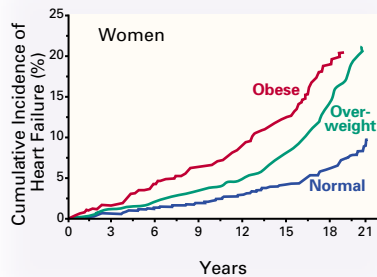




This Week in the Journal

August 1, 2002

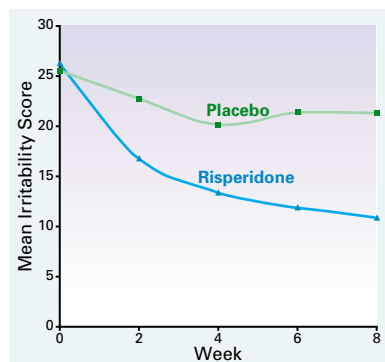


Obesity and the Risk of Heart Failure

Extreme obesity is a risk factor for heart failure. This analysis from the Framingham Heart Study assessed the risk associated with lesser degrees of obesity and overweight. There was a continuous increase in the risk of heart failure with increases in the body-mass index (an increase in risk of 5 percent for men and 7 percent for women for each increment of 1 in the body-mass index). Obesity accounts for about 11 percent of heart failure among men and 14 percent among women in the Framingham population.

Obesity may increase the risk of heart failure by virtue of its relation to established risk factors, such as hypertension, diabetes, and hyperlipidemia, but obesity may also have a direct negative effect on myocardial function.

see page 305 (editorial, page 358)



Risperidone in Children with Autism and Serious Behavioral Problems

Serious behavioral problems in children with autism are common and difficult to manage. Atypical antipsychotic medications are effective in treating adults with schizophrenia and have fewer side effects than traditional antipsychotic medications. This randomized trial examined whether risperidone improved behavior in children between the ages of 5 and 17 years who had autistic disorder with severe tantrums, aggression, or self-injurious behavior. At eight weeks, 69 percent of the children treated with risperidone had substantial improvement in behavior, as compared with 12 percent of those who received placebo. Fatigue, drowsiness, tremor, drooling, and increased appetite were mild but were more common among children taking risperidone.

This eight-week study suggests that atypical antipsychotic medications improve moderate-to-severe behavioral problems in children with autism. The long-term risks and benefits of treatment with risperidone in children with autistic disorder are not yet known.

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PERSPECTIVE

The Autistic-Spectrum Disorders

Any person, talented or handicapped, whose social skills have been severely deficient since very early childhood, who started to talk late or whose communicative use of language is inadequate, and who perseverates and lacks cognitive and behavioral flexibility meets the diagnostic criteria for an autistic-spectrum disorder. The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), published by the American Psychiatric Association, and the *International Classification of Diseases, 10th Revision* (ICD-10), published by the World Health Organization, use the term “pervasive developmental disorder” to encompass the broad spectrum of developmental disorders with these characteristics (see Table). Pervasive developmental disorders are more common in boys than girls. Autistic disorder is classic autism, one of the more severe disorders on the spectrum. Persons with autistic disorder have substantial impairment in social skills, verbal communication, and cognitive and behavioral flexibility. About 70 percent of such persons are mentally retarded, and a third have had at least two unprovoked epileptic seizures by the time they reach late adolescence. About half are nonverbal or have grossly impaired speech. Most persons with autistic disorder are not able to live independently as adults.

