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## Epidemiology and Etiology of Mental Retardation

**SUZANNE McDERMOTT, MAUREEN S. DURKIN,  
NICOLE SCHUPF, and ZENA A. STEIN**

Mental retardation (MR) is a manifestation of a heterogeneous set of impairments and conditions that result in cognitive limitation. It is a condition of medical, educational, and social importance. Physicians identify profound, severe, and moderate MR but rarely diagnose mild MR unless it is associated with a genetic or medical syndrome. From a medical perspective, the quest for etiology and the possibility of medical or surgical intervention to minimize deterioration are paramount. Educators, on the other hand are less concerned with causation than with academic achievement and school success. The majority of cases of mild MR is identified in school settings. Finally, the public uses the label to describe poor adaptive skills. Adults with MR who hold jobs, live independently, and participate in society are not always described as having MR. Thus some individuals characterized in childhood or adolescence as having mild MR become indistinguishable from the general population in adulthood.

There are numerous definitions of MR but the two most widely used in textbooks and research articles are the American Association on Mental Retardation [AAMR] (AAMR, 2002), recently revised and most often used in the United States, and the *International Classification of Diseases* (ICD-10) (World Health Organization [WHO], 1992) the most widely used classification in other countries of the world. The AAMR definition is a practical tool for the determination of service eligibility; the ICD-10 allows for levels of disability and is based on a medical model of classification.

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**SUZANNE McDERMOTT** • Family Practice Center, Department of Family and Preventive Medicine, USC School of Medicine, Columbia, South Carolina 29208. **MAUREEN S. DURKIN** • University of Wisconsin—Madison, Madison, Wisconsin 53726. **NICOLE SCHUPF and ZENA A. STEIN** • Columbia University—New York, New York 10032.

Identification of the causes of MR has been a U.S. goal since the 1960s when the President's Committee on Mental Retardation was first formed by President John F. Kennedy. The search for etiology was fueled by the desire to prevent incident cases and this was coupled with the belief that scarce resources were needed for the lifelong care of individuals with MR. Research related to the search for causation requires a multidisciplinary approach, including the fields of neuroscience, genetics, epidemiology, and numerous medical specialties.

## DEFINITIONS AND CLASSIFICATIONS

There are differences among the conceptual bases for defining MR and variations in the methods of ascertaining cases. The primary source of population-based data is household surveys. The United States conducts the *National Health Interview Survey* (NHIS) (National Center for Health Statistics, n.d.) which includes questions about impairments including MR. Administrative registries are often used to describe population rates of MR but these should be carefully interpreted because the criteria for participation in the program and its registry of needs vary. Some state and local programs are entitlements for eligible citizens, but not all citizens with the condition agree to be tested and deemed eligible. Other state programs are need-based with both economic and disability determinations. Thus, administrative registries are often not complete counts of individuals with MR but represent a combination of needy citizens and selective eligibility.

Age-specific rates of MR vary widely across different surveys. In order to appreciate the reasons for variability among age-specific rates of MR, definitions and classification systems must be considered. There are three main classification schemes used in the United States: the AAMR version is used by most adult service providers, the medical community uses the ICD-9 or ICD-10, the psychiatric practitioners use the *Diagnostic and Statistical Manual* (DSM) (American Psychiatric Association [APA], 1994), and state public education systems use variations of these. In addition, there has been a movement away from strict case-definitions that rely on standardized testing to a more functional and dynamic definition. Both the AAMR and the medical/rehabilitation international communities have moved from testing-based criteria to an assessment of needed supports.

## CLASSIFICATION SCHEMES

Both national and international organizations have developed classifications for MR. These are summarized in Table 1.1.

In the United States the most widely accepted definition is taken from the 2002 version of the *Classification of Mental Retardation* published by the AAMR (AAMR, 2002): "MR is a disability characterized by significant limitations both in the intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills. This

**Table 1.1.** Principal Classification Systems for Mental Retardation in Common Use: 2005

Organization	Groups	Use
American Association on Mental Retardation (AAMR, 1992, 2002)	Mild, moderate, severe/profound intellectual deficit combined with intermittent, limited, extensive, and pervasive need for support	U.S. service agencies and institutions
World Health Organization (WHO, 1980a, 1980b, 1992), International Classification of Disease ICD-9 and ICD-10	Code groups: 317, 318, 319	Medical practice and research
World Health Organization (WHO, 1980a, 1980b, 2001), International Classification of Functioning (ICF) and ICIDH	Classification of functioning, disability, activity, and participation	International service agencies
American Psychiatric Association, Diagnostic and Statistical Manual (DSM-IV) (APA, 1994)	Multi-axial system of five domains—clinical mental disorders, general medical conditions, psychosocial and environmental problems, overall functioning	Psychiatry
Schools	Mild or educable, moderate or trainable, severe/profound	Public schools

disability originates before age 18.” The AAMR classification recognizes that intellectual functioning is still best represented by IQ scores when obtained from appropriate assessment instruments. The criterion most widely used for labeling and diagnosis is two standard deviations below the mean score of a group of people thought to be representative of the entire population. Older definitions of MR have focused primarily on age at onset and intelligence. Adaptive behavior has become a second measurable component of the definition over the last 25 years and is viewed as a set of social and practical skills that have been learned by people to function independently. The classification of the AAMR commonly includes four categories of MR based on the statistical distribution of IQ scores. This categorization groups mild MR to an IQ range of 55–69, moderate MR to an IQ range of 40–54, severe MR to an IQ range of 25–39, and profound MR to an IQ below 25, although these subcategories have been omitted from the definition developed by AAMR (1992, 2002) and retained in a definition disseminated by the MR/DD division of the APA (Editorial Board, 1996).

The ICD, now in its 10th edition, was developed by the WHO to code health disorders, including impairments and disabilities (WHO, 1992). The ICD-10 is widely used by physicians and other health-care providers to code specific syndromes and impairments associated with MR, such as Down Syndrome (DS), Prader–Willi, Fragile X, and to code the level of intellectual disability (mild, moderate, and severe). The ICD codes are often combined with clinical procedure and therapeutic codes that are used for billing purposes. The DSM (APA, 1994) is used by U.S. psychiatrists to

classify mental illnesses and is often considered analogous to the ICD for the field of psychiatry. The DSM includes MR (IQ and age of onset), the use of IQ ranges for levels of MR, and the assessment of adaptive skills as the defining criteria for diagnosis.

The WHO *International Classification of Functioning, Disability, and Health* (ICF) is the newest schema for classifying disability, including MR, and it was developed to describe a dynamic system in which impairment, function, and the environment interact (WHO, 2001). The ICF states that “an individual’s disability may be characterized by marked and severe problems in the capacity to function (‘impairments in body functions and structures’), the ability to function (‘activity limitations’), and the opportunity to function (‘participation restrictions’).” The ICF codes have been used in some European countries since the early 1990s, and in selected sites in the United States.

The range of MR prevalence differs notably by etiology, degree of ability and disability, and behavioral characteristics. Individuals with mild MR predominate and constitute 75–90% of the group, and individuals with moderate to severe and profound MR make up 10–25%. The proportion in each category varies by the method of case acquisition, with school-based records favoring high proportions of mild cases and institutional registries reporting high proportions of severe and profound cases. Registries for adult services tend to report relatively more cases with moderate to severe MR than indicated by the proportions above. In addition, there are different proportions of severity by underlying impairment. For example, girls with Rett syndrome have a high proportion with severe and profound MR, while the range of intellectual disability is much wider for individuals with DS. There are also geographic and temporal variations that are a function of epidemics (e.g., rubella, influenza), poverty levels, environmental conditions (e.g., lead and mercury exposure), and access to prevention programs (e.g., early intervention for infants at risk, immunizations, dietary and therapeutic interventions).

It has been shown for the general population that IQ scores are relatively stable (Vernon, 1979; Zigler & Butterfield, 1966). Changes in scores greater than one standard deviation are usually attributed to removal of deprivation followed by intervention involving social and learning stimulation during early childhood (Clarke & Clarke, 1976; Dennis, 1973; Lazar & Darlington, 1982). In addition, the assumption of a normal distribution of IQ scores that underlie the assignment of an IQ of 70 as a cut point for MR is not based on epidemiological investigation. The empirical distribution obtained by researchers doing large-scale studies (e.g., Vernon, 1979; Zigler, 1967) has been bimodal with a second smaller peak in the lower tail of the curve. The explanation for this phenomenon is that there are two distributions of intelligence. One is for those whose intelligence is the result of an interaction of genetic and environmental influences and the other in which the brain has been damaged and the biological side of the interaction dominates (Lewis & Goldberg 1969; Zigler, 1967). The smaller mode in the left end of the distribution represents biologically induced MR. Many critics of intelligence testing and assignment of mental age argue that abstract intelligence cannot be forced into a linear model. The same argument has

been applied to tests of adaptive functioning, which have been shown to have nonlinear progression (Jacobson & Mulick, 1996).

In general, in the field of MR there is a definite shift in the focus of classification schemes away from static definitions to dynamic models of functioning. These definitions, however, are not yet consistently used in the epidemiologic literature and there is little uniformity in their use in the service, medical, or educational arenas. Thus, it is important to recognize that although the AAMR definition of MR is widely known, many epidemiological studies of the prevalence of MR do not use measures of adaptive behavior and they most commonly report two categories of IQ. Epidemiologists use the term "mild" for an IQ between 50 and 70. They categorize all IQs below 50 as "severe" MR.

Epidemiologic research is based on the ability to count exposures and outcomes based on well-defined case definitions. When the outcome of interest is MR, the epidemiologist must specify the criteria used for designating cases and how the criteria were applied. Depending on whether the individuals were identified by a research testing protocol or ascertained from an administrative source such as a clinic, school, or service provider, the definition used was likely influenced by the year and the prevailing definition at that time.

## INCIDENCE AND PREVALENCE

There have been extensive efforts to quantify the magnitude of the population with MR through the study of incidence and prevalence, a process that had used a number of approaches and yielded different results. The distinction between incidence and prevalence of MR is difficult to specify since MR identified at birth occurred during conception or gestation and many cases identified throughout childhood were probably also present at birth but not identified until delays in development were observed. There are a number of categories of causes that represent incident cases during childhood, such as postnatal encephalitis or trauma.

Prevalence is a function of incidence and duration and population dynamics such as immigration and emigration. Uneven prevalence rates throughout the lifespan are a result of delayed diagnosis for some mild cases, early death for some severe cases, and omission of mild cases from service registries during adulthood. These factors also make it impossible to determine incidence. The prevalence of MR in the United States during late childhood has been reported to be 1-2% of the population during the past decade, but there is substantial variation in the literature (Durkin & Stein, 1996). In the Netherlands, Sweden, and other countries, national registries track people throughout their lifetime in an effort to identify health, social problems, and service utilization and thus the disability associated with MR is captured more effectively (Kiely, 1987; Stein, Susser, & Saenger, 1976; Stein, Susser, Saenger, & Marolla, 1976). The United States has a birth defects surveillance system that captures only those cases identified in the first days of life, but the United States does not have a national disability registry; therefore prevalence rates for MR are

usually calculated from cross-sectional data on children in public schools (Frankenberger & Harper, 1988; McDermott, 1994; McLaren & Bryson, 1987; Yeargin-Allsopp & Boyle, 2002).

Public school data on MR prevalence are not entirely reliable since intelligence tests are not administered universally and procedures for referral practices for testing and placement of children into special education vary among schools and by states, although they are all within guidelines from the U.S. Department of Education. Reports from the U.S. Department of Education include the number of children, aged 5–21, enrolled in special education programs and there are two and sometimes three programs for children with MR: Educable Mental Deficiency (EMD), Trainable Mental Deficiency (TMD), and Severe Mental Deficiency (SMD). In addition, some children with multiple disabling conditions are placed in other special education programs, i.e., multiply disabled, speech and language, orthopedic, or vision or hearing impairment, and are only counted in the one program with the highest level of reimbursement to the district, leading to an undercount of MR. Federal guidelines for placement of children with MR provide a definition of MR that includes significantly subaverage general intellectual functioning, with deficits in adaptive behavior. States provide guidance to local school districts in matters of referral, testing, and placement procedures. Research has shown that there are small-area (school district and county level) and large-area (national and state level) variations in MR prevalence rates (Baird & Sadovnick, 1987; Kiely, 1987; McDermott, 1994). The most widely used U.S. estimate of school-aged prevalence of MR is given in the *Healthy People 2010 Objectives for the Nation* (U.S. Department of Health and Human Services, 2000). The Metropolitan Atlanta Developmental Disabilities Surveillance System (MADDS) has set the benchmark for national prevalence of childhood MR at 131/10,000 8-year-old children, using an estimate from the 1991–1994 MADDS data (Yeargin-Allsopp & Boyle, 2002; Yeargin-Allsopp, Murphy, Cordero, Decoufle, & Hollowell, 1997).

Although MR is usually considered a lifelong disability, analysis of prevalence rates, especially for mild MR, indicates that the condition is less frequently identified in early life and it peaks during the school years, and that the label is not as often applied in later adulthood. Using the 1994/1995 *National Health Interview Survey Disability Supplements*, Larson et al. estimated the combined prevalence of MR or developmental disability to be 14.9 per 1000 in the noninstitutionalized population of the United States (Larson et al., 2001). Other estimates range from 1 to 10%, depending on the population surveyed and the methods used (Drillien, Pickering, & Drummond, 1988; Massey & McDermott, 1995; McLaren & Bryson, 1987; Simeonsson & Sharp, 1992; Stevenson, 1996).

## ETIOLOGY

The AAMR 2002 states “etiology is a multifactorial construct composed of four categories of risk factors (biomedical, social, behavioral, and

educational) that interact across time, including across the life of the individual and across generations from parent to child" (p. 123). Even gross genetic factors such as DS or mutation of a gene, can be viewed as highly associated with MR although not absolutely causal. In fact, with early intervention services some children with DS function in the low normal range on tests of IQ are not classified as having MR until they qualify for services later in childhood. Even more importantly, the cause of many genetic impairments remains unknown even when the underlying molecular pathways that cause neuronal processes involved in cognitive functions are understood.

In approximately half of the cases of MR the cause is unknown. Algorithms have been suggested for the evaluation of individuals that rely on family history, physical findings, and neurological functioning. The evaluation should include karyotyping and identification of anomalies. Then depending on the resources available to pursue the investigation there are a growing range of methods and technology available to make a diagnosis. Diagnostic techniques include chromosome microdissection, fluorescence in situ hybridization (FISH), interferometer spectral karyotyping (SKY), primed in situ labeling (PRINS), subtelomeric screening, magnetic resonance spectroscopy (MRS) of the brain, and other techniques in molecular genetics, neuroimaging and dysmorphology (Battaglia & Carey, 2003). The time when an insult occurs and leads to MR ranges from the time of conception through late childhood. A range of conditions associated with, and less often causally linked to MR, are described below in Table 1.2, in chronological order of occurrence.

