

## Chapter 2

# Causative Factors

ADHD is a highly heritable disorder but in addition to genetic causes, acquired and environmental factors are sometimes uncovered that may be amenable to prevention or specific treatment. The causes of ADHD may be characterized as *idiopathic*, arising spontaneously from an unknown cause, *symptomatic* and secondary to a brain structural abnormality, or familial and presumed *genetic*. A majority of cases of ADHD are idiopathic or of uncertain cause. A delay in development or maturation of the nervous system is sometimes proposed as an explanation for ADHD, especially in children with mild or “soft” neurological deficits.

### Etiological Classification

The etiologies of ADHD are sometimes classified by the time of their occurrence: (1) *prenatal*; (2) *perinatal*; and (3) *postnatal* (Table 2.1). The syndrome may be *genetic* and *familial*, or *acquired* and *environmental*. Rarely, a chromosomal anomaly is the underlying cause of ADHD.

*Prenatal* causes include developmental cerebral abnormality, maternal anemia, toxemia of pregnancy, alcohol and cocaine abuse, and tobacco smoke. Other environmental factors sometimes suspected are exposure to lead, PCBs and pesticides in the water and diet, lack of iodine and hypothyroidism. The season of birth may be a risk factor, and exposure to viral infections, especially influenza and viral exanthema, in the first trimester of pregnancy or at the time of birth has been correlated with the diagnosis of ADHD.

*Perinatal* etiological factors include the following: premature birth, breech delivery, anoxic-ischemic-encephalopathy, cerebral hemorrhage, meningitis, and encephalitis.

*Postnatally*, the infant may have suffered a head injury, meningitis, encephalitis, frequent attacks of otitis media, or low blood sugar. Drugs used to treat childhood illnesses, asthma and epilepsy, frequently cause or exacerbate hyperactive behavior and result in attention and learning deficits. The role of diet in the cause of ADHD is controversial, but the ingestion of food additives and sucrose, lack of omega 3 fatty acids, and allergies to certain foods are occasionally significant. A lack of iron

**Table 2.1** Causes of ADHD

Time of effect	Causative factors
Prenatal	Cerebral maldevelopment, chromosome anomaly, infections, toxins, drugs, metabolic, endocrine disorder
Perinatal	Premature birth, encephalopathy, infection, hemorrhage
Postnatal	Infection, trauma, toxins, drugs, nutritional, endocrine disorder

Modified from Millichap (2008).

in the diet and anemia are documented potential causes and rarely, thyroid hormone dysfunction is associated with ADHD (Millichap, 2008). An abnormality in sensory input alleviated by oral potassium is proposed as a novel mechanism of ADHD in a 9-year-old boy with symptoms of sensory overstimulation and potassium sensitivity (Segal et al., 2007).

## Evidence for a Neurological Basis for ADHD

The neurologic or anatomic theory of hyperactivity and ADHD is based on numerous experimental studies in animals, neurological and electroencephalographic (EEG) examinations, and magnetic resonance imaging (MRI) of the brain. Positron emission tomography (PET) studies, showing changes in glucose metabolism in the frontal lobes of the brain, point to a localized cerebral abnormality in adults who were hyperactive since childhood.

*Neurological “soft” signs*, including motor impersistence (an inability to maintain postures or movements), distractibility (an inability to maintain attention), and attentional control and response inhibition, are indicative of right-sided frontal cerebral lesions. Frontal cerebral lesions and their connections with the basal ganglia or striate cortex produce the greatest number and degree of hyperactive behavioral responses. The right prefrontal cortex has a role in attentional control and inhibiting responses, whereas the basal ganglia are involved in motor control and the execution of behavioral responses. Distractibility and impulsivity in ADHD children reflect deficits in response inhibition.

Injury or abnormal development of areas of the brain other than the frontal lobes may also be associated with the syndrome of ADHD and impairment of language and social skills. Cognitive dysfunction and ADHD are reported in children with temporal lobe lesions, and a connection with the fronto-striatal circuitry is possible in these cases.

At *Duke University Medical Center, Durham, NC*, deficits of cognitive function, language development, and social skills were reported in 4 children with bilateral medial temporal lobe (hippocampus) sclerosis, associated with severe epilepsy beginning in early childhood. MRI showed abnormal signals and 25% loss of hippocampal volume (DeLong and Heinz, 1997).

*Temporal lobe arachnoid cyst* is reported in association with ADHD in several childhood patients (Millichap, 1997). Although rare, the diagnosis of this

association and syndrome points to the potential importance of prenatal factors in the cause of ADHD. The cause of arachnoid cyst is usually undetermined, but an injury to the fetal brain is likely, stemming from trauma, bleeding, or virus infection. In patients with increased intracranial pressure and complicating headaches or seizures, treatment sometimes requires surgery to drain the cyst, but generally the symptoms can be controlled by other more conservative measures.

*MRI brain volume analyses.* Measurements of various structures in the brain, using MRI quantitative techniques, have revealed changes in the development of the corpus callosum, a decreased volume of the right prefrontal cortex and basal ganglia, a smaller cerebellar vermis, and small cerebral volume. MRI measures of the right prefrontal cortex and basal ganglia correlate with response inhibition and task performance in ADHD children. Decreased cerebral volumes in some ADHD children may explain lower scores on IQ tests.

At the *Western Psychiatric Institute, University of Pittsburgh, PA*, MRI volumetric analyses in 26 children with ADHD compared to 26 normal controls showed correlations between task performance and prefrontal and caudate volume in the right hemisphere. Only right prefrontal measures correlated with performance of responses involving inhibition (Casey et al., 1997).

