

Mental Retardation and Developmental Disabilities Influenced by Environmental Neurotoxic Insults

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This paper sets a framework for the discussion of neurotoxicity as a potentially major contributor to the etiology of many types of mental retardation and developmental disabilities. In the past the literatures on developmental neurotoxicology and on mental retardation have evolved independently, yet we know that the developing brain is a target for neurotoxicity in the developing central nervous system through many stages of pregnancy as well as during infancy and early childhood. Our definitions and theories of mental retardation and developmental disabilities affect the models of neurotoxicity we espouse. For instance, models of developmental risk in neurotoxicology have guided environmental regulation to reduce the likelihood of neurotoxic effects. On the other hand, models of developmental risk for mental retardation aim not only at primary prevention, but also at secondary and tertiary prevention through early intervention. In the future, dynamic models of neuroplasticity based on the study of gene-brain-behavior relationships are likely to guide our views of developmental neurotoxicology and prevention of mental retardation and other disabilities. *Key words:* brain development, developmental disability, environmental toxins, mental retardation, neurotoxicity, risk assessment. — *Environ Health Perspect* 108(suppl 3):395-399 (2000). <http://ehpnet1.niehs.nih.gov/docs/2000/suppl-3/395-399schroeder/abstract.html>

The goal of this overview is to set a framework for the discussion of neurotoxicity as a potentially major contributor to the etiology for many types of mental retardation and developmental disabilities (MRDD). It is odd that these two literatures have not intersected more than they do. The *American Journal on Mental Retardation* (American Association on Mental Retardation, Washington, DC) is generally considered one of the leading interdisciplinary research journals on MRDD in the United States. Yet, out of over 1,000 submissions in the past 5 years, only a handful of them dealt with neurotoxicity and its contribution to mental retardation (MR). Similarly, the neurotoxicology literature does not reveal the dynamic conceptualizations of MRDD that exist in the MRDD research literature. The present paper examines the overlap and some potentially mutually beneficial contributions from these two literatures. Three broad topics are covered: definitional and theoretical issues of MRDD; pre- and perinatal biological and environmental risk factors and their interactions; and issues in neurotoxicity and MRDD.

Definitional and Theoretical Issues in MRDD

Mental Retardation

There are two widely accepted definitions of MR in the United States. One definition was adopted by the American Association on Mental Retardation (AAMR) in 1992 (1):

Mental retardation refers to substantial limitations in present functioning. It is characterized by significantly subaverage intellectual functioning, existing concurrently with related limitations in two or more of the

following applicable adaptive skill areas: communication, self-care, home living, social skills, community use, self-direction, health and safety, functional academics, leisure, and work. Mental retardation manifests before age 18.

The other definition was adopted by the American Psychiatric Association in 1994 in the fourth edition of its *Diagnostic and Statistical Manual of Mental Disorders (2) (DSM-IV)*:

a. Significantly subaverage intellectual functioning: an IQ [intelligence quotient] of approximately 70 or below on an individually administered IQ test (for infants, a clinical judgment of significantly subaverage intellectual functioning).

b. Concurrent deficits or impairments in present adaptive functioning (i.e., the person's effectiveness in meeting the standards expected for his or her age by his or her cultural group, in at least two of the following skill areas: communication, self-care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health and safety).

c. Onset before the age of 18.

Code based on degree of severity reflecting level of intellectual impairment:

317: Mild mental retardation—IQ level 50–55 to approximately 70;

318.0: Moderate retardation—IQ level 35–40 to 50–55

318.1: Severe mental retardation—IQ level 20–25 to 35–40

318.2: Profound mental retardation—IQ level below 20 or 25

319: Mental retardation, severity unspecified—when there is a strong presumption of mental retardation but the person is untestable by standard intelligence tests.

There is considerable overlap between the two definitions, but there are also important differences. The similarities include: *a*) they both still emphasize subaverage intellectual functioning occurring during the developmental period before 18 years of age; *b*) they both include concurrent impairments in adaptive functioning in at least two of ten social skill areas; and *c*) they both use multi-dimensional systems incorporating intellectual, adaptive, emotional, physical, health, and environmental considerations. Both of these definitions have changed several times over the years—the AAMR nine times, and the *DSM-IV* four times—to incorporate contemporary thinking and theory on MR.

