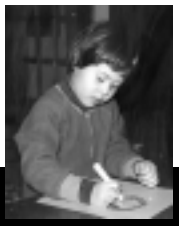
Chapter 5



Multiple Causes of Developmental, Learning and Behavioral Disability

Introduction

Diverse influences contribute to developmental, learning and behavioral disability. These influences are generally divided into two broad groups: genetic factors, determined by hereditary information contained in human chromosomes, and environmental factors, which include all non-genetic influences. Environmental influences can be further subdivided into several categories, including physical, chemical, infectious and social. Chemical factors, which are the focus of this report, are broadly defined as synthetic and naturally occurring substances to which an individual is exposed. Social-environmental factors are defined as encompassing family, cultural and socioeconomic variables.

It is widely recognized that influences from various domains interact in very complex ways,[1,2,3] though research has generally focused on one domain at a time. As a result, a truly over-arching framework and methodology have yet to be developed to examine the real-world interactions of these influences.

Genes or the Environment: An Outdated Dichotomy

Over the past 20 years, studies of twins and adopted children have clarified important genetic contributions to a variety of cognitive, behavioral and personality traits. Altogether these studies suggest that for many of these traits, heredity accounts for about 50% of the observed differences among individuals.[4,5] Some mistakenly take this as evidence that these traits are genetically determined. According to Robert Plomin, director of the Center for Developmental and Health Genetics at Pennsylvania State University, "research into heritability is the best demonstration…of the importance of the environment." If heredity accounts for 50% of the variability in a trait, the other 50% of variability must be due to environmental influences.[6,7] In other words, genetic and environmental influences seem to be roughly equal in determining many neurocognitive characteristics.[8]

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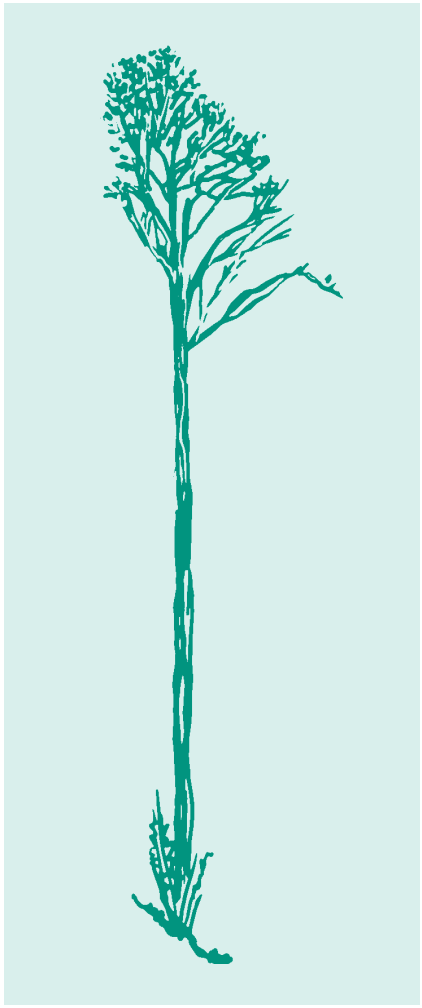
DEFINITION - *Genotype:*

The genetic makeup of an individual.

PHENOTYPIC PLASTICITY

Genotype is a term that refers to the specific genetic makeup of an individual, whereas phenotype refers to the traits or characteristics of that individual as they actually appear. For many traits, phenotype is only partially a result of the genotype. Environmental factors encountered during fetal development, or even after birth, also affect the phenotype. The variability of phenotypes for a given genotype or within populations of genetically similar individuals is called phenotypic plasticity.



Among the most dramatic examples of phenotypic plasticity are the marked differences in genetically similar individuals in different environments. For example, in the illustration, the tall thin tree actually grew in a dense forest, where rapid vertical growth was essential in order to compete successfully for light. The genetically similar, short, branched tree grew on a south-facing open slope where there was no competition for light, allowing the tree to grow in a very different manner. In general, phenotypic plasticity is a result of

both the environmental cues that trigger the variable phenotypes and the individual's capacity to respond to those cues, based largely in the genotype. In other words, phenotypic plasticity is a result of gene-environment interactions.

