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Prader–Willi Syndrome: Genetics and Behavior

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Abstract

Since its inception, the John F. Kennedy Center has attempted to overcome developmental problems, which create restrictive barriers to the participation of individuals with specific disabilities in our broader society. Some of Nicholas Hobbs's earliest efforts involved developing strategies for preventing children's emotional and behavior problems, which interfered with their later full participation in society. Other investigators in the Kennedy Center explored ways of reducing dysfunctional repetitive movement problems and self-injury commonly associated with autism and severe mental retardation. We have become concerned about a group of people who have the potential to live largely independently (or semi-independently), to work at meaningful jobs in the community, and to make full use of the same recreational and leisure opportunities as other members of society but who are prevented from doing so because of a life-threatening behavior problem. Prader–Willi syndrome (PWS) is a genetic developmental disability characterized by a group of specific behavioral features of which an insatiable appetite is the most striking. PWS is the most commonly known genetic cause of obesity. The eating disorder associated with PWS can be so severe as to be life threatening, including eating to the point of stomach rupture and death. Though a cluster of commonly covarying clinical features are exhibited by people with this syndrome, only the eating disorder is common to all affected individuals.

PWS shares behavioral features with other disorders and disabilities, such as obsessive compulsive disorder and autism, but only PWS includes the unique combination of characteristics that distinguish this syndrome. Because eating disorders such as bulimia and anorexia nervosa also

share features with PWS, any light that could be shed on the causes and treatment of the eating disorder in PWS could potentially have far-reaching implications for other eating disorders as well. In this article, we review the behavioral, cognitive, and other psychological features of PWS and explore their relationships to known genetic mechanisms.

History and Prevalence

PWS was first described by Prader, Labhart, and Willi in 1956, and since that time over 800 cases have been reported in the literature (Butler, 1990, 1994; Butler, Meaney, & Palmer, 1986; Greenswag & Alexander, 1995). The main clinical features included poor muscle tone during infancy with improvement by 9 months of age and obesity with onset between 6 months and 6 years of age, with an average age of onset by 2 years of age. In addition, children with PWS have underdeveloped sex organs, and as adults, they are usually infertile. Though people with PWS have a developmental disability, they do not necessarily have mental retardation. Slightly less than half of the people with PWS function in the low to average range of intellectual functioning, and somewhat more than half test in the mild to moderate range of mental retardation. People with PWS have short stature, small hands and feet, and often light skin and hair coloration (sometimes albino). Roughly 60% to 70% have a partial deletion of a section of the long arm of chromosome 15. The diagnosis is easier to make in males than females, particularly during infancy; therefore, more males are reported with this disorder. PWS affects about one in every 10,000 to 20,000 individuals (Butler, 1990; Greenswag & Alexander, 1995). This syndrome has been reported in all races and ethnic groups, although it is reported disproportionately in Whites. It is not known whether this reflects differences in reporting by different racial and ethnic groups or whether it reflects actual base rate differences.

Prenatal Development

Most pregnancies of children with PWS are uneventful, though reduced fetal movement is noted in the majority of PWS pregnancies. About one fourth of babies with PWS are in an unusual position, such as breech presentation, at delivery. About one half of babies with PWS are born either earlier or later than the anticipated date of delivery. There is an overrepresentation of babies with PWS born in the autumn months—specifically October—for reasons that are unclear.

Birth and Early Infancy

Because of generalized poor muscle tone, PWS babies are often described as having a floppy appearance. Medical evaluations (such as standard blood tests, brain coaxial tomograph [CT] scans, etc.) are usually either normal or not diagnostic for a specific syndrome. Most infants with PWS have a weak cry, display little spontaneous movement, sleep excessively, and have a poor suck reflex, which may require tube feedings. Ironically, failure to thrive and poor weight gain are common features of infants with PWS. These babies may also have temperature instability, and their body temperature may rise or fall for no known reason. It is thought that these changes in body temperature and abnormal appetite may be due to a hypothalamic abnormality.

Mild atypical facial features emerge during infancy including a narrow forehead; small upturned nose; thin upper lip and down-turned corners of the mouth; a long, narrow appearing head; and upward slanting of the palpebral fissures (Butler, 1989, 1990; Butler et al., 1986). In addition, babies with PWS often have excessively sticky saliva (see Figure 1).

Genetics

Maps now exist for all 23 pairs of human chromosomes. Each chromosome has a short arm (called the *p arm*) and a long arm (or *q arm*). Locations along each arm are labeled numerically beginning at the centromere, which separates the long and short arm of each chromosome. In 1980, Ledbetter et al. (1980) reported a small section missing from the proximal long arm of chromosome 15 in a group of people with PWS. Using newly developed, high-resolution chromosome methods, Ledbetter et al. found that the deleted section extended from the 11th to the 13th band of chromosome 15, which is designated as the 15q11q13 region (see Figure 2). Butler and Palmer (1983) found that chromosomes of the parents of the affected individuals were generally normal, but the chromosome 15 deletion originated with the father in all PWS families studied. This puzzling observation was studied later using newer molecular genetic techniques. In addition, Strakowski and Butler (1987) found an overrepresentation of fathers working in occupations where they were exposed to hydrocarbons (e.g., paint thinners, dry cleaning fluid) at the time of conception, compared with the general population. The chromosome 15 deletion was seen in about 60% of people with PWS, whereas the remaining patients showed normal chromosome 15s, or translocations or other anomalies involving chromosome 15.

Butler et al. (1986) found clinical differences in people with PWS who had normal appearing chromosomes from those with the visible chromosome 15 deletion. Individuals with the chromosome 15 deletion had lighter hair and eye color and fairer complexion than other similarly aged family members; individuals reported that they burned very easily in the sun. The people with PWS who showed visible deletions were more homogenous in their clinical features than the individuals with PWS who did not have chromosome 15 deletions.

Nicholls, Knoll, Butler, Karam, and Lalande (1989) used newer molecular genetic techniques to study chromosomes of individuals with PWS that appeared normal—that is, which had no deleted section. They reported a fascinating finding. People with PWS who had normal-appearing chromosome 15s received both members of the chromosome 15 pair from their mother and no chromosome 15 from their father. This phenomenon was called *maternal uniparental disomy* of chromosome 15.

Thus, there are two genetic causes of PWS: (a) a deletion of the 15q11q13 region of the father's chromosome 15 or (b) two copies of chromosome 15 from the mother, which is observed in about 25% of people with PWS (Mascari et al., 1992). An intact chromosome 15q11q13 region is required from the father to prevent the findings recognized as PWS. If this chromosome region had been deleted or if the entire chromosome 15 from the father was absent, the offspring had PWS.