At the *National Institute of Mental Health, Bethesda, MD*, quantitative MRI studies in 46 right-handed boys with ADHD and 47 matched healthy controls found a smaller cerebellar vermis, especially involving the posterior inferior lobules, in the ADHD group. A cerebello-thalamo-prefrontal circuit dysfunction is postulated in ADHD (Berquin et al., 1998).

Localized cerebral hemisphere and cerebellar anomalies of development in ADHD are correlated with abnormal fronto-striatal-cerebellar function and sometimes with response to stimulant medication.

At the *University of California, Irvine*, volumetric MRI brain analyses in 15 male ADHD children compared to 15 normal controls showed smaller volumes of localized hemispherical structures. Smaller left basal ganglia (caudate nucleus specifically) was correlated with response to stimulant medication, whereas nonresponders had reversed caudate asymmetry (Filipek et al., 1997).

At the *University of Barcelona, Spain*, MRI measurements of the head of the caudate nucleus correlated with neuropsychological deficits and behavioral problems in 11 adolescents with ADHD. The ADHD group had a larger right caudate nucleus and a reversal of the normal L>R caudate asymmetry (Mataro et al., 1997).

The different anatomical sites of injury or lesion in the brain, sometimes detected in children with ADHD, can account for the varying symptoms and complications of the syndrome. The role of the right hemisphere and especially the right frontal lobe in the neurological basis for ADHD is stressed by Voeller (1990), my colleague, Charles Swisher (personal communication), and other neurologists, and is reviewed in "Progress in Pediatric Neurology I, II, & III" (Millichap, 1991, 1994, and 1997).

A *frontal-motor cortex disconnection syndrome*, or "lazy" frontal lobe, in ADHD is hypothesized on the basis of cerebral blood flow, EEG studies, and MRI volumetric analyses (Niedermeyer and Naidu, 1997). This concept is developed from the function of the frontal lobe as an inhibitor of excessive motor activity, children with

ADHD having disinhibited motor activity. The calming effect of methylphenidate may stem from a stimulatory effect on the frontal lobe causing motor inhibition.

*EEG Abnormalities and ADHD.* Epileptiform discharges in the EEG are reported in children with ADHD with varying frequencies, from 6% to as high as 53%. The indications for an EEG in ADHD include the following: (1) a history of seizures; (2) frequent “daydreaming”; (3) a history of head trauma, encephalitis or meningitis; and (4) as a precursor to treatment with stimulants in patients with a past or family history of epilepsy. A proportion of patients with ADHD have an increased susceptibility to seizures, based on EEG data.

Computerized power spectral analysis permitting statistical analysis of the EEG shows that boys, aged 9–12 years, with ADHD have increased theta (4.75 Hz) and decreased beta 1 (12.75–21 Hz) activity, when compared to controls matched for age and grade level (Mann, 1992). The increased theta is found in the frontal and central locations, and decreased beta in posterior and temporal locations.

EEG data from 184 boys with ADHD-combined type found three distinct EEG clusters or subtypes of children characterized by (a) increased slow wave activity and deficiencies of fast wave, (b) increased high amplitude theta with deficiencies of beta activity, and (c) an excess beta group (Clarke et al., 2001). Children with ADHD do not constitute a homogeneous group in EEG profile terms. Quantitative EEG data may provide more objective measurements of attentive difficulties in children with ADHD than are currently available from subjective questionnaires or rating scales. Variability of EEG characteristics must be recognized if the EEG is used as a reliable ADHD diagnostic tool sometime in the future.

## Role of Genetic Factors in Etiology of ADHD

Parents will often admit that fathers and, less often, the mothers were hyperactive or had a learning problem during childhood. Occasionally, they will deny any childhood behavior or attention problem, despite their inability to sit quietly during the consultation. A history of siblings and cousins who have been diagnosed with ADHD and who have had a favorable response to stimulant medications is not uncommon.

The clear distinction between the effects of nature and nurture in the cause of ADHD is difficult to prove, and both genetic and acquired factors are important. In some patients, the cause may be purely inherited, in others, mainly acquired and environmental, and in many, a combination of both. Several methods are employed by epidemiologists to demonstrate the role of genetic factors as compared to environmental influences (Omen, 1973).

(1) ADHD prevalence in different geographic, ethnic, or racial populations.

In a study of 145 children diagnosed with ADHD at the Shaare Zedek Medical Center, Jerusalem, Israel, boys outnumbered girls by 3:1, 30% had siblings with learning disabilities compared to only 7% among control children without ADHD, and 34% were of North African descent, an ethnic background present in only 12%

of the population of Jerusalem. A familial-genetic factor in this group of patients was expressed by the preponderance of males, the increased frequency of learning disabilities in siblings, and an ethnic-related propensity to ADHD (Gross-Tsur et al., 1991).

(2) Risk of ADHD in first-degree relatives (parents, siblings, and children) of patients with ADHD compared to the general population.

Among 457 first degree relatives of children and adolescents referred to the Child Psychiatry Service, Massachusetts General Hospital, Boston, the risk of ADD, as well as antisocial and mood disorders, was significantly higher than among normal controls (Biederman et al., 1990).

(3) *Twin studies.* Identical, monozygotic (MZ) twins may be compared with fraternal, dizygotic (DZ) twins. If genetic factors are important, both MZ twins are affected (concordant), whereas concordance in DZ twins is lower and similar to that for ordinary siblings. DZ twins must be of the same sex in studies of ADHD, since there is a male preponderance. The extent to which MZ twins may be discordant (i.e. only one affected) is an indication of the influence of environmental factors in the cause of ADHD.