## SELECTED PERICONCEPTIONAL CAUSES

### Telomeric Rearrangements

Chromosomal anomalies may be *numerical* or *structural*. Structural changes result from the breakage and rearrangement of chromosome parts, and animal experiments have shown that they can be induced by a variety of exposures, including ionizing radiation and certain viral infections and toxic substances. They occur as duplications, deletions, translocations, insertions, or inversions of chromosome parts or as rings on selected chromosomes. Numerical anomalies arise through nondisjunction during meiosis or mitosis, through lagging of chromosomes at anaphase of cell division, or through fertilization by two sperm (i.e., triploidy). Chromosomal anomalies as a whole contribute more to fetal loss than to live births and MR. Kline, Stein, and Susser (1989) estimated that from 8 weeks after the last menstrual period, the proportion of chromosomal aberrations lost by miscarriage exceeds 90% for all but trisomy 21 (DS), XXX, XXY (Klinefelter syndrome), and XYY. In survivors after birth in developed countries, chromosomal anomalies cause more than 30% of the cases of severe MR, with the majority of these having DS (Gustavson, Hagberg, Hagberg, & Sars, 1977a, 1977b).

**Table 1.2.** Categories of Causes of Mental Retardation, by Time of Insult (Adopted from Durkin et al., 2001)

Time	Category	Examples
Periconceptual	Genetic-chromosomal	Down syndrome, telometric rearrangements
	Sex linked-single gene	Fragile X syndrome, Rett syndrome
	Autosomal dominant	Phenylketonuria, neurofibromatosis, Tay Sacks
	Metabolic	Hypothyroidism
	Segmental autosomal syndromes	Prader-Willi syndrome, Angelman syndrome
Intrauterine	Genetic and nutritional	Neural tube defects
	Infection	Toxoplasmosis, rubella, cytomegalovirus, herpes, gonorrhea, group B streptococcus, Chlamydia, trichomonas vaginalis, bacterial vaginosis, herpes simplex virus, HIV
	Substances- prescribed and lifestyles	EtOH, antimicrobials (e.g., sulfonamides, isoniazid, ribavirin), anticonvulsants (e.g., phenytoin, carbamazepine), and other drugs- (e.g., warfarin, aminoptein, accutane)
Perinatal and postnatal Childhood	Metals and chemicals	Lead, mercury
	Nutritional	Iodine
	Birth complications and effects	Prematurity, low birth weight, asphyxia
	Infections	Encephalitis, meningitis, varicella
	Environmental exposures	Lead, mercury
Childhood	Injury	Traumatic brain injuries from vehicle crashes, child abuse and neglect
	Deprivation	Insufficient stimulation

In humans, *de novo* (presumed mutant) chromosomal rearrangements, whether balanced or unbalanced, occur in 2/1000 live births. This estimate is based on 63,000 fetal amniocenteses, which were diagnosed in the New York State Chromosome Registry (Hook & Cross, 1987). Of these, about 0.5 per 1000 are *de novo* markers; about 0.5 per 1000 other *de novo* unbalanced translocations and about 1.0 per 1000 *de novo* balanced rearrangements. The rate of inherited rearrangements was about 2.9 per 1000, including 0.3 per 1000 inherited markers, 0.2 per 1000 other inherited unbalanced rearrangements, and about 2.4 per 1000 inherited balanced abnormalities. Among fetuses studied because of maternal exposure to putative mutagens, there was an excess of mutants, 2.9–5.7 per 1000 versus 1.7–2.2 per 1000 (Hook & Cross, 1987). These findings suggest that workplace or environmental exposures may increase risk of structural cytogenetic abnormalities in the fetus that, in turn, may be associated with birth defects and neurodevelopmental delay in the infant.

Warburton (1984, 1987, 1991) reported the results of a 10-year collection of data from a series of over 377,000 amniocenteses in which the



occurrence rate of *de novo* balanced reciprocal translocations, Robertsonian translocations, and inversions was estimated to be about 1 per 1000. The most common *de novo* balanced chromosomal anomalies were *de novo* reciprocal translocations (1 per 2000). The overall risk of a serious congenital anomaly, including but not limited to MR, for balanced reciprocal translocations and inversions was 6.7% (95% CI 3.1–10.3%). In this same study, *de novo* supernumerary markers were found in 1 in 2500 amniocenteses, and had a risk of approximately 15% of being associated with an abnormal fetal outcome. *De novo* unbalanced rearrangements, including supernumerary small markers, have been estimated to occur in about 1 in 1000 amniocenteses which were carried out for reasons other than suspected fetal anomalies (Hook & Cross, 1987). This rate increased to 1.8 per 1000 when amniocentesis was performed because of known or suspected fetal pathology.

However, these rates are based on cytogenetic methods that may miss small deletions or translocations and underestimate the impact of chromosomal anomalies on neurodevelopmental disorders. There is mounting evidence that chromosomal rearrangements involving the subtelomeric regions of chromosomes contribute to moderate to severe MR and are associated with dysmorphic phenotypic features (Flint et al., 1995; Knight et al., 1999). Flint and his colleagues (Knight et al., 1999) reported that subtelomeric abnormalities, requiring microassays or FISH to be detected, occurred in 7.4% (95% CI 4.4–10.4) of 284 children with previously unexplained moderate to severe MR. About half of the subtelomeric rearrangement cases were familial and the other half were isolated, apparently *de novo* cases. Approximately 10% of the *de novo* rearrangements had abnormal outcomes. In both the familial and *de novo* groups approximately 60% of the chromosomal anomalies were paternal and 40% were maternal in origin. If cases are selected to include dysmorphic features as well as developmental delay, chromosomal aberrations may be found in as many as 13.0% (Popp et al., 2002). On the other hand, van Karnebeek et al. (2002) screened 266 children in a consecutive cohort of cases with unexplained MR presenting to an academic tertiary center for diagnosis and found that the total frequency of cytogenetic anomalies was 10%, but the frequency of subtelomeric rearrangements was low (0.5%, van Karnebeek et al., 2002). Thus, screening for subtelomeric rearrangements is likely to be most effective when combined with targeted selection criteria, including unexplained MR, dysmorphic features, and a positive family history with two or more affected individuals (Popp et al., 2002).

## DOWN SYNDROME

DS is the most common genetic cause of MR and the leading known cause of severe MR in developed countries (Nicholson & Alberman, 1992). All cases of DS result from partial or complete duplication of chromosome 21 in the genome (Epstein, 1986). The most common form (95% of cases at birth) is standard trisomy, involving duplication of chromosome 21. In

over 90% of these cases, the extra chromosome is of maternal origin, due to nondisjunction during meiosis (Hassold, Chiu, & Yamane, 1984; Sherman et al., 1991; Stewart et al., 1988). Translocation of chromosome 21 material to another chromosome (usually 13 or 18) and mosaicism (transmission of a cryptic trisomy 21 cell line from an unaffected parent) are rare causes of DS (Hook, 1982; Staples, Sutherland, Haan, & Clisby, 1991).

The most striking epidemiological characteristic of DS is the marked increase in risk with increasing maternal age, from 1 per 1550 live births at ages 20–24 years to 1 per 700 live births at ages 30–34 years to 1 per 50 live births at ages 41–45 years (Cuckle, Wald, & Thompson, 1987). Despite this strong association with maternal age, most DS births are to women aged less than 35 years because younger women contribute the great majority of births. Thus, the crude birth rate of DS in a population will depend on the maternal age distribution and the availability and use of prenatal diagnosis followed by selective abortion.

Except for advanced maternal age, factors that increase risk for having a child with DS are not well established. Recently, variants in two folate metabolizing enzymes, the 677C → T polymorphism in the gene for methylenetetrahydrofolatereductase (MTHFR) and the 66A → G polymorphism in the gene for methionine reductase (MTRR), have been found to be more prevalent among mothers of children with DS than among control mothers (Hobbs et al., 2000; James et al., 1999; O'Leary et al., 2002). The combined presence of both the MTHFR and MTRR polymorphisms increased risk of having child with DS to a greater extent than either polymorphism alone (Hobbs et al., 2000; O'Leary et al., 2002). The MTHFR 677C → T mutation affects both folate metabolism and cellular methylation reactions. James and colleagues hypothesized that gene–nutrient interactions associated with abnormal folate metabolism and reduced DNA methylation might increase risk of nondisjunction DS (Hobbs et al., 2000; James et al., 1999). As Hobbs has noted, the reduction in enzyme activity in carriers of the 677C → T mutation may raise dietary requirements for folic acid. This is the first risk factor to be identified for DS in young women and raises the possibility of intervention and prevention for DS (Hassold et al., 2001).

Virtually all persons with DS have a cognitive impairment, with the majority functioning in the moderate to profound range of MR. Observations of children living at home with their families or enrolled in infant stimulation programs suggest that the cognitive intellectual potential of children with DS may have been underestimated (Bennett, Sells, & Brand, 1979; Centerwall & Centerwall, 1960; Clements, Bates, & Hafer, 1976; Connolly, Morgan, & Russell, 1984; Melyn & White, 1973; Rynders, Spiker, & Horrobin, 1978; Sharav & Shlomo, 1986). However, early intervention has not been effective in altering the trajectory of development for all children who receive it, and some children with severe MR do not benefit substantially from it.

Adults with DS show a variety of age-related changes in physical and functional capacities suggestive of premature or accelerated aging (Martin, 1978), including changes in skin tone, hypogonadism, increased frequency of cataracts, increased frequency of hearing loss, hypothyroidism, seizures,

degenerative vascular disease, and Alzheimer's disease (AD) (Oliver & Holland, 1986; Sare, Ruvalcaba, & Kelly, 1978; Schupf & Sergievsky, 2002; Wisniewski, Wisniewski, & Wen, 1985; Zigman, Schupf, Sersen, & Silverman, 1996). The most extensively studied aspect of aging in DS is their high risk for the development of AD. Virtually all individuals with DS have key neuropathological changes consistent with a diagnosis of AD by the time they reach 40 years of age, including deposition of beta amyloid ( $A\beta$ ) in diffuse and neuritic plaques (Wisniewski, Wegiel, & Popovitch, 1994), and most will develop dementia by the end of their seventh decade of life (Lai et al., 1999). The neuropathological manifestations of AD in DS have been attributed to triplication and overexpression of the gene for amyloid precursor protein (APP) located on chromosome 21 (Rumble et al., 1989). The increased risk of dementia in DS may be mediated by an increased substrate for cellular production of  $A\beta$ . Neuropathological studies have shown that diffuse plaques, the most prevalent "Alzheimer-type" lesion seen in individuals with DS before age 50, are not associated with dementia. In contrast, increase in the numbers of neuritic plaques, containing substantial amounts of fibrillized  $A\beta$  peptides, is observed in adults with DS predominantly after 50 years of age (Wisniewski et al., 1994) and all incidence studies agree that risk of AD increases primarily after 50 years of age (Holland, Hon, Huppert, & Watson, 1998; Lai et al., 1999; Visser et al., 1997). In addition, not all adults with DS will develop dementia even if they reach ages when the presence of high densities of neuritic plaques and neurofibrillary tangles can be presumed. Thus, factors, which modify the rate and degree of  $A\beta$  deposition, rather than overexpression of APP, may be the important determinants of risk for dementia in DS (Schupf & Sergievsky, 2002).

### **SEX-LINKED SINGLE GENE**

Mutations in 14 X-linked genes have been identified in both syndrome and nonsyndrome conditions. These are AGTR2, ARHGEF6, ATRX, FAFL4, FMR2, GD11, ILRIRAPL, MECP2, OPHNI, PAK3, RSK2, TM4SF2, and VCXA. Other X-linked genes and those that map to X will likely be identified in the future (Chechlac & Gleeson, 2003). The fragile X syndrome, a nonsyndrome MR with a transcription factor (FMR2), primarily affects males. This syndrome, which results from mutations in the MECP2 gene located at Xq28, is both syndromic and nonsyndromic and the prevalence is estimated to be at least as high as 1 in 10,000 females (Hagberg & Hagberg, 1997; Kerr & Ravine, 2003).

#### **Fragile X Syndrome**

The fragile X syndrome is the most common form of inherited MR. In addition to cognitive disability, the fra(X) phenotype includes macroorchidism, a long face, prominent jaw, large ears, thickening of the nasal bridge, and joint hypermobility. Behavioral abnormalities may

include autistic-like features, repetitive speech patterns, social anxiety, perseveration, and gaze aversion (Brown, Jenkins, & Friedman, 1982; Hagerman & Silverman, 1991; Opitz & Sutherland, 1984; Reiss & Freund, 1990). Neuroimaging has demonstrated a small posterior cerebellar vermis, and enlarged hippocampus, caudate nucleus, thalamus, and lateral ventricles and Reiss and colleagues have shown correlations between these structural abnormalities and IQ (Reiss, Abrams, Greenlaw, Freund, & Denckla, 1995; Reiss, Aylward, Freund, Joshi, & Bryan, 1991; Reiss, Lee, & Freund, 1994). A fragile site on the X chromosome, fra(X), was first identified in males from families with X-linked MR (Lubs, 1969; Sutherland, 1977). The proportion of cells showing the fragile X site in cytogenetic studies is quite variable and may be characteristic of each individual. About 80% of male carriers of the mutation and about 30% of female carriers show some degree of MR (Chudley et al., 1983; Sherman, Morton, Jacobs, & Turner, 1984).

An unusual pattern of inheritance emerged from segregation analysis of families affected with fra(X), which followed the intergenerational passage of the gene (Sherman, Jacobs, et al., 1985; Sherman, Morton, et al., 1984). About 20% of males who carry the genotype are clinically unaffected and do not express the fra(X) site on cytogenetic testing. Mothers of these nonpenetrant males are rarely affected. These nonpenetrant normal transmitting males transmit the mutation to daughters who, although unaffected themselves, will have affected children. Thus, grandsons of nonpenetrant normal transmitting males have MR and granddaughters may show some cognitive impairment (Sherman, Jacobs, et al., 1985; Sherman, Morton, et al., 1984). Brothers of nonpenetrant normal transmitting males are at low risk (approximately 9%) while grandsons and great grandsons are at high risk (approximately 40–50%).

The molecular basis of Fragile X syndrome was elucidated with the isolation of the fra(X) gene, *FMR1*, in 1991 (Bell et al., 1991; Fu et al., 1991; Kremer et al., 1991; Oberle et al., 1991; Verkerk et al., 1991; Vincent et al., 1991). At the molecular level the FRAXA site contains an exon of the *FMR1* gene responsible for the fragile X, a repetitive CGG sequence, which demonstrates length variation in normal and in fra(X) individuals, and a cytidine phosphate guanosine (CpG) island that shows preferential methylation in fra(X) cases (Bell et al., 1991; Vincent et al., 1991). The length of the CGG repeat in genomic DNA is correlated with risk for the fragile X syndrome (Kremer et al., 1991). Normal individuals have CGG repeat lengths of 6–50 repeats and affected individuals show dramatic amplification of the CGG repeat (from 200 to 1000) and hypermethylation of the repeat and adjacent CpG region, resulting in a shutdown of transcription of *FMR1* and absence of the FMR1 protein (Bell et al., 1991; Oberle et al., 1991; Pieretti et al., 1991; Sutcliffe et al., 1992; Verheij et al., 1993). The full mutation, when fully methylated, results in cognitive disability in all males and in 50–70% of affected females (de Vries et al., 1997; Hagerman et al., 1992; Rousseau et al., 1994).