In the late 1980s, several people were reported who had the same apparent chromosome 15q11q13 region deleted but who did not have the classic features of PWS. They had unsteady gait; seizures; and a wide-appearing head, nose and mouth. They lacked speech, had severe mental retardation, and often displayed peculiarly inappropriate laughter. This condition is called Angelman syndrome (named after Dr. H. Angelman, who first described people with these findings in 1965). Molecular genetic studies of chromosome 15 showed the deletion, when present (70% of people with Angelman syndrome have a 15q11q13 deletion, and the remaining people have normal appearing chromosome 15s), was from the child's mother, and the intact chromosome 15 was from the father (Williams, Gray, Hendrickson, Stone, & Cantu, 1989; Zackowski et al., 1993). A small percentage of individuals with Angelman syndrome (about 5%) received both copies of chromosome 15 from the father and no chromosome 15 identified from the mother. Thus, PWS and Angelman syndromes represent the first examples in humans of genetic imprinting, or the differential expression of genetic information whether inherited from the mother or from the father. Therefore, a gene or genes may only be functional on one member of a chromosome pair. This newly reported genetic phenomenon may play a significant role in other poorly understood genetic conditions.

Increasing evidence suggests that the cluster of features composing PWS may be determined by more than one gene from the chromosome 15q11q13 region. That is, it is a *contiguous gene syndrome*. There are several candidate genes on chromosome 15 that appear to contribute different features of PWS. The locations and names of candidate genes on chromosome 15 from the 15q11q13 region and their possible role in PWS are shown in Figure 2. One important candidate gene is SNRPN (small-nuclear ribonucleoprotein polypeptide N), which is received from the child's father (not active on the mother's chromosome 15) and is found in the smallest deletions recognized in PWS patients (Buiting et al., 1995; Ozcelik et al., 1992). Additional studies are needed to identify and characterize genes from the 15q11q13 region that may cause PWS and Angelman syndrome.

Eating Disorder

Many Americans eat too much too often, but the eating disorder with PWS has an entirely different magnitude. Individuals with PWS have a voracious appetite, never satiated and rarely vomiting. The resulting obesity is substantial and highly resistant to change (Holm, 1981). As many as one third of PWS patients weigh more than 200% of ideal body weight (Meaney & Butler, 1989; Schoeller, Levitsky, Bandini, Dietz, & Walczak, 1988). Food-related behavior problems often become prominent around age 4. Temper tantrums related to attempts to satisfy an insatiable appetite are common (e.g., Bray et al., 1983). When thwarted in their attempts to obtain food, many individuals with PWS display "rages" (Cassidy, 1984). Holm (1981) reported that 74% of the sample of children and adults with PWS had "violent outbursts" related to obtaining food. The home lives of families of adolescents and young adults with PWS are often made intolerable by the struggle over controlling their food intake. These individuals can weigh 250 to 300 lb by late teens if the food intake is not controlled, and they are generally short when considered within their family's height history (Butler et al., 1988). The average man with PWS is 5 ft 1 in. tall, and women with PWS average 4 ft 10 in.

Additional problems during adolescence and adulthood include sleep disturbances and sleep apnea, which may correlate with the degree of obesity. Scoliosis, or curvature of the spine, and osteoporosis may also occur, and PWS patients should be monitored for these problems and treated accordingly. Table 1 includes the frequency of clinical findings seen in PWS patients.

People with PWS may have 40% to 50% body fat, which is two or three times more than normal individuals, whereas the lean body mass is lower than for normal individuals. A sex-reversed fatness pattern (i.e., males have more fat than females) is also observed (Meaney & Butler, 1989). The heaviest deposition of subcutaneous fat is in the trunk and limbs.

People with PWS usually avoid physical exercise (e.g., Greenswag, 1987; Hill, Kaler, Spetalnick, Reed, & Butler, 1990; Schoeller et al., 1988); however, it is unclear whether this is more of a problem in people with PWS than other people with comparable obesity and body build. People with PWS not only need fewer calories to maintain their weight than do lean people, they require fewer calories for maintenance than others who are equally obese (Cassidy, 1984). Schoeller et al. (1988) reported that even after weight loss, children with PWS could consume no more than an average of 60% of a typical diet and still maintain their weight.

Behavioral and Cognitive Development

Childhood

Most children with PWS have delayed developmental milestones in early childhood. Infants with PWS typically sit independently at 11 to 12 months, crawl at 15 to 16 months, walk independently at 24 to 27 months, use their first word at 23 to 28 months, and have 10-word vocabularies at 38 to 39 months (Butler et al., 1986; Dunn, Tze, Alisharan, & Sulzbacher, 1981; Greenswag, 1987). The delay in achieving motor milestones appears to be due in large part to slowed psychomotor development and not to excessive weight. Language appears to be the most delayed of the developmental milestones (Butler et al., 1986).

About one half of children with PWS develop temper tantrums and stubbornness between 3 and 5 years of age and may also display depression by adolescence. Behavioral problems are commonly precipitated by with-holding of food; however, increasing evidence indicates many behavior problems may not be food related. Intolerance for changes in routine is a severe problem for many youth and adults with PWS. Controlling food intake, managing the obesity, and behavioral problems are often very difficult for parents to handle. Early diagnosis and intervention with dietary restrictions (about 60% of normal) and increased physical activity and family counseling are needed to control the obesity and its life-threatening complications.

Adolescence and Adulthood

Adolescents with PWS do not sexually mature as rapidly as their peers, though interest in dating and participation in typical heterosexual friendships appear similar to those of matched peers. External signs of adulthood such as beard growth in boys, underarm and pubic hair, and enlargement of breasts in girls may not be apparent or are delayed.

Approximately one third of appropriately aged girls with PWS have menstrual periods, although not regularly. Adolescent girls are unlikely to become pregnant, and boys with PWS are not known to produce sperm. Some female and male adolescents have undergone hormone therapy with some success in developing secondary sexual characteristics. Typical adolescent rebelliousness is often exaggerated in these individuals, with a constant struggle with parents and other adults over access to food.

More Serious Behavior Problems and Psychiatric Symptoms

The early literature on psychiatric symptoms in PWS relied heavily on anecdotal case reports using retrospective interviews and symptom questionnaires. These findings emphasize a variety of personality problems manifested as frequent temper tantrums, stubbornness, manipulative behavior, depression, emotional lability, arguing, worrying, compulsive behavior, skin picking, difficulty adapting to new situations, difficulty relating to peers, poor social relationships, low self-esteem, and difficulty in detecting social cues from other people (Cassidy, 1984; Greenswag, 1987; Hall & Smith, 1972; Hermann, 1981; Holm, 1981; Peri, Molinari, & DiBlasio, 1984; Sulzbacher, Crnic, & Snow, 1981; Whitman & Accardo, 1987).

Several studies have included comparison groups. Turner and Ravacabu (1981) compared the maladaptive behavior of people with PWS and mental retardation who were residing in an institution with controls matched for age, sex, and intellectual level, but not obesity status. The PWS participants were more verbally aggressive, self-assaultive, and regressive but less sexually inappropriate than the controls. Taylor and Caldwell (1983) compared PWS participants and a group of intellectually similar, obese persons on Part 2 (Maladaptive Behavior) of the American Association on Mental Deficiency (AAMD) Adaptive Behavior Scale (ABS). People with PWS were more self-abusive (often displaying skin picking), exhibited less stereotyped behavior, and were less sexually aberrant than the controls, although these latter differences did not reach the $p < .05$ confidence level.