An evaluation of 10 pairs of twins, at least one having the hyperactive syndrome, showed that all four pairs of MZ twins were concordant, whereas only one of six DZ pairs was concordant. The MZ twins were all boys (Lopez, 1965). This study supports a genetic basis for ADHD.

*The Minnesota Twin Family Study*, involving 576 twin boys, aged 11 and 12, and analyses of teacher and maternal reports, confirmed the importance of genetic factors in the mediation of both inattention and hyperactivity-impulsivity subtypes of ADHD. Environmental factors had lesser contributions to the etiology of ADHD (Sherman et al., 1997).

At the *UCLA School of Medicine, Los Angeles, CA*, twin studies using interview assessment of ADHD showed 79% concordance in 37 monozygotic twins compared to 32% in 37 same sex dizygotic twins. ADHD is a familial disorder, with frequency five to sixfold greater among first-degree relatives than in the general population. Relatives of ADHD probands have increased rates of comorbid conditions, especially oppositional and conduct disorders, anxiety, mood disorders, and learning disabilities. Adoption studies support both a genetic basis for ADHD and environmental factors (Smalley, 1997).

(4) *Influence of environmental upbringing among MZ twins.* Comparison of MZ twins reared together versus MZ twins reared apart, in foster homes, allows epidemiologists to distinguish the influence of genetic from environmental factors within a family. Also, the incidence of ADHD in the biological vs the adoptive relatives or half-sibs can be determined.

In a study of full sibs and half-sibs of 14 children with minimal brain dysfunction (ADHD), all reared in foster homes, 50% of the full sibs vs 14% of the half-sibs had hyperactive behavior and attention deficits (Safer, 1969). These findings were more in favor of genetic than environmental influences in the cause of ADHD, although the study was flawed by a higher incidence of prematurity and neonatal difficulties among the full sibs, environmental factors known to cause ADHD.

## Chromosomal Anomalies Associated with ADHD

Chromosomal syndromes are rare among ADHD-clinic patients. They include fragile X, velocardiofacial (22Q.11.2 deletion), Williams, Turner and Prader-Willi syndromes, and neurofibromatosis type 1 (Moore et al., 1996). In a study of 100 children (64 boys) with ADHD (combined type) and normal intelligence, 1 girl had a sex chromosome aneuploidy (47.XXX) and 1 boy had a permutation-sized allele for fragile X, but none showed the full mutation. Tests for 22q11.2 microdeletion were negative. In the absence of clinical signs or family history, routine chromosome analysis in children with ADHD is not generally recommended (Bastain et al., 2002).

## Molecular Genetic Studies

The above reports point to the role of genetic factors in the cause of ADHD. The identification of a specific metabolic or enzyme marker is also required to prove an inherited predisposition. Studies focused on catecholaminergic candidates support the involvement of the dopamine receptor and dopamine transporter genes (*DAT1*). Deficits in dopamine-modulated frontal-striatal circuits are correlated with subtypes of ADHD. The relation of dopamine deficits to fetal and perinatal stresses may explain the mechanism of environmental etiologies of ADHD (Swanson et al., 2007). Preterm birth complicated by susceptibility to cerebral ischemia may contribute to increased dopamine receptor availability, deficient dopaminergic transmission, and subsequent development of ADHD (Lou et al., 2004).

Evidence of environmental mediators in ADHD has been demonstrated in twin studies. Affected twins have greater exposure to risk factors such as maternal smoking, lower birth weights, and delayed growth and development compared with unaffected co-twins (Lehn et al., 2007). Gene-environment interaction is increasingly recognized as an important mechanism in the etiology and development of ADHD, with some genes (e.g. *DAT1*) affecting the individual sensitivity to environmental etiological factors (Thapar et al., 2007).

## Environmental Factors in Etiology

The evidence for environmental and acquired factors, although often presumptive, is perhaps stronger than the genetic data in the search for causes of ADHD (Millichap, 2008). *Pregnancy- and birth-related risk factors* include maternal smoking and nicotine, exanthema, maternal anemia, breech delivery, prematurity, low birth weight, hypoxic-ischemic-encephalopathy, small head circumference, cocaine and alcohol exposure, and iodine and thyroid deficiency. *Childhood illnesses* linked to ADHD include viral infections, meningitis, encephalitis, otitis media, anemia, cardiac disease, thyroid disease, epilepsy, and autoimmune and metabolic disorders. Head injury involving the frontal lobes, toxins and drugs, and nutritional disorders

are additional risk factors. The relation of dietary factors to ADHD is often controversial, especially food additives, food allergies, sucrose, gluten sensitivity, and fatty acid and iron deficiency. Of all the environmental factors implicated, maternal smoking and nicotine exposure attract the most attention in the literature, but in practice, cigarette smoking is almost invariably denied.

## **Role of Adverse Home and School Environments**

Adverse home environments and overcrowded classrooms may contribute to and exacerbate hyperactivity and inattentiveness in a child with ADHD. However, these factors alone are rarely the explanation, and intrinsic genetic or acquired causes must always be investigated.

The influence of parents with psychiatric illness on the functioning of children with ADHD and normal control children was studied at the Pediatric Psychopharmacology Unit in Psychiatry, *Massachusetts General Hospital, Boston, MA*. The frequency of adverse family environments, including chronic family conflict, poor family union, and mothers with psychiatric problems, was greater among 140 ADHD compared to 120 normal children (Biederman et al., 1995).

Early recognition of these environmental factors should lead to prompt intervention and improved outcome.

In a study of psychiatric disorders in families of children with ADHD, at the Department of Pediatrics, *Wyer and La Rabida Children's Hospitals, University of Chicago*, alcoholism, drug abuse, depression, learning disabilities, and/or ADHD were more common among parents of ADHD than control children (with Down syndrome) (Roizen et al., 1996).

