Background

What is autism?

Treatment successes for some children diagnosed early and treated intensively have increased attention toward making the diagnosis of autism as early as possible.

Autism is a neurological or brain disorder that profoundly affects a person's ability to communicate, form relationships with others, and respond appropriately to the environment. Most autistic children look perfectly normal, but they may have behaviors, such as hand flapping, finger flickering, body rocking or spinning, which attract notice and cause concern. They may also be more sensitive to certain sights, sounds, textures, smells, and tastes. Autism has an onset before the age of 3 and ranges in its effect on development. Along the spectrum, some persons with autism are considered "high-functioning"; many can be mainstreamed into regular school classrooms, some attend college, and some find and maintain employment. At the other end of the spectrum are severely affected persons who may not have any means of communicating with others, or communicate only by repeating words or phrases. They may lack eye contact or regard for faces. They can have additional developmental problems, such as mental retardation. Aggressive and/or self-injurious behavior may be present in some cases.

The diagnostic criteria for autism are listed in the Diagnostic and Statistical Manual-IV (DSM-IV) of the American Psychiatric Association. For a detailed definition, please see Appendix 1. The diagnosis can be difficult to make, but usually results after a parent or another caretaker raises concerns about the child's development. The process of getting a diagnosis may start with a primary care doctor, then often involves developmental specialists (such as developmental pediatricians or developmental psychologists), neurologists, or specially trained social workers or registered nurses. In California, the diagnosis is often made following an evaluation of the child at the local Regional Center (described below). Treatment successes for some children diagnosed early and treated intensively have increased attention toward making the diagnosis of autism as early as possible.

History of the Regional Center System in California

In 1969, the Lanterman Mental Retardation Services Act established regional coordination of care for persons with mental retardation. This care was overseen and managed through an association of Regional Centers located throughout California. In 1973, this act was extended to serve persons with cerebral palsy, epilepsy, autism and other conditions similar in severity to mental retardation. In 1976, the Lanterman Developmental Disabilities Services Act was amended to establish the right to treatment and habilitation services for person with developmental disabilities. Children and adults are referred to their local Regional Center by health-care providers or other health or service organizations, or families may self-refer their children. An assessment is undertaken to determine if the person qualifies for services as outlined in the Lanterman Act. Typical services that are coordinated through the Regional Center include therapies such as physical therapy, occupational therapy, and speech therapy; planning for educational goals; provision of necessary medical devices, such as wheelchairs; and the provision of respite care for the family or guardians. Twenty-one Regional Centers located throughout California coordinate these services through a array of case managers, community service providers, and professional staff (i.e. psychologists, social workers, and nurses). (See Appendix 2 for locations of Regional Centers.) The Regional Center system in California is unique as a service mechanism through which the needs of developmentally disabled citizens are addressed.

Collection of Information in the Regional Center System

California's Regional Center System has compiled over 20 years of data from annual assessments of individuals who qualify for service. The Client Development Evaluation Report (CDER) is the assessment instrument that is administered to each client at intake, and yearly thereafter, to determine developmental and functional status. The types of information collected on the CDER form include reporting date, who prepared the form, developmental diagnostic information (documentation of mental retardation, cerebral palsy, autism, seizure disorder, and/or other), mental disorders, chronic major medical conditions, medications, and categorization of deficits in use of muscles, independent living, social, emotional, cognitive, and communication skills. A copy of the CDER form is included in Appendix 3.

The CDER database, a potentially rich source of statewide data regarding autism, has been primarily used for administrative purposes. Many potential problems exist in using these data for more than their primary purpose. The major drawback of these data for tracking changes in autism over time is the lack of specific and uniform criteria in establishing a diagnosis of autism across the State's Regional Centers and across time. The written guidelines for determining whether a child has autism are that "the diagnosis in this section must be provided by a person qualified to diagnose autism." The presence or absence of autism is recorded on page 3 of the CDER with one of four different codes — CDER Status 0, CDER Status 1, CDER Status 2 and CDER Status 9. CDER Status 0 is None (no evidence of autism). CDER Status 1 is labeled "Full Syndrome" autism and is believed to be roughly equivalent to meeting DSM-IV criteria for autism, but this assumption has not been validated prior to this

study. CDER Status 2 is labeled "Autism, residual state," but this designation lacks a DSM-IV equivalent. CDER Status 9 is labeled "Autism suspected, not diagnosed." An additional category for autism was coded in the data, CDER Status 4, based on diagnostic coding made on the CDER that captures other conditions along the autism spectrum, such as Pervasive Developmental Disorders (PDD), including PDD, not otherwise specified (PDD-NOS); Asperger's Disorder; Rett's Disorder; and Childhood Disintegrative Disorder. These data were used in the DDS Report discussed below. There are additional potential problems with using CDER data to track changes over time in autism. The CDER database tracks children who qualify for developmental services, but has no record of children who were assessed but did not qualify for services. By anecdotal report, the database is not always updated, even when evaluations change over time, but the extent of this problem is unknown.