The AAMR definition is designed to deemphasize people's limitations related to lower IQ and to emphasize their strengths and capacities facilitated by supportive environments. These assumptions reflect the current national policy promoting independence, productivity, and inclusion of people with MRDD in the mainstream of American society.

The main differences between the *DSM-IV (2)* and AAMR (1) definitions are the IQ cutoff of 70 for *DSM-IV* versus 70–75 for AAMR and the retention of IQ levels of MR (mild, moderate, severe, and profound) for *DSM-IV* but not for the AAMR definition. In the case of the AAMR definition, raising the IQ cut-off functionally to 75 has the potential of doubling the population of people with a label of MR (3). Therefore, eligibility for special educational and vocational services as well as Medicaid benefits would

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also increase. This is an important social policy change, especially since the new federal Child Welfare Reform Legislation, passed in 1997, will actually reduce the eligibility of needy families who have children with disabilities (4,5).

Discarding the levels of MR in the AAMR definition has also had several effects. First, the differentiation between children with mild MR or learning disabilities has become blurred in school placement decisions (6). Second, IQ is used less than the discrepancy between a student's behavior and his or her expected achievement in teacher decision-making. Third, IQ alone, usually without the use of adaptive behavior measures, is used mostly for determining eligibility for services to meet the letter of the law only. Fourth, researchers, especially those in biomedical fields, tend to favor the *DSM-IV* definition because it preserves the different levels of MR that are useful in differentiating various organic conditions and because it maintains an emphasis on differential diagnosis.

The federal definition of developmental disabilities as enacted in the Developmental Disabilities Act of 1990 (7) is:

Developmental Disabilities. Developmental disabilities means a severe and chronic disability that is attributable to a mental or physical impairment or combination of mental and physical impairments, and is manifested before the person attains age 22, and is likely to continue indefinitely, and results in functional limitation in three or more of the following areas of major life activity: self-care, receptive and expressive language, learning, mobility, self-direction, capacity for independent living, economic self-sufficiency, and reflects the person's need for a combination and sequence of special, interdisciplinary or generic care, treatment, or other services that are of life-long or extended duration and are individually planned and coordinated.

The federal definition was really the forerunner to the AAMR (1) 1992 and *DSM-IV* (2) 1994 definitions. The cut-off age for the developmental period in the federal definition is 22 instead of 18 years. Although approximately half of the functional limitation categories overlap with the definitions for MR, there are also several differences. By this definition, it is possible to have a developmental disability without MR, e.g., autism, cerebral palsy, spina bifida, epilepsy, mental illness, etc. Similarly, it is possible to have MR but not a developmental disability. In fact, the majority of people with mild MR do not carry either label into adulthood and do not receive specialized services for their developmental disabilities. This is much less frequently the case for people with moderate, severe, or profound MR.

Because of the great overlap between MR and other developmental disabilities, we increasingly tend to combine them under the heading MRDD.

Contemporary Theories of MRDD

Since World War II, there have been several comprehensive theories of MR. One group of theories, typified by Ellis' deficit theory (8), viewed intelligent behavior as a general ability, the so-called "g" factor, which consists of a set of intellectual processes, one or more of which may be deficient among people with MR. The goal was to find a small subset of deficient processes while the rest remained intact, thus differentiating people with and without MR.

Zigler's developmental theory (9), on the other hand, hypothesized that people with MR develop more slowly and reach a lower asymptotic level of development than do their intellectually normal counterparts. However, when they have equal mental age, no intellectual differences are found. Differences in developmental rate are due to genetic variation, whereas the remaining differences are due to sociocultural factors. Zigler's theory applies mainly to individuals with IQs above 50. The developmental versus deficit theories of MR are being debated even today.

More recent theories of retarded intellectual functioning, e.g., Detterman (10), consider mental ability as a complex system of interrelated primary abilities. To understand MR, we must study how the individual primary abilities function together as a whole system. The task is to find an optimum set of measures that reveal how the system functions as a whole with a view to understanding the underlying mechanisms. Although there are currently several variations of theories of intelligence relevant to MR, e.g., Sternberg (11), Ceci (12), and Gardner (13), they all pursue strategies similar to this one.