Children with a family history of psychiatric disorders should be screened for ADHD.

## **ADHD in Adopted Children**

In a previous analysis of the author's patients, the incidence of adoption among children with the hyperactive syndrome was 12% and more than three times the national incidence of adoption in that year (Millichap, 1975). A 17% rate of adoption was reported in another study of ADD children, 8 times that found in a normal control group or in the general population (Deutch et al., 1982). Behavioral and psychiatric problems are not increased in the foster families of hyperactive adoptive children, according to another study (Morrison and Stewart, 1973).

Although it is generally believed that behavior problems are more prevalent among adopted children, the occurrence of adverse psychological environments in foster or adoptive placements must not be assumed. An increased likelihood of insults to the fetus or newborn baby during unwanted pregnancies and births and possible genetic anomalies are more plausible explanations. In the author's ADD



clinic at *Children's Memorial Hospital, Chicago*, cocaine exposure during pregnancy and birth is frequently reported by adoptive parents of foster children but is only rarely admitted by a biological parent.

## Biochemical Basis for ADHD

Evidence is accumulating that changes in the brain chemistry – the catecholamine *neurotransmitters* (dopamine, norepinephrine, and serotonin) – might account for hyperactivity, inattentiveness, and other symptoms of ADHD. The central nervous system stimulants, dextroamphetamine and methylphenidate (*Ritalin*®), benefit ADHD by increasing catecholamine concentrations in the brain. Catecholamine metabolism and levels of norepinephrine are related to arousal, attention span, and motor activity.

The biochemical studies in children with ADHD are experimental. Measurements of metabolites, or breakdown products, of dopamine and norepinephrine in the urine or of enzymes in the blood are not of practical significance in the diagnosis and treatment of ADHD, but they increase our understanding of the neurobiology of ADHD (Yehuda, 1986; Zametkin and Rapoport, 1987).

## Infectious Causes of ADHD

Viral infections during pregnancy, at birth, and in early childhood are linked to an increased risk of ADHD. In a case-controlled study in Italy, the frequency of measles, varicella, or rubella, in mothers of children who developed ADHD is significantly higher than in controls (Arpino et al., 2005). Other viral infections associated with an increased prevalence of ADHD and learning disorders include HIV, enterovirus 71, and varicella zoster encephalitis. Febrile seizures, frequently associated with human herpesvirus 6 infection in the United States and with influenza A in Asia, are a risk factor for development of ADHD (Millichap, 2008). A possible relation between ADHD and streptococcal infection and a causative role for otitis media require confirmation.

## Perinatal and Early-Life Risk Factors

Various centers internationally have reviewed the roles of premature birth and perinatal hypoxic-ischemic encephalopathy in the pathophysiology of ADHD. At the *John F Kennedy Institute, Glostrup, Denmark*, up to one-third of premature infants with birth weights of <1500 g have ADHD by 5–7 years of age (Lou, 1996). Birth histories of 196 children with ADHD followed in Iceland showed a statistically significant increased risk associated with low birth weight, young maternal age, and cesarean delivery (Valdimarsdottir et al., 2006). Advances in NICU nursing care



and improved survival rates among premature infants have lead to an increase in the importance of perinatal risk factors for ADHD. In contrast, a case-control study at the *Mayo Clinic* found that pregnancy and labor, low birth weight, and twin birth were not correlated with ADHD, while male gender and low parental education levels were positive risk factors (St Sauver et al., 2004).

## Postnatal Risk Factors

Cerebral trauma, meningitis, encephalitis, metabolic and endocrine disorders, especially thyroid dysfunction, toxins and drugs, and nutritional deficiencies, additives, and food sensitivities are factors known to be associated with ADHD. A genetic factor and inherited predisposition are likely basic causes, and environmental factors are probably secondary, acting as a trigger. Some potentially preventable ADHD environmental causes include hypoglycemia, iron, zinc, and iodine deficiencies.

## Head Injury as a Cause of ADHD and Learning Disorders

Head injury, even mild in degree, in young children warrants observation and follow-up for possible behavior and cognitive impairments. Hyperactive behavior was directly correlated with the severity of head injury in a study of 95 children, aged 5–15 years, followed at the *Johns Hopkins University, Baltimore* (Greenspan and MacKenzie, 1994). The risk of functional limitations following injury was increased in children with previous chronic health problems and those who sustained lower extremity injuries in addition to head injury.

Mild head injury, not sufficient to require admission to hospital for observation, can result in learning deficits and impairment of reading and school performance in young children. Compared to a control group of preschool children with minor injury not involving the head, 78 head-injured preschoolers tested at one year after injury had visual perception problems and an increased incidence of dyslexia (Wrightson et al., 1995). The development of visual skills necessary for reading was interrupted by the mild head injury.

Math and spelling abilities were impaired in a 17-year-old boy who had sustained a right hemisphere injury in infancy. Investigations using a functional MRI at the *University of Maryland, Baltimore*, showed activation of the left hemisphere while the patient performed arithmetic calculations. Visuospatial skills normally subserved by the right hemisphere had been transferred to the left hemisphere after the injury, causing a “crowding effect” and disproportionate impairment of math and reading skills in comparison to language development (Levin et al., 1996).

At *Columbia University and New York State Psychiatric Institute*, low-birth-weight children, with neonatal cranial ultrasound abnormalities suggestive of white matter injury, were at increased risk for neuropsychiatric disorders, especially ADHD, by the age of 6 years (Whitaker et al., 1997).