A 273% increase in reported cases of autism from 1987 through 1998 is far in excess of population changes of approximately 20% for the State during the same time.

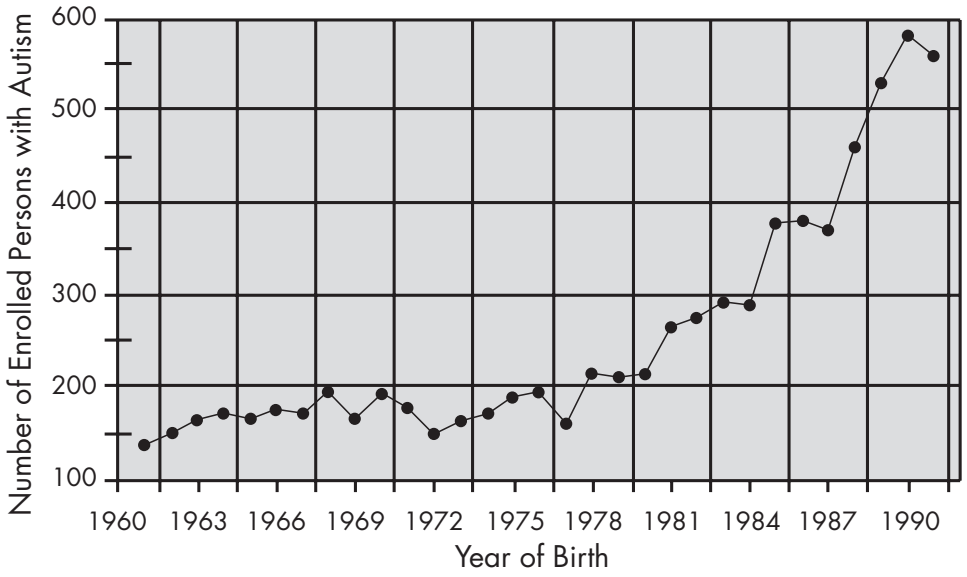
The March 1999 DDS Report to the State Legislature

In March 1999, the California Department of Developmental Services issued a report entitled "Changes in the Population of Persons with Autism and Pervasive Developmental Disorders in California's Developmental Services System: 1987 through 1998" (this report will be referenced as "the DDS Report").[1] During the 12-year period covered in the report there was a substantial (273%) increase in reported cases of autism (CDER status 1 and 2) from 2,778 to 10,360. This is far in excess of the population increase of approximately 20% for the State during this period. The report also documented a 69% increase in the total Regional Center consumer population of 80,483 to 136,383 during the same period. The number of Regional Center consumers with any designation of autism (CDER status 1, 2, 4, and 9) increased from 3,864 to 11,995, an increase of 210%. In comparison, the number of consumers with cerebral palsy increased from 19,972 to 28,529 (43%), consumers with epilepsy increased from 22,683 to 29,645 (31%), and consumers with mental retardation increased from 72,987 to 108,563 (49%). In 1988, consumers with autism in all forms accounted for 4.9% of all consumers of Regional Center services in the state. In 1997, this proportion had increased to 9.4%. These numbers pointed to increases in the total number of

children with autism and increases in the proportion of developmental disorders that are due to autism in California.

The number of cases of autism per birth year is shown in Figure 1. This figure shows relatively stable numbers of Regional Center consumers with autism until 1981, after which time the number of consumers with autism steadily increased.

Figure 1. *Distribution of birth dates of regional center eligible persons with autism*



(from "Changes in the Population of Persons with Autism and Pervasive Developmental Disorders in California's Developmental Services System: 1987 through 1998")

Legislation Authorizing This Study

The findings from the DDS Report generated much concern and controversy. In order to answer many of the questions that were raised by that report, as well as independent observations of increases in autism, the State Legislature allocated $1,000,000 for the Department of Developmental Services to "enter into an interagency agreement with the University of California's Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute to prepare a comprehensive pilot study to examine all factors surrounding the increased number of persons with autism and autism spectrum disorders in California from 1977 to 1999." (SB 160) This document reports the findings from the statewide comprehensive pilot study conducted by researchers at the University of California, Davis, and their colleagues at the University of California, Los Angeles.