Importance of Definitions and Theories of MRDD to Neurotoxicology

Why are these definitions and theoretical accounts of MRDD important to the field of neurotoxicology? These definitions and theories affect the models of neurotoxicity we espouse. Do we adopt a strict research definition or do we try to incorporate the much more difficult definition that combines policy and practices? Relying on a standard test or an experimental measure may yield cleaner results, but will it have ecological and social validity? Do we adopt a deficit model of neurotoxicity? Experience from research on MR suggests that we will find most of the defects we look for. So what? The trick is to find a differentiated subset and show their dynamic

interactions with other biological and environmental variables over time, perhaps the life span. For instance, Weiss (14) notes that there are some neurotoxins that appear to accelerate the aging process. Bellinger (15), in an excellent commentary on interpreting the literature on lead and child development, chides researchers for "neglecting the role of the experimental system" when comparing and reconciling disparate findings. He suggests looking at the field of behavior toxicology as a model experimental system. His final comment says it well:

Although available data provide a solid empirical foundation for current public health policy, they do not provide very satisfactory answers to the most fundamental questions about the impact of lead on a child's nervous system. Now that the basic policy issues seem largely settled, it is time to rethink our assessment goals and strategies and our interpretational approaches so that we may gain greater insight into the pathophysiology of lead's behavioral toxicity in children.

Interactions of Prenatal and Perinatal Factors in MRDD and Its Prevention

What are some of the dynamic interactions we can expect to find in linking gene-brain-behavior relationships found in MRDD with environmental neurotoxic insults? How will this knowledge aid in the prevention of MRDD?

Genetic Conditions and MRDD

There are approximately 6,000 known genetic disorders whose effects are also related to MRDD (16). Thanks to the Human Genome Project (17), the number is growing rapidly. Some of the most interesting genetic disorders are those related to MRDD. Lesch-Nyhan Syndrome, for instance, is a sex-linked disorder of purine metabolism that also results in a depletion of dopamine in the basal ganglia. Breese et al. (18) hypothesized that neonatal depletion of dopamine receptors is responsible for the distinctive phenotype of self-biting exhibited by most Lesch-Nyhan cases. It appears that the combination of a genetic susceptibility, abnormal brain development, and environmental reinforcement combines at about the age of 6-18 months to develop this intransigent self-biting for which there is no satisfactory intervention to date.

Recently Rodier et al. (19) reported that some forms of autism arise from toxic insults. Thalidomide or valproic acid effects during neurulation in a window of time just after neural tube closure is another example of how gene-brain-environmental interactions can cause MRDD.

Environmental Conditions Affecting Biological Risk for MRDD

There are a host of environmental conditions that affect biological risk for MRDD in the pre- and perinatal period: *a*) maternal infections, e.g., rubella (20); *b*) suboptimal pregnancy conditions, e.g., substance abuse (21); *c*) immune system response, e.g., pediatric acquired immunodeficiency syndrome (22); *d*) maternal exposure to toxins, e.g., heavy metals (23); and *e*) psychosocial conditions, e.g., caregiving environment, socioeconomic status, and parental education (24). Most of these conditions are preventable. In several cases, we as a society have been remarkably successful in preventing their effects. Congenital rubella syndrome is a case in point. In 1963–1965 there was an epidemic of > 25,000 cases of congenital rubella syndrome in the United States. However, since the development of the rubella vaccine in 1969, incidence has dropped markedly. In 1996 only two cases of congenital rubella syndrome were

reported in the United States (25). In other cases, we have not been so successful.

Various points of known insult and intervention during the prenatal development cycle can result in MRDD. Abnormal development of gametes, or immunologic and/or endocrinologic imbalances during early embryo development, are important determinants of MRDD (26). Many researchers are now focused on filling in major gaps in our knowledge of risk factors during pregnancy that are related to MRDD. For instance, the Dalton et al. (27) knockout mouse model showed that metallothionein genes are critical to protection of the developing embryo from zinc deficiency and from the toxic effects of cadmium (27). Elevated cadmium levels have been related to learning disabilities (28) and impaired cognitive function in school-aged children (29).