Phenotypic plasticity is of two types.[1] One is the spectrum of phenotypes that may be expressed by a given genotype in a range of different but relatively stable environments. To study this, one would look for the appearance of different traits in genetically similar populations located in different environments. The other type of plasticity refers to the response of individual organisms to variations in a single environment. In this case, either the ability to adapt, or conversely, the susceptibility to adverse effects from even minor environmental fluctuations, particularly during development, reflects the plasticity of the individuals.

In this report, we are largely concerned with the second type of plasticity when we note that, at most, genotype accounts for about 40-60% of the variance in neurodevelopmental traits or disorders, while the remainder is more persuasively explained by environmental factors and gene-environment interactions.

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Observers also point out that inferences from these studies are based on the simplistic assumption that genes and the environment have simple additive effects. [9] [10] In fact, current research shows that gene-environment interactions can be extremely complex. As summed up by Plomin and his colleague Gerald McClearn, also from the Center for Developmental and Health Genetics, in a recent review article: "simple approaches to complex phenotypes may lead to misleading or erroneous conclusions. Particularly inappropriate are questions couched in either -or ter ms: Is such and such a trait the result of genes or of environment? Unfor tunately , this type of thinking was promoted for decades by the natur e-versus-nur ture contr oversy , which convinced many academicians that they had to choose sides. W e hope that this brief overview has made apparent the intellectual bankruptcy of this either -or for mulation." [11]

Our approach to developmental disabilities can be informed by medical models for addressing other complex problems with multiple contributing factors. Atherosclerotic heart disease, the cause of heart attacks, is one example of a multifactorial problem in which modern medicine has had relatively good success, markedly reducing the incidence of the disease over the past several decades. [12] [13] [14] [15] Like developmental disability , ather oscler otic heart disease is influenced by a variety of factors, most of which have both genetic and environmental components.

The medical model for approaching atherosclerotic heart disease entails addressing all of the risk factors that are amenable to inter vention: obesity , smoking, elevated blood pressure and cholesterol, diabetes, diet and sedentary lifestyle. Identifying a genetic marker for risk of heart disease, (such as the apolipoprotein E4), does not as of yet trigger specific therapy , but it does indicate the need for more vigorous control of other risk factors. Applying such a model to learning and developmental disorders would argue for eliminating toxicant exposures, since they are readily preventable, and for improving the social environment of children at risk. While genes themselves cannot be altered, the environmental triggers for some genetic diseases can be reduced or eliminated. Clarifying genetic risks factors can also identify the children most in need of additional protection from toxicants and other adverse environmental factors, including social factors.

Rare Diseases Governed by Powerful "OGOD" Genes: the PKU Prototype

In 1984, for the first time, a gene associated with developmental disability was identified and localized within human chromosomes: the gene that causes phenylketonuria, (PKU), a rare disorder that occurs in 1 in 10,000 births. PKU is a prototype "single gene disor der." Such genes ar e also called OGOD genes, a term which stands for "one gene, one disor der."[16] The genetic component of a disease caused by an OGOD gene is controlled by one gene only, unlike the common developmental

DEFINITION - *Phenotype:*

The traits or characteristics of an individual as they actually appear. Phenotype results from the interaction of genotype and the environment.

DEFINITION - *Gene:*

The basic unit of heredity, consisting of a segment of DNA that codes for a particular product, such as an enzyme. Each gene occupies a certain location on a chromosome.