Curfs, Hoondert, Van Lieshout, and Fryns (1995) compared children with PWS and regular school children matched on sex and age but not intellectual level using a Dutch translation of the California Child Q-set—a measure of behavior and personality characteristics. Children with PWS were less agreeable, less conscientious, less open to new ideas and experiences, less motorically active, more irritable, and more dependent than children in the comparison group. However, it is not clear to what degree the obtained findings were influenced by differences in functioning level and not PWS per se. The personality dimensions were not systematically related to with the presence or absence of a 15q11q13 deletion.

Dykens, Hodapp, Walsh, and Nash (1992) reported Child Behavior Checklist (CBCL) data for adolescents and adults with PWS. They report elevated scores, as compared with normative values, for three age groups (13–19, 20–29, 30–46 years). Externalizing broadband scale scores were significantly greater than Internalizing scale scores primarily during adolescence. The behavior problems most often reported were those generally regarded as characteristic of PWS (e.g., temper tantrums, arguing, irritability, stubbornness, lying, skin picking, obsessions, defiance). Curfs, Verhulst, and Fryns (1991) performed a similar study of children and adolescents with PWS who were 6 to 18 years of age; the study

revealed that 81% of youth with PWS had CBCL total behavior problem scores greater than the 90th percentile.

Considerable recent attention has been directed toward the compulsive behavior exhibited by people with PWS. People with PWS often hoard, repetitively count, arrange, check, and clean repetitively and excessively as assessed by scales such as the Yale–Brown Obsessive Compulsive Scale (Dykens, Leckman, & Cassidy, in press; Stein, Keating, Zar, & Hollander, 1994). Dykens et al. found compulsive symptoms in up to 60% of persons with PWS studied. Increasing evidence points to the possibility that some people with PWS may have obsessive–compulsive disorder, which suggests it may be profitable to explore the neurobiological basis of the two conditions further in an effort to identify a common pathway.

Cognitive Characteristics

Decreased intellectual functioning was among the four original defining characteristics of PWS (Dunn, 1968; Prader et al., 1956; Zellweger & Schneider, 1968). IQs have ranged from 12 to 100 in those studies in which individual test results or ranges have been reported (Butler et al., 1986; Crnic, Sulzbacher, Snow, & Holm, 1980; Dunn et al., 1981; Dykens et al., 1992; Hall & Smith, 1972; Jancar, 1971; Zellweger & Schneider, 1968). The average IQ is typically in the mild range of mental retardation (55 to 70). The distribution includes few cases within the average range of intelligence or profound range of mental retardation.

Early reports suggested IQ values in PWS declined with age in cross-sectional (Crnic et al., 1980) and longitudinal studies (Dunn et al., 1981). However, a more recent study failed to reveal an IQ decrease over time (Dykens et al., 1992). On the contrary, test scores were remarkably similar over testing sessions 3 years apart for subjects ages 3 to 30 years.

Other correlates of IQ in this population include body weight and chromosomal factors. Crnic et al. (1980) reported individuals with PWS who were never obese had significantly higher IQs ($M = 80.25$) than PWS subjects who were currently obese ($M = 57.33$) or had been obese and had lost weight while participating in a comprehensive weight management program ($M = 59.90$). Differences in the groups were not associated with differences in parent education. However, as Dykens et al. (1992) pointed out, Crnic et al. did not take into account variability in height of their subjects. The relation between obesity, assessed as body mass index, and IQ in 18 persons with PWS was $r = -0.21$ and statistically nonsignificant in their study. Butler et al. (1986) compared IQs of their patients based on presence or absence of a chromosome 15 deletion and found subjects with the deletion had higher IQs ($M = 69.6$) than patients without the deletion ($M = 59.2$).

Some consideration has been given to relative strengths and weaknesses in intellectual or cognitive abilities among people with PWS. Typically, these analyses are based on psychological test profiles and include comparisons of verbal and performance portions of intelligence tests, variation in subtest scores, and styles of cognitive processing such as the simultaneous and sequential scores from the Kaufman Assessment Battery for Children (K–ABC; Kaufman, 1983). Many people with PWS score significantly higher on the performance subtests (Curfs et al., 1991), but this has not been a universal finding (Gabel et

al., 1986). Block Design on the Wechsler test (WISC-R; Wechsler, 1974) appears to be strength for some subjects (Curfs et al., 1991) and suggests an ability to recognize and evaluate figural relations greater than would be expected based on other aspects of cognitive functioning. Dykens et al. (1992), using the K-ABC, found significant weakness in sequential processing relative to simultaneous processing—a finding consistent with the view that people with PWS have strengths in tasks “requiring the integration of stimuli in a spatial mode” (p. 1128). Anecdotal reports of superior puzzle-solving ability in PWS patients are also consistent with this hypothesis (Holm, 1981).

Warren and Hunt (1981) compared cognitive capabilities of adults with PWS and controls matched on mental age and IQ. The PWS subjects had difficulty with short-term memory processing, and they lost more information that they had learned over time as compared with controls. Warren and Hunt speculated that stimulus encoding may be limited. There were no significant differences in long-term memory.

Branson (1981) reported that 52% of her sample of 21 children with PWS demonstrated language comprehension and production abilities commensurate with overall cognitive level. The remaining children had uneven receptive language (comprehension) profiles relative to their expressive (production) abilities. Seventeen of 21 children exhibited atypical speech-sound production skills. There was considerable variability ranging from unintelligible speech in some cases to extremely subtle difficulties in others. These difficulties included nasal air emission, oral-motor difficulties, and other articulation deficits. Branson concluded there was a lack of common features in the speech and language abilities of children with PWS and that individualized assessment and therapy (where necessary) were recommended. A recent study by Kleppe, Katayama, Shipley, and Foushee (1990) revealed multiple articulation errors (dysarthria), reduced intelligibility, and delayed language skills (vocabulary, syntax and morphologic abilities) in children with PWS.

Academic Achievement

Early studies suggested that children with PWS may have concomitant learning disabilities given their frequent placement in learning disabilities educational programs (cf. Sulzbacher et al., 1981). Such placements were apparently based on the observed variability in relative skills and deficits in academic performance. It was reported that reading abilities were generally better developed than arithmetic abilities. A subsequent analysis of 232 people with PWS conducted by Greenswag (1987) found that 75% of the participants had received special education services. These persons typically performed at the sixth grade level or lower in reading and the third grade level or lower in mathematics. However, the degree to which referral for special education services was based primarily on delayed cognitive functioning versus presentation of behavior problems (e.g., tantrums, stealing food, skin picking, and other self-injury) is unclear.

Studies that included standardized achievement testing generally support the view that PWS subjects have somewhat higher reading than math scores, although the magnitude of the differences is small (Dykens et al., 1992; Taylor & Caldwell, 1983). Contrary to the learning disabilities hypothesis, Taylor and Caldwell reported no differences in level of academic achievement between the PWS participants and a comparison group of intellectually similar,

obese persons. Moreover, the achievement test scores were fairly consistent with the intelligence scores. Dykens et al. (1992) reported that among adolescent and adults with PWS, there was a significant difference in Academic Achievement section of the K-ABC as compared with the sequential and simultaneous processing components of the test. However, the difference was attributable to the fact that overall academic achievement scores were higher than the ability measures, which raises questions concerning the learning disabilities hypothesis of PWS.