Risk Models of MRDD

Environmental neurotoxicology has become a component of environmental risk assessment. Risk assessments in environmental neurotoxicology are aimed primarily at prevention by environmental regulation. The main risk models in the MRDD field, on the other hand, are aimed at prevention through early intervention. They all incorporate intervention strategies organized around primary, secondary, and tertiary prevention as exemplified in Table 1. They all assume considerable neuroplasticity on the part of the child and modifiability of the environment. Both strategies are needed.

Horowitz's (30) developmental prevention model (Figure 1 is an outgrowth of Sameroff and Chandler's (31) continuum of caretaker casualty. The Horowitz model is a transaction model of risk that assumes the organism affects the environment (and vice versa) differently at different points in life to yield developmental outcomes in the areas of motor behavior, cognition/language,

social/emotional, and behavioral development, i.e., learning and performance. The transactional model assumes that these influences do not occur in a linear fashion. Rarely is a single risk factor related to a single outcome. Rather, they can be facilitated or mitigated by resilience factors that affect an organism's vulnerability by early intervention and by environmental modification. Biological factors are important early in life, whereas the environment becomes more important later. Universal behaviors, e.g., walking, are less modifiable by the environment than nonuniversal behaviors such as language acquisition. The model is based on a number of risk literatures in addition to neurotoxicology (Table 2). It is more of a descriptive scheme that tries to organize a large body of risk research as it relates to child development and MRDD.

The Biosocial Systems Model by Ramey et al. (32) comes out of the authors' research on early educational intervention with high-risk socially disadvantaged infants and young children (33) (Figure 2). Two well-known intensive center-based interventions, the Abecedarian Project (34) and the Infant Health and Development Program (35), a large multisite replication of the Abecedarian Project, showed lasting effects after 10 years of follow-up. The first children are nearing high school graduation and are still being followed.

The optimal timing for intervention proved to be during infancy and preschool years. In this model, risk is viewed as the disequilibrium resulting from adverse effects and the inability to control them. Interventions are adaptations that make the person less vulnerable to the risk condition. Biological risk factors, such as neurotoxic risks, are seen as stressors on the system to be removed or mitigated. This model is relatively silent about biological risk factors. It is used more to delineate secondary and tertiary prevention. The effects

Table 1. Prevention of mental retardation.

Prevention services	Target group
Primary prevention	
Genetic services	Women medically at risk
Genetic counseling	Low-income women
Nutritional supplements	Teenage mothers
Family planning	Older women
Prenatal care	Births genetically at risk
Maternal education	
Medical services	
Secondary prevention	
Newborn intensive care	Newborn
Intervention programs	Infancy/early childhood
Developmental follow-up	Low-income families with children
Special care	Premature births
Family/infant care	
Medical services	
Social services	
Tertiary prevention	
Special education	Individuals with severe/profound MR
Sex education	Victims of accidents
Driver education	Victims of catastrophic illness ^a

^aFor example, encephalatic, Reyes syndrome.

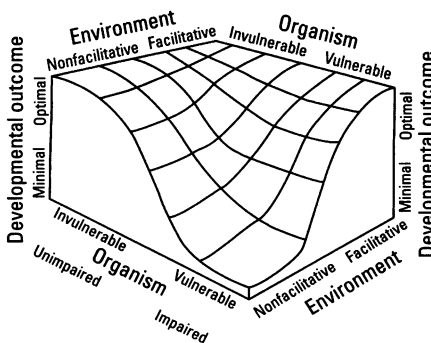


Figure 1. Horowitz's developmental prevention model (30).

Table 2. Risk literatures.

Risk literature	Terms	Ages
High-risk infant	At-risk Biological risk Social risk	Prenatal Neonate Infants
Conduct disorder	Deviant Delinquent Aggressive	Middle childhood Adolescent
Behavioral toxicology and teratogenesis	Specific risk elements: lead, methylmercury, alcohol, etc.	Animal analogs Infants Preschool Middle childhood
Developmental psychopathology	Emotionally disturbed Specific syndromes Vulnerable/resilient	Middle childhood Adolescent
Sensitive periods	Critical, optimal sensitive epochs for environmental events	Animal analogs Infants Adolescents