Brain injury at an early age can lead to reorganization of the locations in the brain where attention, language, and cognitive function are represented.

## Hypoglycemia and ADHD

Hypoglycemia in a newborn infant, if unrecognized and untreated, can cause convulsions and brain damage that later may result in mental retardation or learning disorders and ADHD. Transient hypoglycemia may occur in infants with birth anoxia or other forms of perinatal stress or in neonates born to mothers with diabetes or toxemia.

Early onset childhood diabetes, before the age of 5 years, is often complicated by episodes of severe hypoglycemia that result in mild cognitive dysfunction, whereas late-onset diabetes, after the age of 5 years, and occasional episodes of severe hypoglycemia have no effect on cognitive function, according to a study in 28 diabetic children at the *Trondheim University Hospital, Norway* (Bjorgaas et al., 1997).

Transient reactive hypoglycemia, following a diet of high sugar content, may be associated with behavioral symptoms seen with ADHD. A rapid rise in blood glucose can result in a heightened insulin secretion, with resultant hypoglycemic symptoms.

## Role of Sugar and Other Dietary Factors in ADHD

Parents frequently note a worsening of hyperactivity and distractibility after the child with ADHD has eaten a high carbohydrate meal or a lot of candy. While the majority of scientifically controlled studies have failed to demonstrate a significant adverse effect, isolated reports tend to support the parents' observations.

In a study at *Yale University School of Medicine, New Haven, CT*, a fall in blood glucose at 3–5 h after a glucose drink was accompanied by symptoms of hypoglycemia (shakiness, sweating, weakness, and tachycardia) in children but not in adults. The reactive lowering of the blood glucose had stimulated a rise in plasma epinephrine, twice as high in children as in adults, sufficient to induce the symptoms of hypoglycemia. A measure of cognitive function, using evoked potentials, was significantly reduced when blood glucose was lowered below 75 mg/dl in children, but was preserved in adults until the level fell to 54 mg/dl (Jones et al., 1995).

Children appear to be more vulnerable to the effects of hypoglycemia on cognitive function than are adults. A diagnosis of excess sugar ingestion and reactive hypoglycemia as a cause of ADHD may be entertained when the child also suffers from more characteristic symptoms, including nervousness, tremor, sweating, dizziness, or palpitations.

At the *Child Psychiatry Branch and Laboratory of Developmental Psychology, NIMH, Bethesda, MD*, the effects of glucose, sucrose, saccharin, and aspartame on aggression and motor activity in 30 boys, aged 2–6 years, were compared. Eighteen

boys were classed as “sugar responders” on parent questionnaires and 12 were “non-responders.” Single dose challenges with sugar or sweetener, in a randomized, double-blind study, produced no significant differences in aggression or activity levels, as measured by teacher and parent ratings. The base-line duration of aggression in the alleged sugar responders correlated with the daily total sugar consumption, but acute sugar loading did not increase aggression or activity in preschool children (Knesi et al., 1987).

At the *Schneider Children’s Hospital, New York*, the effect of a sucrose challenge on aggressive behavior and attention was studied in a sample of hyperactive boys with ADD and age-matched control subjects (Wender and Solanto, 1991). Aggression was not modified, but inattention measured by a continuous performance task was increased following sugar ingestion in the ADHD group. Conners CK at the *National Children’s Hospital, Washington, DC*, reports that behavioral effects of sugar in children with ADHD may be demonstrated if the sucrose challenge follows a high carbohydrate breakfast. The effects are reversed or blocked if the child has a protein meal before or with the ingestion of sugar (Yehuda, 1987).

An analysis of 16 published studies on the effects of sucrose on behavior and cognition of children with ADHD, conducted at *Vanderbilt University, Nashville, TN*, failed to demonstrate a significant adverse effect in the group as a whole, but a small effect in some sets of ADHD children could not be ruled out (Wolraich et al., 1995). Aspartame (Nutrasweet®) used as a control in these studies was considered to have no adverse effect on behavior or cognition (Shaywitz et al., 1994), but further investigation of the safety of aspartame may be indicated. Some authorities have demonstrated an exacerbation of EEG seizure discharges and of migraine headaches following aspartame ingestion.

## Feingold Theory of Food Additives as a Cause of ADHD

Controlled studies of the additive-free, Feingold diet have failed to demonstrate a significant benefit in children with ADHD, except in an occasional pre-school child. However, some parents still believe that their children are reactive to foods containing artificial coloring, flavoring agents, and preservatives. They avoid apples, luncheon meats, sausage, hot dogs, gum, candies, cake mixes, oleomargarine, and ice cream. Flavored cold drinks, soda pop, and medicines containing aspirin are also excluded from the Feingold diet (1975).

The evidence for and against the Feingold theory is reviewed in Chap. 10. Scientific panels, established to study the efficacy of the diet and sponsored by the FDA, criticized the treatment and theory for lack of controls and statistical validity. Numerous studies of the effects of food additives on behavior followed, including additive-containing challenges. Small subgroups of younger children were found to react adversely to color additives in short-term trials, but the overwhelming benefits claimed for the Feingold diet were not substantiated (National Institutes of Health Consensus Panel, 1982).

The proof of food additive toxicity and relation to hyperactive behavior is difficult to determine. Questionnaires completed by parents, teachers, and psychologists may be biased, for or against, and may not address behavioral symptoms susceptible to the additive-free diet. Interest in the Feingold hypothesis and dietary treatment of ADHD has waned in the United States but waxes in Europe and Australia, where research continues on the use of elimination and hypoallergenic diets for the treatment of a variety of childhood neurobehavioral disorders.

