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Evidence for Behavioral Teratogenicity in Humans

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Central to both the scientific development of behavioral teratology and the attention paid to this field as an important area of study is establishing that prenatal exposure of pregnant females to exogenous agents leads to neurobehavioral disorders in their offspring. This tenet may not be questioned by the majority of toxicologists, but others may not be convinced. This paper serves as a brief review of the accumulated evidence that prenatal exposure to a number of drugs and environmental/industrial agents produces behavioral disorders in human infants.

A central issue in behavioral teratology or developmental neurotoxicology is the establishment of prenatal causes of developmental behavioral disorders. Only in recent years has sufficient evidence accumulated to document a linkage between prenatal exposure and adverse postnatal outcome for a series of drugs and industrial chemicals in both humans and animals. This linkage is crucial to the scientific development of the field of behavioral teratology, and also has implications for the extent of research support that this field will obtain. These linkages, however, do not appear to be well recognized, and this lack of recognition may contribute to the lack of widespread support of research in the field of developmental neurotoxicology. This paper summarizes the published evidence of neurobehavioral disorders in humans induced by prenatal exposure to exogenous agents to encourage further the development of the field of developmental neurotoxicology.

Huge societal costs result from the array of childhood disorders and dysfunctions identified in the United States, and many of these disorders persist into adulthood. Some 15–20% of American children have some form of ongoing physical health problem, many of which may be of prenatal origin.[1] Mental retardation (defined as an IQ score of <70) afflicts some 6 million people in America (about 3% of the population), and over 100 000 newborn children are added to this population each year.[2] Developmental disabilities (e.g. asthma, diabetes, epilepsy, speech or hearing impairment) affect some 3.9 million Americans under the age of 22, and it is estimated that 25% of the total US population has some form of psychological disorder.[3,4] Learning disabilities plague ca. 4% of the school children in the United States.[5]

The degree to which prenatal factors contribute to the childhood disorders and dysfunctions noted above has not been established. However, the incidence of some correlated problems has been established. It is generally accepted that the incidence of birth defects is 2–3% of liveborn babies.[6] In 1985, birth defects were the leading cause of infant mortality in the United States and the fifth leading cause of shortened life span.[7,8] Birth defects contribute significantly to chronic disease morbidity and related medical costs; ca. 30% of all admissions to pediatric hospitals are associated with birth defects, and expenditures for medical care have been estimated at $1.4 billion per year;[9] these figures may not include costs of otherwise normal babies born prematurely or with low birth weight. In addition to these figures for birth defects, another 7–8% of babies have malformations or mental deficiencies that are identified only after birth but before one year of age. In fact, this figure would be higher if other behavioral dysfunctions, for which prenatal factors may play a contributory role, were added to the total. These dysfunctions include seizure disorders, autism, childhood schizophrenia, early onset emotional disturbances and attention deficit disorders.

Despite the fact that birth defects and functional disorders affect a significant portion of the human population, the causes of these problems are not well established. The period between exposure to a causative agent and detection of the resulting functional pathology interposes numerous confounding factors, which may mask the etiological agent. Despite the difficulties inherent in detecting behavioral teratogens in humans, several such agents have been identified, frequently because the behavioral effects accompany other congenital malformations (at least at high exposure levels). Human infants who show evidence of growth retardation have a 33–50% chance of having a learning disability and some 26–61% of infants with mental retardation have associated congenital anomalies.[10] For example, mental retardation resulting from prenatal ethanol abuse has been associated with the abnormal appearance of the children (often, microcephaly). As noted below, evidence from animal research and/or isolated reports in human infants suggest other agents as possible human behavioral teratogens.

Vorhees and Mollnow[11] have reviewed the evidence that various drugs and environmental agents are human behavioral teratogens (see also Refs 12 and 13). Based

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on published animal and clinical evidence of behavioral teratogenicity (excluding non-specific causes, such as birth trauma accompanied by hypoxia), agents were categorized as established, probable or suspected behavioral teratogens; these agents are presented in Table 1. The 'established' category is based on evidence for both animals and humans published in the peer-reviewed research literature. The category of 'probable' behavioral teratogens identifies those agents for which the published evidence of behavioral teratogenesis in animals is strong but cannot yet be considered conclusive because of the scarcity of human data. The third category, 'suspected' behavioral teratogens, includes those agents for which evidence is only suggestive of behavioral teratogenicity, usually from published work involving a limited number of animal experiments.

The accumulated evidence described above (from animal research, as well as human observations) clearly establishes the existence of human behavioral teratogens. What is less clear is the extent to which these and other, as yet undiscovered, behavioral teratogens contribute to the overall incidence of behavioral disorders among humans. The discovery of a broad range of pharmacological agents that produce such disorders resulted directly from the extensive testing requirements imposed on drugs. These tests have provided much evidence regarding behavioral teratogens.[14–18] A similar, aggressive program of testing for environmental and industrial agents would likely reveal a number of behavioral teratogens for these agents as well.

