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Similarities in Genetic Mental Retardation and Neuroteratogenic Syndromes

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ADAMS, J. *Similarities in genetic mental retardation and neuroteratogenic syndromes.* PHARMACOL BIOCHEM BEHAV **55**(4) 683–690, 1996.—Principles and mechanisms of neurobehavioral teratogenesis are used to show commonalities between manifestations of abnormal development consequent to genetic abnormality or teratogenic exposure. A comparison and contrast of both the neuropathological and neuropsychological characteristics of children with early embryonic exposure to isotretinoin (Accutane) or with selected mental retardation syndromes is presented. Putative mechanisms of retinoid teratogenesis through the disruption of normal retinoid-triggered embryogenesis and the alteration of homeobox gene expression are discussed. Interference with homeobox gene expression as an avenue to the perturbation of early developmental processes and the production of hindbrain and craniofacial abnormalities is then proposed as a common basis for the translation and expression of several genetic mental retardation syndromes. Finally, dose-response effects and other modulators of vulnerability to abnormal development are used to provide a conceptual framework for the understanding of variability in the expression of genetically caused abnormalities. **Copyright © 1996 Elsevier Science Inc.**

Isotretinoin Retinoid teratogenesis Williams Syndrome Hindbrain abnormalities Mental retardation Neurobehavioral teratology Fragile X syndrome

HISTORICALLY, neurobehavioral teratology has been better understood in terms of applied significance and general principles governing vulnerability, than with regard to basic developmental mechanisms that may be relevant to all forms of neurodevelopmental disorders. In the last decade, however, information has accumulated which alters this state of affairs and suggests similarities in the etiology and expression of several genetic and teratogen-induced neurodevelopmental disorders. Potential similarities in etiology are suggested by the molecular mechanisms of action of certain teratogens that alter the regulation of embryonic developmental processes, the role of homeobox genes in the control of embryonic development, and the more thorough elaboration of the neuroanatomical and neuropsychological characteristics of children with genetic and teratogenic syndromes. This is an exciting time in which multidisciplinary collaborations may provide: (a) knowledge about mechanisms active in producing developmental stage- and dose-specific neural and behavioral pathology; (b) knowledge linking the teratogenic mechanisms underlying malformation and mental retardation with those controlling neurobehavioral dysfunction in lesser affected individuals who experienced the same exposure; and (c) information that may bridge the gap in understanding the mechanisms which produce genetic as well as teratogenic effects upon brain structure and function. This latter possibility suggests that research directed at the etiology of teratogenic and genetic disorders, and the commonalities in the expression of these disorders may be mutually informative. Such research may provide a fuller understanding of the relationships between developmental events, resultant neuroanatomy and neurochemistry, and consequent manifestations upon specific neuropsychological processes on which cognitive functioning depends.

Rodier (62) first suggested commonalities between teratogenic and other neurodevelopmental disorders with respect to the disorder of autism, a disorder of unknown etiology. The DSM-IV (6) defines autistic disorder on the basis of behavioral symptomatology which onsets prior to the age of 3. Symptoms include markedly abnormal development of social interaction and communication, delayed language development, a restricted repertoire of activity and interests, and the presence of certain stereotypical or highly unusual motor behaviors. Seventy-five percent of individuals with autism have moderate mental retardation (IQs of 35-50) and the disorder is 4-5 times more common in males than in females (6).

The critical underlying neuropathology responsible for autistic disorder has not been elucidated (6), however, numerous studies report certain features (62,64). Autopsy data show increased brain weight on the order of 100g, limbic system abnormalities with elevated neuron packing density, and cere-

bellar abnormalities marked by reduced Purkinje and granule cells, reduced deep nuclei, and reduced neuronal size in the inferior olive (8,9,32). Imaging studies have reported that the midbrain, pons, and medulla are smaller, the neocerebellar vermis (lobules VI and VII) is abnormal, and gyral abnormalities have been described in the cerebral cortex (13,14,28, 33,57,61). However, Rodier (62,63) points out that no consistent pattern has been shown across subjects, thus questioning which abnormalities are both necessary and sufficient for the behavioral symptomatology.

Awareness of thalidomide-induced cases of autism (67) led Rodier to undertake an evaluation of the specific features of these children in order to shed light on the relevant neuropathology of autism. She has presented a compelling argument that these thalidomide-induced autistic cases show neuropathological similarities to other cases of autism. Following thalidomide exposure between gestation days 20-24, an unusually high incidence (5/15) of autism with accompanying mental retardation occurs (67). Based on the pattern of brain and cranial motor nerve abnormalities present in these cases, Rodier (62,63,64) has argued that thalidomide-induced autism results from interference with pattern formation of the rhombomeres from which the brainstem nuclei arise and/or from interference with neuron production of cranial nerve motor nuclei. These abnormalities reflect injury to basal plate derivatives of the neural tube. The abnormalities of hindbrain structures which have been reported in autistic individuals are argued as consistent with a severe developmental injury to these same structures. Thus, Rodier argues that early insult to the basal plate can cause the development of the brain to deviate in a way that leads to autism. She suggests that specific disruptions in the early embryogenesis of the hindbrain and cranial motor nerve nuclei may account for the disorder of autism. Further, Rodier argues that the presence of a Hoxa-1 transgenic knockout mouse with similar neuropathology suggests that the failure of formation of the 5th rhombomere may be particularly relevant. Rodier (62,63,64) has now developed a valproic acid-induced animal model of autism in which early embryonic exposure produces a consistent neuropathological profile.

Rodier's arguments regarding the embryologic disturbance that may produce autism are well-elaborated, empirically documented, and quite compelling. It is unclear, however, whether the teratogen-induced autistic symptomatology includes the cognitive features that are shown in non-retarded autistics, or whether it is restricted to the behavioral symptomatology seen in mentally retarded individuals with autism. Regardless, this work offers a model for exploring the etiology of autism from a new perspective and provides an animal model for the study of a disorder previously thought to defy animal modeling.