Adaptive Behavior

There has been very little formal assessment of adaptive behavior functioning in persons with PWS. Taylor (1988) reported AAMD ABS data from an unpublished study conducted by Taylor and Caldwell (1983). ABS scores of adults with PWS were compared with those of a group of intellectually similar, obese individuals without the syndrome. The only significant difference between the groups on Part 1 of the ABS was in the physical development category, where the subjects with PWS had scores that were 34 percentile points below those of the control group.

In an attempt to establish the developmental profile of adaptive behavior of adolescents and adults with PWS, Dykens et al. (1992) used the Vineland Adaptive Behavior Scales. Adaptive strengths were apparent for the group as a whole in daily living skills, and a relative weakness was in socialization particularly in coping skills. Dykens et al. also reported that daily living skills become more of a strength with increasing age. They suggested that strengths in domestic skills might reflect selective interest and experience with food-related behavior (e.g., meal preparation), which would show up on the test as a domestic skill strength.

Laboratory Assessments of Learning and Memory

Historically, studies of cognitive ability in populations with mental retardation have often used standardized intellectual assessments to investigate cognitive functioning. Recently it has been suggested that a more profitable approach to understanding cognitive features of individuals with mental retardation emphasizes differences in cognitive features as a function of the etiology of the mental retardation, rather than the degree of an intellectual impairment, per se (Burack, Hodapp, & Zigler, 1988). This strategy encourages exploration of variables that may have significance for a specific population. This may be an especially promising approach to take in studies of PWS, owing to the unique behavioral aspects of the syndrome, especially those relating to food.

Few studies of learning address specific aspects of cognition in PWS. Warren and Hunt (1981) found that children with PWS did less well on a picture recognition task than did children with mental retardation of unknown etiology matched for chronological age and IQ. The two groups of children performed similarly on a letter comparison task meant to measure access to overlearned items in long-term memory. The authors concluded that children with PWS have a deficit in short-term visual memory, but not in visual long-term storage. Visual perception, organization, and puzzle-solving skills have been reported as relative strengths in people with PWS. Taylor and Caldwell (1983) reported subscores from

the Wechsler Adult Intelligence Scale (WAIS) for adults with PWS and obese control subjects matched for overall IQ. The highest subtest scores for the subjects with PWS were on picture completion, object assembly, and block design. Similarly, Curfs, Wieggers, Sommers, Borghgraef, and Fryns (1991) found that 9 of 26 children with PWS scored significantly higher on the Block Design subtest of the WAIS.

A possible weakness in auditory attention was reported by Gabel et al. (1986) based on results from the Detroit Tests of Learning Aptitude subtests. Children with PWS performed at a level more than 3 years lower on the auditory attention span subtest than on the visual attention subtests. Matched control subjects had only a 1-year discrepancy for the same subtests. Another potential cognitive weakness was revealed by scores on the K-ABC reported by Dykens et al. (1992). A significant weakness in scores on the scale for sequential processing was found for adults and adolescents with PWS. Sequential processing is important for tasks whose execution requires performing the steps making up the task in a temporal sequence or specific order (e.g., dialing a telephone number).

Methods that make use of controlled laboratory testing and computer technology exist for studying learning in people who have disorders associated with mental retardation. We discuss two of these methods: the repeated acquisition of behavioral chains and stimulus equivalence learning. The repeated acquisition of behavioral chains procedure was developed to address an important problem in the study of learning: how to assess the effects of variables, such as drug dose, on learning in a single individual (Boren & Devine, 1968). The solution is for an individual to learn a new sequence of responses during each experimental session so that a new learning curve is produced, permitting multiple assessments of learning. The typical apparatus has several response options (e.g., buttons, levers, or keys) which the participant must learn to select in a specific order in response to unique stimuli at each step in the sequence. Each step in the sequence is referred to as a *link*, and the terminal link is followed by reinforcement. A distinct cue is associated with each link in the sequence. The participant is required to learn to choose a new sequence of responses in each session, eventually producing a similar learning curve each time. Effects of additional variables can then be assessed using this acquisition baseline.

This procedure has been adapted for participants with mental retardation by presenting the task on the screen of a computer monitor fitted with a touch-sensitive screen. Each screen is divided into quadrants that each contain a photograph of a familiar object (e.g., lamp, car). Several of these screens are shown in a given order to the participant, who must learn to touch the quadrants that are designated as “correct” in the session. The same sequence of screens is repeated throughout the learning session. Figure 3 shows an example of a three-link chain.

The task can be divided into two components: acquisition of the new response sequence and the steady state behavior shown after the new sequence is learned. The data can be plotted as percent correct responses as a function of trial, and a curve can be fitted to them. The typical result is a negatively accelerated curve that yields a measure of speed of learning (the half-life) and stable performance once learning is complete (the asymptote). The half-life value is the number of trials it takes the participant to reach 50% of their asymptotic performance.

Figure 4 shows a typical learning curve produced with the repeated acquisition of behavioral chains procedure for a participant with mental retardation.

It is often of interest to determine if there are procedural aspects of the learning situation that facilitate or impede learning. In PWS, an obvious experimental variable is food-related stimuli. Using food in learning situations for people with PWS has been admonished (Lupi, 1988); however, there are no published studies systematically examining this question. The involvement of food-related stimuli in a learning task in persons with PWS may be such a case. We are currently investigating the repeated acquisition of behavioral chains procedure comparing pictures of food with pictures of salient nonfood objects. We found faster learning and more rapid stable performance when food pictures were used for adults with PWS (Joseph & Thompson, 1996).

The second method for studying new learning by people with mental retardation uses a procedure called matching-to-sample to teach new categories of items and is referred to as stimulus equivalence learning. Matching to sample is a familiar procedure used in many children's books in which the child is asked to point to one of two words (e.g., *dog* vs. *cat*) along the bottom of the page that is the same as shown in the picture (e.g., of a Collie) at the top of the page. In the laboratory version, a person is taught at least two relations, such as the Arabic numeral 3 corresponds to both a set of three objects and the Roman numeral *III*. As an indirect result of this learning, the person is usually capable of matching the Arabic numeral 3 and the Roman numeral *III* to each other, even though these relations were not explicitly taught. A demonstration of this sort of response transfer has come to be called stimulus equivalence learning, because the stimuli are equivalent in meaning in the appropriate context. A formal demonstration of stimulus equivalence relations requires a demonstration of three logical properties: reflexivity, symmetry, and transitivity (Sidman & Tailby, 1982). Reflexivity refers to the ability to match a stimulus to itself (identity matching). Symmetry is shown when the roles of sample and comparison are reversed (i.e., if taught to select 3 when shown *III*, one is also able to select *III* when shown 3). Transitivity can be seen when one is able match two stimuli correctly that have both been related to third stimulus. In the previous example, this would entail choosing the array of three objects in response to the Roman numeral *III* and the reverse.

Stimulus equivalence relations are one form of abstract symbolic relations and may be a basis for many basic conceptual skills involved in academic learning. Because equivalence relations involve both directly taught and inferred relations, they are a good preparation to study the effect that food may have on learning in people with PWS, either as instructional cues or as reinforcing consequences for correct choices. Stimulus equivalence learning may depend on how reinforcers are presented during teaching: Reinforcers may be correlated with a specific problem or set of relations to be learned, or the same reinforcer may follow all problems being taught, which is the typical practice.