Expansion of the premutation to the full mutation occurs only in female meiotic transmission (Oberle et al., 1991; Smits et al., 1992; Yu et al.,

1991) and risk for expansion to the full mutation increases with the number of repeats (Fu et al., 1991). As amplification of the gene increases, it becomes more unstable, leading to mitotic instability as well as meiotic instability (Fu et al., 1991; Oberle et al., 1991; Pieretti et al., 1991). The mitotic instability of the full repeat causes longer and shorter expansions, resulting in mosaicism with respect to size (premutation together with a full mutation) or with respect to degree of methylation (from 10 to 100% of leukocytes with an unmethylated full mutation). Several cases of intellectually normal males with a high proportion of unmethylated leukocytes have been reported, suggesting that methylation is critical for lack of transcription of FMR1 gene and expression of the phenotype (de Vries et al., 1996; Hagerman, Hull et al., 1994; Nolin, Glicksman, Houck, Brown, & Dobkin, 1994; Rousseau et al., 1994). In addition, several cases have been found with atypical mutations at the FRAXA site, two involving a deletion and one a point mutation in the FRM1 gene (Gedeon et al., 1992; Wohrle et al., 1992). Other fragile sites (FRAXE, FRAXD, FRAXF) are found close to the FRAXA site. FRAXE is associated with learning disabilities, but is caused by a different expanding trinucleotide repeat (Feldman, 1996).

### **Prevalence of the Fragile X Syndrome**

Prevalence studies in defined populations have employed cytogenetic or DNA testing for fra(X) among individuals with MR. Prevalence estimates from these studies have ranged from 0.5 to 4.2% of patients with MR (de Vries et al., 1997; Hagerman, Wilson, et al., 1994; Jacobs et al., 1993; Meadows et al., 1996; Murray et al., 1996; Turner, Webb, Wake, & Robinson, 1996; van den Ouweland et al., 1994). The wide range of these estimates is likely to be due to differences in the distribution of MR causes in the samples studied, as well as variability in the DNA analysis. Within the general population, the prevalence of fra(X) has been estimated to range from 1/4000 to 1/6045 males (de Vries et al., 1997; Morton et al., 1997; Turner et al., 1996). Estimates of the prevalence of the FRAXA premutation carrier frequency among females in the general population have also ranged widely, from 1/248 women to 1/1000 women (Holden, Percy, et al., 1999; Reiss et al., 1994; Rousseau, Rouillard, Morel, Khandjian, & Morgan, 1995; Spence et al., 1996).

## **SEGMENTAL AUTOSOMY SYNDROMES**

Segmental autosomy syndromes result from abnormalities in gene dosage caused by structural defects (deletion, duplication) or functional imbalance (imprinting defects, uniparental disomy) of critical genes (Budarf & Emanuel, 1997). Recent molecular studies have shown that three syndromes involving early onset cognitive disability are within this class of disorders: Williams, Prader-Willi, and Angelman syndromes.

## Williams Syndrome

Williams syndrome (WS) is a multisystem disorder characterized by developmental and language delays, pixie-like facial features, cardiovascular abnormalities, elevated calcium levels, problems in gross motor skills, and a distinctive cognitive profile that includes mild MR with relatively good language and face-processing skills. The frequency of WS has been estimated to be about 1/10,000 live births (Beuren, Apitz, & Harmajanz, 1962; Williams, Barratt-Boyes, & Lowe, 1961). Individuals with WS have an approximately 2 Mb deletion of chromosomal region 7q11.23 (Ewart et al., 1993; Perez-Jurado, Peoples, Kaplan, Hamel, & Francke, 1996). Variability in deletion size may be related to variable phenotypic presentation. The majority of patients with WS is hemizygous for 7q11.23 and in more than 90% of cases, the deletion includes the locus for the elastin gene (*ELN*), a protein kinase LIM-kinase 1 (*LIMK1*), and a replication factor C subunit (*RFC2*) (Frangiskakis et al., 1996; Osborne et al., 1996; Peoples, Perez-Jurado, Wang, Kaplan, & Francke, 1996). Families with "partial WS," involving smaller deletions that include only *ELN* and *LIMK1*, show the cognitive and cardiovascular profiles but lack other features of WS, suggesting that the loss of at least three genes is required for the full WS phenotype (Budarf & Emanuel, 1997; Frangiskakis et al., 1996). There is no evidence of imprinting in WS, but if the gene deletion is of maternal origin, patients have more severe growth retardation and microcephaly (Perez-Jurado et al., 1996).

## Prader-Willi/Angelman Syndrome

Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are characteristics of disorders resulting from genomic imprinting in which the phenotypic expression of the disorder depends on the parent from whom the genetic abnormality is inherited. Both syndromes involve structural or functional loss of expression of genes in the chromosome 15q11-q13 region, including deletions, uniparental disomy, and mutations in an imprinting center. Paternally inherited abnormalities result in PWS while maternally inherited abnormalities result in AS (Knoll et al., 1989; Ledbetter et al., 1981). PWS is characterized by developmental delay, hypotonia, and feeding problems in infancy followed by excessive and rapid weight gain resulting in severe obesity, cryptorchidism, short stature, and mild MR. Behavioral characteristics include temper tantrums and ritualistic or obsessive-compulsive behavior (Clarke, Boer, Cheung, Sturney, & Webb, 1996; Dykens, Leckman, & Cassify, 1996; Webb et al., 2002). The frequency of PWS is approximately 1/15,000 live births. In contrast, AS is characterized by severe MR, microcephaly, hypermotoric behavior with hand-flapping, and jerky movements in association with outbursts of laughter, short attention span, hypopigmented skin and eyes, and seizures with onset under 3 years of age.

It appears that different genes are responsible for the two syndromes, all of them imprinted in the germ line. The 15q11-q13 region contains four paternally expressed genes whose loss of expression causes PWS;

small nuclear ribonucleoprotein-associated polypeptide N (Ozcelik et al., 1992), zinc finger protein (Mowery-Rushton, Driscoll, Nicholls, Locker, & Surti, 1996), a gene designated as imprinted in Prader-Willi (Wevrick, Kerns, & Francke, 1994) and two less well-characterized transcripts, PARI and PAR5 (Sutcliffe et al., 1994). The 15q11-q13 region also contains the gene for E6-AP ubiquitin-protein ligase 3A (*UBE3A*) which is biallelically expressed in somatic tissue but is imprinted with preferential maternal expression in the brain (Albrecht et al., 1997; Jiang, Tsai, Bressler, & Beaudet, 1998; Matsuura et al., 1997); mutations in *UBE3A* are found in a small subset of patients with AS.

The effects of imprinting are also seen in cases of uniparental disomy (UPD) where maternal UPD represents loss of paternally expressed genes and is associated with PWS, while paternal UPD represents loss of maternally expressed genes and is associated with AS. Seventy percent of cases in PWS are associated with a 4 Mb deletion in 15Q11-q13, an additional 27% display maternal uniparental disomy and 1-2% of cases are associated with mutations and deletions in the imprinting center (Sutcliffe et al., 1994). As in PSW, 70% of AS cases have maternal deletions in the 15q11-q13 region, 3-5% have paternal uniparental disomy, 7-9% have imprinting mutations, 2-4% have mutations in *UBE3A*, while in 10-20% of cases, the molecular defect is still unknown (Nicholls, 1993; Wagstaff et al., 1992).

## COMBINATIONS OF GENETIC AND NUTRITIONAL FACTORS

Neural tube defects (NTD), including spina bifida, anencephaly, and meningomyelocele, result from failure of neural tube closure during the third to eighth week of gestation. The cause of a majority of cases of NTD is related to a nutritional deficit of folate and a small proportion of cases is related to a genetic problem (Czeizel, 1995; MRC Vitamin Study Group, 1991; Wild et al., 1986). The incidence of all levels of NTDs in the United States is 1-3 per 1000 births and 2-5% in children with a previous affected sibling (Cohen, 2000). NTDs are associated with a wide range of intellectual function and only a small proportion of MR is attributable to NTDs. Hydrocephalus occurs in 95% of high lumbar and thoracic lesions and 60-85% of low lumbar and sacral defects. Since shunting of cerebral spinal fluid is now a well-established surgical intervention, only a small proportion of these children has MR. The use of preconception and early conceptual folate supplementation through diet or vitamin pills can prevent a substantial proportion of occurrence and reoccurrence of NTDs.

Phenylketonuria (PKU) deficiency is a rare defect of amino acid metabolism with a frequency of about 1 per 15,000 in White populations. Because it is a single gene defect and PKU deficiency is identified during newborn screening in all states in the United States, the sequella of MR can be prevented with adherence to a strict diet during infancy and early childhood. The realization that the sequella of PKU can be prevented by strict diet during childhood unfortunately overlooked the fact that the female survivors who then became pregnant needed to go onto the diet perinatally,

so the intrauterine environment of the fetus is not toxic with phenylketones (Baumeister & Woodley-Zanthos, 1996; Hanley et al., 1999; Lenke & Levy, 1980; Levy & Ghavami, 1996; Levy & Waisbren, 1983; Rouse et al., 1997; Waisbren, Chang, et al., 1988; Waisbren, Doherty, Bailey, Rohr, & Levy, 1998). Severe MR and microcephaly are observed in 75–90% of children of mothers with classic PKU (defined as blood phenylalanine level > 1200 mol/l). Less severe cognitive deficit may affect children of mothers with atypical PKU (elevations of blood phenylalanine levels to between 594 and 1194 mol/l, Levy & Ghavami, 1996). Dietary restrictions during pregnancy to reduce maternal blood phenylalanine levels and prevent phenylalanine metabolite accumulation can improve the outcome in offspring if the diet is started prior to conception and maintained throughout pregnancy.

A third nutritionally related cause of MR is hypothyroidism during pregnancy. A genetic form of hypothyroidism (which, when untreated is referred to as cretinism), unrelated to iodine deficiency, can result in progressive neurological deficits after 3 months of age. In the United States, screening of all newborns is mandatory in all states and thus the occurrence of cretinism is rare. Cretinism can also result when there is maternal, fetal, or neonatal nutritional thyroid hormone deficiency; the supplementation of iodine in the mother needs to occur prior to conception. Cretinism can result in neurodevelopmental deficits in the newborn, including MR and a number of other sensory and motor impairments. When both fetal and maternal hypothyroxinemia are present, such as in iodine-deficient regions of China, it has been shown that iodine replacement in the first trimester of pregnancy was necessary to prevent neurological deficits (Cao et al., 1994; Liu, Momotani, & Yoshimura, 1994; O'Donnell et al., 2002; Wasserstrum & Anania, 1995). Iodine deficiency can range from mild to severe, and the associated outcomes range from mild cognitive impairments and cerebral palsy to death. Worldwide iodine deficiency is estimated to affect over 20 million people and it has been reported as a leading cause of MR (Hetzl, 1989).

Children with PKU and hypothyroidism can be identified at birth, so their parents can receive instruction about the appropriate diet or medication needed to prevent the onset of MR. The effectiveness of newborn screening strategies to identify and treat infants with PKU and hypothyroidism has resulted in a significant decline in children with MR from these causes in the United States during the past 25 years.

## INFECTIONS

Infections during pregnancy have long been recognized as contributors to maternal and infant mortality and morbidity, including long-term neurological impairments. The significant role of infection in early child survival and wellness has led to the development of a number of vaccines. During the later part of the 1990s and in the decade of 2000–2010 the infective process during gestation has received a significant amount of attention.



The route of infection of the fetus following maternal infection is through transplacental transmission or from the genital tract by the cervical amniotic route. The effect of a maternal infection on the fetus may be due to direct actions of toxins or organisms or it can be an indirect consequence of interference with placental or uterine function (Leviton & Gilles, 1996; Leviton & Paneth, 1990). The effect of a specific infection on fetal development is likely to depend on maternal and fetal factors including genetics, nutrition, stage of development, anatomical site of the infection, and the integrity of the placenta. After implantation interaction between the mother and fetus is mediated through the trophoblast, which has distinct immunological characteristics. In addition, the endometrium of pregnancy is unique and the general maternal response to major histocompatibility complex (MHC) antigens in the conceptus is downregulated by maternal antifetal HLA (human leukocyte antigen) antibody production (Johnson, 1995). Other factors that influence the outcome include the characteristics of the organism, portal of entry, time of exposure, and dose of the infectious organism. One group of intrauterine infections, which has contributed to MR and other adverse consequences, is collectively known by the acronym TORCH: toxoplasmosis, other, rubella, cytomegalovirus (CMV), and herpes. The impact of these infections is dependent on the time of exposure during gestation.

CMV is one of the most ubiquitous viral infections in humans in the world, with prevalence rates reported from 20 to 95%. In some countries of Southeast Asia, Africa, and the South Pacific islands prevalence rates are reported above 90%, while in the United States and parts of Europe the prevalence is reported to be around 50%. Transmission occurs through shedding of the virus from nasopharyngeal secretions, urine, saliva, tears, genital secretions, breast milk, and blood. Maternal infections usually occur because of sexual transmission, and high number of sexual partners and early age of intercourse are predictors of occurrence of CMV. Perinatal transmission occurs through exposure of the fetus, in utero, to virus from reactivated or acute maternal disease. The virus can remain dormant in the host and cause latent infection and its sequella are exacerbated if the host has immune compromise. Exposure of the fetus to a primary CMV infection poses a risk of adverse outcome at any stage of pregnancy (Peckham, 1991). Approximately 10% of infants with asymptomatic infections at birth develop serious sequella, such as optic atrophy, learning disabilities, and MR (Faro & Soper, 2001). Congenital CMV is reported in 0.2–2.2% of all live births (Baumeister & Woodley-Zanthos, 1996). The mortality rate among symptomatic newborns is about 30%, and more than 90% of survivors have neurological impairments including microcephaly, seizures, MR, and hearing and vision problems. The pathway of transmission of congenital CMV is probably through the placenta and the critical period of exposure appears to be in the first trimester.

Toxoplasmosis is a disease caused by a protozoan, often transmitted through maternal handling of cat feces when changing a litter box or through the ingestion of raw or undercooked meat that contains the protozoa. It can be acquired either pre- or postnatally although the prenatal

infection appears to have the most critical impact during the first trimester. Transmission of toxoplasma to the fetus occurs only when the mother has been infected for the first time during gestation, except if the mother has severe immune compromise. The outcomes associated with untreated prenatal exposure to the fetus include microcephaly, hydrocephalus, cerebral palsy, epilepsy, and MR (Baumeister & Kupstas, 1991; Remington, McLeod, & Desmots, 1995; Roizen, Swisher, & Stein, 1995). Infant sequella of a maternal infection can be prevented if it is detected and treated with spiramycin early in gestation or with pyrimethamine and sulfadiazine later in gestation. Although prevalence of congenitally infected infants in the United States is not available it has been estimated that 1–10 per 10,000 infants born annually have toxoplasmosis, and the majority is asymptomatic at birth and does not develop the sequella until later in life (Dunn et al., 1999; Guerina et al., 1994; Lebech et al., 1999).

The viral disease rubella has severe consequences when the infection occurs early in pregnancy. When a mother is infected in the first 12 weeks of pregnancy the fetus has an 80% chance of getting the infection, and the rate declines progressively to 25% during the 26th week. In infected fetuses, rubella-associated defects occur in all cases during the first 11 weeks and 35% of cases infected during weeks 13–16; risk to the fetus is negligible after the 16th week (Martin & Schoub, 2000; Morgan-Capner, 1999). The last major epidemic of rubella in the United States occurred in 1964–1965 and resulted in approximately 31,000 cases of rubella and congenital rubella infections. It is reported that 11,000 of these cases resulted in fetal death or therapeutic abortion and 20,000 infants were born with congenital rubella syndrome (CRS). Since 1969 the incidence of rubella declined by more than 99% (Centers for Disease Control and Prevention [CDC], 1997a).