Inherent or implicit in Rodier's hypothesis for autism are 3 major points: 1) understanding the embryonic origin of the neuroanatomical abnormalities present in a disorder helps to clarify the timing of its etiology, 2) teratologic events and abnormal genetic events may be expressed through disruptions of similar mechanisms of abnormal development, and 3) the disruptions may result from interference with regulatory processes controlled by specific genes and their regulatory proteins.

This paper adheres to the reasoning put forth by Rodier, but broadens its relevance (and reduces its precision) to incorporate genetic mental retardation and teratogen-induced malformation syndromes into a common mechanistic etiological framework. Despite teratogenic or genetic causation, it is argued that embryonic development may proceed abnormally in certain syndromes due to the disruption of common mechanisms critical to normal development. Thus, shared underlying mechanisms are argued to potentially translate genetic or teratogenic "insult" into similar physical *and* neuropsychological sequelae. While it is important to acknowledge that there are multiple mechanistic avenues that likely converge in final common characteristics, this paper will focus upon a single multifaceted path that may be useful to explore as central to, or playing a part in, the induction of particular outcomes. The neuropsychological similarities in children exposed to isotretinoin during early embryogenesis and in children with Fragile X Syndrome and Williams Syndrome will be discussed as well as their physical similarities and differences. Like the continuum over which teratogenesis is expressed, a great deal of variation exists in the characteristics of children with documented genetic mental retardation syndromes. Indeed, it is now recognized that a subset of individuals with Fragile X or Williams Syndrome are not mentally retarded and have reduced dysmorphology. This paper will focus upon the neuroanatomical features that have been identified in the more severely affected children in each group (isotretinoin exposed, Fragile X, and Williams Syndrome), whereas neuropsychological characteristics will be described for the less severely affected, nonretarded children.

Isotretinoin teratogenicity will first be discussed followed by a review of its putative mechanisms and their potential generality. The characteristics of Fragile X and Williams Syndrome children will then be presented. Finally, the variability in the expression of the genetic disorders will also be addressed as consistent with principles governing vulnerability to neurobehavioral teratogenesis.

I. CHARACTERISTICS OF CHILDREN EXPOSED TO ISOTRETINOIN DURING EARLY EMBRYOGENESIS

Isotretinoin (tradename Accutane, Hoffman-LaRoche, Inc.) has been available by prescription since 1982 in the United States for the treatment of severe recalcitrant cystic acne and other dermatologic problems. Lammer and colleagues (42) documented the human teratogenicity of isotretinoin based on the outcome of 36 prospectively ascertained pregnancies with exposures during the first 60 days of gestation. Risks associated with human exposure during embryogenesis include a 40% risk for spontaneous abortion, 4-5% perinatal mortality, 16% premature birth, and 25% major malformations (42, 43). The characteristic pattern of malformations involves craniofacial, cardiac, thymic, and central nervous system (CNS) structures. Major malformations of the CNS include cerebellar hypoplasia, agenesis of the vermis, enlargement of the 4th ventricle, malformation-induced hydrocephalus, cortical abnormalities, and microcephaly in some cases. It is important to note that these CNS abnormalities have not been systematically evaluated but instead emerge from clinically-indicated evaluations. Autopsies of the brains of affected fetuses or infants have revealed abnormalities in the cerebellum, pons, medulla, thalamus, hippocampus, heterotopias in frontal cortex, and white matter gliosis (41).

The craniofacial abnormalities induced by isotretinoin exposure include external ear abnormalities (anotia or microtia), abnormal ear canals, mild facial assymmetry, facial nerve paresis, and mild mandibular hypoplasia (42). The craniofacial, cardiac, and thymic abnormalities have been explained as consistent with disruption of normal cranial neural crest cell migration prior to and around the time of neural tube closure (42). The CNS abnormalities are consistent with disturbances

in derivatives of neuroectodermal origin during early embryogenesis of the rhombencephalon. Both the CNS and the neural crest cell-derived malformations place the time of insult as within the first 30 days of gestation. Such disturbances likely result from the action of retinoic acid on responsive elements on certain homeobox genes. This etiology and mechanisms are discussed more thoroughly later in this paper.

A subset of the prospectively ascertained children (44 exposed, 40 controls) from Lammer's sample are being followed longitudinally to examine neuropsychological characteristics (2–4). At 5 years of age, 13.6% (6/44) of the exposed children were found to be functioning in the mentally retarded range of general intelligence (< 70 on the Stanford-Binet IV) as compared to only 2.5% of the controls (1/40). Major malformations are present in all of the isotretinoin-exposed mentally retarded children. An additional 29.5% (16/44) of the exposed children performed in the borderline intelligence category as compared with 7.5% (3/40) of controls. Among the exposed children with borderline intelligence were children who did as well as did not have major abnormalities. Clearly a continuum of effect upon physical structure and mental ability was present and significant intellectual impairments were seen in children with and without major malformations. This is consistent with the results from neurobehavioral teratology studies in rodents exposed to retinoids (1).

Delineation of neuropsychological strengths and weaknesses is necessary to suggest brain systems that may be most vulnerable to exposure. Neuropsychological profiles are difficult to evaluate in mentally retarded populations due to floor effects. Thus, neuropsychological characteristics were evaluated by the examination of subtest scores in the 5 year old children whose fullscale IQ scores were between 71 and 95. A predominant pattern (61.5% of the exposed children in this mental ability range vs 14.3% of controls) of strengths and weaknesses was present (3). Language-based strengths existed alongside weaknesses in visual-motor integration and visual-spatial ability, and in the planning and organization of behavior (3). When this learning disability profile is used to identify affected children in the normal range of intelligence, an additional 16% of exposed cases demonstrate the significant learning disability profile whereas only 7% of the control children met the defining criteria.