PHENYLKETONURIA (PKU)

In the past PKU was responsible for about 1% of cases of institutionalized mental retardation.[17] When a child inherits the PKU gene from each parent, the child cannot produce the enzyme phenylalanine hydroxylase, which is required to break down the amino acid phenylalanine.[18] This leads to the build up of phenylalanine in the blood, and, since high levels of phenylalanine are harmful to the developing brain, severe brain damage results. As another consequence of high blood phenylalanine levels, a related compound for which the disease is named, phenylketone, appears in the urine.

Simply by reducing phenylalanine in the diet, the build up of toxic metabolites is prevented, and neurologic development proceeds normally. Since phenylalanine, like other amino acids, is a building block of protein, it is found in all protein foods, particularly those high in protein such as fish, eggs, meat, cheese, and peanuts. By lowering the amount of protein in the diet, the trigger for the disease is removed, and the defective gene becomes harmless.

DEFINITION -
Amino acids:

Organic compounds, (marked by the presence of both an amino and a carboxyl group), which are the building blocks of proteins. 20 amino acids are used by the body for growth and metabolism. Some of these can be produced by the liver. The rest must be supplied in the diet.

disorders that are genetically influenced by the combined tiny contributions of a myriad of genes. Diseases that arise from single gene defects are in theory, at least, particularly amenable to intervention since they are associated with a single etiology.

Many rare disorders affecting neurodevelopment have been identified as OGOD disorders by a characteristic inheritance pattern. These rare disorders include other syndromes which, like PKU, are caused by the inability to metabolize various nutrients, including other amino acids and fatty acids. Like PKU, many of these disorders, as well as their developmental effects, are preventable if the problematic nutrient is reduced in the diet, beginning in early life. Specific genes responsible for many of these disorders have been identified. Dietary interventions to prevent these disorders, however, were developed on the basis of clinical studies long before the defective genes were identified. A newborn screening program for PKU, in fact, was in place in Massachusetts more than 20 years before the discovery of the PKU gene. Currently Massachusetts is piloting a newborn screening program that tests for 20 rare, metabolic diseases associated with developmental disability. Dietary interventions for these disorders also predated the identification of their respective OGOD genes.

While molecular genetics has allowed us to identify specific genes and to understand their chemical structure, it has not yet resulted in specific treatments for neurodevelopmental disability. Once a gene is identified, however, molecular genetics studies can begin to clarify how the gene causes disease. While no "quick fixes" have yet resulted from such investigations, it is believed the identification of genes will eventually lead to the development of specific preventions and treatments including environmental and pharmaceutical interventions.

Common Diseases Influenced by Multiple "Puny" Genes

In contrast to the powerful OGOD gene of PKU, genetic influence over the common disorders of learning and development appears to be controlled by the cumulative impact of innumerable genes. Such genes, which "act together in a probablistic fashion to influence a common trait" are referred to as "quantitative trait loci" (QTLs). The implication of this finding is that traits relevant to learning and development are influenced not by single genes, but by many genes, each of which makes a very small contribution towards the trait. In

the words of a prominent behavioral geneticist, each of these genes has a "puny effect on phenotype," that is, the trait as it's actually expressed. [19]

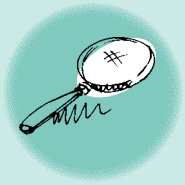
Gene-Environment Interactions: A Spectrum of Complexity

The complexities of gene-environment interactions in neurodevelopment are just beginning to be unraveled. However, it is already clear that there are an astounding variety of ways that genes and the environment can interact. PKU illustrates a straight forward "simple trigger" interaction involving one gene and one environmental factor. The three examples that follow illustrate more complex interactions.

Example 1: Complex Gene-Environment Interactions Mediate Some Effects of Organophosphate Pesticides

The gene-environment interactions that mediate the effects of organophosphate pesticides are extremely complex, and not yet completely understood. Some of the effects of organophosphate pesticides are mediated by at least five different enzymes, [20] some of which have been shown to be influenced by their own set of environmental and/or genetic factors. [21] [22] [23] [24] [25] [26] To illustrate the complexity of this interaction, we will focus on the two enzymes that have been most extensively researched to date: paraoxonase and acetylcholinesterase.