In laboratory studies, improved learning and better terminal performance is usually seen in situations using a specific, different reinforcer for each relation being taught, which has been called the Differential Outcomes Effect (Trapold, 1970). Joseph, Overmier, and Thompson (in press) examined the use of food and nonfood reinforcers in stimulus equivalence learning

by five adults with PWS, presenting both types of reinforcers differentially and nondifferentially. The performance on test trials for the relations composing equivalence indicated that food reinforcement resulted in superior transfer if the reinforcers were presented nondifferentially; however, if the reinforcers were presented differentially (i.e., each reinforcer is uniquely associated with only one potential stimulus class, e.g., animals vs. plants), the two types of reinforcers resulted in equal amounts of concept transfer. Figure 5 summarizes the results of data for five adult participants with PWS. The data indicate that the use of food reinforcers in adults with PWS can facilitate the learning of complex symbolic relations; however, it is not necessary to use food reinforcers to achieve this result if the reinforcers are strictly associated with a unique set of relations being taught. This strategy of associating reinforcers with a set of problems to be learned has promise as an instructional strategy for people with PWS and perhaps for others populations with mental retardation.

Gene Behavior Relationships

There is strong evidence that PWS is a contiguous gene syndrome. Several DNA loci in the 15q11q13 region appear to regulate specific features of the syndrome, such as the voracious appetite, partial crossing of visual pathways, hypopigmentation, and other behavioral and emotional problems. A project currently underway at the Kennedy Center in collaboration with colleagues in the Vanderbilt University Medical Center is designed to clarify the relation between chromosome 15 abnormalities of people with PWS (macro and specific submicroscopic deletions) or disomy and the resulting neurochemical, metabolic, and behavioral phenotypic expression. We know that approximately 95% of all people with PWS will have a discriminable chromosomal abnormality (60% macrodeletion, 15% microdeletion, 20% disomy, and 5% no detectable abnormality).

There are thought to be approximately 100 genes between the common breakpoints on the proximal long arm of chromosome 15. Although it is theoretically possible that within any group of people with PWS, each person could have a deletion in a different area of chromosome 15, in practice, that is not the way deletions occur. They group in some areas that overlap across affected individuals. In our research project, we are looking for patterns of neurochemical, physiological, and behavioral differences in those people with PWS as compared with all other people with PWS who do not share that deletion. If, for example, all individuals with a given overlapping deletion—say at the D15S63 locus—had elevated endogenous opioid blood levels, lowered total energy expenditure, increased frequency of skin picking, and increases in relative preference for high fat foods, then we are attempting to determine whether other individuals with PWS who do not have deletion of D15S63 fail to share some or all of these characteristics. We then determine that the probability is that those differences would occur by chance in only those subjects with the D15S63 locus deletion. If the differences are statistically meaningful, we are then able to say that DNA within the locus in question must code for a protein that somehow regulates all of those processes in common, which is an invaluable lead in tracking down the common mechanism responsible for the group of features. The foregoing configural strategy allows us to determine patterns of cognitive, behavioral, physiological, and neurochemical outcomes that

covary with specific genetic lesions among a group of people with PWS and the degree to which those features differ from matched controls.

Implications

It is reasonable to ask whether it makes sense to invest the resources of a substantial federally funded research project to study a condition with a prevalence of 1 in approximately 12,000 births. There are three reasons why this is an appropriate investment: (a) It could reduce the human suffering associated with the syndrome itself and reduce the economic costs associated with the care of people with PWS; (b) there is the possibility of discovering a gene-controlled amino acid or neurochemical mechanism underlying PWS that is shared with other eating disorders (e.g., anorexia and bulimia) or other generic forms of obesity; and (c) we achieve the thorough evaluation of a model for studying specific gene-behavior disorder relationships, which can subsequently be modified to explore other genetically based behavior disorders associated with developmental disabilities (e.g., autism, de Lange syndrome).

Parents of children with PWS describe the lives they and their children lead as trapped in a food-oriented world, a life in which nearly every moment of every day revolves around a struggle to prevent the child from overeating (Wett, 1988). The anguish many families experience leads them to conclude that placing their son or daughter with mild or moderate mental retardation in a highly restrictive institutional treatment setting is more humane than confronting them with the daily battle of deciding what to eat or not eat, in a less controlled community setting (Thompson, Greenswag, & Eleazer, 1988). As a result, many very capable young women and men find themselves living in unnecessarily restrictive settings in other respects, surrounded by people with severe and profound mental retardation who often display very severe behavior problems (violent aggression and self-injurious behavior). This is an unacceptable choice to be forced to make, but it is the only available alternative for many.

Approximately 1 out of every 12,000 births are of children with PWS, and there are 3.5 million children born each year in the United States; therefore, approximately 250 children are born each year with PWS. The average life expectancy of people with PWS is not precisely known, though we believe it is somewhat shorter than the average for the general population. If one assumed the average life expectancy (for the general population) was 50 rather than in the mid-70s and that most of the adult life is spent in closely supervised institutional settings (in order to restrict access to food), one can estimate the lifetime cost per person and for a generation of people with PWS. We further assume that not all people with PWS receive such costly care and that as many as one third manage without specialized community or institutional care. The total number of individuals with PWS in the United States should be around 12,000 to 12,500 (i.e., 250 children born per year with PWS and each person lives to 50 years; therefore, 250 times 50 equals 12,500 individuals). Braddock, Hemp, Fujira, Bachelder, and Mitchell (1990) summarized the cost of institutional services, and the daily per diem for institutional care was \$153, or an annual cost of \$55,845 per person. If one assumed that only half of the life of a person with PWS is spent in a restrictive residential setting (e.g., 25 years), the per-person cost would be \$1,396,125. If one further

assumes that two thirds of the 12,000 people receive such residential services (9,000 people), the lifetime cost would be \$12,565,125,000 for residential services alone for the current group of people with PWS. These figures would not include the costs associated with specialized health expenses, additional professional consultation, acute hospitalizations, and so on. In short, if research on the causes and treatment of PWS brings the uncontrollable eating under even modest control, the cost of a research project such as that currently under way at the Kennedy Center would be paid for 200 to 300 fold.

Our research on PWS explores several plausible gene-regulated mechanisms that may account for, or be intimately involved in, the voracious eating and the weight gain associated with PWS. It is possible one or more of these processes may be shared with other eating disorders, such as forms of bulimia, anorexia nervosa, pica, or other forms of genetically regulated obesity. Because obesity is one of the major health problems facing the United States, any contribution to preventing these eating and weight control problems could be a significant public health contribution.

Finally, it is clear that emotional and behavior disorders associated with developmental disabilities account disproportionately for the cost of care of people with mental retardation in the United States. Destructive behavior is a burden on the health care, the educational, and the social service systems, to say nothing of the individuals and families involved. Much as the eating disorder associated with PWS is related to specific genetically mediated neurochemical or metabolic problems, the same is likely to be true of other developmental disabilities commonly associated with self-injury and aggressive behavior (e.g., autism, de Lange syndrome, fragile X syndrome). We believe our experience with PWS will provide a strategy that could serve as a model for understanding other genetically mediated behavior disorders associated with developmental disabilities.