Irritability, restlessness, and sleep disturbance rather than attention deficit were the behavioral patterns associated with the ingestion of azo dye food colorings (tartrazine and carmoisine) in a small, double-blind controlled study at the *Royal Children's Hospital, Victoria, Australia* (Rowe, 1988). The author concluded that behavioral rating questionnaires not including sleep habits may fail to identify specific reactors to food additives.

## **Role of Food Allergy in ADHD**

Food allergy is proposed as a possible factor in the cause of ADHD. Chocolate, cow milk, egg, citrus, wheat, nuts, and cheese have triggered hyperactive behavior in some susceptible patients. A hyposensitization treatment with intradermal injections of food allergens (EPD) in 40 children with ADHD was conducted at the *Universitätskinderklinik, Munchen, Germany*, and the *Great Ormond Street Hospital, London* (Egger et al., 1992). Of 20 children receiving the EPD injections, 16 no longer reacted toward hyperactivity-provoking foods, compared to 4 of 20 who received placebo shots. A hypoallergenic, elimination diet has been used occasionally in practice, with variable results (Millichap, 1986). The role of food hypersensitivity as a cause of ADHD is difficult to document, the cooperation of neurologist, allergist, and dietician being essential. The hypoallergenic diet deserves further study.

## **Iron Deficiency and ADHD**

Researchers in Paris, France report evidence of iron deficiency in children with ADHD. Serum ferritin levels were <30 ng/ml in 84% of children with ADHD vs 18% of control non-ADHD children; 32% had levels of <15 ng/ml vs 3% of controls. The authors report improvements in attention and behavior following supplemental iron (Konofal et al., 2004).

In contrast, our experience in Chicago shows that a mean serum ferritin level of  $39.9 \pm 40.6$  ng/ml in ADHD children is not different than that of control children with no ADHD, but 18% of children with ADHD have levels below 20 ng/ml that are considered abnormal. None had evidence of iron-deficiency anemia.

A comparison of clinical characteristics of children with the lowest serum ferritin levels (< 20 ng/ml) and those with highest serum ferritin levels (> 60 ng/ml) show

no significant difference in severity or frequency of ADHD and comorbid symptoms or response to medications (Millichap et al., 2006). An uncontrolled trial of iron supplement was ineffective and did not provide a substitute for medication in the management of ADHD. A causative role for low serum ferritin levels in ADHD was not confirmed in our patient cohort. Differences in mean iron storage levels in the French and Chicago-based studies may explain the variation in response to iron supplements. Further controlled trials of iron supplements may be indicated. Routine serum ferritin levels in children with ADHD may be justified.

## **Role of Zinc in ADHD**

Several controlled studies, mainly in Turkey and Iran, countries with suspected endemic zinc deficiency, demonstrate a deficiency of zinc in patients with ADHD and a beneficial response to zinc sulfate supplements (Arnold et al., 2005). In another study, low serum zinc levels were correlated with inattention but not with hyperactivity/impulsivity (Arnold and DiSilvestro, 2005). Some researchers recommend zinc sulfate supplements as adjunctive therapy with methylphenidate. In the United States, routine serum zinc levels in children presenting with ADHD are probably not warranted.

## **Iodine Deficiency, Thyroid Function and ADHD**

*Iodine deficiency* and hypothyroidism are prenatal and postnatal risk factors for ADHD in some environments. Optimal iodine intake is essential for normal thyroid function and the prevention of learning disabilities and academic underachievement. In the United States, iodine is present in the diet in adequate amounts but in underdeveloped countries, iodine deficiency is a common occurrence. Estimates find 200 million people affected by iodine deficiency diseases and 800 million at risk worldwide, a total of 1 billion at risk of brain maldevelopment or malfunction. A prospective study of the neuropsychological development of offspring of women from an iodine-deficient area in Italy found ADHD in 69%; no cases of ADHD were reported in an iodine sufficient area. The mothers were hypothyroxinemic at early gestation, resulting in reduction of triiodothyronine available to the developing fetal brain (Vermiglio et al., 2004). Endemic cretinism (congenital hypothyroidism) is the most serious complication of iodine deficiency. Milder forms of iodine deficiency can result in impaired cognitive function and learning disabilities in later childhood. Iodine deficiency, a major international public health problem especially affecting underdeveloped countries, may be prevented by iodized salt in the diet.

At the *University of Groningen, The Netherlands*, continuous performance tasks, measures of the ability to sustain attention, were used to study 48 children with early treated congenital hypothyroidism and 35 healthy controls. Impairments of sustained attention were correlated with low pre-treatment thyroid hormone levels but

not with onset of treatment for hypothyroidism. Declines in sustained-attention task performance were related to cognitive, motor, and motivational deficits (Kooistra et al., 1996).

At the *Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India*, 100 boys with prolonged iodine deficiency, not suffering from cretinism and selected for their ability to read and write, were slow learners and had impaired motivation to achieve (Tiwari et al., 1996).

Iodine deficiency not resulting in cretinism can cause learning disabilities and poor academic motivation.

*Thyroid dysfunction.* Impairments of cognition, attention, and behavior may occur with hypo- or hyper-thyroidism. Case reports of thyrotoxicosis and ADHD are rare, and symptoms may be subtle, leading to a missed diagnosis. In 3 patients with no characteristic signs of hyperthyroidism, treatment resulted in control of hyperactivity, increased attention span, and improved language function (Suresh et al., 1999). The authors recommend routine thyroid screening in children with ADHD. In the neurology ADHD clinic at *Children's Memorial Hospital, Chicago*, using routine thyroid screening we have encountered four cases of hyperthyroidism in one year, two with goiter.