Since their development in the 1930s, organophosphate chemicals have been known to interfere with the function of acetylcholinesterase, an enzyme critical to the proper functioning of the nervous system. Acetylcholinesterase, which is found throughout the nervous system and the body in general,[27] is responsible for breaking down the neurotransmitter acetylcholine. Organophosphate pesticides (OPs), however, inhibit the enzyme and prevent it from performing this critical function.



ACUTE HIGH DOSE ORGANOPHOSPHATE POISONING, AN EXPRESSION OF MAJOR CHOLINESTERASE INHIBITION

Acetylcholinesterase inhibition has long been recognized in acute pesticide poisoning that follows high dose exposures to pesticides. This syndrome consists of over-activation and dysfunction of the considerable portion of the nervous system that uses the neurotransmitter acetylcholine. The consequences of this over-activation/dysfunction are comparable to the clinical effects of "nerve gas" agents designed for chemical warfare, chemicals from which some modern pesticides are derived. The grim picture of acute OP poisoning includes excessive secretions (salivation, tears and bronchial secretions), slowing of the respiratory rate, wheezing and respiratory distress, unstable pulse and blood pressure, muscle twitches followed by weakness or paralysis, vomiting and diarrhea, urinary and fecal incontinence, drowsiness, confusion and ultimately coma and death.[65]

DEFINITION - *Enzymes:*

Protein molecules, coded for by genes, that facilitate chemical reactions.

As a result, acetylcholine builds up at the junctions between nerve cells, first causing over-stimulation, and then complete dysfunction of the involved nerve pathway. At high exposures, this results in the characteristic symptoms of OP poisoning, which are identical to those caused by organophosphate chemical warfare agents.

While large exposures to OPs have long been recognized as causing the nerve gas syndrome, more recent animal studies have suggested that low dose exposures can cause more insidious injury to the developing fetus, and can do so at exposure levels that do not cause clinical symptoms in the mother. Concern about fetal toxicity arises from the fact that very small alterations in acetylcholinesterase function alter levels of acetylcholine in the developing brain. Because the multiplication and differentiation of brain cells are guided by local neurotransmitters, small changes in the concentration of acetylcholine caused by OP exposure may alter the developing architecture of the exposed brain, and impair a variety of behaviors later in life. (OPs also cause other forms of fetal neurotoxicity that are independent of the acetylcholinesterase mechanisms discussed here. See Chapter 6 for details.)

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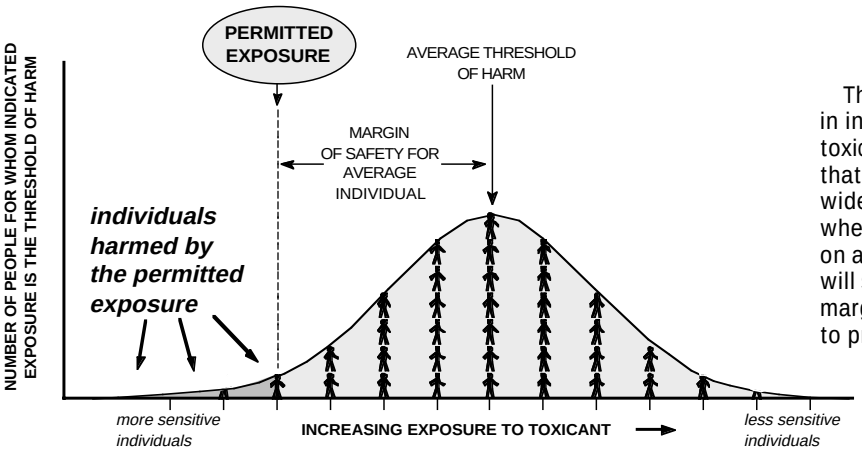
Genetic factors markedly modify these OP effects that are mediated through acetylcholinesterase. About 4% of the population carries a gene that produces a poorly functioning form of acetylcholinesterase.[28 29 30 31] This greatly increases an individual's vulnerability to cholinesterase inhibition by OPs, since the diminished reservoir of functioning enzyme is more easily overwhelmed by OPs. Cholinesterase levels are also affected by a variety of other factors including age, body weight, height, gender, pregnancy and liver disease.[32] Thus a host of antecedent factors, both environmental and genetic, interact to determine acetylcholinesterase levels, which in turn help determine the vulnerability of the fetal brain to environmental toxicants, in this case OPs.