Of interest is the determination of whether this neuropsychological profile is somehow unique to effects induced by isotretinoin exposure or whether it is seen in other developmentally disordered groups. At the grossest level, one may characterize this profile as verbal strength and nonverbal weakness during the preschool period. Longitudinal followup of these children at 10–11 years of age is ongoing. In an early quest to identify an appropriate contrast group from which to examine the specificity of the neuropsychological profile of isotretinoin-exposed 5 year old children, I was quickly humbled by the overrepresentation of the verbal strength-nonverbal weakness profile in children with several different developmental disorders of genetic origin. Nonretarded individuals with Fragile X Syndrome (19,24,48,50), Turners Syndrome (66), and mentally retarded or learning disabled individuals with Williams Syndrome (10,49) display a similar profile when grossly defined as disparity between scores on verbal (relative strength) vs performance (relative weakness) subtests at young ages. While there are undoubtedly many differences in the specific nature of the deficits, similarity at a categorical level is striking. This is particularly noteworthy since "nonverbal learning disabilities" are estimated to be present in less than 10% of the general learning disabled population: a population for whom causes are mostly unknown and defining physical features are not present (56). This sharp contrast may be accounted for by the period-specific nature of the developmental disruptions that, through phenotypic expression, define these mental retardation syndromes. A prototypical co-occurence of craniofacial defects, hindbrain abnormality, and major organ malformations in the severely affected individuals with these mental retardation syndromes is consistent with disruption of embryonic events occurring within the first 30 days of human pregnancy. Likewise, isotretinoin embryopathy and dysfunction are consistent with this early disruption of embryonic events. Can one then assume that specific, clinically relevant cognitive profiles might be associated with period-specific disruptions? This is an open question due to the lack of availability of information on different profiles (language-based learning disorder, attention deficit disorder, socioemotional disorders). Nevertheless, animal studies have demonstrated the tenability of this hypothesis with respect to behavioral indices (71,72,54).

The possibility that the neuropsychological characteristics of children exposed to isotretinoin during embryogenesis may have features in common with genetic disorders involving abnormalities in hindbrain and craniofacial structures will be explored following a discussion of the mechanisms through which retinoids act as teratogens. The former discussion will focus upon Fragile X Syndrome and Williams Syndrome.

II. MECHANISMS THROUGH WHICH ISOTRETINOIN IS BELIEVED TO INDUCE ABNORMAL DEVELOPMENT

Retinoic acids are known to play an important role in the morphogenesis of the embryo, especially for limb and nervous system development (47). All of the retinoid compounds (this precludes beta carotene) are teratogenic at some level (35 36,38). In humans, the conversion of 13-cis-retinoic acid to the trans isomer and trans metabolites is believed to play a major role in the teratogenicity of isotretinoin (15,16,34,37). Just as the putative agents of retinoid teratogenesis have been proposed, inroads have also been made toward an understanding of the actual mechanisms of teratogenesis. Binding substrates exist in the embryo in order to support the role of endogenous retinoids in morphogenesis (74). Retinol and retinoic acid have been shown to serve as endogenous ligands for cellular retinol-binding protein (CRBP) and cellular retinoic acid-binding protein (CRABP). The exact functions of these cytosolic binding proteins are unknown, but they have been proposed to serve as substrates to bind, store, and/or perhaps transport retinoids to the nucleus (74,75). Once in the nucleus, retinoic acid interacts with nuclear receptors for retinoic acid (retinoic acid receptors, RARs) and following this interaction, proteins are expressed which modify rates of gene transcription by binding to specific sequences on the cell's DNA (74,20). Such receptor interactions are known to play a regulatory role on DNA function in nervous system and craniofacial development for both the mouse and the rat embryo (17, 47,51). The normal role of retinoids during embryogenesis is believed to be disturbed by the high levels which follow exogenous administration, and abnormal development of relevant structures results (58,73).

Retinoid teratogenesis primarily reflects disruption of hindbrain and cranial neural crest structures. Structures of the face, cranial motor nerves, parts of the heart and thymus gland share common embryonic primordia in their origination from cranial neural crest cells. Hindbrain structures are derived from rhombomeres specified by neuroectodermal tissue at the

time of neural tube closure (39,55). Rhombomeres and cranial neural crest cells appear to be organized in a pairwise fashion such that an orderly relationship exists in the migration of the neuroectodermal cells which form certain rhombomeres as well as in the migration of cranial neural crest cells emergent from these neuroectodermal cells (40,45,46,53).

The formation of rhombomeres and associated neural crest cells also appears to be controlled by a common family of regulatory genes (18,29,39,44,55,68). Sets of embryologically significant genes appear to provide assembly rules which orchestrate the development of the various structures. These regulatory genes are expressed in precise spatial patterns during early embryogenesis and determine segmental anatomical patterns and precise positioning of structures. Such genes, known as homeobox-containing regulatory genes or HOX genes, are expressed in overlapping domains along the anterior-posterior axis of the embryo (20,53,68). The development of each segment of the hindbrain and related crest cell derived structures depends upon the expression of a unique combination of HOX genes.

Various regulatory molecules are important at different stages in the orchestration of development: the activation of HOX genes, the production of homeodomain proteins that specify the anterior-posterior body axis and the particular properties of the cells within a segment, and the expression of other substances that enhance or inhibit development. Retinoic acids play an important molecular role in achieving regional specificity of the hindbrain and related neural crest-derived structures. Exogenous retinoic acids have been shown to alter the expression of homeobox genes in both ectodermal and mesodermal tissues during early embryogenesis (20). Mouse embryos given retinoic acid show a different pattern of homeobox gene expression with alterations in the differentiation of structures along the anterior-posterior axis (7,18,21). It is believed that exogenous retinoic acid alters the normal concentration gradient and induces the anterior expression of HOX genes that would normally be expressed only more posteriorly.

When these same retinoic acid responsive HOX genes are mainipulated in transgenic or knockout mouse models, a pattern of malformation similar to that induced by retinoic acid disruption occurs. For example, Chisaka and Capecchi (11) have shown that knocking out the Hoxa-1 gene in mouse embryos causes neural tube defects, abnormal development of inner ear structures, and abnormalities in certain hindbrain ganglia that form certain cranial motor nerves. Chisaka, Musci, and Capecchi (12) have produced defects in the ear, cranial nerves, and hindbrain of mice through disruption of the homeobox gene, Hox-1.6.

Studies in other transgenic animals with certain missing or abnormal HOX genes have produced animals with syndromic abnormalities of the face, brain, heart, and thymus gland. Further, certain human malformation syndromes involving the head, brain, face and other neural crest derived structures (parts of the heart, the thymus) have been associated with abnormal chromosomal loci related to HOX and other regulatory genes (68).

