Associates.)
Gottlieb, G. (1995). Some conceptual deficiencies in 'developmental' behavior genetics. *Human Development, 38,* 131–141.
Gottlieb, G. (1996). A systems view of psychobiological development. In D. Magnusson (Ed.), *The lifespan development of individuals: Behavioral, neurobiological, and psychosocial perspectives* (pp. 76–103). Cambridge, England: University of Cambridge Press.
Gottlieb, G. (2002). Emergence of the developmental manifold concept from an epigenetic analysis of instinctive behavior. In D. Lewkowicz & R. Lickliter (Eds.), *Conceptions of development: Lessons from the laboratory* (pp. 31–56). New York: Psychology Press.
Gottlieb, G., & Halpern, C.T. (2002). A relational view of causality in normal and abnormal development. *Development and Psychopathology, 14,* 421–435.
Greenough, W.T., & Black, J.E. (1992). Induction of brain structure by experience: Substrates for cognitive development. In M.E. Gunnar & C.A. Nelson (Eds.), *Developmental behavioral neuroscience* (pp. 155–200). Hillsdale, NJ: Erlbaum.
Griffiths, S.C., Owens, I.P.F., & Burke, T. (1999). Environmental determination of a sexually selected trait. *Nature, 400,* 358–360.
Gupta, A.P., & Lewontin, R.C. (1982). A study of reaction norms in natural populations of *Drosophila pseudoobscura. Evolution, 36,* 934–948.
Hinde, R.A. (1990). The interdependence of the behavioral sciences. *Philosophical Transactions of The Royal Society, London B, 329,* 217–227.
Ho, M.W. (1984). Environment and heredity in development and evolution. In M.W. Ho & P.T. Saunders (Eds.), *Beyond neo-Darwinism: An introduction to the new evolutionary paradigm* (pp. 267–289). San Diego, CA: Academic Press.
Hood, K. (in press). Development as a dependent variable: Robert B. Cairns on the psychobiology of aggression. In D.M. Stoff & E.J. Susman (Eds.), *Developmental psychobiology of aggression*. New York: Cambridge University Press.
Hughes, K.R., & Zubek, J.P. (1956). Effect of glutamic acid on the learning ability of bright and dull rats. I. Administration during infancy. *Canadian Journal of Psychology, 10,* 132–138.
Johannsen, W. (1909). *Elemente der Exacten Erblichkeitslehre* [Elements of the scientific doctrine of heritability]. Jena: G. Fischer.
Johnston, T.D., & Edwards, L. (2002). Genes, interactions, and the development of behavior. *Psychological Review, 109,* 26–34.
Kuo, Z.Y. (1970). The need for coordinated efforts in developmental studies. In L.R. Aronson, E. Tobach, D.S. Lehrman, & J.S. Rosenblatt (Eds.), *Development and evolution of behavior* (pp. 181–193). San Francisco: Freeman.
Lehrman, D.S. (1970). Semantic and conceptual issues in the nature–nurture problem. In L.R. Aronson, E. Tobach, D.S. Lehrman, & J.S. Rosenblatt (Eds.), *Development and evolution of behavior* (pp. 17–50). San Francisco: Freeman.
Lerner, R.M. (1991). Changing organism–context relations as the basic process of development: A developmental contextual perspective. *Developmental Psychology, 27*, 27–32.
Lerner, R.M. (2002). *Concepts and theories of human development* (3rd ed.). Mahwah, NJ: Erlbaum.
Loehlin, J.C. (1996). Genes and environment. In D. Magnusson (Ed.), *The lifespan development of individuals: Behavioral, neurobiological, and psychosocial perspectives* (pp. 38–51). Cambridge, England: Cambridge University Press.
Mackay, T.F.C. (2001). Quantitative trait loci in *Drosophila*. *Nature Reviews-Genetics, 2,* 11–20.
Magnusson, D., & Törestad, B. (1993). A wholistic view of personality: A model revisited. *Annual Review of Psychology, 44,* 427–452.
Molenaar, P.C.M., & Boomsma, D.I. (1987). Application of nonlinear factor analysis to genotype-environment interaction. *Behavior Genetics, 17,* 71–80.
Molenaar, P.C.M., Huizinga, H.M., & Nesselroade, J.R. (2003). The relationship between the structure of inter-individual and intra-individual variability: A theoretical and empirical vindication of developmental systems theory. In U.M. Staudinger & U. Lindenberger (Eds.), *Understanding human development* (pp. 339–360). Boston: Kluwer.
Newman, S.A., & Müller, G.B. (2000). Epigenetic mechanisms of character origination. *Journal of Experimental Zoology, 288,* 304–317.