Varicella and herpes zoster are different manifestations of the same virus. The primary infection produces chickenpox during childhood in the United States, although varicella is a disease of the reproductive years in subtropical and tropical climate countries. Chickenpox is a highly contagious disease and humans are the only reservoir. It is transmitted by droplets from vesicular fluid or secretions from the upper respiratory tract. There are approximately 1–7 cases per 10,000 pregnancies (Freij & Sever, 1997; Gilstrap, 1997; Paryani & Arvin, 1986; Preblud, Cochi, & Orenstein, 1986). The manifestations of congenital varicella include cortical atrophy and other neurological findings. *Varivax*, the live attenuated varicella vaccine, was approved in the United States in 1995 (Gibbs & Sweet, 1999).

Another important maternal infection that has consequences for the developing fetus is urinary tract infection. Urinary tract infections represent the most common medical complication of pregnancy, occurring in approximately 4–7% of all pregnancies. When all potentially offending genitourinary pathogens are included, and when the spectrum of asymptomatic bacteriuria is considered, these factors may increase the frequency of maternal bacteriuria to 25%. Recent research using an inception cohort design with Medicaid maternal and infant-linked records and Vital Records for 41,090 pregnancies during 1995–1998 found the relative risk

(RR) for MR or developmental delay among children of mothers with urinary tract infection without an antibiotic (i.e., based on Medicaid pharmacy reimbursement claims) was significantly elevated compared to the group without an urinary tract infection and compared to children of mothers with urinary tract infection and an antibiotic claim. Similar analyses of the National Collaborative Perinatal Project provide comparable results (McDermott, Callaghan, Szwejbka, Mann, & Daguise, 2000; McDermott, Daguise, Mann, Szwejbka, & Callaghan, 2001).

There is an increasing body of evidence suggesting that prematurity is a consequence of maternal infections including those that are sexually transmitted: gonorrhea, Group B streptococcus, *Chlamydia trachomatis*, *trichomonas vaginalis*, bacterial vaginosis, and herpes simplex virus. Premature rupture of the membranes (PROM), a precursor of early delivery, is often accompanied by the presence of one of these organisms, which could cause the fetal membranes in utero to weaken and rupture. Thus it is often suggested that PROM is a symptom of an existing infection, which was not treated (Creasy & Iams, 1999; Iams, Talbert, Barrows, & Sachs, 1985). Bacteria in amniotic fluid are found in approximately 10% of women with PROM and PROM occurs in approximately 5% of all pregnancies (Aries, Rodriguez, Rayne, & Kraus, 1993; Romero, Yoon, et al., 1993).

Worldwide another serious and widespread threat to cognitive development results from the transmission of human immunodeficiency virus (HIV) infection from the mother to the developing fetus. Perinatally acquired HIV infection and pediatric autoimmune deficiency syndrome (AIDS) emerged as a cause of MR in the late 1980s (Boylan & Stein, 1991). AIDS has become a major public health problem in many countries of Africa, where high HIV prevalence among childbearing women is combined with lack of access to antenatal antiretroviral therapy and cesarean delivery, causing vertical transmission of HIV (*intrauterine*, *intrapartum*, or neonatal) (European Mode of Delivery Collaboration, 1999). The neurodevelopmental effects of pediatric AIDS include microcephaly and significant delays in cognitive and motor development (Belman, 1992; Macmillan et al., 2001). These effects have been reported to be greater when transmission of the virus from mother to child occurs in utero versus during parturition (Smith et al., 2000). In developed countries, improvements in postnatal treatment and survival of children with HIV may be associated with a reduction in adverse neurodevelopmental outcomes. One U.S. study of HIV infected children aged 3–5 years found no detriment in verbal or performance IQ when compared to controls matched on ethnicity and prenatal drug exposure (Fishkin et al., 2000). Another study, without controls, of children with AIDS surviving to school age in Philadelphia, found no more than 12% to have developmental scores in the range for MR (Mialky, Vagnoni, & Rutstein, 2001). Estimates are not available of the prevalence of pediatric HIV-associated neurodevelopmental disorders from low-income countries, where the vast majority of HIV-infected children reside but where few have access to antiretroviral therapy. In addition to direct effects of AIDS on the developing nervous system, the AIDS epidemic may be a causal factor in mild MR to the extent that it increases children's exposure to social,

emotional, and economic deprivation during critical periods of development. Cost-effective and accessible methods of prevention and treatment of HIV in developing countries are needed to control this emerging cause of MR. Although administration of antiretroviral therapy and other medications to the pregnant woman can dramatically reduce HIV transmission, this form of treatment and preventive intervention is not widely practiced in the continents of Asia and Africa, due to poverty and political will (Amar, Ho, & Mohan, 1999; Boylan & Stein, 1991). In low-income countries which include the majority of HIV-infected women worldwide and in which prenatal screening, counseling, and treatment options are limited, the probability of vertical transmission from mother to infant is 30–40%.

In addition to infections known to directly damage the developing nervous system, other prenatal and perinatal infections associated with perinatal complications may contribute to developmental disabilities either directly or indirectly. Perinatal complications that occur more frequently in the presence of maternal and fetal infections include premature birth, low birth weight, intrauterine growth restriction, and asphyxia (Donders, Desmyter, De Wet, & Ban Assche, 1993). Infants born with perinatal complications, in turn, are at increased risk for developmental disabilities (Broman, Nichols, Shaughnessy, & Kennedy, 1987). The role of maternal and intrauterine infections in the etiology of perinatal brain disorders is an area of active investigation (O'Shea & Dammann, 2000).

### **PREMATURITY AND LOW BIRTH WEIGHT**

Some of the risk factors associated with MR are a mixture of causes that are highly correlated. These include poverty, prematurity, low birth weight, and intrauterine infection. Since the 1970s the proportion of infants born in the United States weighing less than 2500 g has remained around 7% of all births. Premature and low birth weight infants have three times the risk for neurodevelopmental impairments compared to babies weighing more than 2500 g at birth (Teplin, Burchinal, Johnson-Martin, Humphry, & Kraybill, 1991; Whitaker et al., 1996). It is not clear, in most cases, if intrauterine problems precipitated the premature birth or the early delivery was responsible for the development of subsequent problems. However, it is clear that the relationship between birth weight and risk for developmental delay is inverse, so the greatest risk is at the lowest weight. Risk factors associated with prematurity include young maternal age, minority racial or ethnic status, poverty, and unmarried status, several of which are likely to be concurrent factors. As noted previously, the role of bacteria in premature labor has been an important area of research in the last decade. Bacteria are found in the amniotic cavity in over 10% of patients with PROM, which occurs in approximately 5% of all pregnancies and accounts for 30–40% of all premature deliveries (Baumeister & Woodley-Zanthos, 1996; Cohen, 2000). However when Romero and colleagues compared randomized antibiotic treatment

to placebo, in a multicenter trial, there was no difference between the two groups in postponing birth (Romero, Sibai, et al., 1993).

### **FETAL STROKE**

Fetal stroke has emerged as another identifiable pregnancy event that can result in MR. Fetal stroke is defined as an ischemic, thrombotic, or hemorrhagic event occurring between 14 weeks of gestation and the onset of labor. A recent literature review suggests that in 50% of the identified cases, the cause of the stroke is unknown. For the cases where risk factors were identified the most common maternal condition was ischemic injury, hemorrhagic disturbances of coagulation, and fetal disorders such as pyruvate carboxylase deficiency (Ozduman et al., 2004).

### **BIRTH TRAUMA AND ASPHYXIA**

Birth injuries occur at the rate of approximately 2–7 per 1000 live births. The risk factors include macrosomy, prematurity, amniocentesis, cordocentesis, fetal surgical manipulations, dystocia, cephalopelvic disproportion, and the prolonged labor (Fanaroff & Hack, 1999). The most common consequences of birth injuries include blood clots, paralysis, and fracture. Neurological consequences are considered rare and are usually attributed to asphyxia.

Asphyxia is a combination of acidemia, hypoxia, and metabolic acidosis. An infant who exhibits acute neurological injury proximate to asphyxia usually has had profound metabolic or mixed acidemia (pH < 7) on an umbilical cord arterial blood sample, an Apgar score of 0–3 for longer than 5 min, neonatal neurological manifestations of seizures, coma, or hypotonia, and dysfunction on a multisystem level. The neurological outcome of asphyxiated infants is difficult to determine in the immediate postnatal period since the sequella are related to the period during development when the event occurred. Fetal asphyxia is associated with cerebral palsy although experts estimate that no more than 15% of cases of CP are explained by this mechanism (Goldenberg & Nelson, 1999).

### **HARMFUL CHEMICAL AND COMPOUNDS**

A number of common chemicals and compounds, e.g., alcohol (EtOH) and lead, are known to be teratogenic and neurotoxic to human embryo and fetal development. Many other chemicals, such as mercury and polychlorinated biphenyls (PCBs), are known to have neurodevelopmental effects that cannot be detected until later in life; therefore they are not classified as teratogens (substances that produce harmful effects detected at birth).

## **Alcohol**

Alcohol has been shown to be associated with a wide array of birth defects ranging from dysmorphia, growth deficiency, and behavioral and cognitive deficits. Heavy alcohol exposure or binge drinking has been associated with fetal alcohol syndrome (FAS) and lower doses of alcohol exposure have been associated with the milder version of symptoms characteristic of fetal alcohol effects (FAE) and alcohol-related neurodevelopmental disorder (ARND). Establishing the rates of these effects is dependent on the admission of alcohol use during pregnancy and the identification of the syndrome by an examining physician. The CDC has estimated FAS affected 6.7 per 10,000 live births in the United States in 1993 (CDC, 1995a). Research indicates that the outcome of intrauterine exposure is associated with the time of exposure and the sensitivity of the mother and fetus to EtOH (Sampson, Streissguth, Bookstein, & Barr, 2000).

## **THERAPEUTIC AND DIAGNOSTIC AGENTS**

The Food and Drug Administration (FDA) has established five categories of drugs based on their potential for causing birth defects in infants born to women who use the drugs during pregnancy. Birth defects are structural defects that can be recognized at birth, and thus exclude cognitive deficits, which cannot be detected until later infancy and early childhood. Five categories (A, B, C, D, X) range from the safest, (A) controlled studies in women fail to demonstrate a risk to the fetus in the first trimester, and fetal harm appears remote, to (X) studies or experience have shown fetal risk that clearly outweighs any possible benefits. For each presenting problem there are medications that are preferred by most prescribing physicians, based on the FDA categories. Few of the drugs considered unsafe for use during pregnancy that have possible links to MR, include antimicrobials (e.g., sulfonamides, isoniazid, ribavirin), anticonvulsants (e.g., phenytoin, carbamazepine), and warfarin, aminopterin, and accutane. Unfortunately, the inability to detect subtle cognitive limitations in infants results in inconclusive recommendations for many drugs (Jones, 1999; McGuigan & Bailey, 2001) and, more generally, knowledge of potential fetal risk presented by a wide range of medications is incomplete.

## **ENVIRONMENTAL CHEMICALS**

The fetus and the developing child need special consideration in the assessment of safety of environmental chemicals since the mitotic activity of cerebral neuronal development occurs prenatally and in the first 2 years of postnatal life. Dose and timing of the chemical exposure are critical variables in predicting neurotoxic outcomes and in many cases human data are insufficient to make accurate assessments of metals and chemicals (Sullivan & Krieger, 2001). Toluene, nitrous oxide, carbon monoxide,

organochlorines, organophosphates, methanol, xylene, trichloroethylene, perchloroethylene, carbon disulfide, lead, mercury, arsenic, manganese, thallium, aluminum, carbon tetrachloride, methylene chloride, *n*-Hexane, and ethylene glycol have all been associated with some neurobehavioral dysfunctions (Filley & Kelly, 2001). In addition, others report that only 7% of high-volume chemicals have actually been tested for potential neurodevelopmental toxicity (Goldman & Koduru, 2000). In humans, the environmental metals and chemicals for which there are the most data are lead, methyl mercury (MeHg), and PCBs.

Lead has been one of the most widely studied neurotoxic substances with respect to neurodevelopmental disorders and recommendations for lead screening, abatement of environmental exposures, and activities for the prevention of lead poisoning in children are numerous. Lead can cross the placenta beginning at 12 weeks of gestation and it accumulates in fetal tissues. Reports of neurobehavioral problems have been associated with blood lead levels higher than 10 mg/dl (Baghurst et al., 1992; CDC, 1997b; Keogh & Boyer, 2001; Tong, 1998). In the last 30 years lead levels in children have decreased in the United States due to the abandonment of leaded gasoline use; however, children living in older homes with leaded paint and other exposures continue to be exposed. Attention deficits and hyperactivity, IQ decreases, and memory deficits are among the neurologic manifestations of lead exposure (Agency for Toxic Substances and Disease Registry [ATSDR], 2000; Wasserman, Graziano, et al., 1994; Wasserman, Liu, et al., 1997). The ATSDR also indicates that pregnant women and children can absorb far more ingested lead than the general adult population: up to 70% of lead is absorbed by the former group compared to 20% by the latter group.

Mercury is found in three states—elemental mercury, inorganic mercury salts, and organic mercury. Small amounts of elemental mercury are found in dental amalgams, thermometers, sphygmomanometers, and batteries. In addition, there are natural sources of elemental mercury such as the degassing of the earth's crust, forest fires, the evaporation of seawater, and volcanoes. Mercury also gets into the environment as a result of the combustion of fossil fuels that contain mercury. Inorganic mercury salts are present in some pesticides and disinfectants and in some medications as a preservative. Mercury is constantly cycling through the environment, evaporating into the atmosphere, and returning to the ground and water sources as the result of gravity or precipitation. Both elemental and inorganic mercury can be transformed by microorganisms in water and soil into organic mercury; and the most common organic mercury in the environment is MeHg. Bioaccumulation in the food chain results from MeHg taken up by bacteria and plankton eaten by small fish, subsequently eaten by larger fish, which are caught and eaten by humans and animals. All forms of mercury cross the placenta into the fetal circulation. Maternal exposure usually occurs from the consumption of fish containing MeHg and through inhalation and skin absorption of elemental and inorganic mercury. All forms of mercury can be toxic to the developing brain and the spectrum of effects range from deficits in learning and memory to a

cerebral palsy-like syndrome, MR, and microcephaly (McGuigan & Bailey, 2001). The effects on infants born to mothers with high exposure to MeHg are mainly neurological, including developmental delay and altered muscle tone and tendon reflexes. At low doses, expected in human consumption of fish, there is no population-based evidence of risk (Davidson et al., 1998). There is human evidence of neural degeneration and glial proliferation occurring throughout the cerebral and cerebellar cortices at high exposure levels, and the clinical manifestations are related to the age of fetal exposure with the effects most pronounced in the second and third trimesters.