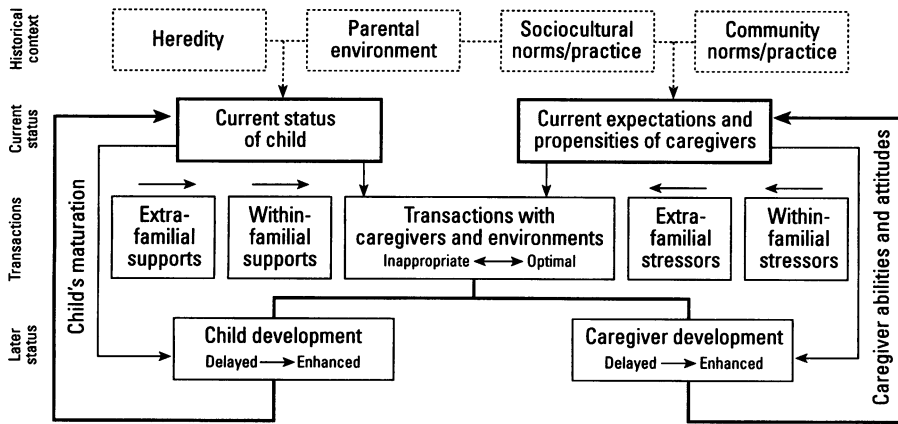


Figure 2. The biosocial systems model for early development. Reproduced from Ramey et al. (32), with permission of the American Psychological Association.

of biological risk factors are usually controlled by statistical modeling strategies or through sampling tactics in these studies.

“The new morbidity” (Figure 3) was a term coined by Haggerty et al. (36) and updated by Baumeister and Kupstas (37) to refer to the multivariate constellation of risk factors that lead to MRDD. The new morbidity model has been adopted by the President’s Committee on Mental Retardation (38) and by many states in their plan for prevention of developmental disabilities. In contrast to the previous model developed by Ramey et al. (32), the new morbidity model aims at primary prevention. It specifies five major types of variables: a) predisposing variables, i.e., demographic, behavioral, and genetic/biological; b) catalytic variables, including acute and chronic poverty and related political, economic, and social conditions; c) resource variables, i.e., quality of life enhancers, backup systems, and empowerment; d) proximal variables, i.e., variables immediately relevant to a risk condition such as low birthweight, prematurity, etc.; and e) outcome variables, i.e., the results of the combinations and interactions of the other four groups of variables.

Of the three models, perhaps the new morbidity model is most suited to neurotoxicology research in that it is heuristic in its description of the many variables relevant to neurotoxicology and it stresses dynamic interactions and timing of variables. Its testability remains to be seen. Nevertheless, it is food for thought that reflects the complexity of our task.

Issues of Neurotoxicity Related to MRDD

Developing Brain as a Target of Neurotoxicity

By definition, the developing brain is central to the issues of neurotoxicity and MRDD.

Almost all birth defects involve impaired central nervous system (CNS) functioning. Rodier (39) showed how neurotoxins may interfere with various specific developmental CNS processes during neuron proliferation, cell migration, synaptogenesis, cell death, formation of transmitters and receptors, trimming of connections, myelination, and development of the blood–brain barrier. All of these developmental processes are necessary for a well-timed and fine-tuned CNS. Each of them is impaired by at least one neurotoxin, any one of which could lead to scrambled or impaired behavioral function. Our knowledge of these functional impairments grows daily. We know a substantial amount about only a few neurotoxins, such as lead and methylmercury. There is a vast area that mostly remains to be explored and exposure to environmental neurotoxins could account for a wide variety of cases of MR currently classified as due to unknown causes.

Dimensions of Risk of MRDD Due To Neurotoxic Agents

Weiss (40) succinctly summarizes the dimensions of neurotoxic risk for MRDD. a) A neurotoxin may elevate the incidence or prevalence of some disease or disability. Even a low incidence distributed over a large population is a significant adverse effect. b) A neurotoxin may cause a shift in population distribution of scores on a particular measure or test. A small shift may have large implications for public health. c) Gestational exposure may exert lifetime consequences. In some cases, they may be delayed until adulthood or senescence. d) The aging process may be accelerated. e) The insult may take the form of reduced compensatory capacity. f) Rate of recovery from a reversible effect may be impeded. Two more items should be added to this list: g) age of vulnerability, e.g., child versus adult and h) type of exposure, e.g., acute versus chronic.