Commonalities in mechanisms which may produce aberrant development following teratogenic exposure or genetic abnormality are clearly illustrated in the above discussion. Similar outcomes may be produced following abnormal activation of HOX genes by exogenous retinoids or subsequent to genetic alterations in the HOX genes themselves. Disturbances in the HOX-coded, assembly rules could occur due to abnormalities in genes that produce molecular triggers for HOX gene expression, abnormalities in the levels of regulatory molecules, or in the amounts or characteristics of substances produced by HOX gene activation. Through this mechanistic path, both teratogenic agents and genetic abnormalities may produce craniofacial, brain, and certain major organ abnormalities. Thus, a teratogen may interfere with cellular or molecular activity relevant to the intiation or implementation of HOX gene activity. Likewise, a genetic abnormality relevant to the production of regulatory chemicals or in the HOX genes themselves might disrupt normal HOX gene expression. Shared embryologic primordia and regulation through HOX gene activities begins to explain the co-occurrence of the syndrome of abnormalities so prominent among neurobehavioral teratogenic and mental retardation syndromes: craniofacial abnormalities, hindbrain abnormalities, and certain organ malformations. Likewise, it contributes to an understanding of how and why the abnormal face may indeed reflect an abnormal brain.

III. PHYSICAL AND NEUROPSYCHOLOGICAL CHARACTERISTICS OF CHILDREN WITH FRAGILE X SYNDROME AND WILLIAMS SYNDROME

To better connect the concept of shared mechanisms of embryogenesis with shared physical and neuropsychological characteristics, it is important to examine data on mental retardation syndromes in greater detail. Since space delimits scope, Fragile X Syndrome and Williams Syndrome will be the focus of this discussion. This brief review captures only certain highpoints relevant to etiology, characteristics, and variability in expression of these disorders.

A. Fragile X Syndrome

Fragile X Syndrome is the most common cause of inherited mental retardation, but is expressed across a spectrum of severity ranging from profound mental retardation (most often in boys) to learning disabilities (most often in girls) (23,24). As reviewed by Hagerman (24), estimates of the prevalence of this disorder range from 1 in 2200 school-aged children to 1 in 4000. The variability in expression of Fragile X Syndrome has been studied subsequent to the identification of the fragile X mental retardation I gene, FMR1 (69). Cytogenetic testing of families in which some members have the disorder has revealed that the number of repeats of the Cytosine-Guanine-Guanine trinucleotide within the 5′ untranslated region of the FMR1 is related to the expression of the disorder (22,27). Unaffected carriers of Fragile X Syndrome have 53-200 repeats of this sequence whereas affected individuals have greater than 230 repeats. The current belief is that methylation associated with the full abnormality prevents the production of the FMR1 protein which is critical to normal brain development. Males are more severely affected by this mutation and are usually moderately to severely mentally retarded (IQs less than 50). The characteristics of females (who have 2 X chromosomes) appear to be determined by the percentage of cells that have the normal vs the abnormal X chromosome as the activated one (25). Thus, a gene-dosing model has been discussed whereby the activation ratio is negatively correlated with intellectual dysfunction and degree of neuroanatomic abnormalities (48,59).

Males with the full mutation display a characteristic phenotype (23). Male features include a long face, large prominent ears, increased head circumference, high arched palate, and macroorchidism. Strabismus, seizures, and mitral valve prolapse exist as medical complications. Several of these charac-

teristics are not evident until adolescence or adulthood. Marked mental retardation, hypersensitivity to environmental stimuli, short attention span, impulsivity, hyperactivity, and mood instability have all been described. "Autistic-like" behaviors such as poor eye contact, hand flailing, perseveration, and tactile defensiveness are often displayed, but only 15% of Fragile X males meet the criteria for the diagnosis of autism (26). In samples of autistic males, 6% have been shown to have Fragile X Syndrome, all being mentally retarded (26).

Among girls with the full mutation (but varying activation ratios), similar but milder facial features than that in boys have been described. Among these females, 53% are mentally retarded and and the rest are cognitively affected to varying degrees from borderline to above average general mental ability with a specific pattern of learning deficits (65).

Since, in general, girls are less affected than boys, the neuropsychological characteristics of non-retarded girls have been studied (48). A cognitive profile marked by verbal strengths and visual-spatial, mathematical, and attentional (including hyperactivity) weaknesses has been documented. Additionally, girls show higher levels of shyness, mood disorders and anxiety, and poorer social skills than age-matched controls.

Among males and females with Fragile X Syndrome, decreased volume of the posterior cerebellum (particularly vermal lobules VI and VII) and increased size of specific brain regions has been reported (48,60). Specific areas of enlargement include the caudate nucleus, the hippocampus, the 4th and lateral ventricles. Mazzocco and Reiss (48) report that across males and females, and thus varying degrees of phenotypic expression, incremental degrees of neuroanatomical abnormality and psychological dysfunction are shown. Again, this supports the gene-dosing model and the authors argue that a gene-brain-behavior model of Fragile X Syndrome can be based on estimates of the degree of FMR1 protein that is expressed.

Based on the above information, it appears that individuals with Fragile X Syndrome share some similarity with the characteristics of children affected by isotretinoin exposure during embryogenesis. General similarities in the pattern of cognitive strengths and weaknesses are evident as well as some shared neuropathology of the cerebellum, particularly the vermis, and of the 4th ventricle. Craniofacial characteristics are dissimilar but may reflect developmental disruptions consistent with origin during early embryogenesis.

B. Williams Syndrome

Williams Syndrome has been studied in some detail both with respect to its defining physical characteristics and the cognitive characteristics of the children. Like isotretinoin teratogenesis and the Fragile X Syndrome, Williams Syndrome is manifest over a continuum of severity ranging from life-threatening malformations and severe mental retardation to a milder retardation or learning disability (10). In the case of the "mildly" affected, a characteristic neuropsychological profile has been substantiated. First, the etiology of the disorder and physical characteristics of the children will be presented. Then, neuropsychological characteristics will be discussed.