PCBs are a group of more than 100 chemicals, which are fat soluble and bioaccumulate in the food chain. The consumption of fish and shellfish is thought to be a major route of human exposure (Landrigan, 2001). Some of the earliest evidence of neurodevelopmental deficits produced by PCBs is from an incident in Taiwan where prenatal exposure to PCB-contaminated cooking oil resulted in lower IQs, spatial reasoning deficits, and developmental delays (Longnecker, Rogan, & Lucier, 1997). However at least one published study (Schell, Budinsky, & Wernke, 2001) refutes the association between PCBs and neurodevelopmental effects in humans. Long-term environmental exposures have been studied in pregnant women eating contaminated fish from Lake Michigan and the results suggest a long-term impact on intellectual function (Buck, 1996; Jacobson & Jacobson, 1996; Jacobson, Jacobson, & Humphrey, 1990). Children with PCB exposures were at greater risk of fetal and postnatal growth deficit and had lower full-scale and verbal IQs in infancy and at age 11 when compared to non-exposed children (Ribas-Fito, Sala, Kogevinas, & Sunyer, 2001). The latest study (Walkowiak et al., 2001; Winneke, Walkowiak, & Lilienthal, 2002) estimated the prenatal and perinatal PCB exposures of newborns in cord blood and maternal milk and followed the infants until 42 months of age, when PCB concentrations were measured in serum. This study found lower cognitive function in the children with higher levels of PCBs, after controlling for the home environment.

## POSTNATAL INFECTIONS

Postnatal meningitis and encephalitis are associated with a variety of infectious agents and leave a proportion of children with permanent cognitive disability, particularly in less developed countries where access to vaccination and treatment is limited or delayed. In the U.S. immunization of infants against tetanus, pertussis, diphtheria, and influenza have reduced the occurrence of these vaccine-preventable diseases.

*Hemophilus influenzae* type b (HiB), an invasive bacterium that can cause meningitis, was one of the most significant infectious causes of MR, deafness, and death in the United States from 1980 to the mid-1990s. The peak incidence, 150/100,000 per year, was in 1986 among children 6–7 months of age. Since 1991 the conjugate vaccine has been available for



infants at 2 months of age and the incidence has dramatically declined (CDC, 1995b; Wenger et al., 1990).

### **ENVIRONMENTAL EXPOSURES IN INFANCY AND EARLY CHILDHOOD**

Lead exposure in early childhood, through ingestion of paint chips, inhalation of lead in dust, and ingestion of ground dirt contaminated with lead from automobile and industrial emissions, is associated with learning and behavior problems. Lead is ubiquitous in the environment and in many parts of the world a significant level of lead has been detected in breast milk (Rabinowitz, Leviton, & Needleman, 1985). Several studies have found higher blood lead levels in formula-fed infants than in breast-fed infants probably because of contaminated formula cans or tap water with high lead levels. Lead is known to affect the central nervous system and leads to reduction in cognitive functioning. The impact of lead exposure is reported to impact the cognitive functioning of 1.7 million children, 1–5 years of age, in the United States.

### **INJURIES**

Severe, traumatic brain injury (i.e., with loss of consciousness for longer than 24 h) during childhood can result in long-term cognitive deficits and thus is a preventable cause of MR. In the United States, the leading causes of traumatic brain injury include falls, motor vehicle collisions, sport-related injuries, and assaults (including shaken-baby syndrome and gunshot wounds, Ewing-Cobbs, Prasad, Kramer, & Landry, 1999; Kraus, Fife, Cox, Ramstein, & Conroy, 1986; Thurman, Alverson, Dunn, Guerrero, & Sniezek, 1999). Despite the relatively high incidence of traumatic brain injuries to children in the population (2–3/1000 per year), evidence from epidemiologic studies indicates that trauma is an infrequent cause of MR (Annegers, Grabow, Kurland, & Laws, 1980; Blomquist, Gustavson, & Holmgren, 1981; Bower, Leonard, & Petterson, 2000; Durkin, Olsen, Barlow, Virella, & Connolly, 1998; Durkin, Schupf, Stein, & Susser, 1998; Gustavson et al., 1977a, 1977b; Kraus et al., 1986; Thurman & Guerrero, 1999). One possible explanation for the relatively minor role of trauma in the etiology of MR is that the majority of head injuries severe enough to result in MR is fatal. Another is that nonfatal brain injuries during childhood are followed by considerable recovery of function (Tomlin, Clarke, Robinson, & Roach, 2002). From a review of the literature, it appears that: (a) long-term sequella of traumatic brain injuries to children commonly include problems with memory, behavior, mood, and sleep, but rarely include significant deficits in general cognition (i.e., intelligence per se) and adaptive behavior (Emanuelson, von Wendt, Lundalv, & Larsson, 1996; Luis & Mittenberg, 2002); and (b) most studies of

the relationship between trauma and MR focus on MR as a risk factor for trauma rather than trauma as a risk factor for MR (Konarski, Sutton, & Huffman, 1997; Sherrard, Tonge, & Ozanne-Smith., 2002). The fact that cognitive disability is a risk factor for injury makes it difficult from follow-up studies of brain-injured children to distinguish cognitive sequella from preexisting cognitive deficits.

## DEPRIVATION

Deprivation in childhood includes children living in extreme poverty, those who experience disordered parenting because of mental illness or MR of a parent, and children faced with family stress, crisis, or neglect for any reason. The actual parent-child problems can include inadequate stimulation, deficient interpersonal nurturance, physical abuse, or malnutrition. In addition, there can be a confounding effect when children with disabilities and low cognitive function live in family chaos or in families with insufficient support systems. Societal advances that decrease the percentage of children living in poverty or increase the proportion of children attending stimulating child care can reduce deprivation and the exacerbating effect it has on children with established developmental deficits. Efficacious programs targeted at families without adequate resources to provide early stimulation can improve outcomes in these children. However, research has shown variability in the effectiveness of in home and out of home programs, and the effects do not extend far beyond the length of attendance (Garber, 1988; Gorman & Pollitt, 1996; Ramey & Ramey, 1998).

Effective prevention of MR must be accomplished by a multifaceted approach of both health-care delivery and educational interventions involving parents and young children. For example, an existing program, WIC—*The Special Supplemental Food Program for Women, Infants, and Children*, is a potentially effective, existing mechanism to define and reach the population at high risk. Expanding WIC services, already in place and staffed, to provide parent education or referral to high quality child stimulation programs would represent an adjustment of that program rather than the creation of a new bureaucratic service and delivery system. An MR-prevention intervention associated with WIC could reach children early in life, motivate both parent and child involvement, and combine health and education service components.

## CONCLUSION

It is essential to take into account the synergistic effect of environmental and biologic factors which determine MR. The interplay among child and parental medical and social characteristics, poverty, and deprivation must be addressed both in program planning and in research. At the present time, there are established strategies to prevent some environmental and heritable causes of MR, although for religious, social, and ethical reasons

they are not always carried out. Identification of causation is fundamental to developing prevention strategies. Prevention of MR challenges the established domains of education, medicine, basic science, and social service to work across discipline and organizational lines.

## REFERENCES

- Agency for Toxic Substances and Disease Registry. (2000). *Case studies in environmental medicine: Lead toxicity*. Atlanta, GA: Author.
- Albrecht, U., Sutcliffe, J. S., Cattanach, B. M., Beechey, C.V., Armstrong, D., Eichele, G., et al. (1997). Imprinted expression of the murine Angelman syndrome gene, *UBE3A*, in hippocampal and Purkinje neurons. *Nature Genetics*, 17(1), 75–78.
- Amar, H. S., Ho, J. J., & Mohan, A. J. (1999). Human immunodeficiency virus prevalence in women at delivery using unlinked anonymous testing of newborns in the Malaysian setting. *Journal of Paediatrics and Child Health*, 35(1), 63–66.
- American Association on Mental Retardation. (1992). *Mental retardation: Definition, classification, and systems of supports* (9th ed.). Washington, DC: Author.
- American Association on Mental Retardation. (2002). *Mental retardation: Definition, classification, and systems of supports* (10th ed.). Washington, DC: Author.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- Annegers, J. F., Grabow, J. D., Kurland, L. T., & Laws, E. R. (1980). The incidence, causes, and secular trends of head trauma in Olmsted County, Minnesota, 1935–1974. *Neurology*, 30(9), 912–919.
- Aries, F., Rodriguez, I., Rayne, S. C., & Krausu, F. T. (1993). Maternal placental vasculopathy and injection: Two distinct subgroups among patients with preterm labor and preterm ruptured membranes. *American Journal of Obstetrics and Gynecology*, 168(2), 585–591.
- Baghurst, P. A., McMichael, A. J., Wigg, N. R., Vimpani, G. V., Robertson, E. F., Roberts, R. J., et al. (1992). Environmental exposure to lead and children's intelligence at the age of seven years. *New England Journal of Medicine*, 327(18), 1279–1284.
- Baird, P. A., & Sadovnick, A. D. (1987). Life expectancy in Down's syndrome. *Journal of Pediatrics*, 110(6), 849–854.
- Battaglia, A., & Carey, J. C. (2003). Diagnostic evaluation of developmental delay/mental retardation: An overview. *American Journal of Medical Genetics*, 117C, 3–14.
- Baumeister, A. A., & Kupstas, F. D. (1991). The new morbidity: Implications for prevention and amelioration. In A. D. B. Clarke & P. Evan (Eds.), *Combating mental handicap: A multidisciplinary approach* (pp. 46–72). London: A.B. Academic .
- Baumeister, A. A., & Woodley-Zanthos, P. (1996). Prevention: Biological factors. In J. W. Jacobson & J. A. Mulick (Eds.), *Manual of diagnosis and professional practice in mental retardation*. Washington, DC: American Psychological Association.
- Bell, M. V., Hirst, M. C., Nakahori, Y., MacKinnon, R. N., Roche, A., Flint, T. J., et al. (1991). Physical mapping across the fragile X: Hypermethylation and clinical expression of the fragile X syndrome. *Cell*, 64, 861–866.
- Belman, A. L. (1992). Acquired immunodeficiency syndrome in the child's central nervous system. *Pediatric Clinics of North America*, 39(4), 691–714.
- Bennett, F. C., Sells, C. J., & Brand, C. (1979). Influences on measured intelligence in Down's syndrome. *American Journal of Diseases in Children*, 133(7), 700–703.
- Beuren, A. J., Apitz, J., & Harmajanz, D. (1962). Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance. *Circulation*, 26, 1235–1240.
- Blomquist, H. K., Gustavson, K. H., & Holmgren, G. (1981). Mild mental retardation in children in a northern Swedish county. *Journal of Mental Deficiency Research*, 25(Pt. 3), 169–186.
- Bower, L., Leonard, H., & Petterson, B. (2000). Intellectual disability in Western Australia. *Journal of Paediatrics and Child Health*, 36(3), 213–215.

- Boylan, L., & Stein, Z. (1991). The epidemiology of HIV infection in children and their mothers—vertical transmission. *Epidemiologic Reviews*, 13, 143–177.
- Broman, S., Nichols, P. L., Shaughnessy, P., & Kennedy, W. (1987). *Retardation in young children: A developmental study of cognitive deficit*. Hillsdale, NJ: Erlbaum.
- Brown, W. T., Jenkins, E. C., & Friedman, E. (1982). Autism is associated with the fragile-X syndrome. *Journal of Autism and Developmental Disorders*, 12(3), 303–308.
- Buck, G. M. (1996). Epidemiologic perspective of the developmental neurotoxicity of PCBs in humans. *Neurotoxicology and Teratology*, 18(3), 239–241; discussion 271–276.
- Budarf, M. L., & Emanuel, B. S. (1997). Progress in the autosomal segmental aneusomy syndromes (SASs): Single or multi-locus disorders? *Human Molecular Genetics*, 6(10), 1657–1665.
- Cao, X. Y., Jiang, X. M., Dou, Z. H., Rakeman, M. A., Zhang, M. L., O'Donnell, K., et al. (1994). Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. *New England Journal of Medicine*, 331(26), 1739–1744.
- Centers for Disease Control and Prevention. (1995a). Update: Trends in fetal alcohol syndrome—United States, 1979–1993. *JAMA*, 273(18), 1406.
- Centers for Disease Control and Prevention. (1995b). Progress toward elimination of *Haemophilus influenzae* type b disease among infants and children—United States, 1993–1994. *Morbidity and Mortality Weekly Report*, 44(29), 545–550.
- Centers for Disease Control and Prevention. (1997a). Rubella and congenital rubella syndrome—United States, 1994–1998. *Morbidity and Mortality Weekly Report*, 46(16), 350–354.
- Centers for Disease Control and Prevention. (1997b). Update: Blood lead levels—United States, 1991–1994. *JAMA*, 277(13), 1031–1032.
- Centerwall, S. A., & Centerwall, W. R. (1960). A study of children with Mongolism reared in the home compared to those reared away from the home. *Pediatrics*, 25, 678–685.
- Chechlacz, M., & Gleeson, J. G. (2003). Is mental retardation a defect of synapse structure and function? *Pediatric Neurology*, 29, 11–17.
- Chudley, A. E., Knoll, J., Gerrard, J. W., Shepel, L., McGahey, E., & Anderson, J. (1983). Fragile (X) X-linked mental retardation. I. Retardation between age and intelligence and the frequency of expression of fragile (X) (q28). *American Journal of Medicine Genetics*, 14(4), 699–712.
- Clarke, A. M., & Clarke, A. D. B. (1976). *Early experience: Myth and evidence*. New York: Free.
- Clarke, D., Boer, H., Cheung, M., Sturney, P., & Webb, T. (1996). Maladaptive behavior in Prader-Willi syndrome in adults life. *Journal of Intellectual Disability Research*, 40(Pt. 2), 159–165.
- Clements, P. R., Bates, M. V., & Hafer, M. (1976). Variability within Down's syndrome (trisomy-21): Empirically observed sex differences in IQs. *Mental Retardation*, 14(1), 30–31.
- Cohen, W. (Ed.). (2000). *Cherry and Merkatz's complications of pregnancy* (5th ed.). Philadelphia, PA: Lippincott.
- Connolly, B. H., Morgan, S. B., & Russell, F. F. (1984). Evaluation of children with Down syndrome who participated in an early intervention program. *Physical Therapy*, 64(10), 150–151.
- Creasy, R. K., & Iams, J. D. (1999). Preterm labor and delivery. In R. K. Creasy & R. Rasnik (Eds.), *Maternal-fetal medicine* (4th ed., pp. 498–531). Philadelphia, PA: Saunders.
- Cuckle, H. S., Wald, N. J., & Thompson, S. G. (1987). Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. *British Journal of Obstetrics and Gynaecology*, 94(5), 387–402.
- Czeizel, A. E. (1995). Folic acid in the prevention of neural tube defects. *Journal of Pediatric Gastroenterology and Nutrition*, 20(1), 4–16.
- Davidson, P. W., Myers, G. J., Cox, C., Axtell, C., Shamlaye, C., Sloane-Reeves, J., et al. (1998). Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: Outcomes at 66 months of age in the Seychelles Child Development Study. *JAMA*, 280(8), 701–707.
- Dennis, W. (1973). *Children of the crèche*. New York: Appleton-Century-Croft.
- de Vries, B. B., Jansen, C. C., Duits, A. A., Verheij, C., Willemsen, R., van Hemel, J. O., et al. (1996). Variable *FMR1* gene methylation of large expansion leads to variable phenotype