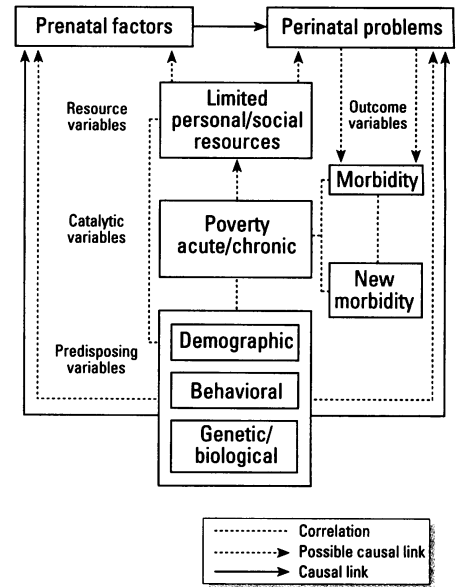


Figure 3. The new morbidity model of risk for mental retardation (37): proximal variables.

Specific Classes of Environmental Toxins Researched among Humans

We know a sufficient amount about only a few environmental neurotoxins and their effects on MRDD. The various classes of neurotoxins, in the approximate order of the amount we know in humans, are heavy metals, polychlorinated biphenyls, pesticides and herbicides, organic solvents, environmental tobacco smoke, radiation, and endotoxins. By far the most researched in terms of behavioral and neurotoxic effects related to MRDD are the heavy metals, especially lead and methylmercury. This work has been very productive in implementing public health regulations as well as in developing our methodological sophistication. However, now it is time to extend this work to other known neurotoxins and newly suspected toxins, such as endotoxins. Looming large on the horizon are the combined effects of a variety of neurotoxins as exemplified in the Superfund cleanup projects. On a basic science level, we know of many cumulative interactive effects of several environmental toxins, but the assessment technology in humans remains to be worked out. This is the technology we are likely to need in the next century.

Conclusion

The naturalist E.O. Wilson wrote *Consilience: The Unity of Knowledge* (41). According to Wilson (41), the concept of consilience is

a jumping together by linking of facts and fact-based theory across disciplines to create a common groundwork of explanation. The consilience of inductions takes place when an induction, obtained from a class of facts, coincides with an induction obtained from another different class. This consilience is the test of the truth of a theory.

Wilson then applied his notion to the sciences, the humanities, the arts, and religion. His point is that we must cast a wide interdisciplinary net if we are going to save our planet. We are not exempt from evolution: We are part of it. He then mobilizes data from world population growth rates, food production capacity, and the loss of important ecosystems to illustrate how interdependent these systems are.

Here are some disturbing facts according to Wilson (41):

- In 1950, 68% of the world population lived in developing countries. By 2000, it will be 78%. Setting aside the problem of hunger and poverty, how will that affect the gene pool? The stakes are high.
- The global population is precariously large and will grow even more before peaking around 2050. If the average woman bore 2.1 children (currently it is 2.6), it would level off at 8.5 billion by 2150. If 2.2, then 20.8 billion by 2150.
- The world can probably support 4–16 billion people. By 1990, Canada, the United States, Argentina, the European Union, and Australia accounted for more than 75% of the world's grain resources. Most of the world is not arable.
- With global warming, food production will become more variable. Competition for food and natural resources was the cause of the recent local struggles in Africa. Rwanda is a case in point.
- We do not know how to restore ruined ecosystems on a large scale. An environmental bottleneck is unfolding in the next century. We have to use our resources more carefully to survive.

How does neurotoxicity fit into this Orwellian scenario? Easily: environmental pollutants continue to grow in prevalence and amount at an exponential rate. Early (developmental) exposure to environmental pollutants can lead to increased likelihood of MRDD. People with MRDD are some of the most vulnerable members of our society. Studying the effects of neurotoxicity on their development can be an early warning system of what is happening to all humans and their sustainabilities on our planet. The Human Genome Project (17), new morbidity model of prevention

(36,37), and Wilson's consilience model (41) suggest strongly that this is the case.

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