Williams Syndrome occurs at an estimated rate of 1 in every 25,000 livebirths (10,49). This rare disorder usually occurs sporadically but may also be manifest as an inherited autosomal dominant disorder. The underlying genetic etiology appears to involve chromosome 7q11.23 and contains the elastin gene locus (Mervis et al, in press). A critical region of deletion in this area that is associated with the expression of complete Williams Syndrome features has not yet been identified.

Williams Syndrome is normally diagnosed on the basis of a constellation of facial features and mental retardation. This discussion is taken from an excellent review by Mervis et al (49). Craniofacial features include periorbital fullness, bitemporal narrowing, low nasal bridge, long philtrum, full cheeks, small jaw, strabismus, wide mouth, full lips, malocclusion, prominent ear lobes, long neck, and broad brow. It is unclear what minimal features must be present to define the syndrome, but craniofacial features are reported to be present in 100% of individuals with Williams Syndrome. Mental retardation or significant learning disabilities and hoarse voice are present in 98% of cases. Congenital cardiac abnormalities are present in 74% of cases, with supravalvular stenosis being most frequent. Inguinal hernia is present in 46%, and hypercalcemia in 15%. This variability in expression also characterizes the cognitive features where children range from profoundly to mildly retarded or learning disabled.

The characteristic neuropsychological profile of verbal strength and non-verbal weakness has been carefully evaluated (10, 49). Language abilities and auditory short term memory are relative strengths, while visuoconstructive spatial abilities are a marked weakness. This is similar in terms of score profiles to that of children exposed to isotretinoin during early embryogenesis, and overlaps with certain characteristics of Fragile X Syndrome as well. Further work will be necessary to determine if the reasons for reduced performance are qualitatively similar. Also superficially similar to isotretinoin embryopathy and Fragile X Syndrome is the presence of craniofacial abnormalities (though they differ).

Studies of neuropathology have been more limited, but some overlap occurs between the structures affected in Williams Syndrome, isotretinoin exposure, and Fragile X Syndrome. Children with Williams Syndrome have been reported to have a 20% reduction in cerebral volume (consistent with microcephaly) relative to controls but no volumetric differences in cerebellar size have been reported (31). However, vermal areas VI and VII (neocerebellar areas) were significantly larger than that of controls (31). Thus, cerebellar vermal abnormalities and alterations in cerebral volume are present, but they are in the direction opposite to what has been discussed for isotretinoin teratogenesis or Fragile X Syndrome. In the isotretinoin sample, however, the vermis has not been examined systematically in all children, instead indications of cerebellar hypoplasia and frank absence have emerged from medically indicated, clinically rated examinations in infants with multiple major malformations.

Questions are raised by the presence of neuroanatomical similarities and differences in the context of somewhat similar neuropsychological profiles across the three groups discussed. First, is disturbance in the normal development of the vermis (in either direction) sufficient to produce mental retardation? If so, is the vermal abnormality associated only with decreased general mental ability but unrelated to specific neuropsychological characteristics? A tentative affirmative answer to the first question may be parsimonious. Vermal hypoplasia and other cerebellar abnormalities have also been reported for other mental retardation syndromes: Down Syndrome (52), Joubert Syndrome (30), and autism (14). With the exception of autism, language based strengths and visuospatial weaknesses describe the neuropsychological profile of higher functioning children with these disorders. Craniofacial anomalies are also used as defining features in all of the syndromes except autism. Thus, abnormalities in the cerebellar vermis appear to be

somewhat common in mentally retarded populations, though specific anatomy varies across disorders. While most of the disorders share the verbal strength-visuospatial weakness profile that has been described, individuals with autism have relative strength in visuospatial processing. Similar across all disorders, however, are effects upon executive control functions such as attention, organization, and planning abilities. Akshoomoff and Courchesne (5) have argued for a role of the cerebellum in attention based on difficulties with attentional shifting in autistics and in individuals with cerebellar disorders. Thus, the second question about the central role of the vermis in specific neuropsychological features has some support, but cannot account for the differing strength/weakness profile with respect to visuospatial processing. The global approach to the definition of this profile may mask greater similarities in the integrity or dysfunction of underlying cognitive operations relevant to the different areas evaluated; alternatively, it may overestimate the similarities. It should be remembered that approximately 15% of males with Fragile X Syndrome have autistic disorder and others have autistic features but do not meet diagnostic criteria. Thus, additional similarities in behavioral phenotype are not represented by the narrow window of description captured by a strength/weakness profile description.

IV. WITHIN-GROUP VARIATION IN OUTCOME MAY BE PARTLY EXPLAINABLE THROUGH PRINCIPLES OF NEUROBEHAVIORAL TERATOGENESIS

While specific causes vary, the mechanisms through which genetic variations/abnormalities translate into manifestations of developmental aberrations are argued to be similar to those provoked by certain environmental insults. Common ground may be the disruption of HOX gene activities as previously discussed. If one thinks of genetic abnormalities as translating into the production or disruption of regulatory chemicals of potential relevance to HOX gene expression, one must assume that alterations in the levels of these chemicals might conceptually result in expression along some type of dose-response curve. Indeed, a gene-dosing model has been proposed for Fragile X Syndrome (48, 59) but the relevance of the FMR1 protein to HOX gene activation or action has not been discussed. At any rate, the basic period-specific, dose-response principle demonstrated for neurobehavioral teratogenesis (1,70) appears to be relevant to the expression of genetic disorders as well. Dose-response effects relevant to the events of early embryogenesis may be demonstrated through variations in outcome ranging from lethality to mental retardation to learning disabilities.

Other factors known to be important modulators of vulnerability to teratogenic insult are the genotype of the mother (and the conceptus), as well as the metabolic, endocrine, dietary, and general health status of the mother during (and prior to) pregnancy (70). Collectively, these factors interact to determine the nature of the intrauterine environment and the consequent nature of response to developmental perturbations. As a result, even an identical genetic abnormality might show variation in phenotypic expression across individuals. Such variation could cover the spectrum from death to malformation to varying degrees of behavioral abnormality. Thus, one need not assume that variation in the expression of a genetic mental retardation syndrome might be fully explained by a precise understanding of differential genetic characteristics of the developing infant. These genetic characteristics still must interact with the prenatal as well as the postnatal environment. Indeed, Mazzocco and Reiss (48) report a case of monozygotic twins with the full Fragile X mutation who are phenotypically discordant with respect to cognitive and behavioral sequelae.