- in three males from one fragile X family. *Journal of Medical Genetics*, 33(12), 1007–1010.
- de Vries, B. B., van den Ouweland, A. M., Mohkamsing, S., Duivenvoorden, H. J., Mol, E., Gelsema, K., et al. (1997). Screening and diagnosis for the fragile X syndrome among the mentally retarded: An epidemiological and psychological survey. Collaborative Fragile X Study Group. *American Journal of Human Genetics*, 61(3), 660–667.
- Donders, G. G., Desmyter, J., De Wet, D. H., & Ban Assche, F. A. (1993). The association of gonorrhoea and syphilis with premature birth and low birthweight. *Genitourinary Medicine*, 69(2), 98–101.
- Drillien, C. M., Pickering, R. M., & Drummond, M. B. (1988). Predictive value of screening for difficult areas of development. *Developmental Medicine and Child Neurology*, 30, 294–305.
- Dunn, D., Wallon, M., Peyron, F., Peterson, E., Peckham, C., & Gilbert, R. (1999). Mother-to-child transmission of toxoplasmosis: Risk estimates for clinical counseling. *Lancet*, 353(9167), 1829–1833.
- Durkin, M., Schupf, N., Susser, M., & Stein, Z. (2001). Epidemiology of mental retardation. In M. Levene, R. Lilford, M. J. Bennet & J. Punt. (Eds.), *Fetal neurology and neurosurgery* (3rd ed., pp. 719–818). London: Churchill Livingstone.
- Durkin, M. S., Olsen, S., Barlow, B., Virella, A., & Connolly, E. S. (1998). The epidemiology of urban, pediatric, neurological trauma: Evaluation of, and implications for, injury prevention programs. *Neurosurgery*, 42(2), 300–310.
- Durkin, M. S., Schupf, N., Stein, Z. A., & Susser, M. W. (1998). Mental retardation. In R. B. Wallace (Ed.), *Public health and preventive medicine* (pp. 1049–1058). Stamford, CT: Appleton & Lange.
- Durkin, M. S., & Stein, Z. A. (1996). Classification of mental retardation. In J. W. Jacobson & J. A. Mulick (Eds.), *Manual of diagnosis and professional practice in mental retardation*. Washington, DC: American Psychological Association.
- Dykens, E. M., Leckman, J. F., & Cassify, S. B. (1996). Obsession and compulsions in Prader-Willi syndrome. *Journal of Child Psychiatry*, 37(8), 995–1002.
- Editorial Board. (1996). Definition of mental retardation. In J. W. Jacobson & J. A. Mulick (Eds.), *Manual of diagnosis and professional practice in mental retardation* (pp. 13–38). Washington, DC: American Psychological Association.
- Emanuelson, I., von Wendt, L., Lundalv, E., & Larsson, J. (1996). Rehabilitation and follow-up of children with severe traumatic brain injury. *Childs Nervous System*, 12(8), 460–465.
- Epstein, C. M. (1986). *The consequences of chromosome imbalance*. Cambridge, UK: Cambridge University Press.
- European Mode of Delivery Collaboration. (1999). Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: A randomized clinical trial. *Lancet*, 353(9158), 1030–1031.
- Ewart, A. K., Morris, C. A., Atkinson, D., Jin, W., Sternes, K., Spallone, P., et al. (1993). Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. *Nature Genetics*, 5(1), 11–16.
- Ewing-Cobbs, L., Prasad, M., Kramer, L., & Landry, S. (1999). Inflicted traumatic brain injury: Relationship of developmental outcome to severity of injury. *Pediatric Neurosurgery*, 31(5), 251–258.
- Fanaroff, A. A., & Hack, M. (1999) Periventricular leukomalacia—prospects for prevention. *New England Journal of Medicine*, 341(16), 1229–1231.
- Faro, S., & Soper, D. E. (2001). *Infectious diseases in women* (1st ed.). Philadelphia, PA: WB Saunders.
- Feldman, E. J. (1996). The recognition and investigation of X-linked learning disability syndromes. *Journal of Intellectual Disability Research*, 40(Pt. 5), 400–411.
- Filley, C. K., & Kelly, J. P. (2001). Clinical neurotoxicology and neurobehavioral toxicology. In J. B. Sullivan & G. R. Krieger (Eds.), *Clinical environmental health and toxic exposures*. Denver, CO: Lippincott, Williams & Wilkins.
- Fishkin, P. E., Armstrong, F. D., Routh, D. K., Harris, L., Thompson, W., Miloslavich, K., et al. (2000). Brief report: Relationship between HIV infection and WPPSI-R performance in preschool-age children. *Journal of Pediatric Psychology*, 25(5), 347–351.

- Flint, J., Wilkie, A. O., Buckle, V. J., Winter, R. M., Holland, A. J., & McDermid, H. E. (1995). The detection of subtelomeric chromosomal rearrangements in idiopathic mental retardation. *Nature Genetics*, 9(2), 132–140.
- Frangiskakis, J. M., Ewart, A. K., Morris, C. A., Mervis, C. B., Bertrand, J., Robinson, B. F., et al. (1996). LIM-kinase1 hemizyosity implicated in impaired visuospatial constructive cognition. *Cell*, 86(1), 59–69.
- Frankenberger, W., & Harper, J. (1988). States' definitions and procedures for identifying children with mental retardation: Comparison of 1981–1982 and 1985–1986 guidelines. *Mental Retardation*, 26(3), 133–136.
- Freij, B. J., & Sever, J. L. (1997). Varicella. In J. T. Queenan & J. C. Hobbins (Eds.), *Protocols for high risk pregnancies* (3rd ed., pp. 387–397). Cambridge, MA: Blackwell Science.
- Fu, Y. H., Kuhl, D. P., Pizzuti, A., Pieretti, M., Sutcliffe, J. S., Richards, S., et al. (1991). Variation of the CGG repeat at the fragile X site results in genetic stability: Resolution of the Sherman paradox. *Cell*, 67(6), 1047–1058.
- Garber, H. (1988). *The Milwaukee project: Preventing mental retardation in children at risk*. Washington, DC: American Association on Mental Retardation.
- Gedeon, A. K., Baker, E., Robinson, H., Partington, M. W., Gross, B., Manca, A., et al. (1992). Fragile X syndrome without CGG amplification has an *FMR1* deletion. *Nature Genetics*, 1(5), 341–344.
- Gibbs, R. S., & Sweet, R. L. (1999). Maternal and fetal infectious disorders. In R. K. Creasy & R. Rasnik (Eds.), *Maternal-fetal medicine* (4th ed., pp. 685–689). Philadelphia, PA: Saunders.
- Gilstrap, L. C. (1997). *Infections in pregnancy* (2nd ed.). New York: Wiley.
- Goldenberg, R. L., & Nelson, K. G. (1999). In R. K. Creasy & R. Rasnik (Eds.), *Maternal-fetal medicine* (4th ed., pp. 1194–1214). Philadelphia, PA: Saunders.
- Goldman, L. R., & Koduru, S. (2000). Chemicals in the environment and developmental toxicity to children: A public health and policy perspective. *Environmental Health Perspectives*, 108(Suppl. 3), 443–448.
- Gorman, K. S., & Pollitt, E. (1996). Does schooling buffer the effects of early risk? *Child Development*, 67(2), 314–326.
- Guerina, N. G., Hsu, H. W., Meissner, H. C., Maguire, J. H., Lynfield, R., Stechenburg, B., et al. (1994). Neonatal serological screening and early treatment for congenital *Toxoplasma gondii* infection. *New England Journal of Medicine*, 330(26), 1858–1863.
- Gustavson, K. H., Hagberg, B., Hagberg, G., & Sars, K. (1977a). Severe mental retardation in a Swedish county. I. Epidemiology, gestational age, birth weight and associated CNS handicaps in children born 1959–1970. *Acta Paediatrica Scandinavica*, 66, 373–379.
- Gustavson, K. H., Hagberg, B., Hagberg, G., & Sars, K. (1977b). Severe mental retardation in a Swedish county: Etiological and pathogenic aspects of children born 1959–1970. *Neuropadiatrie*, 8(3), 293–304.
- Hagberg, B., & Hagberg, G. (1997). Rett syndrome: Epidemiology and geographical variability. *European Child and Adolescent Psychiatry*, 6(Suppl. 1), 5–7.
- Hagerman, R. J., Hull, C. E., Safanda, J. F., Carpenter, I., Staley, L. W., O'Connor, R. A., et al. (1994). High functioning fragile X males: Demonstration of an unmethylated fully expanded *FMR-1* mutation associated with protein expression. *American Journal of Medical Genetics*, 51(4), 298–308.
- Hagerman, R. J., Jackson, C., Amiri, K., Silverman, A. C., O'Connor, R., & Sobesky, W. (1992). Girls with fragile X syndrome physical and neurocognitive status and outcome. *Pediatrics*, 89(3), 395–400.
- Hagerman, R. J., & Silverman, A. C. (Eds.). (1991). *Fragile X syndrome, diagnosis, treatment and research*. Baltimore: Johns Hopkins University Press.
- Hagerman, R. J., Wilson, P., Staley, L. W., Lang, K. A., Fan, T., Uhlhorn, C., et al. (1994). Evaluation of school children at high risk for fragile X syndrome utilizing buccal cell *FMR-1* testing. *American Journal of Medical Genetics*, 51(4), 474–481.
- Hanley, W. B., Platt, L. D., Bachman, R. P., Buist, N., Geraghty, M. T., Isaacs, J., et al. (1999). Undiagnosed maternal phenylketonuria: The need for prenatal selective screening or case finding. *American Journal of Obstetrics and Gynecology*, 180(4), 986–994.
- Hassold, T. J., Burrage, L. C., Chan, E. R., Judis, L. M., Schwartz, S., James, J., et al. (2001). Maternal folate polymorphisms and the etiology of human nondisjunction. *American Journal of Human Genetics*, 69(2), 434–439.

- Hassold, T., Chiu, D., & Yamane, J. A. (1984). Parental origin of autosomal trisomies. *Annals of Human Genetics*, 48(Pt. 2), 129–144.
- Hetzel, B. S. (1989). *The story of iodine deficiency: An international challenge in nutrition*. Oxford: Oxford University Press.
- Hobbs, C. A., Sherman, S. L., Yi, P., Hopkins, S. E., Torfs, C. P., Hine, R. J., et al. (2000). Polymorphisms in genes involved in folate metabolism as maternal risk factors for Down syndrome. *American Journal of Human Genetics*, 67(3), 623–630.
- Holden, J. J., Percy, M., Allingham-Hawkins, D., Brown, W. T., Chiurazzi, P., Fisch, G., et al. (1999). Conference Report: Eighth International Workshop on the fragile X syndrome and X-linked mental retardation, August 16–22, 1997. *American Journal of Medical Genetics*, 83(4), 221–236.
- Holland, A. J., Hon, J., Huppert, F. A., & Watson, P. (1998). Population-based study of the prevalence and presentation of dementia in adults with Down syndrome. *British Journal of Psychiatry*, 172, 493–498.
- Hook, E. B. (1982). Epidemiology of Down syndrome. In S. M. Pueschel & J. E. Rynders (Eds.), *Down syndrome: Advances in biomedicine and the behavioral sciences* (pp. 11–18). Cambridge, MA: Ware .
- Hook, E. B., & Cross, P. K. (1987). Rates of mutant and inherited structural cytogenetic abnormalities detected at amniocentesis: Results of about 63,000 fetuses. *Annals of Human Genetics*, 51, 27–55.
- Iams, J. D., Talbert, M. L., Barrows, H., & Sachs, L. (1985). Management of preterm rupture of the membranes: A prospective randomized comparison of observation versus use of steroids and timed delivery. *American Journal of Obstetrics and Gynecology*, 151(1), 32–38.
- Jacobs, P. A., Bullman, H., Macpherson, J., Youings, S., Rooney, V., Watson, A., et al. (1993). Population studies of fragile X: A molecular approach. *Journal of Medical Genetics*, 30(6), 454–459.
- Jacobson, J., & Jacobson, S. (1996). Intellectual impairment in children exposed to polychlorinated biphenyls in utero. *New England Journal of Medicine*, 335(11), 783–789.
- Jacobson, J., Jacobson, S., & Humphrey, H. (1990). Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. *Journal of Pediatrics*, 116(1), 38–45.
- Jacobson, J. W., & Mulick, J. A. (1996). *Manual of diagnosis and professional practice in mental retardation*. Washington, DC: American Psychological Association.
- James, S. J., Pogribna, M., Pogribny, I. P., Melnyk, S., Hine, R. J., Gibson, J. B., et al. (1999). Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductase gene may be maternal risk factors for Down syndrome. *American Journal of Clinical Nutrition*, 70(4), 495–501.
- Jiang, Y.-H., Tsai, T.-F., Bressler, J., & Beaudet, A. L. (1998). Imprinting in Angelman and Prader–Willi syndromes. *Current Opinion in Genetics and Development*, 8(3), 334–342.
- Johnson, P. M. (1995). Immunology of pregnancy. In G. Chamberlain (Ed.), *Turnbull's obstetrics* (2nd ed., pp. 143–159). Edinburgh, UK: Churchill Livingstone.
- Jones, K. L. (1999). Effects of therapeutic, diagnostic and environmental agents. In R. K. Creasy & R. Rasnik (Eds.), *Maternal-fetal medicine* (4th ed., pp. 132–144). Philadelphia, PA: Saunders.
- Keogh, J. P., & Boyer, L. V. (2001). Lead. In J. B. Sullivan & G. R. Krieger. (Eds.), *Clinical environmental health and toxic exposures* (pp. 879–889). Baltimore: Lippincott Williams & Wilkins.
- Kerr, A. M., & Ravine, D. (2003). Review article: Breaking new ground with Rett syndrome. *Journal of Intellectual Disability Research*, 47(8), 580–587.
- Kiely, M. (1987). The prevalence of mental retardation. *Epidemiologic Reviews*, 9, 194–218.
- Kline, J., Stein, Z., & Susser, M. (1989). *Conception to birth: Epidemiology of prenatal development*. New York: Oxford University Press.
- Knight, S. J., Regan, R., Nicod, A., Horsely, S. W., Kearney, L., Homfray, T., et al. (1999). Subtle chromosomal rearrangements in children with unexplained mental retardation. *Lancet*, 354(9191), 1676–1681.