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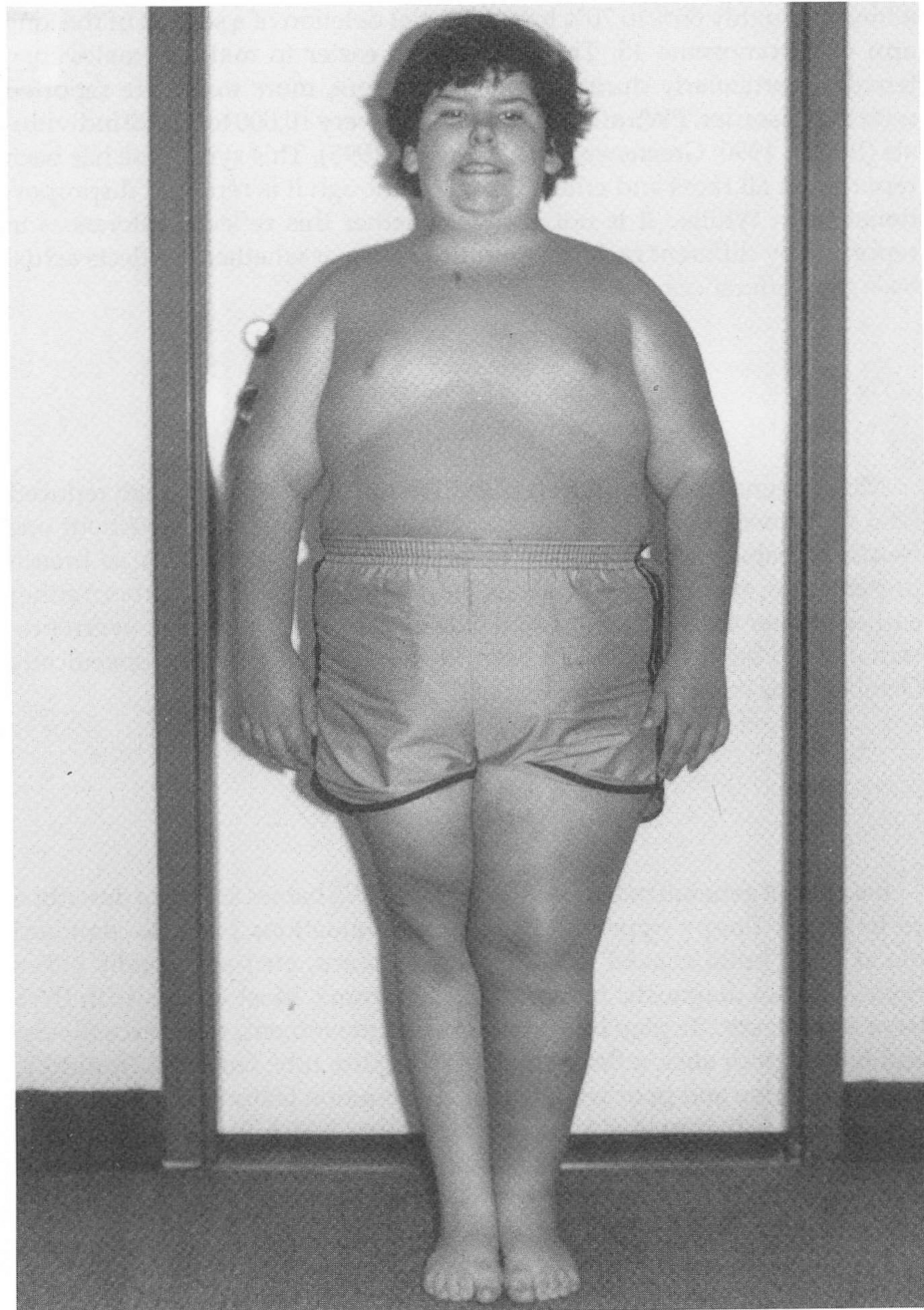


Figure 1.
A photograph of a typical 10-year-old male with Prader–Willi syndrome with uniparental maternal disomy of chromosome 15 (both 15s from the mother).

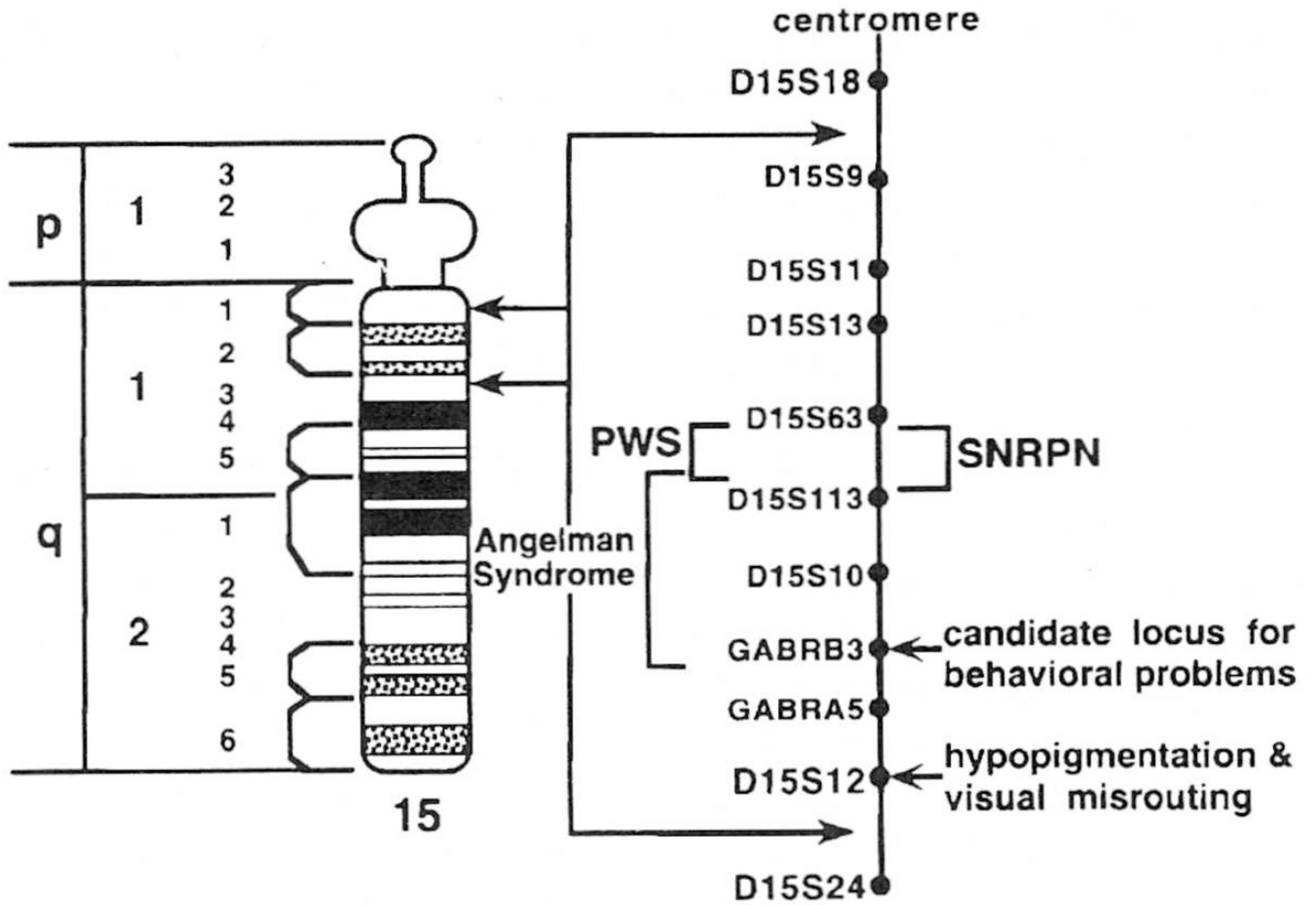


Figure 2.