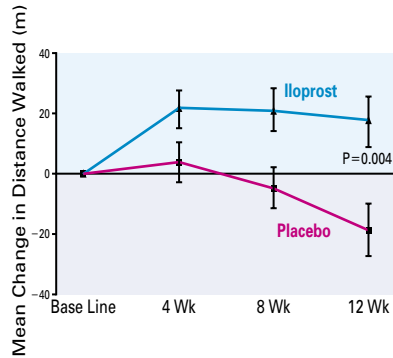
As long as autistic disorder was the only recognized subtype on the spectrum of autistic disorders, autism was considered to be rare (0.4 case per 10,000 persons). In the early 1940s, however, Kanner and Asperger independently described children whose speech was notable

Characteristics of Pervasive Developmental Disorders	
Disorder	Characteristics
Autistic disorder (classic autism)	<ul style="list-style-type: none"> • Presence of ≥ 6 of 12 potential deficits involving all three behavioral domains that define the autistic spectrum: <ul style="list-style-type: none"> ≥ 2 deficits in sociability, empathy, and insight into other persons' feelings and agendas ≥ 1 deficit in communicative language and imagination ≥ 1 deficit in behavioral and cognitive flexibility • Detectable before the age of 3 years • Diagnosis not excluded by the level of cognitive competence or the existence of other handicaps
Asperger's disorder	<ul style="list-style-type: none"> • Troublesome social ineptness, lack of insight • Behavioral inflexibility with a narrow range of interests • IQ ≥ 70 (affected children may be normally intelligent or gifted) • No delay in the emergence of speech • Often clumsiness
Pervasive developmental disorder not otherwise specified	<ul style="list-style-type: none"> • Applies to less severely affected children who do not meet criteria for either autistic disorder or Asperger's disorder
Disintegrative disorder	<ul style="list-style-type: none"> • Early development entirely normal, including speech • Severe regression between the ages of 2 and 10 years, affecting language, sociability, cognition, and competence in skills of daily life
Rett's syndrome	<ul style="list-style-type: none"> • Severe global regression in infant girls (rarely in boys), resulting in lifelong severe mental retardation, lack of language and purposeful hand use, and other neurologic deficits

for its stilted quality and unusual vocabulary and who had many autistic characteristics despite average or superior intelligence. Since then, widespread use of improved, standardized questionnaires and observational scales has resulted in the identification of many persons with less severe disorders on the autistic spectrum, some of whom have received a diagnosis such as developmental language disorder, attention-deficit disorder, or obsessive-compulsive disorder. Their cognitive skills are typically uneven. The least severely affected may not come to medical attention at all or not until mid-childhood or adolescence, despite aberrant types of behavior that are evident to family members, educators, and peers. According to the DSM-IV and ICD-10 classifications, such children who are not retarded and who started to speak at the ex-

pected age have Asperger's disorder, and those who do not meet the criteria for either autistic disorder or Asperger's disorder have pervasive developmental disorder not otherwise specified.

DSM-IV and ICD-10 list two other rare, very severe disorders with a poor prognosis. The first, disintegrative disorder, is diagnosed in previously normal children who do not have a degenerative disease yet inexplicably undergo a catastrophic global regression, with or without epilepsy, and become autistic, most often between the ages of three and six years. Mutations of the *MECP2* gene on Xq28, identified in 1999, cause the second disorder, Rett's syndrome, which affects girls almost exclusively. This disorder is characterized by post-natal reduction in brain growth, with hand stereotypy, seizures, sen-



Inhaled Iloprost for Severe Pulmonary Hypertension

The number of effective, long-term treatments for pulmonary hypertension is limited. In this double-blind, randomized trial, an aerosolized form of iloprost, a stable analogue of the pulmonary vasodilator prostacyclin, was assessed over a 12-week period. Iloprost had a beneficial effect on the combined end point of the distance walked in six minutes and an improvement in the New York Heart Association functional class.

The advantage of iloprost is that it can be administered by inhalation, thus avoiding the intravenous infusion required for the administration of prostacyclin and allowing delivery of the drug directly to the lungs.

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soromotor and autonomic deficits, and curtailment of social, language, cognitive, and neurologic development.

A puzzling feature reported by about a third of the parents of children with autism is stagnation or regression of early language, usually between the ages of 18 and 24 months, and regression of sociability and play, with the appearance of stereotypy. Some parents blame the problem on an intercurrent illness or a traumatic environmental change, but in most cases, it is insidious and unexplained. Clinical or subclinical epilepsy (the latter diagnosed on the basis of epileptiform electroencephalographic features in the absence of clinical seizures) occurs in no more than 10 to 20 percent of children with autism, whether or not they have a history of regression. The value of treatment with antiepileptic medications has not been determined. The natural course of autistic regression is an improvement, although full recovery is rare.