- Knoll, J. H., Nicholls, R. D., Magenis, R. E., Graham, J. M., Jr., Lalande, M., & Latt, S. A. (1989). Angelman and Prader-Willi syndromes share a common chromosome 15 deletion but differ in parental origin of the deletion. *American Journal of Medical Genetics*, 32(2), 285-290.
- Konarski, E. A., Sutton, K., & Huffman, A. (1997). Personal characteristics associated with episodes of injury in a residential facility. *American Journal of Mental Retardation*, 102(1), 37-44.
- Kraus, J. F., Fife, D., Cox, P., Ramstein, K., & Conroy, C. (1986). Incidence, severity, and external causes of pediatric brain injury. *American Journal of Diseases of Children*, 140(7), 687-693.
- Kremer, E. J., Pritchard, M., Lynch, M., Yu, S., Holman, K., Baker, E., et al. (1991). Mapping of DNA instability at the fragile X to a trinucleotide repeat sequence p(CCG)<sub>n</sub>. *Science*, 252(5013), 1711-1714.
- Lai, F., Kammann, E., Rebeck, G. W., Anderson, A., Chen, Y., & Nixon, R. A. (1999). APOE genotype and gender effects on Alzheimer disease in 100 adults with Down syndrome. *Neurology*, 53(2), 331-336.
- Landrigan, P. J. (2001). Pesticides and polychlorinated biphenyls (PCBs): An analysis of the evidence that they impair children's neurobehavioral development. *Molecular Genetics and Metabolism*, 73(1), 11-17.
- Larson, S. A., Lakin, K. C., Anderson, L., Kwak, N., Lee, M., & Anderson, D. (2001). Prevalence of mental retardation and developmental disabilities: Estimates from the 1994/1995 National Health Interview Survey Disability Supplements. *American Journal of Mental Retardation*, 106(3), 231-252.
- Lazar, I., & Darlington, R. (1982). Lasting effects of early education: A report from the consortium for longitudinal studies. *Monographs of the Society for Research in Child Development*, 47(2-3), 1-151.
- Lebeck, M., Andersen, O., Christensen, N. C., Hertel, J., Nielsen, H. E., Peitersen, B., et al. (1999). Feasibility of neonatal screening for toxoplasma infection in the absence of prenatal treatment. Danish Congenital Toxoplasmosis Study Group. *Lancet*, 353(9167), 1834-1837.
- Ledbetter, D., Riccardi, V., Airhart, S., Strobel, R., Keenean, B., & Crawford, J. (1981). Deletions of chromosome 15 as a cause of the Prader-Willi syndrome. *New England Journal of Medicine*, 304(6), 325-329.
- Lenke, R. R., & Levy, H. L. (1980). Maternal phenylketonuria and hyperphenylalaninemia: An international survey of the outcome of untreated and treated pregnancies. *New England Journal of Medicine*, 303(21), 1202-1208.
- Leviton, A., & Gilles, F. (1996). Ventriculomegaly, delayed myelination, white matter hypoplasia, and "periventricular" leukomalacia: how are they related? *Pediatric Neurology*, 15(2), 127-136.
- Leviton, A., & Paneth, N. (1990). White matter damage in preterm newborns—an epidemiologic perspective. *Early Human Development*, 24(1), 1-22.
- Levy, H. L., & Ghavami, M. (1996). Maternal phenylketonuria: A metabolic teratogen. *Teratology*, 53(3), 176-184.
- Levy, H. L., & Waisbren, S. E. (1983). Effects of untreated maternal phenylketonuria and hyperphenylalaninemia on the fetus. *New England Journal of Medicine*, 309(21), 1269-1274.
- Lewis, M., & Goldberg, S. (1969). Perceptual-cognitive development in infancy: A generalized expectancy model as a function of mother-infant interaction. *Merrill-Palmer Quarterly*, 15, 81-100.
- Liu, H., Momotani, N., & Yoshimura, J. (1994). Maternal hypothyroidism during early pregnancy and intellectual development of the progeny. *Archives of Internal Medicine*, 154(7), 785-787.
- Longnecker, M. P., Rogan, W. J., & Lucier, G. (1997). The human effects of DDT and PCBs and an overview of organochlorines in public health. *Annual Review of Public Health*, 18, 211-244.
- Lubs, H. A. (1969). A marker-X chromosome. *American Journal of Human Genetics*, 21(3), 231-244.



- Luis, C. A., & Mittenberg, W. (2002). Mood and anxiety disorders following pediatric traumatic brain injury: A prospective study. *Journal of Clinical and Experimental Neuropsychology*, 24(3), 270–279.
- Macmillan, C., Magder, L. S., Brouwers, P., Chase, C., Hittelman, J., Lasky, T., et al. (2001). Head growth and neurodevelopment of infants born to HIV-1 infected drug-using women. *Neurology*, 57(8), 1402–1411.
- Martin, D., & Schoub, B. (2000). Rubella infection in pregnancy. In M. L. Newell & J. McIntyre. (Eds.), *Congenital and perinatal infections: Prevention, diagnosis and treatment*. Cambridge, UK: Cambridge University Press.
- Martin, G. M. (1978). Genetic syndromes in man with potential relevance to pathobiology of aging. *Birth Defects Original Articles Series*, 14(1), 5–39.
- Massey, P. S., & McDermott, S. (1995). State-specific rates of mental retardation—United States, 1993. *Morbidity and Mortality Weekly Report*, 45, 61–65.
- Matsuura, T., Sutcliffe, J. S., Fang, P., Galjaard, R. J., Jiang, Y. H., Benton, C. S., et al. (1997). De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (*UBE3A*) in Angelman syndrome. *Nature Genetics*, 15(1), 74–77.
- McDermott, S. (1994). Explanatory model to describe school district prevalence rates for mental retardation and learning disabilities. *American Journal of Mental Retardation*, 99(2), 175–185.
- McDermott, S., Callaghan, W., Szwejbka, L., Mann, H., & Daguise, V. (2000). Urinary tract infections during pregnancy and mental retardation and developmental delay. *Obstetrics and Gynecology*, 96(1), 113–119.
- McDermott, S., Daguise, V., Mann, H., Szwejbka, L., & Callaghan, W. (2001). Perinatal risk for mortality and mental retardation associated with maternal urinary-tract infections. *Journal of Family Practice*, 50(5), 433–437.
- McGuigan, M. A., & Bailey, B. (2001). In J. B. Sullivan & G. R. Krieger (Eds.), *Clinical environmental health and toxic exposures* (pp. 289–299). Baltimore: Lippincott Williams & Wilkins.
- McLaren, J., & Bryson, S. E. (1987). Review of recent epidemiological studies of mental retardation: Prevalence, associated disorders, and etiology. *American Journal of Mental Retardation*, 92(3), 243–254.
- Meadows, K. L., Pettay, D., Newman, J., Hersey, J., Ashley, A. E., & Sherman, S. L. (1996). Survey of the fragile X syndrome and the fragile X E syndrome in a special education needs population. *American Journal of Medical Genetics*, 64(2), 428–433.
- Melyn, M. A., & White, D. T. (1973). Mental and developmental milestones of noninstitutionalized Down's syndrome children. *Pediatrics*, 52(4), 542–545.
- Mialky, E., Vagnoni, J., & Rutstein, R. (2001). School-age children with perinatally acquired HIV infection: Medical and psychosocial issues in a Philadelphia cohort. *AIDS Patient Care and STDS*, 15(11), 575–579.
- Morgan-Capner, P. (1999). Rubella. In D. J. Jeffries & C. N. Hudson (Eds.), *Viral Infections in obstetrics and gynaecology*. London: Arnold.
- Morton, J. E., Bunday, S., Webb, T. P., Macdonald, F., Rindl, P. M., & Bullock, S. (1997). Fragile X syndrome is less common than previously estimated. *Journal of Medical Genetics*, 34(1), 1–5.
- Mowery-Rushton, P. A., Driscoll, D. J., Nicholls, R. D., Locker, J., & Surti, U. (1996). DNA methylation patterns in human tissues of uniparental origin using a zinc-finger gene (*ZNF127*) from the Angelman/Prader-Willi region. *Human Molecular Genetics*, 6(2), 140–146.
- MRC Vitamin Study Group. (1991). Prevention of neural tube defects: Results of the Medical Research Council vitamin study. *Lancet*, 338(8760), 131–137.
- Murray, A., Youings, S., Dennis, N., Latsky, L., Linehan, P., McKechnie, N., et al. (1996). Population screening at the FRAXA and FRAXE loci: Molecular analyses of boys with learning difficulties and their mothers. *American Journal of Medical Genetics*, 5(6), 727–735.
- National Center for Health Statistics. (2000). National Health Interview Survey. Retrieved December 3, 2002, from National Center for Health Statistics, National Health Interview Survey (NHIS) Web site: <http://www.cdc.gov/nchs/nhis.htm>

- Nicholls, R. D. (1993). Genomic imprinting and candidate genes in the Prader-Willi and Angelman syndromes. *Current Genetic Developments*, 3(3), 445-456.
- Nicholson, A., & Alberman, E. (1992). Prediction of the number of Down's syndrome infants to be born in England and Wales up to the year 2000 and their likely survival rates. *Journal of Intellectual Disability Research*, 36(Pt. 6), 505-517.
- Nolin, S. L., Glicksman, A., Houck, G., Brown, W. T., & Dobkin, C. S. (1994). Mosaicism in fragile X affected males. *American Journal of Medical Genetics*, 51(4), 509-512.
- Oberle, I., Rousseau, F., Heitz, D., Kretz, C., Devys, D., Hanauer, A., et al. (1991). Instability of a 550-base pair DNA segment and abnormal methylation in fragile X syndrome. *Science*, 252(5010), 1097-1102.
- O'Donnell, K. J., Rakeman, M. A., Zhi-Hong, D., Xue-Yi, C., Mei, Z. Y., DeLong, N., et al. (2002). Effects of iodine supplementation during pregnancy on child growth and development at school age. *Developmental Medicine and Child Neurology*, 44(2), 76-81.
- O'Leary, V. B., Parle-McDermott, A., Molloy, A. M., Kirke, P. N., Johnson, Z., Conley, M., et al. (2002). MTRR and MTHFR polymorphism: Link to Down syndrome? *American Journal of Medical Genetics*, 107(2), 151-155.
- Oliver, C., & Holland, A. J. (1986). Down syndrome and Alzheimer's disease: A review. *Psychological Medicine*, 16(2), 307-322.
- Opitz, J. M., & Sutherland, G. R. (1984). Conference report: International Workshop on the fragile X and X-linked mental retardation. *American Journal of Medical Genetics*, 17(1), 5-94.
- Osborne, L. R., Martindale, D., Scherer, S. W., Shi, X. M., Huizenga, J., Heng, H. H., et al. (1996). Identification of genes from a 500-kb region at 7q11.23 that is commonly deleted in Williams-syndrome patients. *Genomics*, 36, 328-336.
- O'Shea, T. M., & Dammann, O. (2000). Antecedents of cerebral palsy in very low birth weight infants. *Clinics in Perinatology*, 27(2), 285-302.
- Ozcelik, T., Leff, S., Robinson, W., Donlon, T., Lalande, M., Sanjines, E., et al. (1992). Small nuclear ribonucleoprotein polypeptide N (SNRPN), an expressed gene in the Prader-Willi syndrome critical region. *Nature Genetics*, 9, 395-400.
- Ozduman, K., Pober, B. R., Barnes, P., Copel, J. A., Ogle, E. A., Duncan, C. C., et al. (2004). Fetal stroke. *Pediatric Neurology*, 30, 151-162.
- Paryani, S. G., & Arvin, A. M. (1986). Intrauterine infection with varicella-zoster virus after maternal varicella. *New England Journal of Medicine*, 314(24), 1542-1546.
- Peckham, C. (1991). Cytomegalovirus infection, congenital and neonatal disease. *Scandinavian Journal of Infectious Diseases*, 80(Suppl.), 82-87.
- Peoples, R., Perez-Jurado, L., Wang, Y.-K., Kaplan, P., & Francke, U. (1996). The gene for replication factor C subunit (RFC2) is within the 7q11.23 Williams syndrome deletion. *American Journal of Human Genetics*, 58(6), 1370-1373.
- Perez-Jurado, L. A., Peoples, R., Kaplan, P., Hamel, B. C. J., & Francke, U. (1996). Molecular definition of the chromosome 7 deletion in Williams syndrome and parent-of-origin effects on growth. *American Journal of Human Genetics*, 59(4), 781-792.
- Pieretti, M., Zhang, F. P., Fu, Y. H., Warren, S. T., Oostra, B. A., Caskey, C. T., et al. (1991). Absence of expression of the *FMR-1* gene in fragile X syndrome. *Cell*, 66, 817-822.
- Popp, S., Schulze, B., Granzow, M., Keller, M., Holtgreve-Grez, H., Schoell, B., et al. (2002). Study of 30 patients with unexplained developmental delay and dysmorphic features or congenital abnormalities using conventional cytogenetics and multiplex FISH telomere (MTEL) integrity assay. *Human Genetics*, 111(1), 31-39.
- Preblud, S., Cochi, S., & Orenstein, W. (1986). Varicella-zoster infection in pregnancy. *New England Journal of Medicine*, 315(22), 1415-1417.
- Rabinowitz, M., Leviton, A., & Needleman, H. (1985). Lead in Milk and Infant Blood: A dose-response model. *Archives of Environmental Health*, 40(5), 283-286.
- Ramey, C. T., & Ramey, S. L. (1998). Prevention of intellectual disabilities: Early interventions to improve cognitive development. *Preventive Medicine*, 27(2), 224-232.
- Reiss, A. L., Abrams, M. T., Greenlaw, R., Freund, L., & Denckla, M. B. (1995). Neurodevelopmental effects of the *FMR-1* full mutation in humans. *Nature Medicine*, 1(2), 159-167.
- Reiss, A. L., Aylward, E., Freund, L. S., Joshi, P. K., & Bryan, R. N. (1991). Neuroanatomy of fragile X syndrome: The posterior fossa. *Annals of Neurology*, 29, 26-32.

- Reiss, A. L., & Freund, L. (1990). Fragile X syndrome, DSM-III-R and autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, 29(6), 885–891.
- Reiss, A. L., Lee, J., & Freund, L. (1994). Neuroanatomy of fragile X syndrome: The temporal lobe. *Neurology*, 44(7), 1317–1324.
- Remington, J. S., McLeod, R., & Desmonts, G. (1995). Toxoplasmosis. In J. S. Remington & J. O. Klein (Eds.), *Infectious diseases of the fetus and newborn infant* (4th ed., pp. 140–267). Philadelphia: WB Saunders.
- Ribas-Fito, N., Sala, M., Kogevinas, M., & Sunyer, J. (2001). Polychlorinated biphenyls (PCBs) and neurological development in children: A systematic review. *Journal of Epidemiology and Community Health*, 55(8), 537–546.
- Roizen, N., Swisher, C. N., & Stein, M. A. (1995). Neurologic and developmental outcome in treated congenital toxoplasmosis. *Pediatrics*, 95, 11–20.
- Romero, R., Sibai, B., Caritis, S., Paul, R., Depp, R., Rosen, M., et al. (1993). Antibiotic treatment of preterm labor with intact membranes: A multicenter, randomized, double-blinded, placebo-controlled trial. *American Journal of Obstetrics and Gynecology*, 169(4), 764–774.
- Romero, R., Yoon, B. H., Mazor, M., Gomez, R., Diamond, M. P., Kenney, J. S., et al. (1993). The diagnostic and prognostic value of amniotic fluid white blood cell count, glucose, interleukin-6, and Gram-stain in patients with preterm labor and intact membranes. *American Journal of Obstetrics and Gynecology*, 169(4), 805–816.
- Rouse, B., Azen, C., Koch, R., Matalon, R., Hanley, W., de la Cruz, F., et al. (1997). Maternal Phenylketonuria Collaborative Study (MPKUCS) offspring: Facial anomalies, malformations, and early neurological sequelae. *American Journal of Medical Genetics*, 69(1), 89–95.
- Rousseau, F., Heitz, D., Tarleton, J., MacPherson, J., Malmgren, H., Dahl, N., et al. (1994). A multicenter study on genotype–phenotype correlation in the fragile X syndrome, using direct diagnosis with probe StB12.3: The first 2253 cases. *American Journal of Human Genetics*, 55(2), 225–237.
- Rousseau, F., Rouillard, P., Morel, M. L., Khandjian, E. W., & Morgan, K. (1995). Prevalence of carriers of premutation-size alleles of the *FMR1* gene and implications for the population genetics of the fragile X syndrome. *American Journal of Human Genetics*, 57(5), 1006–1018.
- Rumble, B., Retallack, R., Hilbich, C., Simms, G., Multhaup, G., Martins, R., et al. (1989). Amyloid A4 protein and its precursor in Down's syndrome and Alzheimer's disease. *New England Journal of Medicine*, 320(22), 1446–1452.
- Rynders, J. E., Spiker, D., & Horrobin, J. M. (1978). Underestimating the educability of Down's syndrome children: Examination of methodological problems in recent literature. *American Journal of Mental Deficiency*, 82(5), 440–448.
- Sampson, P. D., Streissguth, A. P., Bookstein, F. L., & Barr, H. M. (2000). On categorization in analyses of alcohol teratogenesis. *Environmental Health Perspectives*, 108(Suppl. 3), 421–428.
- Sare, Z., Ruvalcaba, R. H., & Kelly, V. C. (1978). Prevalence of thyroid disorder in Down syndrome. *Clinical Genetics*, 14(3), 154–158.
- Schell, J. D., Jr., Budinsky, R. A., & Wernke, M. J. (2001). PCBs and neurodevelopmental effects in Michigan children: An evaluation of exposure and dose characterization. *Regulatory Toxicology and Pharmacology*, 33, 300–312.
- Schupf, N., & Sergievsky, G. H. (2002). Genetic and host factors for dementia in Down syndrome. *British Journal of Psychiatry*, 180, 405–410.
- Sharav, T., & Shlomo, L. (1986). Stimulation of infants with Down syndrome: Long-term effects. *Mental Retardation*, 24(2), 81–86.
- Sherman, S. L., Jacobs, P. A., Morton, N. E., Froster-Iskenius, U., Howard-Peebles, P. N., Nielsen, K. B., et al. (1985). Further segregation analysis of the fragile X syndrome with special reference to transmitting males. *Human Genetics*, 69(4), 289–299.
- Sherman, S. L., Morton, N. E., Jacobs, P. A., & Turner, G. (1984). The marker X syndrome: A cytogenetic and genetic analysis. *Annals of Human Genetics*, 48(Pt. 1), 21–37.