Review of research on the causes of autism and other current issues

Epidemiology of Autism

Autism affects neurodevelopment in multiple and profound ways, yet much remains to be learned about what causes autism or even how common autism is. Estimates of the prevalence of autism vary, with higher rates reported in more recent studies. Prior to 1985, autism was believed to be a rare condition with an estimated prevalence of 4-5 per 10,000.[2] Since that time, prevalence estimates have been in the range of 10-12 per 10,000, but prevalence studies done in the United States have shown lower rates.[3] It is suggested that the changes in rates are due in part to changes in how autism is diagnosed. The lower prevalence estimates in the past were based on Kanner's description of the classic autism prototype, where autism usually affects children with an IQ range of 50 to 70. Most recent prevalence studies are based on DSM III-R, DSM-IV, or ICD-9 criteria, which define autism more broadly.† The prevalence of other autism spectrum disorders is much higher than that of autism, with estimates ranging from 1.8 per 1,000 to 5 per 1,000.[3,4] An investigation of children aged 5 to 11 years in Cambridgeshire (UK) provided an estimate of 1 in 175 for the prevalence of autism spectrum disorders, including Asperger's Disorder.[5]

Autism produces profound effects in neurodevelopment in multiple ways, yet much remains to be learned about what causes autism or even how common autism is.

Epidemiological studies demonstrate a strong genetic component. The relative sibling recurrence risk is 45-90 times that of the general population.[6] (Recurrence risk to young siblings of children with autism is 4.5% compared to the occurrence in the general population of 0.05-0.1%.) Autism occurs in males 3 to 4 times more frequently than females.[2-4] Studies of families with multiply affected members have identified many chromosomes that are highly associated with autism, but not universally found in children with autism. Twin studies have found a concordance of 36% to 91% in identical twins compared to a less than 1% concordance rate in fraternal twins.[7,8]

Many children with autism also have other medical and developmental conditions. According to previous data, the majority of children with autism (about 75%) have

† It should be noted that the change in diagnostic criteria from the Kanner definition to DSM or ICD criteria predates the increases noted in the DDS Report, which spans 1987 to 1998.

mental retardation.[9] (Whereas, the majority of children with autism spectrum disorders without "full" autism do not.[2]) Other conditions associated with autism include epilepsy, visual and auditory sensory impairments, neurofibromatosis, tuberous sclerosis, Angelman's syndrome,[10] untreated phenylketonuria, and fragile-X syndrome. However, most children with autism do not have a recognizable genetic syndrome.

The question as to when autism begins in any child remains to be answered. Some studies provide support for a prenatal or perinatal origin for autism. Data from analyses of neonatal blood spots taken from children later diagnosed with autism showed that 95% of a small sample of children with autism have elevated levels of four neuropeptides and neurotrophins.[11] However, these findings were not specific to autism and were also found in children with mental retardation, but not in children with cerebral palsy.[11] A study of morphologic changes noted at birth found that 42% of children with autism had posteriorly rotated ears, which would suggest changes that occur at least by the first month of gestation for a large number of children with autism.[12] While most children with autism display delayed development from birth, regression of development (i.e. a period of normal development then an apparent loss of developmental milestones) is reported in 30% to 35% of cases,[13-16] leading some to suspect postnatal factors contribute to the development of autism for at least some children.

The question as to when autism begins in any child remains to be answered.

Many other associations have been suggested by prior studies of autism, including viral exposures, vaccinations,[17] immunologic factors,[18] autoimmune disorders,[19,20] gastrointestinal disorders,[21] prenatal exposure to thalidomide,[22] anticonvulsants,[23] and food allergies.[24,25] The interaction between a genetic predisposition and early environmental insults has also been suggested.[26]

Viral causes have been suggested due to early findings that suggested an association between month of birth and autism,[27-29] but other studies have failed to confirm this association.[30,31] One study found that prenatal or neonatal exposure to chickenpox, measles, mumps or rubella was associated with autism, but further concluded that the attributable risk associated with these exposures is small.[32]

The possible association of autism with vaccinations has received increased scrutiny following the case series presented by Wakefield, *et al* describing regression in previously normal children, development of autism and enterocolitis, and temporal association of the MMR vaccination.[21] Vaccine strain measles in peripheral mononuclear cells was detected in three of nine children with autism in one study.[33] How-

ever, population studies have not found a causal association between MMR vaccination and autism.[13, 34] The issue is far from resolved for parents of children with autism, especially for those considering immunizations for their later-born children.

Implications of Current Understanding About Autism in the Context of the Current Study

One of the most controversial aspects of the DDS Report is whether the significant increase in numbers of Regional Center individuals with autism is due to increased rates of autism or to some other factor (or combination of factors) that artificially increases the number of children with autism presenting for services. These factors include increases in the overall population of children, loosening the criteria used to establish the diagnosis of autism, prior misclassification of autism as mental retardation, increases in the number of children with autism moving in from out-of-state, and improved case finding.

Only a small portion of the apparent increase in autism cases can be explained by the increase in the State's population.