V. CONCLUSIONS

This perspective has emphasized mechanisms and governing principles that may be shared in the production of syndromes involving cognitive dysfunction and craniofacial abnormality, whether they result from genetic or environmental causes. An implication of these direct or conceptual commonalities is that the study of each causative category should inform the understanding of the other. Given this assumption, researchers should begin to consider the benefits of designing studies which compare the neuropsychological features of children with physical abnormalities that reflect a similar embryologic disruption regardless of its cause. The use of matched contrast groups to examine the specificity of purported disorder-specific, neuropsychological profiles also appears essential. In this approach, the cause of the disorder present in the contrast group becomes somewhat irrelevant. What matters is the nature of the common embryology suggested by somewhat common manifestations, and the relationship between structural and functional abnormality. The questions become, "when anatomic manifestations suggest a particular prenatal stage in which development was disrupted, is this disruption also reflected in a similar resultant neuropsychological profile?". Approaching this question through the use of contrast groups may lead to a more rapid understanding of the relationships between neuropathology and neuropsychological characteristics.

Basing comparisons on similarities in neuropathological manifestation regardless of the cause also allows the use of animal models of cognitive developmental disorders based on neuropathological similarities alone. This approach as advanced by Rodier's animal model of autism (62,63,64) may provide information about the etiology of disorders which have remained unexplained despite years of effort, and may lead to the development of relevant animal models of behavioral symptomatology as well.

In both human and animal studies, determining whether similar neuropathology linked to stage-specific embryonic mechanisms is associated with a similar neuropsychological profile would advance our understanding of all neurodevelopmental disorders. Likewise, it should inform the selection of both medical and educational therapeutic interventions on behalf of mentally retarded and learning disabled individuals.

REFERENCES

1. Adams, J. Structure-activity and dose-response relationships in the neural and behavioral teratogenesis of retinoids. Neurotox. Ter. 15:193–202; 1993.
2. Adams, J.; Lammer, E. J. Relationship between dysmorphology and neuropsychological function in children exposed to isotretinoin "in utero." In: Fujii, T.; Boer, G. J., eds. Functional neuroteratology of short term exposure to drugs. Tokyo: Teikyo University Press; 1991:159–170.
3. Adams, J.; Lammer, E. J. Human isotretinoin exposure: The teratogenesis of a syndrome of cognitive deficits. Neurotox. Ter. 17(3):386; 1995.
4. Adams J.; Lammer, E. J.; Holmes, L. B. A syndrome of cognitive