Another genetically determined enzyme further modifies an individual's susceptibility to OP toxicity. This enzyme, paraoxonase, which is found in the blood, plays an important role in detoxifying several organophosphate pesticides.[33 34] For example, individuals vary 11-fold in the ability to deactivate the pesticide parathion depending on which gene they carry for this enzyme. Studies in mice show that low levels of paraoxonase increase susceptibility to chlorpyrifos (Dursban),[35 36] a pesticide to which the US population is widely exposed. High paraoxonase activity thus acts as a first line of defense against organophosphate effects. However, those with the relatively inactive form of paroxonase, an estimated 30%-38% of the population,[37 38] will be slower to break down these OPs and consequently more vulnerable to acetylcholinesterase inhibition. If in addition the individual has low levels of acetylcholinesterase, due to either genetic or environmental factors, the individual will have further increased susceptibility to acetylcholinesterase inhibition by organophosphate pesticides.

Thus, as demonstrated in animal studies, levels of OP exposure that are

Spectrum of Vulnerability



There is wide variation in individual sensitivity to toxicant exposure. This means that in a large population with widespread exposures, even when the dosage is acceptable on average, many people will still be hurt. A significant margin of safety is required to prevent such injuries.

well tolerated by some individuals may cause permanent alterations in brain development and behavior in those who are more vulnerable due to a complex mix of genetic, age-related and environmental factors.

Individual differences in vulnerability are widely recognized by scientists, but may be vastly under -estimated by r egulatory agencies. In chemical regulation, for example, EP A has typically used a standard tenfold uncertainty factor to account for all known and unknown human variability in susceptibility to that chemical, including differences between adults and childr en. Yet as pr eviously discussed, paraoxonase activity alone varies by a factor of 11. Since there are four other enzymes that mediate OP toxicity whose variability has not yet been characterized, individual differences in vulnerability to OPs may be several orders of magnitude greater than the 10-fold variation currently recognized by regulatory agencies.

Only after specific research on a particular chemical has been conducted to demonstrate greater differences in vulnerability will regulatory agencies consider implementing policies that are more protective than the standard practice. Unfortunately such "after the fact" regulation allows generations to be harmed in the time required to clarify the complex interactions that create vulnerability .

Example 2: Gene-Environment Interactions in "PANDAS," Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection

Another important area of gene-environment interactions involve antibody reactions to infection. One example of this interaction has recently been recognized in subsets of patients with several neuropsychiatric disorders. These patients, whose symptoms markedly worsen following infections with Group A streptococcus, (the cause of "strep throat") are considered to have PANDAS. Post-str eptococcal exacerbations have been shown to occur in several disorders in which repetitive behaviors are a prominent feature. These include the neuropsychiatric

DEFINITION - *Obsessive compulsive disorder:*

A disorder characterized by recurrent and persistent thoughts or impulses that are experienced as intrusive and cause marked anxiety. May be accompanied by repetitive behaviors (such as hand washing, ordering, counting) the person feels compelled to do according to rigid rules.

DEFINITION - *Tics:*

Sudden, rapid, recurrent, stereotyped, involuntary motor movements or vocalizations. May include actions such as eye blinking, neck jerking, facial grimacing, stamping, and repeating words out of context. They are typically exacerbated by stress, and stop during absorbing activities and sleep.

DEFINITION - *Tourette's Disorder:*

A syndrome consisting of multiple motor and vocal tics causing significant impairment in social or occupational functioning.