ADHD is reported in patients with generalized resistance to thyroid hormone (GRTH), a disease caused by mutations in the thyroid receptor B gene. GRTH is characterized by reduced responsiveness of peripheral and pituitary tissues to thyroid hormone. In families with a history of GRTH studied at the *National Institutes of Health, Bethesda, MD*, 70% of affected children met the criteria for ADHD (Hauser et al., 1993). In another study, the prevalence of ADHD in patients with GRTH was 46% (Weiss et al., 1993). Despite some reports of a lack of association between GRTH and ADHD (Elia et al., 1994), screening of patients with a family history of thyroid dysfunction is recommended.

## Lead Exposure as a Cause of ADHD

Clinical reports suggest that lead-exposed children may be distractible and hyperactive, but few studies have examined the effects of lead on behavior using statistical controls. A characteristic "behavioral signature" associated with lead exposure has not been identified (Bellinger, 1995). Proof of cause and effect is often lacking, especially for conditions such as pervasive development disorder and speech articulation problems.

Although the research is controversial, cognitive deficits have been correlated with blood lead levels of 10 mcg/dl or higher. Questions regarding risk of lead exposure at home, the school, or playground are important in children presenting with learning and behavior disorders. Preschool blood lead determinations are mandatory in some communities, but testing is appropriate in children diagnosed with ADHD and living in high-risk environments.

At the *Department of Community Medicine, University of Adelaide, Australia*, a study of low level lead exposure and effects on intelligence, which began in 1979,

has been followed into the primary school age range. In 494 children, aged 7 years, from a lead smelting community, the IQ was inversely related to antenatal and post-natal blood lead concentrations, even at 10 mcg/dl levels. An increase in blood lead from 10 to 30 mcg/dl caused deficits in verbal IQ and full scale IQ of 6 and 5 points, respectively (Baghurst et al., 1992).

Three longitudinal studies in different locations (Australia, Boston, and Cincinnati) have demonstrated that lead-associated decreased intelligence is persistent across cultures, racial and ethnic groups, and social and economic classes. The finding is not limited to socially and economically disadvantaged children (Mahaffey, 1992).

## Cocaine-Exposed Infants at Risk of ADHD

Cocaine-exposed infants require careful follow-up for early diagnosis and therapy of neurobehavioral complications. A history of prenatal cocaine exposure is common in foster children with ADHD attending our ADD clinic. A cause and effect is presumed but not proven.

At the *University of Miami School of Medicine, FL*, a study of 30 preterm cocaine-exposed infants compared to normal controls found smaller head circumference at birth, and a higher incidence of cerebral hemorrhage, restless sleep, agitated behavior, and tremulousness (Scafidi et al., 1996). The signs of abnormal brain development and excitation in cocaine-exposed infants were associated with higher levels of norepinephrine and dopamine in the urine, neurotransmitter chemicals important in the mechanism of ADHD. Hormonal changes, with higher cortisol levels and lower plasma insulin levels, were also reported in the cocaine-exposed newborns.

At the *University of Florida, Gainesville, FL*, cranial ultrasound examinations of 134 cocaine-exposed compared to 132 control newborns found an increased incidence of brain cysts and enlarged ventricles, possibly related to cocaine effects on brain development (Behnke et al., 1998).

At the *Women and Infants Hospital, Brown University School of Medicine, Providence, RI*, increased muscle tone and motor activity, jerky movements, startles, tremors, and back arching were observed in 20 infants with prenatal exposure to cocaine, alcohol, marijuana, and nicotine cigarettes (Napiorkowski et al., 1996). Signs of brain excitability were related only to cocaine and were neither apparent in the 17 infants exposed to alcohol, marijuana, and nicotine without cocaine, nor in the 20 drug-free infants.

At the *Children's Hospital, Boston, MA*, dose-related effects of cocaine on neurobehavior were demonstrated in exposed infants examined at 3 weeks of age. Heavily exposed infants showed impaired regulation of arousal and greater excitability than lightly or unexposed infants (Tronick et al., 1996).

Effects of prenatal cocaine on behavior and development noted in infancy are likely precursors of ADHD in later childhood. A combination of cocaine



exposure and poor nutrition is a cumulative risk factor for impaired infantile motor performance and later cognitive development in inner-city minority infants.

## **Fetal Exposure to Alcohol, Marijuana, or Cigarettes and Increased Risk of ADHD**

Behavioral problems are one of the characteristics of the “fetal alcohol syndrome” (FAS). Alcohol use during pregnancy and breast-feeding may cause delay in an infant’s development and even an increased risk of brain hemorrhage (Holzman et al., 1995).

In a study of 64 alcoholic families at the *Karolinska Institute, Stockholm, Sweden*, children were retarded in development and had more behavioral problems than controls up to 4 years of age. Boys were more vulnerable than girls. Behavioral disorders were more pronounced when both parents were alcoholic (Nordberg et al., 1994).

At *Sahlgren University Hospital, Goteborg, Sweden*, 26 children of mothers who abused alcohol during pregnancies were followed throughout childhood and were examined at 11–14 years of age for neuropsychiatric, psychological, and social problems. Of 24 children seen at follow-up, 10 had ADHD, 2 had Asperger syndrome, and one had mild mental retardation and autistic spectrum disorder. The severity of the disorder was correlated with the degree of alcohol exposure in utero. Children whose mothers discontinued alcohol consumption by the 12th week of gestation developed normally and had no learning problems in school (Aronson et al., 1997). Biological, not psychosocial, factors are responsible for ADHD in children with fetal alcohol syndrome.