- Sherman, S. L., Takaesu, N., Freeman, S. B., Grantham, M., Phillips, C., Blackston, R. D., et al. (1991). Trisomy 21: Association between reduced recombination and nondisjunction. *American Journal of Human Genetics*, 49(3), 608–620.
- Sherrard, J., Tonge, B. J., & Ozanne-Smith, J. (2002). Injury risk in young people with intellectual disability. *Journal of Intellectual Disability Research*, 46(Pt. 1), 6–16.
- Simeonsson, R. J., & Sharp, M. C. (1992). Developmental delays. In R. A. Hockelman, S. B. Friedman, N. M. Nelson & H. M. Seidel (Eds.), *Primary pediatric care* (2nd ed., pp. 867–870). St. Louis, MO: Mosby-Year Book.
- Smith, R., Malee, K., Charurat, M., Magder, L., Mellins, C., Macmillan, C., et al. (2000). Timing of perinatal human immunodeficiency virus type 1 infection and rate of neurodevelopment. The Women and Infant Transmission Study Group. *Pediatric Infectious Disease Journal*, 19(9), 862–871.
- Smits, A., Smeets, D., Dreesen, J., Hamel, B., de Haan, A., & van Oost, B. (1992). Parental origin of the Fra(X) gene is a major determinant of the cytogenetic expression and the CGG repeat length in female carriers. *American Journal of Medical Genetics*, 43(1–2), 261–267.
- Spence, W. C., Black, S. H., Fallon, L., Maddalena, A., Cummings, E., Menapace-Drew, G., et al. (1996). Molecular fragile X screening in normal populations. *American Journal of Medical Genetics*, 64(1), 181–183.
- Staples, A. J., Sutherland, G., Haan, E. A., & Clisby, S. (1991). Epidemiology of Down syndrome in South Australia, 1960–1989. *American Journal of Human Genetics*, 49(5), 1014–1024.
- Stein, Z. A., Susser, M. W., & Saenger, G. (1976). Mental retardation in a national population of young men in The Netherlands: 2. Prevalence of mild mental retardation. *American Journal of Epidemiology*, 104(2), 159–169.
- Stein, Z. A., Susser, M. W., Saenger, G., & Marolla, F. (1976). Mental retardation in a national population of young men in The Netherlands: 1. Prevalence of severe mental retardation. *American Journal of Epidemiology*, 103(5), 477–489.
- Stevenson, R. (1996). Mental retardation: Overview and historical perspective. *Proceedings of the Greenwood Genetic Center*, 15, 9–18.
- Stewart, G. D., Hassold, T. J., Berg, A., Watkins, P., Tanzi, R., & Kurnit, D. M. (1988). Trisomy 21 (Down syndrome): Studying nondisjunction and meiotic recombination by using cytogenetic and molecular polymorphisms that span chromosome 21. *American Journal of Human Genetics*, 42(2), 227–236.
- Sutcliffe, J. S., Nakao, M., Christian, S., Orstavik, K. H., Tommerup, N., Ledbetter, D. H., et al. (1994). Deletions of a differentially methylated CpG island at the SNRPN gene define a putative imprinting control region. *Nature Genetics*, 8(1), 52–58.
- Sullivan, J. B., & Krieger, G. R. (2001). *Clinical environmental health exposures* (2nd ed.). Philadelphia: Lippincott Williams & Wilkins.
- Sutcliffe, J. S., Nelson, D. L., Zhang, F., Pieretti, M., Caskey, C. T., Saxe, D., et al. (1992). DNA methylation represses FMR-1 transcription in fragile X syndrome. *Human Molecular Genetics*, 1(6), 397–400.
- Sutherland, G. R. (1977). Fragile sites on human chromosomes. Demonstration of their dependence on the type of tissue culture medium. *Science*, 197(4300), 265–266.
- Teplin, S. W., Burchinal, M., Johnson-Martin, N., Humphry, R. A., & Kraybill, E. N. (1991). Neurodevelopmental, health, and growth status at age 6 years of children with birth weights less than 1001 grams. *Journal of Pediatrics*, 118(5), 768–777.
- Thurman, D., Alverson, C., Dunn, K., Guerrero, J., & Sniezek, J. (1999). Traumatic brain injury in the United States: A public health perspective. *Journal of Head Trauma and Rehabilitation*, 14(6), 602–615.
- Thurman, D., & Guerrero, J. (1999). Trends in hospitalization associated with traumatic brain injury. *JAMA*, 282(10), 954–957.
- Tomlin, P., Clarke, M., Robinson, G., & Roach, J. (2002). Rehabilitation in severe head injury in children: Outcome and provision of care. *Developmental Medicine and Child Neurology*, 44(12), 828–837.
- Tong, S. (1998). Lead exposure and cognitive development: Persistence and a dynamic pattern. *Journal of Paediatrics and Child Health*, 34(2), 114–118.

- Turner, G., Webb, T., Wake, S., & Robinson, H. (1996). Prevalence of fragile X syndrome. *American Journal of Medical Genetics*, 64(1), 196–197.
- U.S. Department of Health and Human Services. (2000). *Healthy People 2010: Understanding and improving health and objectives for improving health* (2nd ed., 2 Vols). Washington, DC: U.S. Government Printing Office.
- van den Ouweland, A. M., de Vries, B. B., Bakker, P. L., Deelen, W. H., de Graaff, E., van Hemel, J. O., et al. (1994). DNA diagnosis of the fragile X syndrome in a series of 236 mentally retarded subjects and evidence for a reversal of mutation in the *FMR-1* gene. *American Journal of Medical Genetics*, 51(4), 482–485.
- van Karnebeek, C. D., Koevoets, C., Sluijter, S., Bijlsma, E. K., Smeets, D. F., Redeker, E. J., et al. (2002). Prospective screening for subtelomeric rearrangements in children with mental retardation of unknown aetiology: The Amsterdam experience. *Journal of Medical Genetics*, 39(8), 546–553.
- Verheij, C., Bakker, C. E., de Graaff, E., Keulemans, J., Willemsen, R., Verkerk, A. J., et al. (1993). Characterization and localization of the *FMR-1* gene product associated with fragile X syndrome. *Nature*, 363(6431), 722–724.
- Verkerk, A. J., Pieretti, M., Sutcliffe, J. S., Fu, Y. H., Kuhl, D. P., Pizzuti, A., et al. (1991). Identification of a gene (*FMR-1*) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in Fragile X syndrome. *Cell*, 65(5), 905–914.
- Vernon, M. (1979). Variability in reading retardation. *British Journal of Psychology*, 70(1), 7–16.
- Vincent, A., Heitz, D., Petit, C., Krietz, C., Oberle, I., & Mandel, J. L. (1991). Abnormal pattern detected in fragile X patients by pulsed field gel electrophoreses. *Nature*, 349(6310), 624–626.
- Visser, F. E., Aldenkamp, A. P., van Huffelen, A. C., Kuilman, M., Overweg, J., & van Wijk, J. (1997). Prospective study of the prevalence of Alzheimer-type dementia in institutionalized individuals with Down syndrome. *American Journal of Mental Retardation*, 101(4), 400–412.
- Wagstaff, J., Knoll, J. H., Glatt, K. H., Shugart, Y. Y., Somer, A., & Lalande, M. (1992). Maternal but not paternal transmission of 15q11-q13 linked nondeletion Angelman syndrome leads to phenotypic expression. *Nature Genetics*, 1(4), 291–294.
- Waisbren, S. E., Chang, P., Levy, H. L., Shifrin, H., Allred, E., Azen, C., et al. (1998). Neonatal neurological assessment of offspring in maternal phenylketonuria. *Journal of Inherited Metabolic Diseases*, 21(1), 39–48.
- Waisbren, S. E., Doherty, L. B., Bailey, I. V., Rohr, F. J., & Levy, H. L. (1988). The New England Maternal PKU Project: Identification of at-risk women. *American Journal of Public Health*, 78(7), 789–792.
- Walkowiak, J., Wiener, J. A., Fastabend, A., Heinzow, B., Kramer, U., Schmidt, E., et al. (2001). Environmental exposure to polychlorinated biphenyls and quality of the home environment: Effects on psychodevelopment in early childhood. *Lancet*, 358(9293), 1602–1607.
- Warburton, D. (1984). Outcome of case of de novo structural rearrangements diagnosed at amniocentesis. *Prenatal Diagnosis*, 4, 69–80.
- Warburton, D. (1987). De novo structural rearrangements at amniocentesis: Outcome and nonrandom position of breakpoints. *American Journal of Human Genetics*, 41(Suppl.), A145.
- Warburton, D. (1991). De novo balanced rearrangements and extra marker chromosomes identified at prenatal diagnosis: Clinical significance and distribution of breakpoints. *American Journal of Human Genetics*, 49(5), 995–1013.
- Wasserman, G. A., Graziano, J. H., Factor-Litvak, P., Popovac, D., Morina, N., Musabegovic, A., et al. (1994). Consequences of lead exposure and iron supplementation on childhood development at age 4 years. *Neurotoxicology and Teratology*, 16(3), 233–240.
- Wasserman, G. A., Liu, X., Lolocono, N. J., Factor-Litvak, P., Kline, J. K., Popovac, D., et al. (1997). Lead exposure and intelligence in 7-year-old children: The Yugoslavia prospective study. *Environmental Health Perspectives*, 105(9), 956–962.
- Wasserstrum, N., & Anania, C. A. (1995). Perinatal consequences of maternal hypothyroidism in early pregnancy and inadequate replacement. *Clinical Endocrinology*, 42(4), 353–358.

- Webb, T., Whittington, J., Clarke, D., Boer, H., Butler, J., & Holland, A. (2002). A study of the influence of different genotypes on the physical and behavioral phenotypes of children and adults ascertained clinically as having PWS. *Clinical Genetics*, 62(4), 273–281.
- Wenger, J. D., Hightower, A. W., Facklam, R. R., Gaventa, S., Broome, C. V., & the Bacterial Meningitis Study Group (1990). Bacterial meningitis in the United States, 1986: Report of a multistate surveillance study. *Journal of Infectious Diseases*, 162(6), 1316–1323.
- Wevrick, R., Kerns, J. A., & Francke, U. (1994). Identification of a novel paternally expressed gene in the Prader–Willi syndrome region. *Nature Genetics*, 3(10), 1877–1882.
- Whitaker, A. H., Feldman, J. F., VanRossem, R., Schonfeld, I. S., Pinto-Martin, J. A., Torre, C., et al. (1996). Neonatal cranial ultrasound abnormalities in low birth weight infants: Relation to cognitive outcomes at six years of age. *Pediatrics*, 98(4 Pt. 1), 719–729.
- Wild, J., Read, A. P., Sheppard, S., Seller, M. J., Smithells, R. W., Nevin, N. C., et al. (1986). Recurrent neural tube defects, risk factors and vitamins. *Archives of Disease in Childhood*, 61(5), 440–444.
- Williams, J. C., Barratt-Boyes, B. G., & Lowe, J. B. (1961). Supravalvular aortic stenosis. *Circulation*, 24, 1311–1318.
- Winneke, G., Walkowiak, J., & Lilienthal, H. (2002). PCB-induced neurodevelopmental toxicity in human infants and its potential mediation by endocrine dysfunction. *Toxicology*, 181–182, 161–165.
- Wisniewski, H. M., Wegiel, J., & Popovitch, E. (1994). Age-associated development of diffuse and thioflavin-S-positive plaques in Down syndrome. *Developmental Brain Dysfunction*, 7, 330–339.
- Wisniewski, K. E., Wisniewski, H. M., & Wen, G. Y. (1985). Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Annals of Neurology*, 17(3), 278–282.
- Wohrle, D., Kotzot, D., Hirst, M. C., Manca, A., Korn, B., Schmidt, A., et al. (1992). A microdeletion of less than 250 kb, including the proximal part of the *FMR-1* gene and the fragile site, in a male with the clinical phenotype of fragile X syndrome. *American Journal of Human Genetics*, 51(2), 299–306.
- World Health Organization. (1980a). *International classification of impairments, disabilities and handicaps*. Geneva, Switzerland: Author.
- World Health Organization. (1980b). *International statistical classification of diseases* (9th ed.). Geneva, Switzerland: Author.
- World Health Organization. (1992). *International statistical classification of diseases* (10th ed.). Geneva, Switzerland: Author.
- World Health Organization. (2001). *International classification of functioning, disability and health (ICF)*. Geneva, Switzerland: Author.
- Yeargin-Allsopp, M., & Boyle, C. (2002). Overview: The epidemiology of neurodevelopmental disorders. *Mental Retardation and Developmental Disabilities Research Reviews*, 8(3), 113–116.
- Yeargin-Allsopp, M., Murphy, C. C., Cordero, J. F., Decoufle, P., & Hollowell, J. G. (1997). Reported biomedical causes and associated medical conditions for mental retardation among 10-year-old children, metropolitan Atlanta, 1985 to 1987. *Developmental Medicine and Child Neurology*, 39(3), 142–149.
- Yu, S., Pritchard, M., Kremer, E., Lynch, M., Nancarrow, J., Baker, E., et al. (1991). Fragile X genotype characterized by an unstable region of DNA. *Science*, 252(5010), 1179–1181.
- Zigler, E. (1967). Mental retardation. *Science*, 157(788), 578–579.
- Zigler, E., & Butterfield, E. C. (1966). Rigidity in the retarded: A further test of the Lewin–Kounin formulation. *Journal of Abnormal Psychology*, 71(3), 224–231.
- Zigman, W. B., Schupf, N., Sersen, E., & Silverman, W. (1996). Prevalence of dementia in adults with and without Down syndrome. *American Journal on Mental Retardation*, 100(4), 403–412.