The DDS Report did not address population growth over the time of the study. California's population increased by approximately 20% from 1985 to 1995, which is an order of magnitude less than the two- to three-fold increase in persons with autism served by the State's Regional Center system. Thus, only a small portion of the apparent increase in autism cases can be explained by the increase in the State's population.

Changes in the diagnostic criteria for a spectrum disorder can change the number of cases identified. If the criteria loosen to include more children who are less severely affected, the number of cases will be artificially increased. Following this line of reasoning, children with autistic features that do not have "full syndrome autism" (meeting DSM-IV criteria) may be given the classification of CDER status 1 autism in order to qualify them for services that would not be available to those classified as CDER Status 9 autism. This process would artificially inflate the number of cases of autism. Furthermore, the Regional Center threshold for establishing a diagnosis of CDER status 1 autism has been assumed to match the criteria from the recognized standard at the time of diagnosis. The current standard is DSM-IV, but the standard was DSM-III and DSM-IIIR during the study period for the DDS Report. Prior to this

study, the extent to which misclassification contributed to the observed increase in autism cases in California was unknown.

Recent data suggest that the increase in cases of autism matches a decrease in cases of mental retardation.[35] Changes in how both autism and mental retardation are classified could cause an artificial increase in autism cases. It is possible that children with both mental retardation and autism could be classified as having mental retardation with autistic features. This might have been recorded as something other than CDER Status 1 in the past, but now similarly affected children may be entered into the data as autistic (CDER status 1 autism) with mental retardation. Presumably, this misclassification occurred more in the past, when the imperative for early diagnosis of autism to allow for early intensive therapies was not as great.

Only a small portion of the apparent increase in autism cases can be explained by an increase in the State's population.

In-migration could contribute to a real increase in the number of cases of autism, but not be due to increased incidence rates of autism among children in California. One might postulate that children with autism from another state may move to California if their home state provides fewer services than California. The extent to which the observed increase in autism can be explained by in-migration was not known prior to this study.

Improved case finding could result in an apparent increase in the number of cases of autism in California. CDER data only describe children included in the State's Regional Center System. Children outside the Regional Center system are not counted in CDER data. Some assume that the Regional Center system captures virtually every case of autism, because the Regional Centers are pivotal in coordinating and financing services for children with autism. Still, improved recognition of autism by both parents and professionals may result in more children with autism being directed to the Regional Centers for services. Autism case finding in California could have been further increased by the implementation of early intervention programs that have increased the diagnosis and treatment of developmental disorders in infants and young children. This study does not examine the extent to which differences in case finding over time have resulted in any changes in the number of autistic children who present to the Regional Centers.

One of the reasons that the DDS Report generated so much concern is that 1) the etiology of autism is unknown and 2) the increase in reported cases of autism could be the result of a new exposure. While genetic factors are strongly associated with autism, the uncertainty about the increasing prevalence rates of autism raises doubts that

genetic factors alone are responsible. The increase in children with autism presenting for care to the Regional Center system is far in excess of what would be expected for a typical genetic condition. This uncertainty, along with parental concerns about other potential causes, has implications beyond the children with autism and their families. Some of the concern is focused on a potential association of autism with vaccinations, especially MMR. This has led to concerns among public health officials that parents will cease to follow recommended vaccination schedules, placing children at risk of contracting vaccine preventable illnesses.

Aims of the Study

The principal aims of this study are listed below:

- **Study Aim 1:** *To investigate whether changes over time in the criteria used to diagnosis CDER status 1 autism account for a significant proportion of the increased numbers of cases of autism.*
- **Study Aim 2:** *To investigate whether the misclassification of some cases of autism as mental retardation in the past has contributed to an apparent increase in the number of children with autism.*
- **Study Aim 3:** *To investigate whether temporal changes in children with autism moving into California for services account for a significant proportion of the increased cases of autism reported to DDS.*
- **Study Aim 4:** *To describe how characteristics of children with autism have changed over time.*
- **Study Aim 5:** *To ascertain what parents of children with autism believe caused their child's autism, and to determine if this has changed over time.*
- **Study Aim 6:** *To determine if vaccination with MMR vaccine is associated with an increase in the recurrence rate of autism in subsequent siblings.*

Scientific Advisory Panel

The M.I.N.D. Institute convened a Scientific Advisory Panel to review and advise the draft research proposal for the Autism Epidemiology Study.

The panel met November 11-12, 2000, in Sacramento, California. Following the recommendations that came out of that meeting, the Principal Investigator and study staff made adjustments to the focus and methodology for the study. A final proposal was sent to the Scientific Advisory Panel for review in April 2001, and some changes were made following the receipt of their comments. The names and affiliations of the Scientific Advisory Panel members are listed in Appendix 4.