A high resolution chromosome 15 idiogram or drawing showing the chromosome bands and the numbers assigned to the band as well as the chromosome breakpoints, designated by arrows at 15q11q13, leading to the 15q11q13 deletion commonly seen in Prader-Willi syndrome (PWS) patients. An expanded view of the 15q11q13 region with assigned locations of DNA loci or markers including known genes in the region. An approximate position for the gene(s) for PWS is shown in the drawing along with the location of SNRPN—a paternally expressed candidate gene for PWS. The approximate site designated where the gene(s) are located that cause Angelman syndrome, an entirely different clinical condition but with a similar 15q11q13 deletion but of maternal origin, is also shown. Other DNA loci that may cause additional features in both PWS or Angelman syndrome are also given.

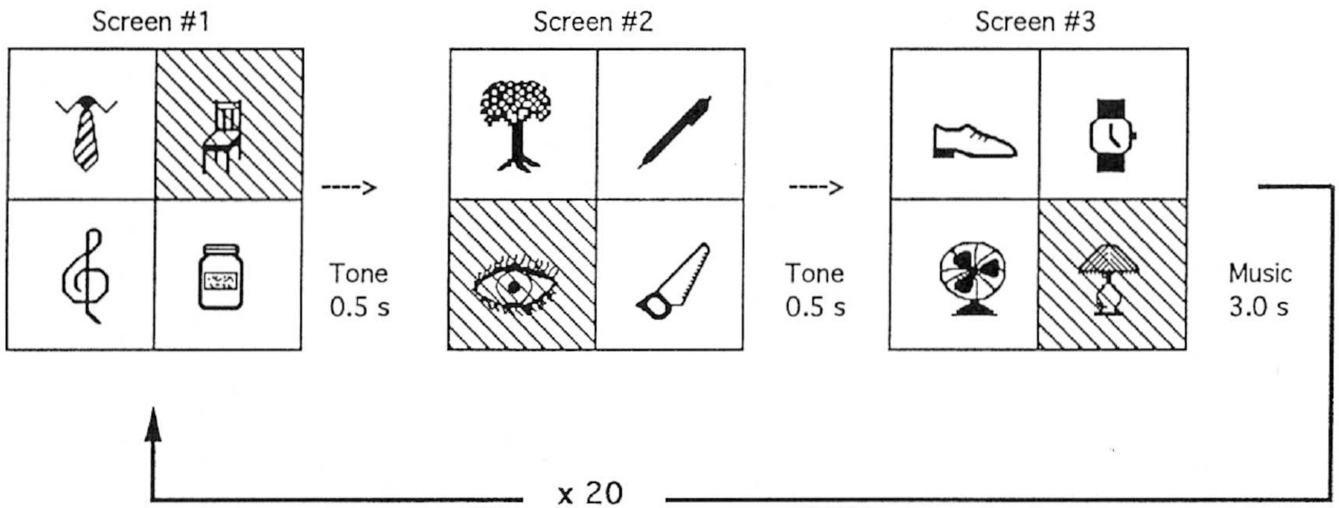


Figure 3. A diagram of the repeated acquisition task showing an example of a session with a three-response chain length. The individual would initially be shown Screen 1 (left). The shaded quadrants of each screen indicate correct responses for the session. A touch to the upper right quadrant of Screen 1 would result in a tone, a 0.5-s interval, followed by the presentation of Screen 2. A touch to the lower left quadrant of Screen 2 would result in the tone, 0.5-s interval, and the presentation of Screen 3. A touch to the lower right quadrant of Screen 3 would result in a musical phrase being played, the 3.0-s intertrial-interval, and the presentation of Screen 1 (Trial 2). Twenty repetitions of the three-response sequence constitute one experimental session.