The focus on therapeutic agents for investigation resulted directly from the thalidomide tragedy of the early 1960s. Some 10 500 malformed infants were born, primarily in Europe, as a result of maternal ingestion of the sedative–hypnotic and antinausea medication, thalidomide, during pregnancy (see Ref. 19). Although this drug was never approved for use in the United States, the Food and Drug Administration (FDA) reacted strongly to this event by establishing guidelines that required teratology evaluations of new drugs with experimental animals. Most industrialized countries subsequently developed similar requirements for new drugs. Had thalidomide also induced behavioral dysfunction, perhaps detection of functional disorders would have been included in the guidelines. Clearly, research interest was concentrated on drugs, both in standard teratology and in the fledgling field of behavioral teratology.[20–24] US regulatory agencies now appear likely to follow the lead of several other developed countries in requiring behavioral teratology evaluations for some classes of drugs and industrial chemicals.[13,25–35]

The thalidomide tragedy was the major stimulus for research in teratology, whereas ethanol was the primary stimulus for research in behavioral teratology. Since Jones and Smith published their paper describing the fetal alcohol syndrome,[36] an extensive literature has accumulated on the behavioral teratogenic effects of ethanol, both in humans and experimental animals.[37–39] The most noted feature of this syndrome is behavioral and intellectual dysfunction characterized by hyperactivity, delayed motor development and mental retardation in human infants.[40] Some researchers have argued that ethanol represents the most preventable cause of mental retardation in humans.[41]

While public and research interest in the 1960s and early 1970s focused on the teratogenicity of drugs, the focus in the late 1970s and the 1980s expanded to include the teratogenicity of environmental and industrial chemicals. With increasing numbers of women entering the workforce,[42,43] and with more

Table 1. Human behavioral teratogens.

Established	Probable	Suspected
Ethanol	Cigarette smoking[b]	Anxiolytics (e.g. diazepam)
Ionizing radiation	Nicotine	Antidepressants (e.g. imipramine)
Organic mercury	Narcotics	Anesthetics (e.g. halothane)
Inorganic lead	Several hormones (e.g. progestin)	Aspirin
Several anticonvulsants[a]	PCBs[b]	Marijuana
Vitamin A[a]		Neuroleptics (e.g. chlorpromazine)
		Thalidomide
		Other[c]

[a] Vorhees and Mollnow[11] included anticonvulsants and vitamin A in the 'probable' category, but subsequent research provides evidence that these drugs now meet the criteria for the 'established' category (see Refs 69, 70, 71). The anticonvulsants include hydantoin, trimethadione and valproate.
[b] As evidence accumulates that cigarette smoking[72] and PCB exposure[73] during pregnancy affects children's performance, cigarette smoking and PCBs should perhaps be shifted to the 'established' category as well.
[c] Includes some maternal infections, other heavy metals (e.g. cadmium and organotins), some industrial solvents and insecticides.

births being delayed until women are in their thirties (i.e. until after a number of years of work exposure), the risk of birth defects in offspring following exposure to industrial chemicals has become a major concern of working women.[44–51]

Concern about exposure of pregnant women to environmental and industrial agents, and the resulting behavioral effects on their offspring, was heightened following several outbreaks of congenital methylmercury poisoning.[52–54] The most widely publicized outbreak resulted from the release of effluent from an acetaldehyde plant into Minamata Bay, Japan.[55] Methylmercury entered the human food supply through fish in Minamata Bay (i.e. the fish were consumed by local villagers). In 1955, some 1600 adult cases of neurological disease were found in the Minamata area of Kyushu, Japan, with symptoms similar to those of cerebral palsy.[56] Several years later, investigators concluded that methylmercury also was responsible for the development of microcephaly, mental retardation and cerebral palsy in 26 infants as a result of *in utero* exposure to methylmercury.[56]

A similar, but less dramatic, event occurred later when pregnant Swedish women mistakenly consumed seed grain treated with mercury. The congenital poisoning resulting from this consumption caused several cases of cerebral palsy with mental deficiency in the children of these women.[55–57] An independent incident in Iraq added evidence to the hypothesis that the Swedish cases could have resulted from mercury exposure. In Iraq, seed grain treated with methylmercury was diverted to make bread, which then was consumed by a large number of Iraqis.[56,58] Thousands of Iraqis were hospitalized and ca. 460 died in hospitals as a result of this exposure. A small number of pregnant women were among those who survived the initial exposure. At least six of the 15 infants born to these exposed women showed gross impairment of motor and mental development, including cerebral palsy, microcephaly, deafness and blindness.[59]

Lead is another industrial chemical with widespread application. The behavioral teratogenic effects of lead have been demonstrated only recently, whereas the neurotoxic and adverse reproductive effects of this metal have been recognized since antiquity.[60–62] These effects have been reviewed recently in the human clinical and experimental animal literature,[62,63] so an extensive coverage of this literature is not attempted here. However, subclinical exposure of children to lead has been shown to be associated with deficits in intelligence, auditory perception, attention and classroom performance.[61] A recent review[62] stated that blood lead levels of 10–15 $\mu g\ dl^{-1}$ in children are known to result in neurobehavioral performance decrements. Centers for Disease Control (CDC) guidelines for lead screening in children were reduced from 30 $\mu g\ dl^{-1}$ in 1978 to 25 $\mu g\ dl^{-1}$ in 1984,[61] and these levels are likely to be reduced further in light of finding positive effects at still lower levels. Owing to lead's persistence in the body, chronic low-level lead exposure of women can result in adverse effects in their progeny born years later.[64]

In summary, numerous drugs and environmental and industrial agents have been documented to produce behavioral teratogenicity in humans.[65] The etiology of the vast majority of human developmental disorders, however, is unknown. If additional etiological agents are to be discovered, data must be obtained from a variety of sources, including surveillance programs,[7,66,67] epidemiological studies, animal research and clinical perspicacity. Clues as to certain chemicals with a high probability of producing developmental disorders can be drawn from structure–activity relationships and from the pattern of toxicological effects observed with adult animals.[68] Finally, the existence of childhood disorders and dysfunctions, accompanied by the lack of knowledge concerning the etiology of such disorders, highlights the need for additional research in developmental neurotoxicology.

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