dysfunctions following human embryonic exposure to isotretinoin. Teratology. 43:497; 1991.
5. Akshoomoff, N. A.; Courchesne, E. A new role for the cerebellum in cognitive operations. Behav. Neurosci.. 106:731–738; 1992.
6. American Psychological Association. Diagnostic and statistical manual of mental disorders, 4th edition. Washington, DC; 1994.
7. Balling, R.; Mutter, G.; Gruss, P.; Kessel, M. Craniofacial abnormalities induced by ectopic expression of the homeobox gene *hox*-1.1 in transgenic mice. Cell. 58:337–347; 1989.
8. Bauman, M. L.; Kemper, T. L. Histoanatomic observations of the brain in early infantile autism. Neurology. 35:866–874; 1985.
9. Bauman, M. L.; Kemper, T. L. Neuroanatomic observations of the brain in autism. In: Bauman, M. L.; Kemper, T. L., eds. The neurobiology of autism. Baltimore: Johns Hopkins University Press; 1994:119–145.
10. Bellugi, U.; Wang, P. B.; Jernigan, T. L. Williams Syndrome: An unusual neuropsychological profile. In: Broman, S. H.; Grafman, J., eds. Atypical cognitive deficits in developmental disorders: Implications for brain function. Hillsdale: Lawrence Erlbaum Associates; 1994:23–56.
11. Chisaka, O.; Capecchi, M. R. Regionally restricted developmental defects resulting from targeted disruption of the homeobox gene *hox* 1.5. Nature 350:473–479; 1991.
12. Chisaka, O.; Musci, T. S.; Capecchi, M. R. Developmental defects of the ear, cranial nerves and hindbrain resulting from targeted disruption of the mouse homeobox gene *hox*-1.6. Nature 355:516–520; 1992.
13. Courchesne, E.; Townsend, J.; Akshoomoff, N. A.; Saitoh, O.; Yeung-Courchesne, R.; Lincoln, A. M. Impairment in shifting attention in autistic and cerebellar patients. Behav. Neurosci. 108:848–865; 1994.
14. Courchesne, E.; Yeung-Courchesne, R.; Press, G. A.; Hesselink, J. R.; Jernigan, T. L. Hypoplasia of cerbellar lobules VI and VII in autism. N. Engl. J. Med. 318:1349– 1354; 1988.
15. Creech Kraft, J.; Kochhar, D. M.; Scott, W. J.; Nau, H. Low teratogenicity of 13-cis retinoic acid (isotretinoin) in the mouse corresponds to low embryo concentrations during organogenesis: Comparison to the all-trans isomer. Toxicol. Appl. Pharmacol. 87:474–482; 1987.
16. Creech Kraft, J.; Lofberg, B.; Chahoud, I.; Bochert, G.; Nau, H. Teratogenicity and placental transfer of all-trans-, 13-cis, 4-Oxo-all-trans-, and 4-Oxo-13-cis-retinoic acid after administration of a low oral dose during organogenesis in mice. Toxicol. Applied Pharmacol. 100:162–176; 1989.
17. Dencker, L.; Gustafson, A.; Annerwall, E.; Busch, C.; Eriksson, U. Retinoid-binding proteins in craniofacial development. J. Craniofacial Gen. Develop. Biol. 11:303–314; 1991.
18. Durston, A. J.; Timmermans, J. P. M.; Hage, W. J., Kendriks, H. F. J.; de Vries, N. J.; Heideveid M.; Nieuwkoop, P. D. Retinoic acid causes an anteroposterior transformation in the developing central nervous system. Nature 340:140–144; 1989.
19. Freund, L. S.; Reiss, A. L. Cognitive profiles associated with the fra(x) syndrome in males and females. Am. J. Med. Genet.:542–547; 1991.
20. Gilbert, S. F. Developmental biology. Sunderland: Sinauer Associates; 1994.
21. Gustafson, A.; Dencker, L.; Eriksson, U. Non-overlapping expression of CRBP I and CRABP I during pattern formation of limbs and craniofacial structures in the early mouse embryo. Development. 117:451–460; 1993.
22. Hagerman, R. J. Molecular and clinical correlations in fragile x syndrome. Ment. Retard. Dev. Disab. Res. Rev. 1:276–280; 1995.
23. Hagerman, R. J. Physical and behavioral phenotype. In: Hagerman, R. J.; Silverman, A. C., eds. The fragile X syndrome: Diagnosis, treatment and research, 2nd edition. Baltimore: Johns Hopkins University Press; 1996:3–87.
24. Hagerman, R. J. Physical and behavioral problems and molecular/clinical correlations in fragile x syndrome. In: Tager–Flusberg, H., ed. Neurodevelopmental disorders: Contributions to a new framework from the cognitive neurosciences. Cambridge: MIT Press; (in press).
25. Hagerman, R. J.; Jackson, C.; Amiri, K.; Silverman, A. C.; O'Connor, R.; Sobesky, W. E. Fragile x girls: Physical and neurocognitive status and outcome. Pediatrics 89:395–400; 1992.
26. Hagerman, R. J.; Jackson, A. W.; Levitas, A.; Rimland, B.; Braden, M. An analysis of autism in 50 males with the fragile X syndrome. Am. J. Med. Genet. 23:359–370; 1986.
27. Hagerman, R. J.; van Housen, K.; Smith, A. C. M.; McGavran, L. Consideration of connective tissue dysfunction in the fragile x syndrome. Am. J. Med. Genet. 17:123–132; 1984.
28. Hashimoto, T.; Tayama, M.; Murakawa, K.; Yoshimoto, T.; Miyazaki, M.; Harada, M.; Kuroda, Y. Development of the brain stem and cerebellum in autistic patients. J. Aut. Dev. Disord. 25:1–18; 1995.
29. Holland, P. Homeobox genes in vertebrate evolution. BioEssays 14:267–273; 1992.
30. Holroyd, S.; Reiss, A.; Bryan, R. N. Autistic features in Joubert syndrome: A genetic disorder with agenesis of the cerebellar vermis. Biol. Psychiatry. 29:287–294; 1991.
31. Jernigan, T. L.; Bellugi, U. Anomolous brain morphology on magnetic resonance images in Williams syndrome and Down syndrome. Arch. Neurol. 47:529–533; 1990.
32. Kemper, T. L.; Bauman, M. L. Neurpathology of infant autism. In: Naruse, H; Ornitz, E. M., eds. Neurobiology of infantile autism. Amsterdam: Elsevier; 1992:43–57.
33. Kleiman, M. D.; Neff, S.; Rosman, N. P. The brain in infantile autism: Are posterior fossa structures abnormal? Neurology 42:753–760; 1992.
34. Klug, S.; Creech Kraft, J.; Wildi, E.; Merker H. J.; Persaud, T. V. N.; Nau, H.; Neubert, D. Influence of 13-cis and all-trans retinoic acid on rat embryonic development in vitro: Correlation with isomerisation and drug transfer to the embryo. Arch. Toxicol. 63:185–192; 1989.
35. Kochhar, D. M. Teratogenic activity of retinoic acid. Acta. Path. et Microbiol. Scandinav. 70:398–404; 1967.
36. Kochhar, D. M.; Penner, J. D. Developmental effects of isotretinoin and 4-oxo-isotretinoin: The role of metabolism in teratogenicity. Teratology 36:67–76; 1987.
37. Kochhar, D. M.; Penner, J. D.; Satre, M. A. Derivation of retinoic acid metabolites from a teratogenic dose retinol (vitamin A) in mice. Toxicol Applied Pharmacol. 96:429–441; 1988.
38. Kochhar, D. M.; Penner, J. D.; Tellone, C. I. Comparative teratogenic activities of two retinoids: Effects on palate and limb development. Teratogen. Carcinogen. Mutagen. 4:377– 387; 1984.
39. Kuratani, S. C.; Eichele, G. Rhombomere transplantation repatterns the segmental organization of cranial nerves and reveals cell-autonomous expression of a homeodomain protein. Development 117:105–117; 1993.
40. Kuratani, S.; Tanaka, S. Peripheral development of avian trigeminal nerves. Am. J. Anat. 187: 65–80; 1990.
41. Lammer, E. J.; Armstrong, D. L. Malformations of hindbrain structures among humans exposed to isotretinoin (13-cis- retinoic acid) during early embryogenesis. In: Morriss–Kay, G., ed. Retinoids in normal development and teratogenesis. Oxford University Press; 1992:281–295.
42. Lammer, E. J.; Chen, D. T.; Hoar, R. M.; Agnish, N. D.; Benke, P. J.; Braun, J. T.; Curry, C. J.; Ferhnoff, P. M.; Grix, A. W.; Lott, I. T.; Richard, J. M.; Sun, S. C. Retinoic acid embryopathy. N. Eng. J. Med. 313(14):837– 841; 1985.
43. Lammer, E. L.; Hayes, A. M.; Schunior, A.; Holmes, L. B. Unusually high risk for adverse outcomes of pregnancy following fetal isotretinoin exposure. Am. J. Hum. Genet. 43:A58; 1988.
44. Lonai, P.; Orr–Urtreger, A. Homeogenes in mammalian development and the evolution of the cranium and central nervous system. FASEB J. 4:1436–1443; 1990.
45. Lumsden, A. The cellular basis of segmentation in the developing hindbrain. Trends Neurosci. 13:329–339; 1990a.
46. Lumsden, A. The development and significance of hindbrain segmentation. Semin. Dev. Biol. 1:117–125; 1990b.
47. Madden, M.; Ong, D. E.; Chytil, F. Retinoid-binding protein distribution in the developing mammalian nervous system. Development 109:75–80; 1990.