The dramatic increase in estimates of the prevalence of autism — to 2 to 5 cases per 1000 children — has raised the possibility of an

“epidemic” of autism, and school systems are hard put to address the problem. More active case ascertainment and changes in diagnostic criteria probably account in large part for the increase. The role of such environmental factors as perinatal injury, vaccines (exposure to minuscule amounts of mercury preservative or the persistence of measles in the enteric lymphatic system), or food allergies is unsubstantiated. In the case of both autism and a broad spectrum of developmental disorders in families, twin and family studies have implicated multigenic influences in the families of many affected persons. Because autism is a behavioral, not a biologic, diagnosis, prenatal diagnosis is not possible except in the rare case in which autism is associated with a single-gene disorder, such as tuberous sclerosis, Rett’s syndrome, the fragile X syndrome, or Angelman’s syndrome. Research requires brain imaging and electrophysiological, biochemical, and genetic investigations, but the yield of these studies is minimal in the clinic, barring specific indications.

In a distressingly large proportion of children with autistic-spectrum

disorders, tantrums, noncompliance, destructiveness, and self-injury impede integration into mainstream social and educational environments. Pharmacologic agents cannot cure autism because, in most cases, the brain has undergone atypical cellular development dating from the earliest embryonic stages. The goal is to alleviate troublesome symptoms that interfere with the most effective intervention — intensive, targeted education. The results of a controlled study of the effectiveness of risperidone, reported by the Pediatric Psychopharmacology Autism Network in this issue of the *Journal* (see pages 314–321), are therefore welcome and encouraging, despite the acknowledged limitations of the study. The search for safe and effective psychotropic medications has been frustrating so far. May this study be followed by larger, longer, and equally rigorous trials of interventions in children with autism. Such studies are sorely needed.

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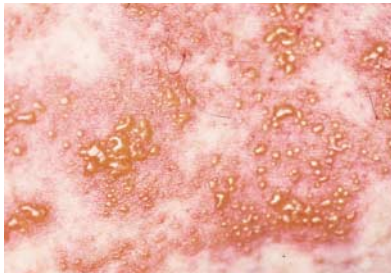
“Diacetyl (2,3 butanedione), a ketone with butter-flavor characteristics, was the predominant compound isolated from air samples.”

Bronchiolitis Obliterans in a Microwave-Popcorn Plant

Bronchiolitis obliterans results in irreversible obstruction of the small airways and has known environmental and occupational causes. An investigation was initiated at a plant that produces microwave popcorn after signs and symptoms of bronchiolitis obliterans developed in eight employees. Among current workers at the plant, those exposed to high levels of diacetyl (2,3-butanedione), the principal additive that is used to give the popcorn its butter flavor, had more than three times the expected rate of airway obstruction and more than twice the expected rate of cough. There were strong relations between the degree of airway obstruction and the level of exposure to diacetyl.

This study provides convincing evidence that occupational exposure to a substance in microwave popcorn, presumably diacetyl, can lead to severe and irreversible airway obstruction.

see page 330 (editorial, page 360)



Clinical Practice: Herpes Zoster

A 77-year-old man has a five-day history of burning and aching pain in his right side and a two-day history of erythema and clusters of clear vesicles, accompanied by headache and malaise. How should he be evaluated and treated?

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Current Concepts: Bites of Venomous Snakes

At least 2000 persons are bitten by venomous snakes in the United States each year. This article reviews the diagnosis and management of bites from venomous snakes encountered in North America, but the same principles apply to management of snakebites elsewhere in the world. The review summarizes the complications of envenomation and explains the current recommendations for the use of antivenoms. It explains how to distinguish venomous from nonvenomous snakes.

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