*Maternal tobacco or marijuana smoking.* A systematic search of the literature found 24 studies concerning maternal tobacco smoking published between 1973 and 2002. All reports indicated an increased risk of ADHD in the offspring (Linnet et al., 2003). Maternal cigarette smoking has been linked to impairments of cognitive function and memory, academic under-achievement, and behavioral problems in children exposed during pregnancy (Drews et al., 1996).

In a follow-up study of 6-year old children studied at *Carleton University, Ottawa, Ontario, Canada*, prenatal marijuana was associated with errors of omission in tasks of vigilance, reflecting a deficit in sustained attention (Fried et al., 1992). Cigarette smoking, marijuana use, and alcohol excess during pregnancy may have adverse effects on the behavior and attention of the infant and child, but a definite causative role in ADHD has not been established.

## **PCBs and Other Environmental Toxins as Potential Causes of ADHD**

Environmental contaminants of our food and water supplies include PCBs (polychlorinated biphenyls), PBBs (polybrominated biphenyls), nitrates, DDT, dioxin,

mercury, and lead. DDT and other pesticides, including dioxin, and PCBs have not been produced since the 1970s. Despite the ban on the manufacture of these chemicals, dangerous concentrations persist in the water of rivers and inland lakes.

PCBs were dumped years ago as waste products from electrical transformer, capacitor, and plasticizer factories. From the sediment at the bottom of harbors, hazardous waste residues pollute the water and are eaten by microscopic organisms and fish. From fish the chemicals are passed to birds and humans, causing various ailments including cancer and reproductive problems (Millichap, 1993, 1995). Man is the final consumer in the food chains, and he is exposed to the greatest concentrations of any environmental poison.

While regulatory control measures have substantially reduced the PCB contamination of animal feeds and food products by spillage, those subgroups of the population who regularly consume fish caught in lakes and streams are still at risk of poisoning. Surveys and analyses of fish from the Hudson River in New York State and from Lake Michigan showed significant levels of contamination with PCBs in excess of 5 ppm.

Studies designed to assess the health hazard of PCB exposure from Lake Michigan fish showed a correlation between the quantity of fish consumed and the concentration of PCB in blood and breast milk of participants in the studies. Those eating higher amounts of fish had significantly higher blood levels of PCB. Children born to women who routinely consumed Lake Michigan sport fish displayed impaired short-term memory function on both verbal and quantitative tests. In a study at *Wayne State University, Detroit, MI*, cognitive function was tested at 11 years of age in 212 children exposed prenatally to PCBs (Jacobson and Jacobson, 1996). Long-term intellectual impairment affected memory, attention, and reading ability, deficits frequently found in children with ADHD.

Developmental neurotoxicity of PCBs is reviewed in a publication from the *Institute of Environmental Studies, University of Illinois at Urbana-Champaign, Illinois* (Schantz, 1996). Studies included reports from Yusho, Japan; Yucheng, Taiwan; Michigan; North Carolina; Oswego, NY; New Bedford, MA; on Inuit people in the Arctic regions of Quebec; and in Faroe Islanders. Methylmercury poisoning could be an additional contaminant in some studies. Children born to mothers exposed to PCBs showed abnormalities in behavior and development, including higher activity levels, lower IQ scores, decreased birth weight and head circumference, deficits in memory at 4 years, and delays in psychomotor development. The public health implications of low-level PCB exposure were compared to those of lead exposure. The effect of PCB was either by direct injury to the brain in the prenatal period or secondary to effects on thyroid function.

At *Odense University, Denmark*, a study of 1022 children born in 1986–1987 in the Faroe Islands to mothers who had consumed methylmercury-polluted pilot whale meat found deficits in language, attention, and memory at 7 years of age (Grandjean et al., 1997).

Subtle alterations in neuropsychological functioning caused by exposure to these environmental toxins are proposed as potential causes for some cases of ADHD and learning disabilities.

## Role of Diet During Infancy in the Cause of ADHD

Diets during infancy have been studied in relation to adult diseases such as hypertension and heart attack. Researchers at *Columbia University, New York*, have studied the rate of weight gain and diet-dependent changes in biochemistry, physiology, and behavior of 142 preterm infants fed varied protein and energy intakes (de Klerk et al., 1997). Rapidly growing infants had increased heart rates, respiratory rates, active sleep time, and decreased EEG frequencies compared to slow growing infants. Shifts in the balance of catecholamine and serotonergic neurotransmitters, similar to those reported with ADHD, were proposed as the cause of the changes in autonomic responses related to diet and rapid growth. Nutrition and weight gain during infancy may be a factor in the etiology of ADHD.

### Summary

The cause of ADHD is frequently unknown or *idiopathic* but in some cases, *symptomatic* and secondary to a brain structural abnormality, traumatic or encephalitic. A familial, genetic factor in an estimated 80% of cases may involve the dopamine receptor and transporter genes, but gene-environment interaction is recognized as the important mechanism in the etiology of ADHD. Environmental factors may occur prenatally, in the perinatal period, or postnatally. They include developmental cerebral abnormalities, infections, toxins, premature birth, encephalopathy, and nutritional and endocrine disorders. A neuroanatomical theory for the symptoms of ADHD is based on the clinical examination and neurological “soft signs,” electroencephalographic abnormalities, magnetic resonance imaging and brain volume studies, and positron emission tomography. Numerous experimental studies in animals have demonstrated hyperactive behavior elicited by prefrontal cerebral lesions. Head injury, even mild in degree, in young children is correlated with learning and behavior disorders. A neurochemical basis for ADHD is also proposed involving catecholamine neurotransmitters, a theory supported by the beneficial effects of stimulant medications.

The recognition of environmental factors in the etiology of ADHD should lead to prompt intervention, improved outcome, and in some cases, prevention of ADHD.

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