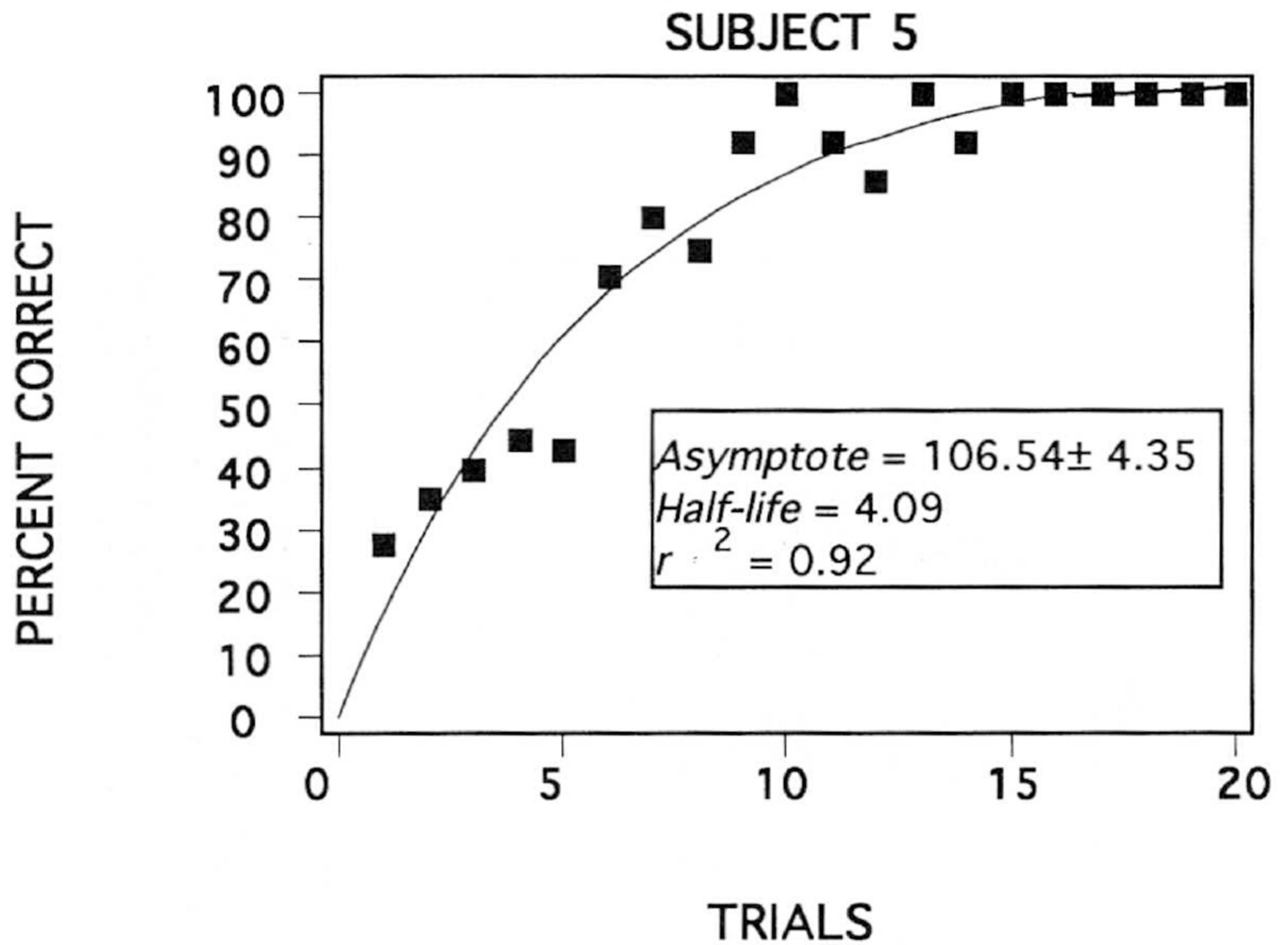


Figure 4.

An example of a curve produced by an individual with moderate mental retardation at a four-response chain length on the repeated acquisition procedure. The half-life indicates the number of trials needed to reach 50% of the asymptotic performance

Performance on Transitivity Probes

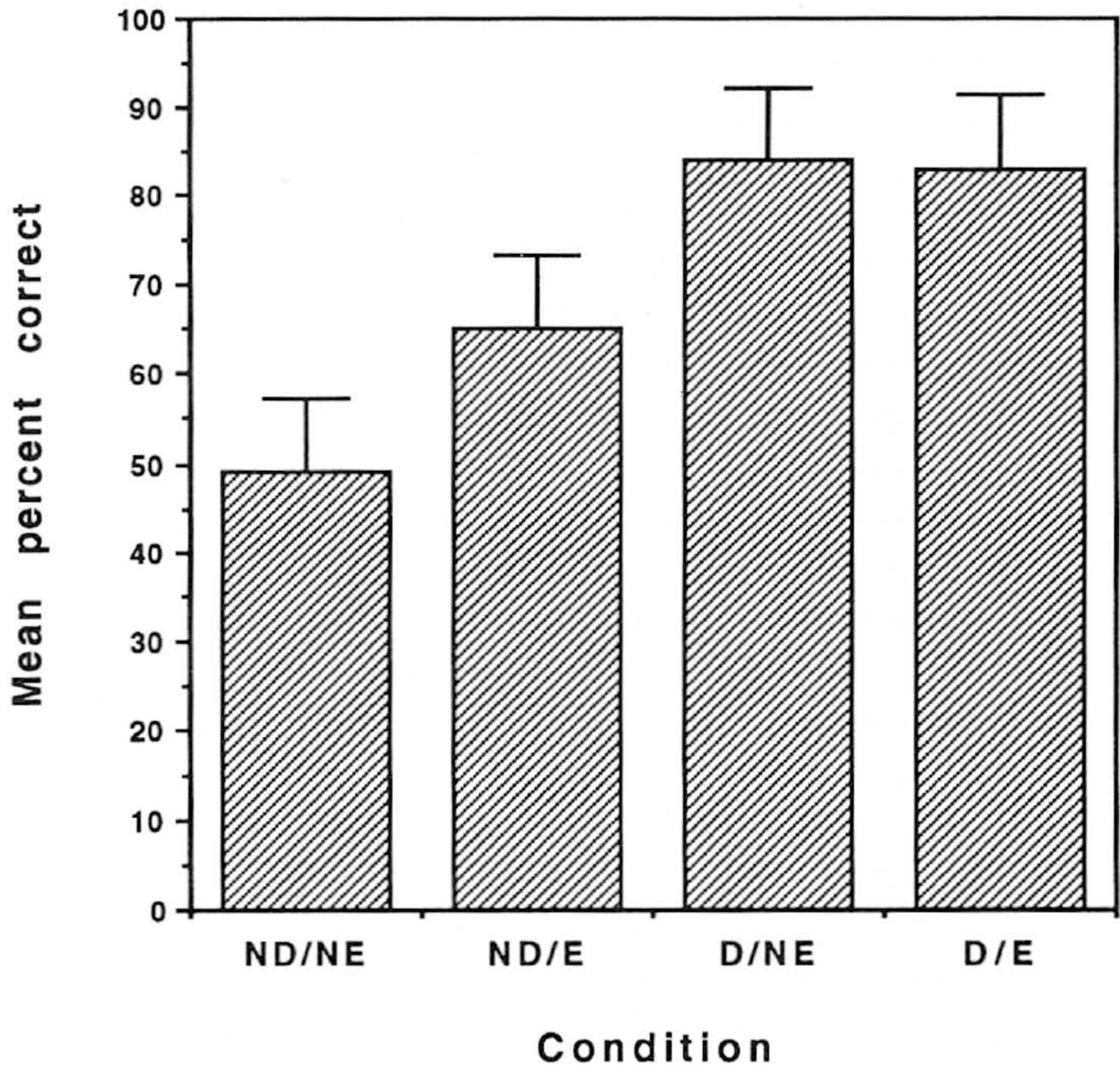


Figure 5.

Results of transfer tests for derived relations (transitivity) for five subjects with Prader–Willi syndrome. The abbreviations for the conditions stand for (from the left), nondifferential, nonedible outcomes (ND/NE), nondifferential, edible outcomes (ND/E), differential, nonedible outcomes (D/NE), and differential, edible outcomes (D/E). Error bars reflect +1 SEM.

Table 1**Clinical Features of Individuals with Prader–Willi Syndrome (PWS)**

Clinical Features	Overall %
Gestation	
Reduced fetal activity	76
Nonterm delivery	41
Breech presentation	26
Early infancy	
Developmental delay	98
Hypotonia (weak muscle tone)	94
Feeding problems	93
Low birthweight	30
Brain function and behavior	
Mental deficiency	97
Personality problems	41
Seizures	20
Growth	
Obesity	94
Short stature	76
Delayed bone age	50
Face	
Narrow forehead	75
Almond-shaped eyes	75
Strabismus	52
Early dental cavities /enamel hypoplasia	40
Sexual development	
Hypogonadism/hypogonadism (underdeveloped sex organs)	95
Cryptorchidism (undescended testicles)	88
Menstruation	39
Skeletal	
Small hands and feet	83
Scoliosis	44
Other	
Skin picking	79
Reduced glucose tolerance/diabetes mellitus	20
Miscellaneous	
Sex: Female/male ratio (about 1:1.5)	
Incidence (about 1 in 10,000–20,000)	

Note. About 70% of PWS individuals have a partial deletion of chromosome 15 (15q11q13 region) that is donated by the father; about 25% have maternal uniparental disomy of chromosome 15 (both 15s from the mother); whereas the remaining 5% have other chromosome 15 abnormalities or genetic imprinting errors. These features are as summarized from the literature from over 500 reported PWS subjects by Butler in 1990.