DEFINITION - *Antigen:*

A protein or carbohydrate marker on the surface of a cell that identifies the cell as "self" or "non self".

syndrome obsessive-compulsive disorder (OCD), and two involuntary movement disorders, tics and Tourette's syndrome. [39] [40] While post-streptococcal exacerbations have not been documented in autistic children, limited immunologic data suggest that many autistic children have the same genetic susceptibility to post-streptococcal immune reactions. [41]

The clinical significance of PANDAS has not yet been clarified. However, several lines of evidence support an emerging consensus that PANDAS represents a valid diagnostic construct[42] and that PANDAS results from a unique gene-enviroment interaction. One line of evidence involves a series of immunologic studies. In these investigations, patients with PANDAS have been shown to carry an immune marker in the blood (B lymphocytes with D8/17 antigen), which has been previously identified as a marker of susceptibility to rheumatic fever, a serious inflammatory disease that occasionally follows streptococcal infection. A high incidence of OCD and involuntary movement disorders in rheumatic fever provides a second, clinical line of evidence supporting a link between streptococcal infection and neuropsychiatric disease.[43] [44]

There is also limited neuroimaging support for the PANDAS construct. This is provided by a case report in which serial magnetic resonance imaging (MRI) studies revealed acute enlargement in a particular area of the brain (basal ganglia) concurrent with post-streptococcal exacerbations of OCD. [45] And finally, the construct is supported by a recent National Institute of Health study that showed therapies that reduce immune reactions (plasma exchange and intravenous immunoglobulin) are effective in reducing symptom severity in children with post-streptococcal OCD, Tourette's syndrome and tic disorders. [46]

An autoimmune mechanism has been proposed that suggests PANDAS result from streptococcal antibodies that cross react with critical brain structures (basal ganglia) in genetically susceptible children. [47] [48] [49] [50] [51] This proposed mechanism as well as the clinical significance of the PANDAS syndrome will need to be further clarified by larger, more comprehensive prospective studies that track infectious, immunologic and neuropsychiatric events and outcomes.

Example 3: Gene-Environment Interactions Affecting Lead Metabolism

Gene-environment interactions have also been identified that affect the way the body handles lead. These interactions involve a gene coding for the delta ALA enzyme (delta aminolevulinic acid dehydratase), which has been shown to affect lead metabolism, bone storage and blood lead levels. While studies have begun to understand how the gene influences the way the body handles lead, the influence of the gene on the neurotoxicity of lead has not yet been clarified. [52] [53] [54] [55] [56] [57] [58] [59] [60]

The Role of the Social Environment

Toxicants and genetics have emerged as important influences in learning and development over the past two to three decades. The important role of the social environment in human development,

however, has been recognized for most of the 20th century.[61] A large body of research documents the associations between social environmental factors and developmental outcomes.[62] For instance, good parental mental health, social supports, education and parenting style characterized by reciprocity have all been associated with improved developmental outcomes. A large scale intervention study has also shown that social supports, parenting skills training and high quality early childhood education improve developmental outcomes in high risk children.[63] [64]

As a practical matter, the importance of the social environment is underscored by the fact that both the assessment of developmental disability as well as management interventions occur mainly in the domain of the social environment. The psychologists and educators who deal with the bulk of learning and developmentally disabled children are generally trained in behavioral traditions that focus on the social environment. In contrast, toxicology and genetics have not yet been routinely translated into the clinical domain, with the notable exception of medical screening programs that test infants for lead, PKU, hypothyroidism and a variety of rare metabolic diseases caused by gene defects.

The importance of the social environment is extensively addressed in other literature. We will therefore not discuss the social environment further in this report except to acknowledge its importance as both a causal factor and as a therapeutic modality in learning and developmental disabilities.

An autoimmune mechanism has been proposed that suggests PANDAS result from streptococcal antibodies that cross react with critical brain structures (basal ganglia) in genetically susceptible children.

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