48. Mazzocco, M.; Reiss, A. A behavioral neurogenetics approach to understanding the fragile x syndrome. In: Tager-Flusberg, H., ed. Neurodevelopmental disorders: Contributions to a new framework from the cognitive neurosciences. Cambridge: MIT Press: (in press).
49. Mervis, C.; Morris, C.; Bertrand, J.; Robinson, B. Williams syndrome: Findings from an integrated program approach. In: Tager-Flusberg, H., ed. Neurodevelopmental disorders: Contributions to a new framework from the cognitive neurosciences. Cambridge: MIT Press: (in press).
50. Miezejeski, C. M.; Jenkins, E. C.; Hill, A. L. Wisniewski, K.; French, J. H.; Brown, W. T. A profile of cognitive deficit in females from fragile x families. Neuropsychologia 24:405–409; 1986.
51. Morris-Kay, G. Retinoic acid and craniofacial development: Molecules and morphogenesis. Bio Essays 15:9–15; 1993.
52. Nadel, L. Down syndrome in cognitive neuroscience perspective. In: Tager-Flusberg, H., ed. Neurodevelopmental disorders: Contributions to a new framework from the cognitive neurosciences. Cambridge: MIT Press; (in press).
53. Noden, D. M. Vertebrate craniofacial development: The relation between ontogenetic process and morphological outcome. Brain Behav. Evol. 38:190–225; 1991.
54. Nolen, G. A. The effects of prenatal retinoic acid on the viability and behavior of the offspring. Neurotoxicol. Teratol. 8:643–654; 1986.
55. Papalopulu, N. Regionalization of the forebrain from neural plate to neural tube. Perspect Dev. Neurobiol. 3(1):39–52; 1995.
56. Pennington, B. F. Diagnosing learning disabilities. New York: The Guilford Press; 1991.
57. Piven, J.; Nehme, E.; Simon, J.; Barta, P.; Pearlson, G.; Folstein, S. Magnetic resonance imaging in autism: Measurement of the cerebellum, pons, and fourth ventricle. Biol. Psychiat. 31:491–504; 1992.
58. Pratt, R. M.; Goulding, E. H.; Abbott, B. D. Retinoic acid inhibits migration of cranial neural crest cells in the cultured mouse embryo. J. Craniofacial Gen. Dev. Bio. 7:205– 217; 1987.
59. Reiss, A.; Abrams, M.; Greenlaw, R.; Freund, L.; Denckla, M. Neurodevelopmental effects of the FMR-1 full mutation in humans. Nat. Med. 1:159–167; 1995.
60. Reiss, A. L.; Aylward, E.; Freund, L. S.; Joshi, P. K.; Bryan, R. N. Neuroanatomy of fragile X syndrome: The posterior fossa. Ann. Neurol. 29:26–32; 1991.
61. Ritvo, E. R.; Freeman, B. J.; Schiebel, A. B.; Duong, T.; Robinson, H.; Guthrie, D.; Ritvo, A. Lower Purkinje cell counts in the cerebella of four autistic subjects: Initial findings of the UCLA-NSAC autopsy research report. Am. J. Psychiat. 143:862–866; 1986.
62. Rodier, P. M. An animal model of autism based on developmental data. MRDD Res Rev. (in press).
63. Rodier, P. M.; Ingram, J. L.; Tisdale, B.; Croog, V. Linking etiologies in humans and animal models: Studies of autism. Reprod. Toxicol. (in press).
64. Rodier, P. M.; Ingram, J. L.; Tisdale, B.; Nelson, S.; Romano, J. An embryological origin for autism: Developmental anomalies of the cranial motor nerve nuclei. J. Comp. Neurol. 370:247–261, 1996.
65. Rousseau, F.; Heitz, D.; Tarleton, J.; MacPherson, J.; Malmgren, H.; Dahl, N.; Barnicoat, A.; et. al. A multicenter study on genotype-phenotype correlations in fragile x syndrome, using direct diagnosis with probe StB12.3: The first 2,253 cases. Am. J. Human Genet. 55:225–237; 1994.
66. Rovet, J.; Ireland, L. Behavioral phenotype in children with Turner syndrome. J. Ped. Psych. 19:779–790; 1994.
67. Stromland, K.; Nordin, V.; Miller, M.; Akerstrom, B.; Gillberg, C. Autism in thalidomide embryopathy: A population study. Dev. Med. Child Neurol. 36:351–356; 1994.
68. Thorogood, P.; Ferretti, P. Heads and tales: Recent advances in craniofacial development. Br. Dental J. 173:301–306; 1992.
69. Verkerk, A. J.; Pieretti, M.; Sutcliffe, J. S.; Fu, Y. H.; Kuhl, D. P.; Pizzuti, A.; Reiner, O.; et. al. Identification of a gene (FMR-1) containing a CGG repeat coincident with a break point cluster region exhibiting length variation in fragile x syndrome. Cell 65:905–914; 1991.
70. Vorhees, C. V. Principles of behavioral teratology. In: Riley, E. P.; Vorhees, C. V., eds. Handbook of behavioral teratology. New York: Plenum Press; 1986:23–48.
71. Vorhees, C. V. Some behavioral effects of maternal hyper- vitaminosis A in rats. Teratology 10:269–274; 1974.
72. Vorhees, C. V.; Brunner, R. L.; McDaniel, C. R.; Butcher, R. E. The relationship of gestational age to vitamin A induced postnatal dysfunction. Teratology 17:271–276; 1978.
73. Willhite, C. C.; Hill, R. M.; Irving, D. W. Isotretinoin- induced craniofacial malformations in humans and hamsters. J. Craniofacial Genet. Dev. Bio. 2:193–209; 1986.
74. Wolf, G. Recent progress in vitamin A research: Nuclear retinoic acid receptors and their interaction with gene elements. J. Nutr. Biochem. 1:284–289; 1990.
75. Wolf, G. The intracellular vitamin A-binding proteins: An overview of their functions. Nutrition. Rev. 49(1):1–12; 1991.