Ordovas, J.M., Corella, D., Serkalem, D., Cupples, L.A., Couture, P., Coltell, O., Wilson, P.W.F., Schaefer, E.J., & Tucker, K.L. (2002). Dietary fat intake determines the effect of a common polymorphism in the hepatic lipase gene promoter on high-density lipoprotein metabolism: Evidence of a strong dose effect in this gene–nutrient interaction in the Framingham study. *Circulation, 106,* 2315–2321.

Overton, W.F. (1998). Developmental psychology: Philosophy, concepts, and methodology. In R.M. Lerner (Ed.), *Handbook of child psychology: Theoretical models of human development* (5th ed., Vol. 1, pp. 107–189). New York: Wiley.

Overton, W.F., & Reese, H.W. (1973). Models of development: Methodological implications. In J.R. Nesselroade & H.W. Reese (Eds.), *Life-span developmental psychology: Methodological issues* (pp. 65–86). New York: Academic Press.

Platt, S.A., & Sanislow, C.A. (1988). Norm-of-reaction: Definition and misinterpretation of animal research. *Journal of Comparative Psychology, 102,* 254–261.

Rampon, C., Tang, Y.P., Goodhouse, J., Shimizu, E., Kyin, M., & Tsien, J.Z. (2000). Enrichment induces structural changes and recovery from nonspatial memory deficits in CA1 NMDAR1–knockout mice. *Nature Neuroscience, 3,* 238–244.

Rutter, M., Pickles, A., Murray, R., & Eaves, L. (2001). Testing hypotheses on specific environmental causal effects on behavior. *Psychological Bulletin, 127,* 291–324.

Sarkar, S. (1999). From the *Reaktionsnorm* to the adaptive norm: The norm of reaction, 1909–1960. *Biology and Philosophy, 14,* 235–252.

Schaffner, K.F. (1998). Genes, behavior, and developmental emergentism: One process indivisible? *International Journal of Behavioral Development, 24,* 5–14.

Schlichting, C.D., & Pigliucci, M. (1998). *Phenotypic evolution: A reaction norm perspective.* Sunderland, Massachusetts: Sinauer.

Schneirla, T.C. (1949). Levels in the psychological capacities of animals. In R.W. Sellars, V.J. McGill & M. Farber (Eds.), *Philosophy for the future* (pp. 243–286). New York: MacMillan.

Thelen, E. (1990). Dynamical systems and the generation of individual differences. In J. Fagan & J. Colombo (Eds.), *Individual differences in infancy* (pp. 19–43). Hillsdale, NJ: Erlbaum.

Thelen, E. (1995). Motor development: A new synthesis. *American Psychologist, 50,* 79–95.

Tobach, E (1972). The meaning of cryptanthroparion. In L. Ehrman, G.S. Omenn & E. Caspari (Eds.), *Genetics, environment and behavior* (pp. 219–239). New York: Academic Press.

Turkheimer, E., Goldsmith, H.H., & Gottesman, I.I. (1995). Commentary. *Human Development, 38,* 142–153.

Valsiner, J. (2001). *Comparative study of human cultural development.* Madrid: Fundación Infancia y Aprendizaje.

*Venter, J.C. et al. (2001). The sequence of the human genome. *Science, 291,* 16 February 2001, 1304–1351.

Vreeke, G.J. (2000). Nature, nurture and the future of the analysis of variance. *Human Development, 43,* 32–45.

Waddington, C.H. (1957). *The strategy of the genes*. London: Allen & Unwin.

Wahlsten, D. (1990). Insensitivity of the analysis of variance to heredity-environment interaction. *Behavioral and Brain Sciences, 13,* 109–161.

Wahlsten, D. (2003). Genetics and the development of brain and behavior. In J. Valsiner & K.J. Connolly (Eds.), *Handbook of developmental psychology* (pp. 18–47). London: Sage.

Weiss, P. (1959). Cellular dynamics. *Reviews of Modern Physics, 31,* 11–20.

Weiss, K.M., & Fullerton, S.M. (2000). Phenogenetic drift and the evolution of genotype-phenotype relationships. *Theoretical Population Biology, 47,* 187–195.

Woltereck, R. (1909). Weitere experimentelle Untersuchungen über Artveränderung, speziell über das Wesen quantitativer Artunterschiede bei Daphniden [Further experimental investigations of species modification, particularly the nature of quantitative species differences in daphnia]. *Verhandlungen der Deutschen Zoologischen Gesellschaft, 19,* 110–173.

Wong, A.H.C., Buckle, C.E., & Van Tol, H.H.M. (2000). Polymorphisms in dopamine receptors: What do they tell us? *European Journal of Pharmacology, 410,* 183–203.

Wright, S. (1968). *Evolution and the genetics of populations: Vol. 1. Genetic and biometric foundations.* Chicago: University of Chicago Press.

*There are well over 200 co-authors of this article.